HDAC-Inhibitor Combination Therapies

Background

Post-translational acetylation is a key regulatory mechanism that can control the activity of various proteins and, in turn, regulate a range of cellular processes. Histone proteins regulate the accessibility of genomic material to the transcriptional machinery. Specifically, acetylation of lysine residues in histone tails reduces net positive charge, causing a relaxation in the chromatin structure and leading to increased transcription and overall gene expression. Acetylation states are altered by two classes of enzymes, Histone acetylases (HATs) and Histone deacetylases (HDACs). Generally, hypoacetylation of histone tails due to HDAC activity has been frequently observed in multiple lymphomas and carcinomas [1].

HDAC inhibitor treatment has been shown to reduce cancer cell viability and affect the characteristics and behaviours of numerous cancer cell lines, including autophagy, cell signalling, cell cycle arrest, cell differentiation and the secretion of pro-angiogenic factors. HDAC inhibitors can sensitize cancer cells to both intrinsic and extrinsic apoptosis pathways, while having no appreciable effect on non-cancerous cells, a concept sometimes referred to as the 'epigenetic vulnerability of cancer' [2, 3]. However, it is likely that HDAC inhibitors reduce tumor growth through multiple simultaneous mechanisms, some of which have yet to be elucidated. While HDAC inhibitors have clearly demonstrable anti-tumoral effects, which have led to regulatory approval of four HDAC inhibiting compounds for cancer treatment, less is known about how HDAC inhibition affects immune cells within the tumor microenvironment and whether such interactions contribute to compensatory mechanisms of cancer survival. For example, global HDAC inhibition has been shown to promote an anti-inflammatory phenotype in immune cells such as macrophages and T-cells, which is likely to yield negative outcomes in the already immuno-suppressive environment of many solid cancers.

HDAC families

The eleven classical HDAC proteins are categorised into four distinct classes. Class I comprises HDACs 1, 2, 3 & 8, Class IIA comprises HDACs 4, 5, 7 & 9) and Class IIB HDACs 6,10. All of these utilise zinc ions for their catalytic activity. Class III HDACs (also referred to as Sirtuins) have an alternative catalytic mechanism that does not require zinc. Class IV has a single member, HDAC11, that also exhibits zinc-dependent enzymatic activity. Pan-HDAC inhibitors are generally understood to inhibit classes I, II and IV HDACs [4]. Specific HDAC protein inhibitors have also been developed in the hope of increasing efficacy and decreasing harmful off-target effects. In Table 1, all currently approved HDAC inhibitor cancer therapeutics, and those undergoing clinical trials in cancers, are summarised.

HDAC inhibitor synergies

Generally, HDAC inhibitors have shown rather limited success as mono-therapies for solid tumors. Vorinostat (also known as suberanilohydroxamic acid) is a good example of this, with a reported efficacy of 10% in AML. Several HDAC inhibitors have undergone clinical trials as combination therapies, often with standard of care agents, in order to create synergistic efficacies in some solid tumors. To date, clinical trials are underway to combine HDAC inhibitors with radiotherapy, DNA repair targeting agents, topoisomer-ase inhibitors, other epigenetic modifying agents, tyrosine kinase receptor inhibitors and immune checkpoint

Drug name	HDAC Class	Indication	Status
Romidepsin	HDAC 1, HDAC 2	Peripheral & cutaneous T cell lymphoma	Approved
Tucidinostat / Chidamide	HDAC1, HDAC2, HDAC3, HDAC10.	Peripheral T cell lymphoma	Approved
Panobinostat	Pan-HDAC	Multiple Myeloma	Approved
Belinostat	Pan-HDAC	Peripheral T cell lymphoma	Approved
Givinostat	Pan-HDAC	Leukaemia & multiple myeloma	Phase II; Phase III
Entinostat	Class I	Hormone receptor positive breast cancer	Phase III
Pracinostat	Class I, II, III	Acute Myelocytic Leukemia	Phase III
Resminostat	Pan-HDAC	Cutaneous T Cell Lymphoma	Phase II
Abexinostat	Pan-HDAC	B-cell lymphoma	Phase II
Quisinostat	Pan-HDAC	Cutaneous T Cell Lymphoma	Phase II
Rocilinostat	Class II	Non-Hodgkin Lymphoma, Multiple myeloma	Phase II
Vrx-3996 / CHR-3996	Class I	Lymphoma	Phase II
Tacedinaline	Class I	NSCLC & pancreatic cancer	Abandoned
Mocetinostat	Class I, IV	Hodgkin's lymphoma	Phase II trial; now being studied with checkpoint inhibitors

inhibitors [5]. Our interests lie in the potential of HDAC inhibitors in immuno-oncology, as single agents and in combination with known checkpoint inhibitors.

HDAC inhibitors & immune-checkpoint inhibitor combos

Immune checkpoint inhibitors have marked a sea change in cancer treatment with the success of anti-programmed cell death 1 (PD-1) and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) therapies. These agents act by improving T cell activation at the tumor site and promoting anti-tumoral leukocyte responses.
To date, anti-CTLA4 (ipilimumab), anti-PD-1 (nivolumab and pembrolizumab) and anti-PDL1 (durvalumab and avelumab) (the endogenous ligand for PD-1) have been approved by the FDA for the treatment of a variety of tumor types. Since the early clinical attempts to combine anti-PD-1 and anti-CTLA-4 agents, there has been a rush to develop other immune checkpoint combinations, specifically ones that can treat solid tumor types that are not considered immunologically 'hot', i.e. where checkpoint inhibitors are expected to have limited effect as their target population is largely absent.
As a compound class, HDAC inhibitors could be good partners for combination with immune checkpoint inhibitors, as they are already known to sensitize cancers to apoptosis and exhibit immune modulating capabilities.

HDAC inhibitors and immune system modulation

Whilst clinical interests in HDAC inhibitors were originally focussed upon anti-cancer applications, more recently these compounds have been found to exhibit strong anti-inflammatory effects. Hence, their indication for autoimmune disease and immune response after transplantation has also been studied [6].
Treatment with the pan-HDAC inhibitor trichostatin (TSA) was shown to enhance macrophage expression of LPS-induced pro-inflammatory genes *cox-2* and *pai-1* as well as IL-6, IL-12, IFNγ and IL-10 [7] [8]. Interestingly, TSA treatment also enhanced glycolysis and OXPHOS in IFNγ / LPS stimulated macrophages [9]. The re-initiation of OXPHOS is known to strongly favour alternative macrophage activation; suggesting that TSA could promote the M2-like, immuno-suppressive, pro-tumoral phenotype in tumor-associated macrophages. In this context, pan-HDAC inhibition might be expected to have a negative impact on cancer progression. However, in a recent key paper, Guerriero *et al.* demonstrated that the Class IIa HDAC inhibitor TMP195 increased the relative proportion of anti-tumoral (classically activated) TAMs in a murine autochthonous mouse model of breast cancer. Consequently, a reduction of the tumor burden was observed, with limited pulmonary metastasis and normalisation of the tumor vasculature. These anti-tumoral TAMs had a highly phagocytic and inflammatory phenotype. The authors showed TMP195 primed newly-recruited monocytes/macrophages from bone marrow to the tumor to be biased against alternative activation once recruited to the TME. The authors demonstrated that TMP195 has no direct tumoricidal effect, suggesting that the observed tumor-killing activity was due to inflammatory macrophage infiltration into the tumor. The reduction of macrophage recruitment to the tumor (using anti-CSF1 antibodies) abrogated the tumoricidal effect of TMP195, further suggesting that TMP195 promotes tumoricidal activities via macrophage activity. This is the first example of HDAC inhibition altering the TAM population within the tumor microenvironment, with corresponding anti-tumoral response by $CD8^+$ T cells [10]. Indeed, there may be an important future role for focused HDAC inhibitors that can target TAMs. In the following section we consider the likely mechanistic consequences of inhibiting individual HDACs enzymes based on their known roles in immuno-oncology.

HDAC1 and HDAC3

Use of the Class I HDAC inhibitor compound MS-275 has been shown to reduce the infiltration of macrophages and T cells in studies of cerulein-induced pancreatitis. The authors also found that MS-275 could decrease IL-6 expression and increase IL-1β expression in RAW264.7 cells [11]. In a second study, MS-275 promoted NFκB mediated IL-10 expression in RAW264.7 cells, but also increased several other pro- and anti-inflammatory genes, suggesting that macrophage polarisation is dysregulated in response to MS-275 treatment [12]. Both HDAC1 and HDAC3 are categorised as Class I HDACs and are known to interact to form a hetero-complex. HDAC3 is involved in promoting expression of a variety of pro-inflammatory genes through the IFN/STAT and NFκB signalling pathways [13]. Hence, inhibition of HDAC3 has been linked with an anti-inflammatory phenotype in macrophages. HDAC3 alone has been shown to bind to enhancer regions of PU.1 target genes, where it can suppress expression of target genes in the IL-4 signalling axis (a potent anti-inflammatory pathway). HDAC3 therefore acts as a brake on M2 macrophage polarisation. Indeed, specific inhibition of HDAC3 has been shown to lead to increased M2 polarisation [14].

The HDAC3 / HDAC1 complex associates with the promotors of IL-12p40, cox-2 and ifnβ genes, thereby suppressing their expression [6]. Inhibition of the HDAC3 / HDAC1 complex should therefore release this inhibitory effect by reinstating expression of these pro-inflammatory genes. The complex of HDAC3 and HDAC1 has also been shown to negatively regulate pro-inflammatory TLR signalling.
It may be important to consider that specific inhibitors for individual HDACs may not necessarily inhibit enzyme activity when in hetero-complex conformation. For

example, the HDAC1, 2 and 3 inhibitor BML-210 does not inhibit HDAC enzymatic activity of the HDAC1/2 complex (HDAC-Sin3A) [15]. Therefore, development of pharmacological interventions to disrupt or inhibit these functional protein complexes may provide more promising specificity and efficacy than targeting the HDAC proteins by themselves [15].

HDAC2

LPS signalling has been shown to increase expression of the enzyme Tet2, which is normally responsible for the hydroxylation of methylcytosine. Tet2 recruits HDAC2 to the promotor of the IL-6 gene, thus suppressing pro-inflammatory IL-6 transcription [16]. Therefore, the inhibition of HDAC2 would be expected to release the suppressive action of HDAC2, thus stimulating IL-6 production. Inhibition of HDAC2 and HDAC3 has been shown to reduce the expression of components of the LPS signalling pathway in macrophages, which would inhibit classical activation [17].

HDAC4

HDAC4, a Class IIa HDAC, has been shown to influence glycolysis and pentose phosphate pathway (PPP) activity. HDAC4 is a mediator of LPS-induced pro-inflammatory gene expression. Prolonged LPS signalling (and consequent glycolysis) results in the degradation of HDAC4, suggesting the enzyme is negatively regulated by LPS and participates in negative feedback. HDAC4 activity suppresses flux through the pentose phosphate pathway (PPP) by suppression of 6-phosphogluconate dehydrogenase (6PGD) activity [18]. The reductive arm of the PPP cycle is critical in promoting the pro-inflammatory classical activated macrophage phenotype. While our understanding of HDAC4 is incomplete, it clear that it plays an important role in connecting LPS signalling, metabolism and the pro-inflammatory macrophage phenotype.

HDAC5

The glycolytic enzyme GAPDH is regulated by acetylation at position K254, which enhances its metabolic activity. In glucose deprivation conditions, HDAC5 (another Class IIa HDAC) deacetylates GAPDH to suppress glycolysis, resulting in a corresponding reduction in inflammatory response capacity in macrophages [19]. Similarly, PGM-1 (of the phosphohexose mutase family) can be post-transcriptionally modified by acetylation of K251, K253 and K254 residues, resulting in conformational change and increased enzymatic activity. Again, in conditions of glucose deprivation, PGM-1 is deacetylated, reducing enzymatic activity and favouring fatty acid oxidation rather than glycolysis for energy utilisation [20]. Utilisation of FAO over glycolysis promotes alternative macrophage activation. These two regulatory mechanisms may be key targets for preventing alternative macrophage activation while promoting classical activation. Inhibition of HDAC5 is likely to favour classical activation of TAMs and their anti-tumoral activity, making HDAC5 a potential target in TAM repolarisation.

HDAC6

HDAC 6 is a member of the Class IIb HDAC family. HDAC6 knock-out has been shown to promote expression of MHC class genes in cancer cells, leading to increased tumor immunogenicity, mediated by CD4+ & CD8+ T cells [21]. HDAC6 knock-out also reduced IL-10 expression [22, 23]. The latter suggests that targeted inhibition of HDAC6 could be advantageous for TAM repolarisation to a classical activated macrophage phenotype. HDAC6 inhibition is also known to suppress STAT3/IL-10 signalling in an array of antigen presenting cells (APCs) [24].

HDAC7

HDAC7 does not have intrinsic HDAC enzymatic activity and is reliant on HDAC3 complexation for its activity (see above). HDAC7 expression is increased in inflammatory macrophages along with its alternatively spliced isoform, HDAC7-u, both of which can stabilise hypoxia inducible factor alpha (HIF1α), resulting in expression of a subset of LPS-inducible genes [25].
It has been suggested that the full form of HDAC7 associates with the transcriptional repressor C-terminal-binding protein (CTBP1). However, the HDAC7-u isoform fails to associate with CTBP1, allowing it to engage in normal transcriptional activation once complexed with HDAC3. Hence, in addressing the functions of some HDACs, the relevance of alternative splice variants and bimolecular complexation must be carefully considered.

HDAC11

HDAC11 is the only member of the Class IV HDAC family. In a non-cancer related model of immune-tolerisation, active HDAC11 has been shown to suppress IL-10 expression in macrophages [22]. Therefore, we posit that the specific inhibition of HDAC11 would be likely to promote unwanted M2-like alternative activation.
Class II HDAC inhibition has been associated with the expansion of Treg populations, but also with an improved anti-tumoral response in murine cancer models. The Class III HDACs, or sirtuins (which are reliant on an NAD+ dependent mechanism of action) have been shown to exert powerful effects upon metabolic activity via modulation of enzyme acetylation. This subject has recently been reviewed by Chang and Guarente [26].

HDAC inhibitor combinations with immune checkpoint inhibitors

An interesting study in a murine model showed that anti-PD-1 and anti-CTLA4 resistance could be overcome by eliminating myeloid derived suppressor cells (MDSCs) within the tumor microenvironment [27]. HDAC inhibition via the use of Entinostat has been shown to specifically target and deplete MDSCs from the tumor environment. Entinostat treatment has been shown to reduce anti-PD-1 and anti-CTLA-4 resistance in murine models of lung and renal cell carcinoma [28]. Beyond murine models, Entinostat has also been shown to reduce MDSC numbers and CD40 expression in breast cancer patients, while also increasing the HLA-DR expression in $CD14^{+}$ monocytes, indicative of biasing infiltrating monocytes to pro-inflammatory monocyte/macrophages phenotypes that correlate with improved anti-tumoral responses [29].

Entinostat and vorinostat have both been demonstrated to sensitize breast and prostate cancer cell lines for T-cell mediated lysis. This adds to the case for combining HDAC inhibitors with immune checkpoint inhibitors not only to control anti-PD-1 and anti-CTLA-4 resistance, but also enhance T-cell lysis of cancer cells. These initial studies have led to multiple clinical trials combining checkpoint inhibitors with HDAC inhibitors, which are listed in Table 2.

Of the studies listed below, only a handful have so-far reported findings. A phase II clinical trial combining vorinostat, cladribine and rituximab (NCT00764517) has recently reported an objective response rate of 97% of patients with mantle cell lymphoma or chronic lymphocytic leukaemia that had been previously untreated. A second group of patients suffering from relapse of indolent Non-Hodgkins lymphoma, mantle cell lymphoma and chronic lymphocytic leukaemia had a 39% objective response rate. Tolerability was reported at 62% in untreated patients with 22% tolerability in the relapse group.

Another phase II study combining vorinostat and rituximab (NCT00720876) reported an overall response rate of 46% in 28 patients suffering from lymphoma. Progression free survival was reported at 29.2% with 13% of patients experiencing serious adverse effects, thrombosis being the most common adverse effect.

A third study combined vorinostat, cyclophosphamide, etoposide, prednisone and rituximab, administered every 4 weeks (NCT00667615). The study aim was to determine maximum tolerated dose and reported a complete response rate of 32% in patients with Hodgkin's disease lymphoma.

Lastly, a phase II trial combining belinostat, rituximab and the radioactive antibody Zevalin (yttrium 90 ibritumomab tiuxetan) for the treatment of diffuse large cell lymphoma (NCT01686165) has just reported promising results. This small study involving 5 patients reported a 100% complete response rate (as well as 100% overall response and progression free survival rate). One patient suffered from a serious adverse event (deep venous thrombosis).

Future direction for HDAC inhibitors

We have already discussed the exciting potential of immune checkpoint inhibitor and HDAC inhibitor combinations in relation to the treatment of solid cancers and we will have a clearer picture when other ongoing clinical trials report more of their findings. There is certainly great potential for HDAC inhibitors to a) limit immune checkpoint resistance by targeting MDSCs; b) directly inhibit the actions of immunosuppressive leukocyte populations such as MDSCs, alternatively activated macrophages and Tregs; c) sensitize tumor cells to apoptosis.

Just as patients can develop resistance to various chemotherapeutic agents and immune checkpoint inhibitor, they may also develop resistance to HDAC inhibitor treatment. The exact mechanisms behind HDAC inhibitor resistance are unknown but it has been postulated to arise via evolutionarily conserved pathways for suppressing prokaryote/fungus secreted naturally-occurring HDAC inhibitors [30]. Here the authors suggested that cancers that are sensitive to HDAC inhibitors may possess mutations in this yet unidentified HDAC inhibitor protection system. The identification of the proteins involved in this protective system could be important for developing targeted strategies to reduce HDAC inhibitor resistance.

In conclusion, there is great clinical interest in utilizing HDAC inhibitors in combination therapy with both small-molecule chemotherapeutics and immune checkpoint inhibitors. Initial results from studies combining HDAC and PD-1 inhibitors are awaited in late 2018. Over the next few years, several phase II clinical trials will report their findings, further informing the field of the potential of HDAC inhibition in combination with immuno-oncology drugs. With a recently concluded trial (NCT01686165) reporting 100% response rate in diffuse lymphoma patients when treated with belinostat in combination with rituximab and Zevalin, it is apparent that there are indeed therapeutic synergies in HDAC inhibitor – I/O combinations.

HDAC inhibitor	Immune check-point inhibitor	Clinical trial identifier	Status	Phase	Cancer type
Belinostat	Rituximab	NCT01686165	Active, not recruiting	II	Diffuse Large Cell lymphoma (DLCL)
Entinostat	Nivolumab and ipilimumab	NCT02453620	Recruiting	I	Metastatic unresectable HER2-negative breast cancer
Entinostat	Pembrolizumab	NCT02909452	Active, not recruiting	I	Multiple solid tumors
Entinostat	Atezolizumab	NCT03024437	Recruiting	I/II	Renal cell carcinoma, Metastatic cancer
Entinostat	Atezolizumab	NCT02708680	Recruiting	I/II	Breast cancer
Entinostat	Pembrolizumab	NCT02697630	Recruiting	II	Metastatic uveal melanoma
Entinostat	Pembrolizumab	NCT02437136	Recruiting	I/II	NSCLC and melanoma
Entinostat	Pembrolizumab	NCT03179930	Recruiting	II	Lymphoma
Entinostat	Nivolumab	NCT01928576	Recruiting	II	NSCLC
Mocetinostat	Durvalumab	NCT02805660	Recruiting	I/II	Advanced solid tumors and NSCLC
Mocetinostat	Durvalumab	NCT02993991	Withdrawn (no safety concern)	I	Squamous cell carcinoma of the oral cavity
Panobinostat	Ipilimumab	NCT02032810	Active, not recruiting	I	Unresectable stage III/IV melanoma
Panobinostat	Rituximab	NCT01282476	Terminated (slow accrual)	II	DLBCL
Romidepsin	Pembrolizumab	NCT02512172	Recruiting	I	Advanced Colorectal Cancer (CRC)
Vorinostat	Pembrolizumab	NCT02538510	Active, not recruiting	I/II	HNSCC and SGC
Vorinostat	Pembrolizumab	NCT02638090	Recruiting	I/II	Stage IV NSCLC
Vorinostat	Pembrolizumab	NCT02619253	Recruiting	I/II	Advanced renal or urothelial cell carcinoma
Vorinostat	Pembrolizumab	NCT02395627	Recruiting	II	Hormone therapy-resistant breast cancer
Vorinostat	Rituximab	NCT00667615	Complete	I/II	DLBCL
Vorinostat	Rituximab	NCT00720876	Complete	II	Lymphoma
Vorinostat	Rituximab	NCT00972478	Active, not recruiting	I/II	DLBCL
Vorinostat	Rituximab	NCT00764517	Complete	II	Lymphoma
Vorinostat	Pembrolizumab	NCT03426891	Recruiting	I	Glioblastoma

1. Fraga, M.F., et al., Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer. Nat Genet, 2005. 37(4): p. 391-400.
2. Bolden, J.E., et al., HDAC inhibitors induce tumor-cell-selective pro-apoptotic transcriptional responses. Cell Death Dis, 2013. 4: p. e519.
3. Nalabothula, N. and F. Carrier, Cancer cells' epigenetic composition and predisposition to histone deacetylase inhibitor sensitization. Epigenomics, 2011. 3(2): p. 145-55.
4. Das Gupta, K., et al., Histone deacetylases in monocyte/macrophage development, activation and metabolism: refining HDAC targets for inflammatory and infectious diseases. Clin Transl Immunology, 2016. 5(1): p. e62.
5. McClure, J.J., X. Li, and C.J. Chou, Advances and Challenges of HDAC Inhibitors in Cancer Therapeutics. Adv Cancer Res, 2018. 138: p. 183-211.
6. Shakespear, M.R., et al., Histone deacetylases as regulators of inflammation and immunity. Trends Immunol, 2011. 32(7): p. 335-43.
7. Halili, M.A., et al., Differential effects of selective HDAC inhibitors on macrophage inflammatory responses to the Toll-like receptor 4 agonist LPS. J Leukoc Biol, 2010. 87(6): p. 1103-14.
8. Hull, E.E., M.R. Montgomery, and K.J. Leyva, HDAC Inhibitors as Epigenetic Regulators of the Immune System: Impacts on Cancer Therapy and Inflammatory Diseases. Biomed Res Int, 2016. 2016: p. 8797206.
9. Van den Bossche, J., et al., Inhibiting epigenetic enzymes to improve atherogenic macrophage functions. Biochem Biophys Res Commun, 2014. 455(3-4): p. 396-402.
10. Guerriero, J.L., et al., Class IIa HDAC inhibition reduces breast tumors and metastases through anti-tumor macrophages. Nature, 2017. 543(7645): p. 428-432.
11. Bombardo, M., et al., Class I histone deacetylase inhibition improves pancreatitis outcome by limiting leukocyte recruitment and acinar-to-ductal metaplasia. Br J Pharmacol, 2017. 174(21): p. 3865-3880.
12. Leus, N.G., et al., HDAC1-3 inhibitor MS-275 enhances IL10 expression in RAW264.7 macrophages and reduces cigarette smoke-induced airway inflammation in mice. Sci Rep, 2017. 7: p. 45047.
13. Chen, X., et al., Requirement for the histone deacetylase Hdac3 for the inflammatory gene expression program in macrophages. Proc Natl Acad Sci U S A, 2012. 109(42): p. E2865-74.
14. Mullican, S.E., et al., Histone deacetylase 3 is an epigenomic brake in macrophage alternative activation. Genes Dev, 2011. 25(23): p. 2480-8.
15. Bantscheff, M., et al., Chemoproteomics profiling of HDAC inhibitors reveals selective targeting of HDAC complexes. Nat Biotechnol, 2011. 29(3): p. 255-65.
16. Zhang, Q., et al., Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. Nature, 2015. 525(7569): p. 389-393.
17. Jeong, Y., et al., Histone deacetylase isoforms regulate innate immune responses by deacetylating mitogen-activated protein kinase phosphatase-1. J Leukoc Biol, 2014. 95(4): p. 651-9.
18. Shan, C., et al., Lysine acetylation activates 6-phosphogluconate dehydrogenase to promote tumor growth. Mol Cell, 2014. 55(4): p. 552-65.
19. Li, T., et al., Glyceraldehyde-3-phosphate dehydrogenase is activated by lysine 254 acetylation in response to glucose signal. J Biol Chem, 2014. 289(6): p. 3775-85.
20. Hallows, W.C., W. Yu, and J.M. Denu, Regulation of glycolytic enzyme phosphoglycerate mutase-1 by Sirt1 protein-mediated deacetylation. J Biol Chem, 2012. 287(6): p. 3850-8.
21. Woan, K.V., et al., Targeting histone deacetylase 6 mediates a dual anti-melanoma effect: Enhanced antitumor immunity and impaired cell proliferation. Mol Oncol, 2015. 9(7): p. 1447-1457.
22. Villagra, A., et al., The histone deacetylase HDAC11 regulates the expression of interleukin 10 and immune tolerance. Nat Immunol, 2009. 10(1): p. 92-100.
23. Cheng, F., et al., Divergent roles of histone deacetylase 6 (HDAC6) and histone deacetylase 11 (HDAC11) on the transcriptional regulation of IL10 in antigen presenting cells. Mol Immunol, 2014. 60(1): p. 44-53.
24. Cheng, F., et al., A novel role for histone deacetylase 6 in the regulation of the tolerogenic STAT3/IL-10 pathway in APCs. J Immunol, 2014. 193(6): p. 2850-62.
25. Shakespear, M.R., et al., Histone deacetylase 7 promotes Toll-like receptor 4-dependent proinflammatory gene expression in macrophages. J Biol Chem, 2013. 288(35): p. 25362-74.
26. Chang, H.C. and L. Guarente, SIRT1 and other sirtuins in metabolism. Trends Endocrinol Metab, 2014. 25(3): p. 138-45.
27. Kim, K., et al., Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells. Proc Natl Acad Sci U S A, 2014. 111(32): p. 11774-9.
28. Orillion, A., et al., Entinostat Neutralizes Myeloid-Derived Suppressor Cells and Enhances the Antitumor Effect of PD-1 Inhibition in Murine Models of Lung and Renal Cell Carcinoma. Clin Cancer Res, 2017. 23(17): p. 5187-5201.
29. Tomita, Y., et al., The interplay of epigenetic therapy and immunity in locally recurrent or metastatic estrogen receptor-positive breast cancer: Correlative analysis of ENCORE 301, a randomized, placebo-controlled phase II trial of exemestane with or without entinostat. Oncoimmunology, 2016. 5(11): p. e1219008.
30. Halsall, J.A. and B.M. Turner, Histone deacetylase inhibitors for cancer therapy: An evolutionarily ancient resistance response may explain their limited success. Bioessays, 2016. 38(11): p. 1102-1110.