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# Creating zinc monkey wrenches in the treatment of epigenetic disorders

Jay Hans Kalin, Kyle Vincent Butler and Alan Paul Kozikowski

The approval of suberoylanilide hydroxamic acid by the FDA for the treatment of cutaneous T-cell lymphoma in October, 2006 sparked a dramatic increase in the development of inhibitors for the class of enzymes known as the histone deacetylases (HDACs). In recent years, a large number of combination therapies involving histone deacetylase inhibitors (HDACIs) have been developed for the treatment of a variety of malignancies and neurodegenerative disorders. Promising evidence has been reported for the treatment of pancreatic cancer, prostate cancer, and leukemia as well as a number of other previously difficult to treat cancers. Drug combination approaches have also shown promise for the treatment of mood disorders including bipolar disorder and depression. In addition to these drug combination approaches, HDACIs alone have demonstrated effectiveness in the treatment of Parkinson's disease, Alzheimer's disease, Rubinstein–Taybi syndrome, Rett syndrome, Friedreich's ataxia, Huntington's disease, multiple sclerosis, anxiety, and schizophrenia. Adverse inflammatory affects observed with traumatic brain injury and arthritis have also been alleviated by treatment with certain HDACIs. Based on the diverse utility and wide range of mechanistic actions observed with this class of drugs, the future development of better drug combination therapies and more selective HDACIs is warranted.

**Address**
University of Illinois at Chicago, Department of Medicinal Chemistry, 833 South Wood Street, Chicago, IL 60612, USA

Corresponding author: Kalin, Jay Hans (jkalin3@uic.edu), Butler, Kyle Vincent (kbutler@uic.edu) and Kozikowski, Alan Paul (kozikowa@uic.edu)

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## Introduction

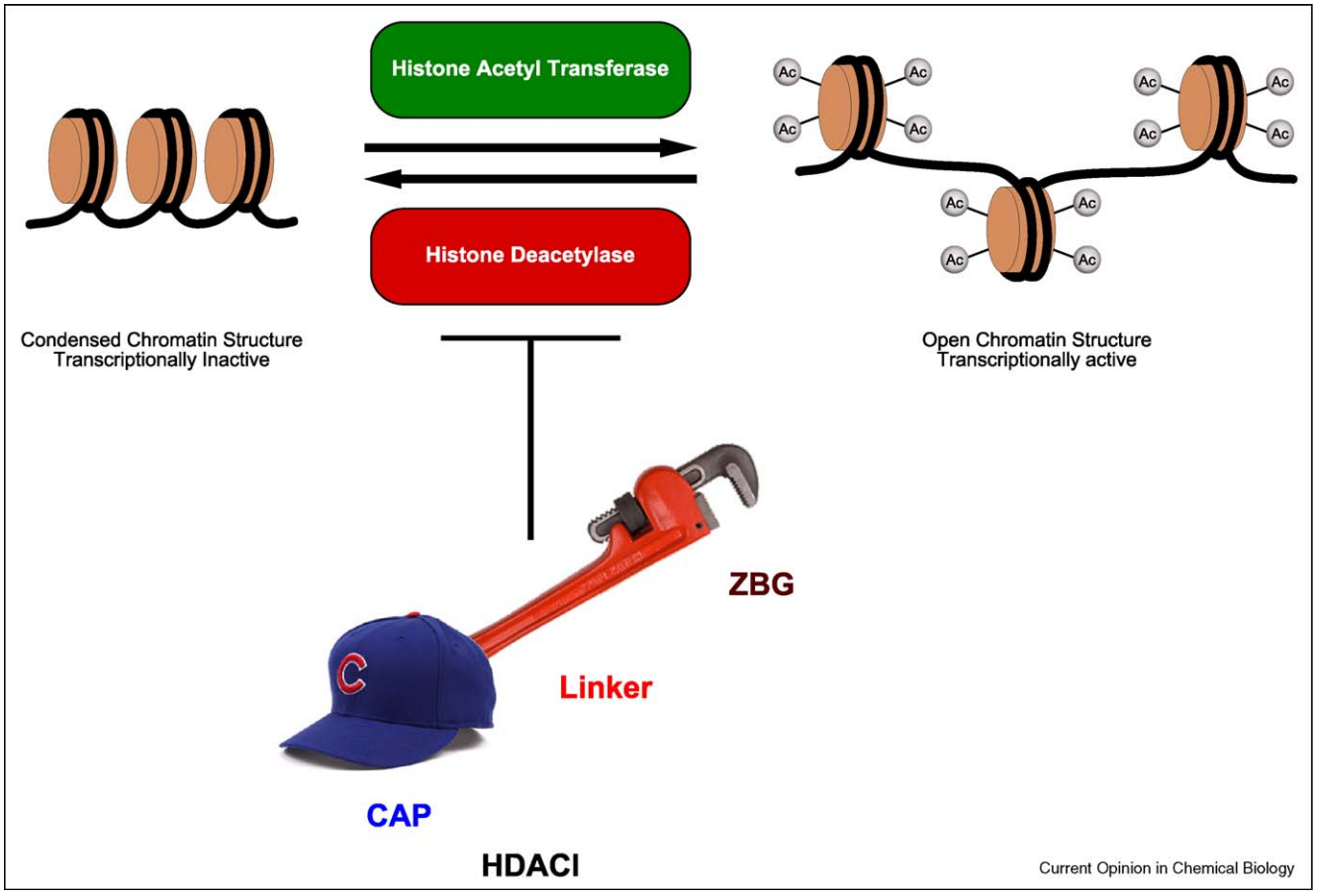
The synthesis of suberoylanilide hydroxamic acid (SAHA) in 1996 and the subsequent identification of its biological target, a class of enzymes known as the histone deacetylases (HDACs), gave rise to a novel class of therapeutic agents, the HDAC inhibitors (HDACIs) [1,2]. On October 6th, 2006, after nearly six years of clinical trials, the FDA approved the use of SAHA for the treatment of cutaneous T-cell lymphoma (CTCL) which provided the scientific community with a testament as to the legitimacy of this new class of drugs [3]. HDACs, along with their counterpart, histone acetyl transferases (HATs), are involved in the regulation of gene expression via deacetylation/acetylation of the N-terminal lysine residues of nuclear histones (Figure 1). HDACs and HATs have also been shown to have a variety of nonhistone substrates including p53, HSP90, α-tubulin, and HMGB1 that are related to gene expression, cell proliferation, and apoptosis [4]. The HDACIs have shown promising results for use in the treatment of a wide variety of disease states including certain neurodegenerative disorders, a wide range of malignancies, and even adverse inflammatory responses [5–7]. Current research regarding the therapeutic uses of the HDACIs has been centered on combination therapies and the synergistic effects of using HDACIs with other known drugs (Table 1). The focus of this review will be to highlight the advances in HDAC research over the past two years and to discuss potential future directions of this research area. Structures of HDACIs referenced in this review can be found in Figure 2.

## HDACI synergism

### Combination therapy for various malignancies

One of the most frequently reported HDAC combination therapies is the use of an HDACI in conjunction with a DNA methyltransferase inhibitor (DNMTI) [8–12]. A recent study has shown that treatment of glioma cells with valproic acid (VPA), a low potency pan-selective HDACI, and 5-aza-2′-deoxycytidine (5Aza-dC), a DNMTI, was able to induce the expression of NY-ESO-1 in cancerous cells. NY-ESO-1, under normal conditions, is only expressed in certain reproductive tissues which lack the major histocompatibility complexes (MHCs) that CD8 T-cells use to recognize pathogens. However, NY-ESO-1 is expressed in a variety of human tumors that do express these MHCs, making it a very attractive target for cancer immunotherapy [10,12]. A similar study involving the treatment of pancreatic cancer cells with a combination of 5Aza-dC and SAHA resulted in upregulation of 30 genes including C/EPBα. C/EPBα is a tumor suppressor protein shown to inhibit pancreatic cancer cell proliferation [10]. The power of combining two drugs was also demonstrated in a study involving human colon cancer cells. The HDACI, scriptaid, in combination with 5Aza-dC was able to induce the re-expression of the tumor suppressor protein, p16, in a dose-dependent manner whereas these

**Figure 1**




Mechanism of transcriptional regulation by HAT and HDAC.

inhibitors, when administered alone, were not sufficient to return p16 expression to its normal level [11]. Interestingly, evidence for the synergistic mechanism exhibited by nucleoside analogs and HDACIs to reduce cell proliferation indicated that the HDACIs are able to reduce the excision of these nucleoside analogs from DNA by suppressing the activity or expression of specific DNA repair enzymes [8].

Other drug combination therapies are also being investigated and show promise for the treatment of breast cancer and acute myeloid leukemia (AML) [13–15]. The marketed HDACI, SAHA, in combination with an antitumor necrosis factor-related apoptosis-inducing ligand receptor (anti-TRAIL-R) monoclonal antibody, MD5-1, safely induced substantial tumor cell apoptosis in a preclinical *in vivo* mouse breast cancer model. Furthermore, the administration of either of these agents alone had little to no effect in regard to inducing tumor cell apoptosis [14]. Another study involving breast cancer cells reported that the combination of 5Aza-dC, SAHA, and ATF-126, an artificial transcription factor for the mammary serine protease inhibitor (maspin), inhibited tumor cell proliferation by 95% *in vitro*. Maspin, an important tumor suppressor gene involved in the suppression of cell growth, angiogenesis, and metastasis, was reactivated 600-fold by this chemical cocktail [13].

Further evidence for the utility of these cocktails can be observed in prostate cancer and medulloblastoma models [16–18]. A large number of prostate cancer cells exhibit gene fusions with certain oncogenes and androgen receptor genes which alluded to the possibility of treating these transformed cells with a combination of antiandrogens and an HDACI. An *in vitro* study demonstrated that apoptosis could be induced in these cells by combinations of various HDACIs including trichostatin A (TSA), *N*-(2-aminophenyl)4-[*N*-(pyridine-3-yl-methoxycarbonyl)aminomethyl]benzamide (MS-275), and SAHA with the antiandrogen, flutamide [16]. Another study involving the evaluation of a novel retinoic acid metabolism-blocking agent (RAMBA), VN/66-1, and the HDACI, MS-275, showed synergistic inhibition of both prostate cancer cells *in vitro* and a reduction in tumor size by 85% in an *in vivo*