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.

PTI-125

Evidence Summary
A small pilot study suggests positive changes on some biomarkers, though larger studies are needed.

Neuroprotective Benefit: A small pilot study suggested some benefits in Alzheimer's biomarkers, though it will need to be replicated in future studies.

Aging and related health concerns: N/A

Safety: No safety issues have been raised in preclinical studies or a pilot study, though no long-term studies have been conducted.

What is it?
PTI-125 is a small molecule that corrects the structure of filamin A (FLNA), a scaffolding protein. It is part of a potential toxic signaling mechanism of beta-amyloid oligomers. In Alzheimer's patients, the FLNA structure is altered, and FLNA independently binds to both the α7-nicotinic acetylcholine receptor (α7nAChR) and toll-like receptor 4 (TLR4). Signaling through α7nAChR is reported to hyperphosphorylate tau and signaling through TLR4 is reported to induce neuroinflammation. In addition, FLNA is a regulator of the actin cytoskeleton, which is important for synaptic function, suggesting another mechanism through which FLNA may contribute to cognitive dysfunction.

PTI-125 is currently under development by Cassava Sciences (previously Pain Therapeutics).

Neuroprotective Benefit for PTI-125: A small pilot study suggested some benefits in Alzheimer's biomarkers, though it will need to be replicated in future studies.

Types of evidence:

- 1 pilot trial in mild-to-moderate Alzheimer's patients
- 2 preclinical studies
- 1 post-mortem study

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

None

Human research to suggest benefits to patients with dementia

Filamin A was reported to be increased in patients with Alzheimer's disease and frontotemporal dementia (FTD) (though not Progressive Supranuclear Palsy – PSP) and associated with tau (n=8 total) (Feuillette et al, 2010).

Cassava Sciences announced (September 9th) the results of a 28-day open-label study of PTI-125 (100mg bid) in 12 individuals with mild-to-moderate Alzheimer's disease. Changes in CSF measures from baseline:

- Total tau decreased by 20% ($p<0.001$)
- P-tau decreased by 34% ($p<0.0001$)
- Neurofilament light chain (NfL – a marker of neurodegeneration) decreased by 22% ($p<0.0001$)
- Neurogranin (a marker for synaptic loss) decreased by 32% ($p<0.0001$)
- YKL-40 (a marker for inflammation) decreased by 9% ($p<0.0001$)
- IL-6 (a marker of inflammation) decreased by 14% ($p<0.0001$)
- IL-1β (a marker of inflammation) decreased by 11% ($p<0.0001$)
- TNFα (a marker of inflammation) decreased by 5% ($p=0.001$)
- The ratio of CSF p-tau/Aβ (a marker of Alzheimer's disease) improved ($p<0.001$)

Although these results are promising (especially the consistent change in all biomarkers), caution must be used to interpret the results as it was an open-label study in few patients.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
A mouse model of familial Alzheimer's disease (PS1 mutation) had increased expression of FLNA in the hippocampus (Lu et al, 2010), and cell culture studies suggest that stimulation of α7nAChR or treatment of cells enriched with α7nAChR with Aβ42 induced tau phosphorylation (Wang et al, 2003).

Wang et al (2012) reported that intracerebroventricular (ICV) infusion of Aβ42 increased the association of filamin A (FLNA) with the α7-nicotinic acetylcholine receptor (α7nAChR) and toll-like receptor 4 (TLR4), and subsequently increased the expression of ptau. These associations were reduced by co-administration with PTI-125. Similar results were seen in Alzheimer's postmortem tissue, with increased association of FLNA with α7nAChR and TLR4 and reduced association after PTI-125 administration. The association of FLNA with α7nAChR and TLR4 were reported to be due to an alteration in its conformation (determined by a change in its isoelectric point).

PTI-125 binds to FLNA at femtomolar concentration in Alzheimer's postmortem tissue versus picomolar concentration in the control post-mortem tissue and displaces naxolone, which was previously shown to bind to FLNA, restoring FLNA to its native form (again, determined by a change in its isoelectric point). PTI-125 also restored FLNA to its native form in Alzheimer's mice and mice with ICV injections of Aβ42. Administration of PTI-125 for two months in young or aged Alzheimer's mice reduced the association of FLNA with α7nAChR, and reduced ptau, beta-amyloid, and inflammatory cytokines. PTI-125 also improved NMDA receptor function, insulin signaling, and increased synaptic density. PTI-125 also improved spatial memory in old mice and working memory in young mice (but not vice versa). Finally, in post-mortem tissue, PTI-125 reduced the association of FLNA with α7nAChR in Alzheimer's tissue and prevented beta-amyloid-induced tau phosphorylation in control tissue (Wang et al, 2017).

APOE4 interactions:
None Reported

Aging and related health concerns: ***N/A.***

Safety: No safety issues have been raised in preclinical studies or a pilot study, though no long-term studies have been conducted.

Types of evidence:

- One pilot clinical trial
- Two preclinical studies

No safety issues have been raised in preclinical studies or in a pilot study. FLNA plays a complicated role in several cancers, both promoting and preventing cancer development. Cytoplasmic FLNA may interact with signaling molecules promoting cancer progression while nuclear filamin A may inhibit cancer progression by interacting with transcription factors (Shao et al, 2016). However, as PTI-125 binds to and stabilizes an altered FLNA conformation in the context of neurodegenerative disease, a potential risk is at this point speculative.

Drug interactions:
Not currently known.
Sources and dosing:
50mg and 100mg bid are currently being investigated in Alzheimer's disease.

Research underway:
There is an ongoing Phase 2b placebo-controlled study in 60 mild-to-moderate patients that will try to replicate the effects of the pilot phase 2a study over 28 days NCT04079803. Patients will take 50mg or 100mg bid.

Search terms:

- PTI-125
- Filamin + alzheimer
- Filamin A [review]

Websites:

- Clinicaltrials.gov
- Pubmed
- Pubchem
- Drugbank.ca

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.