

# Cancer Research



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## Cell, Tumor, and Stem Cell Biology

### Antitumor Effects of a Combined 5-Aza-2'Deoxyctidine and Valproic Acid Treatment on Rhabdomyosarcoma and Medulloblastoma in *Ptch* Mutant Mice

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*Patched* (*Ptch*) heterozygous mice develop medulloblastoma (MB) and rhabdomyosarcoma (RMS) resembling the corresponding human tumors. We have previously shown that epigenetic silencing of

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the intact *Ptch* allele contributes to tumor formation in this model. Here, we investigated whether targeting of epigenetic silencing mechanisms could be useful in the treatment of *Ptch*-associated cancers. A reduction of endogenous DNA methyltransferase1 (Dnmt1) activity significantly reduced tumor incidence in heterozygous *Ptch* knockout mice. A combined treatment with the Dnmt inhibitor 5-aza-2'deoxyctidine (5-aza-dC) and the histone deacetylase (HDAC) inhibitor valproic acid (VPA) efficiently prevented MB and RMS formation, whereas monotherapies with either drug were less effective. Wild-type *Ptch* expression was efficiently reactivated in tumors by 5-aza-dC/VPA combination therapy. This was associated with reduced methylation of the *Ptch* promoter and induction of histone hyperacetylation suggesting inhibition of HDACs *in vivo*. However, the treatment was not effective in clinically overt, advanced stage tumors. This is a first *in vivo* demonstration that targeting of Dnmt and HDAC activities is highly effective in preventing formation of *Ptch*-associated tumors. The results suggest a novel clinical strategy for consolidation therapy of corresponding tumors in humans after completion of conventional treatment. Our data also suggest that epigenetic therapy may be less effective in treating advanced stages of tumors, at least in this tumor model. [Cancer Res 2009;69(3):887–95]

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