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.

Trodusquemine

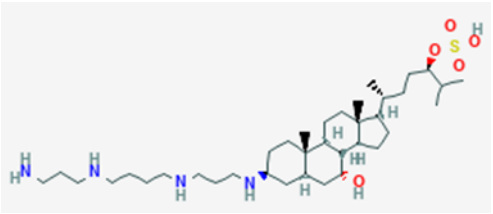
Evidence Summary

PTP1B inhibitor which can enhance insulin and leptin signaling in the context of metabolic dysfunction and may promote tissue regeneration. Reasonable safety based on limited testing in humans.

Neuroprotective Benefit: May help improve insulin signaling in the brain and mitigate inflammation based on ability to inhibit PTP1B, but evidence for a specific effect from trodusquemine is extremely limited.

Aging and related health concerns: May enhance insulin signaling, protect against atherosclerosis, and enhance tissue repair based on preclinical studies.

Safety: Good safety profile in Phase 1 trials, no evidence about long-term safety, and has to be administered IV due to poor oral bioavailability.

Availability: Research use and clinical trials	**Dose**: Not established	**Chemical formula:** $C_{37}H_{72}N_4O_5S$ **MW**: 685.066 g/mol  Source: Pubchem
Half-life: ~ 1 week (rodents)	**BBB**: Penetrant	
Clinical trials: Phase 1 for obesity/Type 2 diabetes (n=22, 25, 42 and breast cancer (n=5)	**Observational studies**: None	

What is it? Trodusquemine, also known as MSI-1436, is a naturally occurring aminosterol which is closely related to the anti-microbial agent squalamine [1]. It consists of a 7, 24 dihydroxylated 24-sulfated 5-cholestane conjugated to spermine. It acts as a reversible allosteric inhibitor of protein tyrosine phosphatase 1B (PTP1B), and has 200-fold selectivity for PTP1B compared to its closest homolog, Tc-PTP [2]. PTP1B dephosphorylates and inactivates receptor activated tyrosine kinases. PTP1B plays a critical role in terminating insulin and leptin signaling, and is considered a very attractive target for metabolic disorders. However, PTP1B has demonstrated to be an extremely difficult drug target, since small molecule activators have generally been highly charged and suffer from poor drug properties [3]. Additionally, most candidates tend to target several PTP family members, which increases the propensity for off-target effects. While trodusquemine has a reasonable pharmacokinetic profile, it is also a charged molecule, and this significantly limits its oral bioavailability. It has been tested in Phase 1 trials for diabetes, obesity, and cancer. Recent preclinical work suggests it may have pro-regenerative properties.

Neuroprotective Benefit: May help improve insulin signaling in the brain and mitigate inflammation based on ability to inhibit PTP1B, but evidence for a specific effect from trodosquemine is extremely limited.

Types of evidence:

- 1 review article on role of PTP1B in AD pathology
- 3 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:

Alzheimer's disease: Potential benefit (preclinical)

PTP1B is associated with a variety of processes implicated in Alzheimer's disease (AD) [4].

ER Stress: PTP1B is involved in endoplasmic reticulum (ER) stress regulation, and mediates the toxicity associated with neuronal ER stress. It also plays a key role in the regulation of insulin and leptin signaling.

Loss of neuroprotection: Defective neuronal insulin signaling, and impaired neuronal glucose utilization are common features in the AD brain. Leptin receptors are highly expressed in the hippocampus and play a role in processes associated with cognition and memory [5]. In the context of AD, leptin signaling is impaired [6], which may impair the resiliency of neurons and make them more susceptible to neurodegeneration. PTP1B activity can further reduce neuroprotection through downregulation of the neurotrophic factor BDNF, which plays a key role in synaptic plasticity, via dephosphorylation and inactivation of its receptor, TrkB [7].

Inflammation: PTP1B activity may also actively promote neurodegeneration by driving chronic neuroinflammation. PTP1B was found to be highly expressed on microglia in the hippocampus in patients with AD and to promote the secretion of pro-inflammatory cytokines [8]. In a mouse model, a PTP1B inhibitor was able to reduce microglial activation following LPS induced inflammation [9].

In a *C. elegans* model of AD, trodusquemine treatment (10 or 20 uM) increased the overall fitness of the worms by 50%, but increased the level of Aβ aggregates and had no effect on total Aβ levels [10]. Trodusquemine has not yet been tested in mammalian models of AD.

Parkinson's disease: Potential benefit (preclinical)

One study found that trodusquemine was protective in a *C. elegans* model of Parkinson's disease (PD). Trodusquemine (10 or 20 uM) treatment inhibited alpha-synuclein lipid induced aggregation [11]. Treatment during the larval stage was able to prevent the formation of alpha-synuclein inclusions, while treatment in adult worms with pre-existing pathology was able to slow the formation of new inclusions.

In this study, the lifespan of the treated PD worms was slightly increased when compared to control worms, and there was also a trend toward a slightly increased lifespan with trodusquemine treatment in control worms. Trodusquemine may also be beneficial for PD based on the neuroprotective effects of PTP1B inhibition, however, it has not yet been established whether trodusquemine can protect against PD-associated pathology in mammals.

Anxiety: Potential benefit (preclinical)

The protein LMO4 acts as an endogenous PTP1B inhibitor, and may exert anxiolytic effects through activation of endocannabinoids [12]. PTP1B activity can reduce endocannabinoid production by inactivating (dephosphorylating) mGluR5. However, the inhibitory activity of LMO4 was found to be reduced in response to stress hormones, such as glucocorticoids. Trodusquemine treatment (intracerebroventricular or i.p.) was able to reduce PTP1B over activation and stimulate endocannabinoid production in the amygdala, and eliminate anxiogenic phenotypes in LMO4 deficient mice [12]. This suggests that systemic administration of trodusquemine may be capable of correcting pathological processes associated with PTP1B overactivation in the brain.

APOE4 interactions: Unknown

Aging and related health concerns: May enhance insulin signaling, protect against atherosclerosis, and enhance tissue repair based on preclinical studies.

Types of evidence:

- 4 clinical trials (Phase 1: Healthy overweight n=42; Diabetes/Obesity n=22, n=28; Metastatic Breast Cancer n=5)
- Numerous laboratory studies

Type 2 diabetes/Obesity: Potential benefit

PTP1B is a negative regulator of insulin and leptin signaling [13]. The endogenous inhibition of PTP1B by LMO4 is reduced in the context of metabolic stressors, such as those associated with a high fat diet [14; 15]. PTP1B activity has been found to be increased in the adipose tissue and skeletal muscle of obese individuals with insulin resistance. It plays a role in the negative regulation of insulin in skeletal muscle in insulin resistant people [16], and improved insulin sensitivity following weight loss in obese people is

associated with a reduction of PTP1B in adipose tissue [17]. PTP1B deficient mice are also resistant to diet induced obesity, and have improved glycemic control and insulin sensitivity [18].

Trodusquemine has been tested in Phase 1 trials examining tolerability and pharmacokinetics in people with obesity and/or Type 2 diabetes (NCT00509132, NCT00606112, NCT00806338). The drug appears to have been well-tolerated and improved glucose tolerance [19], however, the full results of the trials have not been published, and the company sponsoring the trials sold off its assets and ceased operation shortly after the conclusion of these trials. The rights to trodusquemine have subsequently been acquired by other companies, but there is no clear indication that they intend to resume trials in this population.

Trodusquemine (i.p. or i.v. 5-10 mg/kg) has been shown to act as an appetite suppressant, reduce body weight, and improve plasma levels of insulin and leptin in mouse models of obesity and diabetes [1; 2; 12; 14; 15; 20; 21]. The weight loss involved a reduction of body fat [2; 22], and was not associated with a change in dopamine signaling in the brain [23]. Lean tissue was spared, and weight loss was proportional to starting weight in obese rodents [2]. These effects may be mediated primarily through the ability of trodusquemine to inhibit PTP1B and improve insulin sensitivity in hypothalamic neurons. Trodusquemine treatment rescued deficits in neuronal insulin signaling, leading to increased levels of phosphorylated insulin receptor (p-IRS1), and associated downstream signaling components Akt and GSK3 [14; 15]. Similar benefits on peripheral (liver) insulin sensitivity were seen in mice following intracerebroventricular (30 µg/kg) administration of trodusquemine [15], suggesting that it may be necessary to target both brain and peripheral PTP1B to achieve clinically meaningful metabolic improvements.

Regeneration: Potential benefit (preclinical)

Wound healing is impaired in animal models with hyperglycemia, such as diabetes, where there is an upregulation of PTP1B. Vascular endothelial cells usually proliferate and migrate in response to VEGF, but dephosphorylation of VEGFR2 by PTP1B can inhibit this process, and impair wound healing [24]. Administration of a PTP1B inhibitor was able to restore wound healing in a mouse model of diabetes, suggesting that in the context of diabetes, PTP1B inhibitors such as trodusquemine could both improve metabolic function and help promote healing [24].

One recent study found that trodusquemine was able to enhance tissue regeneration in zebrafish and mice [25]. Zebrafish have endogenous regenerative capacity, and trodusquemine was able to accelerate repair processes by stimulating cell proliferation without inducing tissue overgrowth. At a dose of 0.125

mg/kg, trodusquemine increased the rate of tail fin regeneration by 2-3-fold, but had no effect on fin length in uninjured fish at doses up to 1.25 mg/kg (for 40 days). Trodusquemine also enhanced heart regeneration, increasing proliferation by 2.6-fold and tropomysin expression in the injured area by 2-fold. In mice, trodusquemine treatment (0.125 or 1.25 mg/kg i.p. every 3 days for 4 weeks) starting 24 hours after ischemic myocardial infarction improved survival from 55% to 70% and 80%, respectively. Heart function also improved by 2-fold (based on fractional shortening and ejection volume), infarct size was reduced by 53%, and myocardial proliferation increased by 4-fold. Notably, trodusquemine enhanced recovery, but did not mitigate the initial amount of ischemic tissue damage. In skeletal muscle, trodusquemine was also found to be able to activate the stem cell population, satellite cells, by 2-fold following injury. These effects were driven by PTP1B inhibition. This study suggests that trodusquemine may have pro-regenerative properties.

Cardiovascular: Potential benefit (preclinical)

PTP1B modulates ER stress and contributes to arterial endothelial dysfunction, particularly with respect to nitric oxide (NO) mediated vessel dilation. Trodusquemine was protective against arterial ER stress in an *ex vivo* model, through the inhibition of PTP1B, which resulted in increased levels of phosphorylated Akt [26].

In the LDLR (-/-) plus high fat diet mouse model of atherosclerosis, both acute (10 mg/kg i.p.) and chronic (10 mg/kg then 5 mg/kg i.p. weekly for 4 weeks) trodusquemine treatment was able to reverse atherosclerotic plaque formation, decrease adiposity, reduce total cholesterol and triglyceride levels, and improve glucose homeostasis [22]. Treatment was also associated with a reduction in aortic inflammation resulting in less monocytic recruitment, which may underlie some of its benefits in reducing plaque formation. These studies suggest that PTP1B inhibition through trodusquemine may improve vascular dysfunction.

Breast Cancer: Potential benefit (preclinical)

Protein tyrosine kinases are overexpressed in many types of cancer and promote cancer cell survival. Most patients develop resistance to current protein tyrosine kinase inhibitors, thus new alternatives are needed. The protein tyrosine kinase HER2 is overexpressed in approximately 25% of breast cancer tumors and is associated with poor prognosis [27]. PTP1B has also been found to be overexpressed in these tumors and appears to drive HER2 mediated tumor growth and spread. In mouse breast cancer models (xenograft and NDL2 transgenic model) treatment with trodusquemine (5 mg/kg i.p. every 3rd day) significantly reduced tumor growth and prevented metastasis [27]. Although most effective when

administered prior to tumor formation, it still significantly reduced tumor growth when administered after tumor formation. A Phase 1 dose escalation clinical trial was initiated in 2015 (NCT02524951), but only enrolled 5 patients and was terminated in 2017 due to lack of sponsor interest. Therefore, it is unclear whether it can impact breast cancer patient outcomes.

The anti-tumor effects of PTP1B inhibition seen for breast cancer may not extend to all types of cancer, since in most cases PTP1B inhibits/counteracts the activity of protein tyrosine kinases. In an ovarian cancer cell line, PTP1B inhibition with trodusquemine promoted cancer cell proliferation and migration [28]. This suggests that whether trodusquemine is beneficial or harmful may be cancer type dependent.

Safety: Good safety profile in Phase 1 trials, no evidence about long-term safety, and has to be administered IV due to poor oral bioavailability.

Types of evidence:

- 3 clinical trials (Phase 1: Healthy overweight n=42, Diabetes/Obesity n=22, n=28).
- Numerous laboratory studies

The Phase1 safety studies conducted thus far indicate that trodusquemine has a favorable safety profile at the doses tested (up to 15 mg/m^2 for single dose and up to 10 mg/m^2 for multiple (8) doses in diabetics) (NCT00606112, NCT00806338). The maximum tolerated dose was determined to be 40 mg/m^2 based on a dose escalation study in overweight adults without diabetes (NCT00509132) (press release).

The full results have not been published, but at a 2009 American Diabetes Association conference, it was reported that the drug was well-tolerated and had linear pharmacokinetic profiles in the single ascending dose study, and that there was no evidence of drug accumulation or serious adverse events in the multiple ascending dose study [19]. Since trodusquemine has relatively low oral bioavailability, it was administered intravenously (IV), and this route poses a risk for infusion-related reactions. Although trodusquemine acts as an appetite suppressant and can induce weight loss in animal models, the effects have largely been attributed to a correction of metabolic dysfunction, and were proportional to baseline weight [2]. However, the long-term effects of trodusquemine treatment have not been established. The doses that were found to be effective at promoting regeneration in animal models are 5-50 times lower than the doses found to be tolerated in the Phase 1 studies, and did not affect weight in these animals [25].

Sources and dosing:

Trodusquemine (MSI-1436) can be purchased from commercial suppliers for research use, but is not available for human use. The doses most effective for diabetes, regeneration, or cancer have not yet been established in humans.

Research underway:

The clinical trials for the use of trodusquemine in diabetes/obesity were sponsored by Genaera, however, this company ran out of money and closed in 2009 (press release). It sold its assets to Ohr Pharmaceuticals, who subsequently licensed the rights to trodusquemine to DepYmed, a spinout from Cold Spring Harbor Laboratory, which is developing PTP1B inhibitors for use in cancer. DepYmed was the sponsor for the Phase 1 trial in metastatic breast cancer who decided to terminate the trial. They have developed a new PTP1B inhibitor called DPM-1001 which shows enhanced PTP1B inhibition *in vitro* (IC_{50} 100 nM vs 600 nM for trodusquemine) [21]. It also acts as a copper chelator, which appears to play a role in mediating its inhibitory effects on PTP1B. *In vivo*, DPM-1001 was found to exert similar effects to trodusquemine on body weight, insulin signaling, and glucose metabolism. In contrast to trodusquemine, DPM-1001 is orally bioavailable, which makes it a more attractive therapeutic agent. DepYmed is currently working to develop DPM-1001 as an anti-cancer therapeutic.

Novo Biosciences, a spinout from MDI Biological Lab in Maine, is working on developing trodusquemine for promoting regeneration in the context of heart damage, kidney damage, and Duchenne muscular dystrophy.

It is not known when new clinical trials for trodusquemine or DPM-1001 might begin.

Search terms:

Pubmed, Google: Trodusquemine OR MSI-1436 +

- Alzheimer's disease, Parkinson's diseaese, neurodegeneration, aging, lifespan, diabetes, cardiovascular, cancer, clinical trials, safety

Websites visited for Trodusquemine:

- Clinicaltrials.gov
- PubChem
- DrugBank.ca

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