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.

Calmodulin-like skin protein

Evidence Summary

CLSP is secreted by skin cells. It promotes skin repair, healing, and cell survival. It can reach the brain and may impact neuronal survival. Safety regarding its potential therapeutic use has not been established.

Neuroprotective Benefit: CLSP activates cell survival pathways and protects neurons. It can reach the brain, but it is unclear whether it meaningfully impacts neuronal survival in the human CNS.

Aging and related health concerns: CLSP promotes healing in skin and may protect against stressor-induced senescence in skin cells. Overexpression may extend longevity in healthy mice.

Safety: The endogenous CLSP shows beneficial health effects, but dosing and safety has not been established for potential therapeutic use.

Availability: Research use	**Dose**: Not established	**Sequence:** MAGELTPEEEAQYKKAFSAVDTDGNGTINAQEL GAALKATGKNLSEAQLRKLISEVDSDGDGEISF QEFLTAAKKARAGLEDLQVAFRAFDQDGDGH ITVDELRRAMAGLGQPLPQEELDAMIREADVD QDGRVNYEEFARMLAQE **MW**: 15,893 Daltons/ 146 amino acids
Half-life: Not established	**BBB**: Penetrant	
Clinical trials: None	**Observational studies**: CLSP levels elevated in the skin of patients with psoriasis or dermatitis	

What is it?

Calmodulin-like skin protein (CLSP) is a calcium binding protein [1]. The gene is known as calmodulin like 5 (CALML5). CLSP is expressed by keratinocytes in the stratum granulosum and lower layers of the stratum corneum of the skin [2]. CLSP is responsive to changes in the calcium gradient in the epidermis to regulate keratinocyte proliferation and differentiation. In this capacity, it promotes wound healing processes in the skin. Although it is expressed in the skin, **CLSP is a secreted protein that is found in the circulation**. It is also blood-brain-barrier penetrant and can be detected in the cerebrospinal fluid (CSF) [3]. CLSP contains an endogenous humanin-like region at amino acids 40 through 61 (TGKNLSEAG**L**RK**LI**S**E**V**D**SDGD), with key conserved residues shown in bold [3]. This region allows CLSP to bind to the humanin heterotrimeric receptor (α CNTFR, WSX-1 and gp130), and activate cell survival pathways, similar to humanin. CLSP also has greater affinity for this receptor compared to humanin itself (EC_{50} 10-100 pM for CLSP vs 1-10 uM for humanin) [3]. CLSP does not appear to have the metabolism regulating properties of humanin, suggesting that those effects are not mediated through the heterotrimeric receptor, or they involve different coupling through the receptor.

Neuroprotective Benefit: CLSP activates cell survival pathways and protects neurons. It can reach the brain, but it is unclear whether it meaningfully impacts neuronal survival in the human CNS.

Types of evidence:

- Several laboratory 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: None

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

CLSP acts as an **agonist at the humanin heterotrimeric receptor** (*α* CNTFR, WSX-1 and gp130), which is associated with the activation of cell survival pathways, including STAT3 [3]. Although expressed in the skin, CLSP is secreted and is found in the circulation. In healthy humans, blood levels were estimated to be approximately 5 nM [3]. In mice, peripherally administered (i.p.) recombinant hCLSP was capable of traversing the blood-CSF barrier, and CSF levels reached 1/100 of serum levels [3]. Notably, in contrast to intraperitoneal administration, hCLSP could not be detected in the mice when it was administered intranasally. In postmortem human CSF samples, CLSP levels were found to be approximately 5 to 10 nmol/L based on immunoblotting, and measured at 3 to 7 nmol/L based on ELISA [4]. Because the EC_{50} of CLSP for the humanin heterotrimeric receptor was calculated to be 10 to 100 pM, it is expected that circulating levels of CLSP are sufficient to impact neuronal survival in the human brain [3].

While protective against neuronal insults, there is no evidence that CLSP can improve cognition in the otherwise healthy. In wildtype mice, overexpression of CLSP did not enhance spatial learning and memory [5].

Alzheimer's disease: CLSP HAS NEUROPROTECTIVE PROPERTIES (Preclinical)

CLSP has been shown to have humanin-like neuroprotective properties in preclinical Alzheimer's disease (AD) models. In postmortem human CSF samples (n=23), levels of CLSP did not significantly differ between controls and AD cases, but there was a genotype effect with respect to ApoE4 status [4]. CSF CLSP levels were decreased in ApoE4 positive AD cases (P = 0.0486), although there was still overlap between CLSP levels in the two groups. This indicates that CLSP does not confer predictive value as a biomarker for AD.

Transgenic overexpression of CLSP in the APPswe/PSEN1dE9 AD mouse model reduced spatial learning impairments based on performance on the Morris water maze, and attenuated the loss of the presynaptic marker synaptophysin in 15-month-old AD mice. CLSP had no effect on Aβ levels [5]. Instead, the neuroprotective effects were mediated by the activation of the humanin heterotrimeric receptor and associated downstream signaling such as the **cytoprotective JAK2/STAT3 pathway**.

Treatment of 7-week-old ICR mice with recombinant mouse CLSP reduced scopolamine-induced memory impairments on the Y-maze when administered intracerebroventricularly (50 pmol) 15 minutes after scopolamine, or intraperitonially (500 pmol) at the same time as scopolamine [6]. This suggests that peripherally administered CSLP could exert neuroprotective activity.

Recombinant CLSP protects against mutant APP (V642I-APP)-induced neurotoxicity in SH-SY5Y neuroblastoma cells, F11 neurohybrid cells, and primary cortical neurons, which is thought to involve activation of the humanin heterotrimeric receptor [7]. The missense T835M mutation in the *UNC5C* netrin receptor gene increases the vulnerability of neurons to injury as well as the risk for late onset AD. In F11 neurohybrid and SH-SY5Y cells, hCLSP treatment is protective against T835M-UNC5C mediated neuronal cell death. The protective effects appear to stem from inhibition of JNK via CLSP-mediated induction of the endogenous JNK inhibitor, SH3BP5.

APOE4 interactions: CLSP levels were found to be decreased in the CSF from ApoE4 carriers with AD, relative to noncarriers with AD [4]. It is unclear how or why CLSP levels are influenced by ApoE4 status.

Aging and related health concerns: CLSP promotes healing in skin and may protect against stressor-induced senescence in skin cells. Overexpression may extend longevity in healthy mice.

Types of evidence:

- 2 biomarker studies (CLSP expression in skin from patients with dermatitis or psoriasis)
- Several laboratory studies

Lifespan: CLSP OVEREXPRESSION EXTENDED SURIVIAL IN MICE

In wildtype (C57bl/6 background) mice, transgenic overexpression of CLSP enhanced survival, but it did not extend the shortened lifespan of AD (APP/PS1) mice ([5]. Additional work is needed to determine if this is a reproducible finding, and if exogenous supplementation of CLSP in a non-transgenic manner can meaningfully impact lifespan.

Senescence: CLSP COUNTERACTS SENESCENCE IN CELL CULTURE

Treatment with recombinant CLSP reduced senescence-associated β-galactosidase-positivity in H_2O_2 or UV-damaged keratinocytes [8]. CLSP expression was also upregulated in keratinocytes exposed to H_2O_2 or UV damage, which may serve to counteract the progression of cellular senescence. The effect is at least partially dependent on CLSP's activation of the humanin heterotrimeric receptor.

Dermatitis and psoriasis: CLSP ELEVATED IN SKIN

CLSP was originally identified as a calcium binding protein specifically expressed in differentiating keratinocytes. Expression is stimulated in the presence of calcium; thus, its levels are dependent on calcium levels in the epidermis [9]. The calcium gradient is altered in the epidermis in several skin diseases, including atopic dermatitis and psoriasis, which can lead to significantly elevated levels of CLSP [2; 9]. CLSP is involved in barrier formation, and the **elevated levels are thought to be protective in helping restore skin barrier formation and skin repair**. Levels of CLSP have also been found to be four-fold higher in the sun damaged skin from Caucasian females, suggesting the CLSP **may play a role in skin healing following UV damage** [10]. It has not yet been established whether administration of CLSP could be used to treat skin conditions or heal damaged skin.

Safety: The endogenous CLSP shows beneficial health effects, but dosing and safety has not been established for potential therapeutic use.

Types of evidence:

- Several laboratory studies

CLSP is an endogenous protein, and its upregulation in the context of skin diseases appears to have protective properties [2; 9]. Transgenic overexpression of CLSP also extended longevity in wildtype mice [5], suggesting that elevating CLSP is not associated with adverse health effects. However, very few animal studies have been conducted examining CLSP supplementation [3; 6], and a thorough analysis of potential safety effects has not been done. There is no data regarding the potential effects of CLSP supplementation in humans.

The route of therapeutic administration also needs to be established, and could pose its own concerns. Proteins typically need to be administered via injection or infusion, both of which can lead to adverse reactions in some people.

Drug interactions: Potential interactions have not been established for CLSP.

Sources and dosing:

CLSP (CALML5) is available for research use from commercial suppliers, but is not available for human use, and its therapeutic value has not been established in humans. No therapeutic dose has been

established. In animal studies, it was found to be BBB penetrant, and could exert effects in the CNS when administered via intraperitoneal injection [3].

Research underway:

Preclinical research studies into the basic biology of CLSP are still taking place, and clinical translation is still premature at this time.

Search terms:

Pubmed, Google: CLSP

- Alzheimer's disease, neurodegeneration, aging

Websites visited for CLSP:

- NCBI

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