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.

Verdiperstat

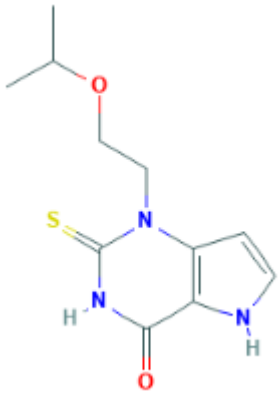
Evidence Summary

There is a rationale for the use of verdiperstat in cardiovascular or neurodegenerative disease, but it is not clear whether myeloperoxidase (MPO) activity is a primary driver of disease progression.

Neuroprotective Benefit: Although there is evidence for the contribution of oxidative stress in neurodegenerative disease and increased expression of MPO in several neurodegenerative diseases, it is unclear to what extent MPO inhibition will slow the progression of the disease.

Aging and related health concerns: Although there is extensive evidence linking myeloperoxidase activity to chronic diseases, it is unknown whether inhibition of myeloperoxidase will improve outcomes.

Safety: One potential concern with MPO inhibition is a risk of infection, though clinical trials are needed to determine the extent of the risk.

Availability: Not available, currently in clinical trials	**Dose**: 600mg twice per day (oral) (currently being tested)	**Molecular Formula:** $C_{11}H_{15}N_3O_2S$ **Molecular weight:** 253.32g/mol **Source:** Pubchem 
Half-life: 2.5 hours	**BBB**: Penetrant (in non-human primates)	
Clinical trials: 2 ongoing, two PET studies completed	**Observational studies**: None	

What is it?

Myeloperoxidase (MPO) is highly expressed in phagocytic cells such as neutrophils and inflammatory lymphocytes. Its physiological role is to protect the body against infectious diseases and detoxify toxins from microorganisms such as diphtheria and tetanus. It possesses a heme group deep within the protein which can react with hydrogen peroxide and chloride ions to produce hypochlorous acid. This can cause a burst of reactive oxygen species that can destroy microbes. However, excessive quantities of these species can damage surrounding tissue. Excessive production of hypochlorous acid can oxidize lipids, protein carbonyls and other species, and interact with the mitochondria leading to a reduction in ATP, NAD and glutathione. MPO activation can also lead to the production of neutrophil extracellular traps (NETs) (Ray and Katyal, 2016; Stefanova et al, 2012).

Although this report is primarily concerned with verdiperstat (the only MPO inhibitor currently in clinical trials), data will also be presented from other MPO inhibitors (tool compounds or pharmaceutical agents). In addition, although increased levels of MPO have been associated with several diseases including cardiovascular disease, rheumatoid arthritis, diabetes, neurodegenerative disease, liver

disease, and cancer, this report will focus on diseases with studies where inhibitors have been tested, rather than the many studies on plasma levels and risk of disease.

Neuroprotective benefit: Although there is evidence for the contribution of oxidative stress in neurodegenerative disease and increased expression of MPO in several neurodegenerative diseases, it is unclear to what extent MPO inhibition will slow the progression of the disease.

Types of evidence:

- Two RCTs measuring neuroinflammation in Parkinson's and multiple system atrophy
- One study on verdiperstat blood brain barrier penetrance in primates
- Seven studies of genetic polymorphisms of MPO and risk of dementia or cognitive decline
- Four studies of MPO expression levels in postmortem tissue from Alzheimer's patients
- Three studies of plasma levels of MPO in patients with Alzheimer's disease
- Multiple preclinical studies on MPO inhibition and expression

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

The G-463A polymorphism in the promoter region of the MPO gene has been inconsistently associated with the risk of Alzheimer's disease. The A allele decreases MPO expression by disrupting an SP1 binding site while the G allele is associated with higher MPO expression. Several studies suggest that the A allele is over-represented in female patients with Alzheimer's disease (Reynolds et al, 1999; Leininger-Muller et al, 2003) and may increase the risk of cognitive decline (Pope et al, 2006). However, the results of the MPO G-463A polymorphism and the risk of Alzheimer's disease are still inconclusive (Reynolds et al, 1999; Leininger-Muller et al, 2003; Crawford et al, 2000; Zappia et al, 2004; Combarros et al, 2002; Usui et al, 2006)

Several studies suggest there is no interaction with ApoE genotype and the MPO G-463A polymorphism (Leininger-Muller et al, 2003; Pope et al, 2006; Crawford et al, 2000).

Human research to suggest benefits to patients with dementia:

Green et al (2004) reported that expression of MPO and its oxidation products are increased in postmortem hippocampal and cortical brain tissue from Alzheimer's patients (no interaction with ApoE4), and that there is an increase in enzymatic activity. Expression was increased around amyloid plaques and neurofibrillary tangles. It was also expressed in neurons around plaques and tangles as well

as some reactive (but not resting) microglia. Reynolds et al (1999) also reported increased expression of MPO around amyloid plaques in the cortex and around blood vessels. This expression was in microglia surrounding plaques and not astrocytes. In 17 Alzheimer's cases, they found a higher expression of MPO surrounding amyloid plaques in ApoE4 patients compared to ApoE3 patients. This may be relevant as ApoE is particularly susceptible to oxidation by MPO (Jolivalt et al, 1996). Gellhaar et al (2017) also reported an increase in MPO in postmortem Alzheimer's tissue compared to controls (n=45). MPO expression was often increased in the proximity of blood vessels, in microglia (but not astrocytes or neurons), and around amyloid plaques in the hippocampus and frontal cortex. Interestingly, *in situ* hybridization did not show an increase in MPO mRNA in the brain and low levels in circulating cells, suggesting the possibility that MPO expression is primarily increased during neutrophil development in the bone marrow and that the increased brain expression comes from peripheral cells. On the other hand, Maki et al (2008) reported increased MPO expression in postmortem Alzheimer's tissue (n=6) that was present around amyloid plaques but was present in astrocytes. Overall, although all studies suggest increased expression of MPO in Alzheimer's patients, there are mixed results concerning which cell type MPO is overexpressed.

Tzikas et al (2013) reported that plasma MPO levels were higher in Alzheimer's patients than in healthy elderly (n=55). MPO levels were also significantly correlated with plasma levels of Aβ and cardiovascular risk factors in both Alzheimer's patients and healthy elderly. Another study also reported an increase in plasma MPO levels in Alzheimer's patients (n=28; 132.8 ng/mL) versus healthy elderly (n=27; 55.0 ng/mL) (Schreitmuller et al, 2013). On the other hand, a proteomic multianalyte profiling study of 190 plasma proteins did not find an association with MPO levels and Alzheimer's disease/mild cognitive impairment (Hu et al, 2012).

Parkinson's disease

In a phase 2a study in 24 patients with Parkinson's disease (randomized 3:1), verdiperstat (600mg b.i.d.) over 8 weeks reduced microglial inflammation (measured with TSPO PET) in treated patients at 4 and 8 weeks compared to baseline while there was no change in placebo-treated patients. In the nigrostriatal pathway, verdiperstat reduced TSPO binding by 13%-16% at both 4 and 8 weeks (effect size from 0.5 to 0.6) (Jucaite et al, 2015). The reduction in TSPO binding in the treated group was significant in all brain regions measured except for the frontal cortex (which was borderline significant). On the other hand, no brain regions in the placebo group showed reduced TSPO binding. There were no differences between the groups, though this could be due to the low numbers analyzed in the placebo group (n=6). However, there was a large variability in the response to verdiperstat.

An ^{11}C PET tracer study confirmed that verdiperstat crossed the blood brain barrier in non-human primates with homogenous distribution throughout the brain (Johnstrom et al, 2015).

Multiple system atrophy (MSA)
In a study of 58 patients with multiple system atrophy, verdiperstat (300mg or 600mg, b.i.d.) had no effect on inflammation (measured with TSPO PET) after 12 weeks (clinicaltrials.gov).

Mechanisms of action for neuroprotection identified from laboratory and clinical research
Alzheimer's disease
Volkman et al (2019) conducted an experiment transplanting bone marrow from either wild type or MPO knockout mice (KO) into an Alzheimer's mouse model. Bone marrow transplantation from MPO KO mice improved cognition compared to wild type transplanted animals while having no effect on amyloid plaques. MPO KO-transplanted mice also had a reduction in astrogliosis, a non-significant reduction in microgliosis, and reduced levels of some (IL1β, VCAM1, but not TNFα) inflammatory cytokines. There was no change in endothelial tight junction markers (markers of blood brain barrier integrity). MPO KO-transplanted mice also showed a reduced expression of ApoE. This suggests that MPO inhibition in the periphery may have some CNS effects on the pathogenesis of Alzheimer's.

Interestingly, Maki et al (2008) reported that MPO was not expressed in the brain of Alzheimer's mice. When they introduced a transgene for human MPO (either the -463G or -463A alleles), only the mice with the transgene containing the -463G allele expressed MPO around amyloid plaques but not mice with the transgene containing the -463A allele. Increased MPO expression also increased lipid peroxidation in the brain.

In hypercholesterolemic rabbits (which develop amyloid plaques), activated microglia expressed MPO in close proximity to amyloid plaques (Chen et al, 2018).

Multiple System Atrophy (MSA)
MSA is characterized by the aggregation of α-synuclein (αSYN) within oligodendrocytes, an increase in microgliosis, and neurodegeneration. In MSA patients and in a mouse model of MSA, there is an increase in MPO expression in microglia, but not astrocytes, in the mesencephalon and basal ganglia. To develop a mouse model of MSA, human αSYN is expressed under the control of an oligodendrocyte promoter (proteolipid protein – PLP) followed by injection of 3-nitropropionic acid (3NP) to increase vulnerability to oxidative stress. Stefanova et al (2012) treated MSA mice with verdiperstat for 28 days at an age when mild neurodegeneration was beginning. MPO inhibition improved behavioral outcomes,

reduced neurodegeneration and microglia (but not astrocyte) activation and reduced the density of nitrated αSYN aggregation.

Treatment of MSA mice with verdiperstat later in the course of the disease had no effect on behavior or neurodegeneration. However, it did reduce neuroinflammation and the density of nitrated αSYN inclusions in the striatum (though not in other regions) (Kaindlstorfer et al, 2015).

APOE4 Interactions:

Several studies suggest no interaction between mutations in the MPO gene, ApoE4, and risk of Alzheimer's disease (Leininger-Muller et al, 2003; Pope et al, 2006; Crawford et al, 2000). One study reported an increase in MPO expression around amyloid plaques in patients harboring an *APOE4* allele (Reynolds et al, 1999). However, further studies are needed to see if ApoE4 patients are more susceptible to neurodegeneration caused by MPO.

Aging and related health concerns: Although there is extensive evidence linking myeloperoxidase activity to chronic diseases, it is unknown whether inhibition of myeloperoxidase will improve outcomes.

Types of evidence:

- One review of MPO and cardiovascular disease
- One study of individuals who are genetically MPO-deficient
- Two meta-analyses of gene mutations in MPO promoter
- One biomarker study of longevity
- One biomarker meta-analysis of risk of acute coronary syndrome
- Eight preclinical studies of MPO inhibitors for cardiovascular/metabolic diseases

Lifespan

In a prospective cohort of individuals over 80 years of age (n=363) living in a mountain community, individuals in the highest tertile of systemic myeloperoxidase levels had an increased risk of mortality after four years (HR = 1.97; 95%CI 1.02-3.80) than those in the lowest tertile (Giovannini et al, 2010).

Cardiovascular disease

MPO is also implicated in the development of atherosclerosis and cardiovascular disease. MPO and its oxidation products are located within atherosclerotic lesions (Nicholls and Hazen, 2005). In a study of 92

patients with MPO-deficiency compared to 92 randomly selected controls in a community cohort, cardiovascular problems occurred in two MPO-deficient individuals vs. nine controls; serious infection occurred in seven MPO-deficient individuals vs. one control; and chronic inflammatory diseases occurred in six MPO-deficient individuals (chronic evolutive polyarthritis) vs. one control (Kutter et al, 2000).

In a meta-analysis of 13 studies with 9,090 individuals with acute coronary syndrome (ACS) followed for an average of 11.4 months, high levels of MPO were significantly associated with an increased risk of mortality (OR = 2.03; 95%Ci 1.40-2.94) but not a major adverse cardiac event or recurrent myocardial infarction. For females, MPO levels were not as good of a prognostic indicator of mortality and recurrent myocardial infarction (Kolodziej et al, 2019). Increased plasma MPO levels have also been associated with adverse outcomes after a cardiovascular event, the need for coronary revascularization, risk of myocardial infarction, chronic heart failure, and other cardiovascular events (Nicholls and Hazan, 2005; Ali et al, 2016; Giovannini et al, 2010).

A meta-analysis of nine studies with 4,744 individuals found that those with the -463A allele were at a decreased risk of coronary artery disease (OR = 0.68; 95%CI 0.54-0.85) but only in Chinese populations. In non-Chinese populations, the relationship was non-significant (Li et al, 2017; Luyao et al, 2014).

Preclinical studies of MPO inhibition
Although few studies exist testing verdiperstat in preclinical models, several tool compounds/pharmaceutical agents have been developed and tested in preclinical models of cardiovascular disease. Below is a summary of different agents tested.

PF-13555: In a mouse model of myocardial infarction in young adult mice, treatment with PF-13555, an MPO inhibitor, reduced the infiltration of inflammatory cells in the infarct area, improved cardiac function, and improved cardiac remodeling after 21 days. Better outcomes were obtained when treatment was started earlier and prolonged (Ali et al, 2016).

PF-06282999: In a mouse model of atherosclerosis (Ldlr -/-, high fat diet), treatment with another MPO inhibitor structurally related to PF-13555 (PF-06282999) over 16 weeks reduced MPO activity in the plasma but had no effect on lesion size. However, PF-06282999 reduced the size of the necrotic core by 37%, increased the collagen content of the lesion area, had no effect on the macrophage content of the lesion (though did reduce the homing of macrophages to the lesion), and reduced inflammation in the lesion (measured with FDG-PET) (Flach et al, 2019).

INV-315: In a mouse model of atherosclerosis (ApoE-/-, high fat diet), high-dose treatment with INV-315 over 16 weeks reduced plaque size (-36%) compared to control mice and improved endothelium-dependent (but not independent) relaxation. In addition, there was a reduction in superoxide production and nitrotyrosine content in the aorta and a reduction in circulating IL-6 (though no significant change in INFγ, MCP-1, or IL-10) (Liu et al, 2012).

AZM198: Cheng et al (2019) tested the effects of AZM198 in three models of inflammation (femoral cuff, tandem stenosis model of plaque rupture in ApoE-/- mice – a model of plaque instability, and a model of insulin resistance) starting prior to vascular injury. In two models (not the model of insulin resistance), treatment with AZM198 improved endothelium-dependent (but not independent) relaxation. It had no effect of circulating neutrophil count or inflammatory cytokines in the ApoE-/- model. In another study with the tandem stenosis model of plaque instability, 13-week treatment with AZM198 had no effect on circulating inflammatory cell count or plasma lipid levels. However, in the unstable plaques, AZM198 increased cap thickness by 65% and increased smooth muscle cells, suggesting that it improved plaque stability. Interestingly, AZM198 had no effect on lipid composition or macrophage number, suggesting another mechanism for improving plaque stability (Rashid et al, 2018).

In an obese/hypertensive mouse model (high fat diet for 16 weeks + infusion of angiotensin II for the last 4), AZM198 treatment reduced bodyweight (independent of food intake), viceral adipose tissue, inflammation in the visceral fat, and attenuated the severity of the nonalcoholic steatoheptitis phenotype. It had no effect on a glucose tolerance test or any effect on measures of cardiac dysfunction (cardiac relaxation and contraction, hypertrophy, and fibrosis) (Piek et al, 2019).

AZD5904: In a rat model of insulin resistance, a two week treatment with AZD5904 had no effect on whole-body insulin resistance but did improve microvascular response to insulin (increased blood flow in the microvasculature) (Chai et al, 2019).

4-ABAH: In a mouse model of atherosclerosis (ApoE-/-, high cholesterol diet), 8-week treatment with 4-ABAH reduced plaque size, improved levels of circulating inflammatory markers (reduced IL-6, increased IL-10), reduced vascular oxidative stress, and improved endothelium-dependent (but not independent) function (Tiyerili et al, 2016).

Safety: One potential concern with MPO inhibition is a risk of infection, though clinical trials are needed to determine the extent of the risk.

Types of evidence:

- One review of genetic mutations in MPO
- Two short RCTs

MPO is one of the defense mechanisms that neutrophils use to kill potential pathogens, and one concern with MPO inhibition is an increased risk of infection. Genetic MPO deficiency occurs in about 1:1000 to 1:4000 individuals in the United States and Europe. It may increase the risk of fungal infections, especially *Candida albicans*. Although there is some increased risk of severe infections, most patients do not seem to be especially susceptible to chronic infections. There are also reports of some cases of chronic inflammatory conditions, such as chronic evolutive polyarthritis. However, MPO deficiency in humans is understudied, and it is not clear that similar effects would occur when taking an MPO inhibitor (Klebanoff et al, 2012; Odobasic et al, 2016; Kutter et al, 2000; Kutter, 1998).

Although there is a potential risk of infections with MPO inhibition, current trials of verdiperstat have reported mild to moderate side effects including headache, nausea, and insomnia.

In the Parkinson's study there were no serious adverse events. Side effects that were mild to moderate and only in the drug group included headache, nausea, and insomnia. There was an increase in mean thyroid stimulating hormone (TSH) in the drug group relative to placebo which returned to baseline by the time of follow-up. There was also a mild decrease in plasma uric acid (a marker of oxidative stress) in some drug-treated patients (Jucaite et al, 2015).

In the MSA study there were only two serious adverse events in the drug group (hip fracture and progression of MSA) and none in the placebo group. Adverse events were balanced between groups (occurring in ~75% of patients) (clinicaltrials.gov).

In a phase 1 safety study, 10% of the participants (4/40) developed a maculopopular rash which was treated with Benadryl (Gan et al, 2019).

It is not known whether inhibition of MPO with a drug would have the same potential risk for infectious disease as individuals who are MPO deficient because of a genetic mutation. However, most studies to

date have been short (<12 weeks) with few patients. Future studies are needed to determine whether verdiperstat is safe and tolerable.

Drug interactions:
Not known

Sources and dosing: Verdiperstat is under development by Biohaven. It is being tested in clinical trials and is not commercially available. In a clinical trial in patients with Parkinson's disease, a 600 mg twice daily dose of verdiperstat has been tested.

Research underway:
There are two ongoing studies with verdiperstat. One is part of a platform trial in patients with amyotrophic lateral sclerosis (NCT04297683). The other study is testing the effect of verdiperstat in patients with multiple system atrophy (NCT03952806).

Search terms:

- myeloperoxidase + alzheimer + lifespan + longevity [title/abstract]
- myeloperoxidase deficiency + cardiovascular
- myeloperoxidase [meta-analysis]
- mpo null
- verdiperstat
- PF-13555
- PF-06282999
- AZM198
- INV-315
- AZD5904
- myeloperoxidase + frontotemporal dementia

Websites visited:

- Clinicaltrials.gov
- Pubmed

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