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.

Tanespimycin (17-AAG)

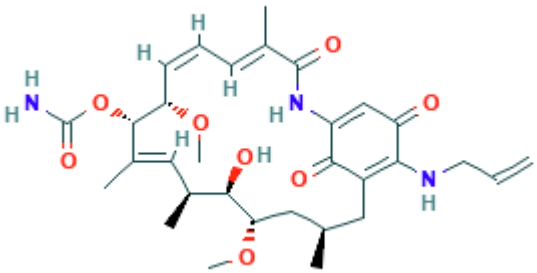
Evidence Summary

Hsp90 inhibition is an interesting target for Alzheimer's and aging, but due to the poor solubility of tanespimycin, better inhibitors are needed.

Neuroprotective Benefit: Tanespimycin is unlikely to reduce the risk of Alzheimer's disease, but other Hsp90 inhibitors may hold promise.

Aging and related health concerns: That tanespimycin emerged from three separate in silico screens for potential pro-longevity drugs and as a senolytic is interesting, but more research on new drugs needs to be conducted to confirm that Hsp90 inhibitors may increase lifespan or healthspan.

Safety: Tanespimycin is tolerable, but its side effect profile is less clear due to the patient populations treated and toxic vehicles used to dissolve it.

Availability: Not available in prescription drug form (pharma company halted development)	**Dose**: No currently established dose	**Chemical formula:** $C_{31}H_{43}N_3O_8$ **MW**: 585.698g/mol  Source: Pubchem
Half life: 3-4 hours	**BBB**: Probably not penetrant	
Clinical trials: None ongoing	**Observational studies**: None	

What is it?

Tanespimycin was identified in three *in silico* screens of drugs that target genes and proteins related to human aging. One study looked at gene expression changes in human brain tissue, and, using the Connectivity Map, identified drugs that altered similar gene products (Donertas et al, 2018). The Connectivity Map is a database of drug-induced gene expression profile changes in multiple cell types. Another study used the Connectivity Map to identify drugs that led to gene expression profile changes that were similar to caloric restriction (Calvert et al, 2016). Another study looked for drugs that targeted genes related to human aging (Fuentealba et al, 2019). In a review of potential lifespan-promoting drugs from 12 *in silico* screens, four were identified in three studies: tanespimycin, geldanamycin, trichostatin, and vorinostat (Donertas et al, 2019).

Tanespimycin is a derivative of the antibiotic geldanmycin, both heat shock protein (Hsp) 90 inhibitors (geldanmycin was soon dropped as a potential drug due to toxicity). Hsp90 is a chaperone protein that can refold misfolded proteins. It fails to refold tau (due to tau's intrinsically disordered structure) and may facilitate aggregation and accumulation of tau. Inhibition of Hsp90 can increase the expression of other heat shock proteins, such as Hsp70 and Hsp27, as well as heat shock factor 1 (HSF1). Hsp90 may also be involved with inflammation and interacts with immune regulators such as NF-kB (Blair et al, 2014).

Neuroprotective Benefit: Tanespimycin is unlikely to reduce the risk of Alzheimer's disease, but other Hsp90 inhibitors may hold promise.

Types of evidence:

- Three preclinical studies in Alzheimer's animal models
- Two studies in preclinical models of ischemia/hemorrhage
- One preclinical study of neurodegeneration in flies

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:
In a mouse model of Alzheimer's disease, Chen et al (2014) reported that tanespimycin has no effect when given systemically (suggesting it does not cross the blood brain barrier – though there are some mixed reports (Egorin et al, 2001; Blair et al, 2014)), but, when infused into the cerebral ventricles over 7 days, it improved memory, increased synaptic density, and increased levels of BDNF. Ortega et al (2014) reported that tanespimycin improved cognition and reduced cell death in animals where amyloid was injected into the brain (thus perhaps it entered the brain due to the damage done during the amyloid injection). In Alzheimer's transgenic models of amyloid and tau, three-month systemic treatment with tanespimycin had no effect on mortality, amyloid, or tau (except for a trend toward reduced tau in males treated with high doses of tanespimycin) (Ho et al, 2013).

Fujikake et al (2008) reported that tanespimycin reduced neurodegeneration and increased survival in fly models of spinocerebellar ataxia and Huntington disease through induction of heat shock proteins.

In a mouse model of subarachnoid hemorrhage, tanespimycin given systemically after hemorrhage improved cognitive and functional outcomes, reduced inflammation (IL-1β and NLRP3 levels), increased neurogenesis, and increased levels of BDNF (Zuo et al, 2018). In a rat model of transient global cerebral ischemia, tanespimycin administered 60 minutes after ischemia reduced infarct volume by ~40%, increased hippocampal neuronal survival, reduced autophagy-induced cell death, reduced levels of inflammatory cytokines (TNFα and IL-1β), and improved cognition 9 days after ischemia (Li et al, 2015).

APOE4
No information

Aging and related health concerns: That tanespimycin emerged from three separate in silico screens for potential pro-longevity drugs and as a senolytic is interesting, but more research on new drugs needs to be conducted to confirm that Hsp90 inhibitors may increase lifespan or healthspan.

Types of evidence:

- Three in silico screens for potential pro-longevity drugs
- One lifespan study in worms
- One in vitro screen for potential senolytics
- Four preclinical studies for cardiovascular disease
- Small clinical studies in cancer

Lifespan

Tanespimycin was identified in three *in silico* screens of drugs that target genes or proteins related to human aging. One study looked at gene expression changes in human brain tissue, and, using the Connectivity Map, identified drugs that altered similar or opposing gene products (Donertas et al, 2018). The Connectivity Map is a database of drug-induced gene expression profile changes in multiple cell types. Another study used the Connectivity Map to identify drugs that led to gene expression profile changes that were similar to caloric restriction (Calvert et al, 2016). Another study looked for drugs that targeted genes related to human aging (Fuentealba et al, 2019). All three reported tanespimycin as a putative pro-longevity drug.

Fuentealba et al (2019) also ranked the drugs based on their expected benefits to longevity and reported tanespimycin was the most promising pro-longevity drug. They subsequently found that it increased lifespan in worms (median: 23%; maximum: 16%).

There was some overlap between the three groups of potential anti-aging drugs, and there were a number of drugs that have previously been shown to increase lifespan in model organisms.

Interestingly, Hsp90 inhibitors, including tanespimycin, 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 disease

Hsp90 was reported to be increased in inflammatory regions of human atherosclerotic plaques, and treatment of a mouse model of atherosclerosis with another Hsp90 inhibitor (17-DMAG) reduced plaque size, inflammation (NF-kβ activation), and lipid and macrophage content (Madrigal-Matute et al, 2010). In two mouse models of atherosclerosis, tanespimycin reduced plaque size, invasion of vascular smooth muscle cells into plaques, and markers of inflammation (IL-6 and ICAM1) (Mu et al, 2017; Kim et al, 2014). In a rat model of pulmonary arterial hypertension, tanespimycin improved arteriole remodeling and increased survival (Wang et al, 2016).

Cancer

Tanespimycin monotherapy has not been reported to be very effective for cancer. Some evidence suggests it may be beneficial in combination with other drugs. For instance, in 72 patients with relapsed and refractory multiple myeloma, tanespimycin in combination with bortezomib led to a clinical response rate of 48% in bortezomib-naïve patients, 22% for bortezomib-pretreated patients, and 13% for bortezomib-refractory patients (Dimopoulos et al, 2011).

Safety: Tanespimycin is tolerable, but its side effect profile is less clear due to the patient populations treated and toxic vehicles used to dissolve it.

Types of evidence:

- One review
- Two clinical studies

The safety of tanespimycin is difficult to assess. It has primarily been used to treat cancer patients, and, because of its low solubility, it is infused with vehicles that have systemic toxicity themselves (e.g. polyoxyl castor oil or DMSO). Side effects reported in clinical trials are relatively frequent (from 10-60% depending on the study) and include diarrhea, back pain, fatigue, nausea, hepatotoxicity, anemia, and thrombocytopenia (Richardson et al, 2010; Burris et al, 2011; Dimopoulos et al, 2011). Although tanespimycin may not be a promising anti-aging drug, itself, less toxic and orally available Hsp90 inhibitors may have promise. On the other hand, there have also been efforts to develop less-toxic formulations of tanespimycin.

Drug interactions: Not known – No Hsp90 inhibitors as a class have been approved, so it is not known what drugs they may interact with.

Sources and dosing: Not currently available and not likely to be developed further. There is currently no established dose (doses have ranged from 56-450mg/m^2 on different dosing schedules – e.g. daily, weekly every 20 days, etc.).

Research underway: ADDF has funded Yuma Therapeutics to develop novel Hsp90 inhibitors.

Development of tanespimycin has stopped, likely due to decreasing patent life and competition from newer Hsp90 inhibitors. Over the years, development of Hsp90 inhibitors for cancer has slowed For more information on Hsp90 inhibitors in cancer see Yuno et al, 2018.

Search terms:

Pubmed:

17-aag + aging, longevity, lifespan, alzheimer, cardiovascular, cognition

tanespimycin[title], 17-aag[title]

tanespimycin + cardiovascular, atherosclerosis, diabetes

Websites visited for

- Clinicaltrials.gov (0)
- Drugs.com
- DrugBank.ca

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