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.

Trichostatin-A

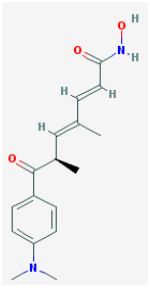
Evidence Summary

Broad-spectrum HDAC inhibitor that can act as a short-term cognitive enhancer. May extend lifespan and protect against acute oxidative stress damage. First human Phase 1 trial for cancer is in progress.

Neuroprotective Benefit: Can induce temporary cognitive boosting effects in animals by modulating expression of synaptic plasticity genes, but does not alleviate disease pathology or neuron loss.

Aging and related health concerns: Can extend lifespan in flies and worms. May be beneficial for cancer in combination therapy, and protective against oxidative stress damage when administered acutely after ischemic injury.

Safety: Limited information about long-term safety in animals, and initial safety testing in humans is ongoing. Has pleiotropic effects, which may include inhibition of oligodendrocyte differentiation and altered expression of pro-atherosclerotic genes.

Availability: Research use	**Dose**: Not established in humans	**Chemical formula:** $C_{17}H_{22}N_2O_3$ **MW**: 302.374 g/mol  Source: Pubchem
Half-life: 10 minutes (plasma, in mice)	**BBB**: low penetrance	
Clinical trials: None	**Observational studies**: None	

What is it? Trichostatin-A is an antifungal antibiotic isolated from *Streptomyces hydgroscopius*. It acts as a potent broad-spectrum reversible inhibitor of class I and class II histone deacetylase enzymes [1]. It also acts as a cell cycle inhibitor. It has not been used in humans, but animal studies provide evidence for neuroprotection, lifespan extension, and anti-tumor activity. It mediates these effects by altering the epigenetic regulation of genes involved in these processes.

Neuroprotective Benefit: Can induce temporary cognitive boosting effects in animals by modulating expression of synaptic plasticity genes, but does not alleviate disease pathology or neuron loss.

Types of evidence:

- Numerous 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:

Neurodegenerative diseases: Potential benefit (rodents)

As a histone deacetylase (HDAC) inhibitor, trichostatin-A, can affect the regulation and expression of genes involved in synaptic function and **act as a temporary cognitive enhancer**. In many

neurogenerative diseases, gene expression is altered due to an imbalance of histone acetylation, and trichostatin-A can help prevent or reverse these epigenetic genes and restore expression of genes important for the maintenance of cognitive function. The cognitive enhancing effects appear to stem primarily from trichostatin-A induced increases in CREB-associated genes, which are critical for regulating synaptic plasticity, and increased expression of brain derived neurotrophic factor (BDNF). However, the **effects of trichostatin-A are pleiotropic**, and only some of these changes are neuroprotective. The specific effects in a given cell population will depend on their epigenetic status, cell type, and tissue-related environmental factors. While trichostatin-A can temporarily improve performance on memory tasks, it **cannot promote regeneration or recover neuronal/synaptic loss** [2; 3].

Alzheimer's disease: Significant overlap was found in the genes regulated by trichostatin-A and those dysregulated in Alzheimer's disease (AD), in a microarray study [4]. Trichostatin-A treatment has shown to have some beneficial effects in rodent AD models by increasing expression of BDNF and rescuing hippocampal synaptic plasticity [5; 6]. However, these **benefits are generally short-lived and not associated with reductions in AD-associated pathology** or recovery of neuronal loss.

In rats injected with amyloid fibrils, hippocampal injection of trichostatin-A three days before testing led to improvements in escape latency on the Morris water maze and preference on the novel object recognition tasks [5]. This was accompanied by a recovery of BDNF expression driven by restoration of histone H3 acetylation at the BDNF promoter. In the APP/PS1 transgenic AD mouse model, acute trichostatin-A administration two hours prior to testing was able to restore hippocampal histone H4 acetylation levels, which are typically reduced by about 50% in these mice, improve performance on a contextual freezing task, and restore synaptic plasticity (Long-term potentiation) [6]. Chronic trichostatin-A administration (i.p. 5 mg/kg every other day for 2 months) promoted brain expression of gesolin, which has anti-amylogenic properties. However, due the pleiotropic effects of trichostatin-A, including an increase in secretase activity, it did not change the overall amyloid load in the brains of these animals [7].

Parkinson's disease: The neuroprotective potential of trichostatin-A depends on the nature of the neuronal insult, and in some contexts may instead exacerbate damage.

Pre-treatment with trichostatin-A, one-hour prior to MPTP, protected against nigrostriatal dopaminergic pathway neurodegeneration. Trichostatin-A relieved the repression on the neuron-restrictive silencer factor (NRSF) target genes, leading to an upregulation of BDNF and thyroid hormone [8]. Thyroid hormone (T3) suppresses expression of APP [9], which helps prevent Aβ production. In cultured SH-SY5Y dopaminergic-like cells, trichostatin-A could protect against MPP+-mediated mitochondrial

fragmentation by preventing the downregulation of Mfn2, but was not protective against rotenone-induced mitochondrial fragmentation [10]. Furthermore, trichostatin-A was found to exacerbate rotenone-mediated neurodegeneration in other dopaminergic cell lines [11].

Huntington's disease: In a transgenic Huntington's disease mouse model (HdhQ7/Q111), acute administration of trichostatin-A improved performance on a novel object recognition task (from 53 ± 3% to 60.5 ± 3.5%) and rescued expression of CREB target genes in the hippocampus [12]. Trichostatin-A also increased vesicular transport of BDNF in striatal neurons via its inhibition of HDAC6 [13].

Stroke: Potential benefit (rodents)

Trichostatin-A is protective in the context of ischemic damage through its ability to promote **induction of the Nrf2 antioxidant system** through P13K/Akt signaling.

In the MCAO stroke model, trichostatin-A pre-treatment reduced infarct volume (from 49.1±3.8 to 21.3±4.6%), edema, and neurological deficit scores [14; 15]. Since the mechanism appears to involve the reduction of oxidative stress damage, it seems likely that trichostatin-A would have to be administered very close to time of damage for it to be effective.

APOE4 interactions:

Trichostatin-A may be beneficial in alleviating ApoE4-associated endosomal dysfunction. Excessive endocytic acidification can promote APP processing and inhibit Aβ clearance [16]. Alkalization of the endosomal compartment can attenuate APP processing and Aβ secretion. The endosomes in ApoE4 astrocytes are too acidic due to the downregulation of the Na^+/H^+ exchanger NHE6, possibly mediated by elevated HDAC4 activity [17]. Epigenetic modification of NHE6 restores its expression, which leads to alkalization of the endosome and restoration of Lrp1 surface expression. Lrp1 is a receptor crucial to the phagocytic activity of astrocytes and helps mediate Aβ clearance.

Aging and related health concerns: Can extend lifespan in flies and worms. May be beneficial for cancer in combination therapy, and protective against oxidative stress damage when administered acutely after ischemic injury.

Types of evidence:

- Numerous laboratory studies

Lifespan: Benefit (flies and worms)

Trichostatin-A has been demonstrated to extend lifespan in *Drosophila* and *C. elegans* in a calorie restriction-like manner.

Trichostatin-A was shown to extend the lifespan of wild-type C. elegans by 22.12% (from 23.1 to 28.4 days), but did not further extend lifespan of long-lived eat-2 mutant worms, suggesting that trichostatin-A promotes lifespan through a similar mechanism to calorie restriction [18]. In Drosophila, trichostatin-A extended the maximum survival of male flies by 37.0% and female flies by 37.9% [19]. Notably, trichostatin-A relieved repression on the Hsp22 and Hsp70 promoters, both of which are more highly expressed in naturally long-lived flies than in short-lived fly strains [20]. This suggests that the optimal dose and effects are likely to vary based on genetic background.

The lifespan extension may involve the same induction of NHE6 mediated vacuolar alkalization shown to be beneficial in promoting Aβ clearance [17]. Trichostatin-A inhibits the HDAC Rpd3, leading to an increase in NHE6, which is a CREB-target gene that regulates cell responses under low-nutrient conditions [21].

Cancer: Potential benefit (rodents, cell culture)

Trichostatin-A has anti-tumorigenic properties due to its ability **to inhibit the cell cycle** and affect the expression of genes dysregulated in cancer. It may be most beneficial by working in a synergistic manner with other therapies to augment their anti-tumor responses.

Based on microarray analysis, the pool of genes regulated by trichostatin-a is largely comprised of cell-cycle and cancer-associated genes [4]. Due to differences in their epigenetic and expression profile, trichostatin-A differentially affects cancer and normal (non-cancer) cells. Trichostatin-A can activate ERK1/2 to prevent TGFβ1 and serum-starvation induced apoptosis in normal cells, while potentiating apoptosis in the cancer cells [22]. It also blocks proliferation in various carcinoma cell lines [22; 23], delays tumor growth in xenograft models [24; 25], and was shown to shift the tumor phenotype from carcinoma to benign in a carcinogen-induced carcinoma model [23]. Trichostatin-A treatment prior to implantation also augmented the innate anti-tumor response in a glioblastoma xenograft model by potentiating natural killer (NK) cell-mediated lysis [24]. While the anti-tumor benefits of trichostatin-A alone appear to be modest, trichostatin-A may be more effective in combination therapy. Trichostatin-A was found to have a synergistic effect with metformin in an osteocarcinoma model [25], re-sensitized breast cancer cells to doxorubin [26], and augmented the ability of oncolytic adenoviruses to impair cell viability in ovarian cancer cells [27].

Human Mesenchymal Stem Cell (MSC) maintenance: Potential benefit (cell culture)
Trichostatin-A treatment of MSCs suppresses the morphological changes and loss of proliferation capacity that typically occurs as they are passaged in cell culture [28]. It also stabilized the expression of pluripotent genes (i.e. Oct4, Sox2, Nanog) and allowed for the maintenance of their multipotent differentiation capacity.

Kidney disease: Potential minor benefit (rodents)

Trichostatin-A helps protect renal function by preventing the loss of Klotho expression that normally accompanies kidney damage (through loss of promoter acetylation). Renal dysfunction is typically associated with the development of proteinuria/albuminuria, and these patients have lower Klotho levels [29]. Trichostatin-A can protect against albumin-mediated downregulation of Klotho in cultured renal cells, and chronic administration (0.5 mg/kg body i.p daily for 6 weeks) was reno-protective in a chronic kidney disease by preserving Klotho expression *in vivo* [30]. As with other agents that mediate protection through Klotho, trichostatin-A would only be expected to be useful in mitigating damage in early stage disease.

Oxidative stress-mediated organ damage: Potential benefit (rodents)

Trichostatin-A has been shown to protect against ischemic/oxidative stress related damage through induction of anti-oxidant and anti-inflammatory pathways.

Cardiovascular: In a coronary-artery ischemia model, trichostatin-A pretreatment reduced myocardial infarct size, and **reduced the level of oxidative stress** markers (ROS, MDA) [31]. The oxidative stress mitigation was related to the induction of SOD and FoxO3a, which was likely mediated by induction of Nrf2 and Klotho, respectively. Trichostatin-A can also suppress aberrant angiogenesis by reducing expression of Nox4 redox signaling [32].

Lung: In a lung ischemia/reperfusion injury model, trichostatin-A dose-dependently reduced vascular permeability, edema, and arterial hypertension [33]. This was associated with a reduction in neutrophil-mediated oxidative stress and inflammation.

Safety: Limited information about long-term safety in animals, and initial safety testing in humans is ongoing. Has pleiotropic effects, which may include inhibition of oligodendrocyte differentiation and altered expression of pro-atherosclerotic genes.

Types of evidence:

- Several laboratory studies

Trichostatin-A **has not yet been tested in humans**, but the first Phase I trial began recruiting patients in October 2018. Most animal studies involve acute treatment with trichostatin-A, so its **long-term safety profile is largely unknown** [34]. A single dose (1 mg/kg) in pregnant mice did not adversely affect the development of the pups [35]. Repeated dosing up to 5 mg/kg has not led to any measurable signs of toxicity in rodents [7; 23; 36]. However, due to the pleiotropic effects of HDAC inhibitors, benefits in one cell type may be offset by harm to another cell type. For example, high dose trichostatin-A has been shown to inhibit oligodendrocyte proliferation and differentiation in culture [37], which could impair myelin repair. Trichostatin-A also regulates the expression of pro-atherosclerotic genes, and could play a role in atherogenesis [38].

Sources and dosing:

Trichostatin-a is available for research use, but not human use, from a variety of commercial suppliers.

Research underway:

Vanda Pharmaceuticals is sponsoring a dose escalation Phase 1 trial for trichostatin-A (VTR-297) for patients with hematological malignancies. The first patient was randomized in October 2018.

Search terms:

Pubmed, Google: Trichostatin-A + neurodegeneration, dementia, Alzheimer's disease, neuroprotection, aging, lifespan, ApoE4, cancer, klotho, cardiovascular, safety, pharmacokinetics, clinical trial

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