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# The Role and Therapeutic Implication of HDAC8 in Neuroblastoma

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## Abstract

Neuroblastoma lineage arises from a neural crest origin and is a typically common tumor among the pediatric population. Survival rate for this disease has improved over the years, however, patients with MYCN amplification correlate with a poor prognosis, warranting improved therapies. The utility and efficacy of pan-HDAC inhibitors for the treatment for various solid tumors has increased with promising results. Isoform-specific HDAC inhibitors have been developed to improve the therapeutic window and reduce side effects. The role of isoform-specific HDAC inhibitors, namely HDAC8 inhibitors, has recently been investigated in numerous tumor histologies, including neuroblastoma, among other neural crest-derived tumors. Long term pan-HDAC inhibition has been demonstrated to induce differentiation and regression to a benign-like phenotype in neuroblastoma *in vivo*. HDAC8 inhibition has been shown to inhibit growth and induce differentiation in neuroblastoma cells. The role of HDAC8 inhibition on neuroblastoma and regression of the disease merits further investigation.

**Keywords:** Neuroblastoma; Neural crest; HDAC inhibitor; HDAC8

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Neuroblastoma is an extracranial tumor that typically occurs in the pediatric population. According the American Cancer Society, neuroblastoma occurs in 700 births per year in the US. The prognosis is multifactorial and the 5-year survival rate has improved from 86-95% for children younger than 1 year and from 34-68% for children between the ages of 1-14 years [1]. Neuroblastoma displays the highest rate of spontaneous regression compared to other tumors; this differentiation is attractive for potential therapeutic intervention [2,3].

The *MYCN* oncogene exhibits amplification in approximately 25% neuroblastoma patients and correlates with poor prognosis [4-6].

Retinoid therapy reduces MYCN expression and induces differentiation in high-risk neuroblastoma patients; however, retinoid therapies yield unwanted toxicities, namely in pediatric patients [7,8]. The role of HDAC isoforms in tumorigenesis and cellular differentiation is well documented [9].

The HDAC family of proteins comprise of 11 known isoforms organized into four classes. These specialized proteins exhibit numerous functions, specifically, the deacetylation of lysine tails on histones and non-histone proteins, among many functions outside of epigenetic regulation [10].

The multifunctionality and known role of HDACs in cancer became the driving force for the discovery and development of HDAC inhibitors as an anti-cancer therapy [11].

Initial, among current, HDAC inhibitors target numerous HDAC isoforms across their various classes with varying affinity [12]. These broad spectrums or pan-HDAC inhibitors induced epigenetic and non-epigenetic changes bringing forth multiple anti-cancer effects [13]. Like all drugs, pan-HDAC inhibitors possess a variety of unwanted side effects [14] and inhibiting multiple HDAC isoforms at once results in a smaller therapeutic window. The emergence and development of isoform-specific HDAC inhibitors may improve therapeutic efficacy with fewer side effects. Isoform-specific compounds targeting HDAC6 and HDAC8 have been developed and studied in various tumor types [15-17], including the neural crest-derived malignant peripheral nerves sheath tumors (MPNST) [18] and neuroblastoma [19-21]. Of note, HDAC8 plays a crucial epigenetic role in skull development of neural crest cells in mice [22].

HDAC8 expression has been shown to correlate with poor outcome in neuroblastoma patients. Biological or pharmacological inhibition of HDAC8 induces neuroblastoma cell differentiation and attenuates cell growth [19,20]. HDAC8 inhibition-induced neuroblastoma cell differentiation may be due to HDAC8 regulation on *MYCN* oncogene expression [21].

Recently, Waldeck et al. [8] demonstrated the efficacy of prolonged exposure of pan-HDAC inhibition-induced differentiation in

neuroblastoma. The group used TH-MYCN mice [23], modelling human neuroblastoma, and treated with pan-HDAC inhibitor panobinostat for 9 weeks, resulting in the murine neuroblastoma to regress to a benign, ganglioneuroma-like tumor.

A unique observation is that panobinostat has an affinity to multiple HDAC isoforms [24] with the ability to induce neuroblastoma differentiation, while only inhibiting HDAC8 also induces differentiation; albeit, in different neuroblastoma models. Testing the effect of prolonged HDAC8 inhibition vs. pan-HDAC inhibition in TH-MYCN mice should be the next step toward potential clinical trials. Unfortunately, the novel emergence of HDAC8 inhibitors has yet to make strides towards human trials. During this intervening time, Braekeveldt et al. [25] have developed an orthotopic neuroblastoma patient-derived xenograft (PDX) model. Their model contains the functionality to study high-risk, *MYCN* amplified, metastatic neuroblastoma. While spontaneous regression is yet to be studied in neuroblastoma PDX models, the dual utility of transgenic and PDX neuroblastoma models can serve as preclinical forecasts for future clinical trials with HDAC8 inhibitors.

While HDAC8 inhibition may appear ideal for the treatment of neural crest-derived tumors, other tumors in this group may not fare so well. Studies have shown that pan-HDAC inhibition upregulates Notch1 expression, in turn, attenuating pheochromocytoma cell growth [26,27]. Recently, HDAC8 inhibition was demonstrated to suppress Notch1 signalling [28], thus targeting HDAC8 for the treatment of pheochromocytoma may not be ideal. In another study, glioma cells were shown to be tolerant to pharmacological HDAC8 inhibition [15].

These important discoveries warrant further investigation applying pan-HDAC inhibition and isoform-specific inhibition for the treatment of neural crest-derived tumors. The current acumen marks a key *terminus a quo* in the role and therapeutic implication of HDACs in neural crest-derived tumors.

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