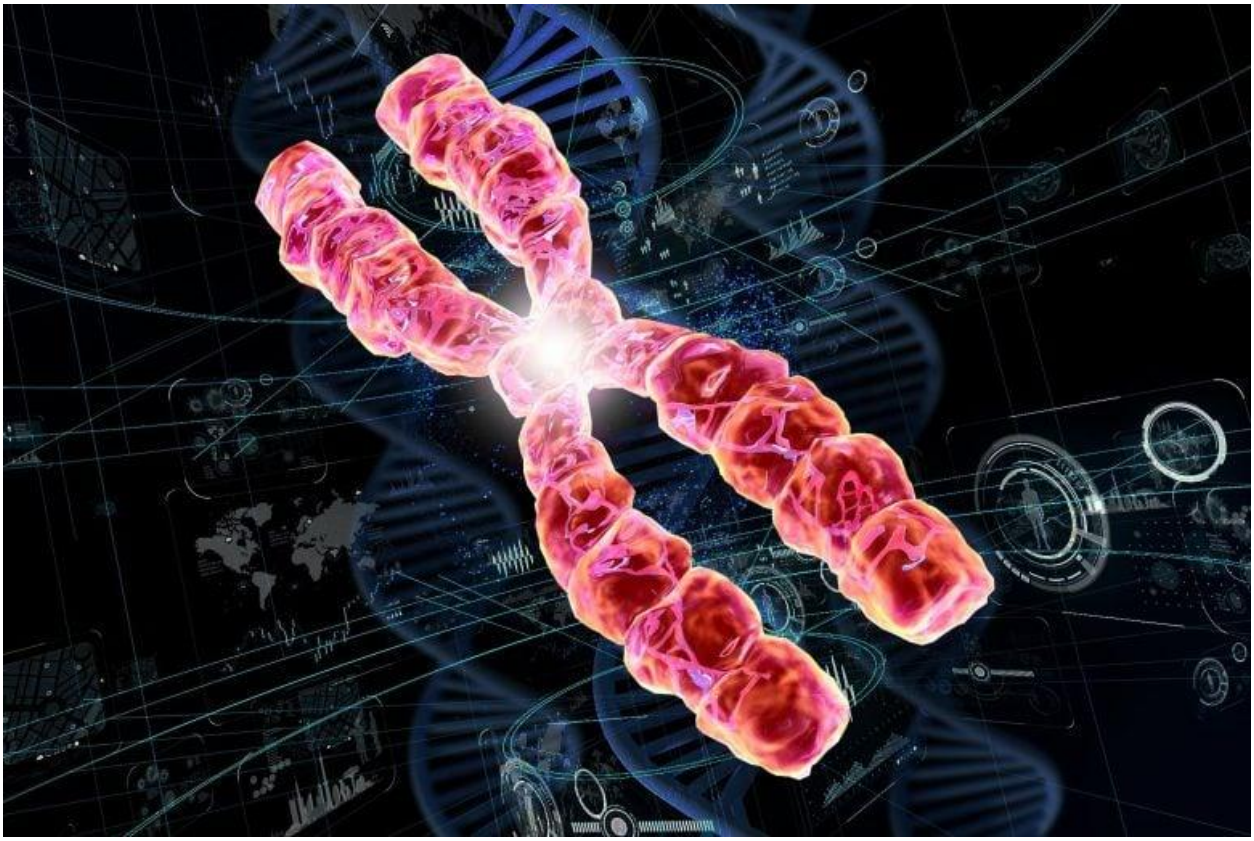
ANTI-AGING VOL 2

Can We Live Longer? Physicist's Breakthrough Discovery in Genetic Protective Layer



Researchers have discovered a new structure of telomeric DNA, which could be key to living longer.

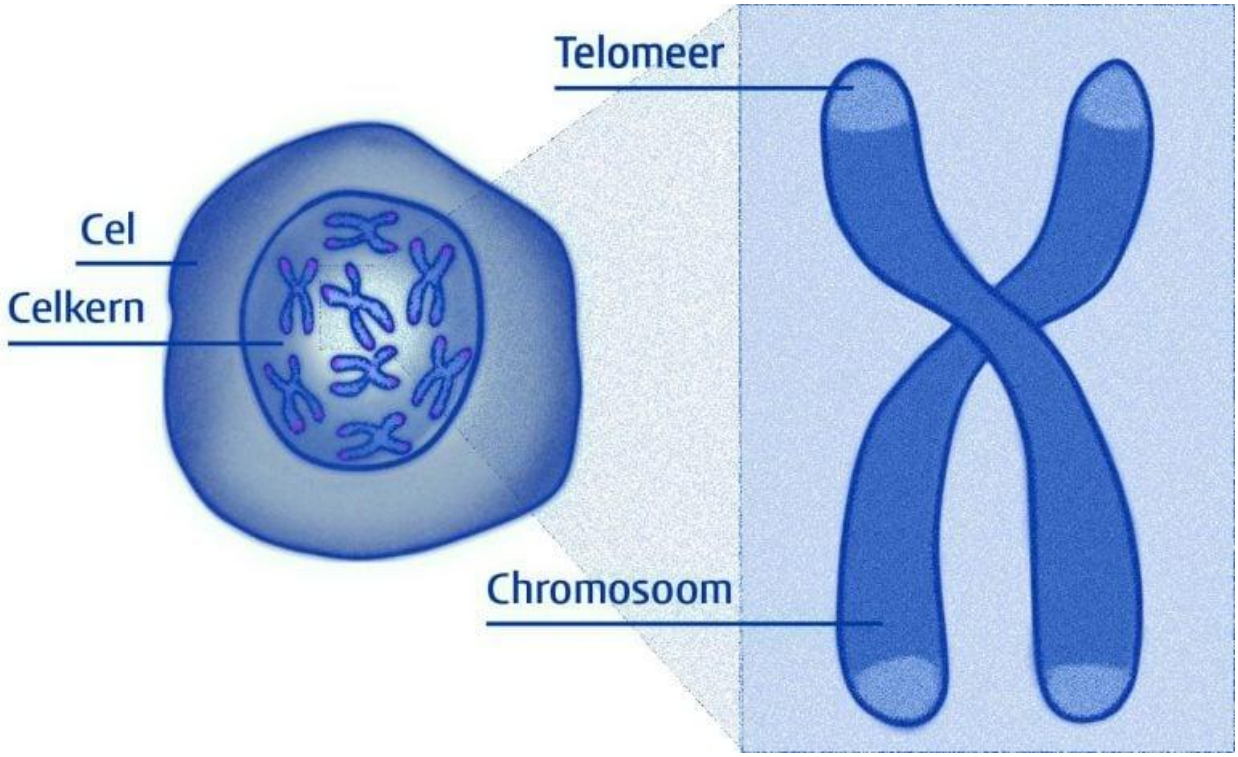
Researchers have discovered a new structure of telomeric DNA with the aid of physics and a tiny magnet. Telomeres are seen by many scientists as the key to living longer. They protect genes from damage but get a bit shorter each time a cell divides. If they become too short, the cell dies. This breakthrough discovery will help us understand aging and disease.

When you hear DNA mentioned, physics is usually not the first scientific discipline that springs to mind. However, John van Noort from the Leiden Institute of Physics (LION) in the Netherlands is one of the scientists who found the new DNA structure. As a biophysicist, he uses methods from physics for biological experiments. This also caught the attention of biologists from Nanyan Technological University in Singapore, who

asked him to help study the DNA structure of telomeres. They published the results on September 14 in the scientific journal *Nature*.

String of Beads

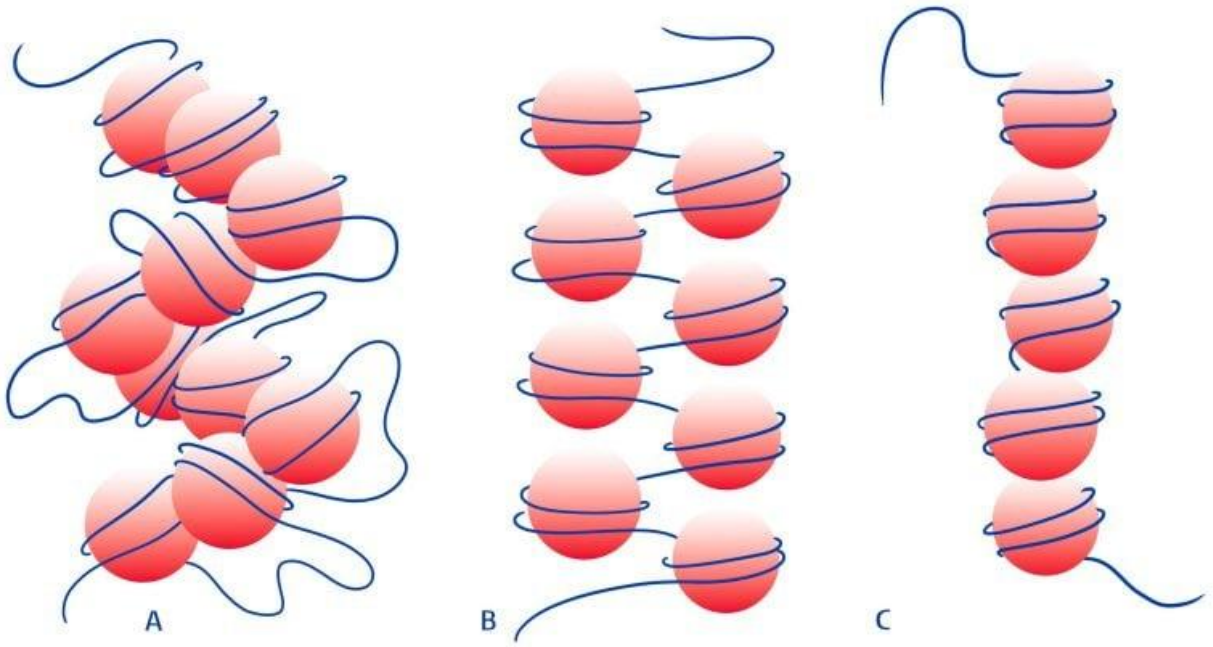
Every cell of our bodies contains chromosomes that carry genes that determine our characteristics (what we look like, for instance). At the ends of these chromosomes are telomeres, which protect the chromosomes from damage. They're a bit like aglets, the plastic tips at the ends of shoelaces.



Because the DNA between the telomeres is two meters long, it has to be folded to fit in a cell. This is achieved by wrapping the DNA around packages of proteins. Together, the DNA and proteins are known as a nucleosome. These are arranged into something similar to a string of beads, with a nucleosome, a piece of free (or unbound) DNA, a nucleosome, and so on.

This string of beads then folds up even more. How it does so depends on the length of the DNA between the nucleosomes, the beads on the string. Two structures that occur after folding were already known. In one of them, two adjacent beads stick together and free DNA hangs in between (figure 2A). If the piece of DNA between the beads is shorter, the adjacent beads do not manage to stick together. Then two stacks form alongside each other (figure 2B).

In their study, Van Noort and colleagues discovered another telomere structure. Here the nucleosomes are much closer together, so there is no longer any free DNA between the beads. This ultimately creates one big helix, or spiral, of DNA (figure 2C).

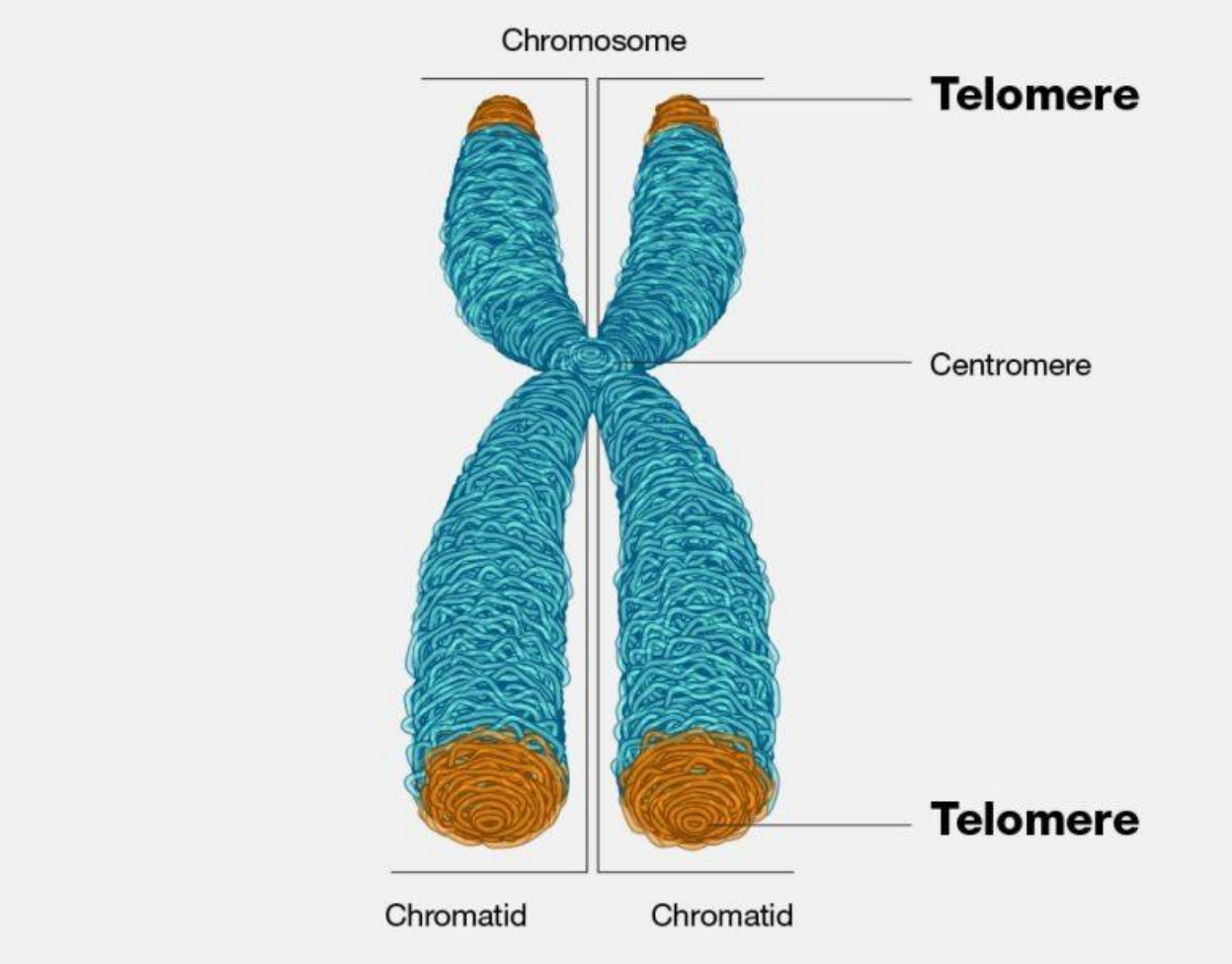


Magnet

The new structure was discovered using a combination of electron microscopy and molecular force spectroscopy. The latter technique comes from Van Noort's lab. Here one end of the DNA is attached to a glass slide and a tiny magnetic ball is stuck to the other. A set of strong magnets above this ball then pull the string of pearls apart. By measuring the amount of force needed to pull the beads apart one by one, you find out more about how the string is folded. The researchers in Singapore then used an electron microscope to get a better picture of the structure.

Building Blocks

Structure, says Van Noort, is "the holy grail of molecular biology." If we know the structure of the molecules, this will give us more insight into how genes are switched on and off and how enzymes in cells deal with telomeres: how they repair and copy DNA, for example. The discovery of the new telomeric structure will improve our understanding of the building blocks in the body. And that in turn will ultimately help us study aging and diseases such as cancer and develop drugs to fight them.



A telomere is a region of repetitive DNA sequences at the end of a chromosome. Telomeres protect the ends of chromosomes from becoming frayed or tangled. Each time a cell divides, the telomeres become slightly shorter. Eventually, they become so short that the cell can no longer divide successfully, and the cell dies. Credit: National Human Genome Research Institute, NIH
Reference: “Columnar structure of human telomeric chromatin” by Aghil Soman, Sook Yi Wong, Nikolay Korolev, Wahyu Surya, Simon Lattmann, Vinod K. Vogirala, Qinming Chen, Nikolay V. Berezhnoy, John van Noort, Daniela Rhodes and Lars Nordenskiöld, 14 September 2022, *Nature*.
DOI: 10.1038/s41586-022-05236-5

Age Reversal Breakthrough: Harvard/MIT Discovery Could Enable Whole-Body Rejuvenation

Scientists from Harvard Medical School, the University of Maine, and MIT have published a groundbreaking study revealing a chemical method to reprogram cells to a more youthful state. This technique offers a potential alternative to gene therapy for reversing aging. The implications of this research are vast, with potential applications in regenerative medicine, treatment of age-related diseases, and whole-body rejuvenation.

In a pioneering study, researchers from Harvard Medical School, University of Maine, and MIT have introduced a chemical method for reversing cellular aging. This revolutionary approach offers a potential alternative to gene therapy for age reversal. The findings could transform treatments for age-related diseases, enhance regenerative medicine, and potentially lead to whole-body rejuvenation.

Groundbreaking Discovery in Aging Reversal

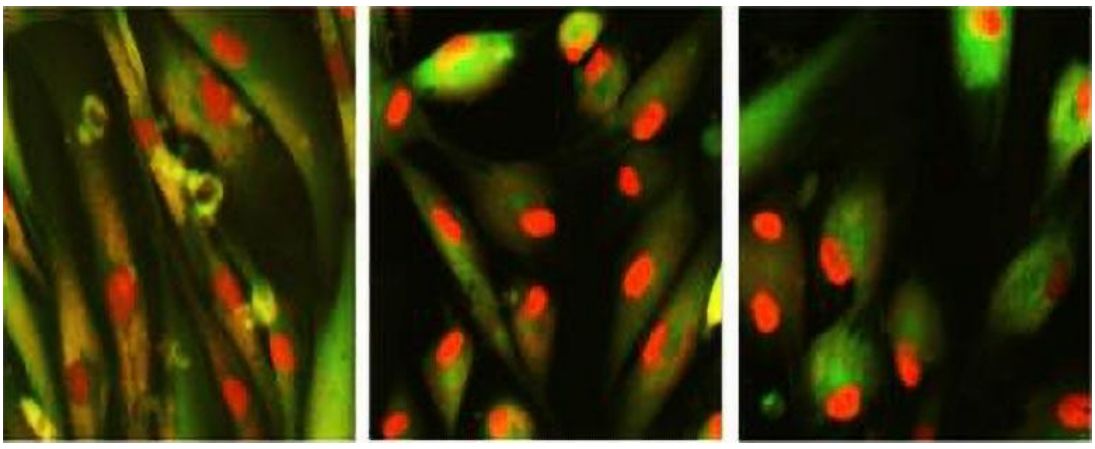
In a monumental study, a team of researchers has revealed a novel approach to combating aging and age-related diseases. This work, undertaken by scientists at Harvard Medical School, introduces the first chemical method to rejuvenate cells, bringing them to a more youthful state. Prior to this, only powerful gene therapy could achieve this feat.

Mice in the Sinclair lab have been engineered to age rapidly to test the effectiveness of therapies to reverse the aging process. The mouse on the right has been aged to 150% that of its sibling on the left by disrupting its epigenome. Photo credit: D. Sinclair, Harvard Medical School. Credit: 2023 Yang et al.

On July 12, 2023, researchers from Harvard Medical School, the University of Maine, and the Massachusetts Institute of Technology (MIT) published a fresh research paper in *Aging*. The paper, titled, "Chemically induced reprogramming to reverse cellular aging," extends upon a previously groundbreaking discovery. The researchers are Jae-Hyun Yang, Christopher A. Petty, Thomas Dixon-McDougall, Maria Vina Lopez, Alexander Tyshkovskiy, Sun Maybury-Lewis, Xiao Tian, Nabilah Ibrahim, Zhili Chen, Patrick T. Griffin, Matthew Arnold, Jien Li, Oswaldo A. Martinez, Alexander Behn, Ryan Rogers-Hammond, Suzanne Angeli, Vadim N. Gladyshev, and David A. Sinclair.

Exploring the Methodology

This discovery builds on the finding that the expression of specific genes, known as Yamanaka factors, can transform adult cells into induced pluripotent stem cells (iPSCs). This breakthrough, which earned a Nobel Prize, prompted scientists to question if cellular aging could be reversed without pushing cells to become too young and potentially cancerous.



Rejuvenation and age reversal of senescent human skin cells by chemical means. Cells in the right two panels have restored compartmentalization of the red fluorescent protein in the nucleus, a marker of youth that was used to find the cocktails, before the scientists

confirmed they were younger, based on how genes were expressed. Image credit: J. -H. Yang, Harvard Medical School. Credit: 2023 Yang et al.

In this recent study, the scientists probed for molecules that could, in tandem, revert cellular aging and refresh human cells. They designed advanced cell-based assays to differentiate between young and old, as well as senescent cells. The team employed transcription-based aging clocks and a real-time nucleocytoplasmic protein compartmentalization (NCC) assay. In a significant development, they identified six chemical combinations that could return NCC and genome-wide transcript profiles to youthful states, reversing transcriptomic age in less than a week.

Relevance and Potential Applications

The Harvard team has previously shown the possibility of reversing cellular aging without causing unregulated cell growth. This was done by inserting specific Yamanaka genes into cells using a viral vector. Studies on various tissues and organs like the optic nerve, brain, kidney, and muscle have yielded encouraging results, including improved vision and extended lifespan in mice. Additionally, recent reports have documented improved vision in monkeys.

These findings have profound implications, paving the way for regenerative medicine and potentially full-body rejuvenation. By establishing a chemical alternative to gene therapy for age reversal, this research could potentially transform the treatment of aging, injuries, and age-related diseases. The approach also suggests the possibility of lower development costs and shorter timelines. Following successful results in reversing blindness in monkeys in April 2023, plans for human clinical trials using the lab's age reversal gene therapy are currently underway.

Views from the Research Team

"Until recently, the best we could do was *slow* aging. New discoveries suggest we can now reverse it," said David A. Sinclair, A.O., Ph.D., Professor in the Department of Genetics and co-Director of the Paul F. Glenn Center for Biology of Aging Research at Harvard Medical School and lead scientist on the project. "This process has previously required gene therapy, limiting its widespread use." The team at Harvard envisions a future where age-related diseases can be effectively treated, injuries can be repaired more efficiently, and the dream of whole-body rejuvenation becomes a reality. "This new discovery offers the potential to reverse aging with a single pill, with applications ranging from improving eyesight to effectively treating numerous age-related diseases," Sinclair said. Reference: "Chemically induced reprogramming to reverse cellular aging" by Jae-Hyun Yang, Christopher A. Petty, Thomas Dixon-McDougall, Maria Vina Lopez, Alexander Tyshkovskiy, Sun Maybury-Lewis, Xiao Tian, Nabilah Ibrahim, Zhili Chen, Patrick T. Griffin, Matthew Arnold, Jien Li, Oswaldo A. Martinez, Alexander Behn, Ryan Rogers-Hammond, Suzanne Angeli, Vadim N. Gladyshev and David A. Sinclair, 12 July 2023, *Aging-US*.
DOI: 10.18632/aging.204896

CRISPR Meets Pac-Man: Powerful New DNA Tool Enables Bigger Gene Edits

A novel tool for cutting larger DNA sections from a cell's genome could expedite gene editing for treatment development and disease study in humans and other organisms.

Gene editing for the development of new treatments, and for studying disease as well as normal function in humans and other organisms, may advance more quickly with a new tool for cutting larger pieces of DNA out of a cell's genome, according to a new study by UC San Francisco scientists.

Publication of the UCSF study on October 19, 2020, in the journal *Nature Methods* comes less than two weeks after two researchers who first used the genetic scissors known as CRISPR-Cas9 were selected to receive this year's Nobel Prize in Chemistry.

Though now employed as a research tool in laboratories around the world, CRISPR evolved eons ago in bacteria as a means to fight their ancient nemeses, a whole host of viruses known as bacteriophages. When bacteria encounter a phage, they incorporate a bit of the viral DNA into their own DNA, and it then serves as a template to make RNA that binds to the corresponding viral DNA in the phage itself. The CRISPR enzymes then target, disable, and kill the phage.

In his latest work exploring this ancient and strange arms race, principal investigator Joseph Bondy-Denomy, PhD, associate professor in the UCSF Department of

Microbiology and Immunology, joined scientists Bálint Csörgő, PhD, and Lina León to develop and test a new CRISPR tool.

The already renowned CRISPR-Cas9 ensemble is like a molecular chisel that can be used to rapidly and precisely excise a small bit of DNA at a targeted site. Other methods can then be used to insert new DNA. But the new CRISPR-Cas3 system adapted by the UCSF scientists employs a different bacterial immune system. The key enzyme in this system, Cas3, acts more like a molecular wood chipper to remove much longer stretches of DNA quickly and accurately.

“Cas3 is like Cas9 with a motor — after finding its specific DNA target, it runs on DNA and chews it up like a Pac-Man,” Bondy-Denomy said.

This new capability to delete or replace long stretches of DNA will enable researchers to more efficiently assess the importance of genomic regions that contain DNA sequences of indeterminate function, according to Bondy-Denomy, an important consideration in understanding humans and the pathogens that plague them.

“Previously, there was no easy and reliable way to delete very large regions of DNA in bacteria for research or therapeutic purposes,” he said. “Now, instead of making 100 different small DNA deletions we can just make one deletion and ask, ‘What changed?'”

Because bacteria and other types of cells are commonly used to produce small molecule or protein-based pharmaceuticals, CRISPR-Cas3 will enable biotechnology industry scientists to more easily remove potentially pathogenic or useless DNA from these cells, according to Bondy-Denomy.

“Large swathes of bacterial DNA are poorly understood, with unknown functions that in some cases are not necessary for survival,” Bondy-Denomy said. “In addition, bacterial DNA contains large stretches of DNA imported from other sources, which can cause disease in the bacterium’s human host, or divert bacterial metabolism.”

CRISPR-Cas3 also should also allow entire genes to be inserted into the genome in industrial, agricultural or even in human gene therapy applications, Bondy-Denomy said.

The UCSF researchers selected and modified the CRISPR-Cas3 system used by the bacterium Pseudomonas aeruginosa, and demonstrated in this *species* and in three others, including bacteria that cause disease in humans and plants, that their more compact version functions well to remove selected DNA in all four species. Other CRISPR-Cas3 systems have been made to work in human and other mammalian cells, and that also should be achievable for the modified P. aeruginosa system, Bondy-Denomy said.

Bondy-Denomy studies a range of bacteria, bacteriophage, and CRISPR systems to learn more about how they work and to find useful molecular tools. “CRISPR-Cas3 is by

far the most common CRISPR system in nature," he said. "About 10 times as many bacterial species use a Cas3 system as use a Cas9 system. It may be that Cas3 is a better bacterial immune system because it shreds phage DNA."

Unlike Cas9, when Cas3 binds to its precise DNA target it begins chewing up one strand of the double-stranded DNA in both directions, leaving a single strand exposed. The deletions obtained in the UCSF experiments ranged in size, in many cases encompassing as many as 100 bacterial genes. The CRISPR-Cas3 mechanism should also allow for easier replacement of deleted DNA with a new DNA sequence, the researchers found.

For DNA deletion and editing in the lab, scientists program CRISPR systems to target specific DNA in the genome of an organism of interest using any guide sequence they choose.

In the new CRISPR-Cas3 study, by manipulating the sequences of DNA provided to the bacteria for repairing the deletions, the researchers were able to precisely set the boundaries of these large DNA repairs, something they were unable to accomplish with CRISPR-Cas9. Bondy-Denomy previously discovered anti-CRISPR strategies that phage evolved to fight back against bacteria, and these might prove useful for stopping the gene editing reactions driven by Cas enzymes used as human therapeutics before side effects arise, or in using phage to remove unwanted bacteria that have populated the gut, he said. Apart from E. coli and a couple of other species, relatively little is known about the 1,000 or so bacterial species that normally reside there.

"Non-model microbes have largely been left behind in the genetics world, and there is a huge need for new tools to study them," he said.

Reference: "A compact Cascade–Cas3 system for targeted genome engineering" by Bálint Csörgő, Lina M. León, Ilea J. Chau-Ly, Alejandro Vasquez-Rifo, Joel D. Berry, Caroline Mahendra, Emily D. Crawford, Jennifer D. Lewis and Joseph Bondy-Denomy, 19 October 2020, *Nature Methods*.
DOI: 10.1038/s41592-020-00980-w

Authors: Bondy-Denomy is senior author. Postdoctoral fellow Csörgő and graduate student León co-led this work, collaborating with other UCSF authors including Joel Berry, Caroline Mahendra, and Emily Crawford.

Funding: The work was primarily funded by UCSF Program for Breakthrough Biomedical Research, the Innovative Genomics Institute, and an National Institutes of Health Director's Early Independence Award to Bondy-Denomy.

Disclosures: Bondy-Denomy is a scientific advisory board member of SNIPR Biome and Excision Biotherapeutics and a scientific advisory board member and cofounder of Acrigen Biosciences. UCSF has filed a patent application relating to various aspects of Cas3-based genome editing.

Genetic Factor Discovery Enables Adult Skin to Regenerate Like a Newborn Baby's

A newly identified genetic factor allows adult skin to repair itself like the skin of a newborn babe. The discovery by Washington State University researchers has implications for better skin wound treatment as well as preventing some of the aging process in skin.

In a study, published in the journal *eLife* on September 29, 2020, the researchers identified a factor that acts like a molecular switch in the skin of baby mice that controls the formation of hair follicles as they develop during the first week of life. The switch is mostly turned off after skin forms and remains off in adult tissue. When it was activated in specialized cells in adult mice, their skin was able to heal wounds without scarring. The reformed skin even included fur and could make goosebumps, an ability that is lost in adult human scars.

"We were able to take the innate ability of young, neonatal skin to regenerate and transfer that ability to old skin," said Ryan Driskell, an assistant professor in WSU's School of Molecular Biosciences. "We have shown in principle that this kind of regeneration is possible."

Mammals are not known for their regenerative abilities compared to other organisms, such as salamanders that can regrow entire limbs and regenerate their skin. The WSU study suggests that the secret to human regeneration might be found by studying our own early development.

"We can still look to other organisms for inspiration, but we can also learn about regeneration by looking at ourselves," said Driskell. "We do generate new tissue, once in our life, as we are growing."

Driskell's team used a new technique called single cell RNA sequencing to compare genes and cells in developing and adult skin. In developing skin, they found a transcription factor–proteins that bind to DNA and can influence whether genes are turned on or off. The factor the researchers identified, called Lef1, was associated with papillary fibroblasts which are developing cells in the papillary dermis, a layer of skin just below the surface that gives skin its tension and youthful appearance.

When the WSU researchers activated the Lef1 factor in specialized compartments of adult mouse skin, it enhanced the skins' ability to regenerate wounds with reduced scarring, even growing new hair follicles that could make goosebumps.

Driskell first got the idea to look at early stages of mammalian life for the capacity to repair skin after learning of the work of Dr. Michael Longaker of Stanford University. When performing emergency life-saving surgery in utero, Longaker and his colleagues

observed that when those babies were born they did not have any scars from the surgery.

A lot of work still needs to be done before this latest discovery in mice can be applied to human skin, Driskell said, but this is a foundational advance. With the support from a new grant from the National Institutes of Health, the WSU research team will continue working to understand how Lef1 and other factors work to repair skin. Also to help further this research, the Driskell lab has created an open, searchable web resource for the RNA sequence data for other scientists to access at skinregeneration.org.

Reference: “Lef1 expression in fibroblasts maintains developmental potential in adult skin to regenerate wounds” by Quan M Phan, Gracelyn M Fine, Lucia Salz, Gerardo G Herrera, Ben Wildman, Iwona M Driskell and Ryan R Driskell, 29 September 2020, *eLife*.
DOI: 10.7554/eLife.60066

Dietary Cocoa Flavanols Reverse Age-Related Memory Decline in Older Adults

A new study from Columbia University Medical Center shows that dietary cocoa flavanols reverse age-related memory decline in healthy older adults.

New York, New York — Dietary cocoa flavanols—naturally occurring bioactives found in cocoa—reversed age-related memory decline in healthy older adults, according to a study led by Columbia University Medical Center (CUMC) scientists. The study, published in the advance online issue of Nature Neuroscience, provides the first direct evidence that one component of age-related memory decline in humans is caused by changes in a specific region of the brain and that this form of memory decline can be improved by a dietary intervention.

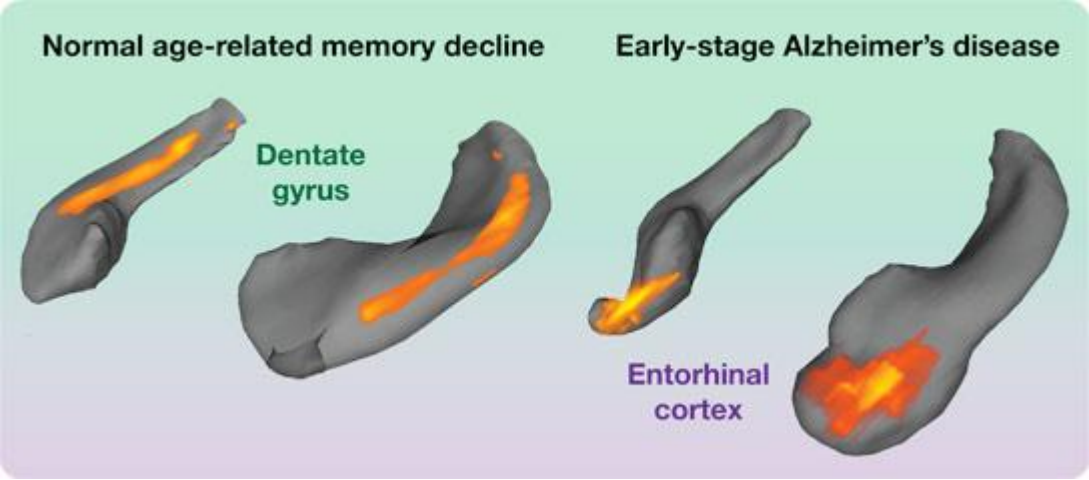
As people age, they typically show some decline in cognitive abilities, including learning and remembering such things as the names of new acquaintances or where they parked the car or placed their keys. This normal age-related memory decline starts in early adulthood but usually does not have any noticeable impact on quality of life until people reach their fifties or sixties. Age-related memory decline is different from the often-devastating memory impairment that occurs with Alzheimer’s, in which a disease process damages and destroys neurons in various parts of the brain, including the memory circuits.

Previous work, including by the laboratory of senior author Scott A. Small, MD, had shown that changes in a specific part of the brain—the dentate gyrus—are associated with age-related memory decline. Until now, however, the evidence in humans showed only a correlational link, not a causal one. To see if the dentate gyrus is the source of age-related memory decline in humans, Dr. Small and his colleagues tested whether

compounds called cocoa flavanols can improve the function of this brain region and improve memory. Flavanols extracted from cocoa beans had previously been found to improve neuronal connections in the dentate gyrus of mice.

Dr. Small is the Boris and Rose Katz Professor of Neurology (in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, the Sergievsky Center, and the Departments of Radiology and Psychiatry) and director of the Alzheimer's Disease Research Center in the Taub Institute at CUMC.

A cocoa flavanol-containing test drink prepared specifically for research purposes was produced by the food company Mars, Incorporated, which also partly supported the research, using a proprietary process to extract flavanols from cocoa beans. Most methods of processing cocoa remove many of the flavanols found in the raw plant.



The dentate gyrus is distinct from the entorhinal cortex, the hippocampal region affected in early-stage Alzheimer's disease. Previous work, including by the laboratory of senior author Scott A. Small, MD, had shown that changes in a specific part of the brain's hippocampus—the dentate gyrus—are associated with normal age-related memory decline in humans and other mammals. (Credit: Columbia University Medical Center)

In the CUMC study, 37 healthy volunteers, ages 50 to 69, were randomized to receive either a high-flavanol diet (900 mg of flavanols a day) or a low-flavanol diet (10 mg of flavanols a day) for three months. Brain imaging and memory tests were administered to each participant before and after the study. The brain imaging measured blood volume in the dentate gyrus, a measure of metabolism, and the memory test involved a 20-minute pattern-recognition exercise designed to evaluate a type of memory controlled by the dentate gyrus.

"When we imaged our research subjects' brains, we found noticeable improvements in the function of the dentate gyrus in those who consumed the high-cocoa-flavanol drink," said lead author Adam M. Brickman, PhD, associate professor of neuropsychology at the Taub Institute.

The high-flavanol group also performed significantly better on the memory test. “If a participant had the memory of a typical 60-year-old at the beginning of the study, after three months that person on average had the memory of a typical 30- or 40-year-old,” said Dr. Small. He cautioned, however, that the findings need to be replicated in a larger study—which he and his team plan to do.

Flavanols are also found naturally in tea leaves and in certain fruits and vegetables, but the overall amounts, as well as the specific forms and mixtures, vary widely.

The precise formulation used in the CUMC study has also been shown to improve cardiovascular health. Brigham and Women’s Hospital in Boston recently announced an NIH-funded study of 18,000 men and women to see whether flavanols can help prevent heart attacks and strokes.

The researchers point out that the product used in the study is not the same as chocolate, and they caution against an increase in chocolate consumption in an attempt to gain this effect.

Two innovations by the investigators made the study possible. One was a new information-processing tool that allows the imaging data to be presented in a single three-dimensional snapshot, rather than in numerous individual slices. The tool was developed in Dr. Small’s lab by Usman A. Khan, an MD-PhD student in the lab, and Frank A. Provenzano, a biomedical engineering graduate student at Columbia. The other innovation was a modification to a classic neuropsychological test, allowing the researchers to evaluate memory function specifically localized to the dentate gyrus. The revised test was developed by Drs. Brickman and Small.

Besides flavanols, exercise has been shown in previous studies, including those of Dr. Small, to improve memory and dentate gyrus function in younger people. In the current study, the researchers were unable to assess whether exercise had an effect on memory or on dentate gyrus activity. “Since we didn’t reach the intended VO2max (maximal oxygen uptake) target,” said Dr. Small, “we couldn’t evaluate whether exercise was beneficial in this context. This is not to say that exercise is not beneficial for cognition. It may be that older people need more intense exercise to reach VO2max levels that have therapeutic effects.”

Reference: “Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults” by Adam M Brickman, Usman A Khan, Frank A Provenzano, Lok-Kin Yeung, Wendy Suzuki, Hagen Schroeter, Melanie Wall, Richard P Sloan and Scott A Small, 26 October 2014, *Nature Neuroscience*.
DOI: 10.1038/nn.3850

Rapid Mental Rejuvenation: Experimental Drug Reverses Age-Related Cognitive Decline Within Days

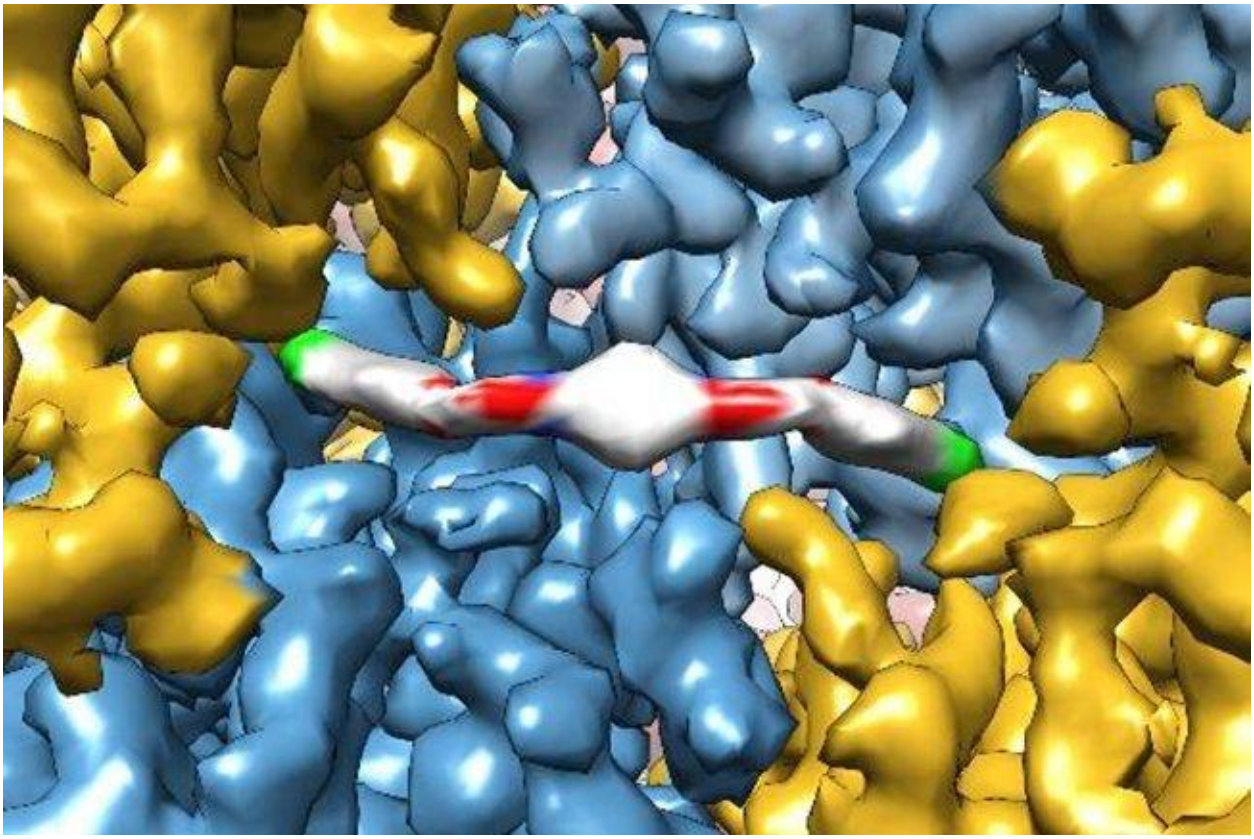
The researchers demonstrated a swift rejuvenation of youthful cognitive abilities in elderly mice, coupled with a revitalization of both brain and immune cells.

Rapid mental rejuvenation in old mice suggests age-related losses may be broadly reversible.

Just a few doses of an experimental drug can reverse age-related declines in memory and mental flexibility in mice, according to a new study by UC San Francisco scientists. The drug, called ISRIB, has already been shown in laboratory studies to restore memory function months after traumatic brain injury (TBI), reverse cognitive impairments in Down Syndrome, prevent noise-related hearing loss, fight certain types of prostate cancer, and even enhance cognition in healthy animals.

In the new study, published on December 1, 2020, in the open-access journal *eLife*, researchers showed rapid restoration of youthful cognitive abilities in aged mice,

accompanied by a rejuvenation of brain and immune cells that could help explain improvements in brain function.



A cryo-electron microscope rendering of an ISRIB molecule. Credit: Adam Frost lab

“ISRIB’s extremely rapid effects show for the first time that a significant component of age-related cognitive losses may be caused by a kind of reversible physiological “blockage” rather than more permanent degradation,” said Susanna Rosi, PhD, Lewis and Ruth Cozen Chair II and professor in the departments of Neurological Surgery and of Physical Therapy and Rehabilitation Science.

“The data suggest that the aged brain has not permanently lost essential cognitive capacities, as was commonly assumed, but rather that these cognitive resources are still there but have been somehow blocked, trapped by a vicious cycle of cellular stress,” added Peter Walter, PhD, a professor in the UCSF Department of Biochemistry and Biophysics and a Howard Hughes Medical Institute investigator. “Our work with ISRIB demonstrates a way to break that cycle and restore cognitive abilities that had become walled off over time.”

Could Rebooting Cellular Protein Production Hold the Key to Aging and Other Diseases?

Walter has won numerous scientific awards, including the Breakthrough, Lasker, and Shaw prizes, for his decades-long studies of cellular stress responses. ISRIB, discovered in 2013 in Walter's lab, works by rebooting cells' protein production machinery after it gets throttled by one of these stress responses – a cellular quality control mechanism called the integrated stress response (ISR; ISRIB stands for ISR InhiBitor).

The ISR normally detects problems with protein production in a cell — a potential sign of viral infection or cancer-promoting gene mutations — and responds by putting the brakes on cell's protein-synthesis machinery. This safety mechanism is critical for weeding out misbehaving cells, but if stuck in the on position in a tissue like the brain, it can lead to serious problems, as cells lose the ability to perform their normal activities, Walter and colleagues have found.

In particular, recent animal studies by Walter and Rosi, made possible by early philanthropic support from The Rogers Family Foundation, have implicated chronic ISR activation in the persistent cognitive and behavioral deficits seen in patients after TBI, by showing that, in mice, brief ISRIB treatment can reboot the ISR and restore normal brain function almost overnight.

The cognitive deficits in TBI patients are often likened to premature aging, which led Rosi and Walter to wonder if the ISR could also underlie purely age-related cognitive decline. Aging is well known to compromise cellular protein production across the body, as life's many insults pile up and stressors like chronic inflammation wear away at cells, potentially leading to widespread activation of the ISR.

"We've seen how ISRIB restores cognition in animals with traumatic brain injury, which in many ways is like a sped-up version of age-related cognitive decline," said Rosi, who is director of neurocognitive research in the UCSF Brain and Spinal Injury Center and a member of the UCSF Weill Institute for Neurosciences. "It may seem like a crazy idea, but asking whether the drug could reverse symptoms of aging itself was just a logical next step."

Improves Cognition, Boosts Neuron and Immune Cell Function

In the new study, researchers led by Rosi lab postdoc Karen Krukowski, PhD, trained aged animals to escape from a watery maze by finding a hidden platform, a task that is typically hard for older animals to learn. But animals who received small daily doses of ISRIB during the three-day training process were able to accomplish the task as well as youthful mice, much better than animals of the same age who didn't receive the drug.

The researchers then tested how long this cognitive rejuvenation lasted and whether it could generalize to other cognitive skills. Several weeks after the initial ISRIB treatment, they trained the same mice to find their way out of a maze whose exit changed daily – a test of mental flexibility for aged mice who, like humans, tend to get increasingly stuck in

their ways. The mice who had received brief ISRIB treatment three weeks before still performed at youthful levels, while untreated mice continued to struggle.

To understand how ISRIB might be improving brain function, the researchers studied the activity and anatomy of cells in the hippocampus, a brain region with a key role in learning and memory, just one day after giving animals a single dose of ISRIB. They found that common signatures of neuronal aging disappeared literally overnight: neurons' electrical activity became more sprightly and responsive to stimulation, and cells showed more robust connectivity with cells around them while also showing an ability to form stable connections with one another usually only seen in younger mice.

The researchers are continuing to study exactly how the ISR disrupts cognition in aging and other conditions and to understand how long ISRIB's cognitive benefits may last. Among other puzzles raised by the new findings is the discovery that ISRIB also alters the function of the immune system's T cells, which also are prone to age-related dysfunction. The findings suggest another path by which the drug could be improving cognition in aged animals, and could have implications for diseases from Alzheimer's to diabetes that have been linked to heightened inflammation caused by an aging immune system.

"This was very exciting to me because we know that aging has a profound and persistent effect on T cells and that these changes can affect brain function in the hippocampus," said Rosi. "At the moment, this is just an interesting observation, but it gives us a very exciting set of biological puzzles to solve."

Broad Effects Exemplify 'Serendipity' of Basic Research

Rosi and Walter were introduced by neuroscientist Regis Kelly, PhD, executive director of the University of California's QB3 biotech innovation hub, following Walter's 2013 study showing that the drug seemed to instantly enhance cognitive abilities in healthy mice. To Rosi, the results from that study implied some walled-off cognitive potential in the brain that the molecule was somehow unlocking, and she wondered if this extra cognitive boost might benefit patients with neurological damage from traumatic brain injury.

The labs joined forces to study the question in mice, and were astounded by what they found. ISRIB didn't just make up for some of the cognitive deficits in mice with traumatic brain injury – it erased them. "This had never been seen before," Rosi said. "The mantra in the field was that brain damage is permanent – irreversible. How could a single treatment with a small molecule make them disappear overnight?"

Further studies demonstrated that neurons throughout the brains of animals with traumatic brain injury are thoroughly jammed up by the ISR. Using ISRIB to release those brakes lets brain cells immediately get back to their normal business. More recently, studies in animals with very mild repetitive brain injury – akin to pro athletes who experience many mild concussions over many years – showed that ISRIB could

reverse increased risk-taking behavior associated with damage to self-control circuits in the frontal cortex.

“Added to this, Karen’s new results in aging mice are just amazing. It’s not often that you find a drug candidate that shows so much potential and promise,” Walter added. “This project also shows the power of the UCSF community – Susanna and I didn’t know each other and were living in different worlds until Regis Kelly brought us together, making this powerful connection that neither of us had realized before.”

“Amazing breakthroughs like this need more than the brilliance and experimental skills of Susanna and Peter,” said Kelly. “They also need donors like the Rogers Family Foundation willing to bridge the gap between great basic research and products that could be highly beneficial to society.”

ISRIB has been licensed by Calico, a South San Francisco, California company exploring the biology of aging, and the idea of targeting the ISR to treat disease has been picked up by many other pharmaceutical companies, Walter says.

One might think that interfering with the ISR, a critical cellular safety mechanism, would be sure to have serious side effects, but so far in all their studies, the researchers have observed none. This is likely due to two factors, Walter says. First, it takes just a few doses of ISRIB to reset unhealthy, chronic ISR activation back to a healthier state, after which it can still respond normally to problems in individual cells. Second, ISRIB has virtually no effect when applied to cells actively employing the ISR in its most powerful form – against an aggressive viral infection, for example.

Naturally, both of these factors make the molecule much less likely to have negative side effects – and more attractive as a potential therapeutic. “It almost seems too good to be true, but with ISRIB we seem to have hit a sweet spot for manipulating the ISR with an ideal therapeutic window,” Walter said.

Reference: “Small molecule cognitive enhancer reverses age-related memory decline in mice” by Karen Krukowski, Amber Nolan, Elma S Frias, Morgane Boone, Gonzalo Ureta, Katherine Grue, Maria-Serena Paladini, Edward Elizarraras, Luz Delgado, Sebastian Bernales, Peter Walter and Susanna Rosi, 1 December 2020, *eLife*.
DOI: 10.7554/eLife.62048

Authors: Other authors on the study were Amber Nolan, Elma S. Frias, Morgane Boone, Katherine Grue, Maria-Serena Paladini, and Edward Elizarraras of UCSF; and Gonzalo Ureta, Luz Delgado, and Sebastian Bernales of Fundación Ciencia & Vida in Santiago, Chile. Bernales is also an employee of Praxis Biotech, LLC.

Funding: The study was supported by continued generous support of the Rogers Family Foundation, as well as the UCSF Weill Innovation Award, the U.S. National Institutes of Health (NIH R01AG056770), National Institute on Aging (NIA F32AG054126); National Center for Advancing Translational Sciences (NCATS TL1 TR001871); ANID Project

AFB 170004; National Institute of Neurological Disorders and Stroke (NINDS K08NS114170) and the Howard Hughes Medical Institute (HHMI).

Disclosures: Gonzalo Ureta works at Fundacion Ciencia & Vida and receives partial funding from Praxis Biotech. Sebastian Bernales is an employee of Praxis Biotech. Peter Walter is an inventor on U.S. Patent 9708247 held by the Regents of the University of California that describes ISRIB and its analogs. Rights to the invention have been licensed by UCSF to Calico.

Turning Back the Biological Clock With Antioxidant Supplements

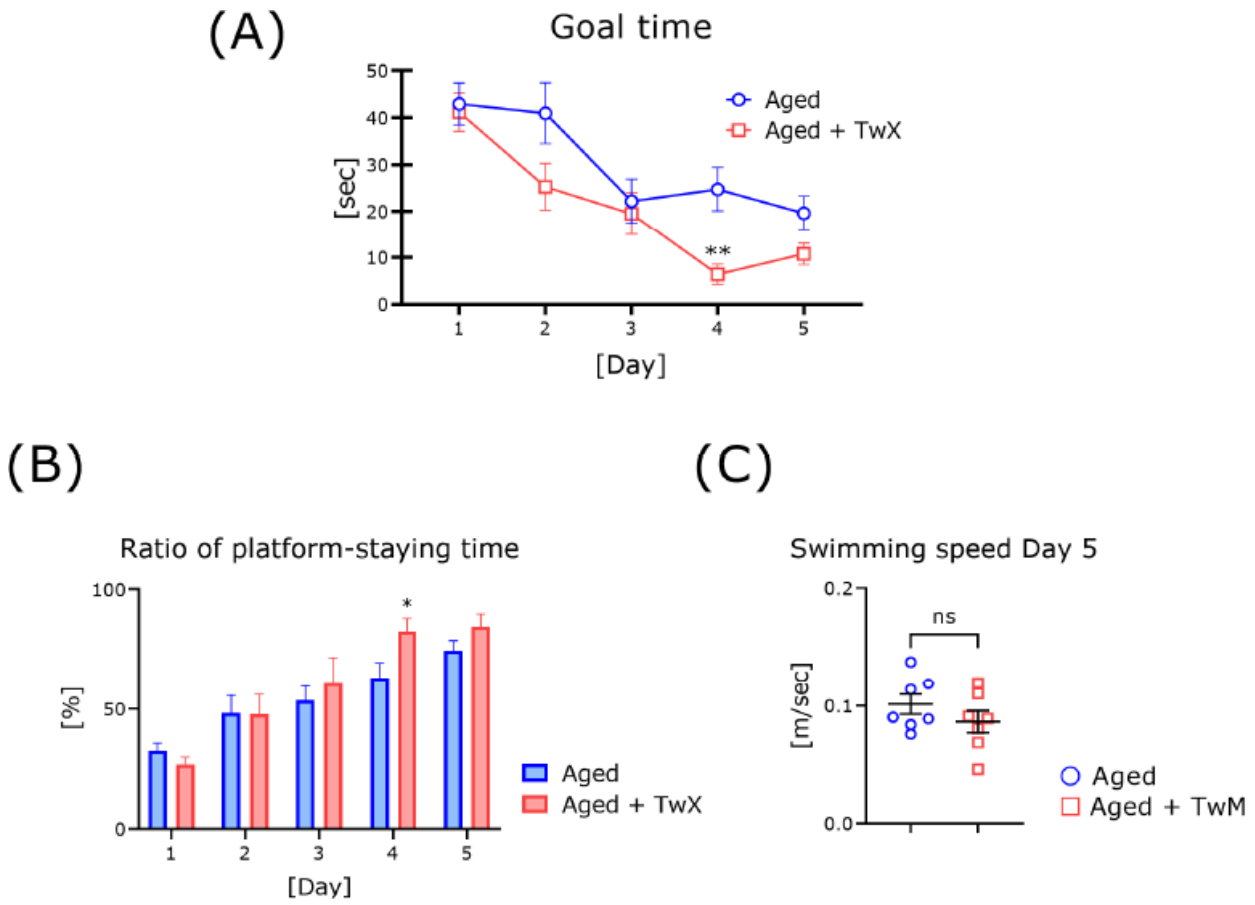
Scientists find that mice administered with blended antioxidant supplement showed significant improvements in spatial cognition, short-term memory, and muscle durability.

Age-related decline in cognitive and muscle function continues to be a significant challenge for the field of healthcare. Healthcare costs associated with treating age-related cognitive decline and muscle weakness are expected to increase substantially in the future. One of the primary underlying mechanisms responsible for age-related health decline is oxidative stress, which refers to the progressive damage inflicted by oxygen-free radicals on cells.

The Role of Antioxidants

Certain compounds in foods, known as antioxidants, are capable of neutralizing oxygen-free radicals. Consuming antioxidant-rich foods is known to reduce cell damage and slow down age-related health decline. In the absence of an antioxidant-rich diet, people often turn to antioxidant supplements that offer comparable or greater health protection.

Now, a team of scientists, led by Professor Koji Fukui affiliated with the Shibaura Institute of Technology (SIT) and including Dr. Fukka You from Gifu University found that administering a blended mix of antioxidant supplements to aged mice significantly improves their spatial cognition, short-term memory, and muscle durability. The paper was published in the Special Issue ‘Antioxidants in health and diseases’ of the *International Journal of Molecular Sciences*.



Administration of Twendee X (TwX) improves spatial learning ability in aged mice. The average goal time (escape latency) in the spatial cognition test is shown in (A). The percentage of time spent in the quadrant is shown in (B). The average swimming speed on Day 5 of the experiment is shown in (C). Credit: Koji Fukui from SIT, Japan

Research Findings and Implications

“In this study, significant improvements were observed in the spatial learning ability and short-term memory in supplement-treated aged mice. Long-term intake of blended antioxidant supplements may be effective, even considering the effects of aging and related increased oxidation in the body,” explains Prof. Fukui, the lead researcher of the study. Memory loss is associated with several debilitating diseases, such as Alzheimer’s, which disproportionately affect older people. The discovery that blended antioxidant supplements improve memory in mice suggests that they may also be beneficial in preventing memory loss in humans.

Sarcopenia, another age-related disease, results in a progressive loss of muscle strength in older individuals. This condition significantly affects people’s mobility, often leading to social isolation. Moreover, sarcopenia can increase the risk of developing cognitive disorders. If blended antioxidant supplements can enhance muscle strength in

mice, they may also hold the potential for mitigating muscle frailty and sarcopenia in humans.

“Frailty and sarcopenia are now serious problems and potent risk factors for dementia. Although the mechanism is unknown, it is groundbreaking that taking supplements may be able to prevent muscle weakness,” notes Prof. Fukui.

Challenges in Antioxidant Supplement Use

Numerous types of antioxidant supplements are available in the market, and determining the right supplements to buy can often be challenging for consumers. The results of this groundbreaking study by Professor Fukui and his colleagues support the use of blended antioxidant supplements to prevent age-related health decline. However, further research is necessary to establish the efficacy and safety of blended antioxidant supplements in humans. Moreover, specific antioxidant blends may have varying effects on the human body, and their use should be ideally based on clinical evidence. The antioxidant blend used in the study was Twendee X, which has a similar composition to the commercially available supplement Oxycut®.

“Although many types of antioxidant supplements are available, the effect is greater if multiple types are taken simultaneously rather than one type. However, it is difficult to know which type and how much to take, as it is possible to take too many of some vitamins,” Prof. Fukui observes. “We recommend only taking multivitamins that are guaranteed to be safe,” he cautions.

Future Directions in Antioxidant Research

Besides choosing the right antioxidant supplement, adopting the right regimen can also confuse consumers. Future research on the individual differences in the effects of antioxidants can reduce confusion around the optimum dose and composition of antioxidant supplements. Over the long term, optimal use of antioxidant supplements may significantly reduce age-related health decline. “In the future, there will come a time when we will provide multi-supplements tailored to each individual. There will be no need to worry about overdosing,” concludes Prof. Fukui.

Reference: “A Blended Vitamin Supplement Improves Spatial Cognitive and Short-Term Memory in Aged Mice” by Koji Fukui, Fukka You, Yugo Kato, Shuya Yuzawa, Ayuta Kishimoto, Takuma Hara, Yuki Kanome, Yoshiaki Harakawa and Toshikazu Yoshikawa, 27 February 2024, *International Journal of Molecular Sciences*.
DOI: 10.3390/ijms25052804

Natural Mineral May Reverse Memory Loss and Boost Learning

Selenium is a mineral found in foods including meat, grains, and nuts.

Selenium – a mineral found in many foods – could reverse the cognitive impact of stroke and boost learning and memory in aging brains, according to University of Queensland research.

Queensland Brain Institute (QBI) lead researcher Dr. Tara Walker said studies on the impact of exercise on the aging brain found levels of a protein key to transporting selenium in the blood were elevated by physical activity.

“We’ve known for the last 20 years that exercise can create new neurons in the brain, but we didn’t really understand how,” Dr. Walker said.

Boosting Neuron Generation with Selenium Supplements

The research team investigated whether dietary selenium supplements could replicate the effects of exercise.

“Our models showed that selenium supplementation could increase neuron generation and improve cognition in elderly mice,” Dr. Walker said.

“The levels of new neuron generation decrease rapidly in aged mice, as they do in humans.

“When selenium supplements were given to the mice, the production of neurons increased, reversing the cognitive deficits observed in aging.”

Selenium is an essential trace mineral absorbed from soil and water and is found in foods such as grains, meat, and nuts, with the highest levels found in Brazil nuts.

Impact of Selenium on Post-Stroke Cognitive Decline

The scientists also tested whether selenium would have an impact on the cognitive decline sometimes experienced following stroke, which can affect people’s memory and ability to learn.

“Young mice are really good at the learning and memory tasks, but after a stroke, they could no longer perform these tasks,” Dr. Walker said.

“We found that learning and memory deficits of stroke-affected mice returned to normal when they were given selenium supplements.”

Dr. Walker said the results opened a new therapeutic avenue to boost cognitive function in people who were unable to exercise due to poor health or old age.

“However, selenium supplements shouldn’t be seen as a complete substitute for exercise, and too much can be bad for you,” she said.

“A person who is getting a balanced diet of fruits, nuts, veggies, and meat usually has good selenium levels.

“But in older people, particularly those with neurological conditions, selenium supplements could be beneficial.”

The research was first published in *Cell Metabolism*.

Reference: “Selenium mediates exercise-induced adult neurogenesis and reverses learning deficits induced by hippocampal injury and aging” by Odette Leiter, Zhan Zhuo, Ruslan Rust, Joanna M. Wasielewska, Lisa Grönnert, Susann Kowal, Rupert W. Overall, Vijay S. Adusumilli, Daniel G. Blackmore, Adam Southon, Katherine Ganio, Christopher A. McDevitt, Nicole Rund, David Brici, Imesh Aththanayake Mudiyan, Alexander M. Sykes, Annette E. Rünker, Sara Zocher, Scott Ayton, Ashley I. Bush, Perry F. Bartlett, Sheng-Tao Hou, Gerd Kempermann and Tara L. Walker, 3 February 2022, *Cell Metabolism*.
DOI: 10.1016/j.cmet.2022.01.005

Experimental Alzheimer’s Drug J147 Shows Anti-Aging Effects

New research from the Salk Institute shows that the experimental Alzheimer’s drug J147 has a host of unexpected anti-aging effects in animals.

The Salk team expanded upon their previous development of a drug candidate, called J147, which takes a different tack by targeting Alzheimer’s major risk factor–old age. In the new work, the team showed that the drug candidate worked well in a mouse model of aging not typically used in Alzheimer’s research. When these mice were treated with J147, they had better memory and cognition, healthier blood vessels in the brain, and other improved physiological features, as detailed November 12, 2015 in the journal Aging.

“Initially, the impetus was to test this drug in a novel animal model that was more similar to 99 percent of Alzheimer’s cases,” says Antonio Currais, the lead author and a member of Professor David Schubert’s Cellular Neurobiology Laboratory at Salk. “We

did not predict we'd see this sort of anti-aging effect, but J147 made old mice look like they were young, based upon a number of physiological parameters."

Alzheimer's disease is a progressive brain disorder, recently ranked as the third leading cause of death in the United States and affecting more than five million Americans. It is also the most common cause of dementia in older adults, according to the National Institutes of Health. While most drugs developed in the past 20 years target the amyloid plaque deposits in the brain (which are a hallmark of the disease), few have proven effective in the clinic.

"While most drugs developed in the past 20 years target the amyloid plaque deposits in the brain (which are a hallmark of the disease), none have proven effective in the clinic," says Schubert, senior author of the study.

Several years ago, Schubert and his colleagues began to approach the treatment of the disease from a new angle. Rather than target amyloid, the lab decided to zero in on the major risk factor for the disease–old age. Using cell-based screens against old age-associated brain toxicities, they synthesized J147.

Previously, the team found that J147 could prevent and even reverse memory loss and Alzheimer's pathology in mice that have a version of the inherited form of Alzheimer's, the most commonly used mouse model. However, this form of the disease comprises only about 1 percent of Alzheimer's cases. For everyone else, old age is the primary risk factor, says Schubert. The team wanted to explore the effects of the drug candidate on a breed of mice that age rapidly and experience a version of dementia that more closely resembles the age-related human disorder.

In this latest work, the researchers used a comprehensive set of assays to measure the expression of all genes in the brain, as well as over 500 small molecules involved with metabolism in the brains and blood of three groups of rapidly aging mice. The three groups of rapidly aging mice included one set that was young, one set that was old, and one set that was old but fed J147 as they aged.

The old mice that received J147 performed better on memory and other tests for cognition and also displayed more robust motor movements. The mice treated with J147 also had fewer pathological signs of Alzheimer's in their brains. Importantly, because of the large amount of data collected on the three groups of mice, it was possible to demonstrate that many aspects of gene expression and metabolism in the old mice fed J147 were very similar to those of young animals. These included markers for increased energy metabolism, reduced brain inflammation, and reduced levels of oxidized fatty acids in the brain.

Another notable effect was that J147 prevented the leakage of blood from the microvessels in the brains of old mice. "Damaged blood vessels are a common feature of aging in general, and in Alzheimer's, it is frequently much worse," says Currais.

Currais and Schubert note that while these studies represent a new and exciting approach to Alzheimer's drug discovery and animal testing in the context of aging, the only way to demonstrate the clinical relevance of the work is to move J147 into human clinical trials for Alzheimer's disease.

"If proven safe and effective for Alzheimer's, the apparent anti-aging effect of J147 would be a welcome benefit," adds Schubert. The team aims to begin human trials next year.

Other authors on the paper include Oswald Quehenberger of the University of California, San Diego; and Joshua Goldberg, Catherine Farrokhi, Max Chang, Marguerite Prior, Richard Dargusch, Daniel Daugherty, and Pamela Maher of the Salk Institute.

This study was supported by the Salk Institute Pioneer Fund Postdoctoral Scholar Award and the Salk Nomis Fellowship Award, fellowships from the Hewitt Foundation and Bundy Foundation, and grants from the Burns Foundation and NIH.

Salk has an issued patent on J147 licensed to Abrexa Pharmaceuticals.

Reference: "A comprehensive multiomics approach toward understanding the relationship between aging and dementia" by Antonio Currais, Joshua Goldberg, Catherine Farrokhi, Max Chang, Marguerite Prior, Richard Dargusch, Daniel Daugherty, Aaron Armando, Oswald Quehenberger, Pamela Maher and David Schubert, 11 November 2015, *Aging*.
DOI: 10.18632/aging.100838

New Synthetic Process Provides a Better View of Diabetes, Inflammation, and Human Aging

Yale University has devised a synthetic process enabling scientists to examine a pivotal molecule implicated in diabetes, inflammation, and human aging. Credit: Yale University

In a newly published research study, scientists describe the new synthesis, as well as a new synthetic methodology, that offers a better glimpse into diabetes and the aging process.

A synthetic process developed at Yale University will allow scientists to study a key molecule involved in diabetes, inflammation, and human aging.

The new process synthesizes glucosepane, which is considered a critical chemical link in both diabetes and aging. It is also an independent risk factor for long-term microvascular complications in diabetes.

“Glucosepane forms in all human beings during the aging process, and also forms during various diseases, including diabetes,” said Spiegel, a professor of chemistry and pharmacology at Yale. “It is unknown what role glucosepane might play in aging and in these diseases, but several hypotheses have been proposed. With access to synthetic glucosepane, we will now be able to generate tools to examine the role this molecule plays in human health and also, perhaps, develop molecules to inhibit or reverse its formation.”

Until now, it has been difficult to study glucosepane effectively. There is a scarcity of chemically homogeneous glucosepane available for scientists to examine — due to its unusual structure and properties — and researchers have been forced to rely on time-consuming extraction protocols to obtain usable material.

Glucosepane contains a rare isomer of imidazole, which has never before been observed in natural molecules, other than those in the glucosepane family. Spiegel and his colleagues developed a new methodology for synthesizing this imidazole form. The process requires only eight steps.

In an accompanying article in Science, Dale L. Boger of the Scripps Research Institute wrote that the Yale study represents “an important, yet largely underexplored, frontier for chemistry with broad implications in human health.” Boger said Spiegel’s methodology “is important in its own right and will find applications well beyond that envisioned by the authors.”

Reference: “Concise total synthesis of glucosepane” by Cristian Draghici, Tina Wang and David A. Spiegel, 16 October 2015, *Science*.
DOI: 10.1126/science.aac9655

The first author of the study is Cristian Draghici, a former postdoctoral researcher at Yale who is now at the Broad Institute of MIT and Harvard. Tina Wang, a former Ph.D. student at Yale who is now at Harvard, is the other co-author.

The work was supported by the SENS Research Foundation, a non-profit organization devoted to research and treatment of age-related diseases that emphasizes a damage repair approach to the diseases of aging.

Study Shows Calorie-Restricting Diets Slow Aging

Research out of NYU Langone Medical Center shows that a low-calorie regimen influences brain gene expression as female mice age.

Neuroscientists show that calorie-reduced diets stop the normal rise and fall in activity levels of close to 900 different genes linked to aging and memory formation in mice.

The adage ‘you are what you eat’ has been around for years. Now, important new research provides another reason to be careful with your calories.

In a presentation prepared for the Society for Neuroscience annual meeting in Washington, D.C., on November 17, researchers say their experimental results, conducted in female mice, suggest how diets with fewer calories derived from carbohydrates likely deter some aspects of aging and chronic diseases in mammals, including humans.

“Our study shows how calorie restriction practically arrests gene expression levels involved in the aging phenotype — how some genes determine the behavior of mice, people, and other mammals as they get old,” says senior study investigator and NYU Langone neuroscientist, Stephen D. Ginsberg, PhD. Ginsberg cautions that the study does not mean calorie restriction is the “fountain of youth,” but that it does “add evidence for the role of diet in delaying the effects of aging and age-related disease.”

While restrictive dietary regimens have been well-known for decades to prolong the lives of rodents and other mammals, their effects in humans have not been well understood. Benefits of these diets have been touted to include reduced risk of human heart disease, hypertension, and stroke, Ginsberg notes, but the widespread genetic impact on the memory and learning regions of aging brains has not before been shown. Previous studies, he notes, have only assessed the dietary impact on one or two genes at a time, but his analysis encompassed more than 10,000 genes.

Ginsberg, an associate professor at NYU Langone and its affiliated Nathan S. Kline Institute for Psychiatric Research, says the research “widens the door to further study into calorie restriction and anti-aging genetics.”

For the study, female mice, which like people are more prone to dementia than males, were fed food pellets that had 30 percent fewer calories than those fed to other mice. Tissue analyses of the hippocampal region, an area of the brain affected earliest in Alzheimer’s disease, were performed on mice in middle and late adulthood to assess any difference in gene expression over time.

Funding support for the study was provided primarily by the US National Institutes of Health. Corresponding federal grant numbers are RR029893, TR000038, GM007238, R01 AG043375, P01 AG014449, and P01 AG017617. Additional funding support was provided by Alzheimer’s Association grant IIRG-12-237253.

Besides Ginsberg, other NYU Langone researchers involved in these experiments were lead study investigator Marissa Schafer, PhD; and co-investigators Igor Dolgalev, MS, and Adriana Heguy, PhD.

Simple & Free: Scientists Find What Enhances Your Immune System and Helps You Live Longer

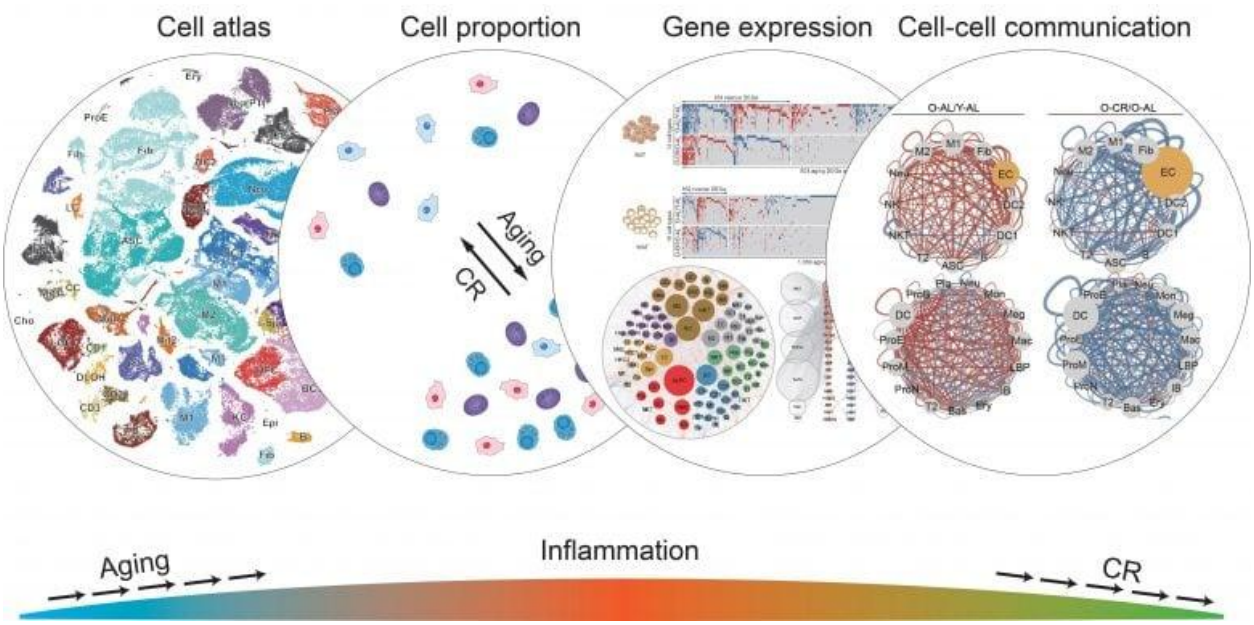
New study that provides the most detailed report to date of the cellular effects of a calorie-restricted diet in rats concludes that eating less food will enhance your immune system, reduce levels of inflammation throughout your body, delay the onset of age-related diseases, and help you live longer.

If you want to enhance your immune system, reduce levels of inflammation throughout your body, delay the onset of age-related diseases, and live longer — eat less food. That's the conclusion of a new study by scientists from the US and China that provides the most detailed report to date of the cellular effects of a calorie-restricted diet in rats. While the benefits of caloric restriction have long been known, the new results show how this restriction can protect against aging in cellular pathways, as detailed in *Cell* on February 27, 2020.

"We already knew that calorie restriction increases life span, but now we've shown all the changes that occur at a single-cell level to cause that," says Juan Carlos Izpisua Belmonte, a senior author of the new paper, professor in Salk's Gene Expression Laboratory and holder of the Roger Guillemin Chair. "This gives us targets that we may eventually be able to act on with drugs to treat aging in humans."

Aging is the highest risk factor for many human diseases, including cancer, dementia, diabetes, and metabolic syndrome. Caloric restriction has been shown in animal models to be one of the most effective interventions against these age-related diseases. And although researchers know that individual cells undergo many changes as an organism ages, they have not known how caloric restriction might influence these changes.

In the new paper, Belmonte and his collaborators — including three alumni of his Salk lab who are now professors running their own research programs in China — compared rats who ate 30 percent fewer calories with rats on normal diets. The animals' diets were controlled from age 18 months through 27 months. (In humans, this would be roughly equivalent to someone following a calorie-restricted diet from age 50 through 70.)



The illustration represents the ways in which caloric restriction affects various aspects of cellular function, with the overall result of reducing inflammation and the activity of many aging-related genes. Credit: Salk Institute

At both the start and the conclusion of the diet, Belmonte's team isolated and analyzed a total of 168,703 cells from 40 cell types in the 56 rats. The cells came from fat tissues, liver, kidney, aorta, skin, bone marrow, brain, and muscle. In each isolated cell, the researchers used single-cell genetic-sequencing technology to measure the activity levels of genes. They also looked at the overall composition of cell types within any given tissue. Then, they compared old and young mice on each diet.

Many of the changes that occurred as rats on the normal diet grew older didn't occur in rats on a restricted diet; even in old age, many of the tissues and cells of animals on the diet closely resembled those of young rats. Overall, 57 percent of the age-related changes in cell composition seen in the tissues of rats on a normal diet were not present in the rats on the calorie-restricted diet.

"This approach not only told us the effect of calorie restriction on these cell types, but also provided the most complete and detailed study of what happens at a single-cell level during aging," says co-corresponding author Guang-Hui Liu, a professor at the Chinese Academy of Sciences.

Some of the cells and genes most affected by the diet are related to immunity, inflammation, and lipid metabolism. The number of immune cells in nearly every tissue studied dramatically increased as control rats aged but were not affected by age in rats with restricted calories. In brown adipose tissue — one type of fat tissue — a calorie-restricted diet reverted the expression levels of many anti-inflammatory genes to those seen in young animals.

“The primary discovery in the current study is that the increase in the inflammatory response during aging could be systematically repressed by caloric restriction,” says co-corresponding author Jing Qu, also a professor at the Chinese Academy of Sciences.

When the researchers homed in on transcription factors — essentially master switches that can broadly alter the activity of many other genes — that were altered by caloric restriction, one stood out. Levels of the transcription factor Ybx1 were altered by the diet in 23 different cell types. The scientists believe Ybx1 may be an age-related transcription factor and are planning more research into its effects.

“People say that ‘you are what you eat,’ and we’re finding that to be true in lots of ways,” says Concepcion Rodriguez Esteban, another of the paper’s authors and a staff researcher at Salk. “The state of your cells as you age clearly depends on your interactions with your environment, which includes what and how much you eat.”

The team is now trying to utilize this information in an effort to discover aging drug targets and implement strategies toward increasing life and health span.

Reference: “Caloric Restriction Reprograms the Single-Cell Transcriptional Landscape of *Rattus Norvegicus* Aging” by Shuai Ma, Shuhui Sun, Lingling Geng, Moshi Song, Wei Wang, Yanxia Ye, Qianzhao Ji, Zhiran Zou, Si Wang, Xiaojuan He, Wei Li, Concepcion Rodriguez Esteban, Xiao Long, Guoji Guo, Piu Chan, Qi Zhou, Juan Carlos Izpisua Belmonte, Weiqi Zhang, Jing Qu and Guang-Hui Liu, 27 February 2020, *Cell*.
DOI: 10.1016/j.cell.2020.02.008

Other researchers on the study were Shuai Ma, Shuhui Sun, Lingling Geng, Moshi Song, Wei Wang, Yanxia Ye, Qianzhao Ji, Zhiran Zou, Si Wang, and Qi Zhou of the Chinese Academy of Sciences; Xiaojuan He, Wei Li, Piu Chan and Weiqi Zhang of Xuanwu Hospital Capital Medical University; Xiao Long of Peking Union Medical College Hospital; and Guoji Guo of Zhejiang University School of Medicine.

The work and researchers involved were supported by grants from the National Key Research and Development Program of China, the Strategic Priority Research Program of the Chinese Academy of Sciences, the National Natural Science Foundation of China, Beijing Natural Science Foundation, Beijing Municipal Commission of Health and Family Planning, Advanced Innovation Center for Human Brain Protection, the State Key Laboratory of Membrane Biology, the Moxie Foundation, and the Glenn Foundation.

Can a Mediterranean Diet Pattern Slow Aging?

A series of six articles in The Journals of Gerontology finds new connections between the Mediterranean diet and healthy aging outcomes. The articles report on the diet's underlying mechanisms, its positive impact on physical and cognitive function, the benefits of taking coenzyme Q10 supplements alongside the diet, and its role in reducing inflammation. However, the studies also emphasize that the level of benefit depends on the method used to measure adherence to the diet.

A series of six articles appearing in the March issue of *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* finds new correlations between a Mediterranean diet and healthy aging outcomes — while also underscoring the need for careful approaches to the use of data in order to measure the diet's potential benefits.

Among their findings, the new articles report on the underlying mechanisms of the diet; the positive relationship between the diet and physical and cognitive function; the value of taking a coenzyme Q10 supplement while adhering to the diet; and the role of the diet in reducing inflammation. But in several of the studies, the level of benefit was dependent on how adherence to the diet was measured.

"Greater clarity on how this diet is defined, in both interventions and observational studies, will be critical in the aim of achieving a consensus on how to optimally apply this dietary pattern towards maximizing healthy aging," state Michelle A. Mendez, Ph.D., and *Journals of Gerontology: Medical Sciences* Editor-in-Chief Anne B. Newman, MD, FGSA, in an opening editorial.

Hallmarks of the Mediterranean diet include: a variety of minimally processed whole grains and legumes as the staple food; plenty of a huge diversity of fresh vegetables consumed on a daily basis; fresh fruits as the typical daily dessert; cold-pressed extra-virgin olive oil, nuts, and seeds as the principal source of fat; moderate consumption of fish; dairy products consumed in low amounts; red and processed meat consumed in very low frequency and amounts; and wine consumed in low to moderate amounts only with meals.

There are a number of scales used to measure adherence to the diet. One of the journal's studies, conducted by researchers at the University of Paris 13, found that among test subjects, higher numbers on the Literature-based Adherence Score to the Mediterranean Diet were associated with higher odds of meeting certain healthy aging criteria. Similar results were found with another index, the Mediterranean Diet Score; however, use of the Mediterranean Diet Scale yielded a weaker correlation. In another study by researchers at the Autonomous University of Madrid, closer adherence to the diet was associated with a lower likelihood of physical function impairment in older adults, although in this case using the Mediterranean Diet Adherence Screener provided more significant results than the Mediterranean Diet Score.

The exact mechanism by which an increased adherence to the diet exerts its favorable effects is still unknown to scientists. However, writing in one of the new articles, researchers from Washington University in St. Louis state there is accumulating evidence of five important adaptations induced by the Mediterranean dietary pattern. These include lipid lowering; protection from oxidative stress and inflammation; modification of growth factors that can promote cancer; inhibition of nutrient sensing pathways by amino acid restriction and gut microbiota-mediated production of metabolites.

Publication:

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Ancient Viruses in Your DNA May Predict How Fast You Age, Study Finds

Researchers at Weill Cornell Medicine and TruDiagnostic have identified DNA markers from retroelements that act as accurate epigenetic clocks, predicting biological age and potentially influencing aging. The study suggests that retroelements may be fundamental to aging and could inform new treatments for age-related diseases. Credit: SciTechDaily.com

Scientists have created the "Retro-Age" clock using ancient viral DNA markers to predict biological age, offering new insights into aging. This discovery could lead to novel anti-aging therapies.

Researchers at Weill Cornell Medicine, in collaboration with the epigenetics company TruDiagnostic, have identified DNA markers linked to retroelements—ancient viral genetic remnants in our genes—that serve as highly precise epigenetic clocks for predicting chronological age. These findings suggest that specific retroelements within the human genome could play a role in the aging process.

Retroelements have been known to impact gene regulation, gene expression, genomic stability, and the trajectory of various human diseases, but their potential as biomarkers for aging had been largely unexplored.

The study, published in the journal *Aging Cell*, concluded that these retroelement clocks embedded in the human genome capture unique signals of aging not previously recognized by other clocks that measure chronological age. Most aging clocks estimate

a person's biological age based on patterns of epigenetic markers—chemical tags called methyl groups that are attached to DNA and affect how genes are expressed. The pattern of methylation on retroelements seems to change as people age causing some genes to be more active which may lead to genomic instability, inflammation, and age-related diseases.

Aging is a complex process influenced by genetic, environmental, and epigenetic factors, with researchers pursuing reliable markers that can predict biological age—a snapshot of a person's age at the biochemical level which impacts health and overall well-being. On the other hand, chronological age represents the number of years a person has lived. Depending on the individual, the two may not correlate.

Building an Aging Clock Based on Retroelements

Researchers used a machine learning model from TruDiagnostic to analyze epigenetic data from 12,670 individuals with ages ranging from 12 to 100. Using the resulting DNA methylation patterns of retroelements, specifically human endogenous retrovirus (HERV) and long interspersed nuclear element (LINEs), they developed a composite retroelement-Age clock called "Retro-Age."

"Now, with Retro-Age, we have greater insight and a fresh perspective into the aging process and a potentially powerful tool to predict biological age," said first author Dr. Lishomwa Ndhlovu, the Herbert J. and Ann L. Siegel Distinguished Professor of Medicine and professor of immunology in medicine in the Division of Infectious Diseases at Weill Cornell Medicine.

The researchers found that the Retro-Age clock remained accurate when testing various human tissues, complemented existing epigenetic clocks, and even extended to other mammalian species. Their findings point to the possibility that retroelement activity might be a fundamental aspect of aging across different species.

Turning Back the Clock—Impact of Environmental Factors

The researchers also found that the DNA methylation patterns they observed were not only predictive of age but also responsive to outside factors like antiretroviral therapy taken by people living with HIV. HIV infection accelerates epigenetic aging, while antiretroviral therapy appears to reverse the clock to some degree. This suggests that retroelement activity is influenced by both the infection and its treatment, affecting the biological aging process in people living with HIV.

"The reactivation of specific retroelements increases with age, potentially leading to biological hallmarks of aging such as inflammation, cellular senescence, and genomic instability," said corresponding author Dr. Michael Corley, assistant professor of immunology in medicine in the Division of Infectious Diseases at Weill Cornell Medicine. "Our findings indicate that retroelement clocks capture previously undetected facets of

biological aging and may open the door to future treatments for these and other age-related conditions."

Monitoring the activity of retroelements could help track the effectiveness of anti-aging therapies, health outcomes in aging populations, and the impact of lifestyle changes on biological aging, said the researchers.

Drs. Ndhlovu and Corley plan to explore new treatments or therapeutic interventions for age-related diseases by targeting the epigenetic states of specific retroelements in the human genome. This approach, they noted, may eventually reverse or mitigate the biological effects of aging, improving an individual's health span and lifespan.

Reference: "Retro-age: A unique epigenetic biomarker of aging captured by DNA methylation states of retroelements" by Lishomwa C. Ndhlovu, Matthew L. Bendall, Varun Dwaraka, Alina P. S. Pang, Nicholas Dopkins, Natalia Carreras, Ryan Smith, Douglas F. Nixon and Michael J. Corley, 02 August 2024, *Aging Cell*.
DOI: 10.1111/acel.14288

The research reported in this story was funded by the National Institutes of Health, with grant awards R01AG082056, R01HL160392, R01MH134391, and UM1AI164559 (ACEL14288).

Eat this food as a late-night snack if you have trouble sleeping — it's full of melatonin and magnesium

You're having trouble sleeping — have you considered turning your insomnia into insom-nom-nom-nom-nia?

Sleep can be hard to come by in the winter because exposure to less sunlight can significantly disrupt internal clocks. There are several ways to restore restful sleep — try maintaining a consistent slumber schedule, basking in morning light and practicing relaxation.

Certain bedtime snacks can also help you catch z's. Brain health researcher Marc Milstein, author of "The Age-Proof Brain: New Strategies to Improve Memory, Protect Immunity, and Fight Off Dementia," said "a few simple tweaks" to your nighttime nosh routine can improve your trips to Sleepy Town.

Sleep can be hard to come by in the winter because exposure to less sunlight can significantly disrupt internal clocks. One particular bedtime snack can help to restore restful sleep.

"Fiber-rich carbs and proteins are the keys to a satiating bedtime snack that will keep you full overnight to improve sleep quality," one registered dietitian said. Getty Images

One of his suggestions is a mash made in heaven — oatmeal.

"Oatmeal is something that is a complex carbohydrate — doesn't cause blood sugar to shoot up or drop,"

"We now know that a lot of the issues that we have with waking up in the middle of the night can be rooted in blood sugar dropping or blood sugar spiking, so we realize that oatmeal is a great choice," he shared.

Oatmeal boasts the hormone melatonin, which promotes sleep, fiber and protein, which significantly contribute to feelings of fullness, and magnesium, which relaxes the muscles.

Milstein is also fond of bedtime bananas and almonds, which are rich in magnesium, and Greek yogurt when it's high in protein and low in sugar.

Johns Hopkins Medicine supports consuming whole-wheat toast or a bowl of oatmeal before bed because they are complex carbohydrates that don't take too long to digest.

They also trigger the release of serotonin, a neurotransmitter believed to play a significant role in regulating sleep quality and duration.

Toronto-based registered dietitian Abbey Sharp likes to make her "hunger-crushing" before-bed oatmeal bowl with oats, hemp hearts, milk, a hand pinch of salt, a ripe banana, a spoonful of almond butter, melatonin-friendly sour cherries and a cut-up protein bar.

"Fiber-rich carbs and proteins are the keys to a satiating bedtime snack that will keep you full overnight to improve sleep quality," Sharp noted on TikTok.

"I also love adding in sour cherries and almond butter for flavor (plus healthy fats) but also because of their evidence-based benefits for a good night's sleep," she added.

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What diseases can we treat with stem cells?

Stem cells help to eliminate the cause of disorders leading to a reduction in symptoms or a full recovery, depending on the initial condition, for (mostly) autoimmune disorders and/or diseases associated with tissue damage.

There is a large percentage of cases with a variety of diseases that have experienced health improvements. Applying only stem cells for some cases may be not enough. Cell therapy works more effectively when combined with other therapeutic methods that help decrease inflammation, restore mobility, activate the tissue repair process. We've seen various levels of recovery after treating the following diseases (not a full list):

Neurological disorders

- Multiple Sclerosis
- Parkinson's disease
- Dementia
- Alzheimer's disease
- Post-stroke condition

- Injuries of CNS
- Lyme disease

Endocrine diseases

- Diabetes type 2
- Diabetic foot
- Erectile dysfunction
- Obesity

Musculoskeletal disorders

- Sports-related injuries complications
- Athletic performance improvement

Digestive System Diseases

- Crohn's disease
- Cirrhosis of the liver
- Peptic ulcer disease
- Chronic pancreatitis

Respiratory diseases

- COPD
- Asthma
- Allergic rhinitis
- Sarcoidosis

Rheumatic diseases

- Systemic scleroderma
- Dermatomyositis
- Lupus
- Vasculitides

It is important to understand that stem cells are not a guaranteed cure for every disease.The patient may be denied stem cell procedures for various reasons. The effectiveness of the therapy for a particular disease depends on multiple factors: duration of the illness, age of the patient, the existence of chronic conditions, hereditary predisposition, lifestyle, etc.

Is stem cell treatment effective for specific disease?

Fill out the form to discuss the disease and treatment options with an expert!
You'll be contacted by a Medical Adviser who will collect information for the doctor and answer your basic questions.

Based on your medical reports, the doctors will assess whether you're a candidate for the therapy and will go over:
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2. What the treatment involves
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"I was looking for a treatment that might give me more hope than I have at home."

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"After the second day of stem cell therapy we noticed unexpected improvement, and now we hope to see more benefits.

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*Patient testimonials provided on this site are for informational purposes only and should not be considered as a guaranteed result for every case of illness. The treatment result depends on the disease, patient's condition, number of treatment procedures, etc.

Mass Media about the results of our patients

Before and after MS treatment documented by UK television

Meet Patrick Van Benthem, 57 years old.
He has had Primary Progressive MS since 2006. For 10 years he was prescribed drugs to minimize its impact. Regardless, the disease quickly progressed. Patrick had to quit his job, couldn't drive a car, and couldn't enjoy regular activities. Steroids did nothing for him. He felt pain at every foot drop and couldn't even raise his legs. His entire arm had gone completely numb.

He went to his neurologist for help, who referred him for NHS stem cell treatment. But, Patrick was denied treatment because his MS had not progressed "enough" to meet the therapy's strict criteria.
So, Patrick made the life-changing decision to go overseas for treatment. UK television documented the entire process — from before treatment to recovery. The results are incredibly encouraging to anyone with MS or someone with a loved one who suffers from MS. Watch this video.

Is stem cells treatments effective?

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Can We Stop Brain Aging? Scientists Uncover Mitochondrial Key

BY AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCEJANUARY 1, 2025

Researchers uncovered a mechanism called excitation-mitochondrial DNA transcription coupling (E-TCmito) linking neuronal activity to mitochondrial DNA transcription, crucial for maintaining brain function. Enhancing E-TCmito in aged mice improved cognition, offering a potential therapeutic target for age-related cognitive decline and neurodegenerative diseases.

New research identifies E-TCmito as a key link between neuronal activity and mitochondrial function, highlighting its potential to address cognitive decline in aging and diseases like Alzheimer's.

New research in mice has identified a critical mechanism that connects neuronal activity with mitochondrial function, offering insight into potential strategies to address age-related cognitive decline. Mitochondria, essential for meeting the energy needs of active neurons, generate adenosine triphosphate (ATP) primarily through oxidative phosphorylation (OXPHOS).

As mammals age, the efficiency of mitochondrial metabolism in the brain declines, significantly impacting neuronal and network function. The disruption of the OXPHOS pathway contributes to oxidative stress and mitochondrial dysfunction, exacerbating these challenges.

Challenges in Understanding Aging-Related Mitochondrial Decline

However, the mechanisms underlying the decline in OXPHOS activity and its impact on mitochondrial efficiency in aging neurons remain poorly understood, which, by extension, has limited the development of targeted interventions for age-related cognitive decline.

To address this, Wenwen Li and colleagues investigated the role of mitochondrial transcription in cognition in the hippocampus of young and aged mice. Li *et al.* identified a novel coupling mechanism, which they dubbed excitation-mitochondrial DNA transcription coupling (E-TC_{mito}), that connects neuronal excitation with mitochondrial DNA transcription.

This coupling, distinct from the traditional excitation-transcription coupling in the nucleus, is essential for maintaining synaptic and mitochondrial health. In aging brains, the effectiveness of E-TC_{mito} declines, leading to cognitive deficits. Notably, by enhancing E-TC_{mito} in aged mice, the authors observed improved cognitive function, highlighting its potential as a therapeutic target for counteracting cognitive decline associated with aging.

“Through an impressive combination of innovative tools, innovative physiology, and behavior experiments, Li *et al.* provide key insights into mitochondrial biology in the aging mammalian brain,” write Deniz Bingul and Scott Owen in a related Perspective. “The findings raise the possibility of identifying targets for age-related neurocognitive disorders associated with mitochondrial dysfunction, including Alzheimer’s and Parkinson’s diseases.”

Reference: “Boosting neuronal activity-driven mitochondrial DNA transcription improves cognition in aged mice” by Wenwen Li, Jiarui Li, Jing Li, Chen Wei, Tal Laviv, Meiyi Dong, Jingran Lin, Mariah Calubag, Lesley A Colgan, Kai Jin, Bing Zhou, Ying Shen, Haohong Li, Yihui Cui, Zhihua Gao, Tao Li, Hailan Hu, Ryohei Yasuda and Huan Ma, 20 December 2024, *Science*.
DOI: 10.1126/science.adp6547

Telomere extension turns back aging clock in cultured human cells, study

Researchers delivered a modified RNA that encodes a telomere-extending protein to cultured human cells. Cell proliferation capacity was dramatically increased, yielding large numbers of cells for study.

January 22, 2015 - By Krista Conger

Helen Blau

A new procedure can quickly and efficiently increase the length of human telomeres, the protective caps on the ends of chromosomes that are linked to aging and disease, according to scientists at the Stanford University School of Medicine.

Treated cells behave as if they are much younger than untreated cells, multiplying with abandon in the laboratory dish rather than stagnating or dying.

The procedure, which involves the use of a modified type of RNA, will improve the ability of researchers to generate large numbers of cells for study or drug development, the scientists say. Skin cells with telomeres lengthened by the procedure were able to divide up to 40 more times than untreated cells. The research may point to new ways to treat diseases caused by shortened telomeres.

Telomeres are the protective caps on the ends of the strands of DNA called chromosomes, which house our genomes. In young humans, telomeres are about 8,000-10,000 nucleotides long. They shorten with each cell division, however, and when they reach a critical length the cell stops dividing or dies. This internal "clock" makes it difficult to keep most cells growing in a laboratory for more than a few cell doublings.

'Turning back the internal clock'

"Now we have found a way to lengthen human telomeres by as much as 1,000 nucleotides, turning back the internal clock in these cells by the equivalent of many years of human life," said Helen Blau, PhD, professor of microbiology and immunology at Stanford and director of the university's Baxter Laboratory for Stem Cell Biology. "This greatly increases the number of cells available for studies such as drug testing or disease modeling."

A paper describing the research was published today in the *FASEB Journal*. Blau, who also holds the Donald E. and Delia B. Baxter Professorship, is the senior author. Postdoctoral scholar John Ramunas, PhD, of Stanford shares lead authorship with Eduard Yakubov, PhD, of the Houston Methodist Research Institute.

The researchers used modified messenger RNA to extend the telomeres. RNA carries instructions from genes in the DNA to the cell's protein-making factories. The RNA used in this experiment contained the coding sequence for TERT, the active component of a naturally occurring enzyme called telomerase. Telomerase is expressed by stem cells, including those that give rise to sperm and egg cells, to ensure that the telomeres of these cells stay in tip-top shape for the next generation. Most other types of cells, however, express very low levels of telomerase.

Transient effect an advantage

The newly developed technique has an important advantage over other potential methods: It's temporary. The modified RNA is designed to reduce the cell's immune response to the treatment and allow the TERT-encoding message to stick around a bit longer than an unmodified message would. But it dissipates and is gone within about 48 hours. After that time, the newly lengthened telomeres begin to progressively shorten again with each cell division.

The transient effect is somewhat like tapping the gas pedal in one of a fleet of cars coasting slowly to a stop. The car with the extra surge of energy will go farther than its peers, but it will still come to an eventual halt when its forward momentum is spent. On a biological level, this means the treated cells don't go on to divide indefinitely, which would make them too dangerous to use as a potential therapy in humans because of the risk of cancer.

This new approach paves the way toward preventing or treating diseases of aging.

The researchers found that as few as three applications of the modified RNA over a period of a few days could significantly increase the length of the telomeres in cultured human muscle and skin cells. A 1,000-nucleotide addition represents a more than 10 percent increase in the length

of the telomeres. These cells divided many more times in the culture dish than did untreated cells: about 28 more times for the skin cells, and about three more times for the muscle cells.

“We were surprised and pleased that modified TERT mRNA worked, because TERT is highly regulated and must bind to another component of telomerase,” said Ramunas. “Previous attempts to deliver mRNA-encoding TERT caused an immune response against telomerase, which could be deleterious. In contrast, our technique is nonimmunogenic. Existing transient methods of extending telomeres act slowly, whereas our method acts over just a few days to reverse telomere shortening that occurs over more than a decade of normal aging. This suggests that a treatment using our method could be brief and infrequent.”

Potential uses for therapy

“This new approach paves the way toward preventing or treating diseases of aging,” said Blau. “There are also highly debilitating genetic diseases associated with telomere shortening that could benefit from such a potential treatment.”

Blau and her colleagues became interested in telomeres when previous work in her lab showed that the muscle stem cells of boys with Duchenne muscular dystrophy had telomeres that were much shorter than those of boys without the disease. This finding not only has implications for understanding how the cells function — or don’t function — in making new muscle, but it also helps explain the limited ability to grow affected cells in the laboratory for study.

The researchers are now testing their new technique in other types of cells.

“This study is a first step toward the development of telomere extension to improve cell therapies and to possibly treat disorders of accelerated aging in humans,” said John Cooke, MD, PhD. Cooke, a co-author of the study, formerly was a professor of cardiovascular medicine at Stanford. He is now chair of cardiovascular sciences at the Houston Methodist Research Institute.

“We’re working to understand more about the differences among cell types, and how we can overcome those differences to allow this approach to be more universally useful,” said Blau, who also is a member of the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

“One day it may be possible to target muscle stem cells in a patient with Duchenne muscular dystrophy, for example, to extend their telomeres. There are also implications for treating conditions of aging, such as diabetes and heart disease. This has really opened the doors to consider all types of potential uses of this therapy.”

Other Stanford co-authors of the paper are postdoctoral scholars Jennifer Brady, PhD, and Moritz Brandt, MD; senior research scientist Stéphane Corbel, PhD; research associate Colin Holbrook; and Juan Santiago, PhD, professor of mechanical engineering.

The work was supported by the National Institutes of Health (grants R01AR063963, U01HL100397 U01HL099997 and AG044815), Germany's Federal Ministry of Education and Research, Stanford Bio-X and the Baxter Foundation.

Ramunas, Yakubov, Cooke and Blau are inventors on patents for the use of modified RNA for telomere extension.

Information about Stanford's Department of Microbiology and Immunology, which also supported the work, is available at http://microimmuno.stanford.edu.

Mitochondria makeover: unlocking the path to healthy longevity

1. Introduction

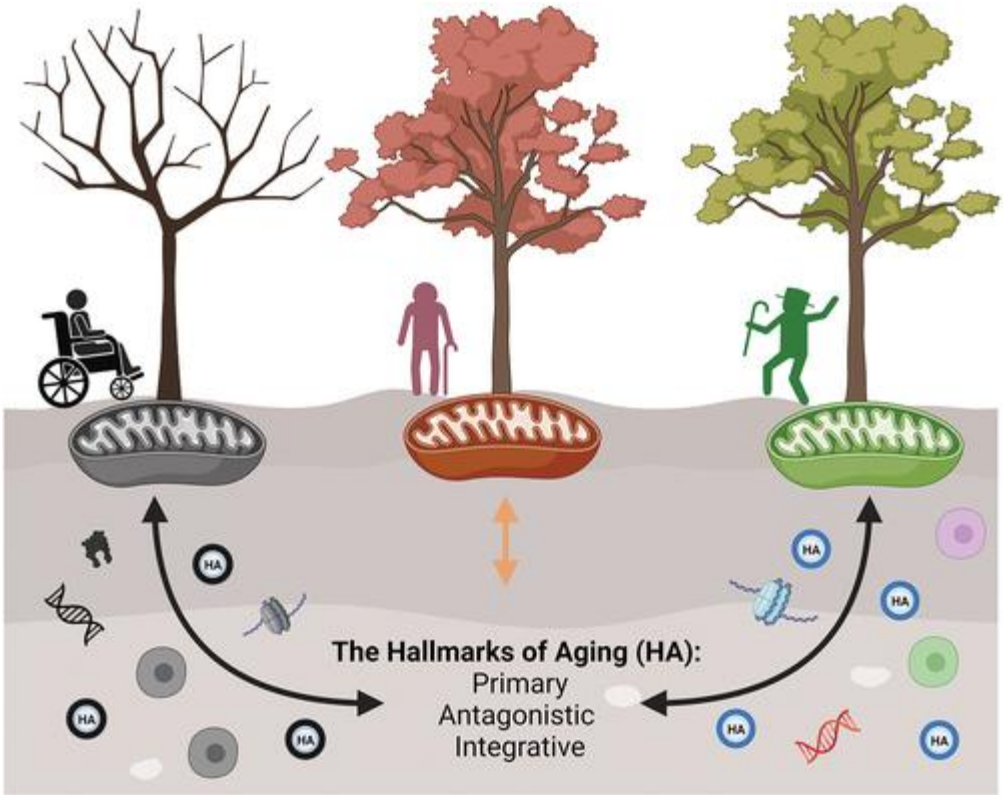
Thanks to biomedical research, significant advances have been made in preventing deaths caused by infectious agents and chronic diseases. Scientific progress has contributed to a remarkable increase in life expectancy, soaring from an estimated 30 years around 1800 to nearly 73 years by 2019 [Citation1]. This unprecedented global rise in life expectancy has resulted in a noticeable shift in the age distribution toward older demographics. However, even with these advancements, we still experience frailty as we age, accompanied by disabilities that reduce our quality of life. While the prospect of an extended lifespan is generally viewed positively, it is essential to recognize that living longer does not automatically guarantee good health. Therefore, developing interventions aimed at promoting healthy longevity has become imperative.

Achieving healthy longevity and mitigating the progressive loss of physiological integrity is a complex endeavor influenced by various factors that contribute to the development of vulnerability and diseases over time [Citation2]. In 2013, Lopez-Otin et al. proposed nine hallmarks of aging, sparking the publication of more than 300,000 articles with the aim of dissecting each hallmark to understand the molecular changes and develop interventions to mitigate aging and aging-associated diseases [Citation3]. Recently 12 hallmarks of aging were described, taking into account age-associated alterations in molecular, cellular, and systemic processes related to the deterioration of biological function over time. These hallmarks include primary (genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, and disabled macroautophagy), antagonistic

(deregulated nutrient-sensing, cellular senescence, and mitochondrial dysfunction), and integrative (stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis) [Citation3]. Notably among these hallmarks is mitochondria, which are interconnected with all of them, potentially offering a pathway to healthy longevity.

Today, our understanding of mitochondria extends beyond cellular boundaries, as they have been identified as viable entities outside of cells existing in circulation [Citation4–6]. Mitochondria transfer seems to play crucial roles in energy management and facilitating inter-organ metabolic adaptation, particularly in response to nutrient stress and possibly caloric restriction [Citation7]. The phenomenon of natural (natural mitochondrial transfer, NMT) and artificial mitochondrial transfer/transplant (AMT/T) between cells opens up the possibility of modifying the metabolism, mitochondrial DNA (mtDNA), and phenotype of recipient cells, particularly those that could be affected by the aging process [Citation8,Citation9]. This suggests that mitochondria, with their multifaceted roles in intracellular molecular interactions, cellular function, and systemic effects by their transfer between cells, may occupy a central position in the study of the hallmarks of aging and the development of interventions (Figure 1). We focus on uncovering and proposing an untested link between the hallmarks of aging and mitochondrial transfer to promote healthy longevity.

Figure 1. Mitochondria exert an influence on the hallmarks of aging, while the hallmarks, in turn, reciprocally impact mitochondria, shaping the aging process. Trees symbolize the diverse ways we experience aging, and they are intricately linked to mitochondrial function. Mitochondrial function, in turn, is influenced by the hallmarks of aging, which can also be influenced by mitochondria. The hallmarks of aging are categorized into three groups: primary (genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, and disabled macroautophagy), antagonistic (deregulated nutrient-sensing), and integrative (cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis). The hallmarks of aging, much like soil, can be differently enriched, leading to changes in mitochondrial function. Created with BioRender.com.



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2. Mitochondrial dysfunction: a central hub linking all other hallmarks of aging

Mitochondria serve as a central hub connecting all other hallmarks of aging and encompassing both their well-understood functions and those crucially remain to be described, such as mitochondrial transfer between cells [Citation10,Citation11]. In light of recent advances in interconnected pathways that may contribute to longevity and reduced age-associated diseases, mitochondria emerge as a key factor of aging decay. Furthermore, it is crucial to delve into how these factors could influence the release and uptake of our 'nomad' mitochondria as they migrate outside the cell and from one cell to another, enriching recipient cells with healthy mitochondria and potentially reducing effects on the aging hallmarks.

Single nucleotide polymorphisms (SNPs) in mtDNA have been associated with healthy longevity in centenarians, providing insights into their key role in the aging process and the importance of genomic stability [Citation12]. In contrast, genomic instability is related to the accumulation of somatic mutations in nuclear and mitochondrial DNA affecting essential genes and transcriptional pathways, leading to cellular dysfunction and compromising our health. Depletion in mtDNA content

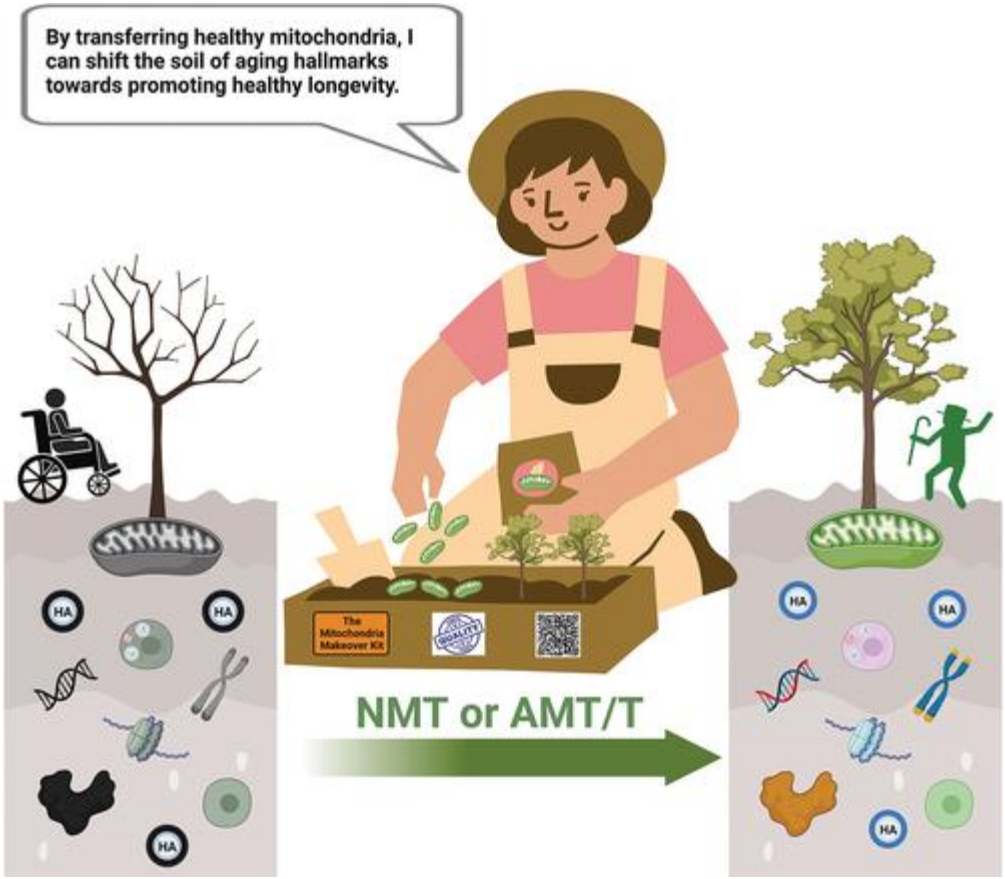
and mitochondrial number is reported during aging [Citation13]. Low mtDNA copy number correlates with frailty and all-cause mortality. Recent research indicates an average loss of four mtDNA copies per decade in humans, linked to age-related physiological changes [Citation14–16]. Additionally, numerous studies affirm the connection between reduced mtDNA content and aging and aging-related diseases [Citation13]. Since the pioneering study conducted by Clark and Shay in 1982, AMT/T has enabled the selective enrichment of a cell's mitochondrial content with a specific type conferring a selective advantage to cells that are less fit or have become unhealthy as a result of the aging process [Citation6,Citation17].

Among the primary hallmarks of aging, the connection between telomere damage and mitochondrial dysfunction is pivotal to understanding cellular decay over time. The relationship between telomere attrition and mitochondrial metabolic malfunction, particularly through the p53-PGC-1α-NRF-1 axis, remains a subject requiring further research [Citation18]. Interestingly, during the reprogramming of induced pluripotent stem cells (iPSCs), which is associated with potential rejuvenation, telomerase is upregulated, resulting in the lengthening of telomeres to embryonic stem cell (ESC)-like lengths. However, mitochondria that have accumulated mutations during the previous somatic life of the iPSCs exhibit diverse responses, leading to the generation of various mtDNA variants and mitochondrial heterogeneity [Citation19]. Some iPSCs appear to be better suited than others, with specific mtDNA variants improving reprogramming efficiency [Citation20]. The question arises: Is it possible to enhance the reprogramming process using specific AMT/T of mitochondria with mtDNA variants to effectively reset the cellular clock and rejuvenate cells? This intriguing avenue of research holds promise for unlocking new insights into cellular rejuvenation and healthy aging.

The other primary, antagonistic and the integrative hallmarks,—altered intercellular communication, stem cell exhaustion, and chronic inflammation – could also be mediated by NMT and AMT/T of healthy mitochondria. Mesenchymal stem cells (MSCs), along with the hematopoietic niche, are key components of tissue stability and function. Currently, it is unknown how MSCs are affected with time and whether the aging process could change their capacity to transfer mitochondria naturally to other cells. NMT and AMT/T could have strong implications for how cells communicate with each other to maintain their function over time and preserve the health of the immune system (Figure 2). Furthermore, observations indicate that the transfer of mitochondria to immune cells, whether through natural processes or via AMT/T from MSCs, can induce an immunoregulatory profile and potentially reduce chronic inflammation. Indeed, Singh et al. (2018) have shown

that restoring mitochondrial function can mitigate the aging process in mice [Citation13].

Figure 2. Mitochondria, playing critical roles in molecular, cellular, and systemic aspects of aging, have the potential to profoundly impact the hallmarks of aging (HA) through both natural mitochondrial transfer (NMT) and artificial mitochondrial transfer/transplant (AMT/T). Mitochondria play a pivotal role in governing the molecular, cellular, and systemic processes associated with aging, both in accelerating and potentially reversing the aging process for healthy longevity. In addition to their vital intracellular functions, both NMT and AMT/T hold promise as tools for gaining deeper insights into the hallmarks of aging and for the development of therapeutic interventions. Created with BioRender.com.



Display full size

It's worth noting that, except for a few exceptions, the spectrum, precise nature and extent of mitochondrial dysfunction concerning the hallmarks of aging remain largely unknown across various cell types and tissues. The factors primarily responsible for the decline in the common core components of the mitochondrial metabolic machinery, leading to dysfunction and subsequent aging in different

tissues, organs, and the entire organism, remain unclear. Intriguingly, not all tissues age in the same manner, adding further complexity to this phenomenon. It could be possible to stimulate NMT between cells in a particular tissue or harness AMT/T with tissue-specific administration of mitochondria. This approach should lead to the utilization of specific mitochondrial transfers in tissues that are particularly affected, offering innovative strategies to rejuvenate and mitigate tissue-specific aging (Figure 2).

Targeting mitochondria and facilitating NMT or AMT/T as a primary approach to extend lifespan and delay aging-associated disease onset necessitates more research. This research should span from basic science to translational and clinical validation. The identification and understanding of core similarities and tissue-specific differences in the nature and scope of mitochondrial dysfunction, along with its connections to the hallmarks of aging, hold the potential to significantly advance our knowledge in the field of healthy longevity (Figure 2).

3. Expert opinion

In the pursuit of achieving healthy longevity, we have discovered that intricate interactions among aging hallmarks converge upon a central player – mitochondria. This dynamic organelle, long recognized for its pivotal role in energy production, management, and metabolism, has now emerged as a linchpin connecting the dots among distinct aging hallmarks. From genomic instability to telomere attrition, from cellular senescence to chronic inflammation, mitochondria stand at the nexus of these age-related processes. Recent breakthroughs in our understanding of NMT and AMT/T have illuminated a path toward restoring mitochondrial function, regenerating cellular vitality, and rejuvenating aging cells, tissues, and organs. These ‘nomad’ mitochondria, migrating between cells, enriching recipient cells with essential functions, and potentially mitigating the effects of other aging hallmarks, present new strategies for extending healthy lifespans (Figure 2). While it is known that the restoration of mitochondrial function can reverse various aging phenotypes [Citation13], it is currently unknown whether cellular rejuvenation through mitochondrial transfer/transplantation can fully reverse the effects of aging. As research advances and synthetic biology opens up new possibilities, we may harness the power of custom-designed mitochondria to re-energize aging tissues and bolster our health over time. In the ever-evolving landscape of aging research, mitochondria must take center stage, offering the prospect of a healthier, more resilient journey through the passage of time.

Declaration of interest

A Caicedo is the leader of Dragon BioMed. KK Singh is the scientific founder of Yuva Biosciences and serves as Chief Scientific Advisor. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

A Caicedo and KK Singh wrote the manuscript, cured, analyze and conveyed the information in the manuscript. A Caicedo and KK Singh proposed natural mitochondrial transfer (NMT) and artificial mitochondrial transfer/transplant (AMT/T) as key mitigators of aging hallmarks. A Caicedo made the figures with comments from KK Singh. A Caicedo and KK Singh conceived this work.

Acknowledgments

We would like to express our gratitude to the School of Medicine at the Universidad San Francisco de Quito (USFQ), the 'Instituto de Investigaciones en Biomedicina, USFQ,' and the Mito-Act Research Consortium in Quito, Ecuador, for their unwavering support of our work and initiatives. Andres Caicedo extends his gratitude to Luisa Páliz for her invaluable support in his personal development and career. AC and KKS thank their laboratory members for their participation in research targeting mitochondria to mitigate aging and aging-associated diseases. The authorship team thanks Reema Azar for her help in ensuring the appropriate use of the English language in the manuscript.

FIGHT AGING!

Do you want to live a longer life in good health? Simple practices can make some difference, such as exercise or calorie restriction. But over the long haul all that really matters is progress in medicine: building new classes of therapy to repair and reverse the known root causes of aging. The sooner these treatments arrive, the more lives will be saved. Find out how to help »

November 13th, 2015

Investigating Mitochondrial Rejuvenation During Cellular Reprogramming and Embryonic Development

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The changes involved in producing induced pluripotent stem cells from ordinary somatic cells, such as those from a skin sample, are accompanied by mitochondrial rejuvenation, a clearance of mitochondrial damage associated with aging. This also occurs in the earliest stages of embryonic development, turning old parental cells into young child cells. It is not beyond the bounds of the possible to suggest that perhaps just this mitochondrial part of the transformation could be split off and used as the basis for a therapy - though other approaches to mitochondrial repair are far closer to realization. Also, it may well be that mitochondria are so vital to cellular function that it is impossible to safely induce such radical changes in adult tissues given the way in which cells are presently structured. As usual, the only way to find out is to dig deeper into what is going on under the hood, as researchers are doing here. The original research release is in PDF format only, unfortunately, but it provides a better explanation than any of the other available resources:

A new study suggests that old mitochondria - the oxygen-consuming metabolic engines in cells - are roadblocks to cellular rejuvenation. By tuning up a gene called Tcl1, which is highly abundant in eggs, researchers were able to suppress old mitochondria to enhance a process known as somatic reprogramming, which turn adult cells into embryonic-like stem cells. Researchers found that Tcl1 does its job by suppressing mitochondrial polynucleotide phosphorylase (PnPase), thereby inhibiting mitochondrial growth and metabolism.

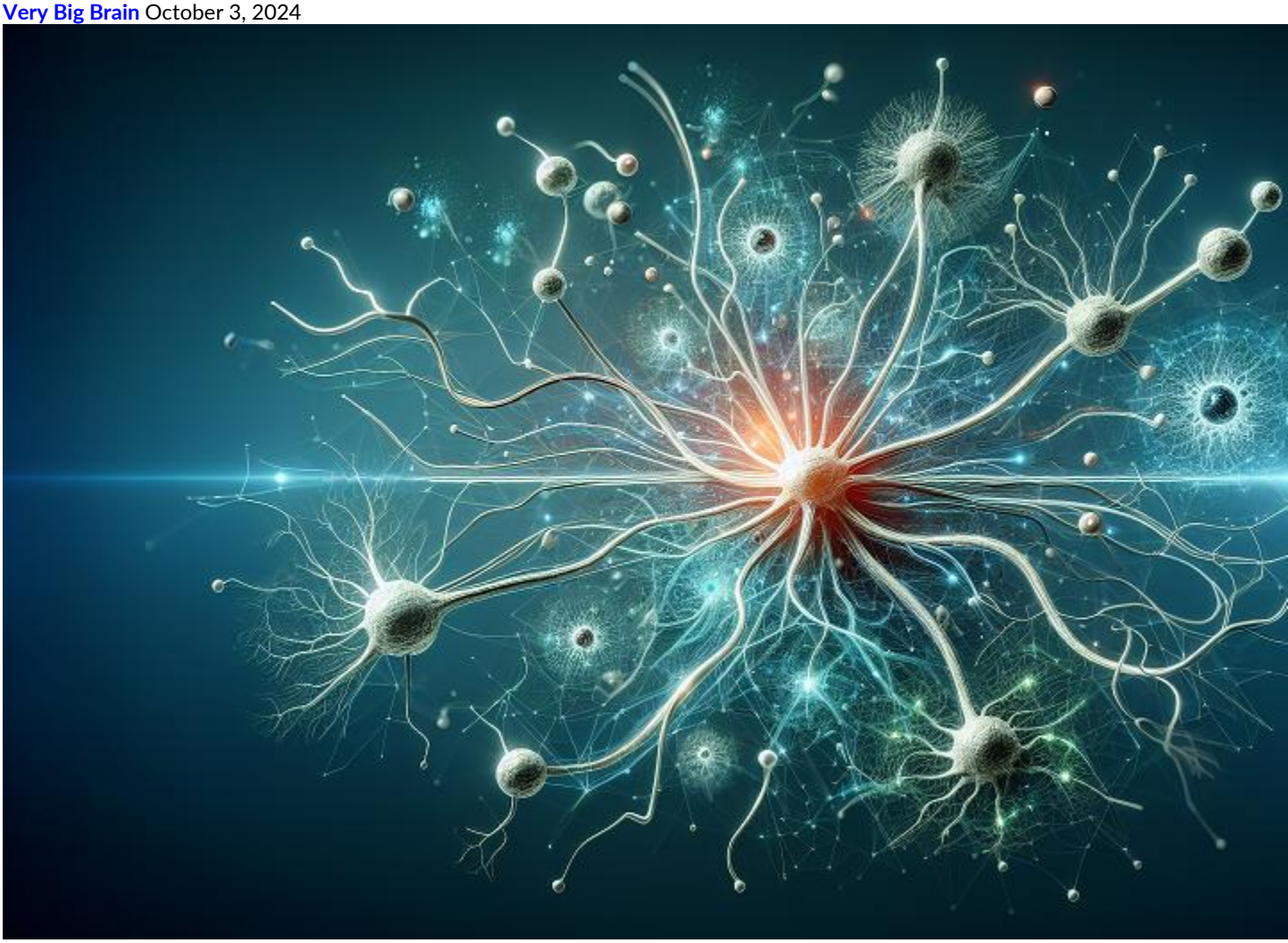
Stem cell researchers had known that egg (or oocyte) cytoplasm contains some special unknown factors that can reprogramme adult cells into embryonic-like stem cells, either during egg-sperm fertilisation or during artificial cloning procedures. While researchers had invented a technology called induced pluripotent stem cell (iPSC) reprogramming to replace the ethically controversial oocyte-based reprogramming technique, oocyte-based reprogramming was still deemed superior in complete cellular reprogramming efficiency. To address this shortfall, researchers combined oocyte factors with the iPSC reprogramming system. Their bioinformatics-driven screening efforts1 led to two genes: Tcl1 and its cousin Tcl1b1. After a deeper investigation, the team found that the Tcl1 genes were acting via the mitochondrial enzyme, PnPase. "We were quite surprised, because nobody would have thought that the key to the oocyte's reprogramming powers would be a mitochondrial enzyme. The stem cell field's conventional wisdom suggests that it should have been some other signalling genes instead."

Tcl1 is a cytoplasmic protein that binds to the mitochondrial enzyme PnPase. By locking PnPase in the cytoplasm, Tcl1 prevents PnPase from entering mitochondria, thereby suppressing its ability to promote mitochondrial growth and metabolism. Thus, an increase in Tcl1 suppresses old mitochondria's growth and metabolism in adult cells, to enhance the somatic reprogramming of adult cells into embryonic-like stem cells. These new insights could boost efficacy of the alternative, non-oocyte based iPSC techniques for stem cell banking, organ and tissue regeneration, as well as further our understanding of how cellular metabolism rejuvenates after egg-sperm fertilisation.

Link: http://www.straitstimes.com/singapore/uncovering-the-secret-of-turning-back-time

The Impact of Nootropics on Mitochondrial Health: Improving Energy Production in Brain Cells

Very Big Brain October 3, 2024



Your brain is a powerhouse, using about 20% of your body's energy to keep you thinking, learning, and functioning throughout the day. But what powers the brain itself? The answer lies in the tiny energy factories inside your cells, known as mitochondria. These microscopic organelles are responsible for producing ATP, the energy currency that fuels brain activity. But as we age, or when we're under stress, mitochondrial function can decline, leading to brain fog, fatigue, and cognitive slowdown. Enter nootropics. These cognitive

enhancers might not just sharpen your mind—they can also support mitochondrial health and boost energy production in brain cells.

What Are Mitochondria, and Why Do They Matter for Brain Health?

Mitochondria are often called the “powerhouses” of the cell, and for good reason. These tiny organelles convert nutrients from the food we eat into ATP, a molecule that cells use for energy. The brain, with its high energy demands, relies heavily on healthy mitochondria to keep neurons firing and cognitive processes running smoothly.

When mitochondria aren’t working at full capacity, brain cells don’t get the energy they need. This can lead to mental fatigue, poor concentration, and even contribute to neurodegenerative diseases. Supporting mitochondrial health is crucial for maintaining cognitive performance, especially as we age. This is where nootropics come into play—they can help optimize mitochondrial function, ensuring your brain stays energized and sharp.

How Nootropics Boost Mitochondrial Function

Nootropics don’t just enhance focus or memory—they can also support the very machinery that keeps your brain running. Certain nootropics boost mitochondrial efficiency, protect them from oxidative stress, and even stimulate the production of new mitochondria. Here’s how these cognitive enhancers help keep your brain cells powered up.

Improving Mitochondrial Efficiency

Efficient mitochondria produce more energy with less effort. Nootropics like **Pyrroloquinoline Quinone (PQQ)** improve mitochondrial efficiency by enhancing the processes involved in ATP production. PQQ promotes the creation of new mitochondria in a process called mitochondrial biogenesis, giving your brain more power to work with.

Think of it this way: when your mitochondria are running efficiently, it’s like upgrading an old, sluggish car engine to a shiny new model. Your brain gets

more energy with less wear and tear, improving everything from focus to overall cognitive stamina.

Protecting Mitochondria from Oxidative Stress

Oxidative stress is like rust for your brain cells, damaging mitochondria and slowing down energy production. This occurs when free radicals (unstable molecules) overwhelm your body's ability to neutralize them. Fortunately, some nootropics act as powerful antioxidants, protecting your mitochondria from oxidative damage.

Nootropics like **CoQ10** and **Alpha-Lipoic Acid (ALA)** help scavenge free radicals, reducing oxidative stress and preserving mitochondrial function. By keeping mitochondria healthy, these nootropics can help maintain consistent energy production, preventing brain fatigue and mental fog.

Top Nootropics for Supporting Mitochondrial Health

Now that we understand how nootropics support mitochondrial health, let's take a closer look at some of the best options available. These nootropics can boost energy production in brain cells, protect mitochondria from damage, and even stimulate the growth of new mitochondria.

Pyrroloquinoline Quinone (PQQ)

Pyrroloquinoline Quinone, or PQQ, is one of the most potent nootropics for enhancing mitochondrial function. PQQ not only helps existing mitochondria work more efficiently but also promotes the growth of new ones. This process, known as mitochondrial biogenesis, increases the overall energy production capacity of your brain cells.

PQQ is often used by people looking to combat brain fog, boost mental energy, and improve overall cognitive function. It's like giving your brain a fresh set of batteries, ensuring that you have the energy you need for sustained mental performance.

Coenzyme Q10 (CoQ10)

CoQ10 is a powerful antioxidant that plays a crucial role in energy production within mitochondria. It's essential for converting food into ATP, and it also helps protect mitochondria from oxidative damage. As we age, levels of CoQ10 decline, which can lead to slower cognitive function and fatigue. Supplementing with CoQ10 helps restore this vital compound, ensuring your brain cells have the energy they need to stay sharp.

Alpha-Lipoic Acid (ALA)

Alpha-Lipoic Acid (ALA) is another antioxidant that supports mitochondrial health by reducing oxidative stress. It works alongside CoQ10 to protect mitochondria from damage while also improving glucose metabolism, which can further enhance brain energy levels. ALA is particularly useful for people looking to maintain cognitive function as they age.

Acetyl-L-Carnitine (ALCAR)

Acetyl-L-Carnitine, or ALCAR, helps transport fatty acids into mitochondria, where they are used to produce energy. ALCAR is well-known for its ability to enhance mental clarity, focus, and energy by supporting mitochondrial function. It's especially beneficial during periods of mental exertion or fatigue, making it a popular choice for students, professionals, and anyone looking to boost their mental stamina.

The Connection Between Mitochondrial Health and Cognitive Performance

Why should you care so much about your mitochondria? The connection between mitochondrial health and cognitive performance is stronger than you might think. When your brain cells are running low on energy, everything from memory to focus can take a hit. By improving mitochondrial function, you can directly boost your cognitive abilities, making it easier to stay focused, think clearly, and process information efficiently.

Mental Fatigue and Mitochondrial Decline

One of the clearest signs of mitochondrial decline is mental fatigue. If your mitochondria aren't producing enough energy, you'll feel mentally exhausted, even if you're not doing anything physically demanding. Nootropics that support mitochondrial health can help combat this fatigue by ensuring your brain cells have the energy they need to perform at their best.

Memory and Learning

Memory and learning also rely heavily on energy-hungry processes in the brain. By supporting mitochondrial health, nootropics like PQQ and CoQ10 can improve your ability to retain and recall information. This is particularly useful for students or professionals who need to stay sharp and learn new information quickly.

Nootropic Stacks for Mitochondrial Health

For those looking to maximize their mitochondrial support, building a nootropic stack that targets mitochondrial health from multiple angles is a smart approach. Here are a couple of stack ideas that can boost energy production, reduce oxidative stress, and enhance cognitive performance.

Stack 1: PQQ + CoQ10 + ALA

This stack is designed for maximum mitochondrial support. PQQ promotes mitochondrial biogenesis, while CoQ10 and ALA work together to protect mitochondria from oxidative damage and ensure efficient energy production. This combination is perfect for anyone looking to enhance mental energy, focus, and overall brain health.

Stack 2: ALCAR + PQQ + Rhodiola Rosea

If you're looking for a stack that boosts both mental and physical stamina, this combination is ideal. ALCAR supports energy production by transporting fatty acids into mitochondria, PQQ promotes the growth of new mitochondria, and Rhodiola Rosea helps reduce mental fatigue and stress, ensuring that your brain cells stay energized even under pressure.

Can Nootropics Really Improve Mitochondrial Health?

So, can nootropics truly support mitochondrial health and improve brain energy? Absolutely. By boosting mitochondrial efficiency, promoting the creation of new mitochondria, and protecting against oxidative stress, nootropics like PQQ, CoQ10, and ALCAR can have a significant impact on brain cell energy production. Whether you're looking to combat brain fog, enhance focus, or improve memory, supporting mitochondrial health is a crucial step in optimizing cognitive performance.

Incorporating nootropics that target mitochondria into your routine could help keep your brain cells powered up, providing the mental energy you need to tackle whatever comes your way. And in the ever-

Aging 'hotspot' found in brain, researchers say: 'Major changes'

The brain plays a big part in the aging process, and scientists think they've pinpointed the specific cells that control it.

In a study of mice, researchers at the Allen Institute identified certain cells that showed "major changes" with age, particularly in one specific "hotspot," according to a press release.

Mice were chosen because their brains share "many similarities" to human brains.

The researchers used RNA sequencing and brain-mapping tools to analyze more than 1.2 million brain cells from young mice (2 months old) and older mice (18 months old).

The 18-month-old mice are roughly equivalent to a "late middle-aged human," the researchers indicated.

The researchers grouped the cells into 847 different types and also identified nearly 2,500 genes that changed with aging, according to Zeng.

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WARDING OFF DEMENTIA MEANS MORE READING, PRAYING AND LISTENING TO MUSIC: STUDY

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The researchers grouped the cells into 847 different types and also identified nearly 2,500 genes that changed with aging, according to Zeng.

Mice (not pictured) were chosen because their brains share "many similarities" to human brains, the researchers said. iStock© iStock

The cells that were linked to aging showed an increase in inflammation and a decrease in "neuronal function."

"Changes in these genes point to deteriorated neuronal structure and function in many neuronal and glial cell types, as well as increased immune response and inflammation in the brain’s immune and vascular (blood vessel) cell types," Zeng detailed.

The cells that experienced the biggest changes were the ones in the hypothalamus, the part of the brain that is linked to food intake, energy balance and metabolism, the researchers noted.

This suggests that this area is a "hotspot for aging," Zeng noted, and that there could be a connection between diet, lifestyle factors, brain aging and risk of age-related cognitive disorders.

"The findings from the study reinforce the notion that maintaining a healthy lifestyle, promoting a healthy metabolic state, and reducing inflammation in the body and brain could slow down or delay the aging process and reduce the risks of aging-associated brain diseases," he said.

The hope is that this discovery could lead to new age-related therapies to improve the function of these cells and help prevent neurodegenerative diseases, according to the researchers.

"Aging is the most important risk factor for many brain diseases," Zeng noted.

"Our study provides a highly detailed genetic map for which brain cell types may be most affected by aging and suggests new gene and cell targets for developing new treatments for aging-related brain diseases."

The study did have some limitations, the authors acknowledged.

"The main limitation of our study is that the findings are correlational," Zeng said.

Inflammation plays a role in chronic age-related diseases such as Alzheimer's, a neurologist noted. AP Images© AP Images

"We don’t know yet if the gene expression changes observed in specific cell types are causal to brain aging. Our study lays the groundwork by providing a detailed genetic map and cell targets."

Zeng called for future studies to investigate the cells’ roles in aging and determine whether the reversal of the changes could delay the aging process.

Dr. Earnest Lee Murray, a board-certified neurologist at Jackson-Madison County General Hospital in Jackson, Tennessee, commented that the new research adds to existing evidence supporting the role of diet in human brain health.

The detailed "brain roadmap" will be very beneficial for future research into aging and possible therapeutics, according to Murray, who was not involved in the study.

The detailed "brain roadmap" discovered in the study will be very beneficial for future research into aging and possible therapeutics, experts agree. iStock© iStock

It's been known for some time that inflammation plays a role in chronic age-related diseases such as Alzheimer's, the neurologist noted.

"More and more evidence is pointing to the fact many chronic diseases can be prevented, and it often comes down to diet and exercise," he told Fox News Digital. "Altering diet to exclude processed foods and initiating some habits such as intermittent fasting have been shown to reduce this cellular inflammation that appears to be leading to so many diseases."

Original article source: Aging 'hotspot' found in brain, researchers say: 'Major changes'

5 major Alzheimer's discoveries scientists made in 2024

The Alzheimer's Association shares some of its most significant dementia findings

Published December 27, 2024

Drug shows promise in treating Alzheimer's

Gillian Turner reports how BAN2401 might help slow the mental decline of Alzheimer's patients.

With an estimated 6.9 million Americans aged 65 and older currently living with Alzheimer's disease, the road to a cure seems long and uncertain.

But as the year comes to a close, experts are reflecting on some of the hopeful advances in diagnosis, treatment and risk management that have been made in 2024.

The Alzheimer's Association — a Chicago-based nonprofit committed to Alzheimer's research, care and support — shared its top five significant discoveries from the year.

DEMENTIA REPORT REVEALS 'SHOCKING' SIGNS AT AGE 60 THAT YOU'LL DEVELOP THE DISEASE BY AGE 80

1. Third new Alzheimer's drug is approved

2024 saw a new drug enter the dementia landscape, as the U.S. Food and Drug Administration (FDA) approved Kisunla (donanemab) in July.

This was the third new approval since 2021.

The Alzheimer's Association — a Chicago-based nonprofit committed to Alzheimer's research, care and support — shared its top five significant discoveries from the year. (iStock)

Kisunla, which is made by Eli Lilly, is designed to "slow progression and change the underlying course of the disease," according to the Association's press release.

The once-monthly injection is intended for adults with early symptomatic Alzheimer's disease.
This is the first medication to target amyloid plaques — the proteins that build up in the brains of Alzheimer's patients, often impairing memory and cognitive function — with evidence to support stopping therapy when amyloid plaques are removed, a company release stated.

'HIDDEN' FAT COULD PREDICT ALZHEIMER'S DISEASE UP TO 20 YEARS BEFORE SYMPTOMS, RESEARCH FINDS
"This is real progress," said Alzheimer's Association President and CEO Dr. Joanne Pike in a statement shared with Fox News Digital at the time.

"[This FDA] approval allows people more options and greater opportunity to have more time. Having multiple treatment options is the kind of advancement we've all been waiting for."

2. Blood tests could improve speed and accuracy of diagnosis

Research this year has helped move Alzheimer's blood tests closer to being used in physicians' offices.
Studies have shown that blood tests can achieve a higher accuracy of diagnosis, which could help fast-track patients' access to clinical trials and treatments, according to the Alzheimer's Association.

> # "This is real progress."

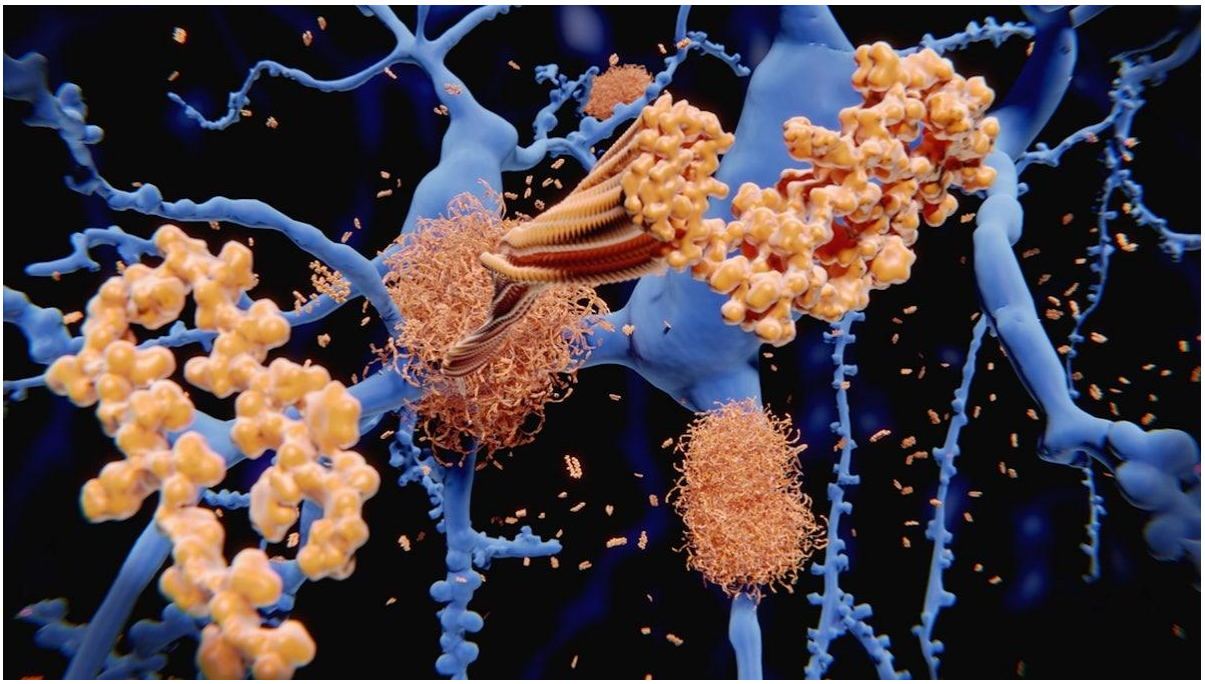
"Blood tests for Alzheimer's are demonstrating in research that they could significantly improve a clinician's accuracy and confidence, provide greater accessibility and a reason for more communication," the same source stated.

In one study reported this year, a specific blood test was around 90% accurate in identifying Alzheimer's in patients with cognitive symptoms seen in primary care and at specialized memory care clinics, per the Association.

3. Individuals and caregivers want more support post-diagnosis

People who are newly diagnosed with Alzheimer's and their caregivers need more support in navigating the health care system.

That's according to a 2024 Alzheimer's Association survey, which found that 97% of dementia caregivers expressed a desire for those support systems.



2024 saw the approval of the first medication to target amyloid plaques, the proteins that build up in the brains of Alzheimer's patients and often impair memory and cognitive function. (iStock)

A majority of dementia caregivers (70%) also noted that "coordination of care is stressful."

To help address this, the Centers for Medicare & Medicaid Services in July 2024 launched an eight-year pilot program in dementia care management, called the Guiding an Improved Dementia Experience (GUIDE) model.

DEMENTIA RISK COULD BE LINKED TO WALKING SPEED, STUDY SUGGESTS

The program aims to work with health care systems to provide supportive services to people living with dementia and their caregivers, with a focus on helping patients remain in their homes and communities, according to the Alzheimer's Association.

4. Wildfire smoke raises risk of dementia

Air pollution has been linked to an increased risk of dementia, according to 2024 research.

The 10-year study, which was presented during the Alzheimer's Association International Conference in Philadelphia in July, found that wildfire smoke can be "particularly hazardous" for brain health.

A 2024 Alzheimer's Association survey found that 97% of dementia caregivers expressed a desire for those support systems. (iStock)

The research included more than 1.2 million people in southern California, an area that experiences frequent wildfire activity.

Air pollution produced by wildfires could be more hazardous to health because it is produced at higher temperatures, contains a greater concentration of toxic chemicals, and is smaller in diameter than other sources, the Alzheimer's Association stated.

5. Alzheimer’s causes physical changes in the brain

In June 2024, scientists and clinicians published research that showed physical changes that happen in the brain due to Alzheimer’s disease. "Defining diseases by the biology has long been standard in many areas of medicine — including cancer, heart disease and diabetes," the Alzheimer’s Association wrote.

In June 2024, scientists and clinicians published research that showed physical changes that happen in the brain due to Alzheimer’s disease. (iStock)

"The new publication defines Alzheimer’s as a biological process that begins with brain changes before people exhibit memory and thinking problems."

These brain changes were found to come ahead of the typical outward symptoms, such as memory loss, confusion, disorientation and trouble with planning or organizing.

Warding off dementia means more reading, praying and listening to music: study

Downtime decisions may have profound health impacts, say researchers

Published January 1, 2025

Could being bilingual help prevent dementia?

Fox News medical contributor Dr. Nicole Saphier joins ‘Fox & Friends Weekend’ to weigh in on a new report that being bilingual could help people ward off dementia.

For long-term brain health, older adults might want to carefully consider how they spend their downtime, according to a new study. Researchers from the University of South Australia assessed the 24-hour activity patterns of nearly 400 people over age 60. When it comes to brain health, the study found that the context or type of activity individuals engage in matters, news agency SWNS reported.

DEMENTIA REPORT REVEALS 'SHOCKING' SIGNS AT AGE 60 THAT YOU'LL DEVELOP THE DISEASE BY AGE 80

Some sedentary behaviors are better for cognitive function than others, according to the findings, which were published in The Journal of Gerontology Series A. Mentally stimulating behaviors, such as reading, listening to music, praying, crafting and playing a musical instrument — as well as social behaviors like chatting with others — are beneficial for memory and thinking abilities, the study noted.

Mentally stimulating behaviors such as reading, listening to music, praying, crafting and playing a musical instrument are beneficial for memory and thinking abilities, a new study noted. (iStock)

The research team referred to the "valuable insights" that could help reduce instances of cognitive impairment. More passive activities, like playing video games or watching TV, do not offer the same benefits as reading, praying and other activities, they noted. More than 55 million people around the globe have dementia, according to estimates from the World Health Organization. Another 10 million new cases are diagnosed each year. Dr. Maddison Mellow, researcher at the University of South Australia, said that not all sedentary behaviors are equal when it comes to memory and cognitive health.

"The context of an activity alters how it relates to cognitive function, with different activities providing varying levels of cognitive stimulation and social engagement." (iStock)

"In this research," she said, "we found that the context of an activity alters how it relates to cognitive function, with different activities providing varying levels of cognitive stimulation and social engagement." She said that scientists "already know that physical activity is a strong protector against dementia risk, and this

should be prioritized if you're trying to improve your brain health," as SWNS reported.

> # "Even small, 5-minute time swaps can help."

"But until now, we hadn't directly explored whether we can benefit our brain health by swapping one sedentary activity for another." She went on, "And while the 'move more, sit less' message certainly holds true for cardiometabolic and brain health, our research shows that a more nuanced approach is needed when it comes to thinking about the link between sedentary behaviors and cognitive function." It's wise to "prioritize movement that's enjoyable and gets the heart rate up," she also said. And "even small, 5-minute time swaps can help."

"A more nuanced approach is needed when it comes to thinking about the link between sedentary behaviors and cognitive function." (iStock)

A recent study published by the RAND Corporation in California also identified several major predictors occurring around age 60 that could likely lead to cognitive impairment and dementia in individuals by age 80, as Fox News Digital previously reported. Researchers evaluated 181 potential risk factors, including demographics, socioeconomic status, lifestyle and health behaviors, health history, psycho-social factors and more. The list of predictors, according to RAND, included "never exercising" and "low engagement in hobbies."
The study results suggested that "maintaining good physical and mental health is beneficial not just to staying in shape, but also to staying sharp and delaying cognitive decline," study co-author Peter Hudomiet, a RAND economist in California, told Fox News Digital.

Why some organs age faster than others: Scientists discover hidden mutations in non-coding DNA

The accumulation of mutations in DNA is often mentioned as an explanation for the aging process, but it remains just one hypothesis among many. A team from the University of Geneva (UNIGE), in collaboration with the Inselspital, University Hospital of Bern and the University of Bern (UNIBE), has identified a mechanism that explains why certain organs, such as the liver, age more rapidly than others.

The mechanism reveals that damages to non-coding DNA, which are often hidden, accumulate more in slowly proliferating tissues, such as those of the liver or kidneys. Unlike in organs that regenerate frequently, these damages remain undetected for a long time and prevent cell division. These results, published in the journal *Cell*, open new avenues for understanding cellular aging and potentially slowing it down.

Our organs and tissues do not all age at the same rate. Aging, marked by an increase in senescent cells—cells that are unable to divide and have lost their functions—affects the liver or kidneys more rapidly than the skin or intestine.

The mechanisms that contribute to this process are the subject of much debate within the scientific community. While it is widely accepted that damage to the genetic material (DNA), which accumulates with age, is at the root of aging, the link between the two phenomena remains unclear.

The liver as the ideal model for studying aging

The group led by Thanos Halazonetis, full professor in the Department of Molecular and Cellular Biology at the UNIGE Faculty of Science, is studying the mechanisms of DNA replication. His team, in collaboration with the groups led by Prof. Stroka and Prof. Candinas at the Inselspital in Bern and UNIBE, has been studying liver cells (hepatocytes), which proliferate infrequently. The scientists analyzed the potential link between the more rapid aging of the liver and the lower frequency of DNA replication in its cells.

"Our study model, the mouse liver, is an ideal organ for studying the mechanisms of DNA replication in vivo. In adult mammals, hepatocytes rarely proliferate unless they have been partially ablated. After ablating two-thirds of the livers of young or old mice, we can study the replication mechanisms in a young or aging organ, directly in the living organism," explains Prof. Deborah Stroka, co-last author of the study.

By mapping for the first time the sites at which DNA replication starts in liver cells that regenerate after ablation, the scientists discovered that these are always located in non-coding regions. It was also observed that replication initiation was much more efficient in young mice than in old mice.

"These non-coding regions are not subject to regular error checking and therefore accumulate damage over time. After removal of the liver in young mice, there is still little damage and DNA replication is possible. On the contrary, when the experiment is carried out in old mice, the excessive number of errors accumulated over time triggers an alarm system that prevents DNA replication," explains Giacomo Rossetti, research fellow in the Department of Molecular and Cellular Biology at the UNIGE Faculty of Science and first author of the study. This block of DNA replication prevents cells from proliferating, leading to degradation of cell functions and tissue senescence.

Hope for slowing down the aging process

These observations could help explain why slowly proliferating tissues, such as the liver, age faster than rapidly proliferating tissues, such as the intestine. In cells that have remained dormant for long periods, too many cryptic DNA lesions have accumulated in the non-coding regions, which contain the origins of replication, and prevent replication from being triggered. In rapidly proliferating tissues, on the other hand, little damage accumulates thanks to frequent cell renewal, and the origins of replication retain their efficiency.

"Our model suggests that by repairing cryptic DNA damage before replication is triggered, certain aspects of aging could perhaps be avoided. It is on this new working hypothesis that our efforts will focus," concludes Halazonetis.

More information: In vivo DNA replication dynamics unveil aging-dependent replication stress, *Cell* (2024). DOI: 10.1016/j.cell.2024.08.034. www.cell.com/cell/fulltext/S0092-8674(24)00963-2

Provided by University of Geneva

New waterproof sunscreen cools skin by 11°F, blocks UV rays and solar heat

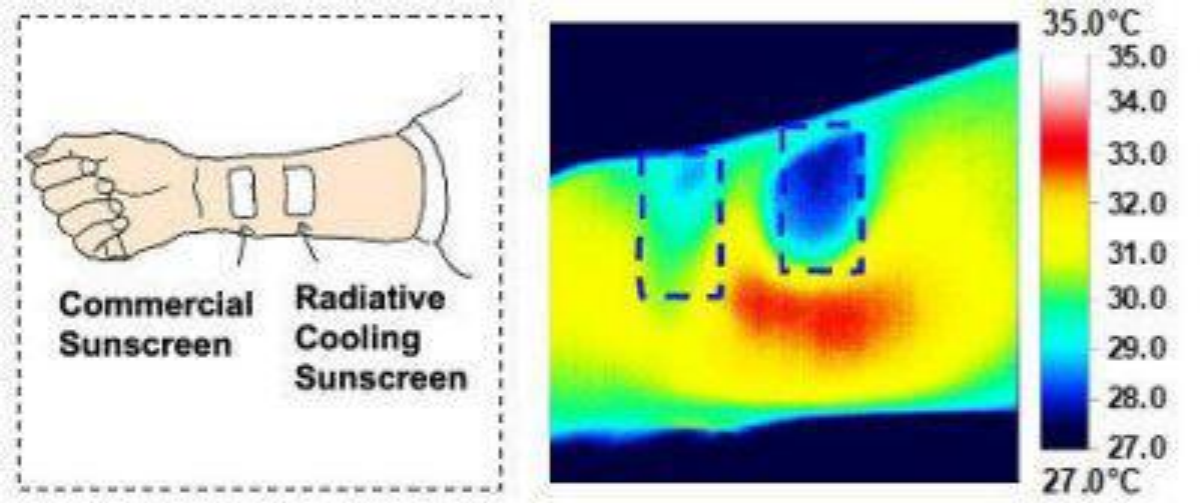
We all know sunscreen is a must for protecting our skin from the sun's harmful UV rays. But did you know that the currently available sunscreen doesn't actually cool you down? In fact, it can sometimes even trap heat.

But now, researchers at Tsinghua University in Beijing have developed a new sunscreen that not only blocks those harmful UV rays but also keeps you feeling refreshingly cool.

Interestingly, it offers a cooling advantage of up to 6 degrees Celsius (11 degrees Fahrenheit) over existing sunscreens.

The new "sunscreen prototype exhibits promising commercial potential, especially as temperatures in the summer continue to rise," the researchers mentioned.

This sunscreen could particularly be beneficial for outdoor workers due to its waterproof nature and its high level of sun protection.



Compared to a commercial sunscreen, the new formula kept the skin cooler when measured under a thermal camera (blue area on right-hand image). Nano Letters

Optimizing the size of particles

Radiative cooling is a technology that cools objects by either reflecting or emitting heat away from them. This technique is already being used to develop innovative materials like cooling fabrics and coatings for buildings.

Titanium dioxide (TiO2), a heat-reflective white mineral, is crucial in certain passive radiative cooling technologies.

Mineral sunscreens use TiO2 to block UV rays, but the particle size is generally not optimized for effective heat reflection and cooling.

This new study focused on optimizing the size of TiO2 nanoparticles to develop a sunscreen with both UV-blocking and radiative cooling properties.

This prototype sunblock was formulated using TiO2 nanoparticles, water, ethanol, moisturizing cream, pigments, and polydimethylsiloxane, a common silicone polymer in cosmetics.

12 hours long protection

This new cooling sunscreen offers a significant advancement in sun protection technology.

The modified size of the TiO2 nanoparticles resulted in a cooling effect by reflecting both UV light and solar heat.

Moreover, it exhibited SPF 50, demonstrated water resistance, and maintained its effectiveness even after 12 hours of simulated sunlight exposure. Importantly, the product showed no signs of irritation when applied to both animal and human skin.

In real-world testing conducted in hot and humid conditions, the new sunscreen demonstrated a significant cooling effect.

Participants wearing the new sunscreen experienced skin temperatures up to 10.8°F (6.0°C) lower than those with bare skin. When compared to the commercially available sunscreens, it was up to 11.0°F (6.1°C) cooler. That's a significant difference, especially on hot summer days.

Interestingly, the sunscreen's color can be customized using kaolin pigments to suit a wide range of skin tones.

"The formulation is inexpensive, costing only $0.92 for 10 grams of the mixture — on par with sunblocks already on the market," the press release stated.

The team highlights the increasing need for heat adaptation strategies as climate change intensifies. They point out that while we can easily layer up for cold weather, extreme heat poses a significant challenge.

This innovation has the potential to significantly improve the working conditions for construction crews, delivery drivers, and farmers in hot climates and provide better protection against heat stress.

The study findings were published in the journal *Nano Letters.*

Junevity Launches to Develop Cell Reset Therapeutics

Feb 13, 2025

Junevity, a biotechnology company on a mission to extend lifespan and healthspan by resetting cell damage from age-related diseases, today announced $10 million in seed funding led by Goldcrest Capital and Godfrey Capital.

The Junevity **RESET platform** is based on exclusively licensed research by co-founder Dr. Janine Sengstack at the University of California at San Francisco. RESET uses large-scale human data and AI to identify genes – or transcription factors – that can regulate cell damage. Then, it develops siRNA therapeutics against these targets to return cells to health. Junevity will use this seed funding to enhance the RESET platform and develop its first therapeutic candidates in Type 2 diabetes, obesity and frailty.

"My research at UCSF showed the power of targeting transcription factors to restore aged human cells back to health," said Janine Sengstack, Ph.D., co-founder and Chief Scientific Officer at Junevity. "Based on these discoveries, we are bringing forward a new class of cell reset therapeutics for diseases, with the ultimate goal of greater human longevity."

Diseases like obesity, diabetes, frailty, neurodegeneration and many others shorten human lifespan and are associated with complex cell damage at the transcriptional level. RESET uses billions of data points from human diseases and AI to rank and evaluate potential targets. Together, the platform outputs the Cell RESET Atlas, a collection of promising transcription factor targets by cell type and by disease for therapeutic targeting. Junevity then develops novel silencing RNA (siRNA) therapeutics to restore cellular transcription back to a healthy state.

Junevity's preclinical data demonstrates the power of the RESET platform. In Type 2 diabetes, Junevity's first siRNA therapeutic candidate improved glucose control and insulin sensitivity in diabetic mice without causing weight gain or other side effects associated with insulin sensitizers. In obesity, Junevity's second siRNA candidate improved adipose tissue metabolism and reduced food intake, leading to 30% weight loss versus controls. Importantly, this weight loss was driven by fat loss with retention of lean mass.

Both drug candidates are siRNA, meaning dosing once every 3-12 months is possible. This approach is patient-friendly and could increase compliance and satisfaction for diabetes and obesity treatments.

"Junevity's RESET platform is a big idea that could broadly impact human health by addressing aging at the cellular level," said John Hoekman, Ph.D., co-founder and Chief Executive Officer at Junevity. "We plan to advance multiple clinical programs, both directly and with partners, to make progress against diseases of aging."

Junevity's team includes world-class operators and advisors driven to extend human longevity, with an "outlier culture"based on mission, excellence, teamwork and intensity/pace. **Junevity's founding executive team includes**:

- Dr. John Hoekman, Ph.D. – Co-founder, CEO – Created the technology for Impel Pharmaceuticals' Trudhesa® nasal spray during his Ph.D. and led it to FDA approval in 2021
- Dr. Janine Sengstack, Ph.D. – Co-founder, CSO – Inventor of the RESET platform during her Ph.D. in Cellular Aging at UCSF
- Rob Cahill – Co-founder, COO – Previously machine learning researcher at UCSF and co-founder and CEO at Jhana, which was acquired by FranklinCovey (NYSE: FC)

"The Junevity team has a novel approach, incredible early data and tremendous potential to treat metabolic and age-related diseases," said Brent Saunders, CEO and chairman of Bausch + Lomb, and an advisor to Junevity. "I'm excited to see how Junevity will advance this innovative platform."

Junevity has exclusively licensed relevant technology from UCSF through its Office of Technology Management and Advancement. Junevity has since filed multiple composition-of-matter patents for its siRNA therapeutic candidates.

About Junevity

Junevity is a biotechnology company developing cell reset therapeutics for longevity. The Junevity **RESET platform** is the first to use large-scale human data and AI to identify transcription factor targets and repress them with siRNA therapeutics. The company is creating siRNA therapeutics to address diseases collectively impacting billions of people worldwide, including Type 2 diabetes, obesity, frailty and more. Based in San Francisco

and founded out of UCSF in 2023, Junevity's mission is to bring cell reset therapeutics to the world for longer lifespan and healthspan. Learn more at **junevity.com**.

Anti-aging guru Bryan Johnson reveals shocking wellness regimen he shares with teenage son: 'Future self'

Published Jan. 4, 2025


Biohacker Bryan Johnson (front), 47, and his son, Talmage, 19, are featured in the new Netflix documentary "Don't Die: The Man Who Wants to Live Forever."Bryan Johnson / Instagram

What a father figure!

Bryan Johnson, the 47-year-old tech millionaire who's poured millions into his quest for immortality, has revealed the strict daily longevity routine that he shares with his son, Talmage, 19.

The pair — who have been praised for looking "like brothers" — shocked the world in 2023 when they announced they had undergone "the world's first multi-generational plasma exchange," along with Johnson's father, now 71, to try to remain forever young.

Following the release of his new Netflix documentary, "Don't Die: The Man Who Wants to Live Forever," Johnson took to X on Thursday to explain how to "build a family culture of health and hard work."

 [4]

The pair shocked the world in 2023 when they announced they had undergone “the world’s first multi-generational plasma exchange,” along with Johnson’s father, now

Start with the basics: Johnson and Talmage wake up at 5 a.m., eat their “final meal of the day,” a combination of veggies, nuts, seeds and berries, at noon and head to bed at 8:30 p.m.

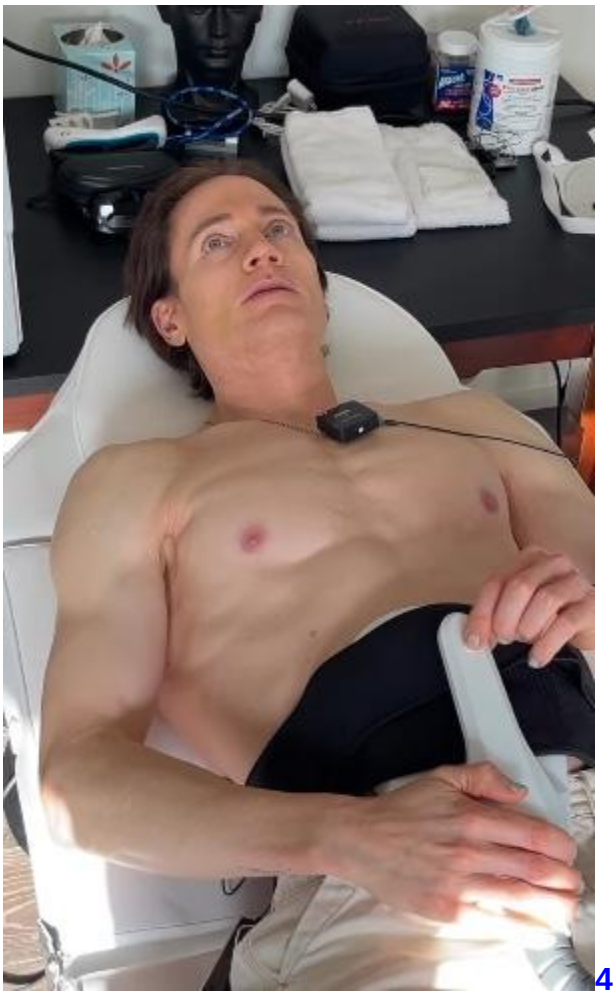
 [4]

Johnson has poured millions into his quest for immortality.YouTube/, The Diary Of A CEO

“By the time I go to bed at 8:30 pm, primary digestion is done and my resting heart rate is around 47-49 bpm,” Johnson recently detailed on his site. “If I eat later in the day, my resting heart rate will be between 55-58 bpm because my body is still digesting food and it will lessen my sleep quality by ~30%.”

When he hits the hay, there’s little tossing and turning as Johnson enjoys lots of deep and REM sleep.

He said he’s been able to achieve “perfect sleep” in part by having an evening wind-down ritual and cutting out late-night activities. He also doesn’t consume caffeine or alcohol.



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Johnson tests out a device he claims can simulate the effects of performing 20,000 sit-ups.Instagram / bryanjohnson_

No surprise that father and son fuel up with Johnson’s Blueprint stack, his comprehensive supplement program that’s available on Amazon. Johnson’s hefty protocol features metformin for blood glucose regulation and proferrin for iron and red blood cell production.

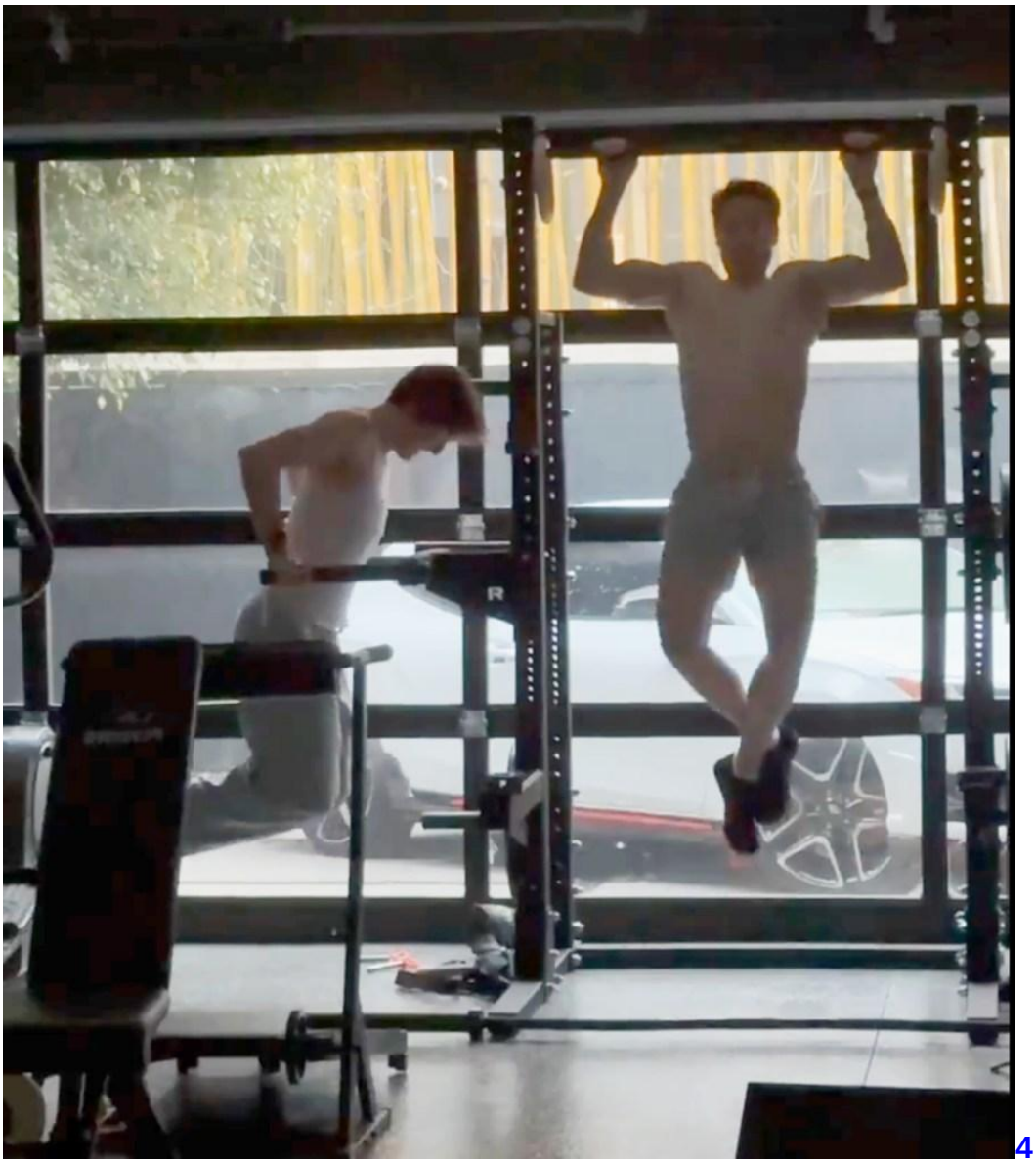
He follows a vegan diet, except for collagen peptides. He typically consumes 2,250 calories a day, 130 grams of protein, 206 carbs and 101 grams of fat.

Breakfast is a protein mix with cocoa, extra virgin olive oil and macadamia nut milk, while lunch at 9 a.m. is a super veggie bowl.

The durability duo does a daily 60-minute workout that blends strength, cardio, flexibility and balance. Reverse pushups, pull-ups, squats, bicep curls and 10 minutes of high-intensity interval training (HIIT) are among the exercises on the docket. And finally, the pair engage in “focused work.”

When asked for the documentary about his relationship with Talmage, Johnson said that, “Talmage views me as his future self, and I view Talmage as my former self.”

“I think we’re both just talking to ourself when we’re engaged in our conversations,” he added.



Johnson and Talmage exercise for an hour a day.Bryan Johnson/X

What do you think? Post a comment.

The Netflix interviewer joked: “I thought you were gonna say that you view Talmage as your future self.”

“Yeah, in many ways, that’s true,” Johnson laughed.

Bryan Johnson ditches longevity drug he took for years over concerns it could have aged him — and given him infections

Published Jan. 9, 2025

Anti-aging advocate Bryan Johnson, who gulps down 54 pills for breakfast, recently discovered a wrinkle in his meticulous approach to dodging death.

Every two weeks, the 47-year-old tech millionaire consumes 13 milligrams of the immunosuppressant rapamycin, which transplant patients take to help prevent organ rejection.

The US Food and Drug Administration has not approved rapamycin for anti-aging therapy, but physicians have been prescribing it off-label because it has been shown to extend the healthy lifespan of mice.

In a new Netflix documentary about him, “Don’t Die: The Man Who Wants to Live Forever,” Johnson called his routine “the most aggressive rapamycin protocol of anyone in the industry.”

But not long after filming the doc, he confessed that he had stopped taking rapamycin — and that it may have done more harm than good.

The video player is currently playing an ad. You can skip the ad in 5 sec with a mouse or keyboard

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Bryan Johnson, 47, revealed his intense anti-aging routine in a new Netflix documentary about him, “Don’t Die: The Man Who Wants to Live Forever.”Bryan Johnson/Blueprint

“I take this because there’s potentially some longevity benefits,” Johnson says in the flick.

“It’s the kind of thing in the longevity community that people are excited about,” he continued. “Outside the longevity community, it’s still kind of crazy, like [if you say], ‘Yeah, I take an immune-suppressing drug.’ [People react], ‘Like, that’s wacky and why would you ever do that?’”

EXPLORE MOR

Johnson said he experimented with rapamycin for nearly five years, until late September. He admitted in November that he dropped the anti-cancer drug from his rigid regimen.

“I have tested various rapamycin protocols including weekly (5, 6, and 10 mg dose schedules), biweekly (13 mg) and alternating weekly (6/13mg) to optimize rejuvenation and limit side effects,” Johnson shared on X.

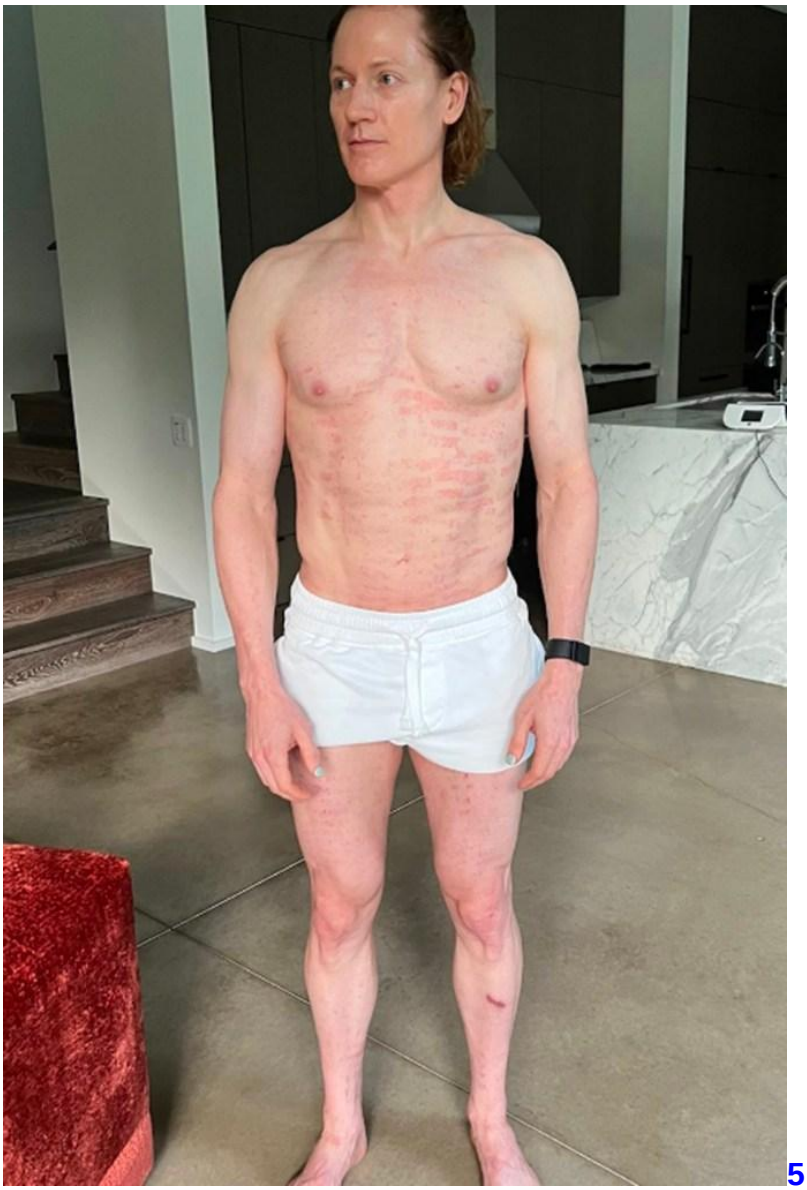
 [5]

Johnson used to take rapamycin with his special vegetable medley and 2 tablespoons of extra virgin olive oil.X / @bryan_johnson

“Despite the immense potential from pre-clinical trials, my team and I came to the conclusion that the benefits of lifelong dosing of rapamycin do not justify the hefty side-effects,” he added.

Johnson said he experienced occasional skin and soft tissue infections, abnormal levels of fats in his blood, elevated blood sugar and a higher resting heart rate.

“With no other underlying causes identified, we suspected rapamycin, and since dosage adjustments had no effect, we decided to discontinue it entirely,” Johnson explained.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Johnson is on a quest to delay death for as long as possible.Bryan Johnson/Blueprint

Medical experts featured in the Netflix doc shared concerns about humans taking the molecule — first isolated in soil collected from Easter Island in the 1960s — for longevity.

Because rapamycin suppresses the immune system, “side effects can include very dangerous bacterial infections, things like pneumonia or cellulitis or pharyngitis,” said Dr. Oliver Zolman, a longevity doctor who works with Johnson.

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Dr. Vadim Gladyshev, a professor of medicine at Harvard Medical School, said there needs to be “properly designed experiments” to test rapamycin’s effectiveness in slowing human aging.

“Then we could make scientific conclusions,” Gladyshev says in the documentary. “What Bryan’s doing, it’s not a scientific approach.”

In explaining why he ditched rapamycin, Johnson pointed to a recent study that “showed rapamycin increased biological aging according to two [measures], while ineffective according to the others.”

Medical experts have criticized his longevity experiments as unscientific.Instagram / bryanjohnson_

5

Rapamycin is primarily prescribed to organ transplant patients.Rpicorp.com

There are other rapamycin studies in the pipeline. One from the University of Washington is assessing if the drug can rejuvenate oral health in older adults.

And physicians at NewYork-Presbyterian/Columbia are investigating if low-dose rapamycin can delay ovarian aging in women. The study is scheduled to conclude by the end of October. Results are expected shortly thereafter, an NY-P rep told The Post.

Rapamycin aside, Johnson has raised eyebrows for a regimen that includes eating dinner at 11 a.m., exposing himself to penis shockwave therapy and undergoing a multigenerational plasma exchange with his teenage son and elderly father.

When he replaced his plasma with albumin protein in the fall, Johnson bragged that the medical specialist who operated the plasma exchange machine marveled that his plasma was "the cleanest he's ever seen. By far."

"He couldn't get over it," Johnson said of the operator. "When we finished, he couldn't bring himself to throw it away. He was imagining all the good that it could do in the world."

A 45-year-old tech CEO is spending millions a year to be 18 again—even though his doctor admits the results are minimal

January 26, 2023

If you had the money to reverse the natural process of aging would you do it?

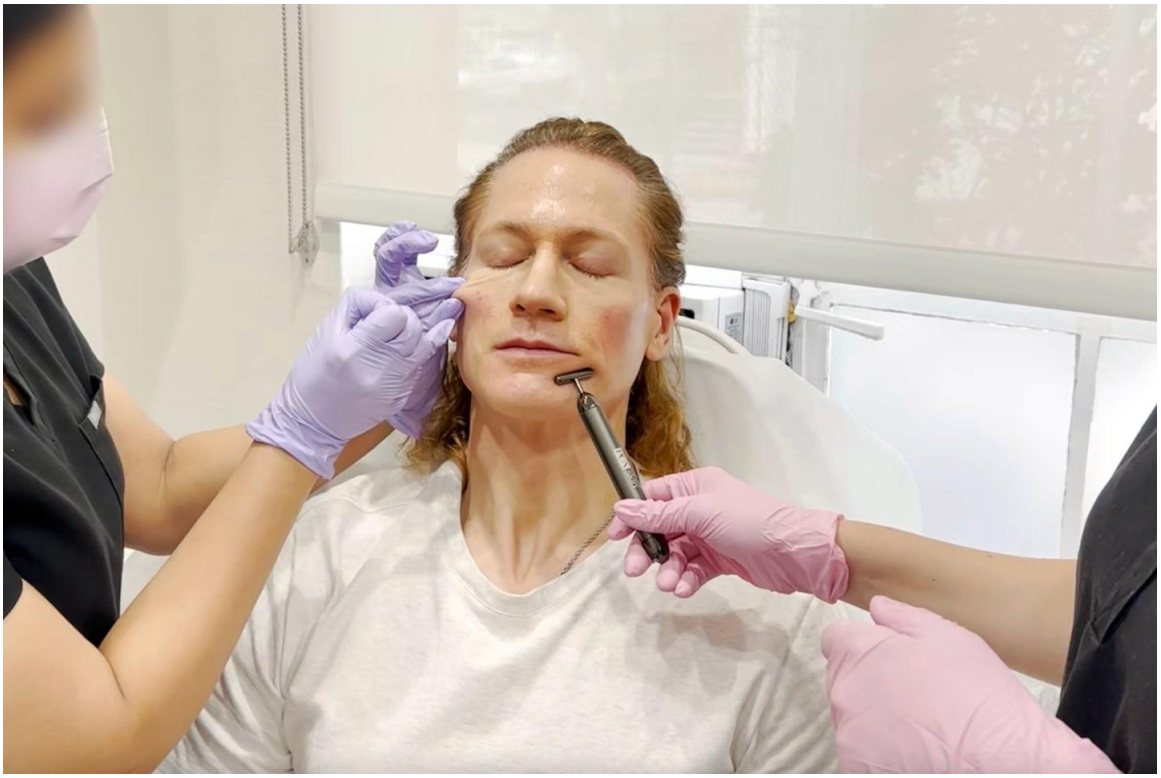
Bryan Johnson, a wealthy entrepreneur based in Venice, Calif., who is 45 going on 18—is enamored with the idea of being biologically young again. So much so that he is on the path to spending over $2 million this year alone on a host of medical interventions and tests aimed at helping him be younger. They range from electromagnetic pulses to improve the muscles in his pelvic floor to a device calculating the number of erections he has per night, according to a recent profile of the software businessman in Bloomberg. Johnson also routinely has MRIs, and has his body fat, heart rate variability, and blood and stool samples examined.

Johnson sees a team of 30 doctors for regular, and sometimes invasive, tests for what they have named Project Blueprint, according to Bloomberg.

Oliver Zolman, the 29-year-old lead doctor and "regenerative medicine physician" on the project, is dedicated "to help reverse the aging process in every one of Johnson's organs" and charges up to $1,000 an

hour for patients interested in the vast testing that Johnson participates in, Bloomberg reports.

While the data is preliminary, Johnson has the heart of a 37-year-old, the skin of a 28-year-old, and the lung capacity of an 18-year-old, according to tests his doctors performed. His overall biological age is at least five years younger, per the report.



Bryan Johnson undergoes a skin treatment.
COURTESY OF PROJECT BLUEPRINT

“We have not achieved any remarkable results,” Zolman tells Bloomberg. “In Bryan, we have achieved small, reasonable results, and it’s to be expected.”

Johnson, who has a medical facility in his own home, also adheres to a hyper-strict exercise and eating ritual, taking two dozen supplements/other medicines at 5 a.m. each day, consuming 1,977 “vegan calories a day,” exercising for an hour, and hitting the hay at the same time after using blue-light-evasive glasses.

“What I do may sound extreme, but I’m trying to prove that self-harm and decay are not inevitable,” he told Bloomberg. Since beginning to see results, he’s continued the project, despite criticism that it’s all a step too far in a way that impedes on the spontaneity that can define living a happy life.

When Bloomberg reporter Ashlee Vance visited Johnson’s home, he writes, “He could have been mistaken for a big, swollen porcelain doll.” (Johnson had recently undergone a fat injecting face procedure, which he says will help him accumulate more youthful cells, though it produced an allergic reaction.)

Johnson has made it clear—whether due to a dream of staying fit and young, outliving his own generation, or to simply explore the untapped potential of emerging longevity technology—he is not stopping anytime soon.

“The whole longevity field is transitioning into a much more rigorous, clinical place,” George Church, a geneticist at Harvard University, tells Bloomberg.

For the majority of people who don’t have the resources to have a medical facility in their home or access a team of doctors and regularly undergo medical tests, there are a myriad of questions: Namely, what will this mean for the rest of us? What is the result of this kind of health care that allows the ultrarich to literally descend in age?

For Johnson, though, it’s all fun for now.

“If you say that you want to live forever or defeat aging, that’s bad—it’s a rich person thing,” Johnson says to Bloomberg. “If it’s more akin to a professional sport, it’s entertainment. It has the virtues of establishing standards and protocols. It benefits everyone in a systemic way.”

Millionaire Known for Extreme Anti-Aging Measures Genuinely Believes He's Not Going to Die

Jan 7th, 2025

Bryan Johnson, the millionaire venture capitalist known for his quest to fight off aging through extreme measures, does not think he's going to die.

Johnson, 47, earned viral fame in 2021 when he announced Project Blueprint, a rigorous experiment to attempt to slow the rate at which his body ages. His anti-aging efforts include regular plasma transfusions from his teenage son, strict diet, exercise, sleep, and an extensive list of daily supplements. He reportedly spends $2 million annually on this quest to prevent aging.

According to test results, Johnson's physical fitness is equal to that of an 18-year-old and the heart of a 37-year-old. Those supposed results have been met with intense scrutiny and skepticism from the scientific community.

On a recent episode of the podcast *Honestly with **Bari Weiss***, Weiss bluntly asked Johnson if he believed he was going to die. Without hesitation, he responded, "No."

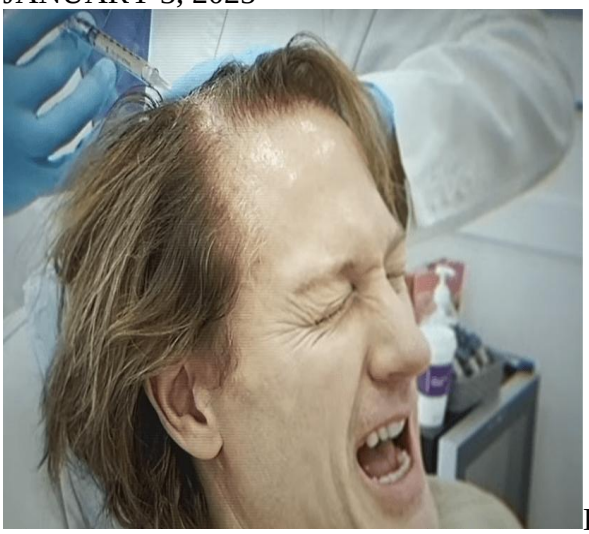
"You think you're going to live forever?" Weiss asked.

"Forever's not a concept the human mind can contemplate," Johnson said. "But will we be able to radically expand life beyond preconceived imaginations? Yes. Will it happen before my natural limit right now, which is — my life expectancy's probably like 80, 90, something like that, if I maintain my health; but the technology's moving so quickly that it will — the species is going to either survive or die in this moment much sooner than my life expectancy would turn up."

Can money buy youth? Meet the tech millionaire spending $20 million to defy father time

Tech millionaire Bryan Johnson, 47, experienced a severe allergic reaction after an experimental anti-aging fat injection for his 'Project Baby Face'.

JANUARY 3, 2025


Don't Die: The Man Who Wants to Live Forever.(photo credit: NETFLIX)

Tech millionaire Bryan Johnson, 47, recently suffered a severe allergic reaction following an experimental anti-aging procedure involving fat injections intended to restore facial volume as part of his 'Project Baby Face'. Johnson, focused on reversing the effects of aging, underwent the procedure to mitigate the gaunt appearance caused by his strict diet and low body fat percentage.

In an Instagram post, Johnson shared his experience: "Immediately after the injections, my face started to explode. And then it got worse, worse and worse, until I couldn't even see," he stated, as reported by El Tiempo. The allergic reaction left his face swollen and his eyes nearly closed, resulting in temporary vision loss.

Despite the side effects, Johnson's face returned to normal after seven days. He acknowledged the failure of the treatment but remained undeterred in his quest for youthfulness. "Seven days later, my face was back to normal and we were back in the trenches reformulating plans for our next attempt. One thing is to make a product and another very different is to be the product," Johnson remarked, according to El País Uruguay.

Johnson's Project Baby Face is part of his larger Project Blueprint, an anti-aging program overseen by a team of more than 30 doctors and health experts. He is spending approximately

$20 million on the endeavor, which combines technology, intensive exercise, vitamins, and strict medical supervision.
His daily routine includes consuming a precise diet of nutrient-rich vegetables totaling 1,977 calories per day to maintain an extremely low body fat percentage. He takes over 100 daily supplements, such as metformin, turmeric, zinc, and lithium for brain health, along with vitamins, minerals, antioxidants, and herbal extracts like resveratrol and NAD+.
Johnson follows sleep protocols, including wearing blue light-blocking goggles two hours before bed to optimize recovery and regeneration. He wakes up at 5 a.m., exercises for an hour to 90 minutes, and avoids excesses like alcohol and sugar in his diet.
His methods have drawn both intrigue and criticism from medical experts. Some label his techniques as pseudoscience, questioning the scientific basis and potential risks of such experimental treatments. Others see him as a living test case for potential anti-aging breakthroughs.
Johnson's journey is documented in the film Don't Die: The Man Who Wants to Live Forever, directed by Chris Smith. The documentary explores his health protocol and his relationships with his father and teenage son. "We may walk into a future where all of us live healthier and longer. I want to live with everything that I am," Johnson says in the film.
Despite setbacks like the recent allergic reaction, Johnson remains resolute. "I'm genuinely trying to map the future of being human. This is not a lackadaisical 'I want to be healthy.' This is, 'I want to evolve with superintelligence into the next evolution of human, and I'm willing to do anything along that path,'" he told The Independent.
Johnson's mission includes experimental practices such as blood transfusions from his teenage son and father in an attempt to slow aging, though he admitted to Futurism that these procedures had essentially "no benefits."

His approach raises ethical concerns over financial barriers and potential risks of such treatments. He insists, however, that his goal is to spark a global shift in how we approach health and wellness. "The problem is not that we don't know what to do. The problem is we are not doing what we know we should do," he stated, according to Variety.
"I genuinely would rather be respected by people in the 25th century than I would be respected right now. Because by definition, the majority of everyone who lives right now is living in the past," he is cited by The Independent.

WHO IS THE AGING-OBSESSED TECH MILLIONAIRE BEHIND NETFLIX'S 'DON'T DIE'?

In the new documentary *Don't Die*, Bryan Johnson shares his ongoing — and pricey — mission towards eternal life.

January 3, 2025

Don't Die: The Man Who Wants to Live Forever. Bryan Johnson in Don't Die: The Man Who Wants to Live Forever *NETFLIX*

There's currently no magic routine that will make humans live forever. But for tech millionaire **Bryan Johnson**, the quest to live longer lies in a routine of pills, shots, blood draws, and experimental therapy regimes he says are rewinding his biological clock. And in **Netflix**'s **new documentary** *Don't Die: The Man Who Wants To Live Forever*, released Jan. 1, filmmakers bring viewers behind the scenes to discover how much work and cash trying to live forever actually takes. It's a fascinating attempt to peel back the psyche of a man who is obsessed with aging, and one who ends up arguing that even with his quirks, Johnson might be building something meaningful to people. But he's also very, very strange.

"Blueprint may seem like it's about diet, sleep, and health. It's not. It's about figuring out how we survive as a species," Johnson told ***Rolling Stone*** in September 2023. "I'm a collection of 35 trillion cells. And before Blueprint, I had a wide variety of goals. There was Morning Me, Evening Me, Ambition Me, Dad Me, they all wanted different things at different times — I had conflicting outcomes. And I just ran this experiment to say, could I effectively align my 35 trillion cells to a single objective?"

Director Chris Smith is known for the controversial stars of his documentaries, which include ***Tiger King***, ***Fyre***, and *Bad Vegan*. In *Don't Die*, which takes its title from Blueprint's slogan, Smith shows the evolution of Johnson from an average Mormon teen to a venture capitalist who lets artificial intelligence run his health — and encourages others to do the same. Johnson was raised in the Church of Latter-Day Saints, a faith he held into adulthood. He joined the tech industry after college, but his most successful creation was Braintree, an e-commerce payment company founded in 2007 right before online shopping became the consumer norm. In 2012, the company purchased Venmo and continued to grow before it was acquired by PayPal for $800 million, according to ***Time***.

In *Don't Die*, Johnson describes being successful on paper but feeling both physically ill and incredibly depressed, a condition that led him to both leave the church and get a divorce. While his ex-wife and two of his children are still Mormon and don't speak to Johnson, according to the **documentary**, his son Talmage, 18, left the church when he was a junior

in high school and moved to California to live with his father. Talmage also follows the Blueprint path, even though he's currently in college.

Now, according to Johnson, he spends upwards of $2 million per year on the anti-aging regimen. But he also believes that the protocols he develops will be helpful for those trying and failing to navigate the healthcare system and develop their own ways of staying young. But what does that mean for Johnson's daily life — and could this million-dollar medical playground actually translate into scientific advancements for the rest of us?

"[There's] probably over a hundred different things I do on any given day that the body has asked for to be in its ideal state," Johnson says in the documentary. "By doing Blueprint, one of the key objectives is to achieve the lowest possible biological age."

This involves a strict routine including over 100 supplements and pills a day, daily medical scans, blood draws, a rigorous and restrictive diet of superfoods, an exercise regimen, and several varying experimental medical procedures like plasma donation from his teen son, penis shockwave therapy, and gene therapy.

In addition to following Johnson's medical treatment, *Don't Die* compiles interviews with journalists, researchers, and doctors in the longevity field, all of whom have varying opinions about the efficacy of Johnson's mission. Some think he's a crook, using the path to shill health kits and $75 sets of olive oil. Others believe he's bringing about the future, one jab at a time. And even more, find themselves caught firmly in the middle, interested in Johnson's process but sure that Blueprint's operating budget could be used to fund more legitimate studies, with more discernible data. But while Johnson notes in the documentary that he has critics, he still believes his algorithm led health plan is a true revolution, one that will happen by trying to build an entirely new framework for living longer. That plan starts by sharing his message with as many people as possible. And what bigger place to spread the word than by participating in a *Netflix* documentary?

I tested biohacker Bryan Johnson's $2M anti-aging lifestyle for 75 days — here's what I learned

A young man followed Bryan Johnson's intense anti-aging lifestyle — and the results are pretty shocking.

Andrew Boyd, 23, spent 75 days following the tech mogul's Blueprint diet and exercise plan to test the highly regimented program.

Johnson, a 46-year-old millionaire, spends a whopping $2 million a year on his bid to reverse the aging process. He eats a strict diet of 2,250 calories per day in a six-hour period, which he combines with a one-hour exercise regimen, 111 supplements daily, a rigid bedtime routine, blood transfusions and daily health tests, among other things, in hopes of achieving the equivalent of an 18-year-old's physique.

To figure out the efficacy of the program, Boyd attempted to follow the plan as closely as possible for an average person.

The young man from Chattanooga, Tennessee, spent about 2½ months following the strict schedule and shared the outcome on his YouTube channel.

"[I] felt incredibly focused and energized," he admitted in the video. "I learned a lot through this experience."'

Boyd ordered from Amazon in bulk, went grocery shopping weekly and purchased the vitamins he thought worked best for his body, spending about $112.34 a week on food and supplements. He followed the meal plan using recipes from Bryan's website and spent about three to four hours a week meal prepping.

He began his day with the "green giant" — which consists of water, chlorella powder, creatine, collagen peptides, cocoa flavanols and Ceylon cinnamon — and then ate the "super veggie," a mix of a "massive amounts of broccoli, cauliflower, mushrooms, ginger, garlic and black lentils."

For a snack, he munched on a so-called "nutty pudding," a mix of nuts topped with fresh strawberries, and then ended his meals with a bowl of roasted sweet potatoes, chickpeas and avocado.

The YouTuber also worked out for an hour a day and went to bed from 9 p.m. to 5:15 a.m. consistently.

“Blueprint is not about the exact diet, it’s not about the exact exercise protocol. It’s not about red light therapy or a bedtime routine or about skincare,” the young man said. said.

“At its core project, Blueprint is about using measurement and data to back up health choices,” Boyd declared.

After 75 days, he claimed that his biological age was 19.2 — at the time of the recording — while his chronological age was 23.7.


5
Boyd spent about $112.34 a week on food and supplements and meal prepped for three to four hours a week.Project Andrew/YouTube

Johnson spends $2 million a year on his bid to reverse the aging process and lower his biological age.Bryan Johnson/Blueprint
5
Bryan Johnson briefly enlisted his 17-year-old Talmage to provide blood transfusions — calling him a “blood boy.”Instagram/@bryanjohnson_

However, he did question the validity of biological age, noting it as a very limited and reactive snapshot of time that can change drastically according to immediate circumstances — such as eating a donut versus an apple.

Boyd lost nearly 30 pounds — dropping an average of 6 pounds a week — going from 192 to 164 pounds and reducing his body fat percentage from 19 to 13.9 percent.

His heart rate variability improved, achieving a lower resting rate, and he stabilized his blood sugar levels and averaged a 95% sleep score.

5
Boyd said that he saw immediate results from the Blueprint program but admitted it was incredibly difficult to follow.Project Andrew/YouTube
What do you think? Post a comment.

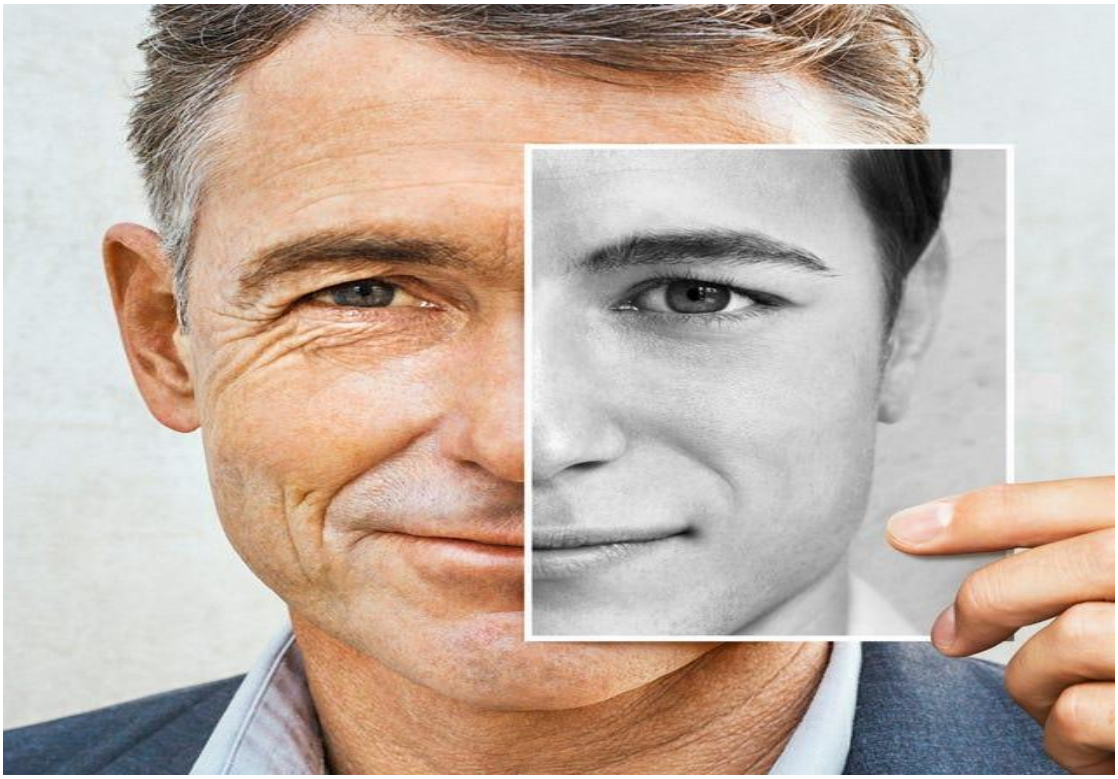
Boyd shared that his “mental clarity and focus went way up” pretty quickly and that he was enticed by how “good” he felt “all the time.”

But being realistic, he admitted that although he had great results, “prioritizing your health to the level that Bryan Johnson does is extremely hard.”

A Guy Is Spending $2 Million to De-Age by 27 Years. It May Be Working.

He won’t stop until he has the brain, heart, teeth, skin, and liver of an 18-year-old.

JAN 25, 2023 2:49 PM EST



Getty Images

- A California man has **employed 30 doctors and experts** to monitor every level of his health.
- He has spent millions of dollars to track his body’s functions to find the “blueprint” for **reversing aging** becoming medically younger.
- His lifestyle is a strict regimen meant to keep him at an optimal wellness level.

Bryan Johnson, 45, doesn’t want to just feel 18 years old. He wants his body to *act* 18 years old.

In an extreme effort—one **chronicled in depth** by *Bloomberg*—Johnson has partnered with more than 30 health professionals and spent over $2 million to track his every level of health and wellness, all with the goal to "have the brain, heart, lungs, liver, kidneys, tendons, teeth, skin, hair, bladder, penis, and rectum of an 18-year-old," according to the article.

"The body delivers a certain configuration at age 18," Johnson tells *Bloomberg*. "This really is an impassioned approach to achieve age 18 everywhere."

Dubbed Project Blueprint, Johnson's endeavor is the latest attempt from scientists and amateurs to figure out **how to reverse aging** and **cure death**. But there's nothing actually revolutionary about Project Blueprint—it just requires a whole lot of extreme, intense, and strict behavior.

Johnson eats a 1,977-calorie vegan diet daily, follows an exacting exercise routine, and sticks to a steadfast sleep routine. But he also tracks his body relentlessly via MRIs, ultrasounds, and more invasive measures like blood tests and colonoscopies.

While Johnson's ultra-healthy—and regimented—lifestyle has produced somewhat expected results, Oliver Zolman, a regenerative medicine doctor on the team, says the wild stuff hasn't even started yet: There may be gene therapies in the offing.

But until then, Johnson takes two dozen supplements and medicines every day and changes his body based on monitoring and testing everything from his body fat, blood glucose, and bowels to his nocturnal erections. He applies creams, undergoes laser therapy, and employs electromagnetic pulses. The list continues on.

Surprise, surprise: Johnson is super healthy. Doctors say the multimillionaire software entrepreneur lowered his biological age by at least five years, including with the lung capacity of an 18-year-old.

"What I do may sound extreme," he tells *Bloomberg*, "but I'm trying to prove that self-harm and decay are not inevitable."

March 19,

In a recent *Fortune* interview, tech CEO Byran Johnson—whose $2 million reverse aging regimen caught the internet's attention—says he wants to live long to enjoy more of what life offers.

"I love life," Johnson says, whose rigid medical interventions have given him the heart health of a 37-year-old, skin of a 28-year-old and lung capacity of an 18-year-old, according to his team of doctors. "If we can dramatically show that aging can be slowed and reversed, it would change everything for the human race."

He adds: "Am I scared of dying? No."

A few years ago, Johnson says he learned to fly a plane, receiving his flying license.

"It was stunning to me how well the autopilot flew the plane," he says. "I wondered, could I build an autopilot for me and my body." In order to do that, he has put faith on medicine and technology.

Bryan Johnson's daily routine

His fascination led him to adhere to a strict approach with the goal of reversing aging with the help of a team of 30 from nutritionists to MRI specialists. He undergoes daily body fat scans, routine MRIs, and often, invasive blood and stool sample tests to see the biological age of his organs.

He has 100 different protocols embedded in his day, he says. Johnson consumes a precise 1,977 calories a day, and over 70 pounds of vegetables a month. His breakfast is a standard mix of broccoli, cauliflower, black lentils, mushroom, garlic, and ginger, followed by a meal of "nutty pudding" with nuts and berries, and finally, a meal of vegetables, berries, nuts, and seeds (along with 15 grams of 100% dark chocolate and 30 milliliters of extra virgin olive oil). He admits to ending his three ounces of red wine a day he used to consume in order to meet the metrics.

With a wakeup at 4:30 each morning, Johnson completes 35 different exercises and takes a list of supplements. It has all been a part of his Blueprint Project, where he measures the health of his organs to determine his rate of aging. He says he plans to continue this regimen forever.

https://www.instagram.com/reel/CpVZh-Esemn/?hl=en

'A walking experiment'

But the data, and the effect his endeavors have on his biological age, is preliminary.

While aging and longevity experts find Johnson's commitment fascinating, they say it poses a concern given the level of discipline and money required to upkeep the routine—not to mention, the limited science available to back up his choices.

In many ways, he is “a walking experiment,” Dan Buettner, longevity expert and founder of Blue Zones LLC, previously told *Fortune*. He adds that he is still “worth paying attention to,” although results in a decade from now will prove more fruitful.

“I applaud anybody who’s tried to use science to live longer…eventually, there’s going to be an intervention that’s going to represent a big leap in life expectancy,” he says. “I don’t think it’s here yet.”

But the uncertainty of whether or not Johnson’s approach will succeed doesn't seem to bother him. "Is the fountain of youth here right now hiding in tens of thousands of scientific publications and really hard work?” he says.

The wealthy CEO does not mind being the guinea pig.

“Let's play an infinite game together,” he tells *Fortune*. “None of this stems from fear; it all comes from an absolute joy for life and a belief that there are majestic things that await us in our next evolution.”

Age-Reversing Tech Millionaire Bryan Johnson Consumes 50+ Pills Daily to Stay Young

Johnson's Netflix film, Don't Die: The Man Who Wants to Live Forever, will release on January 1

Dec. 23, 2024

Netflix has released the trailer for a documentary titled *Don't Die: The Man Who Wants to Live Forever*, which follows Bryan Johnson, a US-based software millionaire on a mission to reverse his biological age. The 47-year-old entrepreneur reveals his costly "anti-ageing protocol," which includes controversial treatments like plasma transfusions, fat transfers, and taking over 50 pills daily in his pursuit of eternal life.

The trailer showcases Johnson’s extreme measures to extend his life, offering a glimpse into his motivations. He explains his drive to explore the limits of science, stating, "I'm trying to be on the

outermost edge of possibility for the science," as he undergoes his first-ever gene therapy in his quest for longevity.

In the trailer, the 47-year-old Johnson shares that his family is the driving force behind his quest for longevity. "I really want to have multiple lifetimes with my son. One hundred years is not enough," he says. The clip also features Johnson, his son, and his father participating in a "multi-generational" plasma exchange, where Johnson's son donates plasma to him, and Johnson donates his plasma to his aging father.

"We may walk into a future where all of us live healthier and longer. I want to live with everything that I am," Johnson explains. He goes on to challenge the idea that aging and death are inevitable, stating, "As a species, we accept our inevitable decay, decline, and death. I want to argue that the opposite is true."

Don't Die: The Man Who Wants to Live Forever will be released on Netflix on January 1. The documentary explores Bryan Johnson's radical approach to reversing aging and potentially conquering mortality. The documentary delves into his obsession with extending life through extreme and costly treatments, capturing the attention of those curious about the science behind defying death.

A former Silicon Valley executive, Bryan Johnson has become a prominent figure in the anti-ageing world through his platform, Blueprint, which investigates innovative methods to reverse aging. His journey includes extreme measures, such as blood transfusions from

his teenage son, and an annual $2 million budget dedicated to medical diagnostics, treatments, and a meticulously designed regimen of diet, exercise, and sleep.

Millionaire Bryan Johnson Claims He Cracked Anti-Aging Code, Selling His Secret for $343

Bryan Johnson said the nutrition stack has been built upon more than 1,000 clinical trials and costs less than fast food at $343 for 30 days.

Bryan Johnson declared it "second only to Mother's milk."

Millionaire tech entrepreneur Bryan Johnson is selling a part of his anti-ageing regime. Mr Johnson claims to have reversed his biological age by following a strict program called Project Blueprint, which includes a special diet and over 100 daily supplements.

One element of Project Blueprint, a "Blueprint stack," is now available for purchase. The stack includes a drink mix, protein, 8 pills, snake oil, 67 powerful therapies, and 400 calories. It is built upon over 1,000 clinical trials.

Mr Johnson says the stack is backed by research and costs less than fast food, at $343 for a month's supply. In a post promoting the drop, Johnson proclaimed it to be "second only to Mother's milk."

Mr Johnson recommends replacing 400 calories from your current diet with the Blueprint stack. The stack is not intended to fully replace meals but rather to supplement deficiencies.

Mr Johnson, a former Silicon Valley executive, is known for his obsession with anti-ageing. Johnson claims to have reversed his biological age by over 5 years and boasts improved health markers. He has invested heavily in Project Blueprint, which includes a special diet, medical monitoring, therapies, and exercise. Earlier this year, Mr Johnson claimed to have reversed hair loss through another self-developed programme.

It is important to note that there is no scientific consensus on the effectiveness of Project Blueprint, and spending $2 million a year on anti-ageing interventions is likely out of reach for most people.

He stated that his product is available for delivery to 23 countries, including the USA, Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, New Zealand, the Netherlands, Norway, Poland, Portugal, Spain, Singapore, Sweden, Switzerland, the UAE, and the United Kingdom.

Bryan Johnson: The tech entrepreneur who spends millions to reverse ageing

The millionaire injects his son's blood on a quest for youth, and has reportedly slowed the pace of ageing by 31 years

25 MAY 2023

Tech millionaire Bryan Johnson has been injected with his 17-year-old son's plasma in a quest to reverse the ageing process and attain the body of an 18-year-old.

Johnson previously hit headlines for revealing he was spending $2 million (£1.6 million) a year on an intense regime to reduce his biological age.

His latest effort to become more youthful has also raised eyebrows, as he revealed he received a plasma infusion from his son, as reported by The Times, inspired by a study that showed that older rodents benefited from sharing a circulatory system with younger mice.

Although the effects on humans is unknown, Johnson has said he will release the results of his own plasma therapy soon.

So who is Bryan Johnson and what is his quest for youth?

Who is Bryan Johnson?

Bryan Johnson, 45, is a tech entrepreneur from Utah who has embarked on a quest to reverse the ageing process.

Johnson was raised in the Church of Latter Day Saints, and was once a Mormon missionary.

When he left the church, he became "partly estranged" from his three children, his son Talmage, 17, revealed to The Times. Father and son now live together in California.

He made his millions selling a tech company to eBay and has since pursued ventures in health tech, including his anti-ageing mission, Project Blueprint.

Tech ventures

His mission began in 2013, when he sold his payment-processing company, Braintree, to eBay for $800 million (£646 million). The year before, Braintree acquired payment app Venmo.

In 2016, he founded Kernel, using $55 million (£44 million) of his own money. Kernel builds hardware to measure brain activity.

Johnson's hope is that the helmets will eventually be used to develop mental-health treatments based on psychedelics, according to The Week, and to assist in the studying of brain ageing, Alzheimer's, and strokes, among other illnesses.

Reversing ageing

BRYAN JOHNSON AND HIS SON, TALMAGE, WITH WHOM HE SWAPPED BLOOD
MAGDALENA WOSINSKA / COURTESY OF BRYAN JOHNSON

The millionaire then announced his next venture, Project Blueprint, in 2021, with the aim of reversing the ageing of his organs. That year, he claimed that his biological age was 36, eight years younger than his then-chronological age of 44. After two years of following his Blueprint algorithm, Johnson has reportedly slowed the pace of ageing by the equivalent of 31 years, and is now ageing slower than the average 10-year-old. His body muscle and fat is "ideal", and he has "perfect" liver fat.

But becoming younger isn't an easy feat — nor is it cheap.

Every day, Johnson follows a strict schedule that dictates what he eats (fewer than 2,000 calories, a vegan diet, plus 16-18 hours of daily fasting), the supplements

he takes (more than two dozen upon waking, plus more with dinner), and his fitness routine (an hour a day, including three HIIT sessions a week).

This intense regime, which involves hundreds of measurements annually (routine measurements include BMI, blood glucose, physical fitness, MRIs, and ultrasounds), costs Johnson around $2 million (£1.6 million) a year.

While the process may sound difficult and tedious for most people, Johnson revealed he derives "tremendous pleasure" from his mission.

"It's funny, because most people hear about this, and the instantaneous reaction is to assume that I must be miserable," Johnson told British GQ.

"It's very hard to understand that I might derive more pleasure from doing this than I would anything else."

UPDATED 1.26.23

ECCENTRIC WEALTHY GUY SPENDS $2 MILLION PER YEAR STAVING OFF AGING

"NO ONE IS PUSHING THE ENVELOPE AS MUCH AS BRYAN."

Tech centimillionaire and middle-aged human man Bryan Johnson, founder of the online payment behemoth Braintree, among other ventures, wants to be 18 again.

Not mentally or spiritually, but physically so — Johnson's on a quest to turn back his biological clock, returning his body's 45-year-old "brain, heart, lungs, liver, kidneys, tendons, teeth, skin, hair, bladder, penis and rectum" to each of their 18-year-old condition. And according to *Bloomberg*, he'll do pretty much whatever it takes — or costs — to get there.

"The body delivers a certain configuration at age 18," Johnson, who again is a middle-aged human man, told *Bloomberg*, detailing his roughly $2 million-per-year approach to anti-aging. "This really is an impassioned approach to achieve age 18 everywhere."

Looking at the entrepreneur's daily and weekly routines, it's not surprising that Johnson's biohacking extremes ring up a multimillion-dollar yearly tab. (Full disclosure, by the way: Johnson was an early investor in Futurism Media, though his involvement ended in 2019.)

He reportedly employs over 30 doctors and health professionals and sticks to an expensive — and incredibly strict — diet, fitness, and supplement regimen. On top of it all, he routinely subjects himself to expensive treatments and procedures, which are sometimes extraordinarily painful, all with the goal of hitting 18-year-old biomarkers.

Of course, Johnson isn't the only rich person obsessed with prolonging his lifespan and vitality. Anti-aging, and even reverse-aging, is common pursuit among the ultrawealthy, particularly in Silicon Valley, elite sports, and celebrity circles. But it could well be argued that Johnson takes longevity to greater extremes than most, not just putting his money, but his body, where his mouth is.

"I treat athletes and Hollywood celebrities," Jeff Toll, an internist on Johnson's very large health staff, said to *Bloomberg*, "and no one is pushing the envelope as much as Bryan."

Pushing the envelope, apparently, has included but not been limited to Johnson taking a lot of pictures — 33,537 in total, per the publication — of his bowels, the undertaking of a "fairly constant stream of blood, stool and urine tests as well as whole-body MRIs and ultrasounds," and extensive daily and weekly skincare routines that involve a lot of lasers and chemical peels. He even employs a device that *tracks his nighttime erections*, just to give a sense of how deep this rabbit hole goes.

Johnson's doctors told *Bloomberg* that they do in fact believe that some of their client's organs are aging backward, with his heart, skin, and lung capacity presenting as 37, 28, and 18 years old, respectively. Overall, the entrepreneur and his team claim that Johnson has wound the epigenetic clock back by 5.1 years over the course of 7 months.

"All of the markers we are tracking," Toll continued, "have been improving remarkably."

And unlike other longevity-hunting zillionaires, Johnson hardly keeps anything he does a secret. Fascinatingly, he tracks his progress openly in something called Blueprint, which reads like a fitness-tracker-meets-personal-diary. Everything, from his monthly food costs to his "notable challenges" to his guiding "principles" — "Principle 4: Look in the Darkness to avoid being blinded by the light" — is carefully maintained in the document, in a possible sign that Johnson is less intent on cracking the reverse-aging code in order to financially capitalize on longevity tech and motivated instead by a personal curiosity. Or, perhaps, a personal need.

"This time, our time, right now — the early 21st century — will be defined by the radical evolution of intelligence: human, AI and biology. Our opportunity is to *be* this exciting future," reads Blueprint's landing page. "Entropy = aging and deterioration. Goal Alignment via your Autonomous Self aims to combat entropy by maintaining perpetual youth. Maximally slowing your pace of aging and reversing the aging that occurs."

Right on, guy. Anyway. We all have our hobbies. And it seems that Johnson has the funds, as well as the sheer willpower, to support his. (We'll continue to work on coming to terms with our mortality, as that suits our particular tax bracket.)

Experts Worried Elderly Billionaires Will Become Immortal, Compounding Wealth Forever

"The longer you're around, the more your wealth compounds."

Let's be clear: modern science has done a lot of incredible things for human health. We live way longer than we used to, and quality of life is remaining far better, for far longer, than at any other point in history.

But there are a lot of wealthy people out there who don't just want to live longer. They want to live forever, and they're using their deep pockets to try to make it happen. In fact, *Wired* just declared that anti-aging research in 2023 could "kickstart the greatest revolution in medicine since the discovery of antibiotics."

Could all that hype fall short? Sure, and it likely will. But it's *also* possible that the quest for immortality could mark a grim new inflection point in the history of wealth.

That's not just because it might mean that humanity will simply have to exist with the glare from an immortal Jeff Bezos' glistening scalp for eternity, but because such technology might mean that people like Bezos, whose money equals a *whole* lot of power, would be able to continue compounding that wealth and power for, well, forever.

"Suppose, for example, we had a kind of vaccine for the pandemic of age," Christopher Wareham, a bioethicist at Utrecht University who studies the ethics of aging, told *The Financial*

Times. "This is going to potentially exacerbate all the kinds of existing inequalities that we have... The longer you're around, the more your wealth compounds, and the wealthier you are, the more political influence you have."

It's a bone-chilling hypothesis, to say the least. Time, of course, is the central reason why anything really changes, politics included. Old leaders and belief systems die, new citizens with fresh ideas are born; in Wareham's dystopian postulation, dictators and autocrats, as well as their donors, would additionally flock to the still-mythic technological fountain of youth.

And seeing as how neither wealth nor power, political or otherwise, are historically something that folks are too keen to share, it's not exactly outlandish to assume that the already-rich makers of such a miracle drug or device might employ some hefty gatekeeping efforts. (Fascinatingly, billionaire SpaceX founder and hopeful Mars colonizer Elon Musk is very much opposed to immortality tech on grounds that leaders should definitely die at some point.)

That being said, some in the field are grappling with these issues, at least in principle. Mehmood Khan, for example, chief executive of longevity nonprofit Hevolution Foundation, told the *FT* that his organization is only funding products that can be "democratized."

"If this is going to be a gazillion dollars' worth of treatment for a handful of people," he told the outlet, "it is of no interest."

Elsewhere, the Bezos-funded Altos Labs, founded with the intention of materializing "cellular rejuvenation programming" to "reverse" disease and injury, says that it's committed to helping as many people as possible.

But of course, as anyone of these organizations has yet to crack the code on immortality, or even an added twenty years to the human lifespan, these are just promises. But any breakthrough would be a financial jackpot in its own rite, and across the board, when that much money — and again, that much power — are involved, promises are easily broken.

Elon Musk Says That Immortality Tech Would Be Very Dangerous

"It is important for us to die because most of the time people don't change their mind, they just die."

SpaceX and Tesla CEO Elon Musk has some strong feelings when it comes to our fate as a civilization.

During an interview at *The Wall Street Journal*'s CEO Council Summit on Monday, Musk warned that letting people live longer — or, presumably, forever — through new technologies may actually be a really bad idea.

"It is important for us to die because most of the time people don't change their mind, they just die," Musk said at the event. "If you live forever, we might become a very ossified society where new ideas cannot succeed."

Musk also added that he's "not aware of any secret technology to combat aging."

His ideas shouldn't come as a shock to anybody. Musk is an ideas man who has benefited immensely from pushing for innovation and change — for better or worse. In his world, there's no room for rigid and obsolete lines of thinking.

Which also explains his continued efforts to push back against the US regulators who have kept an increasingly close eye on his operations. The news also comes after he called for "age limits" to be set for US government leaders earlier this month.

Musk, a 50-year-old father of six, also argued at the event that a "rapidly declining birthrate" on a global scale is "one of the biggest risks to civilization."

Allowing people to live longer lives, in other words, would result in rapidly aging populations, which would lead to further declining birthrates as fewer people are able to have children.

It's far from the first time Musk has warned of declining populations being the eventual cause of our downfall. Earlier this year, he took potshots at fellow space company billionaire Jeff Bezos for investing millions in a mysterious anti-aging research startup in Silicon Valley."And if it doesn't work, he's gonna sue death!" Musk added derisively at the time, referring to Bezos' litigious tendencies.

Despite all of facetiousness and flippant comments in the past, Musk's warnings aren't completely off the mark. Birthrates are indeed declining worldwide — and COVID-19 has only heightened the trend.

Even China, the most populous country in the world, has faced precipitous drops in birthrates, causing leaders to ring the alarm bells.

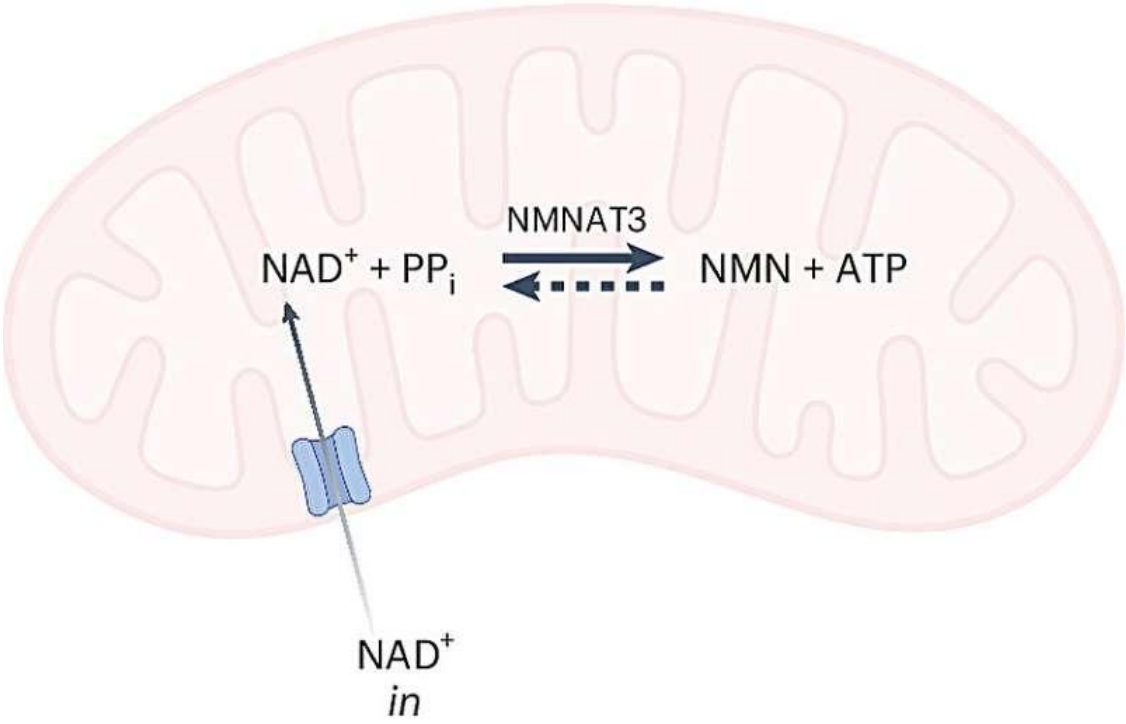
With demographics skewing older in may parts of the world, humanity could really be in for a decline, and it could kick off before the year 2100, according to experts.

But whether that's really a bad thing remains to be seen. The economic impacts of a shrinking labor force may be self-evident, but given our species' immensely harmful footprint on our planet, it may not be such a bad thing after all.

DECEMBER 23, 2024

Newly discovered mechanism reveals NAD's role in aging and disease

by University of Bergen



Proposed model for the cooperation of SLC25A51 and NMNAT3 to buffer cellular NAD⁺ fluctuations. Credit: *Nature Metabolism* (2024). DOI: 10.1038/s42255-024-01174-w

UiB researchers are behind a new discovery that tells us how associated neurodegenerative diseases might develop. At the center of this discovery stands a molecule called NAD, or nicotinamide adenine dinucleotide. The results have been published in *Nature Metabolism*.

Professor Mathias Ziegler from the Department of Biomedicine, University of Bergen (UiB), led the international team of researchers behind the study and explains its significance: "The fascinating thing about NAD is that the molecule is essential to life, as it plays critical roles in all cellular processes.

"Therefore, dysregulated NAD levels are involved in aging processes as well as many pathologies ranging from cancer to diabetes and neurodegenerative diseases. And the reason for this is that it holds a key position in both energy metabolism and the regulation of vital functions," he says.

NAD is like a rechargeable battery

All bodily functions depend on energy. Without energy we can neither run, breathe nor think. The energy that our body, or our cells, need to function comes from the food we ingest. Nutrients, such as sugar or fat, are converted to a universal form of energy that our cells can use to maintain all energy-demanding functions.

"NAD is central to these conversions as it functions like a rechargeable battery. It is charged by the energy retrieved from food and passes it on to fuel all cellular activities. An important part of this energy transfer takes place in cellular structures called mitochondria, which are also referred to as the powerhouse of the cell," Ziegler explains.

Crucially, NAD also contributes to many other vital functions throughout the cell. It serves as a chemical signal to regulate key cellular events including gene expression and DNA repair, which take place in the cell nucleus.

"Interestingly, during aging, our DNA may accumulate damage which, in turn, will increase the demand for NAD molecules. Indeed, we see that cellular NAD levels decrease as we age, and it is assumed that increased DNA repair activity is one of the main reasons for this decline," explains Ziegler. "The problem arises when the mitochondria or their NAD store are affected or tapped over extended periods of time."

But how do cells cope with the increased demand for NAD and do decreased NAD levels necessarily result in pathological conditions?

To answer these questions, Ziegler and his team developed models to study how cells react to reduced NAD levels as they occur during aging.

They had previously developed a method that enabled them to detect cellular NAD molecules and their distribution in living cells. In addition, they implemented advanced analytical techniques, including high-resolution mass spectrometry, to study the cellular dynamics of NAD-dependent processes.

As a result, the researchers discovered a hitherto unrecognized role of mitochondria in the maintenance of cellular NAD levels:

"These organelles serve as an NAD reservoir that is filled when cells function normally, and it supplies the cell with NAD when there is an increased demand," explains Lena Høyland, Ph.D. student and first author of the study.

Employing gene-technological methods such as CRISPR-Cas9 genome editing, they were able to establish the molecular mechanisms of how mitochondria counteract cellular NAD decline.

"Decreased cellular NAD levels thus appear to be generally well tolerated by the cells," she says.

"The problem, however, arises when the mitochondria or their NAD store are affected or tapped over extended periods of time. This can have fatal consequences since the cells may no longer have sufficient NAD 'battery capacity' to drive vital, energy-dependent processes," Professor Ziegler adds.

NAD supplementation has provided encouraging results

Research in recent years has established that mitochondrial dysfunction and lowered cellular NAD levels represent characteristics of aging, and age-related disorders, such as dementia or neurodegenerative diseases.

Based on their new findings, the team of researchers believes that excessive consumption of mitochondrial NAD might constitute a key factor leading to dysfunctional cellular powerhouses and thus aging-associated diseases.

Indeed, initial clinical trials in Norway and internationally using therapeutic supplementation approaches aiming to increase NAD levels have provided encouraging results.

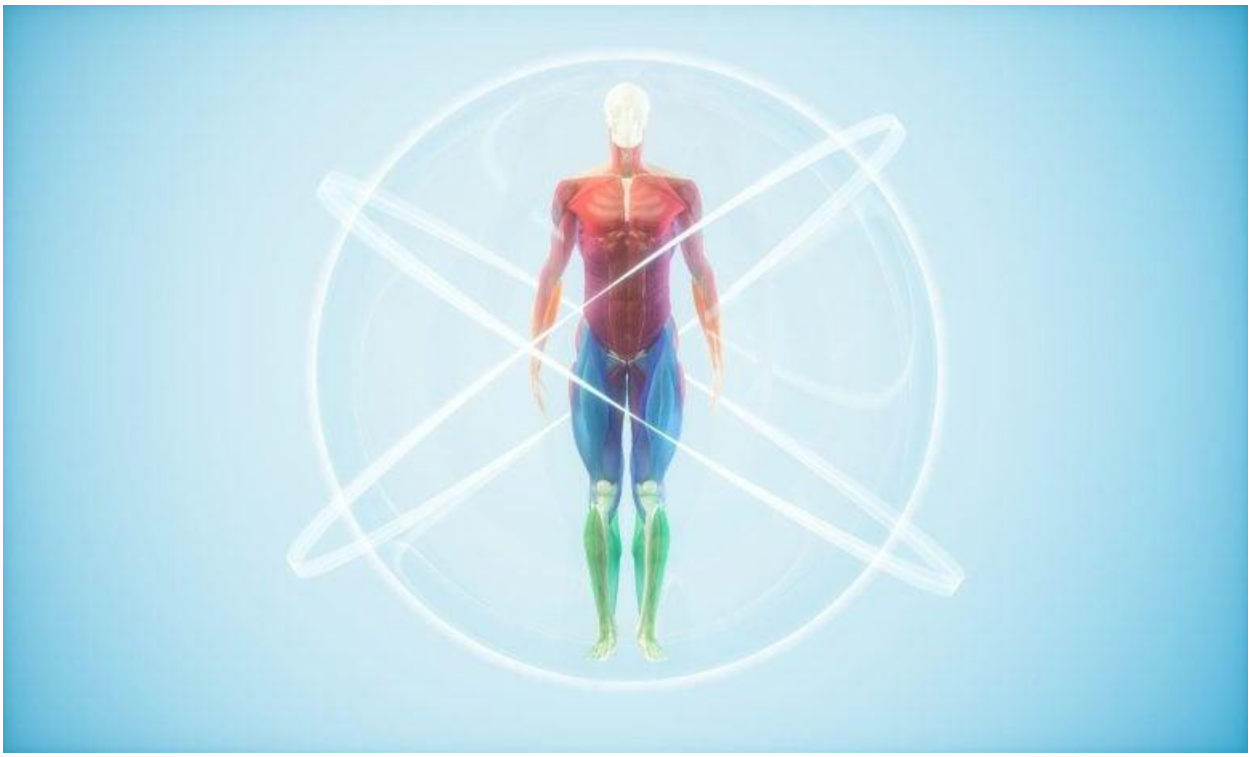
"We are very excited about having discovered yet another mechanism potentially involved in disease development and progression," says Høyland

Ziegler says, "Our study also demonstrates the importance of basic research to identify promising targets to slow aging and to treat aging-related diseases."

More information: Lena E. Høyland et al, Subcellular NAD+ pools are interconnected and buffered by mitochondrial NAD+, *Nature Metabolism* (2024). DOI: 10.1038/s42255-024-01174-w
Journal information: Nature Metabolism
Provided by University of Bergen

Longevity Breakthrough: Scientists Restore “Youthful” Enzyme Activity To Combat Aging

JANUARY 19, 2025



CCM Biosciences has developed groundbreaking compounds that activate the enzyme SIRT3, potentially reversing age-related cellular decline. These first-in-class drugs outperform existing treatments and will enter clinical trials in 2025 to target Alzheimer’s, Parkinson’s, and other age-related diseases.

Innovative therapies revive a once-undruggable mitochondrial aging regulator through a revolutionary enzyme activation mechanism.

Researchers at CCM Biosciences, Inc. have leveraged a novel biophysical mechanism of enzyme activation to discover and characterize groundbreaking enzyme activators for a previously untargetable master regulator of cellular energy production.

These first-in-class compounds restore the enzyme’s activity to levels comparable to those of youthful cells, offering substantial potential for clinical applications in treating age-

related disorders such as Alzheimer's, Parkinson's, cardiovascular diseases, and metabolic conditions.

Enhancing healthy lifespan by even one year is estimated to hold a global economic value exceeding $10 trillion. In line with this potential, the largest XPRIZE in history has recently launched a seven-year initiative focused on cellular rejuvenation.

Many chronic age-associated diseases may be addressed by boosting the activity of enzymes responsible for regulating critical biochemical signaling pathways. Despite the global focus on this area, identifying enzyme activators remains challenging due to their reliance on allosteric modulation—a mechanism that is viable in fewer than 10% of proteins.

Expanding Beyond Traditional Enzyme Activation

Recently, a team of scientists at CCM Biosciences and its affiliated R&D center Chakrabarti Advanced Technology expanded the scope of enzyme activation beyond allosteric modulation by introducing new physical principles for enzyme activation and successfully applied computational and experimental design methods based on these principles to identify new compounds that dramatically enhance the activity of previously undruggable enzyme Sirtuin-3 (SIRT3), which is centrally involved in regulating human aging. This study was published in *Physical Review X*, the flagship journal of the American Physical Society (APS), on October 22, 2024.

Billions of dollars have been invested over the past two decades in efforts to upregulate sirtuin enzymes due to their role in regulating healthspan and lifespan. The biotechnology company Sirtris Pharma, founded based on the work of longevity researchers from Harvard and MIT, was bought by GlaxoSmithKline for $720 million, but the development of its drug candidates, which were allosteric activators, was subsequently terminated due to the observation that they only functioned with a limited number of substrates for one of the seven sirtuin enzymes.

Due to the difficulty of identifying activators that upregulate more sirtuin enzymes under more physiologically relevant conditions, companies such as Elysium Health (MIT) had largely abandoned the efforts to develop targeted sirtuin activators and instead turned to marketing nutraceuticals to increase sirtuin activity.

Unlocking the Potential of SIRT3 Activation

Notably, SIRT3, the major mitochondrial sirtuin enzyme, plays a critical role in determining human health span and lifespan through the regulation of mitochondria—the energy production powerhouses of cells that decline with age—but was considered undruggable due to lack of a known allosteric site. The lead compounds recently discovered by CCM

scientists greatly increase the sensitivity of SIRT3 to the essential metabolic cofactor NAD^+ (nicotinamide adenine dinucleotide), whose levels decrease with age and play a major role in the onset of many age-related diseases. While researchers had identified protein mutations in sirtuins that could increase the sensitivity of a related enzyme SIRT1 to NAD^+, they were not successful in designing drug-like compounds that could achieve this effect.

CCM compounds fully recovered the activity of SIRT3 in the face of NAD^+ levels decreasing by a factor of two, as observed in old age. The scientists have also shown that their compounds increase SIRT3 activity in the face of declining NAD^+ for multiple cell lines employed in aging studies. The proposed compounds are also undergoing animal testing in mice for age-related disorders, including infertility, where they have outperformed both NAD^+ supplements and other sirtuin activators.

In recent years, investment in therapeutic interventions for age-related disorders has surged, with invested capital in 2024 exceeding $5 billion. Notable examples include Calico (an Alphabet company) and Altos Labs, each of which has received over $3 billion in funding.
However, very few proprietary first-in-class drug candidates have been advanced to clinical trials for efficacy in against age-related disorders. By contrast, the drug programs of CCM Biosciences for age-related disorders are entering clinical trials for efficacy in 2025.

Dr. Michael Pollak, Professor of Medicine, Oncology, and Pharmacology at McGill University and an expert on clinical trials for age-related disorders and the biochemistry of sirtuin-regulated signaling pathways, says that “Efforts have been underway for decades to activate signaling pathways regulated by sirtuins to combat age-related disorders, but prior efforts have encountered significant hurdles. The discoveries by CCM Biosciences pertaining to the design of drug candidates that can activate the major mitochondrial pathways regulated by sirtuins, along with the clinical development plan for evaluation of efficacy as well as safety of these drug candidates, revitalize this area of drug development.”

Reference: “Computationally Driven Discovery and Characterization of SIRT3-Activating Compounds that Fully Recover Catalytic Activity under NAD+ Depletion” by Xiangying Guan, Rama Krishna Dumpati, Sudipto Munshi, Santu Chall, Rahul Bose, Ali Rahnamoun, Celina Reverdy, Gauthier Errasti, Thomas Delacroix, Anisha Ghosh and Raj Chakrabarti, 22 October 2024, *Physical Review X*.
DOI: 10.1103/PhysRevX.14.041019
BiotechnologyLifespanLongevityMolecular Biology

JANUARY 21, 2025

Why our biological clock ticks: Research reconciles major theories of aging

University of California - San Diego

Credit: AI-generated image

Researchers at University of California San Diego School of Medicine have published results that shed new light on an old question: what causes aging at the molecular level? Their findings, published in *Nature Aging*, describe a never-before-seen link between the two most accepted explanations: random genetic mutations and predictable epigenetic modifications. The latter, also known as the epigenetic clock theory, has been widely used by scientists as a consistent, quantitative measure of biological aging.

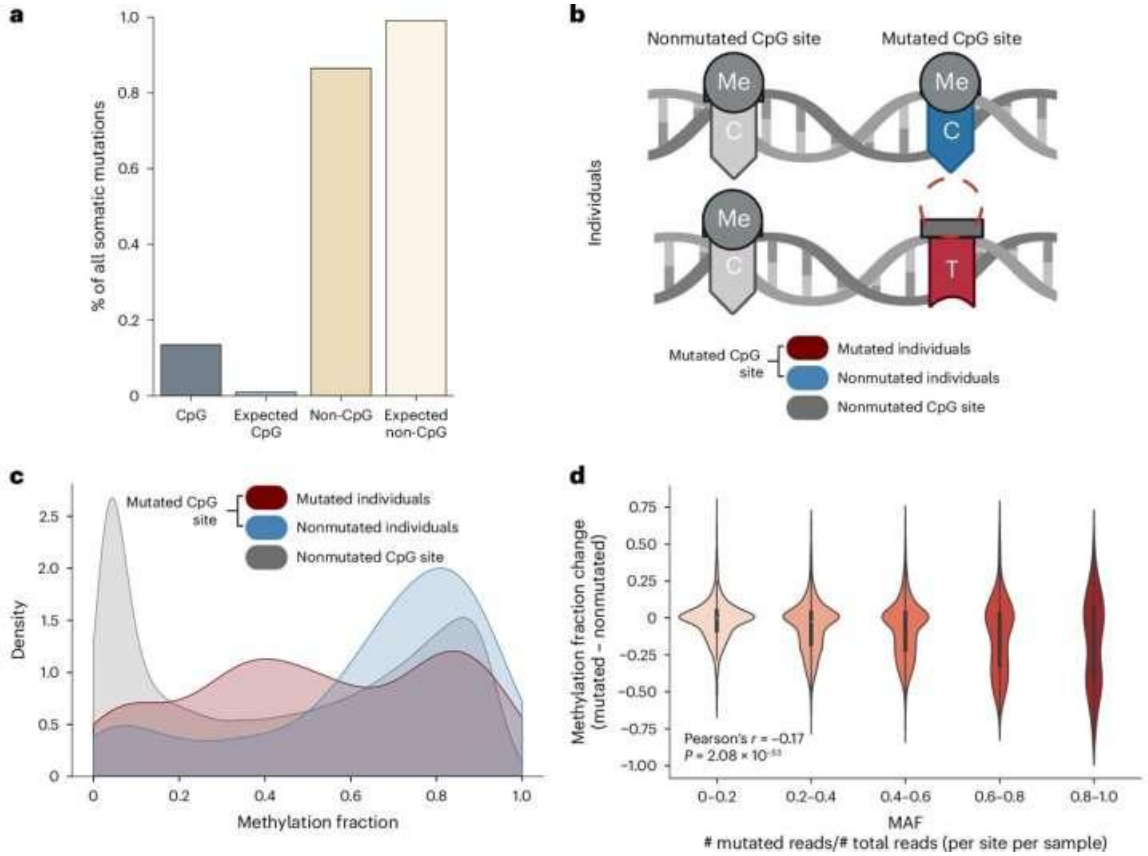
However, the new research suggests that the process may not be so simple.

"Major research institutions and companies are betting on turning back the epigenetic clock as a strategy to reverse the effects of aging, but our research suggests that this may only be treating a symptom of aging, not the underlying cause," said co-corresponding author Trey Ideker, Ph.D., a professor at UC San Diego School of Medicine and UC San Diego Jacobs School of Engineering.

"If mutations are in fact responsible for the observed epigenetic changes, this fact could fundamentally change the way we approach anti-aging efforts in the future."

There are two prevailing theories about the relationship between aging and DNA. The somatic mutation theory suggests that aging is caused by the accumulation of mutations, permanent changes in our DNA sequence that occur randomly. The epigenetic clock theory suggests that aging occurs due to the accumulation of epigenetic modifications, minor changes to the chemical structure of DNA that do not alter the underlying sequence, but instead change which genes are on or off. Unlike mutations, epigenetic modifications can also be reversed in some cases.

Because epigenetic modifications only occur at specific sites on our genome rather than at random locations, they are easier to quantify and have become a go-to way for scientists to determine the "biological age" of cells. However, scientists have long wondered about the source of these epigenetic changes.



Frequency and methylation status of CpG mutation events. Credit: *Nature Aging* (2025). DOI: 10.1038/s43587-024-00794-x

To answer this fundamental question, researchers analyzed data from 9,331 patients cataloged in the Cancer Genome Atlas and the Pan-Cancer Analysis of Whole Genomes. By comparing genetic mutations to epigenetic modifications, they found that mutations were predictably correlated with changes in DNA methylation, one type of epigenetic modification.

They found that a single mutation could cause a cascade of epigenetic changes across the genome, not just where the mutation occurred. Using this relationship, the researchers were able to make similar predictions of age using either mutations or epigenetic changes.

"Epigenetic clocks have been around for years, but we're only now beginning to answer the question of why epigenetic clocks tick in the first place," said first author Zane Koch, a Ph.D. candidate in bioinformatics at UC San Diego. "Our study demonstrates for the first time that epigenetic changes are intricately and predictably tied to random genetic mutations."

The study's authors note that further research is needed to fully understand the relationship between somatic mutations and epigenetic changes in aging. However, the study's findings provide a major breakthrough in our understanding of the aging process and have important implications for the development of new therapies aimed at preventing or reversing aging.

"If somatic mutations are the fundamental driver of aging and epigenetic changes simply track this process, it's going to be a lot harder to reverse aging than we previously thought," added co-corresponding author Steven Cummings, M.D., executive director of the San Francisco Coordinating Center at UC San Francisco and senior research scientist at Sutter Health's California Pacific Medical Center Research Institute.

"This shifts our focus from viewing aging as a programmed process to one that's largely influenced by random, cumulative changes over time."

In addition to Ideker, Cummings and Koch, the study was co-authored by Adam Li at UC San Diego and Daniel S. Evans at California Pacific Medical Center Research Institute and UC San Francisco.

More information: Zane Koch et al, Somatic mutation as an explanation for epigenetic aging, *Nature Aging* (2025). DOI: 10.1038/s43587-024-00794-x
Journal information: Nature Aging
Provided by University of California - San Diego

US scientists gene engineer mice in first-ever model to unlock human aging secrets

WSU researchers developed a new clinical model to study telomeres in humans: genetically engineered mice.

Updated: Feb 04, 2025

After years of hard work, scientists have succeeded in creating genetically-engineered mice that could help accelerate anti-aging research for humans.

A team of scientists from the Washington State University (WSU) have taken one step ahead in the quest to unlock the secrets of extending human lifespan at the cellular level.

As per the team's research, aging occurs gradually due to the shortening of telomeres –the protective caps at the ends of chromosomes that function like shoelace tips to prevent unraveling. s telomeres shorten over time, cells lose their ability to divide for healthy growth, and some eventually begin to die, says the press release.

However, it has been challenging to study the telomeres at the cellular level in humans.

Therefore, the scientists led by WSU College of Pharmacy and Pharmaceutical Sciences Professor Jiyue Zhu have developed mice that have human-like short telomeres.

It should be noted that normally mice have up to 10 times longer telomeres than humans.

First mouse model with humanized telomeres

The genetically engineered mice are being called HuT mice by the scientists. They will help the team to make progress in multiple research projects.

"This is the first mouse model with truly humanized telomeres because telomerase isn't expressed in adult tissues in this model," Zhu said. "Our paper demonstrates that they exhibit human-like telomeres. Now, we aim to observe how these mice age."

The key areas of focus for researchers include studying how short telomeres reduce the likelihood of developing cancer and influence human lifespan, as well as exploring

strategies to extend individuals' health span– the period of life free from age-related diseases.

"One of our goals is to reduce telomerase expression in cancer cells, and this is an active area of research," he added.

It can help in developing new drugs and treatments for the future. As Zhu pointed out, many diseases start at the cellular level, therefore, targeting drugs at that space is a good strategy.

Unlocking anti-aging in humans

In the long run, the research can also help them pave the way for making anti-aging in humans a reality to extend lifespans.

As per Zhu, the mouse model will allow for multiple aging related studies. One of the collaborating scientists studies how sleep impacts human health. The HuT mice will also be studied to understand how the stress of sleep deprivation and other life stresses affect telomere regulation and aging.

It took 10 years for Zhu and his team of scientists to develop the HuT mice. During this period they studied how telomeres differed in humans and other animals.

Mice were finally chosen for the study "as they are similar to humans in terms of organ structures, genes, and genetic makeup."

The scientists also want to share the mice with other researchers to advance studies on similar subjects.

"There are thousands of people studying aging and cancer, and we believe the new mouse model provides a valuable tool for scientists worldwide to explore these processes," Zhu stated.

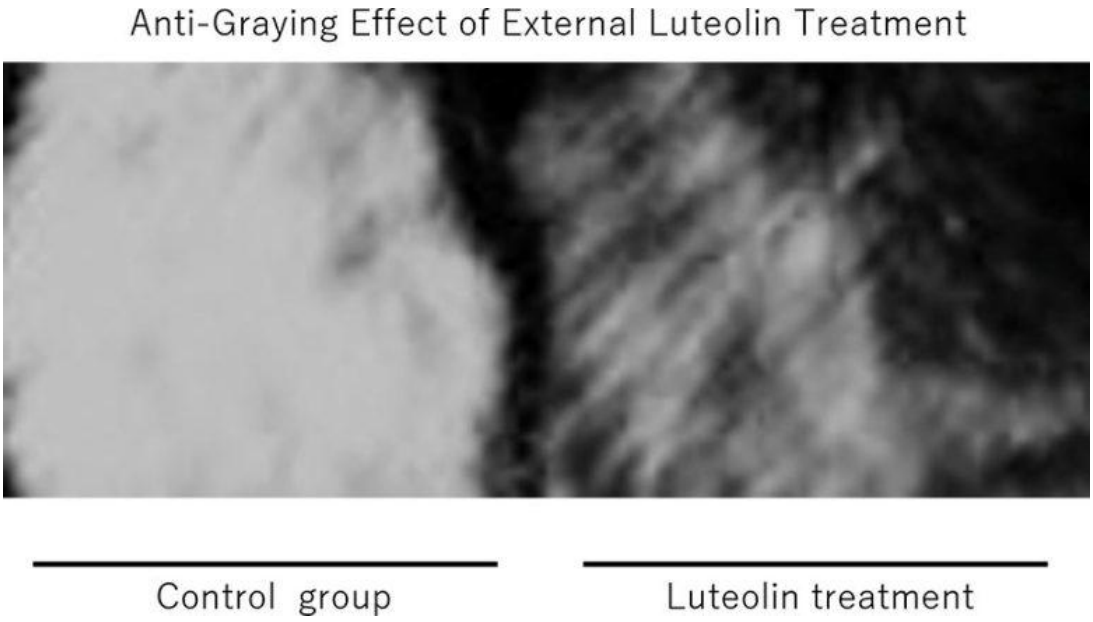
Anti-Aging Breakthrough: Scientists Discover a Natural Antioxidant That Could Stop Gray Hair

Researchers from Nagoya University in Japan have identified luteolin, an antioxidant found in certain vegetables, as a potential solution for preventing hair graying. Their study on mice showed that luteolin helped maintain fur color by preserving endothelin expression, which supports melanocyte activity responsible for hair pigmentation.

A study from Nagoya University found that luteolin, an antioxidant in vegetables, helps prevent hair graying by preserving endothelin expression and melanocyte activity.

Graying hair is a common sign of aging, often seen as unavoidable. However, recent research from Nagoya University in Japan, led by Masashi Kato and Takumi Kagawa, suggests that an antioxidant may help slow this process. The study identifies luteolin, a naturally occurring antioxidant found in vegetables such as celery, broccoli, carrots, onions, and peppers, as a potential agent for preventing hair graying. These findings could lead to new applications in hair care aimed at maintaining natural hair color.

The researcher's study focused on three antioxidants—luteolin, hesperetin, and diosmetin—to assess their anti-graying effects in mice that were bred to go gray like humans. The difference was startling, the mice that received luteolin retained their black fur, even as their cage mates' fur turned gray, regardless of whether the luteolin was given externally or internally.



Anti-graying effect of external luteolin treatment. Credit: Masashi Kato

"This result was surprising," Professor Kato said. "While we expected that antioxidants may also have anti-graying effects, only luteolin, not hesperetin or diosmetin, demonstrated significant effects. This finding suggests that luteolin may have a unique medicinal effect that prevents graying."

How Luteolin Works: The Role of Endothelins

Luteolin's anti-graying effects are closely linked to its influence on endothelins—proteins that play a crucial role in cellular communication. In the study, luteolin treatments preserved the expression of endothelins and their receptor. This preservation supports healthy signaling pathways, preventing the decline in melanocyte activity that typically accompanies graying.

"Interestingly, luteolin had limited effects on hair cycles, indicating that its primary impact is on pigmentation rather than hair growth or shedding," Professor Kato said. "This targeted action makes luteolin a particularly intriguing candidate for addressing age-related hair graying."

The similarities between the hair-graying processes in the model mice and humans offer encouraging prospects for translating these findings into human applications. As well as vegetables, luteolin is already available as a supplement for topical and oral use, making it a viable candidate for further development as an anti-graying treatment. As research progresses, this antioxidant could become a key ingredient in hair care regimens, helping individuals preserve their natural hair color as they age.

Building on these promising results, Dr. Kagawa envisions broader applications for luteolin in age-related research. “It would be interesting to investigate whether luteolin’s anti-aging effects could also be applicable to other age-related changes, including balding.”

Reference: “Anti-Graying Effects of External and Internal Treatments with Luteolin on Hair in Model Mice” by Machiko Iida, Takumi Kagawa, Ichiro Yajima, Akihito Harusato, Akira Tazaki, Delgama A. S. M. Nishadhi, Nobuhiko Taguchi and Masashi Kato, 16 December 2024, *Antioxidants*.
DOI: 10.3390/antiox13121549

Anti-Aging Breakthrough: Cellular Rejuvenation Therapy Safely Reverses the Aging Process in Mice

Anti-aging artist’s concept.
Salk researchers treated mice with anti-aging regimen beginning in middle age and found no increase in cancer or other health problems later on.

Age may be just a number, but it’s a number that often carries unwanted side effects, from brittle bones and weaker muscles to increased risks of cardiovascular disease and cancer. Now, scientists at the Salk Institute, in collaboration with Genentech, a member of the Roche group, have shown that they can safely and effectively reverse the aging process in middle-aged and elderly mice by partially resetting their cells to more youthful states.

“We are elated that we can use this approach across the life span to slow down aging in normal animals. The technique is both safe and effective in mice,” says co-corresponding author Juan Carlos Izpisua Belmonte, professor in Salk’s Gene Expression Laboratory and holder of the Roger Guillemin Chair. “In addition to tackling age-related diseases, this approach may provide the biomedical community with a new tool to restore tissue and organismal health by improving cell function and resilience in different disease situations, such as neurodegenerative diseases.”

Yamanaka Factors in Cellular Rejuvenation

As organisms age, it is not just their outward appearances and health that change; every cell in their bodies carries a molecular clock that records the passage of time. Cells isolated from older people or animals have different patterns of chemicals along their DNA—called epigenetic markers—compared to younger people or animals. Scientists know that adding a mixture of four reprogramming molecules—Oct4, Sox2, Klf4, and cMyc, also known as “Yamanaka factors”—to cells can reset these epigenetic marks to their original patterns.

This approach is how researchers can dial back adult cells, developmentally speaking, into stem cells.

Cellular rejuvenation therapy safely reverses signs of aging in mice. Credit: Salk Institute
In 2016, Izpisua Belmonte's lab reported for the first time that they could use the Yamanaka factors to counter the signs of aging and increase life span in mice with a premature aging disease. More recently, the team found that, even in young mice, the Yamanaka factors can accelerate muscle regeneration. Following these initial observations, other scientists have used the same approach to improve the function of other tissues like the heart, brain, and optic nerve, which is involved in vision.

In the new study, Izpisua Belmonte and his colleagues tested variations of the cellular rejuvenation approach in healthy animals as they aged. One group of mice received regular doses of the Yamanaka factors from the time they were 15 months old until 22 months, approximately equivalent to age 50 through 70 in humans. Another group was treated from 12 through 22 months, approximately age 35 to 70 in humans. A third group was treated for just one month at age 25 months, similar to age 80 in humans.

"What we really wanted to establish was that using this approach for a longer time span is safe," says Pradeep Reddy, a Salk staff scientist and co-first author of the new paper. "Indeed, we did not see any negative effects on the health, behavior, or body weight of these animals."

From left: Juan Carlos Izpisua Belmonte and Pradeep Reddy. Credit: Salk Institute

Compared to control animals, there were no blood cell alterations or neurological changes in the mice that had received the Yamanaka factors. Moreover, the team found no cancers in any of the groups of animals.

Youthfulness Restored

When the researchers looked at normal signs of aging in the animals that had undergone the treatment, they found that the mice, in many ways, resembled younger animals. In both the kidneys and skin, the epigenetics of treated animals more closely resembled epigenetic patterns seen in younger animals. When injured, the skin cells of treated animals had a greater ability to proliferate and were less likely to form permanent scars—older animals usually show less skin cell proliferation and more scarring. Moreover, metabolic molecules in the blood of treated animals did not show normal age-related changes.

This youthfulness was observed in the animals treated for seven or 10 months with the Yamanaka factors, but not the animals treated for just one month. What's more, when the treated animals were analyzed midway through their treatment, the effects were not yet as

evident. This suggests that the treatment is not simply pausing aging, but actively turning it backwards—although more research is needed to differentiate between the two.

The team is now planning future research to analyze how specific molecules and genes are changed by long-term treatment with the Yamanaka factors. They are also developing new ways of delivering the factors.

"At the end of the day, we want to bring resilience and function back to older cells so that they are more resistant to stress, injury, and disease," says Reddy. "This study shows that, at least in mice, there's a path forward to achieving that."

Reference: "In vivo partial reprogramming alters age-associated molecular changes during physiological aging in mice" by Kristen C. Browder, Pradeep Reddy, Mako Yamamoto, Amin Haghani, Isabel Guillen Guillen, Sanjeeb Sahu, Chao Wang, Yosu Luque, Javier Prieto, Lei Shi, Kensaku Shojima, Tomoaki Hishida, Zijuan Lai, Qingling Li, Feroza K. Choudhury, Weng R. Wong, Yuxin Liang, Dewakar Sangaraju, Wendy Sandoval, Concepcion Rodriguez Esteban, Estrella Nuñez Delicado, Pedro Guillen Garcia, Michal Pawlak, Jason A. Vander Heiden, Steve Horvath, Heinrich Jasper and Juan Carlos Izpisua Belmonte, 7 March 2022, *Nature Aging*.
DOI: 10.1038/s43587-022-00183-2

Belmonte is currently an Institute Director at Altos Labs, Inc., in addition to being a professor at the Salk Institute.

Other authors included Mako Yamamoto, Isabel Guillen Guillen, Sanjeeb Sahu, Chao Wang, Yosu Luque, Javier Prieto, Lei Shi, Kensaku Shojima, Tomoaki Hishida and Concepcion Rodriguez Esteban of Salk; Kristen Browder, Zijuan Lai, Qingling Li, Feroza Choudhury, Weng Wong, Yuxin Liang, Dewakar Sangaraju, Wendy Sandoval, Michal Pawlak, Jason Vander Heiden and Heinrich Jasper of Genentech, Inc.; Amin Haghani and Steve Horvath of UCLA; Estrella Nuñez Delicado of Universidad Católica San Antonio de Murcia; and Pedro Guillen Garcia of Clínica CEMTRO.

The study was supported by Universidad Católica San Antonio de Murcia (UCAM), and Fundación Dr. Pedro Guillén.

New Drug Molecules Could Prevent Skin Aging Caused by Ultraviolet Sun Exposure.

Two new molecules that generate minute amounts of the gas hydrogen sulfide have been found to prevent skin from aging after being exposed to ultraviolet light found in sunlight.

Sunburn is a major cause of premature aging in skin, and a primary risk factor for skin cancer, and other skin problems associated with aging. Now, an international research team has made inroads towards being able to reverse or delay this damage for the first time.

The research was led by Professor Matt Whiteman at the University of Exeter Medical School, and Professor Uraiwan Panich at the Faculty of Medicine Siriraj Hospital, Mahidol University, in Thailand. In the study published in *Antioxidant and Redox Signaling,* the team exposed adult human skin cells and the skin of mice to ultraviolet radiation (UVA). UVA is the part of natural sunlight which damages unprotected skin and can penetrate through windows, and even through some clothes. It causes skin to age prematurely by turning on skin digesting enzymes called collagenases. These enzymes eat away at the natural collagen, causing the skin to lose elasticity and sag, resulting in wrinkles. UVA also penetrates deeper into skin than the UV radiation that causes sunburns (UVB)-, and it damages cellular DNA, leading to mutations that can contribute to some skin cancers. Classic sun creams people use on holiday sit on top of the skin and absorb UV radiation, but they do not penetrate the skin where the long-lasting damage occurs.

However, the team's research paves the way for a new way to protect the deeper layers of skin using two compounds invented at the University of Exeter: AP39 and AP123. In the experiments, the compounds did not protect the skin in the same way traditional sun creams prevent sunburn, but instead penetrated the skin to correct how skin cells' energy production and usage was turned off by UVA exposure. This then prevented the activation of skin-degrading collagenase enzymes and subsequent skin damage.

The compounds used in this study were previously shown to have impressive effects in reducing skin inflammation and skin damage after burn injury and atopic dermatitis (eczema). In an anti-aging context, they prevented human skin cells in test tube experiments from aging, but this is the first time the effects of photo-aging have been seen in animals.

Professor Uraiwan Panich, of the Faculty of Medicine Siriraj Hospital, Mahidol University, in Bangkok, a co-senior author on the paper, said: "The compounds AP39 and AP123 specifically target the energy generating machinery inside our cells, the mitochondria, and supply them with minute quantities of alternative fuel, hydrogen sulfide, to use when skin cells are stressed by UVA. The direct result of this was the activation of two protective mechanisms. One is a protein call PGC-1α, which controls mitochondria number inside cells and regulates energy balance. The other is Nrf2, which turns on a set of protective genes that mitigate UVA damage to skin and turn off the production of collagenase, the main enzyme that breaks down collagen in damaged skin tissue and causes skin to look significantly more 'aged'."

Professor Matt Whiteman, of the University of Exeter Medical School, a co-senior author on the paper added: "Some skin sun creams and cosmetics contain ingredients thought to protect mitochondria from UV radiation. However, it isn't clear that these cosmetic skin-applied substances get inside skin cells at all, whereas we found that our molecules penetrate cells and specifically target mitochondria where they are needed. By protecting mitochondria, we also preserve and upregulate the protective mechanisms by which mitochondria control inflammation, protect cells and prevent tissue destruction. Currently, we have no way of reversing or delaying skin ageing caused by sunlight exposure. Our results are a really exciting step towards that goal, and could one day help reduce age-related skin conditions, as well as be useful in other conditions resulting from the aging process."

The important observation noted was the compounds only regulated energy production, PGC-1α and Nrf2 in skin that was exposed to UVA. This suggests a novel approach to treating skin that has already been damaged by UV radiation, and could potentially reverse, as well as limit, that damage.

While more research is now needed, long term implications of this work could be medical as well as cosmetic, where protecting skin from UV light is important. For example, not only premature skin aging and skin cancers, but UV light allergies, solar urticaria (hives) and rare hereditary skin diseases such as xeroderma pigmentosum, although further work is needed. The Exeter team is currently mid-way through testing newer and more potent molecules able to do the same task using newer approaches *via* the University of Exeter spin-out company MitoRx Therapeutics; a company developing highly potent mitochondrial drugs for clinical use.

Reference: "Mitochondria-targeted hydrogen sulfide delivery molecules protect against UVA-induced photoaging in dermal fibroblasts, and in mouse skin *in vivo*" by Miss Jinapath Lohakul, Miss Saowanee Jeayeng, Dr. Anyamanee Chaiprasongsuk, Mrs. Roberta Torregrossa, Dr. Mark Wood, Dr. Malinee Saelim, Dr. Weerawon Thangboonjit, Prof. Matthew Whiteman and Prof. Uraiwan Panich, 8 July 2021, *Antioxidant and Redox Signaling*.
DOI: 10.1089/ars.2020.8255

Scientists Develop New Gene Therapy Strategy to Delay Aging and Extend Lifespan

Researchers have pinpointed new senescence-promoting genes in humans using a genome-wide CRISPR/Cas9 screening system. This discovery offers a fresh therapeutic approach for addressing aging and related pathologies.

Cellular senescence, a state of permanent growth arrest, has emerged as a hallmark and fundamental driver of organismal aging. It is regulated by both genetic and epigenetic factors. Despite a few previously reported aging-associated genes, the identity and roles of additional genes involved in the regulation of human cellular aging remain to be elucidated. Yet, there is a lack of systematic investigation on the intervention of these genes to treat aging and aging-related diseases.

How many aging-promoting genes are there in the human genome? What are the molecular mechanisms by which these genes regulate aging? Can gene therapy alleviate individual aging? Recently, researchers from the Chinese Academy of Sciences have shed new light on the regulation of aging.

Recently, researchers from the Institute of Zoology of the Chinese Academy of Sciences (CAS), Peking University, and Beijing Institute of Genomics of CAS have collaborated to identify new human senescence-promoting genes by using a genome-wide CRISPR/Cas9 screening system and provide a new therapeutic approach for treating aging and aging-related pathologies.

In this study, the researchers conducted genome-wide CRISPR/Cas9-based screens in human premature aging stem cells and identified more than 100 candidate senescence-promoting genes. They further verified the effectiveness of inactivating each of the top 50 candidate genes in promoting cellular rejuvenation using targeted sgRNAs.

Among them, *KAT7* encoding a histone acetyltransferase was identified as one of the top targets in alleviating cellular senescence. It increased in human mesenchymal precursor cells during physiological and pathological aging. *KAT7* depletion attenuated cellular senescence whereas *KAT7* overexpression accelerated cellular senescence.

Mechanistically, inactivation of KAT7 decreased histone H3 lysine 14 acetylation, repressed $p15^{INK4b}$ transcription, and rejuvenated senescent human stem cells.

Cumulative studies have described that age-associated accumulation of senescent cells and proinflammatory cells in tissues and organs contribute to the development and

progression of aging as well as aging-related disorders. Prophylactic ablation of senescent cells mitigates tissue degeneration and extends the health span in mice.

In this study, the researchers found that intravenous injection of a lentiviral vector encoding Cas9/sg-*KAT7* reduced the proportions of senescent cells and proinflammatory cells in the liver, diminished circulatory senescence-associated secretory phenotype (SASP) factors in the serum, and extended healthspan and lifespan of aged mice.

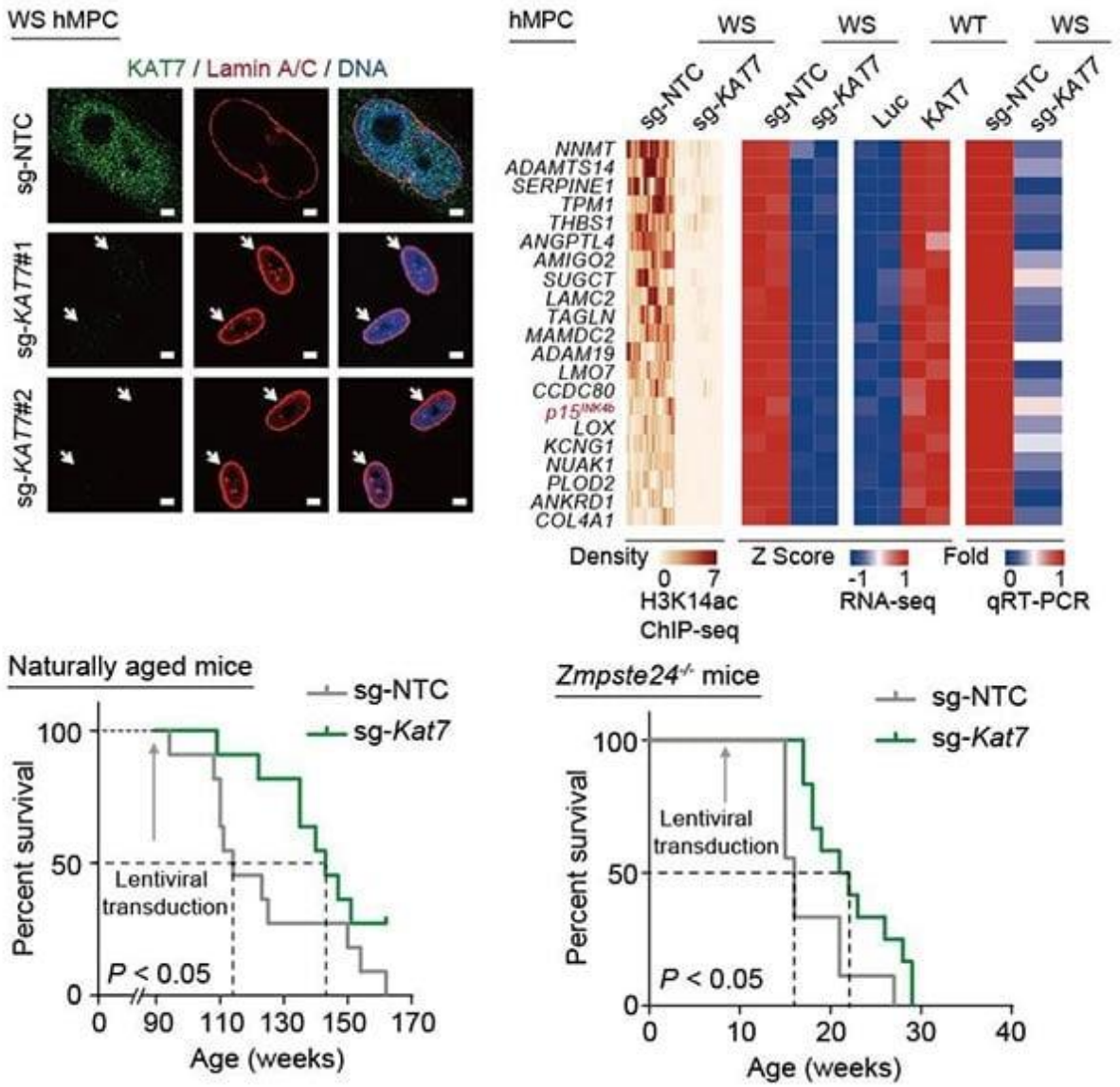


Figure. Gene therapy targeting Kat7 extends lifespan in naturally aged and progeria mice. Credit: IOZ

These results suggest that gene therapy based on single-factor inactivation may be sufficient to extend mouse lifespan. The researchers also found that the treatment with the lentiviral vector encoding Cas9/sg-*KAT7* or a KAT7 inhibitor WM-3835 alleviated human

hepatocyte senescence and reduced the expression of SASP genes, suggesting the possibility of applying these interventions in clinical settings.

Altogether, this study has successfully expanded the list of human senescence-promoting genes using CRISPR/Cas9 genome-wide screen and conceptually demonstrated that gene therapy based on single-factor inactivation is able to delay individual aging. This study not only deepens our understanding of aging mechanism but also provides new potential targets for aging interventions.

Reference: "A genome-wide CRISPR-based screen identifies KAT7 as a driver of cellular senescence" by Wei Wang, Yuxuan Zheng, Shuhui Sun, Wei Li, Moshi Song, Qianzhao Ji, Zeming Wu, Zunpeng Liu, Yanling Fan, Feifei Liu, Jingyi Li, Concepcion Rodriguez Esteban, Si Wang, Qi Zhou, Juan Carlos Izpisua Belmonte, Weiqi Zhang, Jing Qu, Fuchou Tang and Guang-Hui Liu, 6 January 2021, *Science Translational Medicine*.
DOI: 10.1126/scitranslmed.abd2655

Scientists Identify Factor in "Young Blood" That Helps Rejuvenate Aging Muscle

A study demonstrates that extracellular vesicles (EVs) deliver genetic instructions for the longevity protein Klotho to muscle cells. Aging mice show a decline in muscle function and impaired repair due to aged EVs carrying fewer copies of these instructions compared to younger animals.
As we age, our muscles gradually become smaller, weaker, and less able to heal after injury. In a new study, UPMC and University of Pittsburgh researchers pinpoint an important mediator of youthfulness in mouse muscle, a discovery that could advance muscle regeneration therapies for older people.

Published on December 6, 2021, in *Nature Aging*, the study demonstrates that circulating shuttles called extracellular vesicles, or EVs, deliver genetic instructions for the longevity protein known as Klotho to muscle cells. Loss of muscle function and impaired muscle repair in old mice may be driven by aged EVs, which carry fewer copies of these instructions than those in young animals.

The findings are an important advance in understanding why the capacity for muscles to regenerate dwindles with age.

Fabrisia Ambrosio, Ph.D., director of rehabilitation for UPMC International and associate professor of physical medicine and rehabilitation at the University of Pittsburgh. Credit: UPMC

“We’re really excited about this research for a couple of reasons,” said senior author Fabrisia Ambrosio, Ph.D., director of rehabilitation for UPMC International and associate professor of physical medicine and rehabilitation at Pitt. “In one way, it helps us understand the basic biology of how muscle regeneration works and how it fails to work as we age. Then, taking that information to the next step, we can think about using extracellular vesicles as therapeutics to counteract these age-related defects.”

The new study builds on decades of research showing that when old mice are given blood from young mice, youthful features are restored to many cells and tissues. But until now, it was unclear which components of young blood confer these rejuvenating effects.

“We wondered if extracellular vesicles might contribute to muscle regeneration because these couriers travel between cells via the blood and other bodily fluids,” said lead author Amrita Sahu, Ph.D., postdoctoral fellow in the Department of Physical Medicine and Rehabilitation at Pitt. “Like a message in a bottle, EVs deliver information to target cells.”

Ambrosio and her team collected serum, the fraction of blood that remains after removing blood cells and clotting factors, from young mice and injected it into aged mice with injured muscle. Mice that received young serum showed enhanced muscle regeneration and functional recovery compared to those that received a placebo treatment, but the serum’s restorative properties were lost when EVs were removed, indicating that these vesicles mediate the beneficial effects of young blood.

Delving deeper, the researchers found that EVs deliver genetic instructions, or mRNA, encoding the anti-aging protein Klotho to muscle progenitor cells, a type of stem cell that is important for regeneration of skeletal muscle. EVs collected from old mice carried fewer copies of the instructions for Klotho than those from young mice, prompting muscle progenitor cells to produce less of this protein.

Amrita Sahu, Ph.D., postdoctoral fellow in the Department of Physical Medicine and Rehabilitation at the University of Pittsburgh. Credit: UPMC

With increasing age, muscle doesn’t heal as well after damage because scar tissue is deposited instead of restoring original muscle structure. In earlier work, Ambrosio and her team showed that Klotho is an important regulator of regenerative capacity in muscle progenitor cells and that this protein declines with age.

The new study shows for the first time that age-related shifts in EV cargo contribute to depleted Klotho in aged stem cells, suggesting that EVs could be developed into novel therapies for healing damaged muscle tissue.

“EVs may be beneficial for boosting regenerative capacity of muscle in older individuals and improving functional recovery after an injury,” said Ambrosio, who is also a member of

Pitt's McGowan Institute for Regenerative Medicine. "One of the ideas we're really excited about is engineering EVs with specific cargoes, so that we can dictate the responses of target cells."

Beyond muscles, EVs could also help reverse other effects of aging. Previous work has demonstrated that young blood can boost cognitive performance of aged mice. Ambrosio and coauthor Radosveta Koldamova, M.D., Ph.D., professor of environmental and occupational health at Pitt's Graduate School of Public Health, have a grant to explore the potential of EVs for reversing age-related declines in cognition.

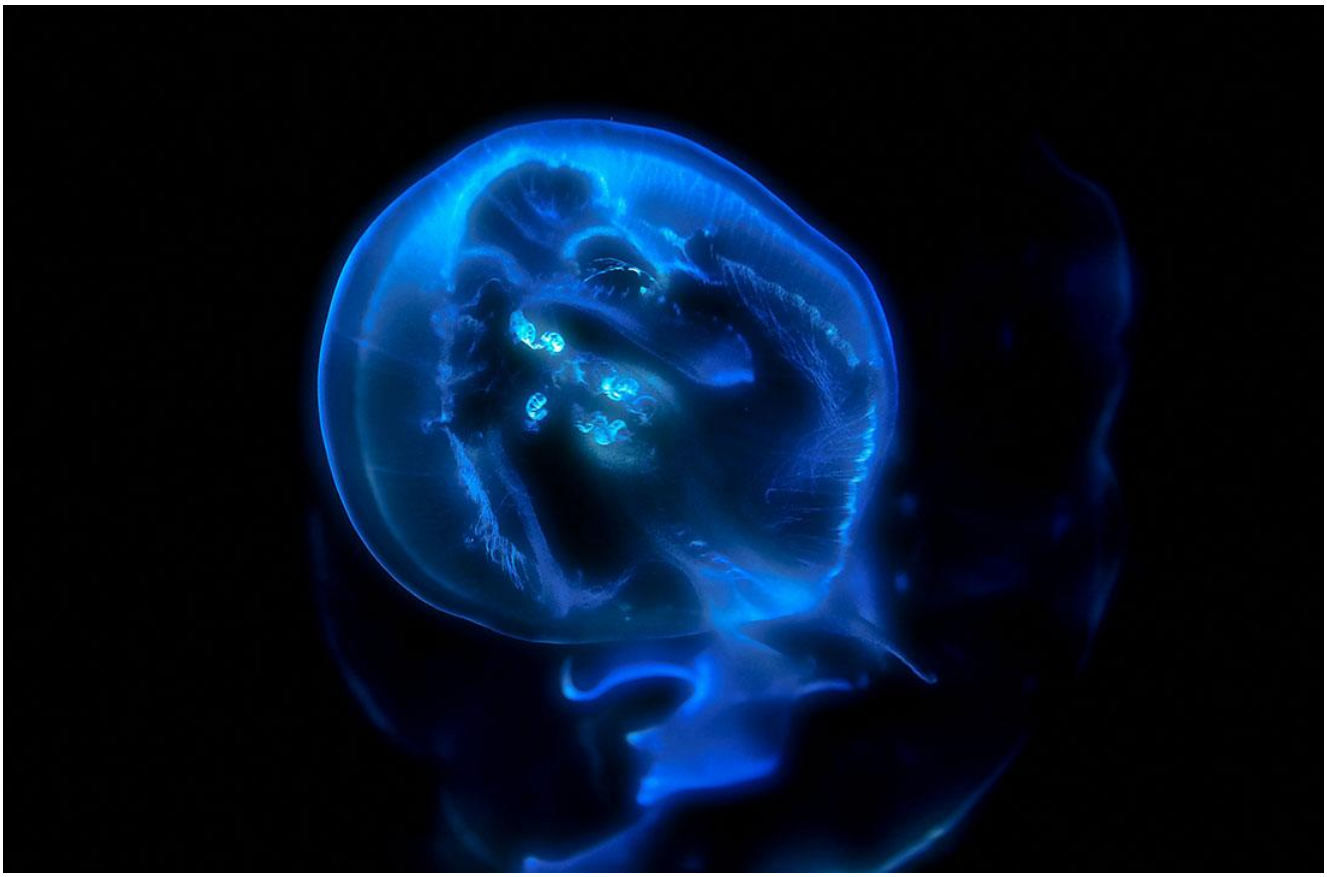
Reference: "Regulation of aged skeletal muscle regeneration by circulating extracellular vesicles" by Amrita Sahu, Zachary J. Clemens, Sunita N. Shinde, Sruthi Sivakumar, Abish Pius, Ankit Bhatia, Silvia Picciolini, Cristiano Carlomagno, Alice Gualerzi, Marzia Bedoni, Bennett Van Houten, Mita Lovalekar, Nicholas F. Fitz, Iliya Lefterov, Aaron Barchowsky, Radosveta Koldamova and Fabrisia Ambrosio, 6 December 2021, *Nature Aging*.
DOI: 10.1038/s43587-021-00143-2

Other researchers on the study were Zachary J. Clemens, Sunita N. Shinde, Sruthi Sivakumar, Abish Pius, Bennett Van Houten, Ph.D., Mita Lovalekar, Ph.D., Nicholas F. Fitz, Ph.D., Iliya Lefterov, M.D., Ph.D., and Aaron Barchowsky, Ph.D., all of Pitt; Ankit Bhatia of Carnegie Mellon University; and Silvia Picciolini, Ph.D., Cristiano Carlomagno, Ph.D., Alice Gualerzi, Ph.D., and Marzia Bedoni, Ph.D., all of IRCCS Fondazione Don Carlo Gnocchi.

This research was supported by the National Institutes of Health (NIA R01AG052978, NIA R01AG061005, NIA R01AG066198-01, R33 ES025606-05 and NIH 1S10OD019942-01) and UPMC Enterprises.

Growing Young: 6 Powerful Exercises for Initiating DNA Repair and Cellular Rejuvenation

BY SONDRA BARRETT



epigenetic research has shown that cellular rejuvenation and DNA repair can be stimulated by our behavior, our environment and our mental and emotional state. photo: robert zunikoff

Each day about a hundred billion cells in the human body divide, making new cells.

Recall what happens to the DNA as a cell divides—the paired strands of DNA separate, unwind, and then are copied, letter by letter, serving as the template for an identical partner to be created.

While this is happening, a mistake can be made by mismatching the triplets, omitting or adding in a wrong letter; such a mistake is a mutation.
A mutation of a single code letter can change which amino acid is placed in the scripted protein. Even one change can alter the shape and function of the protein being produced—an incorrect code can make the protein stiffer or too flexible or a totally different shape from the original. The protein may no longer work the way it is supposed to.

Since even a single, minuscule error such as this can affect the health of the cell, a potent DNA repair mechanism must be available to protect the cell from damage and instigate cellular rejuvenation. In fact, in nature's wisdom, multiple DNA repair systems are present in our cells.

At the genesis of this growth of cells, self-correction is insured by the wavy strands of molecular intelligence held tight unwinding and letting go only after perfection is created.

— Christopher Vaughan, How Life Begins

Much of the time, our cells get it right, yet sometimes they don't. In fact, it's been estimated that at least a thousand errors are committed inside our cells every day. Fortunately, the cell possesses innate wisdom and cellular rejuvenation mechanisms, built into the architecture of the DNA helix, that recognizes when an error has been made. Damage or errors in DNA trigger an astonishing sequence of events as a gene called p53 rides to the rescue in the interest of DNA repair.

The p53 system is both a "spell-checker" and an emergency brake on cell growth, and it has other genes under its command. If an error is created, the p53 gene orders other genes to stop being copied until repairs can be made to the DNA. Once the damaged DNA is repaired and the cell has essentially been rejuvenated, p53 turns on the green light and allows the cell reproduction cycle to continue. But what if the damage is beyond repair? In that case, p53 activate genes that direct the cell to self-destruct; this is known as programmed cell death or apoptosis, which comes from the Latin for "falling leaves." Apoptosis, in contrast to traumatic or necrotic cytotoxic death, is a relatively gentle process in which parts of the cell slough off and are recycled or removed by the scavenger cells—falling leaves are an apt metaphor, with their ability to decompose, be recycled into the earth, and even nourish the tree that once sustained them.

A traumatic or cytotoxic death, by contrast, is one in which the cell is acutely damaged and basically explodes, releasing its contents into the cellular environment. This type of

cell death can damage the surrounding tissues as it sets free potentially dangerous substances from the cell. Cells contain numerous substances that, if released, can harm other molecules; however, within the cell they are compartmentalized to protect against their damaging effects. Apoptosis is a slower process that allows the neighborhood to reclaim or eliminate cell parts, one step at a time, without damaging the area.

To sum up the role of p53, it's the damage-control specialist with the capability to correct gene errors, prevent amplification of unruly DNA, suppress tumor cell growth, and when necessary, push cells into programmed self-elimination. Our cells have other numerous backup systems as well to ensure healthy survival.

How to Increase DNA Repair Rates

The rate of DNA repair—how quickly errors can be fixed—influences our vulnerability to cancer and other illnesses affected by genetic mutations. Long-term stress slows down DNA repair, as does cancer. In China, a study on improving the rate of DNA repair and cellular rejuvenation offers tantalizing and hopeful results. Researchers found that the DNA repair rate of people with cancer in remission compared to healthy people was much slower. The patients in remission were then taught qigong stress-reducing techniques. Following three months of practice, their cell repair rate had nearly doubled.

"Following three months of practice, their cell repair rate had nearly doubled."

It is conceivable that the "new" energy medicines of qigong and vibrational sound can affect the erratic energy of DNA and stimulate cellular rejuvenation. Ancient qigong, tai chi, yoga, and the dance of the whirling dervishes all use spiral movements as part of their energy healing exercises—do they help realign our DNA? Prolonged stress damages the immune system, reproduction, digestion, memory, and even our bones. That is why stress reduction practices, which include the practices just mentioned as well as meditation and imagery, are important to our health at every level.

Imagine That!

The use of guided visualization and imagery is growing in acceptance as a complementary healing modality, particularly in stress reduction, and easing pain, suffering, and other consequences of cancer and its treatment. Significant data indicate that the miserable feelings associated with a cancer diagnosis and the side effects of treatment can be minimized in some people who practice imagery. Many of the first popularized imagery scripts had people visualizing their immune cells coming to the rescue and killing cancer cells. What we have learned since is that the immune cells are not the primary removers of "demon" cells. So what if we instead base our imagery on a new, spiral model of fixing genetic errors? Here I offer two different suggestions for eliminating any abnormal cells in your body, enhancing DNA repair and cellular rejuvenation. They are only suggestions; feel free to use your imagination.

1. Visualization Exercise: Eliminating Unhealthy Cells

1. Take some time to relax and pay attention to your breath. Feel all the places your body touches: the chair, floor, or other surface you rest upon. Allow your breathing to be peaceful.

2. If you know that you have cancer cells in your body, imagine what they look like. Biological accuracy is not necessary—how do you perceive them?

3. Now allow yourself to imagine something that will eliminate those cells.

4. For example, you might imagine the cancer cells as dust mites and the eliminator as a vacuum cleaner. Make sure the eliminating force is larger and stronger than the tumor cells.

5. Once all the abnormal cells are removed, picture new, healthy tissue developing as DNA repair and cellular rejuvenation processes take hold. Take as long as you need for the process and then bring your awareness back to your breath and this present moment.

2. Visualization Exercise: Repair and Cover Up

Since our cells make errors all the time and abnormal cells do exist in our bodies, this script focuses on changing abnormal genes.

1. Take time to relax the same way as for the previous exercise. Now imagine or intend that any errors in your genes or cells are corrected. Picture the spiral DNA pairs being made to match perfectly, removing or correcting all the errors in your genetic repertoire.

2. Alternatively, you can envision preventing these genes from being expressed by covering them up with new proteins that adhere to them, keeping them hidden.

3. Allow your imagination to guide you in the way abnormal genes are taken out of action. See all of your genes as healthy and whole. Take as long as you need for the process and then bring your awareness back to your breath and the present moment.

4. Draw or write what you experienced.

The divine choreography of our DNA—its spiraling strands and ability to program both reproduction, repair, rejuvenation and self-sacrifice—brings us once more to life and death. Embedded within our cells is the ability to detect and correct errors in coded genetic messages. When correction is impossible, a gentle death is initiated. We know that ultraviolet radiation from the distant sun can penetrate and mutate the gene. And what about cigarette smoke that somehow is breathed into the cell, altering the gene structure so that faulty proteins are made? If invisible agents can initiate damaging changes, can we use the invisible laser of our energy or imagination to cut out or hide the damaged sections? Ancient healing practices including walking the labyrinth and chanting may provide valuable assistance for transforming our inevitable cellular errors.

3. Healing Energy Exercise: The Basic Posture: Standing Home Alignment

1. Feel your feet on the earth, grounded and anchored. Place your feet shoulder-width apart, parallel to each other. You can imagine roots from the soles of your feet that reach deep into the earth. To help find that solid and centered place on your feet, rock back and forth and then sideways until you feel yourself grounded in the earth. You can gain strength from the earth's energy when you feel your feet upon her. You may also perceive or imagine that you are drawing up the earth's energy through your feet.

2. Your knees are slightly bent, your butt tucked under. Your shoulders are dropped and relaxed. Your arms hang loose at your sides. Your tongue rests softly on the roof of your mouth behind your teeth. (This is called the inner smile, and you can practice it anytime.) Your chin is parallel to the floor; you can imagine a golden cord connecting your head to heaven, a link to another source of energy.

3. Rock a bit until you feel solid on the ground. All movements of this series start with taking this basic stance.

4. Another option of Standing Home is to assume this posture and then bend your elbows and place them at your sides by your waist. Hands are open and palms are facing each other at the level just below your belly button. This now becomes the Standing Stake, a standing meditation in which you begin to generate qi. Remember to keep your knees gently bent, and when you want to explore this, do it for a few minutes. With some teachers, this is the very first practice a student will be taught. They will work up to standing thirty minutes. It certainly strengthens your legs, body, and resolve.

4. Healing Energy Exercise: Energy Wash

This part of the sequence is perfect to do when you want to relieve the mind of unwelcome thoughts or stress, the act of which plays an important role in cellular rejuvenation and DNA repair.

1. Stand rooted with arms loose at your sides. Raise your arms at your sides, elbows slightly bent and palms facing up, fingertips pointing outward away from the body. Inhale while you are raising your arms until

2. they are directly above your head. Palms now face each other, elbows softly bent. When hands are above your head, fingertips are gently curved, facing up toward the sky.

3. Pause and exhale while you imagine receiving Qi from heaven or the universe.

4. When you are ready, inhale and turn your palms down, toward the crown of your head. Spread open your fingers and with your palms facing downward, slowly lower your hands in front of the midline of your body, imagining clear new qi flowing from your fingertips while the energy you don't need is being washed out. You might imagine that new energy is being sent to every cell. Take as long as you need to lower your hands while you "wash."

5. If you come to a place where you can't feel the energy or it feels dense, keep your hands there until you notice a change. And you may not feel anything at all.

5. Healing Energy Exercise: Integration: Balancing Yin and Yang, Right and Left Hemispheres

This is another tensegrity movement useful for initiating cellular rejuvenation and DNA repair. It also balances the right and left hemispheres of the brain and is equivalent to alternate nostril breathing in yoga.

1. Beginning in the same Standing Home posture as all the other poses, bring your right hand in front of your belly, palm down. Your elbow is gently bent. Your left hand is hanging straight, not rigid, at your side, palm down.

2. Raise both your arms simultaneously. Extend the left arm out to your side while the right rises along the midline of your body. Continue until they both reach above your head, fully extended, palms facing one another. Pause.

3. Turn both palms down, with your left palm now going down the midline and the right arm extended out to the side. Slowly lower both arms.

4. Now reverse the sequence. When your arms reach the level of your belly, raise your left arm up the center while your right arm rises to the side. Repeat this three times on each side or until you get the rhythm of the movement.

This sequence took me weeks to learn, so be easy on yourself. When I recently taught this series, most in the class got it on the first try while one person never got it.

Tip: This is an exercise you have to let your body learn without your mind trying to figure it out.

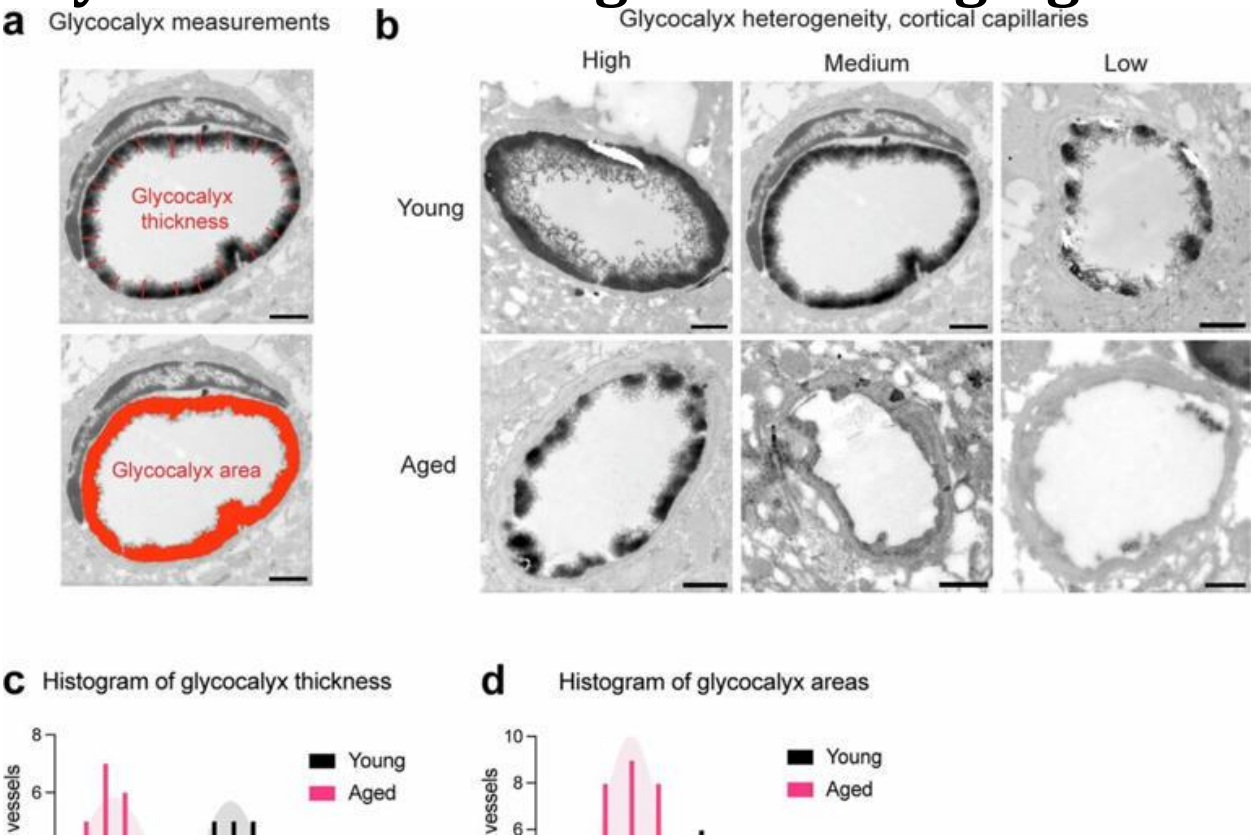
6. Healing Energy Exercise: Gathering and Storing the Qi: Closing the Circuits

When you are finished practicing qigong, you always gather in the qi and "close the circuits."

1. Take the Standing Home pose and cup your hands in front of your lower dantian, your belly. Now widen your stance and reach behind and around you, gathering the qi in a circular embrace. Embrace this qi in front of your belly and then press your palms close to your body, forming an upside down V with your hands. Remain in this position for a few moments. This is another position in which you can simply stand, relaxed, with gently bent knees and inner smile. Close your eyes and let the qi move you, fill you, and replenish your cells. This can be another form of a standing meditation.

If you've never practiced tai chi or qigong, it's always useful to work with an experienced teacher. You may also find it worthwhile to keep a journal and occasionally map your energy and watch what happens.

Changes in brain's 'sugar shield' could be key to understanding effects of aging



Heterogeneity in the brain endothelial glycocalydx layer. Credit: Nature (2025). DOI: 10.1038/s41586-025-08589-9

What if a critical piece of the puzzle of brain aging has been hiding in plain sight? While neuroscience has long focused on proteins and DNA, a team of Stanford researchers dared to shift their gaze to sugars—specifically the complex sugar chains that cover all our cells like chain mail.

Their investigation revealed how changes in this sugary armor on the brain's frontline cells could be key to understanding cognitive decline and diseases like Alzheimer's.

"This is like landing on a new planet," says Nobel laureate Carolyn Bertozzi, professor of chemistry and Baker Family Director of Sarafan ChEM-H, whose research on cell surface sugars and their biological roles laid the groundwork for this interdisciplinary study. "We're stepping outside for the first time and trying to make sense of what's out there."

At the center of this discovery is Sophia Shi, a Stanford Bio-X Graduate Fellow, whose doctoral research bridges the labs of Bertozzi and neuroscientist Tony Wyss-Coray, professor of neurology and neurological sciences and the Director of the Phil and Penny Knight Initiative for Brain Resilience at the Wu Tsai Neurosciences Institute.

In a study in aging mice, Shi has uncovered striking age-related changes in the sugary coating—called the glycocalyx—on cells that form the blood-brain barrier, a structure that protects the brain by filtering out harmful substances while allowing in essential nutrients.

"The glycocalyx is like a forest," Shi explains. "In young, healthy brains, this forest is lush and thriving. But in older brains, it becomes sparse, patchy, and degraded."

These age-related changes to the glycocalyx weaken the blood-brain barrier, Shi found. As the barrier becomes leaky with age, harmful molecules can infiltrate the brain, potentially fueling inflammation, cognitive decline, and neurodegenerative diseases.

"This work lays the foundation for a new field of inquiry into how the aging brain loses its resilience," says Wyss-Coray, the D.H. Chen Professor II of Neurology.

The study, published online in *Nature,* was jointly supervised by Bertozzi and Wyss-Coray, with Shi as lead author.

Decline and resilience in the blood-brain barrier

While Wyss-Coray's lab has extensively studied how aging impacts the blood-brain barrier, Shi's project was the first to investigate how age affects its sugary armor—the glycocalyx.

The results were striking: in older mice, bottlebrush-shaped, sugar-coated proteins called mucins, a key component of the glycocalyx, were significantly reduced. This thinning of the glycocalyx correlated with increased permeability of the blood-brain barrier and heightened neuroinflammation.

When the team reintroduced those critical mucins in aged mice, restoring a more "youthful" glycocalyx, they improved the integrity of the blood-brain barrier, reduced neuroinflammation, and measurably improved cognitive function.

"Modulating glycans has a major effect on the brain—both negatively in aging, when these sugars are lost, and positively, when they are restored," Shi says. "This opens an entirely new avenue for treating brain aging and related diseases."

Bertozzi underscores the significance of the discovery: "Biology is often about looking in the right place. This huge structural change in the glycocalyx was hiding in plain sight because no one had thought to look at it before, or had the tools to do so."

Shi's work also raises new questions. While the glycocalyx is traditionally viewed as a passive barrier that blocks harmful substances from entering cells, its sugars may play a more active role in the brain and how it ages.

Scientists often look to nucleic acids and proteins to understand how biological processes are precisely controlled, but they may be missing the roles that sugar molecules play, Bertozzi explains. "The glycome adds a layer of complexity that allows biological systems to achieve extraordinary fine-tuning."

This is particularly true in the brain, where many sugar molecules are uniquely expressed. Yet, until now, their roles in brain aging and disease have remained largely unexplored, she adds.

Shi's dual expertise in chemistry and biology enabled her to tackle a problem that neither lab could have solved alone. This study also brought together the two interdisciplinary institutes that share the Stanford ChEM-H / Neurosciences Research Complex: Sarafan ChEM-H and the Knight Initiative for Brain Resilience at the Wu Tsai Neurosciences Institute.

The brain's sugar shield and disease

Many questions remain about the glycocalyx—what drives its decline with age, and do similar changes occur in humans? "It's hard to study human brains," Bertozzi notes, "but understanding whether similar mechanisms are at play in humans will be crucial for translating these discoveries into therapies."

The study also offers new opportunities to tackle neurodegenerative diseases like Alzheimer's, a particular interest for Shi. By identifying the molecular pathways behind glycocalyx changes, the team hopes to uncover therapeutic targets that could slow or even reverse disease progression.

Shi, who will soon establish her own lab at the Rowland Institute at Harvard, plans to expand this research to better understand glycans' roles in neurodegeneration and explore their potential for developing new treatments.

Beyond aging and neurodegeneration, the findings have significant implications for effectively delivering drugs to the brain. The blood-brain barrier is notoriously difficult to penetrate, making it challenging to treat many neurological diseases.

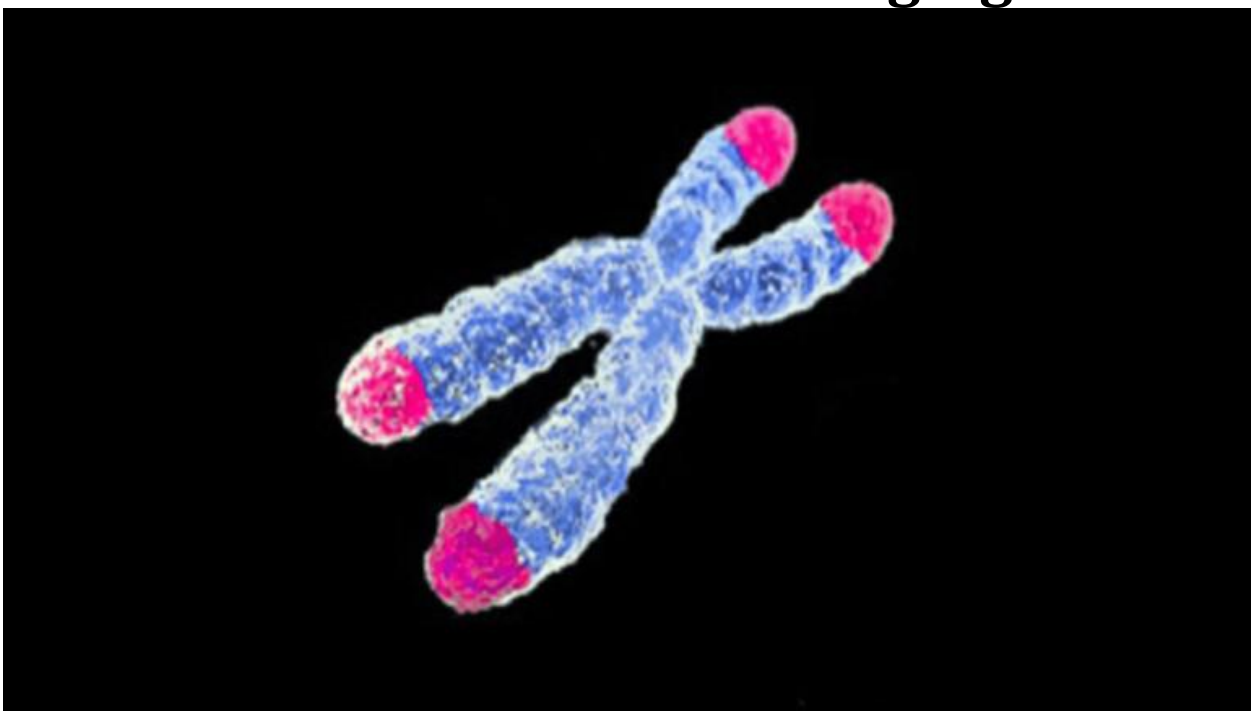
By understanding the role of the glycocalyx, scientists may discover better ways to get medicines into the brain, offering hope for conditions ranging from multiple sclerosis to brain cancer.

For now, this work represents a first step into a new field. As Shi puts it, "I'm excited to unlock the secrets of the glycocalyx in brain aging and neurodegeneration and discover how we can harness its potential to improve brain health."

More information: Sophia M. Shi et al, Glycocalyx dysregulation impairs blood–brain barrier in ageing and disease, *Nature* (2025). DOI: 10.1038/s41586-025-08589-9

Provided by Stanford University

US scientists gene engineer mice in first-ever model to unlock human aging secrets



US scientists gene engineer mice in first-ever model to unlock human aging secrets

After years of hard work, scientists have succeeded in creating genetically-engineered mice that could help accelerate anti-aging research for humans.

A team of scientists from the Washington State University (WSU) have taken one step ahead in the quest to unlock the secrets of extending human lifespan at the cellular level.

As per the team's research, aging occurs gradually due to the shortening of telomeres–the protective caps at the ends of chromosomes that function like shoelace tips to prevent unraveling. s telomeres shorten over time, cells lose their ability to divide for healthy growth, and some eventually begin to die, says the press release.

However, it has been challenging to study the telomeres at the cellular level in humans.

Therefore, the scientists led by WSU College of Pharmacy and Pharmaceutical Sciences Professor Jiyue Zhu have developed mice that have human-like short telomeres.

It should be noted that normally mice have up to 10 times longer telomeres than humans.

First mouse model with humanized telomeres

The genetically engineered mice are being called HuT mice by the scientists. They will help the team to make progress in multiple research projects.

"This is the first mouse model with truly humanized telomeres because telomerase isn't expressed in adult tissues in this model," Zhu said. "Our paper demonstrates that they exhibit human-like telomeres. Now, we aim to observe how these mice age."

The key areas of focus for researchers include studying how short telomeres reduce the likelihood of developing cancer and influence human lifespan, as well as exploring strategies to extend individuals' health span– the period of life free from age-related diseases.

"One of our goals is to reduce telomerase expression in cancer cells, and this is an active area of research," he added.

It can help in developing new drugs and treatments for the future. As Zhu pointed out, many diseases start at the cellular level, therefore, targeting drugs at that space is a good strategy.

Unlocking anti-aging in humans

In the long run, the research can also help them pave the way for making anti-aging in humans a reality to extend lifespans.

As per Zhu, the mouse model will allow for multiple aging related studies. One of the collaborating scientists studies how sleep impacts human health. The HuT

mice will also be studied to understand how the stress of sleep deprivation and other life stresses affect telomere regulation and aging.

It took 10 years for Zhu and his team of scientists to develop the HuT mice. During this period they studied how telomeres differed in humans and other animals.

Mice were finally chosen for the study "as they are similar to humans in terms of organ structures, genes, and genetic makeup."

The scientists also want to share the mice with other researchers to advance studies on similar subjects.

"There are thousands of people studying aging and cancer, and we believe the new mouse model provides a valuable tool for scientists worldwide to explore these processes," Zhu stated.

MARCH 4, 2025

Brown fat tissue could promote healthful longevity and help maintain exercise capacity in aging

by Rutgers University

Credit: Pixabay/CC0 Public Domain
Rutgers Health researchers have made discoveries about brown fat that may open a new path to helping people stay physically fit as they age.

A team from Rutgers New Jersey Medical School found that mice lacking a specific gene developed an unusually potent form of brown fat tissue that expanded lifespan and increased exercise capacity by roughly 30%. The team is working on a drug that could mimic these effects in humans.

"Exercise capacity diminishes as you get older, and to have a technique that could enhance exercise performance would be very beneficial for healthful aging," said Stephen Vatner, university professor and director of the Cardiovascular Research Institute in the medical school's Department of Cell Biology and Molecular Medicine and senior author of

the study in *Aging Cell*. "This mouse model performs exercise better than their normal littermates."

Unlike white fat, which stores energy, brown fat burns calories and helps regulate body temperature. This study revealed brown fat also plays a crucial role in exercise capacity by improving blood flow to muscles during physical activity.

The genetically modified mice produced unusually high amounts of active brown fat and showed about 30% better exercise performance than normal mice, both in speed and time to exhaustion.

The discovery emerged from broader research into healthy aging. The modified mice, which lack a protein called RGS14, live about 20% longer than normal mice, with females living longer than males—similar to the pattern seen in humans. Even at advanced ages, they maintain a healthier appearance, avoiding the typical signs of aging, such as loss of hair and graying that appear in normal elderly mice.

Their brown adipose tissue also protects them from obesity, glucose intolerance, cardiovascular disorders, cancer and Alzheimer's disease, in addition to reduced exercise tolerance.

To test whether the brown fat—rather than some other result from the missing genes—accounted for the benefits, the researchers transplanted the brown fat to normal mice. They noted that the recipients gained similar benefits within days. Transplants using regular brown fat from normal mice, by contrast, took eight weeks to produce much milder improvements.

The discovery could eventually improve human lifespans—the total time when people enjoy good mental and physical health.

"With all the medical advances, aging and longevity have increased in humans, but unfortunately, healthful aging hasn't," Vatner said. "There are a lot of diseases associated with aging—obesity, diabetes, myocardial ischemia, heart failure, cancer—and what we have to do is find new drugs based on models of healthful aging."

Rather than develop a treatment that addresses aging broadly, which poses regulatory challenges, Vatner said his team plans to test for specific benefits such as improved exercise capacity and metabolism. This approach builds on their previous success in developing a drug based on a different mouse healthful longevity model.

"We're working with some people to develop this agent, and hopefully, in another year or so, we'll have a drug that we can test," Vatner said.

In the meantime, techniques such as deliberate cold exposure can increase brown fat naturally. Studies have found such efforts to produce short-term benefits that range from

enhanced immune system function to improved metabolic health, but Vatner said none of the studies have run long enough to find any effect on healthful aging.

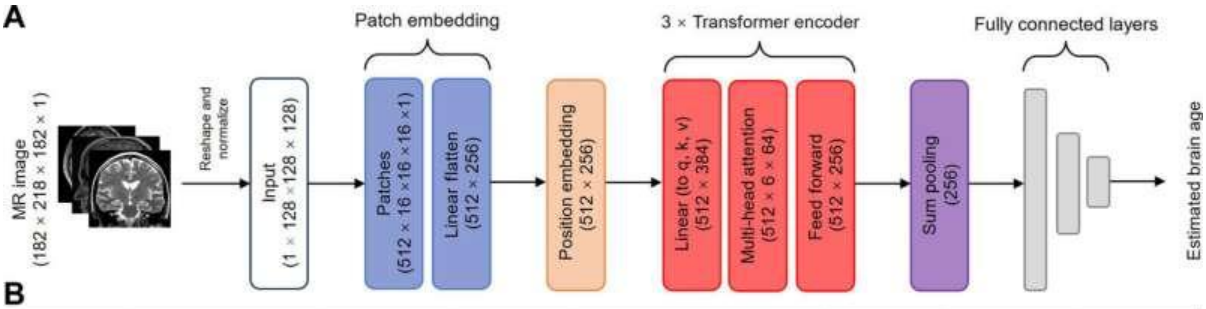
He added that most people would prefer to increase brown fat levels by taking pills rather than ice baths and is optimistic about translating the newest finding into an effective medication.

More information: Dorothy E. Vatner et al, Brown adipose tissue enhances exercise performance and healthful longevity, *Aging* (2024). DOI: 10.18632/aging.206179
Journal information: Aging Cell
Provided by Rutgers University

MARCH 16, 2025

Deep learning uncovers gene targets and potential drugs to slow brain aging

by Sanjukta Mondal , Medical Xpress



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Metrics	Dataset	VGGNet	ResNet	DenseNet	EfficientNet	SFCN	GLT	3D-ViT
MAE	UKB cross-validation	**2.64**	2.68	2.66	3.61	3.93	2.95	**2.64**
	UKB testing	2.79	2.7	**2.56**	3.41	3.13	2.94	2.6
	ADNI	3.67	3.17	3.37	4.73	11.85	6.16	**2.99**
	PPMI	4.08	4.03	5.65	7.58	6.16	10.4	**3.44**
	IXI	5.13	4.04	6.12	6.54	5.45	7.46	**3.61**
MSE	UKB cross-validation	**11.06**	11.35	11.21	20.84	23.79	13.55	11.12
	UKB testing	12.42	11.42	**8.66**	18.73	15.37	13.76	10.74
	ADNI	23.28	18.4	19.02	36.25	163.48	60.39	**15.95**
	PPMI	28.17	29.96	55.28	98.51	69.54	160.03	**20.66**
	IXI	41.94	27.65	59.49	65.09	48.38	84.13	**21.61**
R^2	UKB cross-validation	0.79	0.81	**0.85**	0.68	0.74	0.77	0.82
	UKB testing	0.79	0.81	**0.85**	0.68	0.74	0.77	0.82
	ADNI	0.38	0.51	0.5	0.04	-3.33	-0.6	**0.58**
	PPMI	0.77	0.76	0.55	0.2	0.43	-0.3	**0.83**
	IXI	0.46	0.65	0.24	0.17	0.38	-0.08	**0.72**
	UKB cross-validation	0.9	0.91	**0.94**	0.83	0.89	0.89	0.91

Deep learning models trained on UK Biobank datasets for brain age estimation.
Credit: *Science Advances* (2025). DOI: 10.1126/sciadv.adr3757

In a new study reported in *Science Advances*, scientists analyzed MRI data stored at the UK Biobank and identified seven genes responsible for fast biological brain aging and 13 existing drugs that can target those genes.

Slowing the aging process is a powerful strategy to prevent many diseases and enhance longevity. Previous research has suggested that the ability to delay aging by even 2% could result in $7.1 trillion in health care savings in less than half a century. Over the years, it has become evident that the brain aging pattern significantly impacts overall human aging, as it is responsible for the rise in the risk of neurodegeneration and decline in both physical and cognitive health.

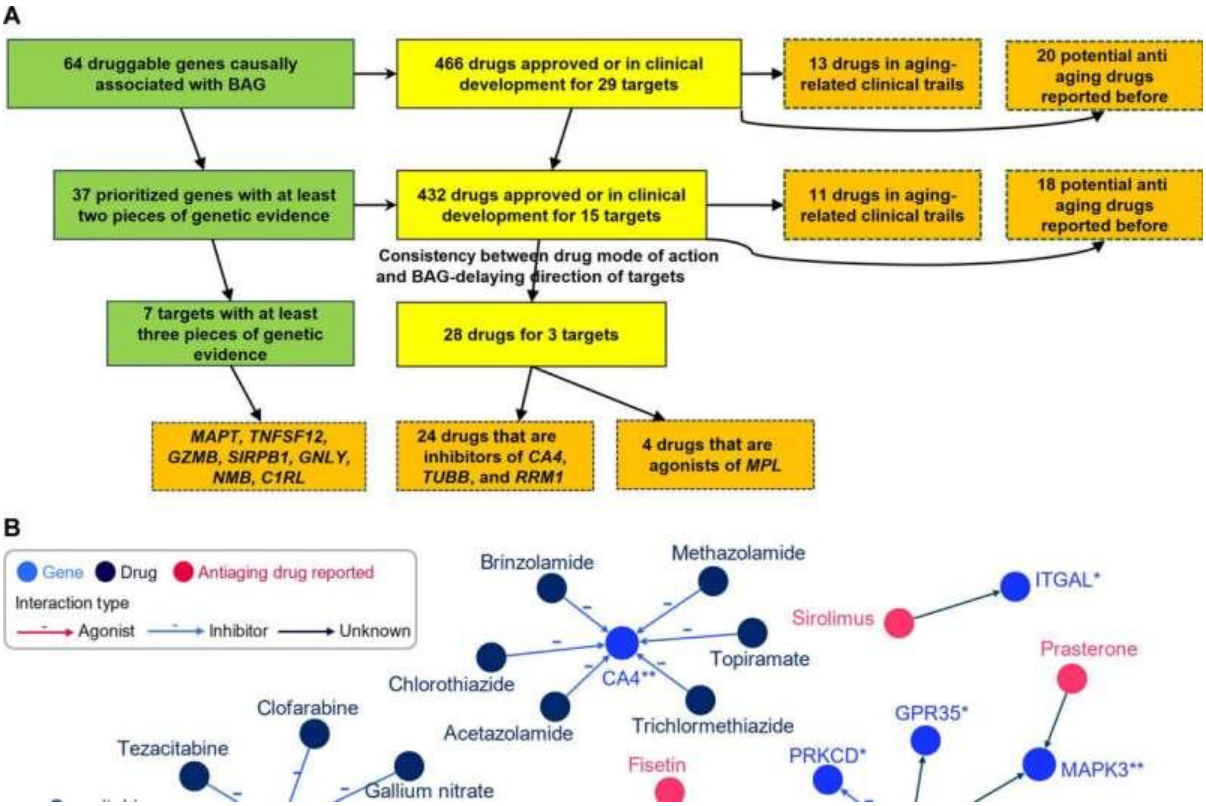
A crucial parameter in brain health research is the brain age gap (BAG), which is the difference between a person's estimated biological brain age and their chronological age. In other words, the BAG measures how old a person's brain appears on MRI or other brain age measurement techniques compared to their actual age.

The brain age gap is also a reliable biomarker (or proxy) for studying brain health. A larger BAG is often seen in individuals with brain disorders like Alzheimer's, demyelination, and schizophrenia and is also linked to lower cognitive test scores.

While the effects of the BAG are well explored, identifying the factors driving the brain's aging process remains a challenge. Genes are known to play a crucial role in shaping how the brain ages.

In this study, researchers used deep learning models trained on MRI scans, lifestyle data, health records, and genetic information from nearly 39,000 UK Biobank participants—averaging 64 years old, with an equal gender distribution—to pinpoint specific genes that contribute to a widening BAG.

Their findings uncovered that seven genes (MAPT, TNFSF12, GZMB, SIRPB1, GNLY, NMB, and C1RL) were promising targets for brain aging.



13 drugs and supplements to target and counter brain aging genes. Credit: *Science Advances* (2025). DOI: 10.1126/sciadv.adr3757

The 3D-ViT model accurately predicted the biological brain age of the participants by analyzing key signatures in their MRI scans. Researchers used saliency map analysis, a technique that highlights the most influential areas in an image or dataset, to identify the brain regions critical for brain age estimation.

The findings pointed to the lentiform nucleus, a region of the brain responsible for cognition such as attention and working memory, and the posterior limb of the internal capsule, which connects many parts of the brain to the cerebral cortex—the brain's outer layer that controls for thinking, memory, and learning.

By combining insights on specific gene targets, brain regions linked to aging, and existing clinical trial data, the researchers identified 13 drugs and supplements, including hydrocortisone, testosterone, diclofenac, and metformin, that can be repurposed to slow down brain aging.

The researchers noted that the genetic basis of aging uncovered in this study can facilitate the development of new drugs to slow brain aging and improve overall health. However, the results of this study were obtained from a population of a specific region. More research needs to be conducted across diverse populations to evaluate the true extent of these findings.

More information: Fan Yi et al, Genetically supported targets and drug repurposing for brain aging: A systematic study in the UK Biobank, *Science Advances* (2025). DOI: 10.1126/sciadv.adr3757
Journal information: Science Advances

At Age 76, Jeannie Rice Just Keeps Running Fast. Now, Scientists Finally Know Why

Rice, who ran a world record in the marathon in the 75-79 age group last year, has an incredibly high V02 max.© Zack Wittman

At 76 years old, Jeannie Rice is still setting age group world records and altering what we thought we knew about aging and running. She currently owns the world record for every distance between the 1500 meters and the marathon. It's not just that Rice is fast for her age—and just plain speedy, full stop. She's also not seeing the decline in speed you'd typically expect for a septuagenarian runner. That's why, when UK-based researchers learned that Rice would be racing

the London Marathon last April, they pounced on the opportunity to study what biomarkers and physical characteristics set her apart from her peers.

➞ **Run like Jeannie Rice!** Try *Runner's World's* **How to Master the Marathon** training program to run your first or fastest 26.2 ever! We'll give you all the tools you need to navigate your entire marathon training journey—from picking a race to crushing your long runs.

Six days after she set a new age-group world record in the marathon, running a time of 3:33:27 (averaging 8:08 miles), Rice agreed to visit an exercise lab in England where she underwent body fat measuring, treadmill testing, and other running and jumping assessments. In the resulting case report, which was published last month in the Journal of Applied Physiology, the authors shared that Rice has the highest V02 max (47.8) ever recorded for a woman aged 75 years or older, and a surprisingly high max heart rate of 180.

"I'm just a normal, average person," Rice insisted in a phone call with *Runner's World* a few days after racing the 2025 Tokyo Marathon. "...I'm not any different than anybody. I don't do anything different, I'm just lucky and I'm blessed, you know," she continued.

However, she added that she regularly runs with friends who are 40-50 years old. "I forget how old I am, because physically, I can keep up with that," she said.

Her very high VO2 max is comparable to that of world-class female and male distance runners who are several decades younger, and what's been reported in male masters world-record holders. Rice's running economy (RE), however, was found to be relatively modest for a runner of her ability.

"That's the same path to success that worked for Joan Benoit Samuelson," wrote Amby Burfoot—who has written about Rice and known her for several years and connected her to the physiologists conducting the study in London—in a Facebook post.

"The very high VO2 max found may explain why the present athlete was able to achieve world-class performances across a wide range of distances (1,500 m – marathon)," the study authors wrote, "as VO2 max is highly important across all middle/long distances, whereas the importance of RE increases with longer running distances."

Trying to make sense of their findings, they wrote that there could be something to the fact that Rice has only experienced one running injury over the course of her 36-year running career, a metatarsal fracture that occurred when she stepped on a rock, about five months after completing lab testing for the study.

"Her resilience to running injuries has likely contributed to her world-class age-group performance," they wrote, "As continuous years of running training has been suggested to be particularly essential for aging athletes. This seems to be due to a possibly more rapid decrease in physiological parameters with prolonged rest (e.g., due to injury) in older individuals, and subsequent reduced response to training as compared with younger individuals observed in some studies."

In other words, her ability to remain consistent has been something of a superpower. If you don't get injured, you can continue improving and stacking one progressive training block on top of another. There's no starting over or rebuilding required, just steady momentum.

Rice, who turns 77 in April, is known for her humble nature, and she demurs about the possibility that she's physiologically special. Her parents were healthy and active, but not impressive athletes. Sometimes when consistent hard work has become so natural to someone, they don't think of it as anything extraordinary, but as Rice said, "If I didn't train, I wouldn't be where I am. Training is 50 percent of it."

She's been running 50 miles per week year round for the past 40 years—keeping her easy days easy, and not typically going for her maximum effort during her thrice weekly interval sessions—and only began accomplishing world-record performances when she entered the 70-74 year-old age category, so the study authors theorize that the training adaptations from all those years of high volume running likely played a major role in her current performances. That, and eating healthy and balanced meals, hydrating well, and keeping her mind strong.

"So I put a lot of miles on my body, and my body probably is like, 'Oh, this is what I do. This is what we do,'" Rice says.

Study authors Bas van Hooren and Michele Zanini suggest that the RE measure may have been affected by the marathon she'd just raced. Rice reported feeling fully recovered at the time of testing, so that could suggest that the impact of

racing the marathon was relatively small on the study's outcomes, but it's probable that it played at least some role. Regardless, the results indicate that her world-class performances "may be primarily attributed to a high VO2 max rather than an exceptional RE," the study says.

Van Hooren and Zanini gave two possible explanations for Rice's relatively modest RE at submaximal running speeds—her weekly training distance and her stature. The male masters marathon world-record holder with a more remarkable RE typically ran 83-87 miles per week in the two years leading up to his world record, whereas Rice says she typically runs around 50 weekly miles, with a maximum of 68 miles in the weeks leading up to her world record at the London Marathon. Her mileage is comparable with a former world-class male middle distance runner who showed similar RE values, potentially making the case that a lower volume of weekly miles could lead to smaller adaptations enhancing RE.

Then, because Rice is relatively short, she required a relatively high step frequency at all speeds throughout the lab tests. And her high step frequency "may increase the cost of leg swing, thereby increasing the energy cost of running."

This case report brings up at least as many questions as it answers, but the researchers gained so much valuable data from Rice, and perhaps it will lead to more testing in this vein. As they acknowledged, studies including world-class masters athletes are rare, and ones that include women are even rarer. And yet, these studies have potential implications for the general population, and are in turn, a public good.

"The study of master athletes, particularly at the world-class level," they write, "can provide essential insights into the ability of humans to maintain a cardiorespiratory fitness with advancing age without the confounding effect of reduced physical activity, and on the training practices eliciting such maintenance."

One of the most illuminating takeaways was the possible suggestion that, based on Rice's stats and her long term training habits, VO2 max might be maintained

as age progresses by running relatively high mileage without a particularly heavy emphasis on high intensity exercise.

The way Rice sees it, she's just happy to keep running, competing, and working towards her personal goals, and she believes that one of these days, it's just a matter of time until somebody new comes along and starts breaking her records. Let there be more Jeannie Rices.

Younger women often approach her at races and ask to take a photo with her. "And you know, it's wonderful," she says, "because they think I'm doing well because of my age. I'm trying to motivate them, be an inspiration for them. They don't know me personally, but they think, 'If she can do it, maybe we could do it.' That's what I want them to think."

How to Look Younger for Men Over 50

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Article Summary

For the article **How to Look Younger for Men Over 50 – Regain Your Edge with 12 anti-aging tips for men.**

- **Adopt Healthy Habit**s: Lose weight and exercise to improve appearance and energy levels.
- **Take Care of Your Skin**: Use sunscreen and moisturizers to protect and rejuvenate your skin.
- **Maintain Good Grooming**: Trim facial, nose, and ear hair; keep teeth clean and white.
- **Prioritize Sleep and Hydration**: Get 7-8 hours of sleep and drink water to enhance mood and skin health.
- **Avoid Smoking and Too Much Sugar**: Quit smoking and reduce sugar intake to prevent premature aging.
- **Dress Appropriately**: Wear well-fitting, age-appropriate clothing that flatters your physique.
- **Consider Professional Treatments**: Explore options like Botox or laser treatments for noticeable improvements.
- **Be Positive**: Boost your confidence and appearance with a positive attitude.

Aging sucks but there are a number of anti-aging tips for men that can help you look younger, perhaps by up to 10 years. If you want to look younger and have a more youthful look check out the following recommendations. Some of these recommendations are lifestyle changes, some cosmetic, and some a change in your attitude. All are ways how to look younger for men.

Unfortunate Realities of Aging

When a guy gets older, their skin changes: they get crow's feet around the eyes, fine lines on the forehead, and dry skin. They begin to lose muscle mass and may appear to have a less than straight posture. They also may begin to lose the hair on their head and get unwanted hair in other places. Finally, they also likely gain weight and

may no longer have a spring in their step. These changes may also have a psychological effect causing lower self-esteem which impacts the way you appear. If this sounds like you, let's make some changes, you and I, to start looking and feeling younger.

Premature Aging

It isn't difficult to look older than your biological age. Premature aging is most noticeable in men that eat poorly, don't exercise, smoke, don't use sunscreen or moisturize their skin, and don't groom themselves.

The appearance of aging is also is brought on by stress and illness, both of which can be beyond one's control and should be discussed with your doctor.

Alter the Aging Process and Discover How to Look Younger for Men Over 50

1. Lose Weight

Weight loss may actually contribute the biggest improvement to reducing and turning back the aging process. Excess weight makes you look older than you are. You may have a double chin and potbelly from eating unhealthy junk food over the years. Your physiology or metabolic age may also be older than your biological age.

The best way to lose weight is to eat a healthy balanced diet including vegetables and protein. An added benefit of eating healthy foods is that your skin will likely improve in appearance, your body water composition and you may have more energy giving you a younger look.

2. Lift Weights

While men begin to lose muscle mass in their thirties it doesn't mean that you can't slow or stop this process. Muscle adds definition and helps give a man a stronger-looking frame. Muscle also gives men confidence which affects their bearing and appearance.

Lifting weights is a way to increase muscle mass. Muscles improve posture, increase energy and improve overall health. It also has the added benefit of stimulating testosterone production which improves your sex drive.

The key to weight training for building muscle is to decrease the repetitions and increase the amount of weight. Heavy weights are what spurs muscle growth. Over time you should increase the amount of weight you lift to see improvement.

If you don't have time or the inclination to go to the gym, work out at home. Buy yourself some resistance bands for strength training.

3. Stand Up Straight

As you age, the weight of gravity has an effect on your posture. Your overall height decreases and your muscles weaken. It becomes more difficult to stand up straight with proper posture. This results in a slouching tired look that impacts your overall appearance. This can be offset by strength training and focusing on maintaining proper posture with your shoulders back, your head up, and straightening your posture.

Some exercises that help improve your posture include exercises that strengthen your back and your core. Strengthening your core is key to improving your posture. You can also reduce your tendency to slouch by stretching by laying down on your stomach and raising your upper body with your hands.

4. Get More Sleep

Getting enough sleep at night will put you in a better mood and will help keep your energy levels up throughout the day. High energy is a sign of youthfulness. 7 – 8 hours of sleep a night is recommended and may also help reduce the facial signs of drowsiness, particularly the dark circles around your eyes.

Make sure you avoid things that may affect your quality of sleep, such as alcohol and caffeine.

5. Avoid Refined Sugar

Sugar:

1. Has a negative compounding effect on your health and the way you appear.
2. Through the process of glycation, which converts sugar to unhealthy free radicals, impacts the look of your skin making it appear older than it is.
3. Tends to sap your energy, after giving you a short sugar rush.

Consider using pure organic stevia, a natural sweetener derived from the stevia plant. It won't make you gain weight like sugar does. It's safe for people with diabetes because it doesn't increase your blood sugar levels. Unlike sugar, pure stevia doesn't cause tooth decay.

6. Wear Sunscreen

UV rays impact the way your skin looks. Although it is important to get some direct sun, which is necessary for the production of vitamin D, too much is bad for your skin. Sun exposure will cause drying, the formation of dark sunspots on your skin, and may lead to skin cancer.

Sunscreen which contains a high Sun Protection Factor (SPF) is ideal and should be worn anytime you expect to be outside for more than a few minutes, especially when it is a sunny day.

If you already have sun spots you may be able to treat these yourself by using lemon juice which will bleach out the sunspots.

7. Tame Your Facial Hair

While some men like to keep a beard, trimming your facial hair will make your face look cleaner and more youthful. If you keep neck hair, shave it, even if you like to keep a 5 o'clock shadow or a short beard. Neck hair, particularly if it is greying makes you look older and untidy.

8. Trim Your Nose and Ear Hair

As guys age, they tend to grow hair in the strangest places. Hair begins growing from their ears and nose. Also, their eyebrows begin growing longer and becoming unruly.

Invest in a hair and beard trimmer to trim your ear and nose hair. Alternatively, you may choose to use tweezers, which involve a bit of pain, if you ask me.

9. Kick the Habit to Reduce Fine Lines

While a lot fewer people smoke in the US and Canada than they did 40 years ago, smoking leads to lung cancer and cardiovascular disease. Smoking also impacts the way you look.

Cigarette smoke ages your skin by prematurely inhibiting collagen and reducing skin elasticity. This makes your skin more wrinkled and worn-looking. it can discolor your skin with yellow patches from the nicotine stain. Quit smoking!

10. Drink More Water

One of the best tips on ways to look younger and have a more youthful glow is to drink more water. When you are dehydrated you lose moisture from your skin and tissues leaving your skin less elastic and making your eyes look darker and your face less youthful.

Drinking water also improves your energy if you are dehydrated and has other benefits such as helping to reduce headaches and flushing toxins from your body. Don't drink too much – 6-8 glasses a day is just fine.

11. Brighten Your Smile

Having white teeth nowadays has the look of healthy youthfulness. While white teeth may make you look better, poorly kept teeth do the exact opposite. Ensure you take proper care of your teeth and even get them straightened, if you have crooked teeth, before putting the focus on them by getting them professionally whitened.

While you may spend money on ways to whiten your teeth make sure you don't undo your progress by drinking too much coffee and tea, both of which will stain your teeth.

12. Dress for Success

The clothes you wear impact the way you look. Baggy and frumpy-looking clothing is not usually attractive, especially for men who have followed the advice in this blog and have lost weight and exercise regularly.

One thing some people do when they want to look younger is they begin dressing younger, sometimes in a clothing style that is much too young or just plain wrong for them. Avoid youthful trendy clothing at all cost!

A conservative style is usually the best option for older guys. Put away the track pants and invest in some trousers and sports jackets. For more ideas check out fashion magazines for guys such as GQ or Men's Fashion Magazine.

Skin Care and Anti-Aging Products for Men

First of all, forget about the perception that skin care is only for women. While the manliest man you knew was probably your grandpa and he would have laughed at the idea of using skin cream, times have changed and people live much longer. Guys are using eye cream and moisturizer more often with product lines being marketed specifically for men.

Skin Care for Men

Taking care of your skin can reduce the look of old age by a few years if done consistently. You will see an even bigger impact if you start earlier.

Washing your face with a face scrub and facial cleanser will remove dead skin cells and dirt that block natural oils. This restores a more youthful appearance while also stimulating the skin's blood vessels. Using moisturizer and eye cream afterward may reduce wrinkles and leave your face looking younger.

Not all moisturizers are the same and most won't remove wrinkles from your skin while most will protect you from the harsh weather.

Using Moisturizers

Aside from drinking more water, the best skin care routine is to use a moisturizer. While most moisturizers will soften your skin not all are

beneficial to reducing wrinkles or other signs of aging. Look for moisturizers that have hyaluronic acid, which is a molecule found naturally in your body that helps reduce the signs of aging. Be sure to avoid products that contain parabens and phthalates which can negatively impact your hormones and endocrine system. Choose carefully!

Freeze Your Face

Botox has become an increasingly common and widespread facial treatment for men and one of the better ways to reduce the look of aging by minimizing wrinkles. Botox enables a temporary regenerative effect on wrinkles by smoothing out the skin and preventing it from creasing by the use of a chemical that inhibits contraction of facial muscles where Botox is injected.

Laser or Surgery

Cosmetic surgery can be used to combat a number of areas of concern. You may opt to have sun spots or other skin discoloration removed using laser surgery. Many men also have liposuction surgery to refine their jawline by removing some fat that gives the look of a double chin.

Plastic Surgery may also be used for “tummy tucks” or even muscle augmentation. It can also be used for something less intrusive, such as removing wrinkles on your forehead. Speak to a doctor about your options.

Conclusion: Bottom Line on How to Look Younger for Men Over 50

We all want to look young. Adopting healthy habits and dropping bad ones may make the biggest difference in your health and the way you look and feel. Simple things like a bright smile, a straight back, and a confident and clean appearance go a long way to making you appear more youthful. Eating healthy, quitting smoking, exercising, taking care of your skin will take you further. For a more profound change in the way you look, cosmetic surgery may even make a bigger difference. You may not be able to go back to your younger days but that doesn't mean you can't look younger.

Ready to regain your edge? Check out Looking Younger for Men Over 50 for more ideas on looking younger. For other ways on how to look younger for men, check out Belly Fat Reduction for Men Over 50: Effective Strategies.

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10 Surprising Benefits of Sleep You Never Knew About

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When you're young you don't give much thought to the benefits of sleep. When I was attending university in my early years, I thought that getting by on 4 hours of sleep while working the night shift during the summers was enough. Or cramming for an exam late into the night was necessary to do well. I didn't realize at the time the harm this was doing to me. I also didn't know that my marks actually suffered from cram sessions. But when you're young, you are resilient.

As you get older you start to realize how necessary sleep actually is. You know that air travel across time zones messes you up for days afterwards. You also know that staying up late into the night, a common thing to do when younger, turns you into a zombie the next day. Still, most of us don't really know the true impact that poor or inconsistent sleep has on the body and mind. Let's explore some of the benefits of sleep and why, as you get older, you need to pay greater attention to your sleep.

1. Sleep Sharpens Your Memory

One of the benefits of sleep is how you are better able to remember things when getting a sufficient quality and quantity of sleep. Ironically, pulling all nighters to cram for those exams was actually detrimental to your scholarly success. As you age, most realize how important maintaining good recall is.

When you sleep your brain is actively organizing and solidifying new information from the day. This allows for clearer thoughts, better

memory and improved learning capability while awake. Of course the flip side of not getting consistent sleep is a forgetful, foggy brain that struggles with learning new things.

Here's what you can do to keep your brain clear and memory sharp:

- Review important notes or concepts right before bed. This allows your brain to consolidate these memories during the night..
- Take a nap for about 20-minutes after learning something important to improve your ability to retain new information.
- Avoid abrupt alarms that impact your sleep cycles. Waking up gently helps avoid disrupting memory consolidation.

2. Sleep Helps Manage Your Emotions

Sleep is especially useful in processing stressful events you had during the day. It leaves you calmer and more balanced when you awake. Not getting enough sleep makes you more emotionally aware and sensitive to stressful events.

Try these strategies to support your emotional health:

- Keep a journal by your bed and record what worries or stresses you out. This helps clear your mind for a better sleep.
- Before bed try meditative breathing or follow your favorite NSDR recording to improve your ability to clear emotional stress from your mind and improve your ability to process stress while asleep.
- Make sure to get enough sleep (7 to 9 hours) in order to have enough REM cycles to process emotional stress from the day.

3. Rest Boosts Your Immune System

If you want to improve your immune system make sure you get a good nights rest. Sleep strengthens your immune system with an increased production of cytokines, a protein which helps identify threats to the immune system, and t-cells which help fight infection.

Want to improve your immune system with sleep? Here's how:

- Get at least 7 hours of sleep to maximize immune cell activity..
- Take brief naps of about 20 to 30 minutes when you don't feel well, which gives your immune system time to recover.
- Remove all distractions which prevent getting a full night's sleep such as noise and uncomfortable bedding.

4. Sleep Cleans Your Brain

While you sleep your brain actively works to remove toxins and waste products through the glymphatic system, a waste removal symptom for the brain similar to the lymphatic system used by the body. This process is necessary for brain health and lowers the risk of cognitive decline and Alzheimer's disease. This waste product removal process is thought to work through Deep, non-REM Sleep.

You can help this process by:

- Giving your brain sufficient time, especially near the start of the sleep cycle, to enter Deep sleep to help maximize toxin removal. This requires a full 7-8 hours of sleep and a well programmed circadian rhythm (regular established sleep times).
- Researchers suggest that sleeping on your side can improve the clearing of toxin and waste from your brain.
- Make sure to stay hydrated throughout the day to give the brain the ability to cleanse itself during sleep.

5. Sleep Increases Testosterone

Testosterone production increases during sleep as part of a natural cycle. A decrease in energy, muscle growth and libido occurs when your sleep suffers. Interestingly, a study of older men showed that sleeping up to 9.9 hours of sleep (and no more) increased testosterone levels.

If you want to boost testosterone naturally try these sleep tips:

- For older guys, sleeping up to 9.5 hours can boost testosterone. Testosterone production is known to increase more so during REM sleep, which occurs in the second half of the sleep cycle.
- Keep to a regular sleep schedule to optimize sleep and testosterone production while sleeping.
- Meditate before bed, focusing on breathing through your nose. This may, over time, improve sleep quality, minimizing breathing issues while sleeping.

6. Sleep Improves Creativity

If you depend on your ability to solve problems, as most of us do, getting sufficient REM sleep is necessary. It builds creativity by helping your brain make new connections. It does this by using different sets of information in memory to make novel connections and build creative solutions.

In order to boost your creativity you need sufficient REM sleep. Here's how:

- Writing down problems you are working on (then meditating to clear your mind) before sleep encourages more productive dreaming.

- Make sure that you don't wake up prior to your regularly scheduled time as REM sleep makes up a good part of the last half of your sleep cycle.
- Keep a journal by your bedside so that you can write down ideas from your dreams when you awake. Great ideas have come from dreams, including the model of the atom and the Rolling Stones song "Satisfaction".

7. Rest Speeds Muscle Recovery

Sleep is a time of renewal and repair, similar to the charging of a battery. During sleep your body repairs muscle tissue damage, healing and accelerating recovery for better physical performance the next day.

You can help this recovery by:

- Trying to time your workouts or sports games earlier in the day to allow more time for your muscles to rest and recover.
- Consider massaging your muscle and using ice baths to aid in muscle tissue repair.
- Ensure you get a full night's rest without distractions to maximize the healing process.

8. Sleep Controls Appetite

Getting a good night's rest helps to regulate appetite by regulating hormones such as leptin and ghrelin that relate to hunger.

To help control your appetite while asleep:

- Make sure you are relaxed and calm by eliminating distractions and using meditation prior to sleep. This will lower cortisol, the

stress hormone which can negatively impact you sleep quality and lead to increased appetite.
- Avoid bright lights and bluescreens (phones, etc) before bed as they disrupt your circadian rhythm, which can disrupt the hormones which control appetite.
- Make sure your diet and workout routine is constant as a deficit of calories can cause hunger pangs, which will impact sleep quality.

9. Sleep Prevents Chronic Diseases

Without regular and adequate sleep, you are at risk of chronic diseases. If your sleep is impacted it can disrupt your hormones which lead to insulin resistance. It can also cause high blood pressure and inflammation. This can lead to heart disease, obesity and diabetes.

To avoid chronic disease:

- Exercise regularly to naturally lower inflammation, insulin resistance and obesity.
- Focus on getting uninterrupted Deep sleep as this stage of sleep helps regulate insulin sensitivity and metabolism.
- Manage your stress levels through exercise and meditation to minimize inflammation and chronic heart disease..

10. Sleep Extends Your Life and Improves Longevity

One of the best ways to live longer and feel young each day is through quality sleep. When your body goes into Deep sleep it repairs cells, fights inflammation, and slows down the aging process. By not getting enough quality sleep, you impact your body on a cellular level, making you look and feel older.

Take these steps to positively impact your sleep habits and improve the healing process:

- Reinforce your body's internal clock – your circadian rhythm – by setting consistent times for going to bed and waking up each day. By doing so this will strengthen your body's internal clock and directly improve hormone balance, immune function, and overall health.
- Make sure to expose yourself directly (go outside) to sunlight first thing each morning to reinforce your internal clock and, in turn, hormone regulation. Just 10-15 minutes of morning sunlight improves your mood, energy, and sleep quality.

- Keep your bedroom cool (around 65°F/18°C), dark, and distraction free to ensure you maximize Deep sleep with its anti-aging repair mechanisms.

Conclusion:

Sleep has a direct impact on a number of health benefits. Getting a full 8 hours of sleep is a good start. Improving not only the quantity of sleep but also the quality of sleep can have an impact on your memory, focus, emotional balance, immune system, hormone levels as well as other health indicators. As you get older, the benefits of sleep can't be more important. Gone are the days where you can pull an all-nighter without much noticeable impact. Try that in your 50s or 60s and you will pay dearly for this choice.

Now is the time to worry about sleep cycles, sleep hygiene, habits that impact sleep and ways to improve it. Better sleep can help you regain and keep your edge.

Check out Keep a Regular Sleep Routine: Reclaim Your Sleep Time.

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Age Reversal Breakthrough: Harvard/MIT Discovery Could Enable Whole-Body Rejuvenation

BY IMPACT JOURNALS LLCJULY 15, 2023

Scientists from Harvard Medical School, the University of Maine, and MIT have published a groundbreaking study revealing a chemical method to reprogram cells to a more youthful state. This technique offers a potential alternative to gene therapy for reversing aging. The implications of this research are vast, with potential applications in regenerative medicine, treatment of age-related diseases, and whole-body rejuvenation.

In a pioneering study, researchers from Harvard Medical School, University of Maine, and MIT have introduced a chemical method for reversing cellular aging. This revolutionary approach offers a potential alternative to gene therapy for age reversal. The findings could transform treatments for age-related diseases, enhance regenerative medicine, and potentially lead to whole-body rejuvenation.

Groundbreaking Discovery in Aging Reversal

In a monumental study, a team of researchers has revealed a novel approach to combating aging and age-related diseases. This work, undertaken by scientists at Harvard Medical

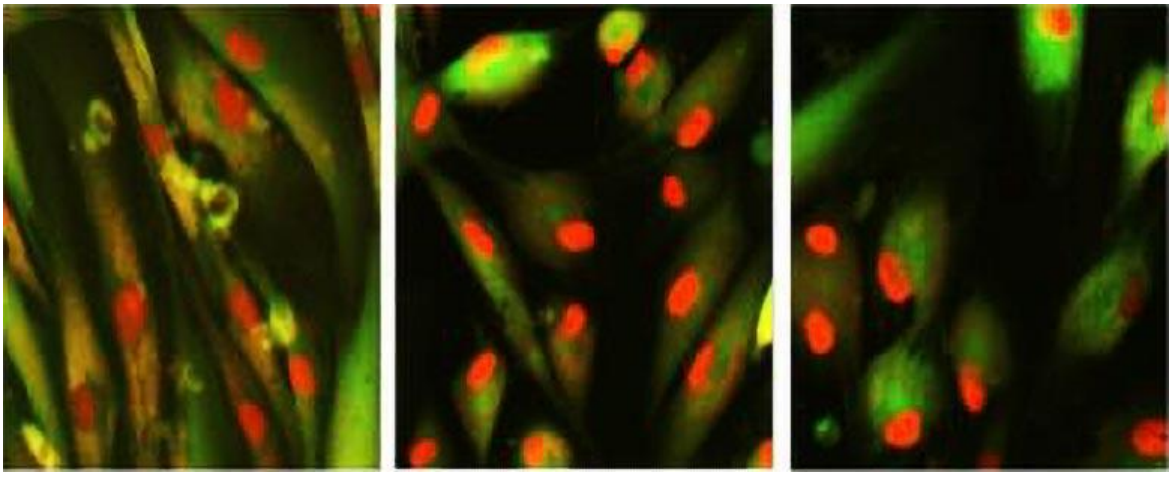
School, introduces the first chemical method to rejuvenate cells, bringing them to a more youthful state. Prior to this, only powerful gene therapy could achieve this feat.

Mice in the Sinclair lab have been engineered to age rapidly to test the effectiveness of therapies to reverse the aging process. The mouse on the right has been aged to 150% that of its sibling on the left by disrupting its epigenome. Photo credit: D. Sinclair, Harvard Medical School. Credit: 2023 Yang et al.

On July 12, 2023, researchers from Harvard Medical School, the University of Maine, and the Massachusetts Institute of Technology (MIT) published a fresh research paper in *Aging*. The paper, titled, "Chemically induced reprogramming to reverse cellular aging," extends upon a previously groundbreaking discovery. The researchers are Jae-Hyun Yang, Christopher A. Petty, Thomas Dixon-McDougall, Maria Vina Lopez, Alexander Tyshkovskiy, Sun Maybury-Lewis, Xiao Tian, Nabilah Ibrahim, Zhili Chen, Patrick T. Griffin, Matthew Arnold, Jien Li, Oswaldo A. Martinez, Alexander Behn, Ryan Rogers-Hammond, Suzanne Angeli, Vadim N. Gladyshev, and David A. Sinclair.

Exploring the Methodology

This discovery builds on the finding that the expression of specific genes, known as Yamanaka factors, can transform adult cells into induced pluripotent stem cells (iPSCs). This breakthrough, which earned a Nobel Prize, prompted scientists to question if cellular aging could be reversed without pushing cells to become too young and potentially cancerous.



Rejuvenation and age reversal of senescent human skin cells by chemical means. Cells in the right two panels have restored compartmentalization of the red fluorescent protein in the nucleus, a marker of youth that was used to find the cocktails, before the scientists confirmed they were younger, based on how genes were expressed. Image credit: J. -H. Yang, Harvard Medical School. Credit: 2023 Yang et al.

In this recent study, the scientists probed for molecules that could, in tandem, revert cellular aging and refresh human cells. They designed advanced cell-based assays to differentiate between young and old, as well as senescent cells. The team employed transcription-based aging clocks and a real-time nucleocytoplasmic protein compartmentalization (NCC) assay. In a significant development, they identified six chemical combinations that could return NCC and genome-wide transcript profiles to youthful states, reversing transcriptomic age in less than a week.

Relevance and Potential Applications

The Harvard team has previously shown the possibility of reversing cellular aging without causing unregulated cell growth. This was done by inserting specific Yamanaka genes into cells using a viral vector. Studies on various tissues and organs like the optic nerve, brain, kidney, and muscle have yielded encouraging results, including improved vision and extended lifespan in mice. Additionally, recent reports have documented improved vision in monkeys.

These findings have profound implications, paving the way for regenerative medicine and potentially full-body rejuvenation. By establishing a chemical alternative to gene therapy for age reversal, this research could potentially transform the treatment of aging, injuries, and age-related diseases. The approach also suggests the possibility of lower development costs and shorter timelines. Following successful results in reversing blindness in monkeys in April 2023, plans for human clinical trials using the lab's age reversal gene therapy are currently underway.

Views from the Research Team

"Until recently, the best we could do was *slow* aging. New discoveries suggest we can now reverse it," said David A. Sinclair, A.O., Ph.D., Professor in the Department of Genetics and co-Director of the Paul F. Glenn Center for Biology of Aging Research at Harvard Medical School and lead scientist on the project. "This process has previously required gene therapy, limiting its widespread use."
The team at Harvard envisions a future where age-related diseases can be effectively treated, injuries can be repaired more efficiently, and the dream of whole-body rejuvenation becomes a reality. "This new discovery offers the potential to reverse aging with a single pill, with applications ranging from improving eyesight to effectively treating numerous age-related diseases," Sinclair said.

Reference: "Chemically induced reprogramming to reverse cellular aging" by Jae-Hyun Yang, Christopher A. Petty, Thomas Dixon-McDougall, Maria Vina Lopez, Alexander Tyshkovskiy, Sun Maybury-Lewis, Xiao Tian, Nabilah Ibrahim, Zhili Chen, Patrick T. Griffin, Matthew Arnold, Jien Li, Oswaldo A. Martinez, Alexander Behn, Ryan Rogers-Hammond, Suzanne Angeli, Vadim N. Gladyshev and David A. Sinclair, 12 July 2023, *Aging-US*.
DOI: 10.18632/aging.204896

What is light therapy?

In short, light therapy is a treatment which has been around for about 30 years. It's the process of exposing skin to red, blue, green, cyan, yellow, orange/amber, purple, white, and near-infrared LED light which each have various benefits.

What does light therapy do?

it's likely that you've heard a little something about LED therapy. In the past, these fancy treatments were only available under the practiced hand of your aesthetician for in-office treatments. Now, this luxury is available for you to use at your leisure.

LED light therapy is actually a NASA technology that was adopted by the medical community when its ability to heal wounds and tame inflammation was noticed. Blue light frequencies are typically used to treat acne, while red light is used for anti-aging concerns. If shooting lights at your face sounds scary, you should know that there are no ultraviolet rays in these devices.

And the benefits go well beneath the skin's surface. In fact, LED light treatments have been applauded for their mental health benefits, too. Client feedback suggests that a short period of time spent under in-clinic LED lamps could dramatically improve mood, lifting spirits and reducing stress levels. Need proof? LED light therapy boosts our ATP so that it can fuel other cells with energy and boost our serotonin count. Needed.

Since the results for your skin and mind are cumulative, you need to have regular treatments to see an effect. If you can't afford regular LED treatments at your local clinic, spa, or salon, at-home light therapy could be the answer. And that's where the best LED face masks come in.

MORE DETAILS INTO EACH WAVELENGTH.

LED LIGHT THERAPY COLOR CHART

RED LIGHT THERAPY

RED: Is the anti-ager color of choice. Studies have shown it reduces fine lines and wrinkles. In addition to this, the body produces more collagen and elastin equating to healthier and younger looking skin. It can also improve overall facial texture and reduce scarring. This is the most common color users select.

BLUE LIGHT THERAPY

BLUE: Is for anti-acne primarily. It kills the bacteria that causes acne in the first place. It's also been shown to help with those who have psoriasis and reduce damage caused by the sun. This is

the favorite for those who have been struggling with Acne and have a hard time with ingredient based solutions.

ORANGE/AMBER LIGHT THERAPY

ORANGE/AMBER: Is used for firming up the skin, reducing dullness and dark spots. Users will often report their skin "glowing" when used regularly and is one of the favorites used leading up to a special occasion.

GREEN LIGHT THERAPY

GREEN: Is for reducing dark spots as well as balancing out skin levels for those with oily skin. Studies have also shown it aids with hyperpigmentation and reducing inflammation. However, the it's most commonly known for reducing bags under eyes by users.

YELLOW LIGHT THERAPY

YELLOW: Is used for calming inflammation and reducing redness. Studies have shown it's a great option for users specifically looking to reduce the redness caused from the sun. It also boosts lymphatic flow which helps remove toxins and increases skin hydration/circulation.

CYAN LIGHT THERAPY

CYAN: Is used for reducing swollen capillaries as well as inflammation. Studies have shown it has also been used to treat mild forms of acne.

WHITE LIGHT THERAPY

WHITE: Is used for accelerating skin metabolism and firming up the skin. It also has many of the same benefits of red such as reducing fine lines, reducing wrinkles and inflammation.

PURPLE LIGHT THERAPY

Not on our chart but...**PURPLE:** Is simply a combination of red and blue light therapy together. It shares both benefits of each at the same time.

And the benefits go well beneath the skin’s surface. In fact, LED light treatments have been applauded for their mental health benefits, too. Client feedback suggests that a short period of time spent under in-clinic LED lamps could dramatically improve mood, lifting spirits and reducing stress levels. Need proof? LED light therapy boosts our ATP so that it can fuel other cells with energy and boost our serotonin count. Needed.

Since the results for your skin and mind are cumulative, you need to have regular treatments to see an effect. If you can’t afford regular LED treatments at your local clinic, spa, or salon, at-home light therapy could be the answer. And that’s where the best LED face masks come in.

If you're curious about the LED face masks that will up your skincare game, read on for some of the best on the market that we have tested..

"*What's wonderful about LED therapy is its versatility. Whether you're combating acne or chasing away wrinkles, there's a light for that.*" *- Sarah Hartman*


RED: Anti-Aging, boosts collagen and elsatin production
BLUE: Anti-Acne, reduces pores and psoriasis
WHITE: Boosts skin metabolism and firms the skin
SCHOOL OF
DERMATOLOGY
LIGHT THERAPY
(FOR SKINCARE)
ORANGE: Firms the skin and reduces dullness
CYAN: Reduces swollen capillaries and inflammation.
GREEN: Reduces dark spots and helps oily skin
YELLOW: Reduces redness and inflammation

SLEEP DISORDERS

15 Warning Signs Your Body Needs More Rest

By Nancy LeBrun
Published on March 28, 2025
Medically reviewed by Daniel Combs, MD

It seems simple. When you feel tired, you need to sleep. However, other signs that you need to get more rest may be less clear. Besides feeling tired or drowsy or seeing dark circles under your eyes, you might notice subtle signs like skin breakouts, achy muscles, or vision changes.

Sleep is vital to life, like eating, drinking, and breathing.[1] These 15 cues mean you may need to give yourself a break and take a rest.

1. Dark Circles

The skin around your eyes is the thinnest and most fragile on your body. If you are not getting enough sleep, your skin cells don't repair themselves as efficiently, and it shows under your eyes. You see the damage as dark circles, which happen as blood pools under your eyes from lack of circulation.[2]

If the skin around your eyes looks slack or pale, it may be due to poor sleep quality, which can weaken the skin barrier and lead to signs of aging like wrinkles or fine lines around the eyes, known as crow's feet.[3]

2. Fatigue

Being tired at the end of the day or drowsy at bedtime is not the same thing as fatigue, which is more severe than simply feeling tired. If you feel weak or lack energy and find you have trouble keeping going during the day, your body could be telling you that you need to find a way to get more rest regularly.[4]

3. Muscle Aches

If you have mysterious aches and pains, it could be that you're lacking sleep. Your body repairs and builds tissues while you sleep.[5] Insufficient rest can also lead to inflammation, which is strongly connected to pain.[6]

Not getting enough rest can make you more sensitive to pain, as well, and it increases the risk of developing chronic pain.[7]

4. Trouble Sleeping

When you were a kid, you might have been told you were "overtired" when you were up past your bedtime. That's a real thing, and it can happen when you have been super active, either through intense physical exercise (like overtraining) or a tough mental workout. Stress can do it, too. Your body can't wind down and let you sleep, no matter how exhausted you are, if you are overstimulated.[8]

5. Poor Daytime Performance

If you're feeling less productive during the day, it could be due to a lack of sleep. You may take longer to do familiar tasks, you make more mistakes, your reaction time is slowed.

Losing just one to two hours of sleep a night over several nights can affect your ability to function just as much as if you pulled an all-nighter. Actions like driving can be more hazardous, and you may act more impulsively. Cognitive functions like learning, memory, and attention are not as sharp.[9]

Motor skills can also be affected. A study showed that tired students could not keep up with the beat of a metronome when walking, compared to students who were getting more sleep.[10]

6. Low Motivation

Sleep deprivation can affect brain circuitry involved in how much you value the amount of effort you make. If you're sleep-deprived, an extra push may not feel worth it. You may not want to put in the work to get the potential rewards from your accomplishments.[11] If you're feeling unmotivated, try getting more rest.

7. Vision Changes

When you sleep, your body and brain are in recovery mode, including your eyes and vision. If you have dry, itchy, or bloodshot eyes, it could be that you are producing fewer tears because you're not sleeping enough.[12]

Your eyesight may be blurred because your eyes are too tired to make rapid adjustments. Eye twitches can be another sign of too-tired eyes, which may feel more sensitive to light.[12]

8. Memory Lapses

Your brain needs rest to file away all that's happened each day for future reference. It organizes neural connections for you while you sleep, and your memory may suffer if you're not getting enough rest.[13]

Lack of sleep can also lead to microsleep, which is when you fall asleep for a few seconds and don't even notice it.[9] If you're in a class or at a work function, you might miss some important information because you had a "micro nap," so get rest to stay sharp.

9. Weight Gain

Sleep deprivation can cause you to confuse tiredness with hunger. Your body is trying to find the energy it needs to get a good night's sleep, so you may make poorer food choices when tired.[14]

Sleep is also important to balance hormones that are connected to hunger. If you are not getting enough sleep, you may produce more of the hormone ghrelin, which can make you want to eat. If you're rested, you may have more leptin, which is associated with feeling full.[15]

10. Moodiness and Feeling Irritated

Sleep and mood are closely related. If you're tired, you are more likely to become irritated. Tired people often respond more strongly to stressful situations and have fewer positive reactions to daily experiences. Poor sleep can make it much more difficult to deal with the stress of daily life and can even distort how you see the world.[16]

11. Increased Anxiety and Depression

If you have chronic insomnia and are not sleeping well for at least three nights a week for three months or longer, your risk of developing anxiety or a mood disorder like depression increases.[17]

Anxiety and mood disorders can also cause insomnia, creating a vicious cycle. If you are experiencing anxiety or feel withdrawn or sad, consider how well you've been sleeping.[17]

12. Sex Drive

If you don't feel inclined toward intimacy, it could be due to a lack of sleep. Sleep deprivation can have a complicated effect on your libido—the desire for sex. Some of it is psychological, and some is physiological.

Not getting enough sleep lowers testosterone levels, the hormone that can reduce sex drive in people of any sex.[18] On the other hand, there is some early evidence that less sleep may increase the desire for sex, though not sexual activity. It may also lead to greater dissatisfaction with sexual activity in women.[19]

Women who get enough sleep may notice an increase in both the desire for sex and physical arousal. One study found that women who increased their sleep by one hour had a 14% increase in sexual activity the next day.[20]

A Note on Gender and Sex Terminology

Verywell Health acknowledges that sex and gender are related concepts, but they are not the same. To accurately reflect our sources, this article uses terms like “female,” “male,” “woman,” and “man” as the sources use them.

13. Increased Resting Heart Rate

If you feel your heart is pounding, or if you measure your heart rate regularly and notice it's been going up, think about how much you're sleeping. Resting heart rate (RHR) is how often your heart beats per minute when you are calmly sitting or lying down.

When you're not sleeping enough, the levels of the hormone cortisol can go up, which can increase your heart rate.[21] In athletes, a higher than usual resting

heart rate is a sign you have not fully recovered from physical activities and may be overtraining.[22] Psychological disorders that can develop from lack of sleep, like chronic anxiety, can also make your heart beat faster.[23]

14. Skin Blemishes and Other Changes

If you notice your skin isn't looking so good, consider how much you've been sleeping. When you sleep, the blood flow to your skin increases, which helps repair and prevent skin damage. If you lack sleep, it can disrupt the skin barrier and affect beneficial bacteria like *Staphylococcus epidermis* that live on your skin and help protect it from drying out.[24][25]

Lack of sleep can lower the production of collagen and elastin (among other proteins) that keep your skin looking plump and healthy.[26] If your cortisol levels are up because you're not sleeping enough, the rapid heartbeat that can result has been shown to worsen acne.[27]

15. Getting Sick More Often

If you are catching colds or other infectious diseases more than you used to, lack of sleep could contribute to it. Your immune system needs sleep to function well. When you're tired, you don't make as many antibodies and other immune system proteins, which fight infection.[28][29]

One older study found that people who typically get less than seven hours of sleep are almost 3 times more likely to catch a cold.[30]

Over time, sleep deprivation can raise the risk of developing serious health problems, including heart disease, high blood pressure, obesity, and stroke.[9]

Summary

Sleep is vital to good health, and if you don't get enough of it, both your physical and psychological health can suffer. There are many signs that you're not getting enough sleep besides feeling simply tired. Understanding them can make you more aware of sleep deprivation, so you can take steps to get the rest you need.

DIET AND NUTRITION

7 Anti-Aging Foods That Can Add Years to Your Life

By Stephanie Brown
Published on March 19, 2025
Medically reviewed by Karina Tolentino, RD

Eating foods rich in antioxidants and anti-inflammatory properties could be part of your anti-aging skin care,[1] but it doesn't mean you'll be wrinkle-free overnight. “When you’re thinking about how to eat for healthier or younger skin, it’s definitely a long-term process,” said Rajani Katta MD, a board-certified dermatologist and a clinical faculty member at the Baylor College of Medicine and the McGovern Medical School.

There isn’t a standard “anti-aging diet” or a miracle cure for skin aging, but here are seven foods that may protect your skin, according to dietitians and dermatologists.

1. Avocados

Walk down any beauty aisle and you’ll find avocado eye cream, sheet masks, and other skincare products touting the green fruit’s ability to moisturize the skin. Research shows that eating avocados might also offer some anti-aging benefits.[2]

A small study published in the *Journal of Cosmetic Dermatology* showed that women who ate an avocado daily for eight weeks had enhanced skin elasticity and firmness.[2]

The researchers suggested that foods rich in monounsaturated fats and the antioxidant carotenoids may promote younger-looking skin. Carotenoids are natural pigments found in many fruits, vegetables, and fungi and they also function as antioxidants that can minimize damage from free radicals and oxidative stress.

2. Tomatoes

Tomatoes are packed with vitamin C and antioxidants that may benefit the skin. Take a scroll on TikTok and you'll find creators blending the fruit with yogurt to make a natural face mask.

Eating tomatoes may also help give the skin a youthful glow. A randomized controlled trial from 2001 found that consuming tomato paste might help make the skin more resistant to sun damage.

This study was one of the exceptions where people noticed some changes to their skin in a short time, according to Katta. "After three months, people were more resistant to sunburn," she said.

3. Berries

Berries are known to benefit heart health[5] and reduce the risk of certain cancers,[6] but they might also support your summer skin protection.

"Strawberries, blueberries, raspberries, blackberries contain antioxidants, which preliminary studies show may prevent skin damage and also protect your skin from UV damage and pollutants," said Kathryn Piper, RDN, LD, NBC-HWC, a registered dietitian at The Age-Defying Dietitian in St. Louis, MO.

Research on how antioxidant-rich foods can protect the skin from UV rays is limited, but some scientists theorize that natural antioxidants might help reduce the damaging effects of UV exposure and protect the skin from photoaging.

4. Dark Chocolate

Dark chocolate contains antioxidants that may offer protection from UV-light damage and promote blood flow in the skin.[8]

If you want to incorporate this into your anti-aging routine, Piper said to look for at least 70% dark chocolate in order to get the most antioxidant effects. Milk chocolate doesn't offer the same benefits and its high sugar content might even be disruptive to your skin.

"High sugar foods can really contribute to the signs of aging like fine lines and wrinkles," Piper said.

5. Green Tea

Green tea is rich in polyphenols, which may support gut health and prevent cell damage.[9] Epigallocatechin-3-gallate (EGCG), the most abundant polyphenolic compound in green tea, has been shown to reduce skin inflammation and fight acne-causing bacteria.[10] But there isn't enough research to determine exactly how much green tea you'd need to see clear benefits in your skin.

6. Fatty Fish

Consuming enough lean protein is important as you age.

Salmon, sardines, and other types of seafood that are packed with omega-3 fatty acids can reduce the risk of heart disease.[11] They're also a great source of protein that can help ease the signs of aging.

"A loss of muscle mass is the norm during the aging process, especially when one doesn't consume enough protein in their diet," Allison Tallman, MS, RD, a registered dietitian based in Nashville, TN, told Verywell in an email.

7. Almonds

Tallman said almonds are one of her favorite anti-aging foods, and they're a great source of healthy fats and fiber.[12]

These nuts are versatile, and "they can be incorporated in smoothies, as a snack on the go, or on top of a yogurt parfait for an added crunch," Tallman added. A study published in 2021 found that consuming almonds daily could reduce facial wrinkles and skin pigmentation.[13] About 50 postmenopausal women with sun-sensitive skin participated in the study and more research is needed to determine if other populations would get the same anti-aging benefits.

In general, foods that are rich in antioxidants and anti-inflammatory properties are best at protecting your skin from oxidative damage. But the key is to focus on eating whole foods and maintaining a balanced dietary pattern, Tallman said. "Focus on what you can add into your diet, like how to add more real, whole foods, rather than what you can take out of your diet," she said. "This makes eating more fun, less stressful, and more nourishing."

APRIL 3, 2025

Exercise as an anti-aging intervention to avoid detrimental impact of mental fatigue

by University of Birmingham

Credit: Monica Silvestre from Pexels

Retired people who habitually exercise are more able to fight the impacts of mental fatigue, new research suggests.

In a paper published in the *Journal of Aging and Physical Activity*, a team of researchers from the University of Birmingham and the University of Extremadura in Spain worked with groups of adults to find out whether age would increase and regular exercise would decrease the impact of mental fatigue on a series of cognitive and physical performance tests.

In the first study, sedentary men between 65 and 79 performed worse in cognitive and physical tests compared to 52–64-year-olds, with these impairments greater when they were tested in a state of mental fatigue.

A second study with retired men and women aged 66–72 found that performance when mentally rested and fatigued was better in the physically active older adults than their sedentary peers.

Professor Chris Ring from the University of Birmingham and corresponding author of the study said, "This study shows how important physical activity is for adults as they get older, and in general for avoiding the worst impacts of mental fatigue on cognitive and physical performance.

"This research from our ongoing international collaborative venture confirms that regular physical activity has a host of benefits, with increased physical fitness associated with improved cognition, increased exercise capacity, and greater mental fatigue resilience.

"For older adults in particular, regular exercise represents a simple but effective means to stave off the effects of age in a host of areas, including avoiding the negative effects of feeling mentally fatigued after a particularly taxing task."

The research team also noted that the research confirmed that mental fatigue impaired performance in older adults and showed that performance when in states of fatigue and relaxation were worsened by aging and inactivity."

Professor Ring suggests the following three active steps can be taken by older adults wishing to perform better in demanding situations:

"First, people can increase their levels of regular physical activity.

"Second, people can warm up using a combination of cognitive and physical tasks to better prepare them for upcoming physical performance overcome, especially when feeling mentally fatigued.

"Third, people can train using a combination of cognitive and exercise tasks—a method called Brain Endurance Training or BET—to improve their mental fatigue resilience and enhance their physical performance."

More information: The detrimental effects of mental fatigue on cognitive and physical performance in older adults are accentuated by age and attenuated by habitual physical activity, *Journal of Aging and Physical Activity* (2025). dx.doi.org/10.1123/japa.2024-0227
Provided by University of Birmingham

Playing the Long Game Towards Radical Life Extension

Significant longevity gains will require an entirely different approach. *May 1, 2025*

- Current techniques can only extend life and health to a limited extent.
- Slightly more advanced therapies may lead to somewhat more healthspan.
- For radical life extension, entirely new approaches are needed.

For most of the history of human civilization, humanity expanded at an astonishing pace: faster than exponential, nearly hyperbolic. This trend was famously described in a 1960 paper by Heinz von Foerster and colleagues, who extrapolated global population data to predict a so-called "Doomsday", a demographic singularity in which human numbers would become infinite by 2026, assuming growth continued unchecked [1].

However, something unexpected happened: birth rates began to fall even as lifespans continued to rise. This shift wasn't directed by any authority; it was a spontaneous outcome of billions of individual choices. It was a striking example of emergent behavior in a complex system. In doing so, humanity collectively dodged what had once been seen as its greatest existential threat: overpopulation.

Yet, the success of this transition has brought a new crisis: as we live longer, we don't necessarily live better. The burden of chronic disease rises sharply with age, driving healthcare costs higher and threatening to destabilize pension systems worldwide. The same demographic shift that saved us from overpopulation now demands a new kind of solution; we must either decouple aging from disease or stop aging altogether.

This imperative has fueled the rise of longevity biotechnology, a modern crusade to unlock the secrets of extended life. Billions of dollars have poured into startups, research labs, and bold promises of reversing aging. We have made progress: we know that human life, and especially the lives of lab animals, can be stretched impressively.

Caloric restriction (CR), cutting food intake while maintaining nutrition, remains the gold standard, consistently extending lifespan in mice, worms, and even monkeys by slowing metabolism and reducing cellular wear. It's a trick that nature has been hinting at for eons. Here's the rub: despite all our high-tech tools, no cutting-edge intervention, whether cellular reprogramming with Yamanaka factors or advanced drug cocktails, has outperformed rapamycin or caloric restriction in animal models, whether tested alone or in combination. As Matt Kaeberlein has emphasized, nothing yet beats the effect of simply eating less.

This stagnation echoes a tale from 800 years ago, when Genghis Khan, the conqueror of empires, turned his gaze to conquering death itself. Around 1222, as he ravaged all of the taxable-at-the-time world, the aging Khan summoned Qiu Chuji, a Taoist monk famed for his wisdom on longevity. Genghis, nearing 60 and feeling the weight of his relentless campaigns, demanded the secret to eternal life: an elixir to defy time.

After a grueling two-year trek to meet the Khan, Qiu offered no potion, no magic. Instead, he counseled moderation: curb your excesses, avoid overindulgence in wine and war, live simply. It was caloric restriction and a balanced life in all but name, pragmatic advice rooted in observation, not mysticism. Genghis, perhaps disappointed, still honored the monk but died just five years later in 1227. Even then, with all his power and the wisdom of the age, nothing better than moderation emerged.

Ironically, it is traditional pharma that has edged closer to practical anti-aging interventions. Drugs like Ozempic, which were originally developed for diabetes and obesity, have shown real, though modest, mortality benefits across a growing list of conditions. These effects are meaningful, but they still fall short of fundamentally altering the aging process.

Meanwhile, the longevity field projects a contradictory message. On one hand, it claims we are close to developing a drug against aging; on the other, it acknowledges that we still lack a shared understanding of what aging actually is. We are like early aviators tinkering with wings and engines, achieving powered flight through trial and error. Drugs that mimic the effects of caloric restriction, like rapamycin and metformin, are our first creaky airplanes: promising, but still crude.

The ambition to truly defeat aging is not just about building better airplanes; it's about realizing that no airplane, no matter how refined, can reach the Moon. To get there, humanity needed rockets, which are based on entirely different principles. Similarly, halting aging will demand not just incremental improvements, but a deep, principled mastery of the fundamental mechanics that drive the aging process.

As with the case of flying machines, nature provides numerous examples of evolutionarily advanced creatures, including some mammals, that exhibit little to no signs of aging and live up to 10 times longer than expected for animals of their size: an effect size far greater than that achieved by CR. This phenomenon, known as negligible senescence, is increasingly recognized as a distinct regime of aging. Notably, recent studies by the Calico team, using increasingly large animal cohorts of naked mole rates, have shown the absence of the acceleration of mortality, a defining feature of aging in humans.

We must begin thinking more deeply to make sense of these observations. In a 2007 paper in *PLOS Genetics*, Leonard Hayflick proposed entropy, the universal force driving systems toward disorder, as the fundamental cause of aging. Building on this idea and using modern molecular-level data, our team developed a comprehensive, quantitative theory of aging that integrates both dynamic (reversible) and entropic (irreversible) components of the aging process.
In a series of peer-reviewed studies, published in *Nature Communications* [2] and *Aging Biology* [3], we demonstrated that human aging is governed by a dual mechanism: a slow, linear accumulation of entropy that expands the footprint in physiological configuration space and leads to irreversible information loss, and, alongside it, dynamic fluctuations—short-term, reversible stress responses—that gradually destabilize the system and drive the onset of chronic diseases with age.

This combined framework not only confirms Hayflick's hypothesis but extends it, providing a coherent and, crucially, quantitative explanation for how different biological systems age over time and eventually fail. Critically, it allowed us to classify organisms into two distinct aging regimes: relatively short-lived ("unstable") species, like mice, whose aging is dominated by dynamic instabilities, and longer-lived ("stable") species, like humans, where aging is driven primarily by the slow, irreversible accumulation of entropic damage. A key insight from this model is that interventions targeting only the dynamic components of aging, such as senescence or inflammation, have little to no effect on the

underlying entropic damage, which is consistent with the expectations of macroscopic irreversibility as dictated by the second law of thermodynamics.

These findings are not merely of academic interest; they form the foundation for a new, quantitative theory of aging: one that explains mortality trends, biomarker divergence, and why long-lived species age differently from short-lived ones. At the heart of this theory lies a simple but powerful principle: aging in humans is driven by the accumulation of microscopic molecular insults—each individually benign and reversible, but collectively irreversible—that gradually erode physiological resilience. As this process unfolds, the organism becomes increasingly fragile, until even small fluctuations (biological noise) can push it past critical thresholds, triggering disease or death.

These findings and the underlying theory not only explain much of what is known about aging biology, but also generate important new predictions. In our 2021 *Nature Communications* publication, we provided one of the first direct measurements of the maximum human lifespan using longitudinal physiological data. By analyzing changes in biological markers, such as blood composition and physical activity patterns, we demonstrated that the variance and recovery time of physiological signals diverge near a critical age, between 120 and 150 years. This divergence signals a fundamental loss of resilience, indicating a hard upper limit on human lifespan. Our results suggest that maximum lifespan is not merely a statistical artifact of demographic data, but an objective, measurable, and potentially modifiable feature of human physiology.

Understanding the physics and biology behind this upper bound on lifespan is critical for evaluating the potential of longevity interventions. Our theory identifies three primary levers for intervention, which we classify into three distinct levels based on their potential effect size [4].

1. **Level-1 therapies** target key molecular hallmarks of aging. These include CR mimetics, cellular rejuvenation therapies, senolytic therapies, telomere activators, and most other areas of research currently in the drug development pipeline. These work well in short-lived organisms where aging is unstable and markers of aging are tightly coupled. Level-1 therapies hold significant promise for addressing individual age-related diseases, including those with the largest market potential. Of those, diabetes alone reduces human lifespan by up to 8 years (depending on the age at diagnosis). This is why we expect that drugs aimed at improving metabolic health are expected to deliver the greatest benefits in this category.

2. We predict the emergence of a new class of drugs, **Level-2 therapies**, designed to reduce physiological noise: the random fluctuations that destabilize health as organisms approach the limits of resilience. By damping this noise, these therapies could decouple aging from the onset of diseases, effectively "squaring" the survival curve. In practical terms, Level-2 interventions could add 30-40 years of healthy life by bridging the gap between today's average lifespan (70-80 years, depending on the country) and the maximum natural lifespan of 120-150 years. However, they would not significantly extend the maximum lifespan itself.
3. **Level-3 therapies** would aim to halt—or, as some hope, reverse—the accumulation of entropic damage itself. These therapies would not merely extend life; they would arrest functional decline and push maximum lifespan beyond the current 120-150 year limit. Because entropic damage accumulates slowly, future experiments and clinical trials will require the development of actionable biomarkers to track it. Targeting or controlling this damage will be challenging and will likely demand novel technologies, such as advanced organ replacement and new animal models of aging. Nevertheless, our theoretical framework provides a solid analytical foundation and brings these ambitious goals within conceptual reach.

Without a clear theoretical understanding of the aging process, drug development efforts often fall into the trap of focusing narrowly on specific disease indications. This is why most researchers, investors, and entrepreneurs in longevity biotechnology are currently centered on Level-1 therapies. These interventions may delay the onset or progression of individual diseases and modestly improve healthspan. However, they will not alter the fundamental dynamics of aging or extend the maximum lifespan.

The theoretical picture sends a dire warning. Level-1 biology addresses diseases in humans but has only a modest effect on lifespan. Level-2 interventions may further reduce the incidence of diseases and mortality. However, neither Level-1 nor even Level-2 therapies alone can alter the rate of functional decline. Aging is not merely the sum of diseases. Even in the absence of illness, humans grow increasingly fragile over time. A 90-year-old free of disease remains a diminished, less resilient version of their younger self.

The reason is that irreversible damage accumulates over time, leading to the progressive and likely irreversible decline of key functional indicators such as IQ, VO_2max, kidney function, and others that collectively define physiological resilience and quality of life. While squaring the curve, extending healthspan toward maximum lifespan, could significantly prolong life compared to current averages, it would not intercept the aging

process itself. Without directly addressing underlying decline, it risks becoming a path to prolonged disability rather than true rejuvenation.

Only a combination of Level-2 therapies that decouple aging from disease—and, even more critically, Level-3 therapies that target or reverse damage accumulation—will extend lifespan *and* preserve function, opening the path to negligible senescence in our species.

The era of low-hanging fruit is coming to an end. Rather than chasing isolated hallmarks of aging or targeting individual diseases, we must now approach aging as a system-level, entropy-driven process. My scientific aspirations are firmly at Level-3, but my instincts tell me that Level-2 therapies, those that reduce biological noise, can be discovered and developed into real medicines much sooner with today's technology.

This is the current focus of our research and development at Gero. We are investigating the biology of physiological noise using longer-lived mammals, such as dogs, as model organisms. Whether it is us or another research team that ultimately cracks the code of Level-2 or Level-3 interventions, true success will come only through a comprehensive understanding of the aging process and by raising the bar for what we expect from interventions. Without that foundation, no amount of billions spent will carry us much farther than the same old wisdom Genghis Khan got almost exactly 800 years ago.

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Rejuvenation Roundup April 2025

Senotherapeutics and extracellular vesicles took center stage last month.

May 1, 2025

While computer technology continues to accelerate, human beings still have to contend with age-related disease and death. Here's some of what's been done to support longer, healthier lives in April.

A Lifespan.io Project Bears Fruit

Results of a Crowdfunded One-Year Human Rapamycin Trial: In *Aging*, Dr. Sajid Zalzala and his team have published the results of Participatory Evaluation of Aging with Rapamycin for Longevity (PEARL), a randomized, controlled human clinical trial that was crowdfunded by Lifespan.io.

Research Roundup

Scientists Discover a New Mitigator of Senescence: Working with flies, mice, and human cells, scientists have demonstrated that a highly conserved protein can modulate cellular senescence, potentially opening a new avenue for future therapies.

Activation of Silent X Chromosome Might Improve Cognition: Using a mouse model, researchers from UCSF have found that the genes that become activated on the silent X chromosome might explain some sex-dependent differences in cognitive abilities during aging.

Extracellular Vesicles Restore Some Heart Function to Mice: Publishing in *Stem Cell Research & Therapy*, researchers have found that small extracellular vesicles (sEVs) derived from young mice alleviate heart dysfunction in older mice.

Reprogramming Epigenetics to Fight Back Pain: A new paper published in the *Nature* journal *Bone Research* has found that reprogramming the epigenetics of spinal disc cells reduces senescence and alleviates pain in a rat model.

Fasting Affects the Immune System via the Brain: A new study has found that the immune remodeling associated with fasting can be recapitulated by activating a subset of neurons in the hypothalamus. The findings could be important in the context of fasting mimicking, metabolic disorders, and cancer.

Dietary Patterns Associated With Healthy Aging: A recent study investigated the impact of eight different mid-life dietary patterns on the odds of healthy aging, including cognitive, mental, and physical health.

How Exercise May Fight Parkinson's Disease: Experimenting on rodents, researchers have found a pathway through which exercise could fight Parkinson's disease and a molecule that might recapitulate this effect.

Neurons Hidden to Immune Cells Improve Parkinson's in Rats: By tweaking genes used by placental and cancerous cells to evade immune detection, scientists have created non-immunogenic neuronal grafts that may help Parkinson's patients.

Senolytics Decrease Low Back Pain in Mice: Researchers have tested a synthetic and natural senolytic combination of RG-7112 and o-vanillin in mice with early-onset low back pain and disc degeneration. They observed reduced signs of back pain; decreased senescence and disc degeneration; and improvements in vertebral bone quality.

Researchers Use Big Data to Find a Longevity Target: Researchers publishing in *Aging Cell* have used large databases to discover a causal relationship between multiple genes and overall mortality risk, finding a new potential target in the process.

A Senescence-Related Target for Blood Vessel Formation: In *Aging Cell*, researchers have linked macrophage senescence to the failure of new blood vessel formation, finding a key target that might make it easier to treat arterial clogs.

Researchers Fight Some Mutations by Targeting Mitochondria: Clonal hematopoiesis, a condition linked to numerous age-related disorders, can be caused by overachieving mitochondria, and it may be susceptible to drugs such as MitoQ and metformin.

Technology Use Associated With Reduced Cognitive Impairment: New research suggests that digital technologies provide beneficial effects on cognition in middle-aged and older adults who did not grow up with such technologies.

How Fisetin May Fight Blood Vessel Calcification: In *Aging*, researchers have described how the well-known supplement fisetin may fight calcification of the blood vessels, seeing significant successes in both cellular and mouse models.

OS-01 Peptide Tested in Skin Aging Pilot Study: A recent study featured in the *Journal of Cosmetic Dermatology* has analyzed the impact of a topical product containing OS-01. This is a senotherapeutic peptide that targets senescence, affecting the skin's barrier function and multiple aging biomarkers.

How Extracellular Vesicles From Stem Cells Fight Senescence: Researchers have discovered a cocktail of micro-RNA strands that make some extracellular vesicles (EVs) effective in reducing cellular senescence and published their findings in *Aging Cell*.

Immune Resilience Is a Strong Determinant of Mortality: A new study defines the concept of immune resilience and positions it as a central determinant of aging trajectories, linking it to survival, inflammation control, and the body's ability to withstand stress.

Impact of Butter and Plant-Based Oils on Mortality: A study published in *JAMA Internal Medicine* suggests that a higher intake of butter is associated with increased mortality while a higher intake of plant-based oils is associated with reduced mortality.

Dietary methionine restriction started late in life promotes healthy aging in a sex-specific manner: The observed benefits provide a translational rationale to develop methionine restriction mimetics as an anti-aging intervention.

Targeting Senescence with Apigenin Improves Chemotherapeutic Efficacy and Ameliorates Age-Related Conditions in Mice: This study demonstrates the feasibility of exploiting a natural compound with senomorphic capacity to achieve geroprotective effects by modulating the SASP.

Niclosamide extends health span and reduces frailty by ameliorating mTORC1 hyperactivation in aging models: It extended lifespan and improved frailty-related phenotypes in C. elegans and effectively ameliorated frailty in aging mice, particularly in muscle aging.

Associations between five indicators of epigenetic age acceleration and all-cause and cause-specific mortality among US adults aged 50 years and older: AAGrimAge and AAGrimAge2 outperformed AAHorvathAge, AAHannumAge and AAPhenoAge in predicting mortality risk, and the association pattern was positive.

Maximum lifespan and brain size in mammals are associated with gene family size expansion related to immune system functions: The researchers conducted a genome-wide analysis not restricted to specific functional gene categories and analyzed the overlap between MLSP-associated genes identified in this study with gene sets previously associated with human longevity and molecular processes relevant to aging and longevity evolution.

AI-Driven Identification of Exceptionally Efficacious Polypharmacological Compounds That Extend the Lifespan of Caenorhabditis elegans: Rationally designing polypharmacological compounds enables the design of geroprotectors with exceptional efficacy.

Life-long microbiome rejuvenation improves intestinal barrier function and inflammaging in mice: Life-long and repeated transfer of microbiota material from young mice improved age-related processes, including coordinative ability (rotarod), intestinal permeability, and both metabolic and inflammatory profiles mainly of macrophages but also of other immune cells.

Social relationships and immune aging in early midlife: Evidence from the National Longitudinal Study of Adolescent to Adult Health: Higher quantity and quality of social relationships may help protect against immune aging, particularly in the CD4+ T cell compartment, prior to midlife.

Compression of morbidity by interventions that steepen the survival curve: A subset of interventions that extend lifespan and steepen the shape of the survival curve are predicted to compress the relative sickspan.

From geroscience to precision geromedicine: Understanding and managing aging: It is anticipated that, pending results from randomized clinical trials and regulatory approval, gerotherapeutics will be tailored to each person based on their genetic profile, high-dimensional omics-based biomarkers of aging, clinical and digital biomarkers of aging, psychosocial profile, and past or present exposures.

Age reprogramming: Innovations and ethical considerations for prolonged longevity: With interdisciplinary collaboration, robust ethical frameworks, and scalable technological innovations, cellular rejuvenation therapies have the potential to transform healthcare.

Evaluation of exploratory fluid biomarkers from a phase 1 senolytic trial in mild Alzheimer's disease: The levels and treatment responses of the analytes identified here may help inform trial design and outcomes for senolytic studies.

News Nuggets

The mTOR Inhibitors Lifespan Project Enters Next Phase: Ora Biomedical, in partnership with Rapamycin Longevity Lab, announces the successful funding of the first subproject under its ambitious initiative to conduct a rapid lifespan analysis of 601 mTOR inhibitors in roundworms. With $50,000 secured, Ora Biomedical will now commence the next phase of the first subproject.

World's First Pig-to-Human Liver Transplant: Chinese scientists announced the world's first successful transplantation of a genetically modified pig liver into a brain-dead patient. This represents an important step towards routinely using pig organs to save human lives.

Coming Up

The Aging Code Summit and Pitch Fest: Longevity Global, Mindvyne, and 3cubed.ai announced that they will be partnering to co-host the Aging Code Summit and Pitch Fest, a two-day event on June 11th and 12th that brings the latest advancements in aging research to Boston and strengthens the East Coast longevity ecosystem.

Immune Resilience Is a Strong Determinant of Mortality

The effect appears to be strongest in middle age.

Apr 29, 2025

- Immune resilience (IR) is defined by how the body handles inflammatory stress.
- People can be categorized as IR-preservers, reconstituters, and degraders.
- The 'degraders' have much higher mortality risk than the other two categories.

A new study defines the concept of immune resilience and positions it as **a central determinant of aging trajectories**, linking it to survival, inflammation control, and the body's ability to withstand stress [1].

Keeping the balance

Geroscientists have long suspected that the immune system plays an outsized role in aging, one that has deep evolutionary roots and stems from the fundamentally double-edged nature of inflammation. On one hand, inflammation is a crucial part of the immune response that helps stave off the incessant, lifelong onslaught of pathogens. On the other, it destroys cells and tissues. Health and lifespan may depend, in large part, on how well

the body performs this balancing act [2]. A well-honed immune system combines effectiveness with relatively low inflammation levels.

A new study by researchers from the University of Texas published in *Aging Cell* proposes immune resilience (IR) as a major determinant of aging trajectories, linking it to survival, inflammation control, and the body's ability to withstand stress. By analyzing about 17,500 participants across multiple cohorts, the researchers identified IR as a dynamic trait that can predict health outcomes more strongly than age alone.

They began by stratifying participants using several standard immune markers, including CD4/CD8 T cell ratios, and longitudinally analyzed how people with different immune profiles react to inflammatory stress events, such as infections or hospitalization. This allowed the team to classify individuals into IR-preservers, reconstituters, or degraders.

IR-preservers maintained robust immune defenses and relatively low inflammation throughout the stress event. IR-reconstituters experienced temporary loss of IR but eventually regained it. In IR-degraders, stress events caused an irreversible exacerbation of the "pathogenic triad", a cluster of processes accelerating biological aging: chronic inflammation (inflammaging), immunosenescence, and the accumulation of senescent cells.

The team then delved deeper into the molecular traits associated with the three subsets. Using transcriptomics and proteomics, the researchers derived two molecular signatures linked to IR status: survival-associated (SAS-1) and mortality-associated (MAS-1). The former was characterized by upregulation of proteins supporting immune competence, and the latter by proteins associated with inflammation and programmed cell death. Interestingly, components of the insulin-like growth factor 1 (IGF-1) pathway were positively associated with SAS-1 and negatively with MAS-1, aligning IR with established aging regulators.

The master regulator

One gene stood out: *TCF7*, a transcription factor essential for maintaining stem-like, multipotent T cells. *TCF7* was strongly associated with the SAS-1 signature and predicted long-term survival across multiple contexts, including chronic conditions like HIV, tuberculosis, and lupus. People with high *TCF7* expression were far more likely to preserve immune function under stress.

Interestingly, in the Framingham Heart Study [3], *TCF7* expression was linked to increased lifespan and reduced cardiovascular risk. *TCF7* is also highly evolutionarily conserved: it is one of only four genes consistently conserved in T cells across species [4].

"Our work shows that immune resilience is associated with *TCF7*, a central master regulator that maintains T cell health," said Muthu Manoharan, MS, co-first author and senior research scientist at UT Health San Antonio.

The researchers view IR as a health-promoting (salutogenic) trait that protects against diseases and aging and can be targeted to increase healthy longevity. "When salutogenesis declines and pathogenesis emerges, this may create a state of inflammation and immune aging that promotes disease," explained Sunil K. Ahuja, MD, professor in the department of medicine at the Joe R. and Teresa Lozano Long School of Medicine. "Individuals with TCF7-linked immune resilience appear better equipped to resist inflammatory stressors and maintain a low-inflammatory immune profile promoting survival and better health."

The warranty period

Importantly, the researchers identified the period between ages 40 and 70 as the one where the differences between the three IR subtypes are most pronounced. People with low IR at 40 faced nearly tenfold higher mortality, equivalent to someone 15.5 years older with preserved immune resilience.

The resilience gap narrowed after age 70, as general systemic aging overtook the benefits of strong immunity. Per the researchers, this suggests a critical intervention window in midlife, when preserving or restoring IR could have the greatest impact. However, even beyond age 70, people with strong IR signatures continued to show molecular signs of better biological aging and some survival advantage.

Framing their findings within human evolution, the researchers proposed that immune resilience evolved to balance the benefits of inflammation with its long-term damage. This "biological warranty period," as the authors call it, extending to around age 70, reflects the span during which IR offers a strong survival benefit. After that, the advantage diminishes as age-related pathologies accumulate. However, the more we know about

how those processes shaped by evolution work, the better we can become at affecting them to promote health and longevity.

"We envision a future in which immune resilience is routinely assessed, much like cholesterol testing," said Justin Meunier, BS, a bioinformatician at the Center for Personalized Medicine. "Optimal immune resilience is associated with a unique blood biomarker profile that reflects higher levels of growth and immune factors, along with lower levels of inflammation."

"The study provides compelling evidence that immune resilience — not just the absence of disease — is a key determinant of longevity," said Dr. David Furman, associate professor at the Buck Institute for Research on Aging, who was not involved in this study, to Lifespan.io. "This work highlights a critical reality: chronic inflammation, cumulative cell stress, and lifelong environmental exposures such as pollutants, diet, and lifestyle factors — what we call the exposome — are central drivers of aging. The exposome relentlessly interacts with our immune system, either preserving resilience or degrading it."

"We've known for years that 'inflammaging' — the chronic, sterile inflammation that builds with age — is a core mechanism behind nearly every age-related disease," Furman explained. "This paper elegantly frames healthy aging as an active, dynamic process. The implications are clear: strengthening immune resilience could be one of the most powerful and actionable strategies we have to extend healthspan, especially as we increasingly recognize that aging is shaped not only by our genes, but by the totality of our lived experiences and exposures."

While the study controlled for major confounders like age, sex, and comorbidities, it remains observational and cannot fully account for unmeasured factors such as lifestyle or medication use. Experimental validation of *TCF7*'s role, which was not performed in this study, will certainly be needed.

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How Extracellular Vesicles From Stem Cells Fight Senescence

A cocktail of four RNA pieces appears to be effective.

Apr 28, 2025

- Extracellular vesicles from stem cells reduce cellular senescence
- miRNAs derived from these cells appear to be responsible for this effect
- A cocktail of four of these miRNAs is effective in reducing senescence in naturally aged mice

Researchers have discovered **a cocktail of micro-RNA strands that make some extracellular vesicles (EVs) effective in reducing cellular senescence** and published their findings in *Aging Cell*.

A new approach to senescence

WHY WE AGE: CELLULAR SENESCENCE

As your body ages, more of your cells become senescent. Senescent cells do not divide or support the tissues of which they are part; instead, they emit potentially harmful chemical signals, collectively known as the senescence-associated secretory phenotype (SASP), which encourages nearby cells to enter the same senescent state. Their presence causes many problems: they degrade tissue function, increase chronic inflammation, and can even eventually raise the risk of cancer and other age-related.

The researchers began their paper discussing the well-trodden ground of senolytics, which kill senescent cells, and senomorphics, which alter them instead. They noted that cellular senescence is often targeted in aging because it is presumably easier to drug than other aspects are, and they listed various senolytics and senomorphics, such as fisetin and the well-known combination of dasatinib and quercetin. They even noted rapamycin's senomorphic qualities [1].

However, they have chosen a different, and possibly more effective, approach. EVs are signaling molecules sent from one cell to another, and they contain various molecules that control how cells behave. We have reported on researchers finding EVs to be effective against a variety of conditions, **such as enlarged hearts**, and even **extending lifespan** in mice. With an eye towards how they affect senescent cells, these researchers took a look at EVs in depth, attempting to find which of their components, specifically micro-RNA strands (miRNAs), lead to such benefits.

A variety of EVs demonstrate benefits

This study began by driving fibroblasts senescent through etoposide for 48 hours, then removing it and waiting for six days. The researchers then confirmed that EVs derived from stem cells, including embryonic stem cell-derived vesicles (AC83) known to be effective in mice, reduce the senescence of these cells. EVs from endothelial stem cells, different embryonic progenitor stem cells, and human liver stem cells were all compared to AC83 and a control group.

All of these cells had some degree of statistically significant effect, although AC83 appeared to be slightly more effective than the other types in rapidly reducing the

proportion of senescent cells, from 100% to approximately 70%, as measured by SA-β-gal. Other senescence biomarkers, including p16, p21, and the inflammatory interleukins IL-1β and IL-6, were also reduced, although AC83 was the only one to reduce p21 and the human liver stem cells were the least effective overall.

Critically, they were all found to be senomorphic rather than senolytic; the number of total cells did not significantly decrease due to EVs derived from any source.

Looking for the right combination

The next step was to take a look at the specific miRNAs involved. Using the miRNA Enrichment Analysis and Annotation Tool (miEAA) and an age-related genetic database called GenAge, the researchers sought to determine which of the miRNAs they extracted from their EVs might be having these beneficial effects, intentionally filtering out miRNAs that also appear in EVs derived from non-stem cell fibroblasts. They found eight different ones that scored highly based on this metric.

Interestingly, none of these miRNAs had complete benefits on their own. One compound decreased SA-β-gal but significantly increased inflammatory interleukins. Another compound did nothing to SA-β-gal but decreased these interleukins. One miRNA that decreased senescence also decreased p16 but provided no benefits elsewhere.

Intrigued by these results, the researchers began testing various combinations and screening them for effectiveness. After multiple attempts, they found that a combination of four of these miRNAs (E5) was sufficient to have broad, positive effects on senescent fibroblasts, reducing the senescent proportion even more than AC83 and having broad benefits against inflammation and other senescence markers.

A genetic investigation found a potential reason why this is the case. Specifically, the genes *PCAF* and *HIPK2* work together to activate p21 in response to genetic damage, beginning a senescence response. These genes were downregulated by E5 at different times, apparently blocking this source of senescence. E5 was also found to affect multiple other pathways, including those related to inflammation, mTOR, and the cell cycle.

Effectiveness in mice

Unsuprisingly, the expression of all four of the E5 miRNAs was downregulated in old mice compared to young mice. To determine its possible therapeutic effectiveness, the researchers injected two-year-old mice with E5 three times over two weeks. They found that, in liver tissue, there was a reduction of both senescence and a DNA damage marker along with reductions in other senescence markers. Inflammation markers trended toward reduction, and the difference was barely outside of statistical significance.

There were several aspects of these miRNAs that went unexplored; for example, it is not known what precise effects they had on other types of cells, and this paper did not include a lifespan study. It may be that miRNA cocktails that specifically instruct cells not to become senescent, delivered through nanoparticles or genetated EVs, may be more potent than senolytic or senomorphic small molecules. Significant work needs to be done to determine the extent of miRNAs' potential effectiveness.

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7 Best Herbs for Memory and Brain Health

Natural (and delicious) ways to build a sharper mind

By Team Verywell Mind
Updated on February 09, 2025
Medically reviewed by
Shaheen Lakhan, MD, PhD, FAAN

We'd all love to have a great memory, especially as we grow older. Perhaps that's why so many of us are looking for different ways to boost our brain power, including natural remedies. But are there really herbs for memory that can improve brain health and prevent memory loss? Several herbs and spices *may* help improve your brain health. In fact, some of them may be already sitting in your fridge or pantry.

Several of these herbs and spices have been studied for their effects on Alzheimer's disease, while others have been tested for their overall effects on cognition (i.e., the mental action or process involved in thinking, understanding, learning, and remembering). The key is to learn more about the research, be aware of potential safety concerns, and take a realistic approach to what these herbs can (and can't) do for your memory.

Feel Good Foods: The Diet-Brain Connection
1

Sage

Sage is an herb for memory that has a number of brain benefits. A spice known for its pungent scent, sage might also improve cognition and aid in the treatment of Alzheimer's disease. In fact, a research review published in 2017, suggests sage contains compounds that may be beneficial for cognitive and neurological function.[1]

Tip

Try adding sage to butternut squash, roasted chicken, turkey, tomato sauce, or in a white bean soup. Sage can also be consumed in tea form.

2

Turmeric

Turmeric is a spice long used in Ayurveda, a holistic, whole-body approach to medicine that originated in India thousands of years ago. This herb contains a compound called curcumin, which has antioxidant and anti-inflammatory effects (two factors that may benefit brain health and overall health).

According to research, turmeric may boost brain health and stave off Alzheimer's disease by clearing the brain of beta-amyloid (a protein fragment).[2] The buildup of beta-amyloid is known to form Alzheimer's-related brain plaques. In addition, turmeric may shield brain health by inhibiting the breakdown of nerve cells in the brain.

Turmeric is a key ingredient in curry powder, which typically includes spices such as coriander and cumin. To increase your intake of turmeric, try adding curry powder or turmeric to stir-fries, soups, and vegetable dishes.

Tip

Include a couple of dashes of black pepper to enhance the absorption of turmeric.

3

Ginkgo Biloba

Long used as a treatment for dementia, ginkgo biloba is a commonly taken remedy in traditional Chinese medicine (TCM) and is well known for its benefits. It's thought that ginkgo biloba might help improve cognitive function in part by stimulating circulation and promoting blood flow to the brain.

Although research on ginkgo biloba has yielded mixed results, there's some evidence that this herb may enhance cognitive function in people with Alzheimer's disease or mild cognitive impairment.[3]

Furthermore, a research review published in the *Journal of Alzheimer's Disease* in 2015 suggests that a ginkgo biloba extract called EGb761 may be especially helpful in slowing the decline in cognition among patients experiencing neuropsychiatric symptoms in addition to cognitive impairment and dementia.[4]

A core feature of Alzheimer's disease and dementia, neuropsychiatric symptoms include depression and other non-cognitive disturbances.
Ginkgo Biloba Benefits, Uses, Side Effects
4

Ashwagandha

Another Ayurvedic herb, ashwagandha has been found to inhibit the formation of beta-amyloid plaques.

What's more, research studies have indicated that ashwagandha may benefit the brain by reducing oxidative stress (a factor that may contribute to the development and progression of Alzheimer's disease)[5].

5

Ginseng

Ginseng is one of the best herbs for memory due to its potential ability to prevent memory loss and reduce age-related memory declines. One of the most popular plants in herbal medicine, ginseng contains anti-inflammatory chemicals called ginsenosides.

According to a review published in 2018, scientists have observed that ginsenosides may help reduce brain levels of beta-amyloid in preliminary lab studies.[6]

6

Gotu Kola

In alternative medicine systems such as Ayurveda and TCM, Gotu kola has long been used to improve mental clarity. Findings from animal-based research suggest that this herb may also help the brain by fighting oxidative stress.[7]

A 2021 review published in the journal Frontiers in Pharmacology suggested that gotu kola may inhibit Alzheimer's-associated oxidative stress and improve cognitive function.[8]

7

Lemon Balm

An herb often taken in tea form and frequently used to ease anxiety and insomnia, lemon balm may help improve cognitive function. Some research suggests that this may be a great herb for memory loss.

Lemon balm contains rosmarinic acid (RA), a compound known for its anti-inflammatory and antioxidant properties, which may have neuroprotective effects.

One 2023 study published in the *Journal of Alzheimer's Disease* found that the administration of 500 mg of Melissa officinalis extract (aka lemon balm extract) may help prevent cognitive decline in older adults who do not have hypertension.[9]

Other research has found that 500 mg per day of lemon balm is safe and well-tolerated and may help prevent the worsening of neuropsychiatric symptoms of Alzheimer's disease.[10]

Should You Use Herbs for Memory and Brain Health?

While certain herbs and spices may have beneficial effects on your brain, no natural remedy should be used as a substitute for standard care in the treatment of a condition affecting brain health.

It is important to note that while adding herbs and spices in the small amounts used in cooking can be healthy and beneficial, using them in larger amounts should not be considered better. Taking herbs and spices in a more concentrated form, as found in supplements, carries more risk of adverse side effects.

Seizures have been reported in children taking sage supplements; cheilitis in adults. Concentrated (supplement) forms of turmeric, ginseng, and ginkgo have a blood-thinning effect thereby increasing the risk of bleeding, especially in people taking other blood thinners or anticoagulants.

Ginseng can cause changes in blood pressure (higher or lower), interacts with many medications, and can cause a severe allergic reaction or liver damage in rare cases. Gotu Kola has been linked to damage to the liver in rare instances.

There is no FDA regulation of the content and purity of supplements. Research has found that some Ayuvedic supplements are contaminated by heavy metals like lead, mercury, or arsenic.[11]

Takeaways

Herbs for memory should be used as an adjunct to other health practices. If you take herbs for memory loss in the form of supplements, you should always talk to your doctor first.

FREQUENTLY ASKED QUESTIONS

- What can I take naturally to improve my memory?

  In addition to herbs for memory, there are also supplements that may have memory-boosting benefits. B vitamins, l-theanine, and omega-3 fatty acids are a few examples. Healthy lifestyle changes such as getting regular exercise, eating a balanced diet, and maintaining an active social life are other changes that can have a positive impact on brain health and memory as you age.

- What herb is good for memory loss?

  Herbs that may help with memory loss include ginseng, ginkgo biloba, ashwagandha, tumeric, and sage.

- What herb stimulates the brain?

  Ginkgo biloba is one of the most well-researched herbs for memory that can potentially stimulate cognitive function and prevent memory loss.[12]

Dietary Patterns Associated With Healthy Aging

With aging, some diets are better than others. *Apr 9, 2025*

A recent study investigated **the impact of eight different mid-life dietary patterns on the odds of healthy aging**, including cognitive, mental, and physical health [1].

You are what you eat

Diet is an easily modifiable intervention in aging, as what we eat has a tremendous impact on our health. There is a wealth of evidence that good diets can be beneficial in preventing cardiovascular diseases [2], type 2 diabetes [3], and premature mortality [4]. Diet also impacts age-related cognitive decline and physical performance [5, 6]. Apart from being used as a tool to prevent diseases, a proper diet can help to achieve healthier aging and a better quality of life for the elderly.

In this study, the researchers aimed to determine which of the many dietary approaches and nutritional recommendations is the best. They compared the associations between various measurements of aging and long-term adherence to eight healthy dietary patterns.

"Studies have previously investigated dietary patterns in the context of specific diseases or how long people live. Ours takes a multifaceted view, asking, how does diet impact people's ability to live independently and enjoy a good quality of life as they age?" said the study's co-corresponding author Frank Hu, Fredrick J. Stare Professor of Nutrition and Epidemiology and chair of the Department of Nutrition at Harvard Chan School.

Eight healthy diets

The dietary approaches included in the study were the **Alternative Healthy Eating Index** (AHEI), te Alternative Mediterranean Index (aMED), Dietary Approaches to Stop Hypertension (DASH), the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), a healthful plant-based diet (hPDI), the Planetary Health Diet Index (PHDI), an empirically dietary inflammatory pattern (EDIP), the empirical dietary index for hyperinsulinemia (EDIH), and ultraprocessed food (UPF) consumption.

Those approaches aim to promote good health by prioritizing healthy foods, such as fruits, vegetables, and whole grains, while reducing red and processed meats; however, there are differences between the diets.

For example, the aMED emphasizes olive oil, fish, and nuts. In the MIND, berries are an essential diet component. The hPDI focuses on plant-based foods, the PHDI focuses on foods that generate low levels of greenhouse gases, and DASH focuses on sodium restriction.

To investigate the impact of those diets on healthy aging, the researchers used the data of 105,015 participants: 70,091 women and 34,924 men from the Nurses' Health Study (1986-2016) and the Health Professionals Follow-Up Study (1986-2016). They noted that since the study participants were health professionals, it limits the generalizability of results, and similar studies should be conducted on a more diverse population.

In 1986, at the beginning of the data acquisition step, the participants filled out the Food Frequency Questionnaire, which was repeated periodically over 14 years. At the end of the study, the participants' health in aging was assessed with self-reported questionnaires that suggested that, after up to 30 years of follow-up, 9,771 (9.3%) of the study participants experienced healthy aging.

Healthy diet, healthy aging

The researchers concluded that "higher adherence to all dietary patterns was associated with greater odds of healthy aging." However, there were differences between dietary patterns.

The strongest association between healthy aging and diet was observed for the AHEI, followed by the reverse EDIH, while the association for the hPDI was the weakest.

When the researchers compared the participants in the lowest 20% of AHEI adherence to those who were in the highest 20%, they reported "86% greater odds of achieving healthy aging using an age cutoff of 70 years and 2.24 times greater odds using an age cutoff of 75 years" that was independent of other lifestyle factors, including physical activity level, smoking, and BMI.

The AHEI was created by the Harvard T.H. Chan School of Public Health researchers. It's similar to the US Department of Agriculture's Healthy Eating Index, a measure of adherence to the federal Dietary Guidelines for Americans. The AHEI focuses on foods that help to reduce the risk of chronic disease.

Different diets for different domains of aging

Aging is not uniform; not everyone goes through it the same way, and its various aspects are affected to different degrees in different people. That's why the researchers analyzed the impact of various dietary patterns on healthy aging in a few different domains. As previously, they noted that higher adherence to all of the tested diets was associated with healthy aging in all tested domains, but there were some differences between the extent of the effects.

Just as in overall healthy aging, the AHEI showed the strongest association with intact physical function and intact mental health. The strongest association for being free from chronic diseases was observed for the reversed EDIH. Intact cognitive health and surviving to 70 are strongly associated with the PHDI.

An apple a day keeps the doctor away

Analysis of individual dietary factors' impact on healthy aging suggested that healthy aging was associated with higher consumption of fruits, whole grains, vegetables, unsaturated fats, nuts, legumes, and low-fat dairy. Meanwhile, consuming ultraprocessed food, trans fats, sodium, total meats, and red and processed meats decreased the odds of healthy aging. Similar results were observed when different aging domains were analyzed.

"Our findings suggest that dietary patterns rich in plant-based foods, with moderate inclusion of healthy animal-based foods, may promote overall healthy aging and help shape future dietary guidelines," said co-corresponding author Marta Guasch-Ferré, associate professor in the Department of Public Health at the University of Copenhagen and adjunct associate professor of nutrition at Harvard Chan School.

Different people, different approaches

The researchers also analyzed different subgroups. The authors found that for both men and women, there was an association between all dietary patterns and healthy aging; however, that association was stronger for women for most diets.

For most diets, the associations were also stronger for smokers, participants with a BMI above 25, and those whose physical activity was below the median.

The researchers also reported significant interactions between socioeconomic status and two dietary patterns, reversed EDIH and reversed EDIP. They did not observe any statistically significant interactions between these diets and having European or non-European heritage.

One size doesn't fit all

While all diets showed benefits, this research has found that different diets have different effects between the sexes and in people with different health concerns. Future studies could address more individualized approaches in detail.

"Our findings also show that there is no one-size-fits-all diet. Healthy diets can be adapted to fit individual needs and preferences," summarized lead author Anne-Julie Tessier, assistant professor in the Department of Nutrition at the University of Montreal, researcher at the Montreal Heart Institute, and visiting scientist at Harvard Chan School.

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Fasting Affects the Immune System via the Brain

This mechanism also affected mTOR.

Apr 8, 2025

A new study has found that the immune remodeling associated with fasting **can be recapitulated by activating a subset of neurons in the hypothalamus**. The findings could be important in the context of fasting mimicking, metabolic disorders, and cancer [1].

Fasting and the immune system

Decades after the modern field of geroscience was born, caloric restriction still holds the crown as the very first and arguably still the most effective intervention. While fasting, a form of caloric restriction, offers numerous benefits [2], there are also many caveats and the practice should be undertaken with caution. For instance, several recent studies tie intermittent fasting to a higher risk of cardiovascular mortality [3].

Fasting can have a profound effect on the immune system. It is known to lower inflammation and reduce the number of circulating pro-inflammatory monocytes – marrow-derived cells that can infiltrate tissue and become macrophages or dendritic cells, part of the innate immune system. However, the mechanisms that drive this immune reorganization are not entirely understood.

In this new study published in *Science Immunology*, researchers from the University of Manchester posed an intriguing question: does this regulation happen via direct sensing of nutrient levels by the immune system, or does it require signaling from the brain? If the latter is the case, can these effects be induced without fasting, solely by neuronal stimulation?

Mind over body

Hunger and satiety are known to be regulated by two distinct subsets of hypothalamic neurons. The first subpopulation, called Agouti-related peptide (AgRP) neurons, promotes the feeling of hunger, while the second one, pro-opiomelanocortin (POMC) neurons, signals satiety.

The researchers genetically engineered mice in order to allow transient activation of these two groups of neurons. When AgRP neurons were activated in mice that had not fasted, the levels of circulating pro-inflammatory monocytes decreased, mirroring the effect of a 20-hour fast (a 4-hour fast did not have that effect). However, unlike in fasting, no drop in blood glucose was detected.

When fasted mice were re-fed, concurrent artificial activation of AgRP neurons prevented the expected monocyte increase, even though feeding restored normal blood glucose levels. This suggests that the brain's perceived hunger state, driven by AgRP neurons' activity, can override the systemic nutrient signal in regulating monocyte abundance.

In another experiment, the researchers activated satiety-promoting POMC neurons in fasted mice. This effectively reversed the fasting effect, increasing the number of monocytes despite the continuing absence of food.

"Our perceptions can shape our bodies in ways we don't always notice. It's easy to see how thoughts guide our actions, but this study reminds us that even our internal body adjustments that are not under conscious control respond to the brain's signals," said the lead senior researcher and coordinator of the study, Dr. Giuseppe D'Agostino. "This study underlines how important the brain is in regulating the immune system. But if internal or external factors alter the brain's perception, these processes can go awry, reminding us how deeply the mind and body are – and should remain – connected."

Collaborator and Manchester immunologist Professor Matt Hepworth added, "This work challenges the long-standing view that fasting's immunological impact is driven purely by nutrient levels. It highlights the nervous system's profound influence on how the immune system adapts during fasting."

The mTOR connection

Activating AgRP neurons mimicked fasting in yet another aspect: by reducing the levels of CCL2, a cytokine known to recruit monocytes from the bone marrow into circulation. Adding exogenous CCL2 partially counteracted this effect.

Since the liver is known to regulate CCL2 levels, the researchers investigated this organ's potential role. Interestingly, key genes that are usually upregulated in the liver during

fasting were not upregulated by activating AgRP neurons. However, the researchers noticed reduced levels of hepatic mTOR activity in what resembled natural fasting. This protein, the mammalian target of rapamycin, is recognized as a potent regulator of longevity in various animal models [4].

Preventing the inhibition of mTOR in the liver blunted the effect of AgRP neuron activation on CCL2 levels and monocyte numbers. "Together, these findings suggest that hepatic mTOR activity is under direct neuronal control via hypothalamic AgRP and POMC neurons and that this control is not exclusively dependent on local nutrient availability," the paper says.

The mechanism the researchers discovered resembles "fly-by-wire," as opposed to a direct mechanical connection: a signal goes into the nervous system, which sends outgoing signals that eventually affect the immune system. The authors suggest that their findings might be important in the context of infections, malnutrition, and muscle wasting in cancer (cachexia).

The study's lead author, Dr. Cavalcanti de Albuquerque, said, "By showing how the brain exerts top-down control over immune cells, we can further explore when and how fasting might deliver health benefits. It also opens up potential ways to treat infectious, inflammatory, metabolic, and psychiatric conditions."

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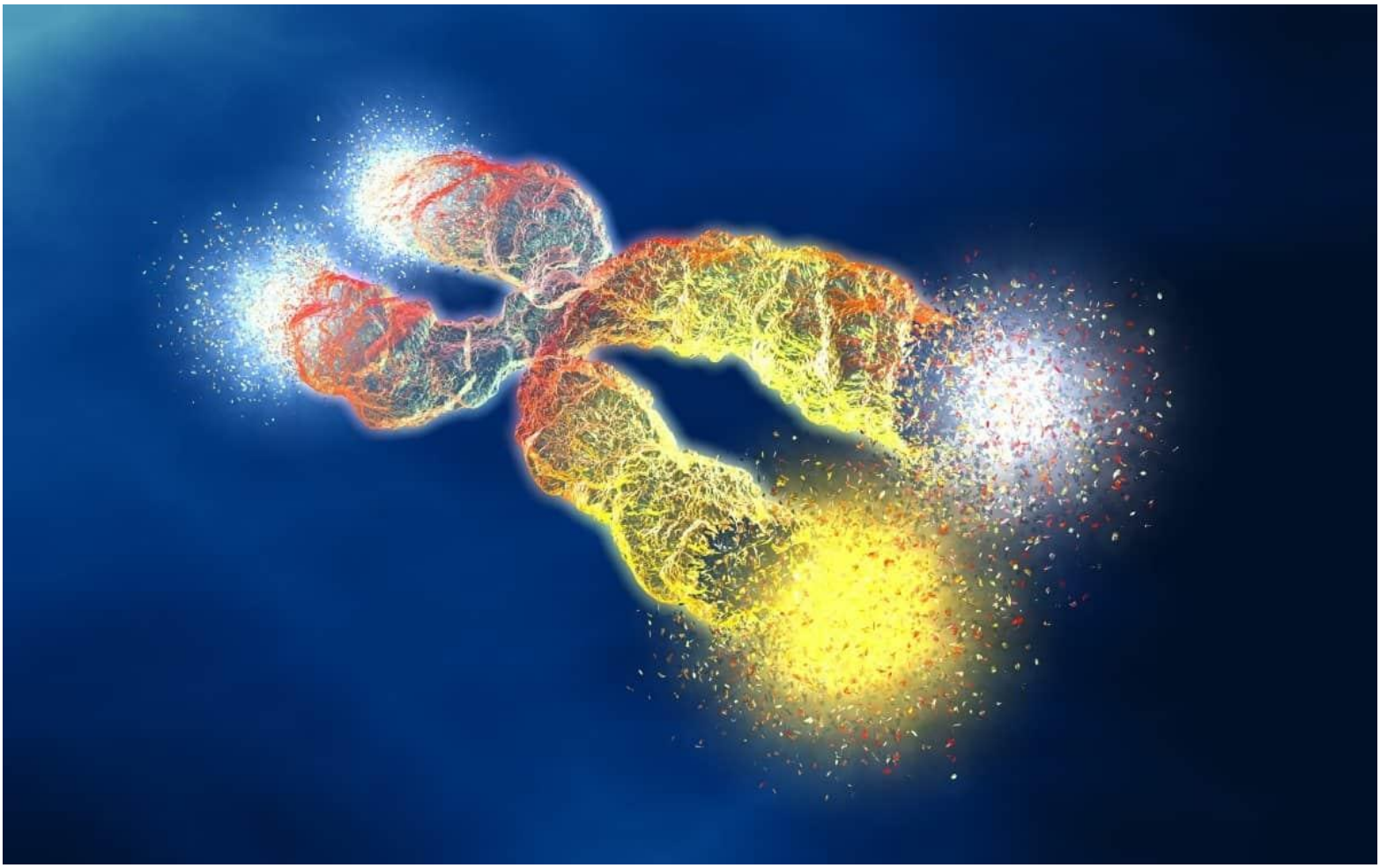
Is It Possible to Lengthen Telomeres With Diet & Exercise?

Rusty Moore

Think of a telomere as being similar to a plastic cap on the end of a shoelace that keeps the chromosome from splitting and fraying as it replicates.

As we age and as chromosomes replicate, these caps – the telomeres, become shorter and shorter. The shorter the telomeres get, the more prone we are to age-related diseases like cancer and cardiovascular diseases (1).

We are really just beginning to understand the significance of telomeres.



In fact, The 2009 Nobel Prize in Physiology or Medicine was awarded to 3 scientists for their discovery of *"How chromosomes are protected by telomeres and the enzyme telomerase."*

These scientists made these discoveries in the late ’70s, but we have just recently recognized the significance of their work.

Speaking of scientists…
For this article, we contacted a Geneticist who has extensive experience in DNA testing and measuring telomere length.

He was formerly a Population Geneticist for *Ancestry.com* and we have a Q&A section with him at the end of this article.

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Is it possible to lengthen the telomeres and potentially extend life?

There is an enzyme called telomerase that keeps telomeres from shortening too early and can even lengthen these structures (2).
Researchers and science still have a lot to learn here, but the thought is that by increasing telomerase we can extend lifespan.

Is TELOMERASE the key to slowing the aging process?

You can’t just take a telomerase supplement.

It's an enzyme produced by the body, so what research is looking into is getting the body to increase telomerase to keep the telomeres from shortening (3).

There are drugs that can increase telomerase activity but unfortunately have been shown to increase the rate of growth of some types of cancer.

This article is going to look at how to lengthen telomeres with diet and exercise.

Let's discuss exercise first.

The trend in fitness today is a heavy focus on weight training and diet alone to get lean.

Cardio is thought of as unnecessary and even counterproductive.

I have never agreed with this approach to fitness and recommend a combo of weight training, a healthy diet, AND cardio.

Cardio can slow and even reverse cellular aging.

A study published in November 2018 in the *European Heart Journal* (4) compared different types of training on the telomere length and telomerase activity.

This involved 124 people over a 6 month period.

The people were split into 4 groups:

- Endurance Training
- HIIT
- Resistance Training
- Control Group

They were instructed to do three 45-minute sessions of their assigned type of training each week.

The telomere length and telomerase activity were measured in the participants' white blood cells before and after the study.

The lead researcher of the study, Ulrich Laufs, said this:

"*Our main finding is that, compared to the start of the study and the control group, in volunteers who did endurance and high intensity training, telomerase activity and telomere length increased, which are both important for cellular aging, regenerative capacity and thus, healthy aging. Interestingly, resistance training did not exert these effects.*"

Endurance training (cardio) and HIIT increased the length of telomeres and resistance training did NOT.

Obviously, resistance training is extremely beneficial.

I believe everyone should do some type of resistance training to maintain muscle as they age.

BUT… *Don't skip out on endurance training.*

An interesting thing is that HIIT was also shown to lengthen telomeres.

It doesn't necessarily have to be done with traditional cardio exercises, I have a detailed article on numerous effective HIIT workout approaches here:
HIIT Workouts | The Definitive Guide to Interval Training

Exercise that increases Nitric Oxide in the blood could POSSIBLY explain why both cardio and HIIT extend telomere length.

In 2000 there was a study (5) showing that Nitric Oxide activates telomerase but in 2007 a study (6) came out with evidence against this.
This seems to be going back and forth…

There's a 2011 study (7) that shows Nitric Oxide positively affecting telomerase activity.
The present work demonstrates that NO affect telomerase activity and cellular replicative capacity in human hematopoietic stem cells. A significant behavior was observed on the telomerase activity and cell proliferation after treatment of cells.

One way to increase Nitric Oxide is to breathe through your nose as much as possible when performing cardio.

I cover this in detail in this article:

3 Unusual Breathing Techniques to Supercharge Your Workout
Nitric oxide production decreases with age.

So make sure you exercise in a way that keeps your levels as high as possible.

Let's talk about diet.

What can you eat to increase telomere length?

I've been following this and for quite a while studies (8) showed no significance when it came to diet and telomere length.
Some of these studies were comparing specific diets like the *Baltic Sea diet* vs the *Mediterranean* Diet.
Then a study (9) published in April 2018 looked at fiber intake and telomere length.

This study used a sample of 5,674 adults in the U.S.

The U.S. is a good population to study because a large portion of the population has a low fiber intake (and getting lower with the rise in popularity of the KETO and Low Carb diets).

People who eat a high fiber diet have been found to have longer telomeres than those who eat very little fiber.

"A *difference of 4.8 to 6.0 years in cell aging was found between those in the lowest compared with the highest quartiles of fiber intake. Overall, the present study highlights the risk of accelerated aging among* U.S. *women and men who do not consume adequate amounts of dietary fiber.*"

This actually may partially explain the results of an earlier study.

In 2014, there was a study (10) showing high fiber intake reduced risk of mortality by 23%.
"*By source of fiber, cereal and, to a lesser extent, vegetable fiber were significantly associated with lower total mortality, while fruit fiber showed no association. In conclusion, high dietary fiber intake may reduce the risk of total mortality.*"

We have known for a while that a high intake of fiber is associated with a lower risk of chronic disease.

Perhaps fiber's effect on telomere length is one of the reasons for the lower incidence of chronic diseases for those who eat a high fiber diet.

Sometimes we figure out something is healthy before we find out exactly why it is healthy.

Here's a list of foods high in fiber:

- Whole wheat spaghetti
- Whole wheat bread
- Brown Rice
- Oatmeal

- Green peas
- Corn
- Potatoes
- Lentils
- Beans
- Berries

Like I mentioned earlier, the rise in popularity of low carb and keto diets mean that people are getting less fiber than ever.
Although these diets can result in fat loss, I just don't think they are healthy long term. It's possible to get lean with a high carb diet.
Whatever diet plan you follow…
Make sure it includes plenty of fiber-rich foods.

How much fiber should you eat each day?

The Dietary Guidelines for Americans (11) recommends 14g of fiber for every 1,000 calories consumed. This comes out to about 21 -25 grams of fiber per day for women and 30 – 38 grams of fiber per day for men.

Only about 10% of Americans hit this recommendation.

I'm not saying the *Dietary Guidelines* are ideal at all, but I think in regards to fiber they have it right.
Here are some other benefits of fiber:

- Reduces cholesterol and blood sugar levels
- Lowers risk of cardiovascular diseases and diabetes
- Increases digestive and bowel health
- Fuels healthy gut bacteria

So the benefits of fiber go beyond extending the lifespan of telomeres.

What about foods that increase Nitric Oxide?

As I discussed earlier an increase in Nitric Oxide is tied to the lengthening of telomeres.

Here are some foods to eat to increase nitric oxide production:

- Leafy Greens
- Beets
- Dark Chocolate
- Citrus Fruit
- Watermelon
- Red Wine
- Rhubarb

Leafy greens like arugula, kale, and spinach top the list.

I would recommend making dishes that combine high fiber foods with these foods shown to boost nitric oxide.

We still have much to learn when it comes to aging, exercise, and diet.

Time to bring in the expert.

Q&A With a Geneticist | DNA, Telomeres, and New Findings

Tim Barclay is the Sr. Editor for the leading DNA testing consumer guide, Innerbody.com. He was also formerly a Population Geneticist for Ancestry.com and earned his Ph.D. in Genetics from Iowa State University.

Question 1: Can you tell how old someone is by telomere length? Is there an average length for each age group?

Answer: It is possible to make an *educated guess* as to how old someone is based on telomere length.

There is an inverse correlation between age and telomere length (measured in TRFs, terminal restriction fragments). By plotting the lengths of thousands of

individuals' telomeres along with their respective ages, we can make educated guesses as to a subject's age based on observed TRF lengths. This plotting method is similar to how we can make an educated guess on how tall a baby will grow up to be based on the heights of the parents.

Question 2: Can I currently have my telomere length tested? I want to find out if I have strong telomeres for a 49-year-old.

Answer: In my opinion, the easiest way to have your telomere length tested is by purchasing a direct-to-consumer test kit from an innovative, Silicon Valley-based company named TeloYears. As far as we know, they are the only company which currently offers such a home test.

On our website, Innerbody.com, we have a detailed review of TeloYears that a colleague of mine wrote earlier this year. In short, our researchers really thought highly of their tests.

Question 3: What is the biggest benefit someone receives by getting their DNA tested?

Answer: Now I am assuming that you are asking about the biggest benefit associated with taking a telomere DNA test (and not a more general DNA test).

There are many benefits. But if forced to choose one, I would say that if you find out that for whatever reason you have significantly shorter than average telomere lengths (which typically affects 5K – 10K Americans), then you will know early on that you have an increased risk for developing many diseases associated with short telomeres such as pulmonary fibrosis. This information can help you and your doctor make more informed medical decisions.

Question 4: I'm guessing things like obesity, smoking, excessive drinking will all negatively affect telomere length. What should we avoid to ensure our DNA isn't negatively impacted?

Answer: You are correct. There have been many reputable studies that appear to show a connection between poor lifestyle choices such as smoking, poor diet, etc. and shorter telomere length. However, the science is not at the point where it can explain why this would be the case. Correlation does not necessarily mean causation, so the truth is that we really don't know for sure. I am not a fitness guru, but from a geneticist's perspective, I would say that that you should not be smoking and should maintain a well-balanced diet to keep your body healthy in general. And if keeping your telomere lengths as long as possible is one of the results of these choices then that is icing on the cake.

Question 5: Are there any effective supplements you would recommend that are especially effective when it comes to affecting our DNA in a positive way?

Answer: As a scientist, I only like making assertions that are strongly backed by diligent research. And at this time, there is not a whole lot of evidence, at least that I know of anyway, that would suggest supplements would help. We just don't know currently, so I would not want to make uninformed guesses. I would say that maintaining a healthy diet would surely not hurt. And I would not be surprised if that sometime in the future, a positive correlation between some vitamins or minerals and telomere health was proven.

Question 6: Do you see a day in the near future where we have the ability to drastically slow down the aging process? It feels like we are getting close.
Answer: This is getting very speculative. I don't know if I would say "near" future, but I do personally believe that sometime within the next 20 or 40 years scientists will have figured out a way to slow down the aging process.
Question 7: What excites you most about this area of research?
Answer: The telescope was invented in the early 1600's. The invention sparked an information revolution about what we learned about the universe. Back then, astronomers saw a blurry object and guessed it was a new planet. They were pretty sure that it was a planet, but they didn't know for sure. And just think how we have come since that time, landing a man on the moon, sending a rover to Mars, and seeing distant galaxies billions of light years away.
Well, genetic science today is about where astronomy and the telescope were in the 1700's. But this time, science is moving much, much faster. I can't wait to see what we uncover about our DNA in the next 10 years. There is so much potential.

More About DNA Tests: Tim has coauthored a short guide which compares all the various DNA testing brands: DNA Health Testing
He covers the best DNA tests for health, nutrition, food sensitivity, ancestry, fitness, telomere health, etc.