

The use of DNA demethylating agent in combination with retinoids shows promise, but further optimization and preclinical studies are required for the treatment of intracranial IDH-mutant gliomas

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Human **IDH1** WT and IDH1R132H cell lines and patient-derived xenografts (PDX) were used to evaluate the FDA-approved DNA **demethylating agent** 5-Azacytidine (5-Aza). Cell growth, protein and gene expression, chromatin immunoprecipitation, and nucleosome position assays were performed in 5-Aza treated cells. To evaluate antitumor activity in vivo, 5-Aza was administered alone and in combination with Temozolomide (TMZ) in a patient-derived xenograft (PDX) glioma models harboring IDH1R132H mutation.

5-Aza treatment has been found to reduce cell growth and increase Glial Fibrillary Acid Protein expression. Chromatin immunoprecipitation and nucleosome position assay showed that the mechanism of increased GFAP expression induction is associated with histone modification and nucleosome repositioning of the GFAP promoter, respectively. In vivo, 5-Aza treatment extended survival in IDH1R132H mutant, but not in an IDH1 WT glioma model. Additionally, 5-Aza enhances the therapeutic effect of DNA damaging agent TMZ in both subcutaneous and orthotopic PDX models of IDH1R132H mutant glioma <sup>3)</sup>.

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da Costa Rosa M, Yamashita AS, Riggins GJ. Evaluation of a DNA demethylating agent in combination with all-trans retinoic acid for IDH1-mutant gliomas. *Neuro Oncol.* 2021 Nov 26;noab263. doi: 10.1093/neuonc/noab263. Epub ahead of print. PMID: 34850159.

2)

Miller JJ, Cahill DP, Arrillaga-Romany I. Enhancing demethylation-induced differentiation in IDH-mutant glioma. *Neuro Oncol.* 2022 Mar 3;noac056. doi: 10.1093/neuonc/noac056. Epub ahead of print. PMID: 35239963.

3)

Yamashita AS, da Costa Rosa M, Borodovsky A, Festuccia WT, Chan T, Riggins GJ. Demethylation and epigenetic modification with 5-Azacytidine reduces IDH1 mutant glioma growth in combination with Temozolomide. *Neuro Oncol.* 2018 Sep 3. doi: 10.1093/neuonc/noy146. [Epub ahead of print] PubMed PMID: 30184215.

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