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.

P110

Evidence Summary

Restores mitochondrial homeostasis in preclinical models by inhibiting pathological mitochondrial fragmentation, but the peptide has not yet been formulated for clinical use.

Neuroprotective Benefit: P110 restores mitochondrial function, improves autophagic flux, and reduces neuroinflammation in preclinical models of neurodegenerative diseases.

Aging and related health concerns: Excessive mitochondrial fragmentation is associated with cardiovascular disease and diabetes. P110 could potentially improve mitochondrial homeostasis.

Safety: Good safety in preclinical models due to its high selectivity, but no long-term studies or human testing have been done. Therapeutic route of administration is unclear and may impact safety profile.

Availability: Research use	**Dose**: Not established	**Chemical formula:** $Drp1_{49-55}$-GG-TAT_{47-57} (Drp1) DLLRPGT-GG-YGRKKRRQRRR (TAT) **MW**: Native P110, 771 g/mol P110-TAT, 2427 g/mol
Half-life: ~ 1 hour (estimated)	**BBB**: Penetrant (TAT conjugated peptide)	
Clinical trials: None	**Observational studies**: None	

What is it?

P110 is a seven amino acid peptide that acts to **inhibit pathological mitochondrial fragmentation**. Drp1 is a member of the dynamin family of GTPases which serves as the master regulator of mitochondrial fission [1]. Under basal conditions it is localized to the cytosol, and upon activation it relocates to the outer mitochondrial membrane where it interacts with adaptor proteins to trigger mitochondrial fission. The P110 peptide targets amino acids 49 through 55 in region 110 of Drp1, which is 100% identical to Fis1 and 80% identical to 16 other proteins [2]. In cells, it acts as a **specific inhibitor of the Drp1-Fis1 interaction** without affecting the interactions with the other adaptors, Mff, MiD49, and MiD51. The Drp1-Fis1 interaction is relatively specific for oxidative stress mediated fission, and blocking it does not appear to interfere with physiological homeostatic mitochondrial fission mediated by interaction of Drp1 with the other adaptors. The peptide is conjugated to TAT_{47-57} in order to make it cell permeable. The P110 peptide has been tested in preclinical models for neurodegenerative diseases.

Neuroprotective Benefit: P110 restores mitochondrial function, improves autophagic flux, and reduces neuroinflammation in preclinical models of neurodegenerative diseases.

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:

Mitochondrial dysfunction is a common feature of neurodegenerative diseases typically characterized by the dysregulation of mitochondrial homeostasis [1]. Mitochondria need to be able to dynamically respond to changes in the environment in order to meet the energy demands of the cell. The number, size, and ATP generating capacity of the mitochondria is determined by regulating the balance between mitochondrial fission and fusion. Cells from patients and/or animal models with various neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, and Amyotrophic lateral sclerosis, show **evidence of excessive mitochondrial fragmentation resulting from increased fission and decreased fusion** [2; 3; 4; 5; 6; 7; 8]. There tend to be increased levels of the activated fission inducer Drp1 and an associated decrease in the fusion regulators Mfn1, Mf2, and Opa1. The activity of Drp1 is regulated through post-translational modifications, and aggregation prone neurotoxic proteins have been shown to drive processes that promote Drp1 activation.

P110 can inhibit hyperactivated Drp1 driven mitochondrial fission by selectively inhibiting the interaction between Drp1 with the adaptor protein Fis1 in response to oxidative stress conditions. Based on preclinical models, inhibiting the Drp1-Fis1 interaction has downstream neuroprotective effects.

Mitochondrial function: A complete inhibition of fission would ultimately be detrimental for neuronal communication, as Drp1 mediated fission is important for the maintenance of axonal and synaptic function [9]. Fission is also essential for eliminating damaged or aged mitochondria, and a complete loss of fission would negatively impact cellular energetics. Thus, it is necessary for Drp1 targeted therapeutics to restore mitochondrial dynamics to a physiologically appropriate level, rather than broadly inhibit fission. It should be noted that in the context of neurodegenerative disease, there is likely to be a higher number of damaged mitochondria, thus the appropriate level of fission may be higher than under basal conditions [10]. Treatment with P110 can restore the balance of fission and fusion by **reducing fission toward more physiologically appropriate levels**. In cell culture, P110 reduces levels of mitochondrial fragmentation, improves mitochondrial interconnectivity, restores membrane polarization, reduces levels of reactive oxygen species (ROS), and restores oxidative respiration capacity and ATP production [2; 4; 7; 8; 11; 12].

Neuroinflammation: P110 was found to be able to **reduce pro-inflammatory cytokine release** and induction of reactivity in microglia and astrocytes that had been exposed to Aβ42, LPS, or expressing mutant Huntingtin or SOD1 [12]. In response to these pathological proteins, microglia and astrocytes undergo increased levels of mitochondrial fragmentation, and they release these fragmented

mitochondria into the extracellular space where they serve to activate the innate immune system. By preventing mitochondrial fragmentation, P110 was able to eliminate the induction of an immune-activating signal.

Proteostasis: P110 was able to **restore autophagic flux** in cultured neurons treated with Aβ42, and to restore autophagic flux and proteasome activity in neurons expressing the mutant SOD1G93A [7; 8]. In these systems there is a buildup of autophagosomes due to lysosomal impairment. Excessive mitochondrial fragmentation reduces ATP production, and thus hinders energy intensive cellular processes. Lysosomal acidification requires high levels of ATP for the maintenance of a H+ gradient. P110 may then promote proteostasis by restoring mitochondrial ATP production to levels sufficient for processes of cellular repair and protein quality control.

Neurodegenerative diseases: Potential benefit (preclinical models)

Alzheimer's disease: Based on postmortem tissue analysis, mitochondrial dynamics homeostasis is altered in the frontal cortex of AD patients (n=15) [13]. The protein levels of fission related proteins Drp1 and Fis1 were found to be significantly increased, whereas fusion related proteins, Mnf1, Mfn2, and Opa1 were decreased. The mitochondrial dyshomeostasis was present at all examined disease stages, and there was an increasing level of interaction between oligomeric Aβ and Drp1 with disease progression.

Aβ42 was shown to facilitate the Drp1-Fis1 interaction in cell culture, resulting in mitochondrial fragmentation and the induction of apoptosis [7]. P110 treatment reduced Drp1 activation, mitochondrial fragmentation, and preserved respiratory capacity in fibroblasts from AD patients. P110 treatment (3 mg/kg/day for 3 months via a subcutaneously implanted osmotic pump) also mitigated the disease-associated decline in mitochondrial integrity and function by restoring the homeostatic balance between fission and fusion [7]. Treatment was also associated with some behavioral improvements including increased nest building and reduced hindlimb clasping.

Parkinson's disease: iPSC-derived neurons from PD patients with LRRK2 mutations had increased mitochondria-associated Drp1, increased mitochondrial fragmentation, increased ROS, loss of mitochondrial membrane potential, and reduced ATP levels [3]. LRRK2 can phosphorylate Drp1 in a manner that promotes its activation. Treatment with P110 was able to **restore mitochondrial structural integrity** and alleviate these deficits in mitochondrial function. The restoration of mitochondrial dynamics was also able to restore autophagic flux by reducing lysosomal hyperactivity driven by excessive mitochondrial-associated autophagy.

P110 (1.5 mg/kg/day via a subcutaneously implanted osmotic pump) was found to be protective in preventing long-term dopaminergic neuron damage in the MPTP mouse model [11]. The dopaminergic nerves and neurons were preserved, and the mice had less locomotor deficits relative to their untreated counterparts. The protective effect appears to be due to a reduction in apoptosis. The mitochondrial localization of Drp1 in response to oxidative stress promotes the mitochondrial localization of p53 and its associated apoptotic signaling cascade, thus P110's inhibition of Drp1 mitochondrial localization and fragmentation inhibits the induction of apoptosis in the stressed dopaminergic neurons. P110 pre-treatment was also shown to protect mitochondrial integrity and cell viability in response to other oxidative stressors (rotenone, H_2O_2, CCCP, MPP+) in cell culture [2].

Huntington's disease: Striatal neurons from HD patients and HD mouse models were found to have increased levels of mitochondria associated Drp1 [4; 14]. Treatment with P110 in cells and animal models was able to reduce mitochondrial fragmentation and correct structural defects [4; 5]. In iPSC-derived GABAergic neurons, P110 was able to **enhance neurite growth as well as improve mitochondrial function** [4]. In a mouse model of HD, P110 treatment (3 mg/kg/day via a subcutaneously implanted osmotic pump) beginning after the onset of symptoms improved mitochondrial respiratory capacity, reduced striatal neuron loss, and slowed disease progression. The treated mice had better motor and cognitive function than their untreated counterparts following 8 weeks of P110.

Amyotrophic lateral sclerosis: Fibroblasts from ALS patients with SOD1, FUS1, or TDP-43 mutations show increased mitochondrial fragmentation and a 50% decrease in interconnectivity, which could be restored by treatment with P110 [8]. P110 treatment reduced ROS, and restored the mitochondrial membrane potential, ATP levels, and autophagic flux in SOD1G93A mutant motor neurons. P110 (3 mg/kg/day via a subcutaneously implanted osmotic pump at symptom onset) also improved locomotor performance, preserved muscle fiber integrity, and delayed disease progression in the SOD1G93A mouse model.

APOE4 interactions: Unknown

Aging and related health concerns: Excessive mitochondrial fragmentation is associated with cardiovascular disease and diabetes. P110 could potentially improve mitochondrial homeostasis.

Types of evidence:

- Several laboratory studies

Lifespan: Unclear

Induction of Drp1 during midlife was found to increase lifespan and healthspan in flies, which was dependent on the induction of autophagy [15]. Studies in mammals have indicated an increase in mitochondrial fragmentation with aging due to age-related increases in oxidative stress [16], therefore, it is unclear whether Drp1 modulation would have a similar effect in mammals. However, this work does provide support for the **necessity of maintaining proper mitochondrial homeostasis for healthy aging**, such that a shift in either direction can compromise health.

Cardiovascular

Mitochondrial fission is a key feature of mitochondrial homeostasis; thus, it needs to be carefully regulated to meet cellular energy demands. Consequently, the function of tissues with high energy demands, such as the heart is highly vulnerable to disturbances in mitochondrial dynamics. Drp1 has been shown to play a role in cardiomyopathies, as Drp1 driven mitochondrial fission is elevated in response to various damage response pathways, and may exacerbate damage by reducing cell survival [17].

Ischemia: Potential benefit (preclinical)

Mitochondrial fission is induced in response to ischemia. P110 was able to protect rat cardiomyocytes exposed to hypoxic conditions in cell culture and an *ex vivo* preparation by reducing mitochondrial fragmentation, maintaining mitochondrial network integrity, preventing a decline in ATP levels, and reducing the induction of pro-apoptotic caspase activation [18]. In a rat myocardial infarction model, acute P110 treatment (0.5 mg/kg i.p.) during reperfusion reduced injury severity and had sustained benefits on mitochondrial energetics up to three weeks later [18]. P110 was also able to reduce right ventricular diastolic pressure in a rat model of pulmonary arterial hypertension [19]. Improvements were associated with the preservation of mitochondrial morphology and the network integrity. In the middle cerebral artery occlusion model of ischemic stroke, pre-treatment with P110 (0.5 mg/kg i.p.) prevented Drp1 hyperactivation, reduced infarct volume, and reduced neurological deficits [20].

HD-associated cardiac dysfunction: Potential benefit (preclinical)

The mutant huntingtin protein is associated with mitochondrial impairments in heart as well as the brain. Treatment with P110 improved cardiac mitochondrial structure and was protective against mitochondrial and lysosomal functional deficits in HD-patient derived cardiomyocytes and in the R2/6

HD mouse model [21]. This suggests that P110 could protect against systemic complications associated with neurotoxic proteins.

Exercise: May reduce aerobic exercise capacity (preclinical)

Exercise induces physiological mitochondrial fission in cardiac muscle, which acts to increase mitochondrial function [22]. Unlike pathological mitochondrial fragmentation, this process was not associated with increased ROS production in mice. Inhibition of Drp1 mediated fission via conditional Drp1 knockout or Mdivi-1, a small molecule Drp1 inhibitor, reduced the ability of the mitochondria to respond to the increase in energetic stress, leading to a decline in exercise capacity.

Notably, treatment with **P110 also reduced maximal and submaximal exercise capacity in the mice**, indicating that the Drp1-Fis1 interaction is involved in this response. Fis1 is also increased in skeletal muscle in response to exercise in mice [23]. The Drp1-Fis1 interaction has been described as dispensable for the maintenance of physiological fission, and instead serves as the primary mediator of oxidative stress driven fission. Since exercise produces non-pathological oxidative stress, chronic treatment with P110 may lead to a decrease in aerobic exercise capacity.

Diabetes: Potential benefit (based on mechanism)

A high glucose environment is associated with increased ROS production and the induction of oxidative stress, which in turn promotes mitochondrial fragmentation [24]. Increased levels of mitochondrial fission and decreased fusion have been described in the cells derived from patients with type 2 diabetes, and these changes in mitochondrial dynamics are linked to poor glycemic control [25; 26]. Through the modulation of cellular bioenergetics, mitochondria have been proposed as master regulators of insulin secretion. In rodents, the inhibition of fusion is associated with insulin resistance and obesity, while the liver targeted inhibition of fission is protective against these conditions [24]. The shift in mitochondrial dynamics may also promote diabetes-associated complications, as **shifting the balance toward fission in mice promotes the induction of hyperglycemia, dyslipidemia, and atherosclerosis** [27].

P110 has not yet been tested in diabetic models, but the protective effects seen with the Mdivi-1 Drp1 inhibitor suggest that P110 may also have therapeutic benefit by inhibiting excessive mitochondrial fragmentation.

Cancer: Potential benefit for proliferative tumors with high Drp1 expression (preclinical)

Metabolic flexibility is a key feature of cancer cells, and the ability to dynamically regulate mitochondrial morphology plays an important role in driving this metabolic plasticity. Several **cancer-related signaling pathways have been shown to activate Drp1** and drive mitochondrial fission [28]. Mitochondrial fragmentation is associated with glycolysis and may help drive Warburg metabolism (aerobic glycolysis) in cancer cells, whereas mitochondrial elongation is associated with a shift toward oxidative phosphorylation. Drp1 serves as a molecular link between several processes that regulate cell growth and survival including cell division and apoptosis. Consequently, whether inhibiting or activating Drp1 is the better therapeutic strategy depends on the tumor type and environment. In general, proliferative cancers dependent on glycolysis tend to have higher Drp1 activity and mitochondrial fragmentation, whereas metastatic cancers tend to be more reliant on oxidative phosphorylation and have lower Drp1 expression [29].

P110 has not been yet been tested in cancer, but the non-specific Drp1 inhibitor Mdivi-1 has been shown to reduce tumor proliferation and/or promote tumor cell apoptosis in various cell culture and preclinical cancer models [28]. The anti-cancer effects appear to be related to its modulation of mitochondrial dynamics, as benefits were associated with reductions in Drp1 mediated fission, and a shift in the metabolic profile away from (aerobic) glycolysis.

Mitochondrial targeted therapies, such as Drp1 inhibitors, are viewed primarily as adjunct therapies that could make tumors more susceptible to proliferation targeted therapies by hindering their metabolic plasticity [28]. Increased levels of Drp1 may help stressed cancer cells resist apoptosis, so inhibiting

Drp1 may increase their vulnerability. However, **Drp1 targeted treatment would need to be personalized for tumor type.**

Colitis: Potential benefit at early stages (preclinical)

P110 (3 mg/kg i.p.) was found to be protective in the dextran sulfate sodium and dinitrobenzene sulfonic acid rodent models of colitis when administered at the time of the colitis-inducing agents [30]. The treated mice had less body weight loss, improved colon morphology, and improved survival. Since P110 was induced starting at the time of disease onset, it is not clear whether the improvements are related to a mitigation of initial damage or whether the treatment would be effective for cases of chronic disease with pre-existing colon damage.

Safety: Good safety in preclinical models due to its high selectivity, but no long-term studies or human testing have been done. Therapeutic route of administration is unclear and may impact safety profile.

Types of evidence:

- Several laboratory studies

P110 has not been tested in humans, but has shown a good safety profile in preclinical rodent models with dosing up to 5 months [8]. In wild-type or control cell and rodent models, P110 treatment did not show significant effects on mitochondrial or cellular function [2; 3; 4; 11; 18]. Non-selective Drp1 inhibitors, which broadly inhibit mitochondrial fission have been shown to have deleterious effects, due to the disruption of mitochondrial homeostasis, indicating that a very selective therapeutic is necessary for a Drp1 targeted approach [9]. P110's very selective inhibition of the Drp1-Fis1 interaction only blocks oxidative stress induced fission, while preserving physiological homeostatic fission mediated by interactions of Drp1 with other adaptor proteins, Mff, MiD49, and MiD51 [2]. However, preclinical rodent models suggest that P110 could potentially reduce aerobic exercise capacity [22].

The small molecule Drp1 inhibitor Mdivi-1 has been more extensively tested in preclinical models than P110, however, some studies suggest that it is non-selective and also inhibits mitochondrial complex I [31]. It is also possible that shifting the fission-fusion balance through modulation of Drp1 has a similar effect on bioenergetics as complex I inhibition [17]. Mdivi-1 also has a longer half-life than P110 (12 hours vs ~1 hour), and poor water solubility [32]. Based on these differences in pharmacokinetics and target, the potential safety of P110 cannot be inferred from studies with Mdivi-1.

The effects of chronic Drp1 inhibition are unknown, as **long-term studies with Drp1 inhibitors have not yet been done**. While acute administration appears safe, it is possible that side effects may emerge with chronic use, particularly in the context of cell stress.

Sources and dosing:

Thus far P110 has only been used in a research setting. The potential therapeutic route of administration or dosing regimen has not been clinically established.

Research underway:

There are currently no clinical trials underway or planned for P110 at this time.

Search terms:

Pubmed, Google: P110 +

- Alzheimer's disease, Huntington's disease, neurodegeneration, mitochondria, fission, Drp1, aging, cardiovascular, diabetes, cancer, safety

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