SOMAGENIX

Klotho

A Guide to the Life Extension Protein

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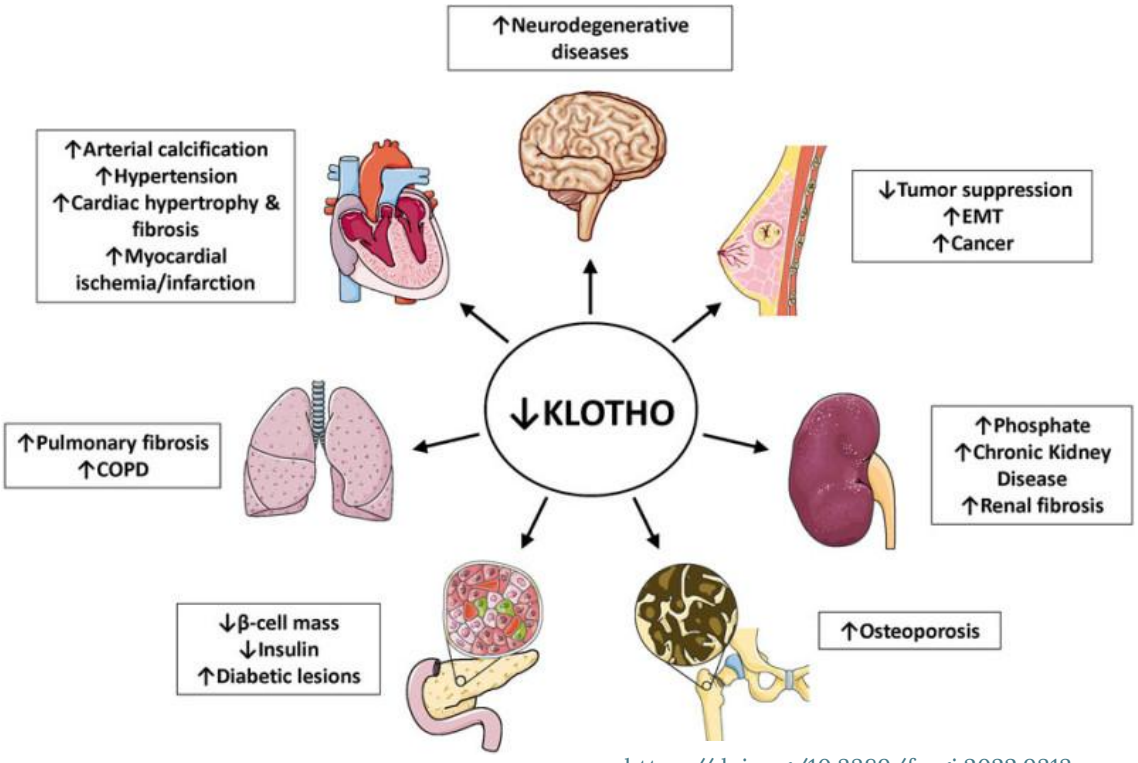
Klotho Research

Klotho protein is linked to longevity, cognitive function, and organ health. Our bodies produce klotho naturally, mainly in our kidneys as well as other organs, however, this declines with age.

Research suggests that increasing Klotho expression could mitigate age-related diseases such as Alzheimer's, cardiovascular disease, and kidney dysfunction, while enhancing overall resilience to aging processes. The Klotho Protein Protocol modifies cells to produce more klotho, improving the opportunity for positive outcomes for individuals with chronic conditions, and potentially extending healthspan.

Though still in early stages, this approach could redefine preventive healthcare and offer a novel strategy for promoting healthier aging.

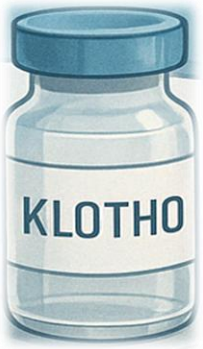


https://doi.org/10.3389/fragi.2022.9313

There are over 3,000 published papers on klotho since it's discovery in 1997.

This guide is designed to be a summary, and is updated with relevant scientific data and breakthroughs as they become available.

A Few Informative Links on Klotho



1. A useful blog with a collection of scientific articles and YouTube videos on Klotho is here: https://healthtechinfo.livejournal.com/451.html

2. An in-depth summary of how Klotho works with scientific links: https://www.wondrousroots.org/klotho

3. A human safety trial in five 80-year-olds with moderate Dementia:

   Safety Study of AAV hTert and Klotho Gene Transfer Therapy for Dementia

   Sewell, Pe & Sewell, Patrick & Ediriweera, D & Rios, Gomez & Guadarrama, E & Gonzalez, Eusebio & Parrish, Elizabeth. (2021). Safety Study of AAV hTert and Klotho Gene Transfer Therapy for Dementia. Journal of Regenerative Biology and Medicine. Volume 3. 1-15. 10.37191/Mapsci-2582-385X-3(6)-097. https://maplespub.com/article/Safety-Study-of-AAV-hTert-and-Klotho-Gene-Transfer-Therapy-for-Dementia

4. A detailed study on Klotho therapy in primates: **Longevity factor klotho enhances cognition in aged nonhuman primates.**

   Castner, S.A., Gupta, S., Wang, D. et al. Longevity factor klotho enhances cognition in aged nonhuman primates. Nat Aging 3, 931–937 (2023). https://doi.org/10.1038/s43587-023-00441-x

5. A 2025 published paper summarises the current research including key animal studies:

   Klotho Protein: A Multifaceted Guardian of Healthy Aging and Its Therapeutic Potential

   Jianlin Shen et al. Int J Nanomedicine. 2025 Jun 9; 20:7251–7270. https://doi.org/10.2147/IJN.S514516

6. **Klotho overexpression protects human cortical neurons from β-amyloid induced neuronal toxicity**

   Shaker, M.R., Salloum-Asfar, S., Taha, R.Z. *et al.* Klotho overexpression protects human cortical neurons from β-amyloid induced neuronal toxicity. *Mol Brain* **18**, 27 (2025). https://doi.org/10.1186/s13041-025-01199-6

7. A further summary paper: **Klotho: a potential therapeutic target in aging and neurodegeneration beyond chronic kidney disease—a comprehensive review from the ERA CKD-MBD working group**

   Mehmet Kanbay, et al. *Clinical Kidney Journal*, Volume 17, Issue 1, January 2024, sfad276, https://doi.org/10.1093/ckj/sfad276

8. **Pathobiology of the Klotho Antiaging Protein and Therapeutic Considerations** Prud'homme GJ, Kurt M and Wang Q (2022) Pathobiology of the Klotho Antiaging Protein and Therapeutic Considerations. *Front. Aging* 3:931331. https://doi.org/10.3389/fragi.2022.931331

9. Human Trials on Klotho Gene Therapy Are Beginning for Alzheimer's, ALS, Parkinsons and Antiaging: https://klothoneuro.com/pipeline/

Video: Klotho Therapy: Extend Lifespan & Increase IQ – GeneHub

Learn about klotho through Somagenix's consultant scientist Diego Garrido's informative video on Klotho: https://youtu.be/lm4G-rcZSZE

Essay: Klotho Protein - A Solution for Improved Cognitive Function and Significant Lifespan Extension

Intro

Klotho, a protein discovered by Japanese scientist Makoto Kuro-O and his team while researching ways to extend the lifespan of animals, has the potential to revolutionize our care of aging related diseases, improve cognition, and extend lifespan significantly. High levels of klotho have been linked to 8-13 year increase in lifespan, improved memory, a lower risk of dementia, increased strength in old age, and a reduced risk of cancer.

Named after one of the Greek Fates, a goddess who controlled the threads of life, klotho levels vary among individuals but most people have levels that are far below the optimum. Fortunately, new protein protocols allow us to modify our cells to produce more of this protein. In this essay, we will explore how the klotho protein works, how to measure its effects on lifespan, and the various gene therapies that can help increase klotho production. All information will be supported by references.

What is klotho?

Klotho is a protein that is produced in the kidneys, livers, and brains of humans and most mammals. It was initially evolved to help animals utilize calcium for building strong bones and muscles, and it continues to be involved in the production of strong tissues such as bones, muscles, and brains. In addition, klotho plays a role in regulating inflammation, blood sugar levels, and the removal of damaged cells in the body. There are three forms of klotho: α, β, and γ- but α-klotho is the most significant and the focus of this discussion.[22]

Alpha-klotho works by binding to another protein called iFGF23, which is present in many tissues throughout the body and in the blood. In the brain, klotho helps to grow gray matter and establish strong neural connections, which can help prevent dementia and mental decline.[22] It is so effective at preventing dementia that it can even counteract other risk factors for developing Alzheimer's disease.[10]

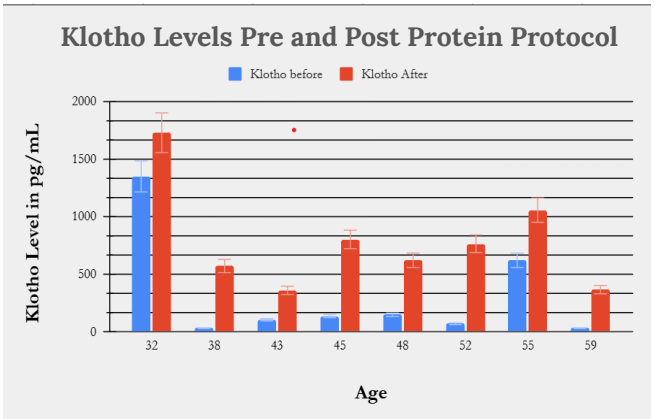
What is the Klotho Replacement Protocol, and what were the results of our studies?

Klotho Replacement Protocol is a promising approach to addressing a variety of health issues, and remains the only way to increase the levels of klotho in the body long term.

The protocol works by inserting a ring of DNA- called a plasmid- into muscle cells, although some of it will also make its way to other tissues. This small circle of DNA tells the muscle cell to begin producing secreted a-klotho protein, which is then excreted by the cell into the bloodstream, where it circulates throughout the body. **This DNA never integrates into the native DNA, staying separate as a plasmid**, leading to a high degree of safety and lasting an estimated 1-2 years. After this time, it is recommended to reapply the protocol for effectiveness. Because of this, it might be more accurate to describe this as a "gene supplement".

The design of the plasmid used in this protocol involves several key components, but the overall design is in nano plasmid form and very compact for maximum biosafety. There are several variations of the klotho gene, including secreted and membrane-bound versions. We have determined that the secreted variation is the most suitable for the protocol, as there is no danger of any other hormonal interactions.

Our lab has been studying the klotho replacement protocol for the past 2 years in animals then humans. We tested the klotho levels before and after the protocol in 8 human individuals in the chart on the left below. You can see levels were much higher following the protocol, allowing a 53 year old male to have a comparative klotho level to a healthy 35 year old. Another 17 humans between the ages of 35 –76 have since received the replacement protocol and 6 are documented in the graph on the right below.



How do we measure increased lifespan?

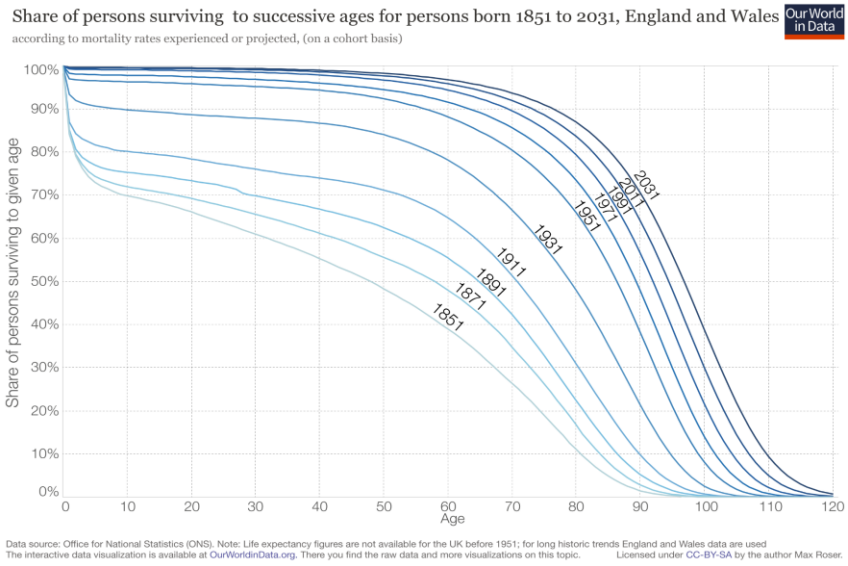
What does it really mean to "increase lifespan"? How can we be sure that a particular intervention is truly extending people's lives?

One way to measure lifespan is to simply wait until an individual dies, but this approach has limitations. To accurately determine the effects of a specific protocol on lifespan, a larger sample size is needed to calculate an average, and even more data is required to be confident that the protocol is effective. It is also important to differentiate between "maximal lifespan" and "average lifespan."

"Maximal lifespan" refers to the oldest age that humans can potentially live to, which is currently estimated at around 120 years. However, by the time an individual reaches this age, they are likely to have developed numerous neurological problems, such as memory loss and impaired reasoning, that make further extension of the body's lifespan less meaningful. Until these issues can be addressed, it may not be practical to increase "maximal lifespan."

On the other hand, "average lifespan" refers to the age at which most people die, which is currently around 80 years. Many people do not reach this age due to serious health problems such as cancer, heart disease, and Alzheimer's disease. If these diseases could be eliminated, it is likely that the average lifespan would increase, and more people would reach very old age in good health, without necessarily increasing the maximum lifespan.

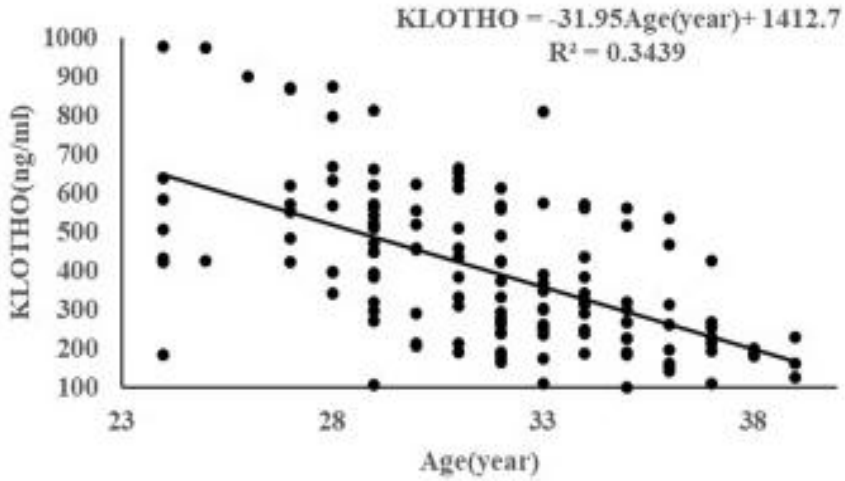
One way to visualize the impact of healthcare on lifespan is through a graph showing the percentage of the population that reaches different ages over time. As healthcare has improved, a larger proportion of the population has reached very old age. As medicine and longevity therapies continue to advance, we can expect this trend to continue, with more people experiencing a longer, healthier "healthspan" and delaying the onset of age-related problems as long as possible.



To understand how klotho may contribute to lifespan extension, it is important to examine the mechanisms through which it functions and the evidence supporting its potential effects on health and longevity.

How does klotho help the body?

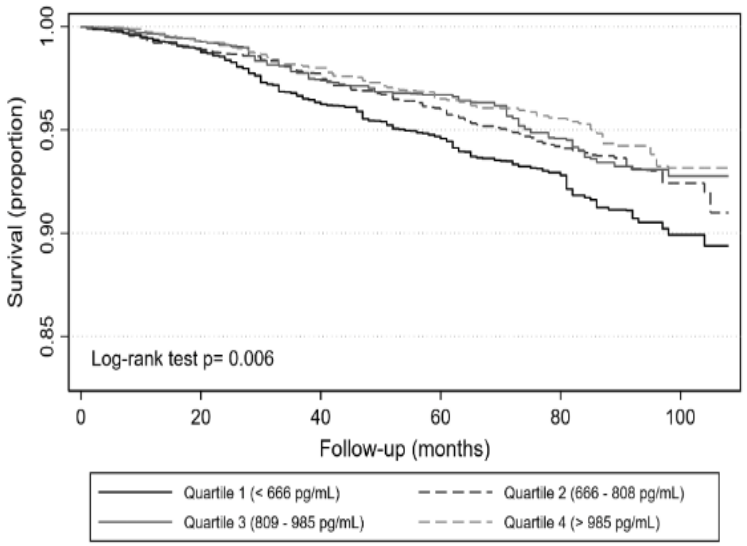
Klotho is typically produced in high quantities by young individuals, but production decreases with age, with most individuals over the age of 50 no longer producing klotho at all. However, there is significant variation in klotho production among individuals, this is just an average. There are plenty of young people with low klotho levels, and plenty of old people that still have some left. You can see here in this graph how widely klotho levels vary, and how it drops with age. There are several genetics and environmental factors contributing to this variation, but genetics are the primary influencer. For example, the KL-VS gene has been identified as a determinant of high klotho levels [1]

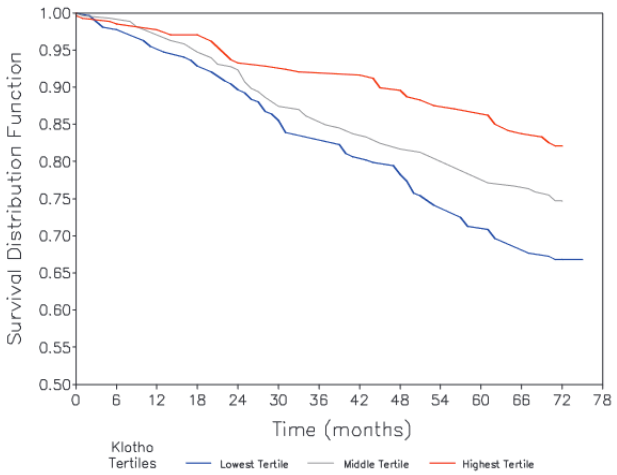


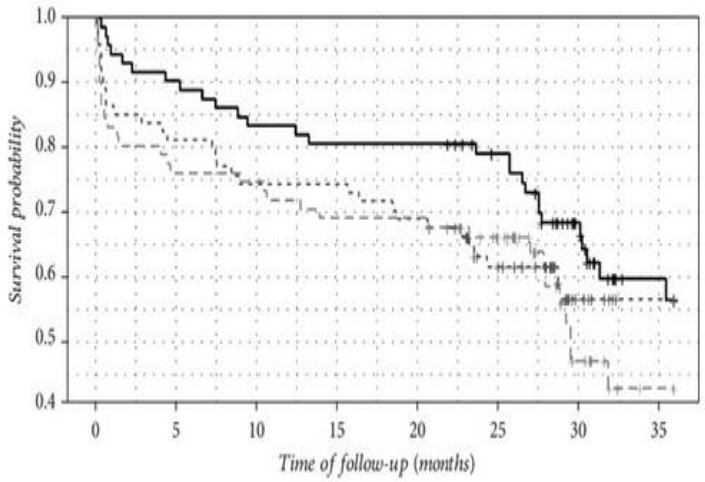
This variation in klotho levels among humans presents a natural experiment that allows us to examine the relationship between klotho and lifespan, cognitive function, and overall health. Repeatedly, research has found that individuals with high levels of klotho tend to have longer lifespans, better cognition, and better health overall. There is no evidence of negative effects from having "too much" secreted klotho, as the protein appears to be able to self-regulate within natural levels.

Even small differences in klotho levels can have significant effects on lifespan, with studies showing that individuals with high klotho levels have better survival rates than those with medium or low levels. Data suggests that optimal klotho levels are beneficial for health, but current research suggests that at least 75% of people have suboptimal levels of klotho.

Even small differences in klotho levels have significant effects on lifespan. Here are three graphs that shows the different survival rates of people with high, medium, and low levels of klotho, from three separate studies.[2][3][4]







You can see that people from the “high klotho” group live longer than the other groups- and this effect becomes more noticeable as time goes on. The data suggests that more klotho is always better for health, but even going strictly by the available studies, we can see that at least 75% of people have suboptimal levels of Klotho.

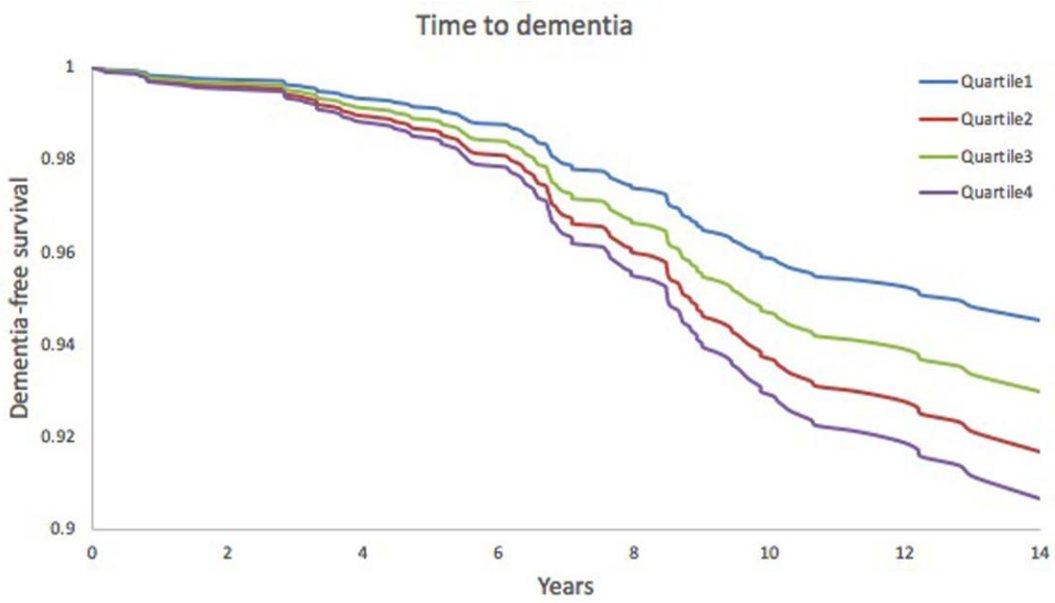
People with very low levels of klotho- more than 25% of the population- had significantly far worse survival rates and many more health problems and dementia. So not only will high klotho levels help you live a longer life, but low levels will drastically diminish your lifespan. Klotho levels even seem to be able to influence cancer rates to a significant degree, with high klotho levels being shown to significantly reduce cancer mortality [5]

Effects on Cognitive function

There is strong evidence to suggest that high levels of klotho may improve cognitive function, particularly in older age. Studies have found that individuals with high klotho levels have a lower incidence of stroke and are less likely to develop Alzheimer's disease and dementia. Klotho may help prevent these conditions by

enhancing overall brain function. Its effect at preventing altzheimers is so significant, it even works against other major risk factors in developing dementia, such as the gene APOE4. [9][10][11][12][13][14][15]

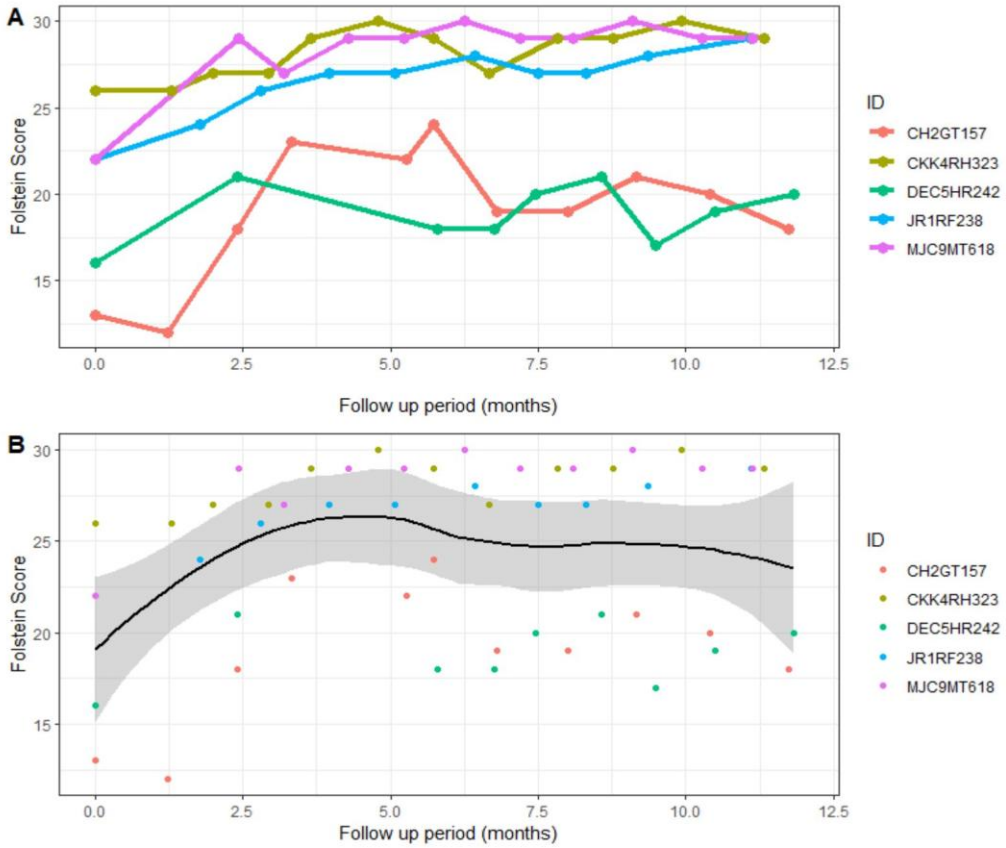
This makes it one of the most effective treatments for preventing and treating cognitive decline and dementia in older people, circumventing the normal routes of dementia. treatment by affecting brain function directly.



Research has also identified a relationship between klotho levels and brain mass and neural connections in areas associated with cognitive processes such as focus, planning, working memory, memory retrieval, perspective-taking, and intelligence.

It has been demonstrated that klotho accounted for approximately 3% of the variation in intelligence between individuals, corresponding to a difference of 6 IQ points between those with high and low klotho levels. This makes it the most significant single genetic factor found for influencing cognitive ability across human populations. [6][7] This relationship has been observed in mice given klotho directly, in both young and old mice, which showed a significant improvement in cognitive abilities.

In a paper from 2019, people with high klotho levels had significantly more brain mass in the areas associated with focus, planning, and working memory (rDLPFC), and they also had more neural connections in the area of the brain associated with memory retrieval, thinking ahead, and taking the perspectives of others (rTEMP) [8]. These findings suggest that klotho may play a role in maintaining and enhancing cognitive function across multiple areas.



Graphical demonstration of the individual Folstein testing results beginning with the pretreatment baseline scores and continuing with the 12-month post treatment results. A) line graphs showing individual patient scores. B) individual scores with locally estimated scatterplot smoothing (LOESS).

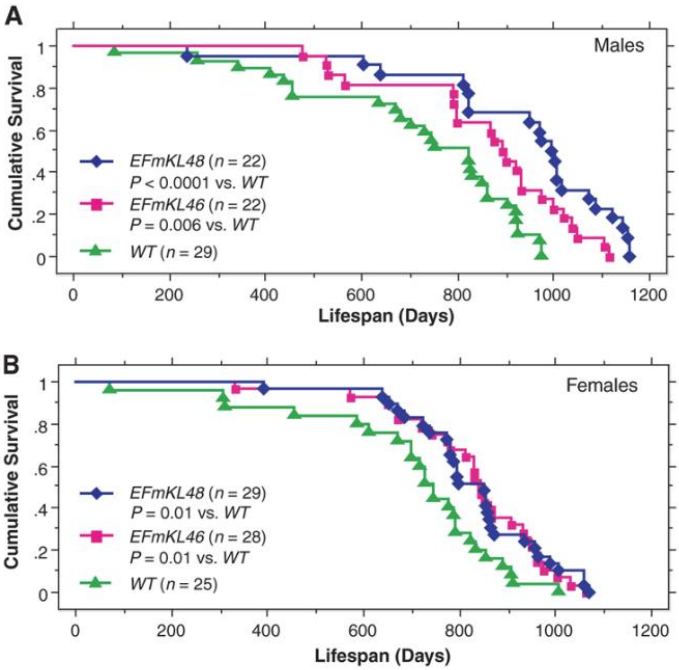
A 2021 study on five patients with mild or moderate dementia (three were males aged 68, 83 and 86 years, two were females ages 83 and 84 years) was performed to primarily evaluate safety. Clinical response data was gathered as a secondary interest.

The therapy demonstrated a very high safety profile with no serious adverse effects identified. Clinical evaluation of the patients over the course of the one year follow up yielded significant findings with all five patients demonstrating evident reversal of Dementia symptoms such as sustained cognitive improvement as measured by the Folstein exam. [24]

How do we establish that klotho is the direct cause of these benefits?

Some readers may be wondering about the relationship between correlation and causation between klotho levels and improved health and longevity. In other words, is it the klotho that is responsible for the benefits, or could it be something else that is causing both improved health and increased klotho levels? To address this question, it is useful to examine studies that have specifically manipulated klotho levels, either through gene therapy or by directly injecting the protein.

One of the first studies to establish a direct link between klotho and longevity was published in 2005, in which researchers created a strain of mice that "over-expressed" klotho, meaning that every cell in the mice produced high levels of klotho[16]. These mice lived 20-30% longer than normal mice, with no other changes made to their biology. It is important to note that these differences in life span demonstrated here mirror the observed differences in lifespan in humans with natural variations of klotho.



Further research has demonstrated that klotho gene therapies can improve overall health in mice, particularly by helping them maintain muscle mass and cognitive abilities as they age [17][19]. Injecting pure klotho protein into mice has also been shown to immediately improve intelligence and health, although these effects are short-lived as the protein is not continuously produced in the body.

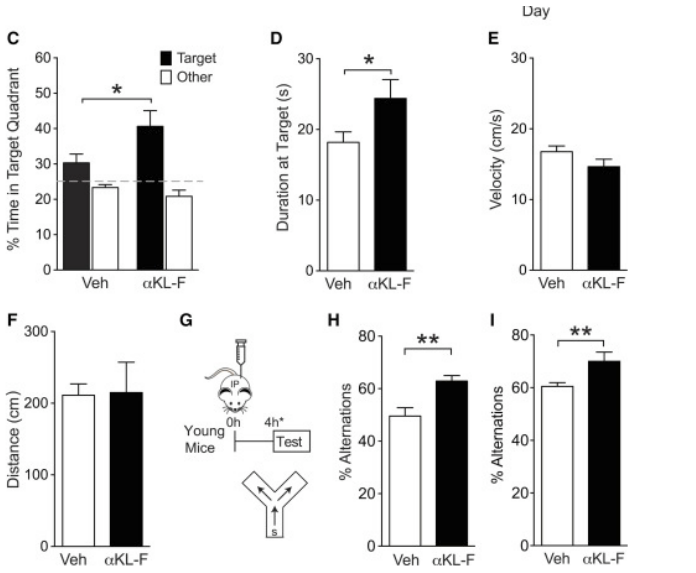


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Figure 2. αKL-F, Delivered Peripherally, Acutely Enhances Cognition in Young Mice

While most research on klotho therapies has been conducted in mice, the relationship between klotho levels and health appears to be similar in humans, as evidenced by the natural variation in klotho levels among individuals. In addition, individuals who have undergone klotho gene therapy report increased energy levels and measured improved performance on cognitive tests

References

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[2] **High klotho levels promote longevity:**

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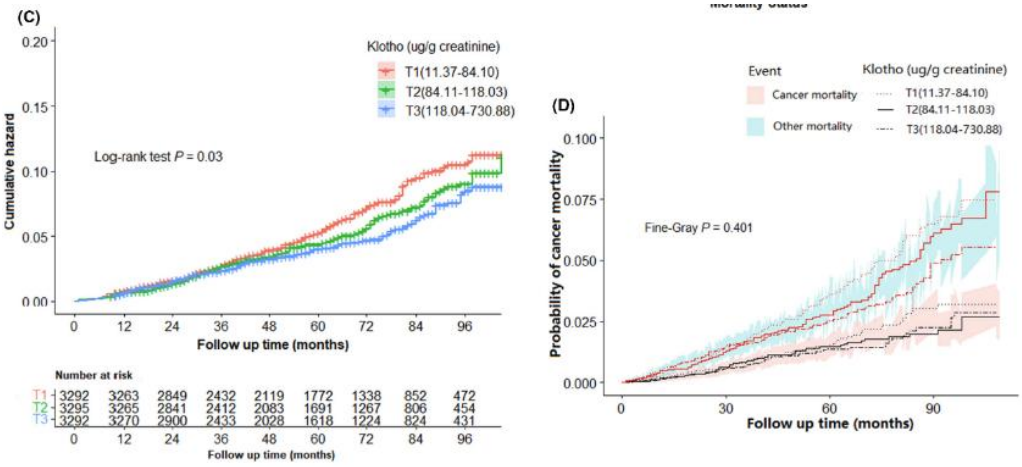
[3] Semba, Richard D., et al. "Plasma klotho and mortality risk in older community-dwelling adults." *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 66.7 (2011): 794-800.

[4] Polat, Yasemin; Yalcin, Ahmet; Yazihan, Nuray; Bahsi, Remzi; Mut Surmeli, Deniz; Akdas, Sevginur; Aras, Sevgi; Varli, Murat (2020). The relationship between frailty and alpha klotho protein in geriatric patients. Archives of Gerontology and Geriatrics, (), 104225–. doi:10.1016/j.archger.2020.104225



[5]Qiao, Yating, et al. "Association of serum Klotho levels with cancer and cancer mortality: Evidence from National Health and Nutrition Examination Survey." *Cancer Medicine* (2022).

C. **High klotho levels promote brain function**

6] Deary, Ian J., et al. "KLOTHO genotype and cognitive ability in childhood and old age in the same individuals." *Neuroscience letters* 378.1 (2005): 22-27.

[7] Dubal, DenaáB, et al. "Life extension factor klotho enhances cognition." *Cell reports* 7.4 (2014): 1065-1076.

[8] Yokoyama, Jennifer S., et al. "Systemic klotho is associated with KLOTHO variation and predicts intrinsic cortical connectivity in healthy human aging." *Brain imaging and behavior* 11.2 (2017): 391-

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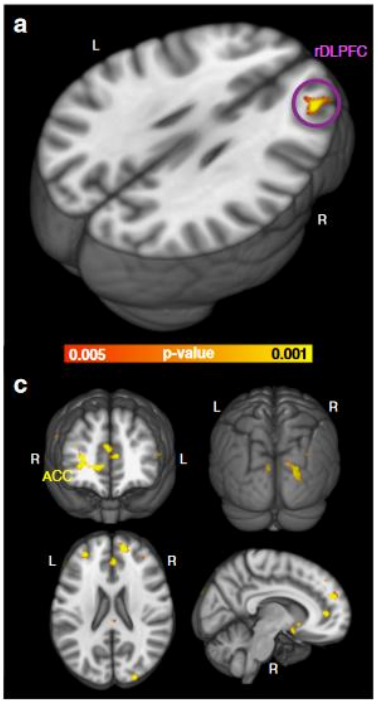
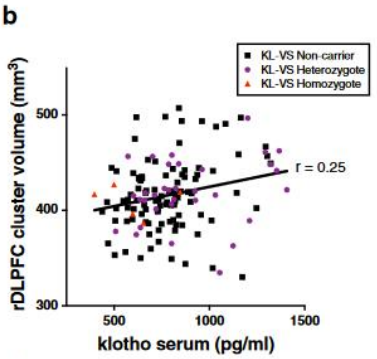




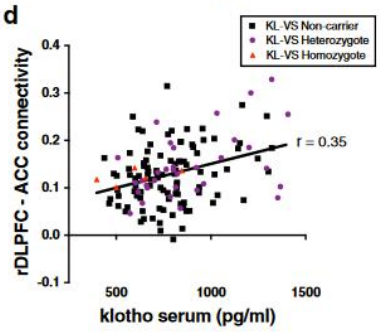
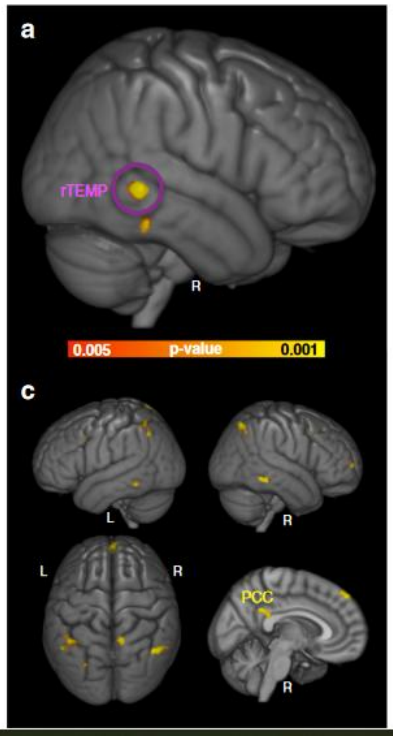
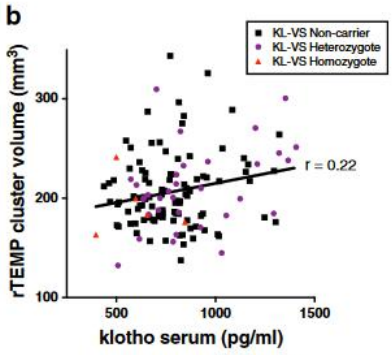


Fig. 2 rDLPFC shows greater volume and connectivity to ACC with higher klotho serum levels. **a** Higher serum klotho levels are associated with greater volume in right dorsolateral prefrontal cortex (rDLPFC), highlighted in purple circle and shown as a red-yellow heat map representing *p*-value of association. **b** Klotho serum level is positively correlated with rDLPFC volume across all genotypes (Pearson's correlation coefficient $r = 0.25$). **c** Higher klotho serum levels are associated with greater intrinsic connectivity (represented by heat map of association *p*-value) between the rDLPFC seed and other regions of the fronto-paricta functional network, including the dorsal anterior cingulate cortex (ACC, yellow text). **d** Representative connectivity between rDLPFC and ACC is positively correlated with klotho serum level across genotypes ($r = 0.35$). All imaging results are overlaid on the MNI152 template





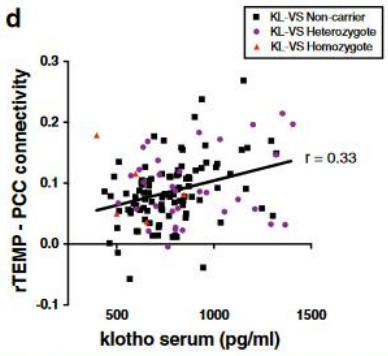


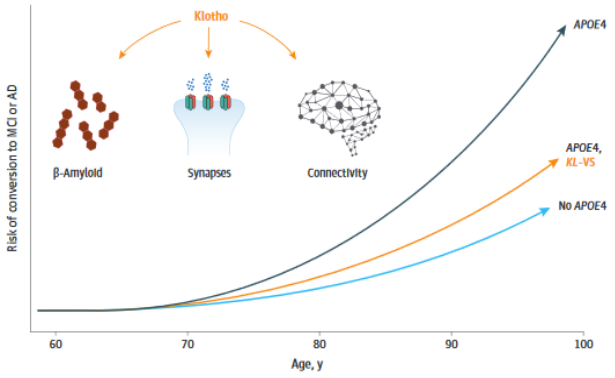
Fig. 3 rTEMP shows greater volume and connectivity to PCC with higher klotho serum levels. **a** Higher serum klotho levels are associated with greater volume in right middle temporal gyrus (rTEMP), highlighted in purple circle and shown as a red-yellow heat map representing *p*-value of association. **b** Klotho serum level is positively correlated with rTEMP volume across all genotypes (Pearson's correlation coefficient $r = 0.22$). **b** Higher klotho serum levels are associated with greater intrinsic connectivity (represented by heat map of association p-value) between the rTEMP seed and other regions of the default mode network, including the posterior cingulate cortex (PCC, yellow text). **d** Representative connectivity between rTEMP and PCC is positively correlated with klotho serum level across genotypes ($r = 0.33$). All imaging results are overlaid on the MNI152 template

D. **Klotho level is associated with prevention of Alzheimer's**

[9] Zeng, Chen-Ye, et al. "Lentiviral vector–mediated overexpression of Klotho in the brain improves Alzheimer's disease–like pathology and cognitive deficits in mice." *Neurobiology of aging* 78 (2019): 18-28.

[10] Zhao, Yue, et al. "Klotho overexpression improves amyloid-β clearance and cognition in the APP/PS1 mouse model of Alzheimer's disease." *Aging Cell* 19.10 (2020): e13239.

Figure. Attenuation of Apolipoprotein E ε4 (*APOE4*)-Associated Alzheimer Disease Risk With *KLOTHO* Variant (*KL-VS*) Heterozygosity



Heterozygosity in *KL-VS*, which leads to higher circulating klotho levels, associates with decreased risk of conversion to mild cognitive impairment (MCI) and Alzheimer disease (AD) among individuals who carry *APOE4*. A hypothetical model of klotho benefits that could counter *APOE4* include protection against pathological β-amyloid production or deposition, enhanced synaptic functions, and increased brain connectivity. This is important because *KL-VS* status could mitigate *APOE4* risks for Alzheimer disease and could be used to further stratify individuals who carry *APOE4* in clinical trials for the disease. Klotho itself could represent a therapeutic for the prevention or treatment of Alzheimer disease in individuals who carry *APOE4*.

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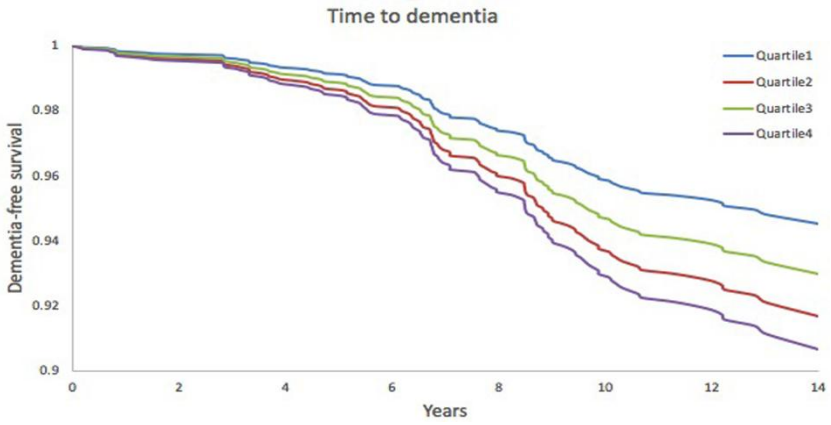
[12] Almeida, Osvaldo P., et al. "Longevity Klotho gene polymorphism and the risk of dementia in older men." *Maturitas* 101 (2017): 1-5.



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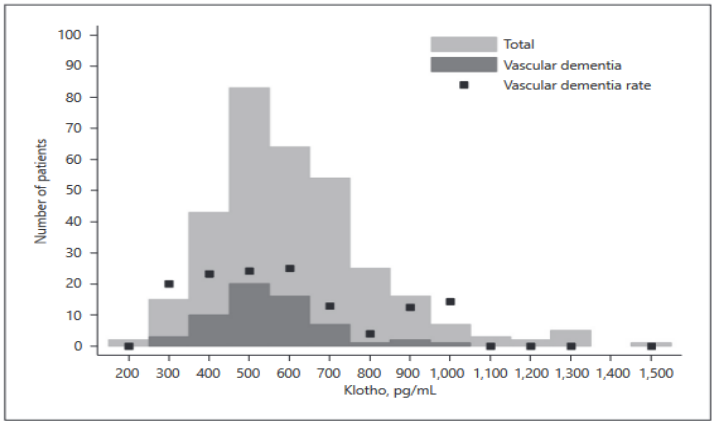

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E. **Increasing klotho levels confers all the advantages of naturally high klotho levels**

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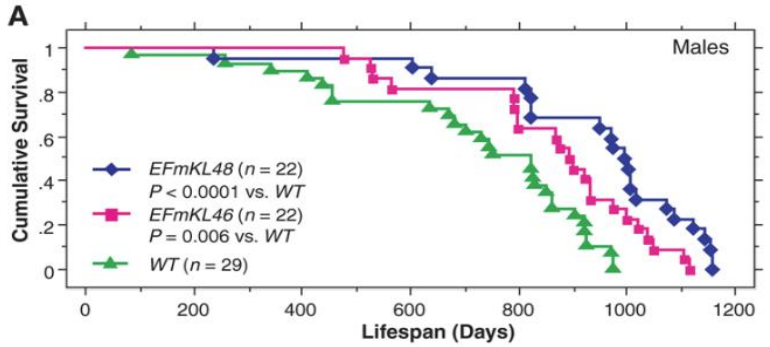

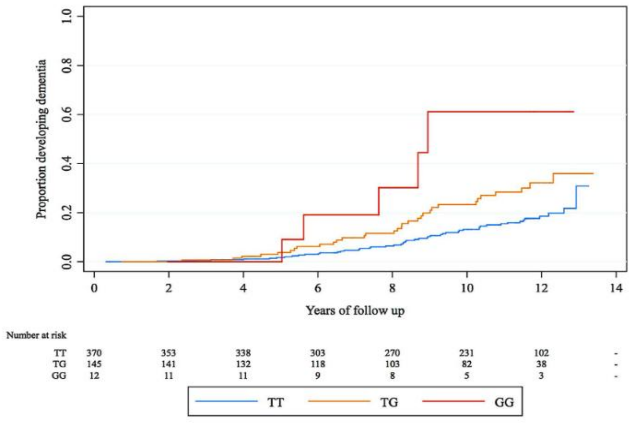

Fig. 1. The figure depicts the proportion of men who develop dementia according to KL-VS genotype over a follow up period of up to 13.4 years (mean ± SD = 9.6 ± 3.3). After considering death as a competing risk, the respective age-adjusted sub-hazard ratios of dementia according to the TG and GG genotypes were 1.6 (95%CI = 1.0–2.5) and 3.5 (95%CI = 1.3–9.1).

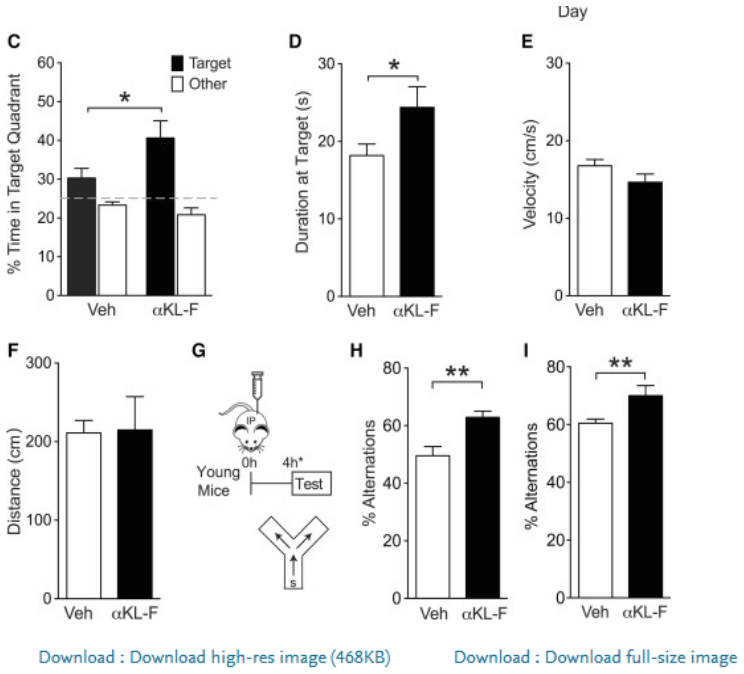

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Figure 2. αKL-F, Delivered Peripherally, Acutely Enhances Cognition in Young Mice

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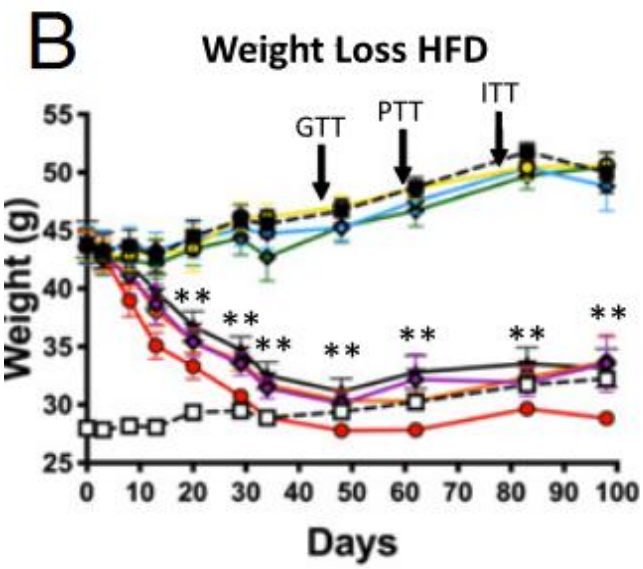

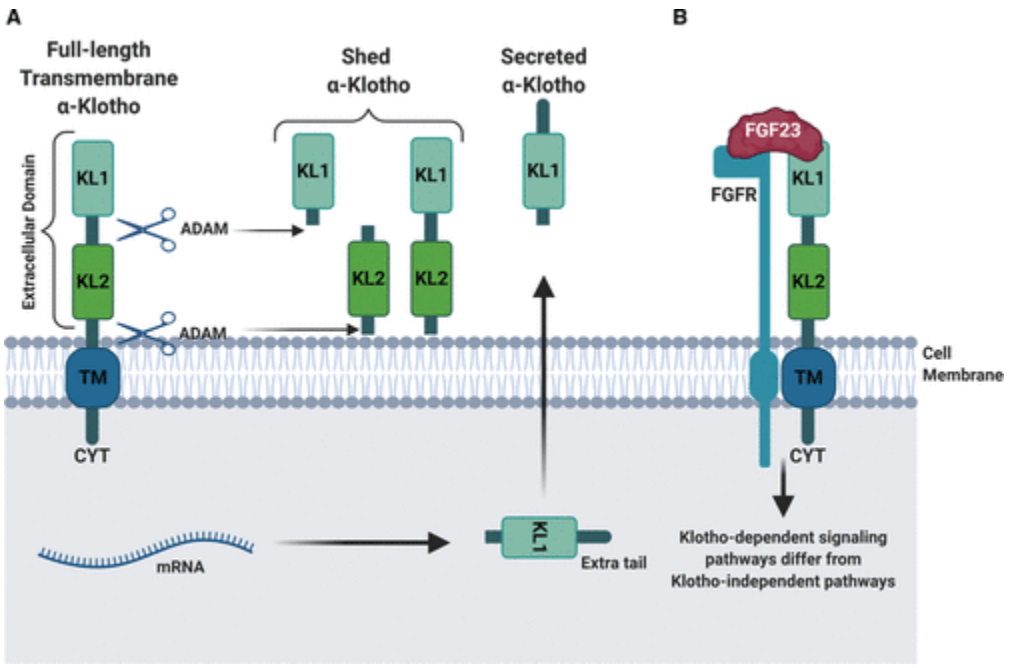

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F. **Human trial demonstrating safety and efficacy of klotho gene therapy**

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Other Relevant Videos on Klotho

Breakthrough Potential of Klotho for Brain Health – Dena Dubal on Peter Attia's Podcast

https://youtu.be/bmBskrX87nU

hTrt and Klotho Gene Replacement for Dementia and Longevity

https://youtu.be/i__oZyxgLC0?si=Ma9Gz7NwjcQbqZ5o&t=2654

THLS2E12 Live long and prosper: Phosphorus, PTH, FGF23, Klotho, CKD & Ageing

https://youtu.be/QOZ7XLMsS0k?si=cMVMp88pPRUJtQlc&t=3685