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.

Hsp90 Inhibitors

Evidence Summary

Hsp90 inhibitors are effective in several age-related diseases in preclinical models, but safety issues still need to be worked out.

Neuroprotective Benefit: Hsp90 inhibitors have been effective in several preclinical studies of neurodegenerative diseases, including Alzheimer's.

Aging and related health concerns: There is some evidence that Hsp90 inhibitors may improve outcomes for age-related diseases, such as atherosclerosis and neuropathy.

Safety: In the clinic, Hsp90 inhibitors have been associated with several side effects. Safety will depend on the particular inhibitor.

Availability: Not available	**Dose**: Not determined, depends on molecule	**Molecular Formula:** N/A **Molecular weight:** N/A
Half-life: Depends on the molecule	**BBB**: Some are penetrant in preclinical studies	
Clinical trials: Many clinical trials in cancer	**Observational studies**: None	

What is it?

Heat-shock proteins (Hsps) are molecular chaperones that bind to non-native proteins and assist in correct folding. They also ensure that native proteins maintain their proper structure when a cell is stressed. Their expression is upregulated in response to stressors such as heat shock, ischemia, hypoxia, and heavy metals. In mammals, they are classified into families based on their molecular weight (e.g., Hsp70, Hsp60, Hsp90, Hsp40, Hsp100, and Hsp27). When Hsps are unable to fix misfolded proteins, they target these proteins for degradation.

Although there is a significant amount of work showing that Hsp70 and Hsp40 may reduce aggregated proteins, the effect of Hsp90 may be mixed. Hsp90 interacts with GSK-3β, and other tau phosphatases, keeping them in the correct conformation and therefore increasing phosphorylated tau. Hsp90 may also increase the production of IL-6 or TNFα. However, Hsp90 still has important physiological roles involved with protein folding. Inhibition of Hsp90 induces the expression HSF-1, which then induces the expression of other Hsps, such as Hsp70. It is estimated that Hsp90 may interact with 60% of all protein kinases with different association strengths. Hsp90 is expressed ubiquitously in the body, so any inhibitor may have systemic effects (Paul and Mahanta, 2013; Thirstrup et al, 2016).

Several Hsp90 inhibitors have been developed including geldanamycin, 17-DMAG (alvespimycin), 17-AAG (tanespimycin), and celastrol. Geldanamycin was the first Hsp90 inhibitor discovered, isolated from bacteria. Although it possessed antibiotic and antitumor activity, development was halted due to toxicity and poor solubility. Hsp90 inhibitors may also bind to different Hsp90 sites such as an N-terminal ATP-binding site (e.g., 17-DMAG) or a C-terminal binding site (e.g., celastrol, KU-32). The downstream effectiveness of binding to the ATP-binding site may be influenced by intracellular ATP concentrations.

The biological response to ATP-binding site inhibitors can be measured *in vitro* by Hsp70 induction. (Jinwall et al, 2012; Paul and Mahanta, 2013).

Another report covers tanespimycin, so this report will cover other inhibitors.

Neuroprotective benefit: Hsp90 inhibitors have been effective in several preclinical studies of neurodegenerative diseases, including Alzheimer's.

Types of evidence:

- Four postmortem studies in Alzheimer's patients
- One plasma study in Alzheimer's patients
- Six preclinical 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:
Gezen-Ak et al (2013) reported a reduction of serum Hsp90 levels in individuals with early- or late-onset Alzheimer's disease and in patients with MCI. They suggested that reduced serum levels of Hsp90 may reflect increased protein aggregation in the brain. Yokota et al (2006) reported a downregulation of Hsp90 in Alzheimer's post-mortem tissue while Domenico et al (2010) reported no changes in Hsp90 levels in the hippocampus of patients with MCI. In one patient with Alzheimer's disease, Dou et al (2002) reported no association between tau tangle staining and Hsp70/90, though Hsp90 staining was found at the periphery of cells containing tau tangles. The authors suggest that this represents regions of nascent tangle development and Hsp90 antagonization. Petrucelli et al (2004) reported that CHIP, a ubiquitin ligase that interacts with Hsp70/90, is associated with tau aggregates in Alzheimer's disease.

Mechanisms of action for neuroprotection identified from laboratory and clinical research
Celastrol
In vitro exposure of cells overexpressing TDP-43 to 17-AAG or celastrol reduced the levels of TDP-43. Celastrol was more effective than 17-AAG, and the investigators posited that it was because celastrol inhibits the interaction of Hsp90 with its co-chaperone Cdc37 rather than binding to the ATP pocket (Jinwall et al, 2012). *In vitro*, celastrol also reduced NFκB and Aβ production in cells overexpressing Aβ.

Four- or 32-day treatment with celastrol (subcutaneous biodegradable pellet) in an Alzheimer's animal model reduced soluble and insoluble Aβ, reduced amyloid plaque burden, and reduced microglial activation (Paris et al, 2010). In mice undergoing major surgery (laparotomy – abdominal incision), pre- and post-treatment with celastrol improved cognition three days later and reduced the levels of astro- and micro-gliosis, reduced amyloid levels, and reduced p-tau levels (Wan et al, 2010).

OS47720

OS47720 is a proprietary Hsp90 inhibitor designed to reduce some of the toxicity of other inhibitors. It is blood brain barrier penetrant. Despite a short half-life (a matter of hours), it induced Hsp70 expression over 48 hours and increased synaptic proteins. Gross pathological examination of the liver did not suggest toxicity (while geldanamycin and tanespimycin caused toxicity). Treatment with OS47720 (three times per week for three or six months) in healthy animals induced dendritic spine formation and increased neuronal activity. In an Alzheimer's animal model, six-month treatment with OS47720 improved cognition (Wang et al, 2016).

PU24FCI, PU-DZ8

Luo et al (2007) reported that either acute or 30-day (five days per week) treatment with the Hsp90 inhibitors PU24FCI or PU-DZ8 reduced tau expression and p-tau in a tau transgenic model.

PU-DZ8, NVP-HSP990, BIIB-021a

A research group at Lundbeck measured the inhibitory constant (Ki) and the biological response (EC50 – induction of Hsp70) of three Hsp90 inhibitors *in vitro*. NVP-HSP990 was the most effective Hsp90 inhibitor. Target occupancy in the brain reached saturation at 7mg/kg and was at 78% and 35% at 6 and 16 hours, respectively. Hsp70 induction remained for 72-96 hours post injection, suggesting that increased Hsp70 has a long half-life.

They then tested two Hsp90 inhibitors (NVP-HSP990 and BIIB-021a) in tau transgenic mice that showed synaptic deficits. The two compounds had different inhibitory constants to Hsp90 which resulted in different levels of Hsp70 induction. Interestingly, acute treatment with NVP-HSP990 increased basal synaptic transmission and synaptic plasticity while treatment with BIIB-021a had no significant effect. This suggests that the effectiveness of an Hsp90 inhibitor may be directly related to its inhibitory constant and thus ability to induce Hsp70 (Thirstrup et al, 2015).

Other neurodegenerative diseases
Hsp90 inhibitors have shown benefits and reduced misfolded proteins in several preclinical studies in other neurodegenerative diseases such as Huntington's, Parkinson's, poly Q, polyglutamine disease, ALS, and spinal bulbar muscular atrophy (Paul and Mahanta, 2013).

APOE4 Interactions:
None reported

Aging and related health concerns: There is some evidence that Hsp90 inhibitors may improve outcomes for age-related diseases, such as atherosclerosis and neuropathy.

Types of evidence:

- One review on cancer studies
- One study on senolytic properties
- Three preclinical studies in cardiovascular disease
- Three preclinical studies in diabetes
- Five preclinical studies on neuropathy

Lifespan
An Hsp90 inhibitor, 17-AAG (see report on tanespimycin), was reported to increase lifespan in *C. elegans*, and it was identified in several *in silico* studies as a potential life extension molecule. No other Hsp90 inhibitors were on the list identified through *in silico* studies.

Interestingly, Hsp90 inhibitors, including 17-AAG, were recently identified as putative senolytics in mouse fibroblasts, and the one Hsp90 inhibitor tested *in vivo*, 17-DMAG, improved healthspan in a mouse model of accelerated aging as measured by a composite healthspan score (Fuhrmann-Stroissnigg et al, 2017).

Cardiovascular
Abdominal aortic aneurysm (AAA) is associated with activation of multiple signaling pathways including JNK, and NFκB. Treatment of a mouse model of AAA with 17-DMAG (three times per week for four weeks) increased expression of Hsp70 and Hsp90, reduced the incidence of AAA, and reduced several pathological factors associated with AAA such as matrix metalloproteinases, MCP-1 (an inflammatory biomarker), and malondialdehyde (a marker of oxidative stress) (Qi et al, 2015).

In human atherosclerotic plaque lesions, Hsp90 expression was increased in close proximity to the lesion site versus further away. In a mouse model of atherosclerosis (ApoE -/- with western diet) treatment with 17-DMAG reduced the lesion size and lipid content of the lesion. It also reduced macrophage infiltration and inflammatory markers in the lesion site (Madrigal-Matute et al, 2010). 17-DMAG also attenuated oxidative stress in a mouse model of atherosclerosis (Madrigal-Matute et al, 2012).

Diabetes

Treatment of streptozotocin-induced diabetic ApoE-/- mice with 17-DMAG over 10 weeks reduced atherosclerotic lesion size. In the lesion, 17-DMAG induced Nrf2, Hsp70, antioxidant, and autophagic protein expression and reduced the expression of NFκB (Lazaro et al, 2017 – full text not accessible). In a mouse model of diabetes and atherosclerosis (streptozotocin + ApoE-/-), ten-week treatment with 17-DMAG every other day improved renal function (decreases in albuminuria and renal lesions), reduced expression of inflammatory and pro-fibrotic proteins in the kidneys, had no effect on glucose or lipid levels, reduced atherosclerotic lesion size and inflammation, and promoted plaque stability (Lazaro et al, 2015).

In another diabetic mouse model (db/+ with high fat diet), mice were treated for fifteen days (three times per week) with AUY922. Treatment increased Hsp70 expression in several tissues (lung, muscle, pancreas, liver) and reduced fasting plasma glucose by 48% in the high-dose group (15mg/kg). In another model of insulin resistant diet-induced obesity, compound A (not clear what this is) improved insulin sensitivity (Lee et al, 2013). In diabetic $Lepr^{db}$ mice, 10 weekly treatments with KU-32 had no effect on serum glucose or insulin levels despite increasing insulin staining on pancreatic islet cells (Farmer et al, 2012).

Neuropathy

Mice were injected with streptozotocin to render them diabetic. After 12 weeks, they were treated with KU-32 or placebo once per week for six weeks (20mg/kg). KU-32 was present in both the plasma and the brain. Treatment with KU-32 reduced pre-existing diabetic sensory neuropathy with no effect on other diabetes measures (e.g., HbA1C, insulin). These results required Hsp70 induction, as KU-32 was ineffective in Hsp70 knockout mice (Urban et al, 2010). In a follow up study where diabetic mice were treated with KU-32 with ten weekly doses, the authors reported an improvement in nerve conduction velocity, improved response to sensory stimuli, an increase in intra-epidermal nerve fiber density (in some mice), and improved mitochondrial respiration (Urban et al, 2012). *In vitro*, KU-32 prevented neuregulin-induced demyelination of dorsal root ganglia explants (Li et al, 2012).

In an *in vitro* study of five Hsp90 inhibitors (geldanamycin, AT13387, AU922, BIIB021, SNX5422, STA9090) on Schwann cell viability, two, AU922 and BIIB021, improved cell survival with AU922 being most effective. Twice weekly injections of AU922 (2mg/kg) over five months in two mouse models of neuropathy (C22 and TremblerJ) improved motor performance, increased nerve fiber diameter, and improved myelination of nerve fibers (Chittoor-Vinod et al, 2019).

In a model of peripheral nerve demyelination (MPZ-Raf mice treated with tamoxifen), treatment with KU-596 (4mg/mL every other day for 14 days), optimized from KU-32, improved motor performance and reduced demyelination (Zhang et al, 2017).

Cancer

Due to the rapid proliferation of cancer cells, they are in a constant state of cellular stress and often require high expression of Hsp90. Hsp90 is thought to be important for tumor progression, differentiation, invasion, metastasis, survival, and therapeutic resistance. Overexpression of Hsp90 has been reported in breast, ovarian, endometrial, lung, esophageal, bone, colorectal, urinary, and prostate cancer. Studies suggests that Hsp90 inhibitors are beneficial in preclinical models.

Hsp90 inhibitors that have been tested in early-stage clinical trials include geldanamycin (terminated due to toxicity and poor solubility), 17-AAG (terminated due to loss of patent protection), AUY992 (non-Hodgkin lymphoma, lung cancer, and relapsed or refractory multiple myeloma), AUY992 + Erlotinib (non-small cell lung cancer), BIIB021 (gastrointestinal stromal tumors), SNX-5422 (TP53-null cancers, and HER2+ cancers), and PU-H71 (solid tumor, lymphoma, and epichaperome addicted tumors). The use of Hsp90 inhibitors for cancer is controversial as there is yet no clear demonstration of efficacy (though some signs of effectiveness) and potential toxicity (hepatotoxicity for geldanamycin and its analogs) (Jafari et al, 2020). There is no evidence for cancer prevention with the use of Hsp90 inhibitors.

Safety: In the clinic, Hsp90 inhibitors have been associated with several side effects. Safety will depend on the particular inhibitor.

Types of evidence:

- One meta-analysis on clinical trials
- One preclinical study

The safety of Hsp90 inhibitors will depend on the specific inhibitor. None have gone far enough along in clinical trials to know a true safety profile. In a meta-analysis of breast cancer trials with Hsp90 inhibitors, 17-AAG was associated with increased liver enzymes, kidney toxicity, hypotension, cough, anemia, dehydration, fatigue among other side effects. BIIB021 was associated with diarrhea, aphasia, hypopituitarism, and retaspimycin was associated with increased liver enzymes, hypokalemia, and nausea. There was no information on 17-DMAG, SNX-5422, AUY922, or ganetespib. Importantly, most of these were small studies, and with the exception of 17-AAG (n=77), all had fewer than 31 patients. In addition, they were open-label studies in cancer patients who may experience adverse events unrelated to the medication (Zagouri et al, 2013).

One potential side effect seen in the clinic for Hsp90 inhibitors is visual disorders. 17-DMAG and NVP-AUY922 were both reported to cause reversible visual disorders in clinical trials while 17-AAG and ganetespib did not. Zhou et al (2013) treated rats with these four drugs for two days. They reported that 17-DMAG and NVP-AUY922 induced photoreceptor cell death 24 hours after the final dose while 17-AAG and ganetespib did not. 17-DMAG and NVP-AUY922 both accumulated in the retina while 17-AAG and ganetespib were rapidly eliminated. This suggests that overexposure of retinal cells to Hsp90 inhibitors may induce cell death.

Drug interactions:
Not known

Sources and dosing:
No Hsp90 inhibitors are currently available. Dosing would depend on the inhibitor, and cancer dose may not be the same as what would be used for Alzheimer's.

Research underway:
There are 17 ongoing clinical trials of Hsp90 inhibitors, mostly in cancer. One study is in psoriasis.

Inhibitors in clinical trials include CUDC-305, HS-201, HS-196, XL888, onalespib, ganetespib, NVP-BEB800, MPT0B640, and PU-H71. All of these studies are currently in phase 1 or phase 2.

Search terms:

- 17-dmag + alzheimer, longevity, lifespan, cardiovascular
- Alvespimycin + alzheimer, longevity, lifespan
- hsp90 inhibitor + alzheimer, lifespan, cardiovascular, neuropathy, cancer, safety, drug interactions

Websites visited:

- Clinicaltrials.gov
- Pubmed