

[P-66]**In2001, Histone Deacetylase Inhibitor, Have a Found Antitumor Activity in Breast Cancer**

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Histone deacetylase inhibitors (HDACIs) are emerging as a promising new treatment strategy in malignancy. The purpose of this study was to evaluate the anti-proliferative activity of a novel HDAC inhibitor, IN2001 in vitro in human breast cancer cell lines and to assess its anti-tumor activity and toxicity in vivo in a female MMTV-erb B2 transgenic mice. We observed that IN2001 treatment inhibited breast cancer cell growth in a dose-dependent manner and induced accumulation of acetylated histone H4. IN2001 treatment also increased expression of the cell cycle regulator p21 in breast cancer cells. IN2001 had pronounced anti-tumor activity in vivo when administered to MMTV-erb B2 transgenic mice at a dose of 15mg/kg by I.P. injection daily for 5 days compared to control mice. The body weights of IN2001-treat animals did not differ significantly from controls, confirming the observation that IN2001 did not cause serious toxicity. Because acetylated histones are generally associated with transcriptionally active chromatin whereas deacetylated histones are often found in conjunction with an inactive chromatin state, we next studied whether HDAC inhibition could alter chromatin structure at the ER gene locus. IN2001 led to re-expression of ER mRNA as detected by RT-PCR in ER-negative MDA-MB-231 breast cancer cells. When MMTV-ErbB2 mice were treated by intraperitoneal injection daily for 1–3 days with vehicle or IN2001 (30 mg/kg), the mammary tumors that develop in these mice was ER negative and IN2001 increased expression of ER in normal ovary and tumor tissues. The present studies confirm the potent anti-tumor activity of IN2001 against breast cancer in vitro and in vivo, strongly supporting HDAC inhibitors as a molecular target for anticancer therapy in breast cancer. Furthermore, It is possible that activation of the silenced ER by HDAC inhibition could open a new avenue for management of a subset of advanced breast cancer with hormonal resistance.

Keyword: HDAC inhibitor, Breast cancer