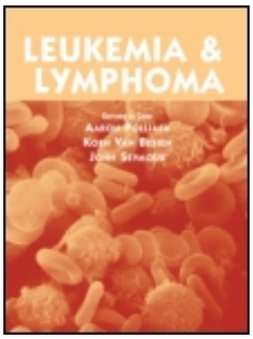

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COMMENTARY

Inhibition of histone deacetylase 6 as a therapeutic strategy for acute lymphocytic leukemia

ELIZABETH A. EKLUND[1,2] & LEONIDAS C. PLATANIAS[1,2]

[1]*The Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA and* [2]*Jesse Brown Veteran's Administration Medical Center, Chicago, IL, USA*

There is emerging interest in targeting histone deacetylase 6 (HDAC6) as a therapeutic approach to hematological and non-hematological malignancies. HDAC6 has a number of substrates in addition to histones, and many of these approaches are based on inhibiting deacetylation of such non-histone substrates. In various experimental models, HDAC6-inhibition induced pleiotropic effects, including a selective decrease in proliferation and a relative increase in apoptosis in malignant cells as compared to non-transformed cells [1–3]. Such effects of HDAC6-inhibition were shown to be independent of histone acetylation state, but were dependent upon acetylation of α-tubulin, one of the alternative HDAC6 substrates.

HDAC6 is a class II histone deacetylase with two putative catalytic domains. The C-terminal domain is responsible for deacetylation of α-tubulin, while the second domain functions as an acetyl lysine binding site to facilitate interaction with the C-terminal domain [4]. Tubulin deacetylation is involved in a number of cellular processes which are essential for cell proliferation and homeostasis. For example, deacetylation of α-tubulin plays an important role in degradation of unfolded and ubiquitinated proteins that are stored in microtubule associated aggresomes. Interaction of α-tubulin with HDAC6 results in α-tubulin deacetylation and assembly of a multi-protein complex which includes the motor protein dynein and the aggresome. After assembly, this complex transports the aggresome to lysosomes or proteasomes for protein degradation (reviewed in [5]). De-acetylation of α-tubulin is also necessary for the assembly of microtubule complexes involved in mitotic cell division. Therefore the acetylation status of α-tubulin influences cell proliferation [5]. In addition, α-tubulin acetylation state influences the activity of some proteins, such as the K^+Na^+-adenosine triphosphatase (ATPase), which are activated by association with the cytoskeleton in an α-tubulin dependent manner [6]. HDAC6 has other substrates that may also impact the anti-neoplastic role of HDAC6 inhibition, including the chaperone protein Hsp90 and redox-related peroxiredoxin proteins.

Tubacin is a HDAC6-specific inhibitor that was identified by screening a chemical library of 1,3-dioxane derivatives for molecules which increase α-tubulin acetylation, but not histone acetylation [4]. Subsequent work demonstrated that tubacin treatment results in rapid α-tubulin acetylation in multiple cell types, but does not alter histone acetylation or gene expression [4]. Based on the functions of acetylated α-tubulin, it was anticipated that tubacin would impair the degradation of aggresome proteins thereby causing stress-induced apoptosis; decrease microtubule function during mitosis thereby impairing proliferation; and inhibit K^+Na^+-ATPase activity thereby disrupting intercellular ion handling. Consistent with the anti-neoplastic potential of tubacin-induced HDAC6-inhibition, tubacin was found to synergize with proteasome inhibitors to increase apoptosis in multiple myeloma cells and prostate cancer cell lines [1,2]. Apoptosis in these cells

Correspondence: E. Eklund, MD, The Feinberg School of Medicine, Northwestern University, 303 E. Superior St, Lurie 5-105, Chicago, IL 60611, USA. Tel: 312-503-3208. Fax: 312-503-0189. E-mail: e-eklund@northwestern.edu

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involved accumulation of ubiquitinated and misfolded proteins, and was Jnk-dependent [2]. In other studies, tubacin induced selective apoptosis of Epstein–Barr virus positive (EBV+) Burkitt lymphoma cells in a manner that required caspase activation and production of reactive oxygen species [7]. This may be related to inactivation of peroxiredoxins in tubacin-treated cells. In other studies, tubacin treatment of prostate cancer cell lines resulted in double-stranded DNA damage, an effect which was synergistic with other DNA damaging agents [1].

In a study published in this issue of ***Leukemia and Lymphoma***, Aldana-Masangkay *et al*. provide important new information regarding the therapeutic potential of HDAC6-inhibition in hematologic malignancies [3]. These authors determine that B- and T-acute lymphocytic leukemia (ALL) cells are significantly more sensitive to the anti-proliferative effect of tubacin relative to normal lymphocytes and bone marrow progenitors [3]. In addition, they demonstrate increased apoptosis in tubacin-treated B- and T-ALL cells in comparison to normal lymphocytes. Apoptosis of ALL cells was associated with rapid acetylation of α-tubulin and accumulation of ubiquitinated proteins. However, unlike multiple myeloma cells, apoptosis in tubacin-treated ALL cells was independent of Jnk activation [3]. The authors further determine that apoptosis in ALL cells is related to K^+Na^+-ATPase inhibition, a novel mechanism for apoptosis induction in hematologic malignancies. This study therefore identifies functionally important differences in the activity of HDAC6 in various malignancies which may be therapeutically exploited.

The authors also substantially advance the potential therapeutic significance of HDAC6-inhibition by performing *in vivo*, murine xenograft studies using samples from relapsed human ALL [3]. These studies establish that tubacin treatment significantly prolongs survival in combination with standard chemotherapy in this model. The studies by Aldana-Masangkay *et al*. also established that HCAC6 expression is increased in ALL cells in comparison to normal lymphocytes [3]. Although many children with ALL are cured, up to 30% relapse and treatment options for these patients are inadequate. The success rate is even lower in adult patients with ALL. This suggests that HDAC6 inhibition might be a rational target for supplementing treatment of this very serious disease.

The studies of the current report provide proof-of-principle for HDAC6 targeting as a unique therapeutic approach to ALL. Although tubacin is a useful compound for research, it lacks many characteristics required for clinical 'lead compound' development [8]. Specifically, the molecule is lipophilic, difficult to synthesize, and does not conform to Lipinski's 'rule of 5.' To address this problem, other investigators used structure and homology based approaches to identify drug-like molecules which specifically inhibit the C-terminal domain of HDAC6 [8]. Based on the results of the report of Aldana-Masangkay *et al*., expanded efforts to identify and clinically develop such compounds may lead to the ultimate development of novel therapeutic approaches for the treatment of ALL and other hematological malignancies.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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