INTRODUCTION: Stem cell-based suicide gene therapy is an attractive modality attributable to inherent tumor-tropic properties of stem cells as cellular vehicles. Multilineage-differentiating stress-enduring (Muse) cells exhibit self-renewal and multipotency within the nervous system, and they do not form teratomas in immunodeficient mice. Besides, when intravenously injected into immunodeficient mice, the cells are integrated into damaged lesions of the respective tissues. Because of these properties including immunotolerance and migratory capability, Muse cells are one of the most attractive vehicles for stem cell-based suicide gene therapy. In the present study, we demonstrated a potent migratory capacity of Muse cells transduced with HSVtk gene (Muse-tk cells) toward glioma. [Methods and Results] In vitro migratory capacity of Muse-tk cells toward brain tumor cells was also examined using Matrigel invasion assay and conditioned medium (CM) of U87 and U251 human glioma cells in the lower chamber. Only Muse-tk cells but not non-Muse-tk cells migrated to the lower chamber filled with CM of U87 and U251. Next, U87-luc cells were implanted in one side of the nude mouse brain and labeled with Muse-tk cells in the opposite hemisphere. Histological examination on day 7 demonstrated numerous labeled Muse-tk cells around the tumor site and also some in the corpus callosum. When GCV was systemically administered, growth of U87-luc tumors was significantly inhibited through the bystander effect between tumor cells and Muse-tk cells that had migrated from the opposite brain (*p<0.05) and the survival time of the mice significantly prolonged (*p<0.05) [Conclusions] Muse-tk cell therapy is still effective when injected at a far distant site to the glioma. P = 0.0343; 8x increase vs. TTFields, P = 0.049). In addition, massive aberrant mitotic figures were visible in the TTFields treatment groups, detected by immunofluorescence microscopy. TTFields are already a promising, well tolerated new treatment modality on top of the standard treatment regimen. Despite advances in genetic knowledge of these tumors the outcome remains fatal. Delta-24-RGD is a safe adenvirus that is currently in clinical trial for adult gliomas with promising results. The main objective of this study is to evaluate the safety and the antitumor effect of Delta-24-RGD alone or combined with radiotherapy in DIPGs. Previously we showed that Delta-24-RGD displayed a potent antiangiogenic effect (IC50 ranging from 5 to 50 MOls) in DIPG cell lines (n=4) that was mediated by an effective proapoptotic activity. Delta-24-RGD effects, including an inducing a synergistic e antitumor ffect (CI<1). Delta-24-RGD is able to infect and to replicate in radiated DIPG cells even at high doses (12 Gy). Virus inhibited key proteins involved in DNA repair that play important roles in the resistance to radiotherapy such as Rad51 or the NMR complex. In vivo studies show that administration of Delta-24-RGD in orthotopic DIPG tumors presented no toxicity. Efficacy studies of the virus alone or in combination with radiotherapy in nude mice are on-going. Our results showed that Delta-24-RGD exerts an effective antiangiogenic effect in vitro with no toxicity in vivo. This adenovirus is able to infect, replicate and to induce tumor cell death. Besides, this vector is able to prove its efficacy in orthotopic glioma models. Delta-24-RGD therapy is better than the chemotherapy alone or combined with radiotherapy and could provide a significant therapeutic advantage.

EXTH-09. LOOKING FOR A CURE: DELTA-24-RDG AND RADIOThERAPY FOR DIPG TREATMENT
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Abstracts
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is a possible agent that can enhance tumor cytotoxicity and radiosensitivity.
We have found that VPA possess mild antitumor activity, may induce apoptosis (mild) as well as autophagy in gloma cell lines, and can increase antitumor activity of TMZ with the capacity to reverse resistance. We investigated the anti-glioma efficacy of dihydroartemisinin (DHA) and combined with temozolomide (TMZ) on human glioma cell lines in vitro and in vivo. Our data suggest that DHA can inhibit proliferation of gloma cell lines and increase antitumor efficacy of TMZ, and TMZ can induce autophagy. We have tested and found that Beta-elemene (β-ELE) could compensate for TMZ to kill both glioma stem-like cells (GSCs) and non-stem-like cancer cells. Notch1 might be a downstream target of β-ELE. In conclusion, repurposing existing drugs which are not antitumor agents could be one of the permission ways for glioma treatment.

EXTH-15. TESVEATINIB MONOTHERAPY EFFICACY AGAINST GBM IS ROBUST IN VITRO BUT RELATIVELY MODEST IN THE INTRACRANIAL GBM12 MODEL, DESPITE EXCELLENT BRAIN PENETRATION
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BACKGROUND: Tesveatinib (TES) is a potent brain penetrant EGFR/VEGFR2 inhibitor. This study evaluated TES monotherapy efficacy in a wildtype EGFR overexpressing, patient-derived xenograft (PDX) glioblastoma (GBM) model of GBM12, a drug resistant cell line U87MG, the early passage GBM10 and M-HBT-161 cultures, and CD133- and SOX2-positive stem cell-like spheres. These inhibitors at 1-8 µM triggered significant inhibition of cell survival and induced apoptotic cell death in GBM cells and GSCs, CAY 10603, Tubastatin A. The ACY-1215 reduced cell survival in U87MG by 50% (IC50) at 1.07, 5.83, and 6.27 µM treatment for 96h, respectively. Moreover, CAY 10603-triggered cell death in U87MG cells as well as CD133/SOX2-expressing spheres was associated with activation of caspases-3, -6, and -9, while β-catenin, a key component of the Wnt pathway, was more activated in GBM10 than in U87MG cells. The results suggest that using HDAC6 inhibitors alone or in combination with other agents may potentially improve the survival of brain tumor patients.

EXTH-12. β-ELEMEHNE SELECTIVELY INHIBITS THE PROLIFERATION OF GLIOMA STEM-CELL-LIKE CELLS THROUGH NOTCH1 DOWNRREGULATION
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BACKGROUND: Beta-elemene (β-ELE) is a compound from a Chinese herb whose anti-cancer effect has been shown in various types of cancer. However, its role in the inhibition of glioma stem-like cells (GSCs) has not yet been reported. METHODS: The inhibitory effect of β-ELE (with or without TMZ) on GBM12 (stem cell-like) and parental U87MG cells was evaluated in vitro and in vivo. The molecular mechanisms were also investigated.
RESULTS: We have found that β-ELE selectively inhibited the proliferation and sphere formation of GSCs other than parental glioma cells, while TMZ exerted its effects on parental cells instead of GSCs. In the in vivo data, we confirmed that the combination of β-ELE and TMZ worked better in the xenografts of GSCs. Notch1 was downregulated upon β-ELE treatment. Our data also demonstrated that the continuous administration of β-ELE produces an ideal effect to control tumor progression in vivo.
CONCLUSIONs: Our finding demonstrated that β-ELE could compensate for TMZ to kill both GSCs and non-stem-like cancer cells. Notch1 might be a downstream target of β-ELE. Therefore, our data shed light on improving the outcome of glioma patients by combining β-ELE and TMZ.