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.

Aha1 Inhibitors

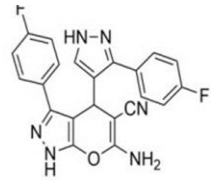
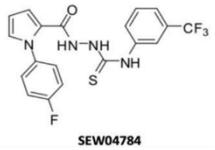
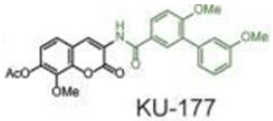
Evidence Summary

Inhibition of the Hsp90-Aha1 interaction may be a less toxic alternative to Hsp90 inhibitors for cancer treatment, and may reduce tau aggregation, but the *in vivo* properties have not been established.

Neuroprotective Benefit: Hsp90-Aha1 inhibition may mitigate tau aggregation, but the optimal time of intervention has not been established, and it could potentially negatively impact other neurodegenerative disease-associated proteins.

Aging and related health concerns: Hsp90-Aha1 inhibitors may benefit cancers where high Aha1 is associated with poor prognosis, but may exacerbate atherosclerosis.

Safety: Hsp90-Aha1 inhibitors are expected to be less toxic than Hsp90 inhibitors, but the full extent of Hsp90-Aha1 client proteins is not known.

Availability: Not available	**Dose**: N/A	Stiegler et al., 2017  HAM-1
Half life: N/A	**BBB**: N/A	Singh et al., 2020  SEW04784
Clinical trials: None	**Observational studies**: Elevated Aha1 expression is associated with poor prognosis in colon and bone cancers.	Shelton et al., 2017  KU-177

What is it?

Aha1 (activator of Hsp90 ATPase) acts as a co-chaperone of the molecular chaperone Hsp90, which plays a role in helping proteins to fold properly [1]. Hsp90 undergoes a series of structural rearrangements during the ATPase cycle, and the transition between these states is influenced by the presence of co-chaperones [2]. Aha1 is the most potent known endogenous activator of Hsp90 ATPase activity and regulates the binding of other co-chaperones. By influencing the kinetics of the ATPase cycle, the presence of Aha1 helps the folding activity of a subset of Hsp90 client proteins. Since it speeds things up, Aha1 can prevent the folding of some difficult to fold proteins [3]. Aha1 competes for binding with other co-chaperones. The composition of co-chaperones bound to Hsp90 regulates which proteins get folded or stabilized, and changes can impact protein aggregation [4]. Inhibiting Hsp90 can be a strategy to target multiple proteins at one time, and has been attempted as a therapeutic approach for cancer [5]. However, inhibition of Hsp90 was found to be too broad of an approach, leading to toxicity. Since different co-chaperone complexes specifically affect certain subsets of proteins, inhibiting the interaction of Hsp90 with specific co-chaperones has been proposed as a potentially less toxic alternative [6]. Due to its dysregulation in various cancers, Aha1 has emerged as a promising candidate, and a series of Hsp90-Aha1 inhibitors have been identified, which are in preclinical development.

HAM-1 was identified in a FRET-based screening assay as an inhibitor of Aha1-mediated stimulation of Hsp90 activity, showing 93.1% inhibition, with an affinity for the complex (K_D) of 24 ± 2 µm [7]. HAM-1 overlaps with a transitory binding site of Aha1 on Hsp90, thereby preventing the interaction, but it does

not dissociate previously formed Hsp90-Aha1 complexes. It does not affect Hsp90 activity in the absence of Aha1.

KU-177 was identified as an inhibitor of the binding of Aha1 to Hsp90, which inhibits Aha1-mediated Hsp90 ATPase activity without impacting Hsp90 activity directly [8]. However, this compound has poor drug properties for *in vivo* use, and efforts are underway to develop and optimize analogs [9].

SEW04784 was identified as an inhibitor of Aha1-stimulated Hsp90 ATPase activity without impacting basal, Aha1-independent, Hsp90 activity [2]. SEW04784 binds to the C-terminal domain of Aha1 to weaken its binding with Hsp90. In cell culture, it was found to reduce expression of the targets of steroid hormone receptors, which are known Hsp90-Aha1 client proteins, in a luciferase assay.

Neuroprotective Benefit: Hsp90-Aha1 inhibition may mitigate tau aggregation, but the optimal time of intervention has not been established, and it could potentially negatively impact other neurodegenerative disease-associated proteins.

Types of evidence:

- 1 study looking at Aha1 expression in postmortem brain tissue for AD
- 1 study looking at chaperone expression changes in brain aging
- Several laboratory studies

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

The network of molecular chaperones regulates the cellular proteome by facilitating the folding or degradation of proteins. The expression profile of this network has been shown to be altered in the brain in the context of aging [4]. There is a trend toward a repression of many of these chaperones, which allows for the accumulation of misfolded proteins [10]. This general pattern overlaps with what is seen in the brains of those with neurodegenerative diseases characterized by misfolded proteins, such as Huntington's disease (HD) and Alzheimer's disease (AD). This suggests that augmentation of the molecular chaperone network may promote healthy brain aging and mitigate the risk for neurodegenerative disease. Due to the complex, intertwined nature of this network, it has been difficult to target. Most attempts have focused on one component of the network but have been stymied in the

effort to find the right balance between promoting proteostasis generally and influencing the processing of disease-specific proteins.

As one of the central components of the chaperone network, Hsp90 plays an important role in the maintenance of proteostasis by stabilizing nascent proteins, referred to as 'clients', to allow them to fold properly and to prevent their aggregation in the context of cellular stress [11]. Many of these clients are associated with disease, such that changes to the structure or abundance of certain sets of these proteins can exacerbate or ameliorate a particular disease [12]. Hsp90 is thought to be a key mediator of the variance in the phenotypic expression of genetic mutations/variants, by allowing or not allowing for the folding of mutated proteins, which dictates the ability of these proteins to influence cellular activity [13; 14]. In some contexts, this can be beneficial by allowing for partial function, while in other cases it can drive pathology. Hsp90 works in concert with approximately 50 co-chaperones, which facilitates the processing of a diverse array of hundreds of clients [12]. Since co-chaperones tend to act on only a subset of Hsp90 clients, changes in the levels or activity of particular co-chaperones may preferentially drive specific disease states.

Major imbalances in co-chaperones have been identified in the aged brain, with certain types being overrepresented and other types being underrepresented. For example, ATP-dependent co-chaperones were found to be decreased by 32%, while ATP-independent co-chaperones were increased by 20% [15]. The co-chaperone Aha1 was found to be slightly decreased in the non-diseased aged brain, while it was elevated in the brains of those with AD [8; 10]. Due to its role in the processing of AD-associated proteins, such as tau, increased Aha1 activity is thought to facilitate the aggregation of pathological misfolded proteins in the brain [8]. However, relative to the other changes in the molecular chaperone network, the impact of Aha1 on disease processes and progression is unclear.

Human research to suggest benefits to patients with dementia:

Aha1 inhibitors have not yet been tested in humans.

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

Tau aggregation: In postmortem brain tissue of the medial temporal gyrus from AD patients, Aha1 was found to colocalize with tau pathology, with a positive correlation between Aha1 and the degree of tau pathology, based on Braak staging [8]. Based on preclinical studies, Aha1 alone does not appear to influence tau levels, but rather its association with Hsp90 influences the formation of tau fibrils [8]. The overexpression of Aha1 in the hippocampus of aged mice (16 months old), led to increased levels of

pathological tau and an impairment in associative learning [15]. The effect of elevated Aha1 appears to be influenced by aging-related factors, as a similar effect was not seen with Aha1 overexpression in younger (5–6-month-old) mice. It may reflect a heightened sensitivity to altered Aha1 levels in the context of age-related changes to the overall network of molecular chaperones. In rTg4510 mice, which overexpress the P301L mutant form of human tau, the overexpression of Aha1 promoted the accumulation of insoluble, oligomeric tau, which exacerbated neuronal loss and cognitive deficits [8]. Treatment with the Aha1 inhibitor, KU-177, reduced the formation of tau fibrils in P301L expressing HEK cells [16]. Similarly, treatment with the Aha1 inhibitor SEW04784 reduced pathological tau cells in HEK293 cells expressing the 0N4R-tau fibrils and primary rat cortical neurons expressing endogenous wildtype tau [2]. Due to the poor *in vivo* drug properties of currently available Aha1 inhibitors [9], it is unclear whether treatment with Aha1 inhibitors can inhibit tau pathology or slow cognitive decline in animal models, and whether treatment needs to be given at a certain stage of disease to be efficacious.

Chaperone activity: In addition to acting as a co-chaperone for Hsp90, there is evidence to suggest that Aha1 can also act as a molecular chaperone independently from Hsp90 [17]. Indeed, the vast majority of Aha1 in the cell is not associated with Hsp90. There is a wide degree of variability in the sequence of Aha1 from different species. Some species, including humans, encode for an Aha1 with an N-terminal fragment that allows for autonomous chaperone activity. It appears to involve non-specific electrostatic interactions via hydrophobic residues [18]. Aha1 can bind to stress-denatured proteins to prevent their aggregation. Rather than promote their refolding, the association with Aha1 appears to promote the ubiquitination and degradation of these proteins [17]. The identities of proteins that interact with Aha1 in this manner have not been established. It is unclear whether Aha1 interacts with a specific subset of proteins, or it can interact with misfolded proteins more generally, in a context-specific manner. One study found that Aha1 was able to inhibit the aggregation of alpha-synuclein, *in vitro* [18]. This suggests that Aha1 autonomous chaperone activity may help promote proteostasis. As such, inhibitors that act on the Hsp90-Aha1 interaction, while leaving autonomous Aha1 activity intact, may have better therapeutic utility.

microRNA regulation: Hsp90 and Aha1 have been shown to be important for the processing of Dicer1, an enzyme involved in the processing of microRNA precursors into mature microRNAs [19]. Knockdown of Aha1 or inhibition of Hsp90 resulted in a reduction in levels of Dicer1 and an associated reduction in the levels of mature microRNAs. This suggests that inhibition of the Hsp90-Aha1 could have a broad impact on gene expression by influencing the levels of functional microRNAs in a given cell. The overall impact of this on cellular function *in vivo* has not been established.

APOE4 interactions: Not established

Aging and related health concerns: Hsp90-Aha1 inhibitors may benefit cancers where high Aha1 is associated with poor prognosis, but may exacerbate atherosclerosis.

Types of evidence:

- 2 studies observational studies examining the relationship between Aha1 and cancer prognosis
- Several laboratory studies

Cancer: POTENTIAL BENEFIT

Hsp90 inhibitors have primarily been developed as anti-cancer agents [5]. Many of Hsp90's clients are overexpressed or mutated in tumors, and can serve as oncogenes to promote cancer progression [6]. Inhibition of Hsp90 could then serve as a way to target multiple cancer promoting proteins at once. Hsp90 complexes show higher activity in cancer cells, and have around 200-fold higher affinity for inhibitors, relative to normal cells [6]. But, due to the wide range of clients and important roles for Hsp90 throughout the body, the impact of these drugs on essential cellular processes results in an untenable side effect profile. Additionally, not all Hsp90 clients are oncogenic, and some may serve as tumor suppressors. Hsp90 co-chaperones only influence the processing of a subset of clients, thus targeting specific co-chaperones has been put forth as a potentially safer and more selective way to target the oncogenic clients [2]. Aha1 is the most potent known activator of Hsp90 ATPase activity, and has been implicated as a prognostic factor in some types of cancer [6]. While only a subset, Aha1 impacts numerous clients, and thus its effects are likely to be tumor-type dependent.

Colorectal cancer: ELEVATED AHA1 IS ASSOCIATED WITH METASTASIS

The expression of Aha1 has been associated with metastasis, but not with survival rates in cases of colorectal adenocarcinoma [16]. Relative to adjacent healthy tissue, the expression of Aha1 in tumor tissue was found to be elevated (n=105 paired tissue samples). Additionally, the expression increased along the trajectory of disease progression toward metastasis, such that tumors with lymph node involvement and metastatic properties had the highest expression. A similar pattern was observed in colon cancer cell lines. Inhibition of Aha1 reduced the invasion and migration capacity of these cancer cells lines.

Osteosarcoma: ELEVATED AHA1 IS ASSOCIATED WITH POOR SURVIVAL

High expression of Aha1 was found to be correlated with poor overall survival and disease-free survival in patients with osteosarcoma (n=109) [20]. The expression of Aha1 was increased at both the mRNA and protein levels in osteosarcoma tissue relative to adjacent healthy tissue. Similarly, Aha1 expression levels were higher in osteosarcoma cell lines relative to healthy bone cell lines. Aha1 promoted the growth and migration of osteosarcoma cells in culture and when implanted into mice, while knockdown of Aha1 reduced tumor growth and metastasis. Mechanistically, Aha1 appears to enhance the cellular bioenergetics of the tumor cells by promoting the processing of the protein isocitrate dehydrogenase 1 (IDH1) in concert with Hsp90 [20]. Similar to Aha1, elevated IDH1 was also found to be correlated with poor overall and disease-free survival, and low expression of both Aha1 and IDH1 was indicative of good prognosis.

Multiple myeloma: AHA1 INHIBITORS MAY INTERACT WITH CURRENT THERAPIES

The mechanism of action of the class of immunomodulatory drugs used for multiple myeloma that includes lenalidomide may involve the modulation of Aha1 activity [21]. These drugs target cereblon, which is a co-chaperone of Hsp90 that impacts the processing of transmembrane proteins. Notably, it counteracts the activity of Aha1. While Aha1 promotes the ATPase activity of Hsp90, cereblon reduces it. The rate of ATPase activity is an important regulator of client protein folding. By slowing it down, cereblon ensures there is sufficient time for the proper folding of transmembrane proteins, and thus can increase the levels of these proteins. By inhibiting the interaction between cereblon and Hsp90, these drugs bias the system toward Aha1. As a result, transmembrane proteins that play an important role in cancer cell survival and signaling, such as LAT1/CD98hc, are destabilized and degraded.

Atherosclerosis: AHA1 INHIBITION MAY EXACERBATE (Preclinical)

The association of Hsp90 with its various co-chaperones is influenced by a variety of post-translational modifications. Phosphorylation on Tyrosine-300 promotes the interaction between Hsp90 and Aha1, while S-nitrosylation on Cysteine 521 inhibits this interaction [22; 23]. Nitric oxide is important for the maintenance of endothelial homeostasis. Pathological induction of nitric oxide can result in the formation of nitrates, leading to protein nitrosylation [23]. The S-nitrosylation of proteins in endothelial cells can lead to endothelial dysfunction. Hsp90 can undergo S-nitrosylation (SNO-Hsp90). Hsp90 acts as a regulator of endothelial nitric oxide synthase (eNOS), and is important for VEGF-dependent nitric oxide production [22]. Modifications that negatively affects the ability of Hsp90 to associate with Aha1 ultimately leading to a reduction of its ATPase and chaperone activity, as well as a reduction in protective VEGF-eNOS signaling in endothelial cells. SNO-Hsp90 has been shown to be elevated in

oxidized-LDL treated endothelial cells, as well as in atherosclerotic artery tissue from humans and rodents [23]. SNO-Hsp90 preferentially interacted with the co-chaperone Cdc37, instead of Aha1, resulting in the induction of pro-inflammatory NF-kB signaling. Preventing the S-nitrosylation of Hsp90 mitigated vascular inflammation and oxidative stress in a rodent model of atherosclerosis (ApoE-/-), suggesting that the inhibition of the Hsp90-Aha1 interaction may exacerbate atherosclerosis [24].

Cystic fibrosis: POTENTIAL BENEFIT (Preclinical)
Aha1 is best understood in the context of the protein mutated in cystic fibrosis, cystic fibrosis transmembrane conductance regulator (CFTR) [3]. The most common mutation associated with cystic fibrosis is the folding deficient CFTR-ΔF508 variant. The folding of CFTR requires Hsp90. Since Aha1 accelerates the ATPase hydrolysis of Hsp90, there is not enough time for the CFTR-ΔF508 mutant to fold properly, so it gets degraded. Inhibiting the Hsp90-Aha1 interaction slows the kinetics of the ATPase hydrolysis to allow for the folding of the mutant CFTR, and a partial restoration of function [7; 24]. These inhibitors may be most useful in the context of drugs that correct the defect in CFTR function [24].

Safety: Hsp90-Aha1 inhibitors are expected to be less toxic than Hsp90 inhibitors, but the full extent of Hsp90-Aha1 client proteins is not known.

Types of evidence:

- Several laboratory studies

The development of Hsp90 inhibitors has been hampered by issues with toxicity [5]. Since targeting the interaction between Aha1 and Hsp90 would only impact a subset of Hsp90 clients, it is expected to be less toxic. Studies in cell culture suggest that Aha1 inhibitors do not induce cytotoxicity [2; 7; 9; 24], however, *in vivo* studies are needed to provide a more comprehensive estimate of their potential side effects, which may vary in a context-dependent manner. The primary issue is that the list of Hsp90-Aha1 clients has not been established. A recent study identified SULT1A1 as an Hsp90-Aha1 client protein [25]. SULT1A1 is a phase-II metabolic enzyme that adds sulfate groups to compounds to make them more soluble for excretion. This process also tends to make the compounds less toxic. As such, it plays an important role in the metabolism of numerous xenobiotics, drugs, and endogenous compounds. Therefore, alterations to SULFT1A1 levels and/or activity could impact drug metabolism and detoxification.

The toxicity profile of a given Aha1 inhibitor will also depend on its individual drug properties, such as the degree and specificity of inhibition, thus compounds with good *in vivo* drug properties will need to be developed in order to determine whether the safety profile is primarily based on class effects or drug-specific effects.

Drug interactions: Aha1 inhibitors may interact with drugs that target Hsp90-Aha1 client proteins. Based on mechanism of action, they would be expected to negatively interact with immunomodulatory drugs for multiple myeloma (thalidomide, lenalidomide, and pomalidomide) [21]. They may also interact with drugs that use SULT1A1 for metabolism or detoxification [25].

Sources and dosing:

Hsp90-Aha1 inhibitors are currently in preclinical development, and have not yet been optimized for *in vivo* use.

Research underway:

Several groups are working on optimizing Aha1-Hsp90 interaction inhibitors.

Search terms:

Pubmed, Google: Aha1

- Alzheimer's disease, neurodegeneration, aging, cancer, inhibitor, Hsp90

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