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Derivative of antiviral agent and histone deacetylase inhibitor selectively targeting viral and non-viral associated malignancies

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Acetylation of histones and other proteinsplay an important role in cancer development and progression. A strong link was found between the level of certain isoforms belonging to histone deacetylase (HDAC) classes I and II and aggressiveness and poor prognosis of some malignancies. Diverse structural classes of HDAC inhibitors (HDACIs) have been shown to exhibit anticancer activity in tumor cells, in cancer animal models and clinical trials. The mechanisms of action of HDACIs include competitive binding to the active site, turnover of the HDAC protein by proteasomal degradation, and HDAC protein inactivation by alkylation/carbonylation.Over-expression of HDACs in cancer disrupts the acetylation of histones and other proteins, affecting many cellular processes, which are employed by cancer cells for survival advantage. Thus, HDACIs have the potential to target multiple cell signaling pathways, including the repair mechanisms in the DNA damage pathway.The encouraging laboratory data, paved the way for clinical trials to test the efficacy of HDACIs. Until now cutaneous T-cell lymphoma (CTCL) is the only approved indication for treatment with HDACIsVorinostat and Romidepsin. However, given the limited clinical efficacy of the two approved HDACIs and their adverse effects, there is an ongoing effort to develop new HDACIs with improved efficacy and selectivity. We studied novel HDAC inhibitory prodrugs that upon metabolic breakdown, release the HDACI butyric acid and aldehyde(s). Of these prodrugs, pivaloyloxymethyl butyrate (AN-9), in a phase I clinical study displayed limited toxicity (Patnaiket al. 2004), and in a phase II clinical trial,improved the well-being and survival of patients with non-small-cell lung carcinoma (Reid et al, 2004). The water-soluble prodrugbutyroyloxymethyl diethylphosphate (AN-7), was found to exhibited significantly better anti-metastatic and anti-angiogenic activities than AN-9. It acted in synergy with doxorubicin (Dox) to augment cancer cell death while simultaneously provides protection against the cardiotoxicity ofDox (Tarasenko et al, 2008, 2012). Recently we developed bifunctional prodrugs composed of HDAC inhibitory and antiviral moieties. AN-446, the valproyl ester-valpramide of acyclovir (ACV) was found to be active against a wide spectrum of cancer cell types in vitro and in vivo. The unique properties of this agent and its potential as anticancer agent will be described and discussed.

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