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.

Drp1 Inhibitors

Evidence Summary

Drp1 inhibitors restore mitochondrial homeostasis in preclinical models by inhibiting pathological mitochondrial fragmentation, but none have yet been formulated for clinical use.

Neuroprotective Benefit: Inhibition of pathological fission restores mitochondrial function, improves autophagic flux, and reduces neuroinflammation in preclinical models of neurodegenerative diseases. They are likely best suited for acute conditions.

Aging and related health concerns: Excessive mitochondrial fragmentation is associated with cardiovascular disease, diabetes, and ischemic injury. Drp1 inhibitors may limit tissue damage with acute use, while chronic use may pose risks.

Safety: Acute use of Drp1 inhibitors shows good safety in preclinical models, but no long-term studies or human testing have been done. Chronic use, particularly with systemic administration, poses a risk to the mitochondrial function in healthy tissues.

Availability: Research use/in preclinical development	**Dose**: Not established	**P110** **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: Varies	**BBB**: Varies	
Clinical trials: None	**Observational studies**: None	

What is it?

Dynamin-related protein 1 (Drp1) is a member of the dynamin family of GTPases which serves as the master regulator of mitochondrial fission [1]. As the energy powerhouse of the cell, mitochondria are dynamically regulated in response to local metabolic demands [2]. One mechanism of regulation is the cycle of fission and fusion, whereby the mitochondria divide or merge with one another. The proper balance between fission and fusion is critical for maintaining the supply of healthy mitochondria. Fission is part of a mechanism to clear damaged mitochondria, so it tends to increase when the proportion of damaged/dysfunctional mitochondria is elevated. Injury, particularly when blood flow is disrupted/insufficient to meet demand, is often accompanied by a shift towards more fission [2]. While this may initially be protective, it often cascades into a pathological feedforward cycle of oxidative stress and excessive mitochondrial fragmentation resulting in lasting damage. Interrupting this process of runaway fission by targeting Drp1 has been proposed as a therapeutic strategy to protect against tissue damage, particularly in the context of ischemic-reperfusion injuries [2].

Under basal conditions Drp1 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 [1]. While general inhibition of its GTPase activity has been utilized in a variety of preclinical models, it is a tenuous clinical strategy, since this approach could disrupt both pathological and physiological fission. An alternative approach is to specifically target types of fission that are most associated with pathological fragmentation. This type of strategy led to the development of the P110 peptide, a seven amino acid peptide that acts to inhibit pathological mitochondrial fragmentation. P110 targets amino acids 49 through 55 in region 110 of Drp1, which is 100% identical to Fis1 and 80% identical to 16 other proteins [3]. 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, which are important for physiological fission. 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 a variety of preclinical models, including models for neurodegenerative diseases.
However, the drug properties of P110 have limited its potential for clinical translation [4]. As such, there have been efforts to develop small molecule inhibitors of Drp1-Fis1-mediated fission [4; 5]. These efforts are currently in the early preclinical development stage, such that much more work will be needed to determine the prospective clinical utility of these compounds. Preclinical studies to date suggest that Drp1 (/Fis1) inhibitors may be best suited for acute use following tissue injury driven by oxidative stress damage.

Neuroprotective Benefit: Inhibition of pathological fission restores mitochondrial function, improves autophagic flux, and reduces neuroinflammation in preclinical models of neurodegenerative diseases. They are likely best suited for acute conditions.

Types of evidence:

- Several studies in postmortem brain tissue indicating mitochondrial dysfunction
- Several laboratory studies

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

Proper mitochondrial function is critical for brain health [2]. Because they could disrupt the physiological balance of mitochondrial dynamics in healthy individuals, Drp1 inhibitors would not be conducive for use in primary prevention. While preclinical studies suggest they may have utility for secondary prevention of neurodegeneration/cognitive decline following brain injury/stroke [6], this class of drugs has not yet been clinically tested, so the potential impacts in humans remain unclear.

***Human research to suggest benefits to patients with dementia*:**

Drp1 inhibitors have not been tested in dementia patients.

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

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 [7]. 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 [8]. Treatment with P110 may 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 ROS, and restores oxidative respiration capacity and ATP production [3; 9; 10; 11; 12; 13].

Neuroinflammation: The release of reactive oxygen species (ROS) and mitochondrial DNA (mtDNA) in response to mitochondrial fragmentation promotes proinflammatory signaling cascades [2]. One mechanism involves the priming of the NLRP3 inflammasome, and downstream pro-inflammatory cytokines, particularly IL-1β, involved in innate immune system activation and polarization. The Drp1-NLRP3 axis is involved in the polarization of macrophages/microglia into a pro-inflammatory M1-like state [2].
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 [13]. 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: Drp1 may impact autophagic flux independent of its effects on mitochondrial fission [14]. Knockdown of Drp1 was found to promote autophagic flux and attenuate protein aggregation in a neuronal cell line [14].
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 [9; 10]. 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.

Potential role of Drp1 in toxin-mediated neurodegeneration/ cognitive impairment

Excessive mitochondrial fragmentation stemming from Drp1 activation has been identified as a potential mechanism mediating organ toxicity, including neurodegeneration and cognitive impairment, downstream of a variety of environmental/industrial toxins. Some of the toxins include the pesticide atrazine [15], the fungicide dithianon [16], the heavy metal cobalt [17], and the mycotoxin deoxynivalenol/vomitoxin [18]. Excessive Drp1-mediated fission has also been implicated in drug-related toxicity [19]. This suggests that excessive Drp1-mediated fission may be a common mechanism of organ toxicity, such that Drp1 inhibition may have neuroprotective effects in the context of both disease-related and toxin-induced mitochondrial dysfunction.

Drp1 inhibition as a therapeutic mechanism

Accordingly, the inhibition of Drp1-mediate excessive mitochondrial fragmentation has been implicated as a neuroprotective mechanism for a variety of agents with therapeutic activity. These agents provide a proof-of-concept for Drp1 inhibitors as potentially neuroprotective therapies. They include various Traditional Herbal Medicines, such as the Qiangji decoction [20], the Buyang Huanwu decoction [21], and Dihuang Yinzi [22]. The active ingredients of the main components of many herbal medicines, such as ligustilide in *Angelica sinensis*, and ginsenosides in *Panax ginseng*, have been found to inhibit Drp1-mediated fission, as part of the modulation of associated signaling pathways [23]. A prominent pathway involved in the regulation of Drp1 activation is AMPK, which acts as a negative regulator of Drp1 through the phosphorylation of its Ser-637 site [24]. As a result, the inhibition of excessive Drp1-mediated inhibition may be one of the mechanisms by which AMPK activating drugs exert their therapeutic effects.

The most notable AMPK-activating therapeutic is the anti-diabetic drug, metformin.

Some of the neuroprotective effects of metformin have been associated with the inhibition of Drp1-mediated mitochondrial fragmentation in preclinical models. Metformin protected against lead (Pb)-induced mitochondrial fragmentation in neuron-like SH-SY5Y cells by preventing Drp1 activation through induction of AMPK/Nrf2 signaling [25]. Inhibition of excessive fission may be a mechanism by which

metformin protects against diabetes-related cognitive impairment [26]. In cell culture, metformin protected against high glucose-induced mitochondrial fragmentation, acting in a similar manner to the Drp1 inhibitor Mdivi-1 [26]. The alleviation of cognitive deficits in a diabetic mouse model (db-/-) in response to metformin treatment was accompanied by the preservation of mitochondrial integrity in the hippocampus stemming from a reduction in Drp1 activation [26].

Drp1 is regulated via numerous post-translational modifications, most notably the phosphorylation of Ser616 which facilitates its interaction with mitochondria and pro-fission activity [2]. In addition to phosphorylation, Drp1 is modified by acetylation, SUMOylation, ubiquitination, nitrosylation, O-GlcNAcylation, s-palmitoylation, and ISGylation [27; 28]. Therefore, therapies which interact with the signaling pathways which modulate these modifications, such as ERK1/2 and sirtuins, may also, at least partially, mediate therapeutic activity through the modulation of Drp1 activation.

Neurodegenerative diseases: POTENTIAL BENEFIT (Preclinical)
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 ALS, show **evidence of excessive mitochondrial fragmentation resulting from increased fission and decreased fusion** [3; 9; 10; 12; 29; 30; 31]. 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. Drp1 inhibitors have typically been tested with acute administration, and show promise under acute injury conditions. Whether they would be suited for long-term use in chronic neurodegenerative conditions, and whether their utility might be restricted to a particular window of early-stage disease remains to be determined.

Alzheimer's disease: Mitochondrial dynamics homeostasis has been shown to be altered in the AD brain, based on postmortem tissue analysis. The specific alternations depend on the brain region and sub-region such as the cortical layer, as well as the stage of disease, and possibly also the sex of the individual [32]. Though a general pattern emerges indicative of a predominance of fission over fusion, with increased Drp1 and variable decreases across the different fusion-related mediators. The increase in fusion-associated proteins in some regions is thought to reflect a compensatory response [32]. Changes in mitochondrial dynamics with regional variation are also observed in the aging brain, with a general trend toward increased fission [32]. The presence of neuropathology may exacerbate some of these aging-related changes, and create additional stress and energy demands that result in further compensatory changes to the machinery involved in mitochondrial dynamics. One study found that the protein levels of fission related proteins Drp1 and Fis1 were found to be significantly increased in the frontal cortex of AD patients (n=15), whereas fusion related proteins, Mnf1, Mfn2, and Opa1 were decreased [33]. Mitochondrial dyshomeostasis was present at all examined disease stages, and there was an increasing level of interaction between oligomeric A and Drp1 with disease progression. Evidence of early dysregulation of mitochondrial dynamics has also been observed in AD models, such that early changes result in waves of further compensatory changes with disease progression [34].

Aβ as a driver of fission: Aβ42 has been shown to facilitate the Drp1-Fis1 interaction in cell culture, resulting in mitochondrial fragmentation and the induction of apoptosis [10]. The cyclin-dependent kinase cdk5 is dysregulated in the context of AD and implicated in AD pathology [34]. Cdk5 was found to regulate Aβ42-induced mitochondrial fission and neuronal apoptosis through the phosphorylation of Drp1 (at Ser579). The activation of Drp1 may then accelerate the further production of Aβ [34]. In SH-SY5Y cells, treatment with P110 reduced the expression of APP and BACE-1, proteins involved in the production of Aβ, while increasing levels of proteins involved in non-amyloidogenic processing and amyloid clearance, such as ADAM10 and Klotho [35].

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 [10]. Treatment was also associated with some behavioral improvements including increased nest building and reduced hindlimb clasping.

Parkinson's disease: Mitochondrial dysfunction, coupled with elevated oxidative stress, is considered a hallmark of PD. Excessive mitochondrial fission may be an important contributor. Inhibition of Drp1 with

Mdivi-1 was associated with the survival of dopaminergic neurons and the activation of the AMPK/Sirt1/PGC-1α axis in PD models [36]. PGC-1α, a master regulator of mitochondrial biogenesis, regulates Drp1 to maintain the balance of mitochondrial dynamics [37].
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 [29]. 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. Similarly, knocking down Drp1 reduced Mn-induced α-synuclein aggregation and restored autophagic flux in a dopaminergic cell line [14].
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 [3].

Huntington's disease: Striatal neurons from HD patients and HD mouse models were found to have increased levels of mitochondria associated Drp1 [12; 38]. Sirt3 is an important regulator of the acetylation of mitochondria-associated proteins [39]. Overexpression of Sirt3 was shown to decrease the mitochondrial accumulation of Drp1 and Fis1, improve neuronal survival, and extend lifespan in a fly model of HD [39].
Treatment with P110 in cells and animal models was able to reduce mitochondrial fragmentation and correct structural defects [12; 30]. In iPSC-derived GABAergic neurons, P110 was able to **enhance neurite growth as well as improve mitochondrial function** [12]. 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: Mitochondrial dysfunction is observed prior to motor neuron degeneration in ALS models [40]. In a fly model (dSod1G85R), a partial reduction in Drp1 prevented mitochondrial fragmentation and mitochondrial defects in synapses [40]. Drp1 was found to be enriched at synapses and accumulated in synaptoneurosomes in postmortem motor cortex brain tissue from patients with various ALS subtypes [41]. Drp1 was co-localized with pTau-S396, suggesting this hyperphosphorylated pathological tau may be a driver of excessive fission [41].
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 [9]. 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.

Stroke: POTENTIAL BENEFIT (Preclinical)
Oxidative stress damage is a prominent feature of cerebral ischemia-reperfusion injury [2]. Calcium overload and excessive production of ROS trigger the activation of Drp1, shifting the balance of mitochondrial dynamics towards increased fission [2]. The accumulation of fragmented mitochondria accelerates the production of ROS, resulting in a feedforward cycle. Therefore, interruption of this cycle by inhibiting excessive Drp1-mediated fission would be expected to limit cellular damage. Drp1 inhibitors have been shown to protect against excessive cell death and damage in a variety of preclinical ischemia-reperfusion models [2]. Acute treatment in response to an ischemic-reperfusion injury may be one of the most clinically relevant uses for Drp1 inhibitors, as acute inhibition may be able to prevent long-term neurological damage while avoiding the potential negative impact on the homeostasis of mitochondrial dynamics with chronic inhibition.
In an endovascular perforation-induced mouse model of subarachnoid hemorrhage, treatment with the Drp1-Fis interaction inhibitor P110 mitigated the injury-induced activation of Drp1, neuronal apoptosis, and disruption to the BBB [42]. These effects were associated with better neurological outcomes.
In the MCAO model of ischemic stroke, pre-treatment with P110 (0.5 mg/kg i.p.) prevented Drp1 hyperactivation, reduced infarct volume, and reduced neurological deficits [43].

Post-operative cognitive decline (POCD): POTENTIAL BENEFIT (Preclinical)
The exacerbation of mitochondrial dysfunction may be a mechanism by which exposure to anesthesia accelerates cognitive decline in individuals with neuropathology at heightened risk for dementia. The anesthetic sevoflurane was found to exacerbate mitochondrial fission in the 5XFAD mouse model

through the further upregulation of p-Drp1-Ser616, the form of Drp1 associated with mitochondrial membranes [44]. Pretreatment with the non-specific Drp1 inhibitor Mdiv-1 preserved mitochondrial metabolism, preventing the compensatory shift to glycolysis and production of ROS. Inhibiting excessive fission also protected against anesthesia-associated Aβ accumulation and synaptic deficits [44]. Mitochondrial bioenergetics are subject to circadian regulation, such that the modification of Drp1 is regulated by the circadian clock [45]. Exposure to the anesthetic, isoflurane, disrupted clock control of Drp1, which negatively impacted energy (ATP) production and cognitive function in the hippocampus of mice [46]. Anesthesia-induced cognitive impairment and mitochondrial dysfunction could be prevented via pretreatment with the non-specific Drp1 inhibitor, Mdivi-1 [46]. Drp1-mediated mitochondrial fragmentation, driven by excessive ROS production, may be a key mechanism underlying propofol-mediated neurotoxicity [47]. Drp1 inhibitors have been shown to dampen propofol's pathological effects on mitochondria, as well as attenuate ROS production and cell death.

Traumatic Brain Injury: POTENTIAL BENEFIT (Preclinical)
Excessive mitochondrial fragmentation may exacerbate tissue damage and precipitate chronic neurodegeneration in the context of brain injury. Levels of Fis1 were found to be elevated in postmortem brain tissue from individuals with TBI [6]. A similar elevation in Fis1 coupled with higher levels of fragmented mitochondria was observed in brain tissue in a mouse model of TBI [6]. Treatment with the Drp1-Fis1 interaction inhibitor P110 (1.5 mg/kg i.p.) for two weeks starting three hours post-injury protected against pathological mitochondrial fragmentation, oxidative stress damage, lipid peroxidation, lipid droplet accumulation, neuronal loss, and BBB dysfunction [6]. Acute P110 had long-lasting neuroprotective effects, including the protection against TBI-related cognitive impairment for at least 17 months post-injury. The protective effects were related to the acute prevention of injury-induced mitochondrial dysfunction, as P110 treatment starting in the chronic phase (8 months post-injury) did not mitigate cognitive deficits. Heat stroke can lead to brain injury. Preclinical models suggest that Drp1 activation during heat stroke may exacerbate heat stroke-induced brain injury by driving proinflammatory microglial polarization [48]. These studies suggest that acute post-injury treatment with a Drp1 inhibitor may have lasting neuroprotective effects.

APOE4 interactions: Not established

Aging and related health concerns: Excessive mitochondrial fragmentation is associated with cardiovascular disease, diabetes, and ischemic injury. Drp1 inhibitors may limit tissue damage with acute use, while chronic use may pose risks.

Types of evidence:

- Several laboratory studies

Lifespan: CONTEXT-DEPENDENT (Preclinical)
Induction of Drp1 during midlife was found to increase lifespan and healthspan in flies, which was dependent on the induction of autophagy [49]. Studies in mammals have indicated an increase in mitochondrial fragmentation with aging due to age-related increases in oxidative stress [50], therefore, it is unclear whether Drp1 modulation would have a similar effect in mammals. In mice, overexpression or knockdown of Drp1 in skeletal muscle during middle age negatively impacted muscle quality and accelerated aging [51]. Studies in *C. elegans* suggest that the impact of Drp1 modulation on longevity depends on the genetic background, timing, and tissue specificity of the Drp1 inhibition [52]. Deletion of Drp1 during adulthood did not meaningfully affect lifespan in wild-type worms or long-lived daf-2 (IGF-1) mutant worms [52]. Meanwhile, Drp1 deletion during development further extended lifespan in daf-2 worms by increasing resistance to chronic stress, but shortened lifespan in wild-type worms. However, neuron-specific inhibition of Drp1 increased lifespan in wild-type worms. This is consistent with the finding that TORC1 signaling in neurons acts as a regulator of aging [53]. Neuronal TORCI signaling can drive systemic mitochondrial fragmentation, while deletion of Drp1 protects against these pro-aging effects in *C. elegans* [53].
AMPK signaling, which acts as an inhibitor of TORC1, is associated with lifespan extension. AMPK negatively regulates Drp1-mediated fission via phosphorylation of the inhibitory site Ser-637 [24]. As such, Drp1 inhibition may be part of the mechanism by which AMPK activating interventions, such as metformin [54], mediates its beneficial effects on lifespan and healthspan.
Overall, the evidence supports the **necessity of maintaining proper mitochondrial homeostasis for healthy aging**, such that a shift in either direction can compromise health.

Cardiovascular: POTENTIAL BENEFIT (Preclinical)
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 [55].

Myocardial ischemia-reperfusion injury: Mitochondrial fission is induced in response to ischemia [2]. 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 [56]. 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 [56]. Treatment of murine atrial HL-1 cells with the novel Drp1 GTPase inhibitor Drp1i27 protected against mitochondrial fragmentation and cell death in a cell model of ischemia-reperfusion injury [57]. Due to the importance of mitochondrial fission as a homeostatic mechanism, Drp1 inhibitors would ideally be delivered in a tissue-targeted manner [58]. Cardiac tissue targeting of the novel inhibitor of Drp1 GTPase activity, Drp1i1 (which appears to be related to Drp1i27), was cardioprotective in a mouse model of acute myocardial ischemic reperfusion injury [58]. Drp1i1 was encapsulated in cubosome nanoparticles conjugated with a cardiac homing peptide (WLSEAGPVVTVRALRGTGSW), and referred to as NanoDrp1i1. Intravenous administration of both Drp1i1 and NanoDrp1i1 during reperfusion reduced infarct size in mice and mitigated the rise in Ser616 phosphorylated Drp1 in the myocardium. However, NanoDrp1i1 showed efficacy at a lower concentration along with more widespread and concentrated distribution throughout the heart tissue. NanoDrp1i1 also potently reduced markers of oxidative stress, injury, and cell death in a human cardiac organoid model of ischemia-reperfusion injury, but did not meaningfully affect these measures under physiological (normoxia) conditions.
The translatability of this approach still needs to be established. The non-specific Drp1 inhibitor, Mdivi-1, has shown cardioprotective effects in a variety of rodent models, however, when administered as an intracoronary bolus ten minutes prior to perfusion, it did not improve outcomes in a clinically relevant adult pig model of acute myocardial infarction [59]. It is unclear whether the lack of efficacy was related to the approach, the drug (Mdivi-1), or the experimental conditions (dosing, follow-up time, etc.). The use of the newer potent and selective Drp1 inhibitors in this type of model may offer more insight into the clinical translatability of Drp1 inhibition for cardiac ischemic injury.

Pulmonary arterial hypertension: Mitochondrial fragmentation is an important metabolic hallmark of the pulmonary vascular remodeling related to the phenotypic switch of pulmonary arterial smooth muscle cells from a contractile to a proliferative state [60]. Inhibition of Drp1 or calcium overload, an important driver of Drp1-mediated fission, protected against this phenotypic switch in cell culture [60]

P110 was also able to reduce right ventricular diastolic pressure in a rat model of pulmonary arterial hypertension [61]. Improvements were associated with the preservation of mitochondrial morphology and network integrity.
Drpitor1a was identified in a screen as an inhibitor of Drp1's GTPase activity and shown to have cardioprotective effects in a model of ischemic-perfusion injury [62]. In a rat model of monocrotaline-induced pulmonary arterial hypertension, Drpitor1a protected against adverse right ventricular remodeling in a sex-specific manner [63]. The pharmacokinetics of Drpitor1a, including oral bioavailability and tissue distribution, differed between male and female rats. The protective effects on pulmonary vascular remodeling and ventricular hypertrophy were only observed in females, consistent with their higher lung concentrations of Drpitor1a.

Hypertension: The phenotypic switch in vascular smooth muscle cells driven by Drp1-mediated mitochondrial fission contributes to the pathogenesis of hypertension [64]. Angiotensin-II, a potent vasoconstrictor, has been shown to induce Drp1 Ser-616 phosphorylation and mitochondrial fission [64]. Treatment with the non-specific Drp1 inhibitor, Mdviv-1, delivered via osmotic pump protected against angiotensin-II-induced phenotypic switching in vascular smooth muscle cells, vascular remodeling and cardiac hypertrophy in mice [64]. Mdivi-1 also suppressed hypertension-related cardiac hypertrophy in Dahl salt sensitive rats [65]. The protective effects are thought to be related to the mitigation of oxidative stress (ROS production).

Atherosclerosis: The polarization of macrophages into a pro-inflammatory M1-like state has been implicated in the progression of atherosclerosis. The uptake of oxidized-LDL promotes Drp1-Fis1-mediated mitochondrial fission and ROS production, which serves as a priming trigger for the activation of the NLRP3 inflammasome, and polarization into a M1 state [66]. Inhibition of Drp1-mediated fission with the non-specific inhibitor Mdivi-1 protects against oxLDL-induced NLRP3 activation, M1 polarization, and foam cell formation in cell culture [66]. Additionally, Drp1 inhibition reduced lipid deposition and the inflammatory profile of aortic tissue in a mouse model of atherosclerosis [66]. Drp1-mediated fission is also associated with oxLDL-induced injury in vascular endothelial cells [67]. The inhibition of Drp1-mediated mitochondrial fragmentation has been identified as a potential mechanism of action for several therapeutics with anti-atherosclerotic properties. Statins are the first-line medications for atherosclerosis. Atorvastatin was shown to inhibit Drp1 activation in cell and animal models [67]. Inhibition of Drp1 downstream of AMPK activation has also been implicated as an anti-atherosclerotic mechanism of the anti-diabetic drug metformin, in animal models [68]. Thus, inhibition

of excessive Drp1-mediated mitochondrial fission may slow the progression of atherosclerosis by protecting against pathological inflammation and preserving the integrity of the vascular endothelium.

Exercise: MAY REDUCE AEROBIC EXERCISE CAPACITY (Preclinical)
Exercise induces physiological mitochondrial fission in cardiac muscle, which acts to increase mitochondrial function [69]. 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 [70]. 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. Notably, the anti-diabetic agent, metformin, has been found to blunt some of the metabolic adaptations to aerobic exercise [71; 72]. Consequently, Drp1 inhibition may be one of the mechanisms underlying these findings.

Diabetes: POTENTIAL BENEFIT (Preclinical)
A high glucose environment is associated with increased ROS production and the induction of oxidative stress, which in turn promotes mitochondrial fragmentation [73]. 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 [74; 75].
Numerous single nucleotide polymorphisms (SNPs) in DNM1L, the gene encoding Drp1, have been associated with type 2 diabetes [76]. 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 [73]. Drp1 has also been shown to play a role in fatty acid metabolism, including the distribution between fatty acids stored in lipid droplets and those utilized for fatty acid oxidation in mitochondria [77].
The inhibition of excessive Drp1-mediated fission may be part of the therapeutic activity of the anti-diabetic drug metformin [78].

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, atherosclerosis, retinopathy, and nephropathy [79; 80].
Drp1 inhibitors, such as Mdivi-1, have been shown to exert protective effects against various diabetes-related complications in preclinical models. P110 attenuated kidney injury in diabetic mouse models without impacting hyperglycemia [81].

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 [82]. 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 [83].
Several Drp1 inhibitors, including Mdivi-1 and Drpitor1a, have been shown to reduce tumor proliferation and/or promote tumor cell apoptosis in various cell culture and preclinical cancer models [62; 82]. The anti-cancer effects appear to be related to the 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.
Drp1-mediated fission has also been implicated in chemotherapy-induced organ toxicity, such that P110 protected against paclitaxel-induced neurotoxicity [84] and cisplatin-induced nephrotoxicity [85] in cell models.
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 [82]. 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.**

Acute kidney injury: POTENTIAL BENEFIT (Preclinical)

Excessive mitochondrial fragmentation has been shown to precede structural damage in models of kidney injury [86]. P110 was found to protect against injury-related excessive fission without meaningfully impacting fission in the kidney under normal physiological conditions [86]. In an ischemic-reperfusion injury model using renal artery occlusion in Bama miniature pigs, pre-treatment with P110 (0.4 mg/kg i.v.) at 24 hours and one hour prior to the arterial occlusion, mitigated structural and functional kidney damage [86]. This was accompanied by a reduction in sterile inflammation. The inhibition of excessive mitochondrial fission prevented cGAS-STING activation triggered by the release of mtDNA. A similar protective effect was observed in several mouse models. However, the clinical utility is unclear, since the therapeutic effects observed with pre-treatment were not achieved when administered 12 hours after injury.

Colitis: POTENTIAL BENEFIT AT EARLY STAGES (Preclinical)
P110 (3 mg/kg i.p.) was found to be protective in the DSS and DNBS rodent models of colitis when administered at the time of the colitis-inducing agents [87]. 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: Acute use of Drp1 inhibitors shows good safety in preclinical models, but no long-term studies or human testing have been done. Chronic use, particularly with systemic administration, poses a risk to the mitochondrial function in healthy tissues.

Types of evidence:

- Several laboratory studies

The small molecule Drp1 inhibitor Mdivi-1 has been the most extensively tested in preclinical models, however, some studies suggest that it is non-selective and also inhibits mitochondrial complex I [88]. It is also possible that shifting the fission-fusion balance through modulation of Drp1 has a similar effect on bioenergetics as complex I inhibition [55]. Mdivi-1 also has a longer half-life than P110 (12 hours vs ~1 hour), and poor water solubility [89].

Novel inhibitors of Drp1's GTPase activity, including Drpitor1a and DRP1i27/Drp1i1 have only undergone limited preclinical testing to date. Drp1i27, identified in a virtual screen, was not tested for off-target

effects on other GTPases [57]. While Drp1i1 was tested in mouse models and human organoids, its safety profile has not been reported [58]. Treatment with Drpitor1a (1 mg/kg i.v.) for 10 days was not associated with significant hematologic, hepatic, or renal toxicity in rats [63]. However, Driptor1a is an analog of ellipticine, an anti-cancer compound with DNA-intercalation properties, thus it carries the risk for cytotoxicity [62].

Broad inhibition of Drp1-medatiated mitochondrial fission carries the risk of disrupting the dynamic balance of mitochondrial fission and fusion needed to respond to changing metabolic demands and to maintain long-term health. As such, these would be best suited for acute treatment, such as immediately following organ injury. Organ targeted delivery may also be necessary to prevent negative impacts to mitochondrial dynamics in other parts of the body.

More specific inhibition of Drp1-Fis1-mediated fission may offer a better therapeutic profile by preserving physiological fission, such as Drp1-Mff-mediated fission, allowing for the maintenance of homeostatic mitochondrial dynamics.

P110 has not been tested in humans, but has shown a good safety profile in preclinical rodent models with dosing up to 5 months [9]. In wild-type or control cell and rodent models, P110 treatment did not show significant effects on mitochondrial or cellular function [3; 11; 12; 29; 56]. 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 [7]. 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 [3]. But, preclinical rodent models suggest that P110 could potentially reduce aerobic exercise capacity [69].

However, the clinical translation of the P110 peptide has been limited due to poor drug-like properties, including lack of oral bioavailability, and susceptibility to serum and cellular proteases [4].

As a result, the team involved in the development of P110 have been working on developing small molecules inhibitors that could disrupt Drp1-Fis1-mediated mitochondrial fission [4]. To date two such inhibitors have been reported.
SP11 is a small molecule which binds to activated Fis1 via engagement with a residue (Cys41) that is structurally important in the formation of the activated Drp1-Fis1 complex [5]. It has been shown to

inhibit pathological mitochondrial fragmentation in response to oxidative stressors in cell culture. This molecule has a phenothiazine core, a framework that is associated with oral bioavailability, BBB permeability, and a durable half-life in other drugs. Further PK and safety testing are needed to determine whether this compound, or a further optimized version, has suitable drug properties for prospective clinical use.
The small molecule SC9 is an allosteric inhibitor of Drp1 which mimics P110 by disrupting the Drp1-Fis1 interaction, while preserving the interaction between Drp1 and Mff. SC9 did not exert overt toxicity in mice at doses up to 50 mg/kg (i.p.) [4]. Additionally, there were no significant differences in serum biomarkers related to hematologic, hepatic, renal, and musculoskeletal damage. Pharmacokinetic (PK) studies in wildtype animals suggest that the drug properties are not ideal, since, at a dose of 20 mg/kg (i.p.), it had a short half-life >0.5 hours, and minimal brain penetration (brain-to-plasma ratio of 2% after 15 minutes). However, its half-life was significantly longer in LPS-treated mice, where it protected against LPS-induced endotoxemia. Further optimization is needed.

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.

Drug Interactions: Interactions have not been established, and will likely depend on the specific drug properties of the inhibitors. However, Drp1 interacts with a variety of signaling pathways, including AMPK, thus Drp1 inhibitors may interact with drugs which modulate these pathways.

Sources and dosing:

Several Drp1 inhibitors, including Mdivi-1 and P110, are regularly used in preclinical research studies. At this time, none of the Drp1 inhibitors have been formulated for human use or clinically tested.

Research underway:

Drp1 inhibitors are currently in early-stage preclinical development.

Search terms:
Pubmed, Google: P110; Drp1 Inhibitor

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

Websites visited for Drp1 Inhibitors:

- PubChem (P110) (Mdivi-1) (Drp1i27)

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