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Differential gene expression-based connectivity mapping identified novel drug candidate and improved Temozolomide efficacy for Glioblastoma

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Abstract

Background: Glioblastoma (GBM) has a devastating median survival of only one year. Treatment includes resection, radiation therapy, and temozolomide (TMZ); however, the latter increased median survival by only 2.5 months in the pivotal study. A desperate need remains to find an effective treatment.

Methods: We used the Connectivity Map (CMap) bioinformatic tool to identify candidates for repurposing based on GBM's specific genetic profile. CMap identified histone deacetylase (HDAC) inhibitors as top candidates. In addition, Gene Expression Profiling Interactive Analysis (GEPIA) identified HDAC1 and HDAC2 as the most upregulated and HDAC11 as the most downregulated HDACs. We selected PCI-24781/abexinostat due to its specificity against HDAC1 and HDAC2, but not HDAC11, and blood-brain barrier permeability.

Results: We tested PCI-24781 using in vitro human and mouse GBM syngeneic cell lines, an in vivo murine orthograft, and a genetically engineered mouse model for GBM (*PEPG* - PTEN$^{flox/+}$; EGFRvIII+; p16$^{Flox/-}$ & GFAP Cre +). PCI-24781 significantly inhibited tumor growth and downregulated DNA repair machinery (BRCA1, CHK1, RAD51, and O^6-methylguanine-DNA- methyltransferase (MGMT)), increasing DNA double-strand breaks and causing apoptosis in the GBM cell lines, including an MGMT expressing cell line in vitro. Further, PCI-24781 decreased tumor burden in a PEPG GBM mouse model. Notably, TMZ + PCI increased survival in orthotopic murine models compared to TMZ + vorinostat, a pan-HDAC inhibitor that proved unsuccessful in clinical trials.

Conclusion: PCI-24781 is a novel GBM-signature specific HDAC inhibitor that works synergistically with TMZ to enhance TMZ efficacy and improve GBM survival. These promising MGMT-agnostic results warrant clinical evaluation.

Keywords: Connectivity map, In silico analysis, Glioblastoma, HDAC, Blood-brain barrier

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