Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

HDAC11 Inhibitors

Evidence Summary

HDAC11 may influence disease trajectories through the regulation of immune system responses. Selective inhibition of HDAC11 appears relatively safe, but the effects are highly context dependent.

Neuroprotective Benefit: HDAC11 inhibitors may modulate the neuroinflammatory profile in a manner that mitigates neurodegeneration, but limited evidence is available.

Aging and related health concerns: HDAC11 is dysregulated in many cancers. Modulation of HDAC11 can impact cancer progression and immune function, but the effects are highly context dependent. HDAC11 inhibitors may enhance metabolic rate.

Safety: HDAC11 inhibitors are expected to have a superior safety profile relative to pan-HDAC inhibitors based on studies in HDAC11 knockout mice and acute preclinical studies with inhibitors. They may affect immunity and long-term safety is unclear.

Availability: In research use only.	**Dose**: Not established	**PB94** **Chemical formula:** $C_{29}H_{33}N_3O_4$ **MW**: 487.59
Half-life: Varies PB94: 5.3 hours (in mice)	**BBB**: Varies (PB94 is penetrant)	
Clinical trials: None	**Observational studies**: HDAC11 expression is altered in a variety of cancers and associated with disease prognosis, but the direction of the associations vary with tumor type.	

What is it?

Histone deacetylase 11 (HDAC11) is the most recently discovered HDAC [1]. HDACs serve as epigenetic regulators by removing acetyl groups from histones, which modulates the accessibility of DNA, and thus the ability of genes to be expressed. In general, the deacetylation of histones decreases gene expression by making DNA less accessible. However, HDACs also modulate the acetylation of various other proteins, which can impact their functional status, thus the effects of HDACs can be wide reaching. Since HDACs tend to regulate the expression/function of a wide array of genes/proteins, their effects tend to be highly context dependent. HDAC11 is the only Class IV HDAC, and its promoter lacks the canonical TATA and CCAAT boxes associated with other HDACs [2]. Whether HDAC11 exerts histone deacetylase activity *in vivo* remains controversial. HDAC11 contains an amino acid substitution of aspartic acid 101 with asparagine in a region (variable loop 2) with a critical role in substrate recognition and catalysis in HDACs, and exhibits extremely low deacetylase activity *in vitro [2]*. However, poor *in vitro* deacetylase activity is a common feature of HDACs, thus it could be an experimental artifact. It has been suggested that its utility as a deacetylase may depend on its association with other proteins, such as HDAC6. In contrast to its unclear/weak deacetylase activity, HDAC11 demonstrates robust defatty-acylase activity, which involves the removal of covalently attached fatty acids from proteins [3]. The most common fatty-acylase modifications are long 14- and 16-carbon saturated fatty acid myristate and palmitate groups. The lysine defatty-acylase activity of HDAC11 was found to be >10,000 fold more efficient than its deacetylase activity [4]. While only a few defatty-acylase targets have been identified to date, this may be one of its predominant activities *in vivo*.

PB94 is a brain penetrant HDAC11 inhibitor that is relatively selective, as its IC_{50} for HDAC11 (0.11 uM) is at least 40-fold lower than its most closely associated partner, HDAC6 [5]. Radiolabeled versions have been demonstrated to distribute into the brain, particularly in the striatum, cortex, and amygdala of mice [5]. It has been tested in preclinical rodent models of neurological conditions [5; 6].

Other HDAC11 inhibitors have been tested in preclinical studies, primarily for cancer, including SIS7, SIS17, FT895, and TD034, however, they have generally been considered suboptimal candidates for clinical translation due to issues with selectivity, stability, or pharmacokinetics [7; 8]. These may serve as scaffolds for further optimization. The literature indicates that research groups are continuing to conduct medicinal chemistry studies to develop novel HDAC11 inhibitors that may be better suited for future clinical use.

Neuroprotective Benefit: HDAC11 inhibitors may modulate the neuroinflammatory profile in a manner that mitigates neurodegeneration, but limited evidence is available.

Types of evidence:

- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function: None

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Neuroinflammation: POTENTIAL BENEFIT (Preclinical)
The prospective ability of HDAC11 to impact disease trajectories in neurodegenerative disorders stems from its capacity to modulate immune responses [1]. HDAC11 is highly expressed in the brain, and, at least in rats, is the most highly expressed HDAC in the brain. While there is evidence to suggest that it plays a role in oligodendrocyte development [9], most studies to date find that the modulation of HDAC11 primarily impacts neuroinflammation. Overall, the studies suggest that HDAC11 activity is associated with an immune profile that drives neurodegenerative processes.

Multiple sclerosis: In the $MOG_{35–55}$-induced mouse model of experimental autoimmune encephalomyelitis (EAE), HDAC11 activity was associated with the chronic progressive phase of the disease [10]. The loss of HDAC11 did not impact disease induction, but it mitigated the chronic progressive phase. Mice lacking HDAC11 had lower levels of pro-inflammatory macrophages and dendritic cell infiltration into the spinal cord stemming from less secretion of the migration promoting chemokine CCL2. This was accompanied by less demyelination and a lower degree of neurological impairment. Notably, HDAC11 mice exhibited similar levels of demyelination in a model of MS (cuprizone-induced) that does not involve adaptive immune responses [10]. This suggests that the inhibition of HDAC11 may mitigate disease severity by attenuating CCL2-mediated immune infiltration and activity. The elevation of HDAC11 expression in female patients with MS suggests that this finding may be translational to human disease [10].

Alzheimer's disease: HDACs have been shown to be dysregulated in the AD brain, and various HDAC inhibitors have been associated with benefit in a variety of preclinical AD models [11]. While the relative contribution of HDAC11 toward AD pathology and progression is unclear, rodent studies suggest that it is one of the more viable HDACs to target therapeutically from a safety perspective. Treatment with the brain-penetrant HDAC11 inhibitor, PB94, was associated with reductions in the levels of Aβ and neuroinflammation based on neuroimaging measures in the 5XFAD mouse model [6].

Depression: Neuroinflammation has been implicated as an inducer of depression-associated behavior. In the context of LPS-induced neuroinflammation, a novel HDAC11 inhibitor (referred to as 5) attenuated depressive-like symptoms on the tail suspension, forced swim, and sucrose preference tests in mice [12]. This was accompanied by a reduction in levels of microglial activation in brain regions involved in emotional processing. At the cellular level, inhibition of HDAC11 prevented the induction of nitric oxide production and reactive nitrogen species in microglia following LPS stimulation.

APOE4 interactions: Not established

Aging and related health concerns: HDAC11 is dysregulated in many cancers. Modulation of HDAC11 can impact cancer progression and immune function, but the effects are highly context dependent. HDAC11 inhibitors may enhance metabolic rate.

Types of evidence:

- 3 observational studies for HDAC11 expression in cancer
- Numerous laboratory studies

Immune modulation: HDAC11 HAS CONTEXT-DEPENDENT FUNCTIONS
HDAC11 has been found to have immunomodulatory properties, but whether it works in a pro- or anti-inflammatory capacity is cell type- and context-dependent, since these effects generally involve the presence (or absence) of other binding partners or downstream players [13].
IL-10: HDAC11 was identified as a negative regulator of IL-10 in antigen presenting cells through regulation of the transcription factor binding to the IL-10 promoter [14]. However, the regulation of IL-10 involves the interplay of HDAC11 and HDAC6, which form a complex [15]. While HDAC11 acts as a negative regulator, HDAC6 acts as a positive regulator of IL-10, such that IL-10 production requires the loss of HDAC11 plus the presence of HDAC6.
Neutrophils: HDAC11 is expressed in neutrophils, where it appears to play roles in their maturation, migration, and phagocytic function [16]. The expression of HDAC11 decreases as neutrophils mature, such that lower expression is associated with higher functional capacity. Neutrophils lacking HDAC11 have greater migratory and phagocytic capacity and a more pro-inflammatory profile. Bone marrow cellularity, or the percentage of hematopoietic cells to fat, tends to decrease with age, which is associated with weakened immunity. In the context of aging, mice lacking HDAC11 exhibit an increase in bone marrow cellularity due to the increased maturation of neutrophils, though the effect of this shift on overall immune function in this context is not clear [16]. These mice also exhibit signs of splenomegaly.
Interferon: HDAC11 was shown to regulate type 1 interferon (IFN) signaling through its defatty-acylation activity [4]. The mitochondrial enzyme, serine hydroxymethyltransferase 2 (SHMT2) was identified as a defatty-acylation substrate of HDAC11 [4]. Lysine fatty-acylation of cytosolic SHMT2 regulates the internalization and stability of IFNαR1 by controlling its de-ubiquitination. Therefore, the defatty-acylation of SHMT2 by HDAC11 inhibits type I IFN signaling by promoting the ubiquitination of IFNαR1. Consequently, mice lacking HDAC11 exhibit increased type 1 IFN responses. This could enhance responses to viral infections, where type 1 IFNs play a role in viral clearance. However, type 1 IFNs have

also been implicated in tissue aging [17], thus the chronic enhancement of IFN responses could also potentially promote age-related tissue dysfunction.

T cells: HDAC11 has been found to play context-dependent roles on T cell function. HDAC11 plays a role in the induction of T cell tolerance. Antigen presenting cells lacking HDAC11 are deficient in activating naïve antigen-specific CD4+ T cells, whereas overexpression of HDAC11 in antigen presenting cells promotes the activation of antigen-specific CD4+ T cells as well as the responsiveness of tolerant T cells [14]. HDAC11 expression is lower in effector and activated T cell populations relative to resting naïve and central memory T cells [18]. Consistently, effector T cell populations are expanded in HDAC11 knockout mice following activation. In the absence of HDAC11, the CD4+ T cells do not develop tolerance, and are less responsive to the suppressive activity of T regulatory cells. These effects may stem from HDAC11's inhibition of the transcription factors, Eomesodermin (Eomes) and TBX21 (Tbet), which regulate effector molecule production [18]. The functional implications of the enhanced effector activity and loss of tolerance are context dependent. The loss of HDAC11 exacerbated inflammatory tissue rejection in a mouse model of acute graft-vs-host disease [12]. However, in a B-cell lymphoma model involving the subcutaneous implantation of (2.2×10^6) FCmuMCL1 cells in mice, the adoptive transfer of HDAC11 deficient T cells reduced tumor burden [12].

Together these studies indicate that the value of an HDAC11 inhibitor will depend on the particular environmental milieu, and will need to be experimentally determined.

Cancer: HDAC11 SERVES AS A PROGNOSTIC MARKER IS VARIOUS CANCERS

HDAC11 is one of the top overexpressed genes in a variety of cancers, but plays a dual role in tumors [19]. In general, HDAC11 appears to promote tumor stemness, but depending on the tumor type, HDAC11 could promote or inhibit the invasive and migratory capacity of the tumor cells [2]. Due to its immunoregulatory roles, HDAC11 also impacts tumor immunity.

A study examining the prognostic effects of HDAC11 expression in 33 different tumor types found that it was aberrantly expressed in 25 of the tested cancers, in which it was overexpressed in 10 types and showed reduced expression, relative to healthy adjacent tissue, in 15 types [20].

HDAC11 expression was associated with better overall survival in uveal melanoma (UVM), kidney renal clear cell carcinoma (KIRC), pheochromocytoma and paraganglioma (PCPG), kidney renal papillary cell carcinoma (KIRP), and brain lower grade glioma (LGG), better disease-specific survival in UVM, KIRP, LGG, KIRC, kidney chromophobe (KICH), and breast invasive carcinoma (BRCA), as well as better progression-free interval in UVM, KIRP, LGG, BRCA, rectum adenocarcinoma (READ), and pheochromocytoma and paraganglioma (PCPG) [20]. Meanwhile, HDAC11 was associated with worse overall survival in liver hepatocellular carcinoma (LIHC) and acute myeloid leukemia (LAML), worse

disease-specific survival in thyroid carcinoma (THCA), and worse progression-free interval in LIHC and lung squamous cell carcinoma (LUSC). A separate study including 145 patients similarly found that high HDAC11 expression was associated with better overall survival in breast cancer, such that knockdown of HDAC11 enhanced the invasion, migration, and proliferation of breast cancer cell lines [21]. A study in 326 patients with non-small cell lung cancer (NSCLC) found that high HDAC11 was associated with poor prognosis in LUSC and lung adenocarcinoma (LUAD) [22].

With respect to tumor immunity, HDAC11 largely had inverse associations with tumor immune components and checkpoint inhibitors, such that its expression may impact responsiveness to immune checkpoint inhibitor therapy [20]. HDAC11 may also impact resistance to other cancer therapies, such as chemotherapy or radiotherapy [20]. Several studies have found that at least in certain tissues, such as the colon, prostate, breast and ovary, treatment with HDAC11 inhibitors selectively affects the cell survival of tumor cells while leaving healthy cells unharmed [2]. Based on these properties, HDAC11 inhibitors may offer clinical utility in the subset of cancers in which high expression is associated with poor prognosis, especially when used in combination with other anti-cancer therapies. A preclinical study in mice using a xenograft model of PC-3 prostate cancer cells suggests that knocking down HDAC11 may improve the anti-tumor efficacy of CAR-T cells by enhancing their proliferation and reducing the expression of cell-exhaustion markers [23].

Metabolism: POTENTIAL BENEFIT (Preclinical)

Preclinical studies indicate that HDAC11 influences metabolic status on a variety of levels, including mitochondrial activity and brown fat activation [7]. Mice lacking HDAC11 are protected against high-fat diet-induced weight gain and white fat accumulation due to a greater proportion of brown adipose tissue [24; 25]. The mice have better insulin sensitivity and reduced accumulation of fat in the liver, which may stem from the enhancement of adiponectin-AMPK signaling [24]. HDAC11 knockout mice have a higher baseline body temperature and metabolic rate [24]. β3-adrenergic signaling is a key driver of brown fat activation, and HDAC11 serves as a negative regulator of β-adrenergic signaling. Consequently, the loss of HDAC11 is associated with the upregulation of downstream targets of β3, such as uncoupled protein 1 (Ucp1). HDAC11 has been shown to negatively regulate β3 via an interaction with the bromodomain and extraterminal acetyl-histone-binding protein, BRD2 [25]. It also regulates β3 via its defatty-acylase activity. Through the de-myristoylation of gravin-α, it plays a role in the β3-mediated upregulation of Ucp1 [26]. The myristoylation of gravin-α promotes its localization to the membrane lipid rafts, allowing it to engage in downstream signaling. Thus, the activity of HDAC11 prevents the signaling required to induce thermogenic genes, such as Ucp1.

Mitochondrial beta-oxidation and oxygen consumption is enhanced in the absence of HDAC11 stemming from the activation of carnitine palmitoyltransferase 1 (CPT1), which serves as a critical regulator of mitochondrial beta-oxidation by initiating the first step of the oxidative pathway [27]. In addition to adipocytes, the promotion of beta-oxidation in the absence of HDAC11 has also been observed in the skeletal muscle of mice, along with the induction of CPT1 and the activation of AMPK signaling. HDAC11 promotes fast twitch muscle fibers such that its absence leads to an increase in the formation of fibers with a slower/oxidative phenotype [27]. Notably, the increased oxidative capacity conferred better resistance to fatigue, as the HDAC11 knockout mice ran 25% longer and 43% further than their wildtype counterparts. A separate study found that the loss of HDAC11 was associated with faster skeletal muscle regeneration, likely through a combination of direct effects of myoblast differentiation and the modulation of the inflammatory environment toward a state more conducive for regeneration [28]. Importantly, the phenotypes associated with HDAC11 manifest in the context of a perturbation, such as a high-fat diet or muscle injury, but the systemic loss of HDAC11 did not impact body weight or muscle integrity under baseline conditions [27; 28]. This suggests that HDAC11 holds superior therapeutic potential for metabolic conditions, relative inhibitors targeting other classes of HDACs.

Neuropathic pain: POTENTIAL BENEFIT (Preclinical)
Alterations in microglial responses have been associated with the induction of neuropathic pain. HDAC11 expression was found to be elevated in the hindlimb region of the primary somatosensory cortex, a region involved in pain processing, in response to chronic constriction injury (CCI) in mice [5]. This region, along with another region involved in pain processing, the anteroposterior region of the thalamus, exhibit increases in microglial activation following injury. This neuroinflammatory microglial response, along with behaviors associated with increased pain sensitivity were attenuated in mice following treatment with the brain penetrant HDAC11 inhibitor, PB94 (10 mg/kg i.p). Inhibition of HDAC11 early on appears to dampen the induction of the pathological microglial response [5]. Amelioration of the pain response was observed following acute administration of PB94 in animals with established neuropathic pain, however, the durability of that effect is not clear.

Safety: HDAC11 inhibitors are expected to have a superior safety profile relative to pan-HDAC inhibitors based on studies in HDAC11 knockout mice and acute preclinical studies with inhibitors. They may affect immunity and long-term safety is unclear.

Types of evidence:

- Numerous laboratory studies (primarily of HDAC11 knockout mice)

HDAC11 inhibitors are still in early phases of drug development, thus limited safety studies are available [7]. The drug-like properties of most of the preclinically tested HDAC11 inhibitors have been suboptimal. The only HDAC11 inhibitor to date that has demonstrated reasonable, though not ideal, drug-like properties and reported preclinical safety testing is the brain penetrant HDAC11 inhibitor, PB94 [5]. It did not inhibit CYP450 enzymes, and did not exert adverse effects at doses up to 200 mg/kg in an acute toxicity study in mice. PB94 did not exert cytotoxicity in a panel of 12 primary human cell lines, but did have anti-proliferative effects in human primary endothelial cells, T cells, B cells, and coronary artery smooth muscle cells. Preclinical studies in cell lines and animal models with other HDAC11 inhibitors highlight that selective inhibitors lack the toxicity observed with pan-HDAC inhibitors [7], suggesting that the selectivity profile of the inhibitor is likely to play a key role in its safety profile.

Our current understanding of the potential safety profile of HDAC11 inhibitors is primarily shaped by studies in HDAC11 knockout mice. These mice are viable, develop normally, and show no overt health effects [3]. This suggests that there may be a variety of compensatory mechanisms for the loss of HDAC11 during development. In preclinical models, phenotypes typically only become apparent in the context of a perturbation, such as the induction of a disease model. The most prominent phenotype appears to be an alteration in immune responses and tolerance, however, these effects are context dependent. Changes to cellular metabolic status are also observed in HDAC11 knockout mice, including an increase in metabolic rate. It is currently unclear the degree to which these phenotypes would be observed with the clinical use of an HDAC11 inhibitor [7].

Drug interactions: Drug interactions have not been established, but similar to other HDAC inhibitors, HDAC11 inhibitors are likely to interact with other immunomodulatory drugs.

Sources and dosing:

HDAC11 inhibitors are not currently available for clinical use. Some HDAC11 inhibitors are available from commercial suppliers for research use.

Research underway:

HDAC11 inhibitors are currently in preclinical development by various research groups.

Search terms:

Pubmed, Google: HDAC11

- Alzheimer's disease, neurodegeneration, cognition, brain, aging, cancer, metabolism, immunity, inhibitors

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