SP5

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Novel binary targeting molecule enhances radiation response in glioma model by induction of DNA damage and delay of DNA repair

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The most common and deadliest primary brain tumor derives from the cells that support neurons in the brain and is called glioblastoma multiforme (GBM). Although glioblastomas are known to be one of the most radioresistant types of tumor, development of new targeted drugs and their combination with radiotherapy have spawned renewed interest and enthusiasm for investigating new treatments possibilities. The aim of this study was to investigate the effect of ZRBA1, EGFR/DNA damage binary targeting molecule, in combination with radiation on proliferation of human glioma cells. The effect of ZRBA1 on the radiosensitivity of U87 and U373 cell lines was evaluated using clonogenic assays and spheroid migration assay whereas DNA damage and cell cycle progression were evaluated by FACS assays. Our data revealed that exposure of GBMs cells to ZRBA1 before irradiation resulted in an increase in radiosensitivity with dose enhancement factors at surviving fraction of 0.1 ranging from 1.3 to 1.7. Additionally, such combinational treatment caused strong cell cycle arrest in the G2/M phase (up to 72h post-treatment), which was accompanied by increased level of phosphorylated H2AX histone (gamma-H2AX). Importantly, in contrast to Temozolomide which enhances radiation response most effectively in MGMT-negative cells, radio-sensitizing proprieties of ZRBA1 does not depend on the MGMT methylation status. Overall, we demonstrated that ZRBA1 can enhance tumor cell radiosensitivity in vitro and suggest that this effect could be related to an inhibition of DNA repair. Therefore we postulate that ZRBA1 may be developed as a potent and innovative radio-sensitizing agent to treat malignant glioma tumors.

SP6

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Preclinical Evaluation of Oral Metronomic Topotecan and Pazopanib for the Treatment of Aggressive Extracranial Pediatric Solid Tumors

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Background: Metronomic chemotherapy with VEGF pathway inhibitors is a highly effective strategy to inhibit angiogenesis and tumor growth. We tested efficacies of daily oral metronomic topotecan and pazopanib, as monotherapy and combination, in three pediatric extracranial tumors mouse models; and the effect of prolonged therapy with the combination on tumor behaviour in a neuroblastoma mouse xenograft model. Findings: In vivo, the combination demonstrated significant anti-tumor activity compared to respective single agents in all models. Reductions in viable Circulating Endothelial Progenitors and tumor microvessel density were correlated with tumor response and therefore confirmed the antiangiogenic activity of the regimens. However, combination also caused significantly higher myelotoxicity. For studying the tumor behaviour to our therapy, a time-response study (28, 56 and 80 days) was conducted in SK-N-BE(2) xenograft model. We found that only combination-treated animals survived till 80 days. However, tumors in these animals started growing gradually after 50 days. Unlike single agents, all three durations of combination significantly lowered microvessel densities, compared to control; with higher pericyte coverage after 56 and 80 days. The combination increased hypoxia, proliferation and glycolysis in the tumor. Conclusion: Combination of metronomic topotecan and pazopanib has superior efficacy than either single agents, which is attributed to superior antiangiogenic activity. However, prolonged treatment with combination can have additive myelotoxicity and may encounter adaptive resistance in neuroblastoma, associated with metabolic reprogramming and increased proliferation of the tumor cells.

SP7 Withdrawn

SP8

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Glioma stem cell specific microRNA-mRNA interaction network

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The role of cancer stem cells in tumor formation and tumor heterogeneity is currently one of the most researched topics in cancer biology. A better understanding of molecular mechanisms regulating the biology of cancer stem cells may ultimately help provide a better management of cancer patients. Various individual or families of microRNAs have been shown to have oncogenic or tumor suppressor function in glioblastoma (GBM). MicroRNAs have functional relevance in regulation of critical genes and pathways implicated in maintenance of glioma stem cell (GSC) properties. To avoid inclusion of inherent bias of miRNA-target prediction algorithms, we have applied biochemical methods to establish direct miRNA-mRNA interaction network relevant and specific to GSCs. We have generated an unbiased global miRNA mediated RNA-RNA interactome by performing RNA-sequencing all RNA species