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Isoform-Selective HDAC Inhibition in Autoimmune Disease

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Abstract

Histone deacetylases are a class of enzymes that play an important role in protein modification and cellular function. Ongoing research suggests that HDAC inhibitors may be efficacious in the treatment of a wide range of diseases from cancer to autoimmune disease. HDACi therapy has shown promising results both *in vitro* and *in vivo* for the treatment of autoimmune disease. To date, 18 isoforms of HDACs have been identified, which exist in four different classes: class I (HDAC1, 2, 3, and 8), class II (HDAC4, 5, 6, 7, 9, and 10) class III (sirtuins1-7), and class IV (HDAC11). The mechanism of action through which HDACs function remains to be fully elucidated. However, the use of isoform-selective HDAC inhibitors has been helpful in determining the physiological role of individual HDACs as well as in decreasing the toxicity of HDACi therapy. This review will focus on isoform-selective HDACs and how they may be effective for the treatment of autoimmune disease.

Keywords: HDAC; Autoimmune disease; SLE

Introduction

Regulation of the immune system is dependent upon both genetic and epigenetic factors. Epigenetics control gene packaging and expression through heritable and stable changes without altering the DNA sequence [1,2]. These changes can be reversible dependent upon environmental factors and thus may provide the link between the environment and genetics that results in autoimmune disease [1]. Epigenetic changes in cellular function include changes in DNA methylation, microRNA (miRNA), and protein acetylation [3]. Proper cellular function requires acetylation of both histone and nonhistone proteins [4]. Abnormal histone acetyl transferase (HAT) and histone deacetylase (HDAC) expression and activity has been associated with a number of autoimmune and inflammatory diseases and may therefore be a potential target to therapeutically modulate disease [5-12].

HATs add an acetyl group to histone proteins allowing for transcriptional activities. Conversely, histone deacetylases (HDACs) are a group of enzymes that catalyze the removal of acetyl groups from lysine residues on histones thereby restricting chromatin availability for gene transcription [13,14]. Traditionally, HDACs were thought to function solely through epigenetic regulation of histone proteins; however, HDACs have more recently been shown to regulate acetylation of over 50 nonhistone proteins and may be more accurately described as lysine deacetylases (KDACs) [15,16]. Of particular interest is the ability of HDACs to regulate transcription factors, signaling molecules, and structural proteins thereby exhibiting an immunomodulatory effect [17].

HDACs have been implicated in immune cell regulation and may therefore be efficacious in the treatment of autoimmune disease [18,19]. Due to the large number of HDACs that are targeted, pan-HDAC inhibitors have been associated with deleterious side effects during clinical trials including fatigue, nausea, thrombocytopenia, and electrocardiograph abnormalities [20,21]. For this reason, a more targeted approach is warranted if HDAC inhibitors are to be used in the treatment of autoimmune disease. This review will discuss the potential use of isoform-selective HDAC inhibitors as therapeutics for autoimmune disease. Isoform-selective HDAC inhibitors may allow researchers to determine not only the biological functions of particular HDACs, but also provide a more specific target for potential therapeutics without adversely affecting normal physiological functions.

HDACs and Autoimmunity

There are 18 known mammalian HDACs, which are grouped into classes I-IV. The classical HDACs consist of HDACs 1-11, which are grouped into classes I, II, and IV [22]. Class III HDACs are comprised of 7 members called seven mammalian silent information regulator two proteins (sirtuins or Sirt) which differ from classical HDACs in that they require NAD^+ as a cofactor and are not dependent upon Zn^{2+} as a catalytic mechanism [23,24]. HDACs are found in both the nucleus and cytoplasm, with some shuttling between the two and others confined to a specific compartment [25].

A nuclear localization signal (NLS) allows HDACs to localize within the nucleus and therefore exert their function on nuclear proteins. HDAC1 and 2 lack a nuclear export signal (NES) and are unable to leave the nucleus [22]. HDAC3 has both a NLS and a NES; however, it is almost always found within the nucleus [22,26]. Conversely, class II HDACs, particularly HDACs 4, 5, 7, 9, and 10, are known to travel back in forth between the nucleus and the cytoplasm and are thought to play an important role in the function of both nuclear and cytoplasmic proteins [22]. HDAC6 is predominantly found within the cytoplasm and mainly influences cytosolic proteins [27]. Similarly to class II HDACs, HDAC11 (class IV), can be found in both the nucleus and the cytoplasm and has been demonstrated to colocalize with

HDAC6 in the cytoplasm [28]. Due to the specificity of HDACs, selective therapeutic targeting may allow for modulation of specific histones or other non-nuclear proteins.

Autoimmunity is characterized by an abnormal immune response during which the body perceives a normal substance as foreign leading to autoantibody production and inflammation [29]. Studies of monozygotic twins discordant for systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and dermatomyositis; suggest a role of non-genetic factors in disease pathogenesis [30,31]. HDAC inhibitors have been shown to modulate a number of key regulators of the immune system including B cells, T cells, and APCs [5,32-36]. During autoimmune disease it is thought that HDAC activity is upregulated leading to increased nuclear translocation and binding of the transcription factors, particularly STAT3 and NF-κB, which promote gene expression of pro-inflammatory genes [37]. HDAC inhibitors have proven to have an anti-inflammatory effect, which may be helpful in the treatment of autoimmune disease during which prolonged inflammation results in tissue destruction and organ failure [36,38].

Due to the anti-proliferative effect that HDAC inhibitors exhibit; they may be effective agents of immunosuppression for the treatment of autoimmune disease. Treatment with pan-HDAC inhibitors including ITF2357, SAHA, and TSA have shown efficacy in treating autoimmune diseases including SLE, RA, and inflammatory bowel disease (IBD) in murine models [34,36,39-43]. We have shown that treatment with ITF2357 is able to reduce disease in lupus-prone mice while increasing the number of Treg cells and decreasing the number of $CD4^+$ T cells [34]. SLE is thought to involve aberrant B and T cell regulation [6,44-47]. Studies showing the regulatory effect of HDAC inhibitors on both B and T cell populations make selective HDACi therapy of particular interest in the treatment of SLE [34,40,48].

Selective HDAC inhibitors are able to provide a more targeted approach to treating autoimmune disease and reduce the risk of complications from unwanted side effects. Pan-HDAC and class I-selective inhibitors, currently undergoing clinical trials, alter physiological functions that require protein deacetylation [20,49]. There are currently two HDAC inhibitors, SAHA (pan-HDACi) and FK228 (selective-class I HDACi), approved by the FDA for the treatment of cutaneous T cell lymphoma (CTCL). Both of these drugs have also been tested for their efficacy in the treatment of autoimmune diseases. SAHA has shown efficacy in the treatment of lupus-prone mice; however, long term treatment resulted in unwanted side effects including possible drug toxicity [41]. SLE is a chronic disease requiring long-term treatment and these results indicate that inhibition of class I and II HDACs by a pan-HDACi may not be optimal [41].

Currently undergoing phase III clinical trials are panobinostat (LBH589) and Valproic acid (VPA) [50,51]. LBH589 is being tested for its use as a CTCL therapeutic and a number of other cancers [50]. VPA is currently in phase III clinical trials for the treatment of cervical and ovarian cancer, but it has recently shown therapeutic potential in the treatment of autoimmune disease [51,52]. HDAC inhibitors currently undergoing phase II clinical trials include Mocetinostat (MGCD0103), Entinostat (MS-275), Belinostat (PXD101), and Givinostat (ITF2357) for the treatment of various cancers [53]. CUDC-101, ACY-1215, CHR-2845, and CG200745 have begun phase I clinical trials for the treatments of cancer [54,55]. Dokamanovic et al. provide a more extensive review of specific HDAC inhibitors currently undergoing clinical trials [15].

Due to the ubiquitous nature of HDACs, not only are the cellular pathways involved with autoimmunity affected, but HDAC inhibition also disrupts the pathways involved with normal cellular function [24]. Furthermore, pan-HDAC inhibitors can be cytotoxic, and it may prove important in clinical treatment for HDAC inhibition to be more selective [56]. The mechanisms through which HDAC inhibitors regulate the immune response are not fully understood. Currently ongoing studies of HDAC inhibitors both *in vivo* and *in vitro* are working to determine the mechanism of both pan-and isoform-selective HDAC inhibitors.

Selective Class I Inhibitors

Class I HDACs (HDACs 1, 2, 3, and 8) play an important role in cell survival and proliferation [57]. While insight has been gained about the function of HDACs through various knockout mouse studies, gene deletion of HDACs 1, 2, and 3, has proven to be embryonic lethal in mice [24]. HDAC1 has been demonstrated to be overexpressed in SLE, RA, multiple sclerosis (MS), and juvenile idiopathic arthritis (JIA) [5]. Furthermore, HDAC3 and HDAC7 have also been shown to play a role in immune regulation during SLE, suggesting the potential importance of targeting these HDACs for treatment of disease [5].

In regard to class I HDACs it is interesting to note that HDAC2 is able to regulate the binding ability of p53, which controls transcription. HDAC2 has been shown to increase p53 binding activity and consequently increase cellular proliferation [58]. HDAC2 was demonstrated to be involved with an anti-apoptotic function following HDAC2 knockdown in cancer cells [59]. Furthermore, p53 activation has been linked to inhibition of autoimmune disease. Studies suggest that p53 expression is able to induce T_{reg} differentiation leading to suppression of the autoimmune response [60]. P53 activation is further thought to inhibit autoimmune disease through downregulation of STAT1 resulting in decreased proinflammatory cytokine production [61]. Autoimmune diseases have been shown to be more severe on a p53-deficient background in mice [60,62]. The studies explain why targeting HDAC2 may be a viable approach for treating autoimmune diseases such as lupus in which T_{reg} cell function may be important to modulate the immune response.

MS-275 is a benzamide-derived selective class I inhibitor currently undergoing Phase I-II clinical trials that has shown promising anti-rheumatic activities including prevention of bone erosion and delayed onset of collagen-induced arthritis (CIA) [24,63]. Studies have demonstrated MS-275 treatment suppressed LPS-induced pro-inflammatory cytokine production in monocytic cells. Treatment led to phase arrest at G_0/G_1 without increasing apoptosis [64]. Treatment with MS-275 after the onset of arthritis in rodents has been demonstrated to halt disease progression suggesting its potential as a therapeutic. Furthermore, MS-275 may have potential as a therapeutic in the treatment of other inflammatory autoimmune diseases based off of its anti-inflammatory effect *in vitro* and in the CIA induced mouse model [63,64]. Following treatment with MS-275, E11 cells and monocytic cells had decreased LPS-induced NF-κB nuclear translocation, decreased production of IL-6, IL-18, NO, VEGF, MMP-2, and MMP-9 [64]. Furthermore, MS-275 has been shown to decrease sera production of pro-inflammatory cytokines IL-6 and IL-1β, which are overproduced during a number of autoimmune

diseases including RA, SLE, autoimmune encephalomyelitis, and IBD [65-71].

The exact mechanism through which MS-275 treatment results in anti-rheumatic and anti-inflammatory effects remains to be elucidated. One proposed mechanism suggests MS-275 increases the stability of histone acetylation associated with the c-Fos promoter which plays an important role in cellular functions including proliferation, differentiation and survival [72]. MS-275 has been shown to increase acetylation of NF-κB p65 leading to decreased nuclear translocation and inhibition of gene transcription [64]. NF-κB activation and nuclear translocation is required for c-Fos expression [72]. These studies suggest that inhibition of NF-κB nuclear accumulation by MS-275 treatment, results in decreased cellular proliferation of osteoclasts induced by c-Fos expression [72,73]. Furthermore, MS-275 has been shown to decrease the chaperone activity of Hsp90 [74]. The ability of MS-275 to inhibit Hsp90 is of particular interest in the treatment of SLE, which has been found to have elevated hsp90 sera levels [75]. Furthermore, use of an Hsp90 inhibitor in lupus-prone mice has shown therapeutic potential [76].

VPA is a selective class I HDACi, effective against HDACs 1-5 and HDAC 7, that has been used as a treatment for seizures and mental disorders [77]. More recently VPA has been tested for its efficacy in the treatment of autoimmune disease using the Fas-deficient MRL/MPJ-Fas^{lpr}/J (MRL/lpr$^{-/-}$) mouse model. MRL/lpr$^{-/-}$ mice injected intraperitoneally with 500 mg/kg VPA for 8 weeks had decreased lymphoid organ weight and cellularity, decreased DN T cells in the spleen, lymph nodes, and blood, and a reduced number of WBCs, particularly lymphocytes, in the peripheral blood compared to vehicle-treated control mice. VPA treatment was found to induce caspase-dependent and independent apoptosis in PBMCs *in vitro* [52]. Furthermore, treatment of glomerulosclerosis in the adriamycin nephropathy mouse model with VPA reduced proteinuria in early phase renal disease [78]. VPA has been demonstrated to inhibit TNF-α, NF-κB, and IL-6 pathways, which have been shown to be dysregulated during many autoimmune diseases [78]. The mechanism of action for VPA in the treatment of autoimmune diseases has yet to be identified. However, treatment of ADR nephropathy with VPA was found to increase glomerular H3K9 acetylation and decrease glomerular apoptosis [78].

MGCD0103 is a selective class I HDAC (HDACs 1, 2, and 3) inhibitor that has also shown selectivity for HDAC11 and is currently undergoing phase I/II clinical trials [79]. MGCD0103 has been demonstrated to have antiproliferative activity in Hodgkin lymphoma cell lines and B-cell chronic lymphocytic leukemia [79-81]. Previous studies indicate that MGCD10103 increases caspase-dependent apoptosis while inhibiting autophagy through the activation of the PI3K/AKT/mTOR pathway [81,82]. Furthermore, MGD10103 increased NF-κB activation and resulted in increased TNF-α expression and production [80]. For these reasons, MGCD0103 may not be optimal for treatment for autoimmune diseases, including SLE and RA, which are characterized by increased PI3K/AKT/mTOR signaling and NF-κB activation [83-85].

Selective HDAC3 inhibition has also been explored for its use in treating inflammatory autoimmune disease. HDAC3 expression has been shown to be elevated in PBMCs from MS patients when compared to healthy controls [86]. MI192 is a selective HDAC3i that has been shown to regulate cytokine production from PBMCs. IL-6 production by PBMCs was decreased in a dose-dependent manner following treatment with MI192; however, the mechanism remains to be elucidated [87]. Studies indicate that overexpression of HDAC3 causes apoptotic-resistant autoreactive lymphocytes that contribute to autoimmune disease [86]. These data suggest that HDAC3 inhibition may be beneficial in the treatment of autoimmunity.

Romidepsin (Depsipeptide, FK288) is a selective HDACi of HDACs 1, 2, 3, and 4 currently undergoing clinical trials for the treatment of T cell lymphoma [88]. Treatment of autoantibody-mediated arthritis (AMA) mice with FK228 reduced inflammation, joint swelling, and bone destruction. Pro-inflammatory cytokines IL-1β and TNF-α were reduced following treatment with FK228 [89]. TNF-α is known to play an important role in the pathogenesis of a number of autoimmune diseases including SLE, RA, and Crohn's disease and anti-TNF-α therapies have proven to be an effective clinical treatment for people with these diseases [38,90-93]. The molecular mechanism through which FK288 reduces inflammation has yet to be determined.

Class IIa HDAC Inhibitors

Class II HDACS are not as ubiquitous as class I, but they are still thought to be essential for regulatory functions of the cell. Class IIa HDACs include HDACs 4, 5, 7, and 9 [24]. Expression of class IIa HDACs is thought to be somewhat tissue specific with increased expression in the brain, muscle, and T lymphocytes [94]. While deletion of HDAC7 is embryonic lethal in mice, deletion of HDACs 4, 5, and 9 produce viable mice, but with defects in cellular hypertrophy, stress response, cardiovascular function, and bone development [24]. Studies suggest a role for class IIa HDACs (HDAC4, 5, and 7) in pro-inflammatory gene expression [95]. Given the pro-inflammatory environment associated with many autoimmune diseases, class IIa HDACs could serve as promising targets for autoimmune therapies. While class IIa HDACs are able to move back and forth between the nucleus and the cytoplasm, they are currently thought to have limited deacetylase function; rather functioning through the recruitment of HDAC3 [56,96].

HDAC9 has been found to be overexpressed in T cells from lupus patients and SLE murine models. HDAC9 deficient MRL/lpr mice had prolonged survival and decreased lymphproliferation, autoantibody production, inflammation, and kidney disease [97]. Furthermore, HDAC9 deficient mice have decreased colitis following dextran sodium sulfate (DSS) treatment compared to wild type (WT) mice [48]. HDAC9 deficiency increased site specific lysine histone acetylation of H3K9, H3K14, and H3K18 localized to IL-4, roquin, and PPAR-γ, respectively in MRL/lpr mice [97]. These results indicate that inhibition of HDAC9 may be able to decrease the inflammatory response through hyperacetylation and stabilization of IL-4 and PPAR-γ.

Inhibition of HDAC9 has also been associated with an increased T_{reg} suppressive function, and studies have shown that HDAC9 is exported from the nucleus upon T_{reg} activation [12,48]. These studies suggest that when located within the nucleus HDAC9 suppresses Foxp3 function and HDAC9 nuclear exportation is required for an effective T_{reg} response [12,48]. SiRNA knockdown of HDAC9 in WT T_{regs} resulted in increased Foxp3 expression and enhanced T_{reg} suppressive function *in vitro*. HDAC9 knockdown in T_{reg} cells caused increased HSP70 expression; however, when HDAC9$^{-/-}$ T_{regs} were treated with triptolide (an HSP70 inhibitor) suppressive function was decreased to levels comparable by WT T_{regs} [48]. Similarly to HDAC9 inhibition, knockdown of HDAC7 increased T_{reg} suppressive ability

[98]. These data suggest the potential of inhibiting HDACs 7 and 9 with isoform-selective inhibitors to decrease autoimmune disease. T_{regs} function to suppress the proliferation of immune cell subsets and regulate cytokine production and the response to self-Ags. Furthermore, the maintenance of self-tolerance. T_{reg} deficiency has been associated with a number of autoimmune diseases including SLE, MS, RA, and IBD [99-103]. Deletion of T_{regs} in animals has been demonstrated to cause autoimmunity [104-107].

Class IIb HDAC Inhibitors

Class IIb HDACs (HDAC6 and 10) are found in both the nucleus and the cytoplasm [24]. The role of HDAC10 has yet to be determined; however, HDAC6 has been shown to regulate acetylation of cytoplasmic and nuclear proteins as wells as deacetylase-independent functions. HDAC6 is thought to play an integral role in a number of cellular functions including regulation of the cytoskeleton, cell migration, and degradation of misfolded proteins through deacetylation of α-tubulin, HSP90, and cortacin [108-110].

During SLE, the number and function of T_{reg} cells is diminished [111,112]. Pan-HDAC inhibitors have been shown to increase the number and suppressive effects of T_{regs}, but treatment with class-I specific HDAC inhibitors, such as MS-275, have been unable to produce the same result suggesting a role of class II HDACs [12,109]. Treatment with a specific HDAC6i leads to increased T_{reg} function. Furthermore, T_{regs} from HDAC6 deficient mice have been demonstrated to have increased suppressive T_{reg} function [109]. T_{reg} cells from HDAC6$^{-/-}$ mice had a T_{reg} effector/memory phenotype with decreased expression of CD44 and CD62L, but increased expression of CD103 [109]. Regulatory effector-memory T cells (T_{REM}) are T_{reg} cells capable of activation, expansion, and memory that function to control the immune response in inflamed tissues [113]. Furthermore, T_{regs} isolated from HDAC6 deficient mice had increased function *in vitro* suppressive of CFSE-labeled WT conventional T (T_{con}) cells [109]. Similarly, treatment with the HDAC6 specific inhibitors tubacin and tubastatin A, resulted in increased suppression of *in vitro* proliferation of T_{con} cells by T_{reg} cells. Although Tubastatin A and tubacin inhibit HDAC6, tubacin is more selective for HDAC6 and may have greater efficacy at lower doses [114].

Crohn's diseases and ulcerative colitis are two forms of IBD and are modeled by the DSS model of colitis. Similarly to other autoimmune diseases, IBD requires a genetic susceptibility coupled with environmental factors leading to an inflammatory response [115]. Studies have demonstrated treatment with tubacin is able to prevent weight loss and diarrhea in the DSS model of colitis in a T_{reg} dependent fashion [109].

Another selective HDAC6i, ACY-738, has minimal reactivity against other class II HDACs and 100-fold less selectivity against class I HDACs [116]. ACY-738 was tested for its efficacy in the treatment of SLE in NZB/W mice. We found that HDAC6 inhibition with ACY-738 was able to decrease a number of hallmarks of SLE disease including splenomegaly, immune complex-mediated glomerulonephritis, and sera anti-dsDNA levels. ACY-738 treatment altered BM B cell differentiation by increasing the percentage of cells in the late pro-B cell and early pre-B cell fractions while decreasing the accumulation of cells in the late pre-B fraction F. Furthermore, ACY-738 also increased the percentage of T_{reg} cells with a concomitant decrease in SLE-associated markers of disease (unpublished data). Studies have shown that treatment with ACY-738 (1 μM) increased the suppressive function of T_{regs} alone and in combination with a sirtuin1 inhibitor, Ex-527 [117].

Compound	Isoform-Specificity	Protein/enzyme/gene	Cellular response	Disease	Reference
MS-275	HDACs 1,2,3,9	↑Foxp3 ↓nuclear NFκB p65, VEGF	↑IL-10 ↓IL-1β, IFN-γ, IL-17, IL-18, TNF-α, IL-18, NO	RA	[64,122]
MI192	HDAC3	ND	↓TNF, IL-6, IFN-γ	RA	[87]
MGCD0103	HDACs 1,2,3,11	Jak/STAT ↑NF-κB activation, *TNFSF4, TNFSF9, TNF* ↓*TNFRSF8*	↑TNF-α	ND	[79,80]
Valproic acid	HDACs 1,2,3,8	PI3K/Akt, mTOR, NF-κB	↓TNF-α	ALPS, SLE, IBD	[52,78]
FK228	HDACs 1,2,3,4	ND	↓IL-1β, TNF-α	AMA, RA, diabetes	[20,88,89]
ACY-738	HDAC6	Foxp3	↑TGF-β ↓IL-1β	SLE	[117] Unpublished data
Tubacin	HDAC6	α-tubulin, HSp90 Foxp3 ↑CTLA-4, PD-1, GITR	↓IL-2, IFN-γ ↑IL-10	RA, IBD	[109,123]
Tubastatin A	HDAC6	α-tubulin, Foxp3	↓TNF-α, IL-6	RA, IBD	[114,124]
ND: No data					

Table 1: Isoform-Selective HDAC Inhibitors and Immune Regulation.

Class IV HDAC Inhibitors

HDAC11 is the most recently identified member of HDAC proteins and is the sole member of class IV [24]. The role of HDAC11 in normal cell function still remains to be fully elucidated and no isoform-selective HDACi has yet been developed [118]. However, HDAC11 has been identified as a potential molecular target for the treatment of autoimmune disease due to its role as a negative transcriptional regulator of IL10 [119]. Overexpression of HDAC11 in a mouse macrophage cell line prevented an increase in IL10 mRNA expression following LPS-stimulation. Furthermore, knocking down HDAC11 using shRNA in human APCs resulted in an increase in expression of IL10 mRNA following immune stimulation. Given the role IL-10 plays in the induction of tolerance, these results suggest targeting HDAC11 in the treatment of autoimmune disease may be beneficial. IL-10 is an anti-inflammatory cytokine with wide-ranging effects from B cell stimulation to limiting the immune response and action of pro-inflammatory cytokines. Dysregulation of IL-10 production contributes to an increased risk for autoimmune diseases including SLE, IBD, and allergic asthma [120]. Specifically during SLE, high sera levels of IL-10 correlate with disease activity [121].

HDAC11 has also been identified as a potential target for regulating APC- mediated immune activation. Primary mouse macrophages overexpressing HDAC11 showed enhanced production of IL-2 and IFN-γ following clonotypic T cell encounter. Conversely, clonotypic T cells that were introduced to APCs with knocked down HDAC11 had reduced IL-2 and IFN-γ production [119].

Summary

Previous studies suggest a complex mechanism of action for HDAC inhibitors; the use of isoform-selective HDAC inhibitors will be helpful in determining the specific roles of individual HDACs. Questions remain about the long-term safety of HDAC inhibitor use for the treatment of chronic diseases. The identification of aberrant HDAC specific isoforms to each autoimmune disease may be important in reducing toxicity. Isoform-selective HDAC inhibition has the potential to correct aberrant immune regulation by altering the function of components of the inflammatory cascades without the deleterious side effects associated with traditional pan-HDAC inhibitors (Table 1).

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