# CRYONICS

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Saul Kent interviewed by Erroll Morris, 2000

# CRYONICS

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# A Time of Transitions


Alcor's facility in Scottsdale, Arizona, June 2023

Welcome, dear reader, to this, the 3rd Quarter, 2023 issue of Alcor's newsletter *Cryonics*. (It is late, and we are trying hard now to catch up!) An important milestone is reported herein: the cryopreservation of Saul Kent, who is one of the pioneering giants in the cryonics field. Together with his business partner Bill Faloon, Saul contributed much to our movement and its important sister, the field of human life extension.

Born in 1939, Saul dedicated his life and self-acquired wealth to overcoming death through rational, scientific means, including halting and reversing aging. It is, needless to say, a tall order. Progress is being made in understanding aging and learning what might be done about it. But the main goal of curing it was too much for one man or a few people to accomplish in one of our presently too-short lifetimes. Saul was enough of a realist to recognize long before that this might be so and made sure he had cryonics arrangements in case the great breakthroughs against aging would not come soon enough to save him. Now his life functions are on hold and future progress must address his needs.

Life presents us with a series of transitions. Once able and prominent people can no longer contribute. New challenges arise that must be met by those who were motivated, informed, supported, and/or trained by those who went before. We would like to see the older ones again someday, vibrant and healthy as they once were. In large part, that is why we are here. To carry through on our mission to eventually revive those we have cryopreserved, we must endure and persevere.

Alcor is undergoing transitions, as we try to offer better services, while at the same time keeping

costs as low as possible. Lower costs mean, for example, less pressure to raise cryopreservation minimums, and more freedom and flexibility to be innovative and improve our operations of standby, cryoprotection, transport, and long-term care.

Among the things we must think about is our newsletter. Currently it is entirely electronic, a move made a few years ago in the interest of saving costs, given that most people now have computers and can access materials online. We thank Aschwin de Wolf who until recently did editing for us on a contractual basis. As another economy measure, we are now doing our editing in-house. As usual, we welcome comments, criticism, and suggestions on Alcor and/or its newsletter readers. Send correspondence to me, Mike Perry: mike@alcor.org or mike.perry@alcor .org.


Alcor's Patient Care Bay, main suite, August 2023. This space is nearly full, and an adjoining suite is now being used increasingly for new arrivals.

# Remembering Saul Kent

by R. Michael Perry

Saul Kent, dust jacket of *The Life Extension Revolution*

On May 6, 2023, Saul Kent became a patient of Alcor. It was after a long and productive career of activism and accomplishment in areas related to extending human lifespan and healthspan. Prominently, it included cryonics, where Saul was a major player almost from the beginning of the movement. Later Saul and his business partner Bill Faloon organized the Life Extension Foundation (LEF; now Biomedical Research and Longevity Society, BRLS) whose revenues from the sale of dietary supplements were used to fund research in cryobiology and organ preservation. In all they stand above all others in their financial backing of research relating to cryonics and life extension, a heroic effort that continues today. We owe them a great debt.

Lately a lot of material has appeared online about Saul. This article is no exhaustive survey of these sources and others. Instead it is my own selection of interesting highlights, with some emphasis on material not easily found elsewhere, and substantial abridgment or omission of other itemsich the interested reader can find in the references given.

**Death not Good**

Asked in an interview with filmmaker Errol Morris, "Why is death so bad?" Saul responded:[3]

> Because it's the end of life. Death is not the second worst thing that could happen to you. It's the worst thing that can happen to you. It's not even a question of death is bad, bad or good isn't the issue. You're just not there. It's the disappearance of everything. There's nothing I can imagine worse than that.

**Early Life**

Saul was born July 19, 1939, in Brooklyn, NY, the only child of William and Dora (Rothbart) Kent, who were Polish-Jewish immigrants.[1,2] Saul in the interview with Errol Morris adds this:[3]

> My mother was around 40 years of age when I was born. So, she was older than most mothers and I was an only child. My father died when I was 10 months old. And of course, I don't recall it at all. And my mother never remarried. So I never really had a father. He died of rheumatic heart disease, which is essentially an infection that attacks the heart and that is readily curable and preventable now. People don't die of rheumatic heart disease anymore. If my father had been frozen, he easily could have been cured of rheumatic heart disease even now or even maybe a year or so after he died.
>
> My mother was both mother and father to me and she was very devoted to me. She brought me up by herself. She stayed in the house and worked as a dressmaker at home. It wasn't until I was about 14 or 15 before she went out and got a job. My mother really believed in being independent and having as much freedom as possible. And I learned a lot of the way I am today from my mother, the independence she showed and the dedication she showed, I learned a great deal from her, and I owe a lot to her. Ultimately, when I arranged to have her frozen, I was really, in a sense, freezing both my parents.

Mother Dora Kent and Saul about 1950

**Education and Early Cryonics Involvement**

Charles Platt in 1991 recorded some conversations with Saul reporting on his schooling, how he got involved in the nascent cryonics movement, and where it went from there.[8]

> I was born in the Bronx. I lived in the New York area until 1975. I went to Hunter College. I was a terrible student, a

misfit in the sense that I wasn't looking for a career. I wanted to be a writer, I had written some short stories, but I hadn't been published. The first book I wrote was called *Future Sex*. But it's largely about life extension, too. There's some fiction in that; every chapter starts out with a fictional episode.

I was a phys-ed major at Hunter, I'm really an athlete. Hunter is part of the City University of New York, and I was one of the worst students ever. It was free at that time, except for books. I revolted against authority and went overboard. When they told me to do something, I wouldn't do it, simply because they told me to do it.

I was a pretty good student till my junior year in high school, and then I started going to the beach. As a senior I arranged my classes so that they were all over by 12 or 1, and then I went to the beach.

I got bored with school because I wasn't motivated. I had problems graduating because in most courses I could do nothing and get a C, but in languages, German in college and French in high school—I would wonder if I'd get any score at all in tests. I did graduate finally from Hunter, but I graduated under 1.8. And 2 is a C, 1 is failure. I also played baseball a lot, till the weather was too hot.

They sent me to a psychologist once, at college, because I was behaving abnormally and wasn't reaching my potential. They gave me a Rorschach test, but I told them that all I could see were ink blots, so I won that one.

In the June 1964 issue of *Playboy* Magazine there's an article titled "Intimations of Immortality" by Fred Pohl, and there's a paragraph about [Robert] Ettinger's book [*The Prospect of Immortality*, that largely started the cryonics movement]. I read that [article], and the next night Pohl was on the Long John Nebel show[, a late-night talk show that used to air on AM radio]. I then went out and bought the book, they'd just gotten it in a few days ago. I was an instant convert, but I didn't get around to doing anything till January 1965, because there wasn't much to do at that point except write to Ettinger.

I had never been a member of anything, I didn't really want to join any organizations.

Ettinger didn't want to have anything to do with any group, his position was that this idea was so logical and important that big companies would get involved—he assumed someone would just run with it. It was only reluctantly, later on, that he decided no big people were going to do anything.

I'd had two real jobs in my life before cryonics. My first term in college was the fall of 1956, and I didn't like it so I dropped out, quit after the first time and got a job at Lehman Brothers brokerage company in Wall Street. I was a runner. I had to deliver things all around Wall Street, such as certified checks for $6 million. Then I went back to school at the beginning of 1957, and then at the end 1959 I was thrown out of school, my marks were low. I got a job as a clerk-typist at Barnes and Noble. And then I went back to school.

After I graduated and got involved in cryonics, I worked for the *Journal of the American Waterworks Association*, then I worked for a publisher of trade journals, then I worked for *Sexology* magazine, writing and editing. Then the only other job I've ever had was around 1972/3 I worked for a year and a half for McGraw-Hill, they had just started a new magazine called *Contemporary ObGyn*. I worked about a year and a half as a writer, and that I enjoyed because I would go out on trips and write them up. Then I became a freelancer.

Finally, I went to Florida to start *Anti-Aging News*.

I'm self-educated in virtually everything, including the legal system.

**Saul Kent and Evan Cooper**

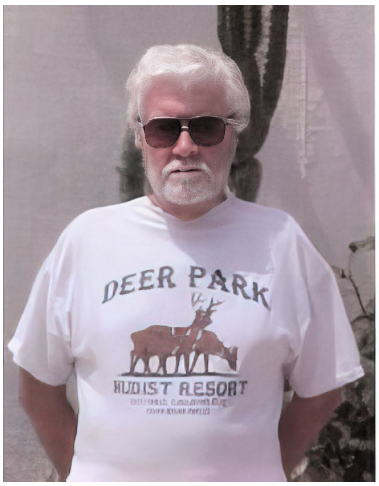
Besides Robert Ettinger, there was another important pioneer in the early cryonics movement, to the point of really being a cofounder. Evan Cooper (birth name: Stanley Edward McBarron, never used or mentioned in his later life as far as I am aware[12]) started the first organization promoting the cryonics idea, the Life Extension Society (LES), in December 1963. Soon LES chapters were being started at different locations around the country, starting from Cooper's home base in Washington, D.C.[15] Saul had interesting things to say about his encounter with Cooper in a 1983 *Cryonics* article, which I've excerpted.[5]

> The cryonics movement did not begin with the publication of *The Prospect of Immortality* by Robert Ettinger in 1964. At the time there was already a cryonics organization in being, although the word "cryonics." had not yet been invented. That organization -- The Life Extension Society (LES) -- was started by Ev Cooper -- a tall, softspoken man who also wrote the first book on cryonics: *Immortality, Physically, Scientifically, Now*, which was published privately.

(Note: I looked up the dates. For the record, Cooper's book was copyrighted Nov. 3, 1962; Ettinger's first version of *Prospect*, also privately issued, appeared six weeks later, Dec. 18. Both writers soon became aware of each other's independent efforts and started corresponding. – RMP.) Saul continues:

> When I read *The Prospect of Immortality* in June of 1964, I was exhilarated to a degree I had never before experienced. Instantly, I knew – beyond a shadow of a doubt – that the most profound and powerful idea in history had been unleashed and that I would devote my life to it. But it wasn't until the following winter that I finally got around to writing a letter to Ettinger to initiate my involvement in the movement.
>
> In that letter, I asked if there were any organizations working to promote the idea. He replied that there were two: The Immortality Records and Compilation Association (IRCA) in Panorama City, California headed by Tom Tierney and The Life Extension Society in Washington, D.C. headed by Ev Cooper.
>
> I wrote a brief note to both organizations and awaited their replies. From IRCA I heard nothing. Two years later, I was to experience hours of intensive questioning from police and the FBI in Las Vegas when Curtis Henderson and I tried to meet with Tierney, who had just been arrested for

counterfeiting and gun fraud. When the police interrogator asked me if we were involved in either of these schemes, I replied: "No, officer, we only freeze dead bodies."




**Stiff Term Faces Bogus Bill Printer**

LOS ANGELES (UPI) — Thomas Tierney, 41, Canoga Park, faces sentencing to up to 30 years in prison Feb. 5 on charges he counterfeited $3 million.

A federal court jury convicted Tierney on two counts of counterfeiting.

Authorities said the bogus bills were printed in 1966 at Consolidated Productions Inc., a mail order firm formerly operated by Tierney in Chatsworth.

Three other persons already are serving time in federal prison in connection with the case.

Tierney, who was convicted at his third trial, faces sentencing before U.S. District Court Judge Harry Pregerson.

**Mail Order Arms Fraud Charged to 3**

LOS ANGELES (UPI) — Two of three Las Vegas men indicted on charges of mail fraud involving a mail-order firearms offer are free today after posting $2,500 bail.

Thomas Tierney, 39, his brother Patrick, 31, and Darrel Shea, 40, were indicted Wednesday by a federal grand jury here on 17 counts of mail fraud.

The three allegedly took part in a scheme which involved mailing 25,000 brochures to all parts of the nation last September and October. The brochures, believed to have been mailed in Van Nuys, Calif., advertised fireams for sale by a firm called "The International Import-Export Co." which listed its base as Rio de Janiero, Brazil. Those wishing to purchase the weapons were instructed to send their money there.

The indictment claimed there were no guns for sale.

The Tierney brothers paid their bail and were freed but Shea was remanded to the custody of the U.S. marshal in lieu of $2,500 bond.

Tom Tierney (Thomas Samuel Tierney, 1927-2020) in later life was open about his shady past, along with early if transient interest in cryonics.[13]

From Ev, on the other hand, I heard a great deal. Several days later I received a Special Delivery letter from him that was a bit overwhelming. Not only did Ev welcome me into his organization with open arms, he actually asked me if I wanted to represent LES in New York as a "Life Extension Coordinator." I wasn't quite ready for that yet and wondered what kind of man would make such an offer so quickly.

About a month later I met Ev Cooper and his wife Mildred for the first time at Grand Central Station in New York. Ev had just participated in a seminar on the freezing idea at Pace Institute in Brooklyn.

**The Gracious Host**

From the beginning I found Ev to be warm, friendly, gracious, and generous. We carried on an exciting and highly stimulating conversation in his car as we drove out to a restaurant in Queens to meet (for the first time) with Jim Sutton and Harry Costello, who were to join with me in becoming coordinators for LES in New York. Three months later, we would resign from LES and six months after that would join with Curtis Henderson and Karl Werner to form the Cryonics Society of New York.

About 6 weeks later, Jim Sutton, Harry Costello, and I took a bus ride to Washington, D.C. to meet with Ev and the other members of LES. Once again, Ev and Mildred greeted us with warmth and good cheer. While Jim and Harry stayed at a local motel, I had the good fortune to be invited to stay with Ev and Mildred at their apartment -- the home base of the Life Extension Society.

That evening Ev and I discussed the idea of achieving immortality with great excitement. It was particularly thrilling for me to discuss the idea with a man who had obviously given great thought to its implications. Ev was well read in philosophy, psychology, and literature. He greatly enjoyed discussing traditional ideas and then speculating about how they might change as the prospect of immortality became more imminent. LES, in fact, had evolved from a discussion group led by Ev that examined the greatest books of the 20th century. Ev and I continued our discussions until well after midnight.

[The next day] Ev took me out about half a mile from shore [in his sailboat]. It was quite windy, and I was soon cold and wet and anxious to get back to dry land. But Ev wasn't about to take me back so quickly. He was truly in his element at sea and was determined to tell me all he could about the glories of sailing, whether I wanted to know or not.

Finally, after about 45 minutes of gliding through the waves, we returned to shore. That was the first and last time I ever saw Ev's sailboat.

Ev Cooper as (1) life extensionist, 1960s; (2, center) "bearded boatman" of later years, with passengers.[12]

**The 1966 Conference**

The first major cryonics event I ever attended was the 2nd Annual LES Conference held on January 1, 1966. …And what a conference it was! Ev had sent out press releases about a frozen dog ("Belle") who would be displayed at the conference. He also made arrangements with Ed Hope of Cryo-Care Equipment Corporation to drive that company's prototype "Cryo-Capsule" to D.C. from Phoenix in order to exhibit the frozen dog.

Hope [had] arrived [the] night [before], but Ev had neglected to make arrangements for a place to put the trailer with the capsule. So he had to leave it in a "no-parking" zone next to the restaurant where the conference was to be held.

The next morning, photos were taken of Belle in the capsule and then the dog was put into a freezer. The conference started bright and early, with the streets of the city deserted (It was New Year's Day, you remember).

At noon we wandered out of the restaurant to find a small crowd gathering around the capsule. The police were questioning Ed Hope about the strange machine in his van. They had perplexed looks upon their faces as they pondered the meaning of the "suspended animation" sign on the side

of the van.

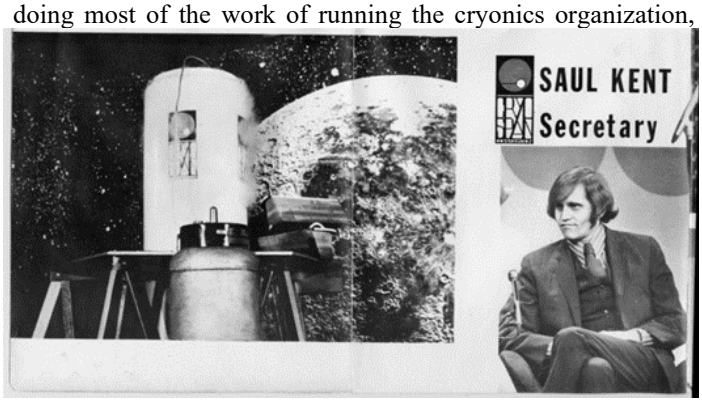
> [More showed up, the crowd got unruly, then] the press arrived. A camera crew from one of the local TV news shows was the prime attraction. One of D.C.'s most popular TV reporters was asking for the person in charge of the festivities. When Ev couldn't be located (he was apparently in the Men's Room), Bob Ettinger consented to an interview to explain what freezing people was all about.
>
> As the interview proceeded, the crowd grew [still larger, the] protesters became more vocal, and the police moved in to break up the proceedings. As soon as the TV interview was over, we returned to the restaurant to resume the conference. That night we watched the late news at Ev's place with a sense of growing excitement. It seemed as if the freezing idea was about to take off and that LES would be in the forefront of the movement.

**The Years with CSNY**

Unfortunately, LES would enjoy only a brief additional tenure as the leading organization promoting the cryonics idea. Cooper wanted desperately to establish a center both for research and for storage of cryopreserved patients and tried heroically, acquiring land and starting construction. But the effort ended in failure after a small laboratory building, built with great effort and much hardship in a marshy area, proved unsuitable.[15] Cooper abandoned the movement around 1970 and focused fully on sailing. (He was lost at sea in 1982.)

Saul meanwhile was energized. His group started the Cryonics Society of New York (CSNY) in the summer of 1965, the first rival to LES. Along with Curtis Henderson, another activist and president of the Society, Saul as corresponding secretary became the major driving force. To Charles Platt, Saul "now embraced cryonics as his grand obsession. … He became a tireless public-relations machine, appearing on local talk-radio shows, responding to information requests, organizing meetings in the New York area, and producing a newsletter."

However, this success also didn't last. Henderson ended up doing most of the work of running the cryonics organization,




From 1972 brochure: Capsule now containing two occupants, being filled with liquid nitrogen; Saul Kent, CryoSpan Secretary. (CryoSpan was a sister organization to CSNY and, by this time, was handling details of storage and maintenance of patients. "Moon and stars" is backdrop curtain.)

while Saul, in 1973, "became disillusioned with the whole thing," and "ended his partnership with Henderson," though did not abandon his aspirations.

Platt continues:

> He simply saw that a different approach was needed. Eventually he decided that if the concept of cryonics was too radical, maybe people would be interested in longevity; and once they accepted that idea, maybe they would take the next step and accept the idea [of] avoiding permanent death completely.

**Florida to California**

Saul moved to Florida, where he started producing a little newsletter titled *Anti-Aging News*. He then went into partnership with another cryonicist named Bill Faloon and started selling anti-aging vitamins via mail-order. At this time, most people in America had never even heard of antioxidants, which placed Kent and Faloon right at the forefront of a growing market for dietary supplements. They appeared on Merv Griffin's nationally networked TV talk show, where they netted a far bigger response than anyone had ever achieved trying to sell cryonics. Soon they were doing a flourishing business, which operated under a separate identity named Life Extension Foundation (LEF).

> They used their profits to put more than $200,000 into an enterprise named Cryovita, where the principals were [Mike] Darwin and a special forces veteran named Jerry Leaf, who had learned hypothermic surgical techniques at UCLA School of Medicine. "I think it's of critical importance," Leaf wrote later, "that we mobilize all we can from clinical medicine to minimize the amount of ischemic injury." At the time, this was an innovative concept.
>
> Darwin and Leaf mapped a protocol that became fundamental in cryonics. If a patient is hospitalized and seems near death, a standby team deploys equipment at the bedside, including an ice bath, a chest-compression device, and medications. The patient is moved to a nearby mortuary, where a surgeon does a cutdown to expose the femoral artery. Tubes are attached, in just the same way as in a conventional extracorporeal bypass. The patient's blood is removed and replaced with an organ preservation solution. The patient is then moved to a cryonics facility for cryoprotective perfusion followed by rapid cooling.

Some, including Robert Ettinger, disputed whether this extra labor and expense was really necessary. As an example, sterile technique was insisted upon and certainly made procedures more complicated and expensive. Would any problems with not using it, such as a few stray bacteria invading the premises, not be resolvable by future technology that could restore a cryopreserved brain to functionality?

Saul was squarely aligned with Leaf's outlook. He lacked a science education but saw the need for cryonics to distance itself from its primitive origins. He also believed that any measure which might improve the future prospect for revival was worth taking.

He and Faloon continued to fund Cryovita, which moved into a facility in a small industrial park in Fullerton, California. Alcor

Foundation, which had been established by Fred and Linda Chamberlain in 1972, joined them as a subtenant.

LEF was increasingly successful, and Alcor relocated to a larger building in Riverside, California. Saul now lived in a big house in the hills overlooking Riverside, and monitored the R&D of cryonics, while Bill stayed in Florida, managing the dietary supplement business that generated the funding.

Again, the future for cryonics looked promising, this time with much more financial backing. Progress was challenged in 1987 by two events: an FDA raid on the offices of Life Extension, and the cryopreservation of Saul's mother Dora, which happened under unusual circumstances that prompted a coroner's investigation. In the end, after years of effort with much credit to Saul Kent and Bill Faloon, all matters were successfully resolved, and both LEF and Alcor continued their operations unhindered.

**Support for Research**

Brian Wowk, Ph.D., is the chief technology officer of 21st Century Medicine, Inc. and a scientist recruited by Saul Kent. In the article excerpted below he reports on Saul's support of scientific research and offers some personal details.[9]

> With his business partner Bill Faloon, Saul has made possible financial support for cryopreservation research over decades costing tens of millions of dollars. This had spinoff benefits in mainstream cryobiology that are not and may never be fully appreciated. Research that they funded when no one else was interested led to new vitrification solutions, ice blockers, improved warming methods, reproducible human cornea vitrification, the first successful vitrification of a vital mammalian organ (rabbit kidney), numerous collaborations that are still ongoing, and scientific publications that have been cited thousands of times. This re-ignited mainstream research interest in organ cryopreservation that had withered after decades without success, leading to the first reproducible vitrification of a vital mammalian organ (rat kidney) as published in Nature in 2023. It used new warming technology developed by the University of Minnesota, but also a vitrification solution from 2004 research supported by Bill and Saul. This is research that could benefit many thousands or even millions of people by cryopreserving products of regenerative medicine. These successes and new excitement in the field of organ cryopreservation wouldn't exist were it not for Saul Kent.
>
> Saul's work was more visible in the controversial field of cryonics, where over many decades he started or supported companies and organizations too numerous to list. Yet even in cryonics, his most important work was invisible. Despite often disagreeing with Alcor leadership, he enthusiastically strategized and marshaled financial support to help Alcor through multiple legal and financial existential crises. So much so, that it's unclear whether Alcor would still exist were it not for Saul Kent.
>
> Saul pursued objectives with great vigor. He wasn't known for letting anything or anyone get in his way, even at the expense of personal relationships when an objective important to him was at stake. With such single-mindedness about cryonics and life extension, it may come as a surprise to some that Saul had friends outside of these fields. He was also capable of great kindness without any expectation of personal gain. Sometimes you don't really know a person until you meet people who visit them while they are ill.
>
> Saul had a lifelong passion for sports, not just as a spectator. He was physically active for most of his life. During his sixth decade, he would still run for miles on the beach of his Florida home in Fort Lauderdale. A few weeks before he was cryopreserved, feeling very frustrated by physical weakness and dependency, he told me of a day in his youth while living in New York where he grew up. He said he ran 15 miles on a beach on Fire Island, then came back to the city and played basketball into the evening for three more hours. He said, "That's the real me." Physicians of the future take note.

**Winding Down**

Saul attemped to start a new cryonics organization (Cryocare Foundation[14]) in the 1990s when he became unhappy with affairs in Alcor and realized he couldn't steer the organization along the path he wished. (After a few years, matters somewhat resolved, and Saul and most of the other "rebels" rejoined Alcor, Saul eventually serving, as once before, on Alcor's board of directors). Coverage is beyond our scope here; however, I include more excerpts, starting with the first impressions Charles Platt had of Saul, and ending with some touching remarks on their last meeting many years later.

> The first time I saw Saul Kent, he was wearing a Hawaiian shirt, khaki shorts, and flip-flops while sitting cross-legged on the carpet in someone's living room. This was during one of Alcor's monthly board meetings, which were unstructured, open events during the 1990s. Saul's hair was long and unkempt, he hadn't shaved in a couple of days, and he could have been mistaken for a homeless person—not that this would have concerned him. I watched him displaying a roguish grin as he counted on his fingers the legal steps he was going to take to sue someone who had run off with some Alcor funds. "I won't bother with a warning letter," he said. "When they receive the law suit, that's the warning."
>
> The last time I visited Saul was in May, 2022. I found him watching basketball, which was one of his favorite recreations. We started reminiscing about cryonics—the adventures and misadventures, the failures and mistakes, the schemes and ambitions. He enjoyed recounting some of his machinations, and he displayed the same rogueish grin I remembered from that first time when I saw him sitting cross-legged on the floor ….
>
> After an hour or so, he gave me an odd look. "You know," he said, "it's good to see you, Charles." He sounded surprised, as if there were few sources of pleasure in his life anymore, and he hadn't expected my visit to be one of them. I think it was the only time I ever heard him express pleasure about a purely social interaction.
>
> Perhaps at this time he could afford to be less driven and more human, because he saw that his grand obsession was not going to be fulfilled in his natural lifetime. When I asked if he still hoped to be cryopreserved, he shrugged. "I no longer think it's going to work," he said, "but I'm going to

do it anyway."

Saul Kent labored more effectively to support the development and implementation of human cryopreservation than anyone else in history, as of the time of his death on May 26, 2023. I cannot express how honored I was to play even a small part in that quest.

**Concluding Remarks**

Cryonics offers hope to its adherents they don't generally find elsewhere: a *possible* means of recovery from clinical death and resumption of healthy life someday. This hope resembles that of a religious believer in an afterlife but with the important difference that it rests on the expectation that revival will occur through scientific means and be engineered by future human or post-human civilization. Another important difference is that cryonics is expensive: money is required, not just faith.

Conventional cryonics wisdom holds that if you are not cryopreserved at clinical death (or otherwise have your remains well-preserved) you are dead, eternally. If you *are* cryopreserved, you still may be dead, eternally, but at least you have a chance of not being. And again, it costs money. Placed alongside a religious hope, it makes a rather unpalatable life stance. This, together with the fact that no person or non-embryonic mammal has yet been revived from cryopreservation, seems to account in large part for the small number of those who choose the cryonics option. (The total is a few thousand signups so far, in a movement that has coexisted for more than half a century with a world population of billions). It also, I think, accounts for much in the way of personality types one does find in cryonics, "motivated by self-interest," often without offspring, et cetera.

By indications Saul (who, though married, had no children and was also not religious) was of the "conventional" outlook in cryonics, as suggested in his remarks at the beginning: death is the "disappearance of everything." Moreover, despite early optimism, in the end he didn't think cryonics would work, though still choosing it "anyway." Charles too notes at one point that he (Charles) thought the chances of his revival occurring through cryonics were "maybe one in 10,000." Time and space limitations prevent going into it much, but for a host of reasons I think estimates like this are way too low. It also begs the question of what is meant by a successful "revival" – and again I take an optimistic view that basically means the "chances" (if that is the right word) are better than one might think.

So, I am optimistic that Saul and many others can be straightforwardly revived from their preserved remains – albeit our technology will have to advance rather considerably.

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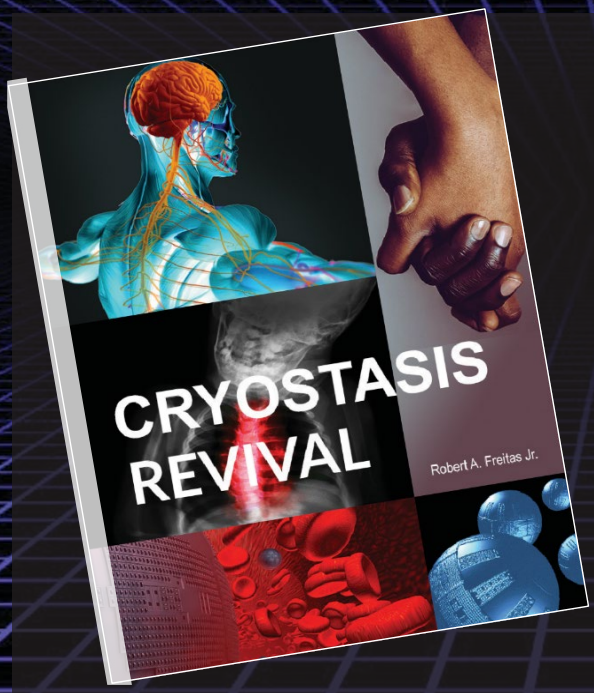
# New Book by Robert A. Freitas Jr.

## Cryostasis Revival: The Recovery of Cryonics Patients through Nanomedicine




Cryostasis is an emergency medical procedure in which a human patient is placed in biological stasis at cryogenic temperatures. A cryopreserved patient can be maintained in this condition indefinitely without suffering additional degradation, but cannot yet be revived using currently available technology. This book presents the first comprehensive conceptual protocol for revival from human cryopreservation, using medical nanorobots. The revival methods presented in this book involve three stages: (1) collecting information from preserved structure, (2) computing how to fix damaged structure, and (3) implementing the repair procedure using nanorobots manufactured in a nanofactory – a system for atomically precise manufacturing that is now visible on the technological horizon.

"Robert Freitas is an extraordinary thinker and author whose previous works have been transformational for our ability to visualize the extraordinary capabilities of future medical technology. In Cryostasis Revival, he now puts his prodigious previous knowledge of nanomedicine to the task of envisioning methods for healing those whose injuries challenge even the ultimate limits of future medicine. His illuminating results and new insights will greatly inform debate over, and may even help to resolve, controversies that have persisted for decades." — ***Gregory M. Fahy, Ph.D., Fellow, Society for Cryobiology & Executive Director, 21st Century Medicine, Inc.***

"Future repair and revival of damaged cryopreserved tissue has been the subject of speculation for decades. This book by a nanomedicine expert examines the problem in detail far beyond anything ever written before. With more than 3000 references, it's both wide-ranging and intensely specific about diverse technical aspects of the problem. It will surely stimulate much discussion, and be an invaluable resource for thinkers about nanomedical cell repair for years to come." — ***Brian Wowk, Ph.D., complex systems cryobiologist, Chief Technology Officer, 21st Century Medicine, Inc.***

"We now have considerable evidence that cryopreserved patients retain the physical structures encoding memory and personality. For most people, the difficulty lies in understanding how it could ever be possible to repair and revive patients. Leading nanomedicine expert Robert Freitas fills in that gap with admirable and remarkable depth. Cryostasis Revival provides an unparalleled clarification of pathways for researchers to explore in the quest to make human cryopreservation reversible." — ***Max More, Ph.D., former president, Alcor Life Extension Foundation***

"Cryostasis Revival is the most magnificent tour de force on cryonics ever done with the signature flair, comprehensive coverage and authoritative style of Robert A. Freitas Jr. It describes all the issues involved in reviving cryopreserved patients: from the philosophical (what is "information theoretic death") to the practical (what damage actually takes place during a cryopreservation) to the technological (how to apply nanotechnology to restore a cryopreserved patient) and more. Nothing else even approaches such a complete and incisive treatment of this life-saving subject. Cryostasis Revival is the book to give anyone who's thinking about cryonics but "isn't sure about the science." — ***Ralph C. Merkle, Ph.D., Senior Research Fellow, Institute for Molecular Manufacturing.***

**Free electronic book and hardback copies for sale at:**
**https://www.alcor.org/cryostasis-revival or Amazon.com**

# Membership Statistics

| 2022-23 | Sep | Oct | Nov | Dec | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cryo Members | 1393 | 1398 | 1401 | 1403 | 1411 | 1412 | 1417 | 1415 | 1415 | 1417 | 1424 | 1419 |
| Basic Members | 27 | 30 | 32 | 32 | 32 | 33 | 36 | 34 | 35 | 35 | 35 | 35 |
| Patients | 200 | 201 | 201 | 203 | 203 | 204 | 205 | 206 | 208 | 212 | 212 | 217 |
| Assoc./Apps | 253 | 233 | 230 | 232 | 218 | 221 | 218 | 223 | 217 | 218 | 219 | 228 |
| Total | **1873** | **1862** | **1864** | **1870** | **1864** | **1870** | **1876** | **1878** | **1875** | **1882** | **1890** | **1899** |

New “Superdewar” cryogenic vessel is delivered to Alcor, mid-July 2023.

# What Should We Be Measuring in Brain Preservation?

**Andrew McKenzie, Ph.D., M.D.**

**Reprinted from *Neurobiology Notes*, 11 Aug. 2023,** https://neurobiology.substack.com/p/what-should-we-be-measuring-in-brain, used with author's kind permission, as is photo.

The goal of brain preservation is to preserve and protect the information in someone's brain indefinitely, with the aim of potential revival if future civilizational capacity ever allows it to be feasible and humane.

Since we're considering a hypothetical outcome in the distant future, a key question is: how can we evaluate the quality of preservation today? We need metrics to avoid wasting time and money on useless rituals.

The first main divide is between people who favor functional vs structural metrics. I tend to be on the side that structural metrics are best. Our hypothetical restoration technology — whether that is via molecular nanotechnology, whole brain emulation, or something else entirely — is likely to be so much better than the technology we have today that trying to test functional read-outs today will not be very dispositive. Instead, I think the best metric we have is to use microscopes and look at the tissue in detail to see whether the structures that seem to be important for memories, personality, and etc are intact.

But that raises the question of *which* structural metrics one should be evaluating when comparing between possible brain preservation procedures. And this gets us to another divide, between people who strictly favor connectome traceability via contemporary electron microscopy and others, like me, who think that is a great ideal goal to aim for, but is probably not strictly necessary. I'm mostly writing this blog post because I keep encountering this disagreement and I want to make my position clear.

**Connectome traceability by contemporary electron microscopy**

Let's first try to understand this position. As far as I can tell, two of the most prominent researchers who have advocated for it are Ken Hayworth and Robert McIntyre.

I always like to try to understand the history of ideas. Let's jump back to around 2011. Although cryonics was first proposed in the 1960s, and many were bullish on near-term revival at the time, it didn't happen. Instead, one of the main justifications for cryonics practice was structural — if you cryopreserve brain tissue in the right way and rewarm it, a lot of the structures still look like they are there, albeit damaged.

Mike Darwin's 2011 blog post, "Does Personal Identity Survive Cryopreservation?", is pretty clearly the best explanation of this stance. The data relied on perfusion of animals with cryoprotectants, either with high concentration or in vitrification protocols. The structures looked intact but also dehydrated.

There also wasn't a report of a whole brain that had been cryopreserved, rewarmed, processed, and imaged in such a way that would allow for the connectome — the set of all neural connections — to be traced. In 2011, Ken Hayworth proposed the brain preservation prize, which leveraged cutting edge neural imaging technology with the goal of measuring ultrastructural quality and connectome traceability.

As Ken put it:

We now understand that the true measure of success should be that a procedure preserves the structural connectivity of the neuronal circuits of the brain along with enough molecular level information necessary to infer the functional properties of the neurons and their synaptic connections.[1]

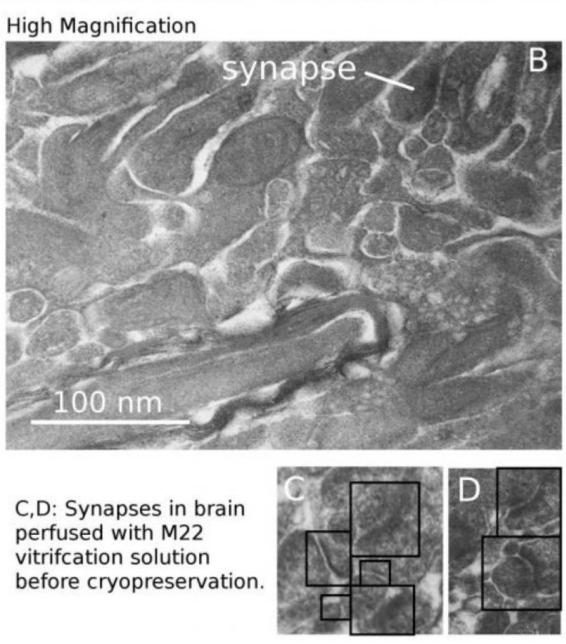
Around the same time, Sebastian Seung also pointed out the necessity of this test to evaluate cryonics in a TED Talk and his book Connectome.

This test is kind of a binary thing: either a procedure preserves the brain in such a way that the connectome is traceable by contemporary standards or it doesn't. The initial goal was to

evaluate the preservation procedure itself, but similar reasoning also can be applied when considering other types of damage occurring during the brain preservation process, such as agonal, postmortem, or storage-associated damage.

Robert McIntyre and Greg Fahy published a paper in 2015 describing aldehyde-stabilized cryopreservation, a procedure that ultimately won the Brain Preservation Foundation prize for preserving the brain in a way that could be stored long-term with connectome traceability intact.

The pure cryopreservation method used in conventional cryonics did not win the prize, and as far as I know, still has not met this standard. The images I have seen from this method applied to whole brains demonstrate dehydration-associated damage, making them difficult to interpret[2]:




C,D: Synapses in brain perfused with M22 vitrifcation solution before cryopreservation.

Electron microscopy data from 21st Century Medicine

The comparison of aldehyde-stabilized cryopreservation vs pure cryopreservation is not the purpose of this post. Instead I just want to point out that deciding upon metrics has very real-world consequences, because it can help to compare the quality of preservation between methods, and also help people to decide whether a procedure is worthwhile at all.

This metric has a lot of advantages. It really seems to include all of what contemporary neuroscientific models tell us could be involved in memory storage. Ken has tried to ask other neuroscientists why it wouldn't be sufficient to preserve engrams, and no compelling counterarguments have been made public, other than general uncertainty about future knowledge and capabilities.

But while it is a great ideal metric, I also think it is too stringent, because it is limited by the capabilities of contemporary imaging modalities. I think we should have more consideration for how reasonable future advances in imaging technology, such as expansion microscopy, might make things easier.

With that in mind, how about this mouthful of a metric instead?:

**Intact cell membrane morphology via light microscopy, as a proxy for connectome traceability by hypothetical molecular imaging**

This metric relaxes the stringency of flawless electron microscopy-level imaging, but still aims to capture the critical structural information.

The reasoning is that if cell membranes, including dendrites, axons, myelin, synapses, and other important structures, maintain their rough shape and location as seen on light microscopy (i.e. are "intact"), then even if they are degraded on the finer electron microscopy level, future molecular imaging may still enable connectome inference.

I want to explain why, but first I have to give a lot of background. Some ballpark resolution numbers might help to ground us. FIB-SEM, which is the type of electron microscopy used to evaluate the brain preservation prize, has a resolution of around 5-20 nm. Routine light microscopy has a resolution of around 200-500 nm. So FIB-SEM has around 10-100x better resolution than routine light microscopy.

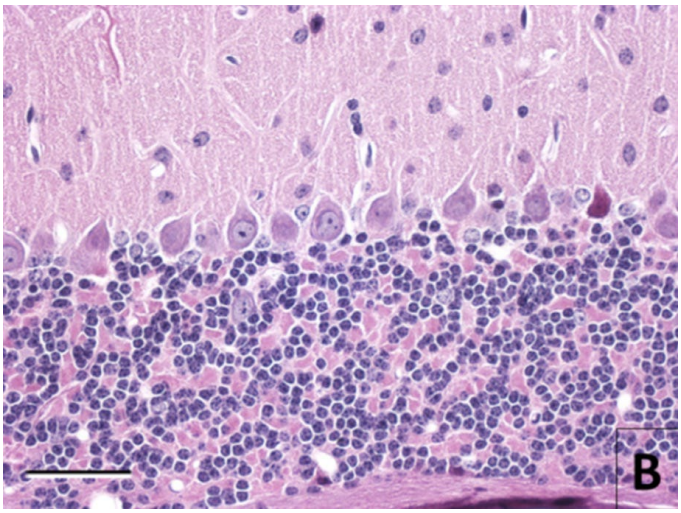
Why focus on cell membrane morphology and not other aspects of morphology, like nuclear shape or organelles? Because it seems to me like cell membrane shape is probably one of the most important parts of the connectome, while organelle shape isn't as critical for memory information.

Of course, one would also need biomolecular information to annotate the connectome, but biomolecular information is largely redundantly stored in the epigenome, other biomolecules, etc, so it doesn't seem as essential to evaluate as cell membrane preservation. So that's why I'm focusing on structures visible under the microscope.

To make it clear that I'm not just accepting "anything", here are a couple of examples of cases that would or would not meet my criteria of intact cell morphology on light microscopy. The first example is any liquefied brain. If something is liquefied at the macroscale level, it seems obvious that the connectome is lost.

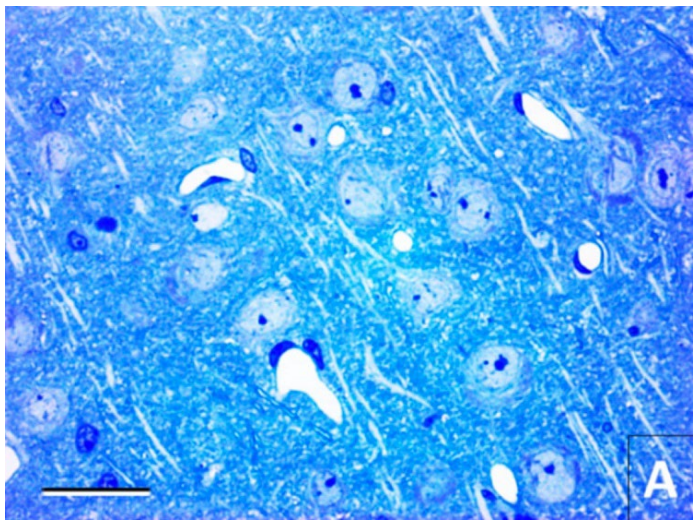
But that's trivial. For a less trivial example, let's consider Monroy-Gómez et al 2020, a nice article that looked at how long rabies virus antigens could be detected in mouse brain tissue after death using different techniques.

First, here is a control image, an H&E-stained light microscopy image from the cerebellum of a mouse whose brain was perfused immediately after death:



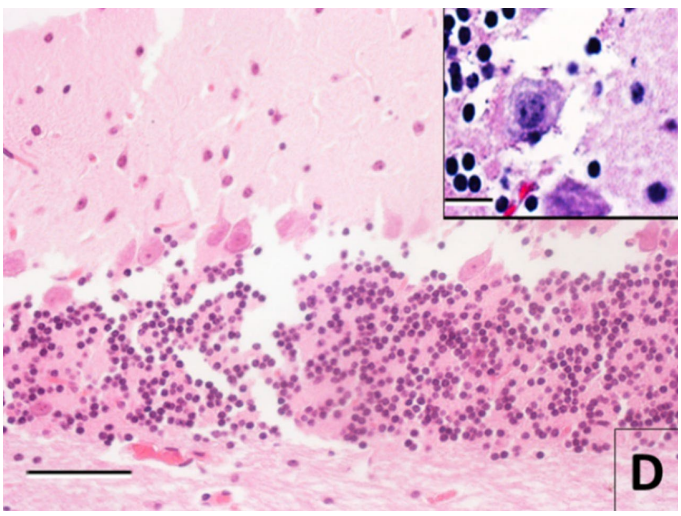

https://doi.org/10.3390/v12090938

And here is an image after 30 hours of storage at room temperature after death prior to immersion fixation and tissue processing:




https://doi.org/10.3390/v12090938

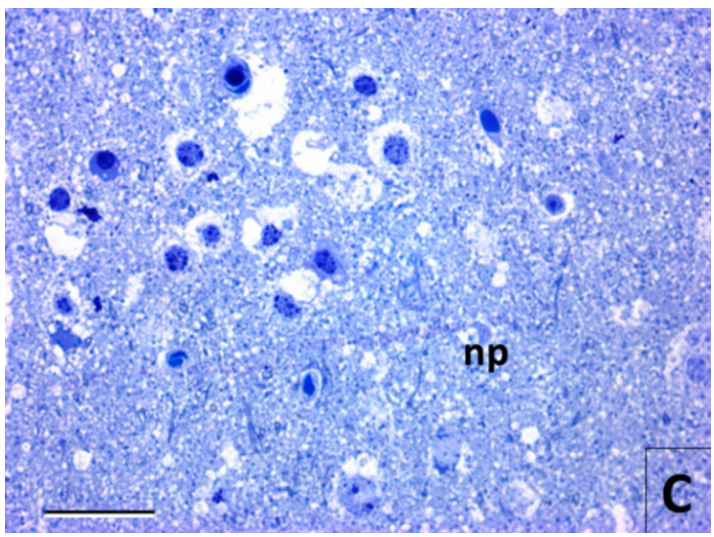
And here's a corresponding image after 30 hours of room temperature storage after death:




https://doi.org/10.3390/v12090938

To me, the original structure seems not inferable based on this image. With the separations, the cell membrane alterations, the changes to the neuropil, and the fact that some cells from the granule layer are reported to be literally gone. Probably too much damage. Am I sure? Definitely not. But this an example of an image that would not pass my subjective sufficient quality threshold.

Here is another example from the same paper. This is an image from the cerebral cortex stained with toluidine blue. Here is the control condition of tissue preserved immediately after death. You can see the normal cellular morphology:




https://doi.org/10.3390/v12090938

In this image, it's no longer possible to identify the cellular morphology.

**What do I mean by molecular imaging?**

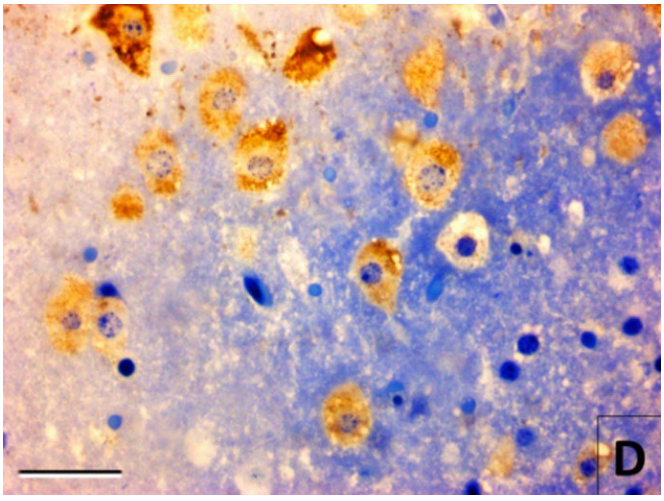
Molecular imaging refers to imaging techniques that can visualize molecules and biomolecules within cells and tissues, like immunohistochemistry. These techniques allow you to see the location and abundance of specific proteins, nucleic acids, lipids, and other biomolecules.

We may one day have imaging technologies that can map the position of every biomolecule in a tissue sample, or even across the whole brain. This extremely high-resolution molecular imaging could allow inference of cell connectomes and other fine structural details, even if the original tissue morphology is disrupted.

Mechanistically, there's a lot of structures preventing biomolecular diffusion during the dying process or during the

preservation procedure, including cell membranes and the extracellular matrix. And empirically, many types of biomolecules do not seem to immediately diffuse away from their original locations after death. So I think there is surface validity to this idea.

As an example of what I mean by using molecular imaging to infer what morphological imaging cannot, here's the same tissue in the most recent image, i.e. mouse cerebral cortex preserved at 30 hours after death. However, this time, there is also immunostaining for a rabies antigen, which appears as a brown color:

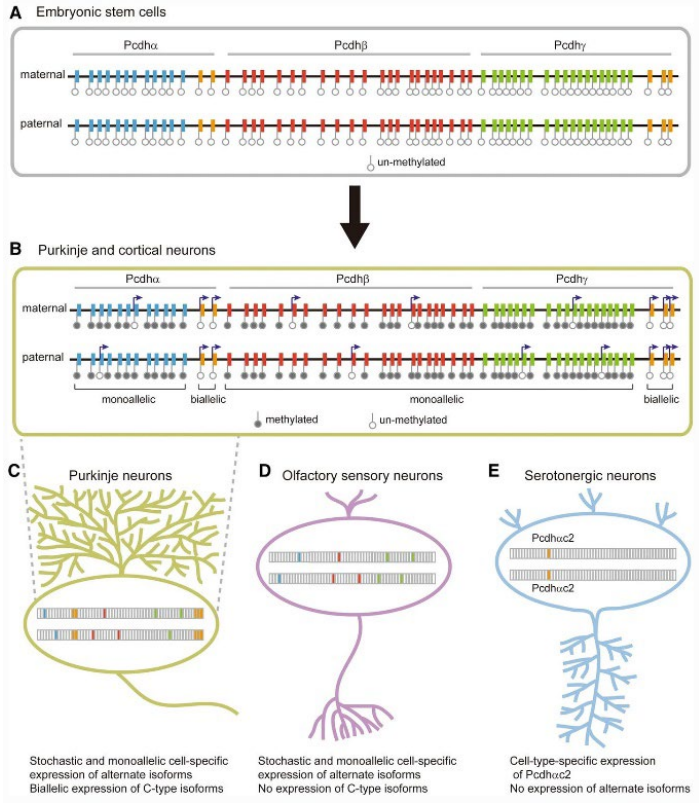



https://doi.org/10.3390/v12090938

In this image, suddenly the cell morphology does seem visible. That's because although the morphological stain — toluidine blue — didn't bind to biomolecules in the cells specifically enough to allow for contrast, the rabies antigen immunostaining did — at least in the subset of cells infected by the rabies virus.

When I think about future molecular imaging technology, I'm imagining something similar to this, but at the level of single biomolecules, down to their atomic composition if need be. And also allowing for deconvolution of the original state in the case that the biomolecules have diffused from their original places.

What type of biomolecules would we be imaging? Well, every cell has a unique composition of biomolecules. This includes cell surface biomolecules like neurexins and protocadherins that have a variety of gene expression mechanisms to allow for variability between cells, in part so that cellular processes can recognize self vs non-self.



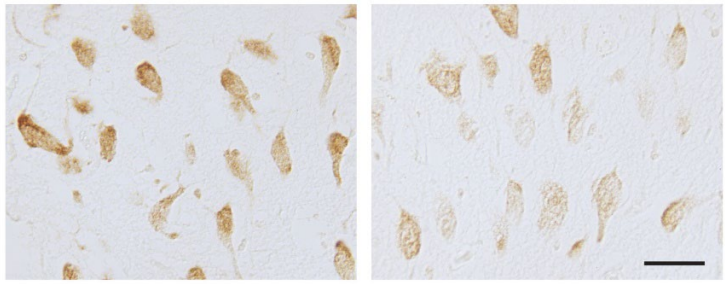

Cell specific expression of protocadherin transcripts, Wu and Jia, 2021

Cells also have a ridiculous number of biomolecules. For example, each neuron has been estimated to have around 50 billion proteins.

Even if there is damage in the dendrites or axons on electron microscopy, so that it's not obvious how to trace it, it still might be possible to trace that neurite following a molecular imaging process. One would need to image the molecules, identify their most likely cellular origin, and deconvolve the most likely original locations of the cells based on predicting where their constituent molecules diffused from.

**What do I mean by deconvolution?**

Let me also give an example here. In microscopy images taken postmortem, one often finds that cell membranes are "blurry". They don't look sharp like they usually do. For example, in Blair et al 2016, you can see the cell membrane morphology stained for rRNA become more blurry as the postmortem interval extends from 22 hours (left) to 41 hours (right):



anti-rRNA Case C PMI 22hr

anti-rRNA Case C PMI 41hr

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0151615

Deconvolution is the idea that if you map enough of the biomolecules at a detailed enough level, you can build an inverse diffusion model to infer what the original state most likely was. In this case, to turn the membranes from blurry to sharp again.

Of course this deconvolution procedure will not be perfect, because molecular diffusion is a random process. That's okay, because the connectome is not static anyway, yet our long-term memories are still stable over a long period of time, suggesting that there is a decent amount of error tolerance in information encoding.

If the brain is liquefied or the local area has undergone too much decomposition, there's going to be a point where attempting to computationally infer the original state based on mapping the diffusion breakdown products is not going to be possible to a sufficient degree of accuracy. Future molecular imaging technologies will still not be magic.

This is why I think it's useful to look at light microscopy images. Although it has a lower resolution, light microscopy bounds how much damage could have occurred to neural structures at the electron microscopy level. My guess is that nanometer scale decomposition that might be occurring beyond what is seen via light microscopy, visible only by electron microscopy, could still potentially be inferred by future molecular imaging technology.

While molecular imaging may be able to recover some information from minor degradation, there will still be a threshold of severe degradation beyond which the original state cannot be accurately inferred. Intact cell morphology on light microscopy provides a proxy for whether tissue degradation has surpassed this threshold.

I think biophysically, there has to be some point at which structures are no longer visible by morphological stains, but they would be visible by molecular imaging. What are the structures under the microscope actually made up of? Mostly, they seem to be collections of biomolecular gel-like networks that are strengthened by fixation. When those gels break down, they're no longer able to be visualized under the microscope. But the biomolecules that make them up don't immediately disappear. Instead, they dissolve and disperse into the local area.

On the other hand, if cell morphology is absent on light microscopy, I think that is a very bad sign suggesting there is a good chance that the information has been lost (i.e. is no longer inferable via classical physics). Light microscopy also has the advantages of being much cheaper, more accessible, and easier to directly measure biomolecules.

**There are plenty of problems with the metric of "intact cell membrane morphology via light microscopy"**

Obviously, this metric is far from perfect. It is subjective and depends on the methods used. There are no definitive thresholds or precise cutoffs to determine how much morphological damage is acceptable. Instead, it relies more on an overall gestalt assessment of the integrity of cell shape. This subjectivity makes it difficult to establish the type of objective, binary prize criteria that connectome traceability provides.

Also, the whole molecular imaging idea is an additional area of uncertainty in the brain preservation project. We cannot say for sure whether it will work. The ideal goal — if it is possible — would be to achieve connectome traceability as seen by electron microscopy today, and thereby avoid this whole discussion.

Finally, relying on an imperfect proxy metric risks complacency in pushing for further advances. Accepting intact morphology as "good enough" could reduce incentives to achieve the ideal of connectome traceability.

Despite these problems, this framework is my best attempt to make sense of a complex issue with the information I have available today. Refining this metric to be more quantifiable and definitive is an important goal of mine for the future. The potential for complacency could be mitigated by continually measuring the effectiveness of preservation techniques and not being satisfied with the status quo.

**Summary**

It seems right to aim for verifiable connectome traceability as seen on electron microscopy as the ideal goal of structural brain preservation. If we have achieved this goal, then I think there is a clear case that the information required for engrams has been preserved, unless there is something very wrong with our theories of neuroscience. The only method that has met this bar is aldehyde-stabilized cryopreservation under ideal laboratory conditions. But, it is a hard bar to reach in most practical cases, where agonal states are severe, perfusion is difficult, and/or the postmortem interval has been too long.

So, for people dying today who can't access that method — either due to it not being available in their area, cost, brain tissue degradation before the procedure can start, or any other reason — I think it's also reasonable to use procedures that meet the criteria of intact cell membrane morphology on light microscopy, as a proxy for connectome integrity by a hypothetical molecular scan.

Which brain preservation methods meet this criteria? I have some opinions, but I'm planning to do some more research and make sure my reasoning is sound before I write publicly about them. In the meantime, I just want to make it clear what criteria I currently think should be used: (a) as the "gold standard", connectome traceability by contemporary electron microscopy, but if that's not achievable, then (b) intact cell morphology via light microscopy also seems like it would have a reasonable chance of being sufficient.

References:

1

When I use the term connectome, I'm using it in the sense of also including molecular information.

2

However, I'm also aware that more recent data using vitrification approaches due to be published is reported to look better.

# Fight Aging!

## Reports From the Front Line in the Fight Against Aging

Reported by Reason

*Fight Aging! exists to help ensure that initiatives with a good shot at greatly extending healthy human longevity become well known, supported, and accepted throughout the world. To this end, Fight Aging! publishes material intended to publicize, educate, and raise awareness of progress in longevity science, as well as the potential offered by future research. These are activities that form a vital step on the road towards far healthier, far longer lives for all.*

January 2nd, 2023

**P2Y6R Inhibition as a Strategy to Reduce Age-Related Memory Loss**

Memory is in some way encoded in the synaptic connections between neurons, with the precise details yet to be determined. Destruction of synapses is a characteristic of neurodegenerative conditions involving loss of memory. Researchers here identify a regulatory receptor that controls the removal of synapses by the innate immune cells known as microglia in the brains of mice. Blocking the activity of this receptor reduces age-related memory loss in mice, suggesting that this aspect of aging is largely a matter of inappropriate microglial activity, destroying synapses that should remain intact.

Removal of synapses is not a bad thing per se, and is thought to be a necessary part of neural plasticity, essential for memory and learning. A range of evidence suggests that excessive synaptic removal might take place in an aged brain, however. This may be driven by chronic inflammation, a state the provokes microglia into excessive activity, but this is by no means certain. There is much yet to explore regarding the underlying mechanisms.

**P2Y6 Receptor-Dependent Microglial Phagocytosis of Synapses Mediates Synaptic and Memory Loss in Aging**

*Microglia are central nervous system macrophages, specialized in the phagocytosis (i.e., engulfment and degradation) of bacteria, synapses, neurons, debris, and aggregated proteins. Microglia can phagocytose synapses during development, neuropathology, and aging, and microglia can also phagocytose dendrites, axons, and intact neurons. Microglial phagocytosis of neuronal structures is mediated by eat-me signals, opsonins, and phagocytic receptors. Interestingly, it has been shown that genetic knockout of the opsonin C3 reduced aging-induced loss of hippocampal synapses, neurons, and memory; and similarly, knockout of the phagocytic receptor TREM2 reduced aging-induced hippocampal synaptic and neuronal loss in mice. Thus, one may hypothesize that the neuroinflammation accompanying aging drives microglial phagocytosis of synapses, resulting in memory impairment and brain atrophy. Microglial biology changes with age, including upregulated expression of phagocytic receptors and opsonins, potentially resulting in excessive phagocytosis of the aging brain.*

*The P2Y6 receptor (P2Y6R, expressed from the P2ry6 gene) is a microglial receptor that mediates microglial phagocytosis of neurons. P2Y6R is expressed by multiple cell types in the body, but within the brain is almost exclusively expressed by microglia. Damaged or stressed neurons release the nucleotide UTP, which is rapidly degraded into UDP by extracellular nucleotide-degrading enzymes, and localized UDP then activates the P2Y6R on microglia to engulf such neurons. We have shown that activating P2Y6R causes microglia to engulf live neurons, and P2Y6R deficiency prevents lipopolysaccharide (LPS)-induced microglial phagocytosis of neurons both in vitro and in vivo. Moreover, P2Y6R knockout mice were also resistant to memory loss induced by beta-amyloid and extracellular tau. These previous studies lead us to ask whether (i) P2Y6R mediates microglial phagocytosis of synapses, and (ii) the synaptic and memory loss induced by natural aging of mice was also mediated by P2Y6R.*

*We found that aging wild-type mice to 17 months of age resulted in synapse and memory loss, whereas P2Y6R knockout mice had preserved memory. Microglia from 17-month-old wild-type mice had an age-associated increase in the internalization of synaptic material, but no such increase was observed in microglia from 17-month-old knockout mice. Moreover, we show here that inactivation of P2Y6R decreases microglial phagocytosis of isolated synapses (synaptosomes) and synaptic loss in neuronal-glial co-cultures. These findings are significant as they support the hypothesis that microglial phagocytosis of synapses contributes to aging-induced memory loss, and, more specifically, that inhibition of the P2Y6R may prevent this*

*memory loss.*

Link: https://onlinelibrary.wiley.com/doi/10.1111/acel.13761

January 4th, 2023

**A Tau-Based Blood Biomarker of Alzheimer's Disease**

The primary approach to assessing neurodegeneration presently involves comparatively expensive imaging technologies. Better, less onerous ways to determine the early onset and later progression of Alzheimer's disease will hopefully enable greater screening of patients in the earliest stages of the condition, and drive greater efforts to find effective ways to prevent and reverse Alzheimer's disease. Researchers here report on an improvement in the assessment of tau protein that finds its way into the bloodstream from the brain, making it a viable biomarker for Alzheimer's disease, where in the past it was difficult to establish a correlation.

The biomarker, called "brain-derived tau," or BD-tau, outperforms current blood diagnostic tests used to detect Alzheimer's-related neurodegeneration clinically. It is specific to Alzheimer's disease and correlates well with Alzheimer's neurodegeneration biomarkers in the cerebrospinal fluid (CSF). Current blood diagnostic methods can accurately detect abnormalities in plasma amyloid beta and the phosphorylated form of tau, but the biggest hurdle lies in the difficulty of detecting markers of neurodegeneration that are specific to the brain and aren't influenced by potentially misleading contaminants produced elsewhere in the body.

For example, blood levels of neurofilament light, a protein marker of nerve cell damage, become elevated in Alzheimer's disease, Parkinson's and other dementias, rendering it less useful when trying to differentiate Alzheimer's disease from other neurodegenerative conditions. On the other hand, detecting total tau in the blood proved to be less informative than monitoring its levels in CSF. Researchers have now developed a technique to selectively detect BD-tau while avoiding free-floating "big tau" proteins produced by cells outside the brain, however.

To do that, they designed a special antibody that selectively binds to BD-tau, making it easily detectible in the blood. They validated their assay across over 600 patient samples from five independent cohorts, including those from patients whose Alzheimer's disease diagnosis was confirmed after their deaths, as well as from patients with memory deficiencies indicative of early-stage Alzheimer's. The tests showed that levels of BD-tau detected in blood samples of Alzheimer's disease patients using the new assay matched with levels of tau in the CSF and reliably distinguished Alzheimer's from other neurodegenerative diseases. Levels of BD-tau also correlated with the severity of amyloid plaques and tau tangles in the brain tissue confirmed via brain autopsy analyses.

Link: https://www.upmc.com/media/news/122722-alzheimers-neurodegeneration

January 6th, 2023

**The Stage is Set for More Rapid Progress Towards Human Longevity in the Next Decade**

Today's popular science article is a tour of a few of the higher profile lines of research and development relevant to treating aging as a medical condition. The state of the field has changed greatly over the last decade, not least of these changes being a vast increase in the funding devoted to clinical translation of age-slowing and rejuvenation therapies. Cynically, I suspect that it is the funding that ensures that the popular science press takes a more respectful tone than they did ten years ago. It is much harder to advance (in writing!) a knee-jerk dismissal of a field of science when billions of dollars of funding and many large, conservative institutions are involved, as they are these days.

As you read the article, spare a thought for the many people - scientists, advocates, entrepreneurs, and philanthropists, some of whom are no longer with us - who spent years to decades laboring in comparative obscurity to build the foundations that led to the present stage of growth and interest in producing viable treatments for degenerative aging. The sudden sea change of public perception, funding, and breadth of research over the past decade, and indeed the advent of the entire longevity industry as it stands today, didn't just happen by accident. Success tends to erase the slow and painful process of bootstrapping that came before it, but that bootstrapping was still necessary and valuable.

**Can Ageing Be Cured? Scientists Are Giving It a Try**

*Scientists are great at making mice live longer. Rapamycin, widely prescribed to prevent organ rejection after a transplant, increases the life expectancy of middle-age mice by as much as 60 percent. Drugs called senolytics help geriatric mice stay sprightly long after their peers have died. The diabetes drugs metformin and acarbose, extreme calorie restriction, and, by one biotech investor's count, about 90 other interventions keep mice skittering around lab cages well past their usual expiration date. The newest scheme is to hack the ageing process itself by reprogramming old cells to a younger state.*

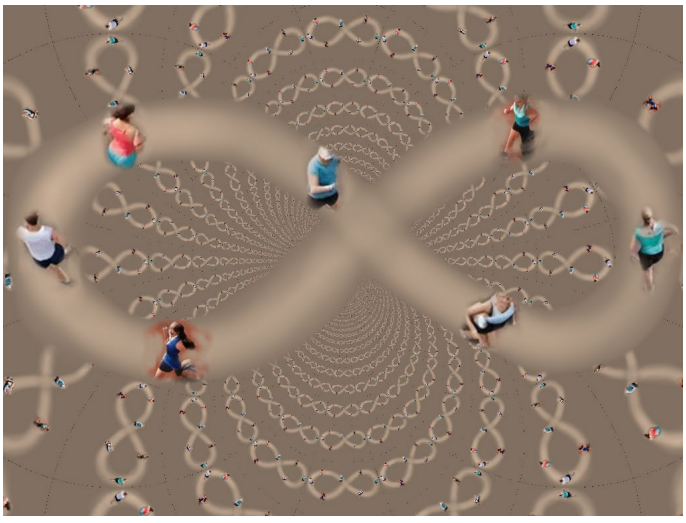
*What about us? How far can scientists stretch our life span? And how far should they go? Between 1900 and 2020, human life expectancy more than doubled, to 73.4 years. But that remarkable gain has come at a cost: a staggering rise in chronic and degenerative illnesses. Ageing remains the biggest risk factor for cancer, heart disease, Alzheimer's, type 2 diabetes, arthritis, lung disease, and just about every other major illness. It's hard to imagine anyone wants to live much longer if it means more years of debility and dependence.*

*But if those mouse experiments lead to drugs that clean up the molecular and biochemical wreckage at the root of so many health problems in old age, or to therapies that slow-or, better yet, prevent-that messy buildup, then many more of us would reach our mid-80s or 90s without the aches and ailments that can make those years a mixed blessing. And more might reach what is believed to be the natural maximum human life span, 120 to 125 years. Few people get anywhere close. In industrialised nations, about one in 6,000 reaches the century mark and one in five million makes it past 110.*

*Human biology, it seems, can be optimised for greater longevity. Unimaginable riches await whoever cracks the code. No wonder investors are pouring billions into trying. This work is powered*

*by artificial intelligence, big data, cellular reprogramming, and an increasingly exquisite understanding of the zillions of molecules that keep our bodies humming. Some researchers even talk about "curing" ageing.*

Link: https://www.nationalgeographic.co.uk/science-and-technology/2022/12/can-ageing-be-cured-scientists-are-giving-it-a-try



February 1st, 2023

**Physical Activity Reduces Dementia Risk**

The quality of data resulting from studies of exercise and disease risk has increased greatly since the advent of low-cost accelerometer devices. Self-reported activity data has many issues, not least of which being the challenge of assessing just how much low intensity activity is actually taking place. Nonetheless, the evidence for a greater degree of physical activity to reduce the risk of age-related disease was extensive even prior to the commonplace use of accelerometers in such studies and has only grown since. The example here is one of a great many studies focused on exercise in the context of dementia risk.

Because few large studies have examined device measures of movement and sitting in relation to mild cognitive impairment and dementia, much of the published research on the associations of physical activity and sedentary behavior with cognitive decline and dementia is based on self-reported measures. For this study, the researchers sampled data from 1,277 women as part of two Women's Health Initiative (WHI) ancillary studies - the WHI Memory Study (WHIMS) and the Objective Physical Activity and Cardiovascular Health (OPACH) study. The women wore research-grade accelerometers and went about their daily activities for up to seven days to obtain accurate measures of physical activity and sitting.

The activity trackers showed the women averaged 3,216 steps, 276 minutes in light physical activities, 45.5 minutes of moderate-to-vigorous physical activity and 10.5 hours of sitting per day. Examples of light physical activity could include housework, gardening or walking. Moderate-to-vigorous physical activity could include brisk walking. The researchers reported that, among women aged 65 or older, each additional 31 minutes per day of moderate-to-vigorous physical activity was associated with a 21 percent lower risk of developing mild cognitive impairment or dementia. Risk was also 33 percent lower with each additional 1,865 daily steps. The study findings also showed that higher amounts of sitting and prolonged sitting were not associated with higher risk of mild cognitive impairment or dementia.

Link: https://today.ucsd.edu/story/more-steps-moderate-physical-activity-cuts-dementia-cognitive-impairment-risk

February 13th, 2023

**Request for Startups in the Rejuvenation Biotechnology Space, 2023 Edition**

It is time once again for my once-yearly set of unsolicited thoughts on biotech startups that I'd like to see join those already working hard on the basis for human rejuvenation. The industry is growing rapidly, but patchily. Partial reprogramming has received enormous attention, as has the development of senolytics. Meanwhile, other important goals in rejuvenation research languish, or presently have only one or two companies involved in clinical translation of promising academic projects. Many plausible paths forward go undeveloped; there are just as many opportunities to make a real difference in the world as there were a decade ago.

**Cell Therapy for Thymus Regrowth**

The thymus atrophies with age, reducing the production of new T cells to a fraction of what it once was. The adaptive immune system declines as a result, becoming cluttered with dysfunctional, broken, and worn cells. One of the more promising approaches to regrowing the aged, atrophied thymus involves intravenous delivery of cells, either progenitor thymocytes or endothelial cells, that home to the thymus. Once there, they promote growth of active thymic tissue. This has been demonstrated in mice, but the groups involved have moved on to try to find small molecule approaches, so far with only very limited progress to show for it. So why not take this cell therapy approach and bring it to the clinic? Production of universal cells from lines engineered to avoid immune rejection is presently a going concern. This is a good time to be innovating in the cell therapy sphere.

**Bring Fecal Microbiota Transplantation into Widespread Use**

One particular implementation of fecal microbiota transplantation was recently approved by the FDA for use in the treatment of C. difficile infection. Beyond this formal arena of medicine, there is a thriving community of individuals attempting to treat their own dysbiosis, and informal clearing houses that attempt to characterize and screen donor samples for safer use. It is well demonstrated in animal models that fecal microbiota transplantation from young to old produces a lasting rejuvenation of the gut microbiome, improved health, reduced inflammation, and extended life span. The timing has never been better to establish a venture that demonstrates the merits of this approach in humans, and then does its best to make fecal

microbiota transplants available to the millions of older people who could benefit.

**A Better Approach to Reversing Tissue Calcification**

The state of the art in reversal of the calcium deposition and consequence loss of elasticity in the aged cardiovascular system and elsewhere is typified by Elastrin's technology, which is to say a focus on ways to improve on the established mode of EDTA chelation therapy by using a far more targeted delivery system. Is there a better way forward that can lead to larger effect sizes, a greater reduction in calcification? One would think that there should be, indeed must be if this aspect of aging is to be fully reversed.

**Solutions to the Systemic Delivery Issues of Gene Therapy**

Presently available gene therapy delivery techniques struggle to achieve a number of important goals. Delivery to the liver may be more or less a solved problem, but many other problems remain unsolved. Sufficient delivery throughout the body without excessive delivery to the lungs or liver following intravenous injection, for example. Or delivery to a specific minor internal organ, with minimal delivery elsewhere, following intravenous injection. Delivery platforms that can provide relatively off the shelf, 80/20 solutions to delivery of gene therapy payloads in these and other important circumstances have yet to be brought into being but are very much needed.

**A Way to Inhibit Alternative Lengthening of Telomeres**

Targeting telomerase and telomeres in the clinical treatment of cancer has started in earnest with Maia Biotechnology. It remains the case that something like ~10% of cancers use alternative lengthening of telomeres (ALT) rather than telomerase to bypass limits on cell replication, however, and there is as of yet no good approach to inhibition of ALT. One of the reasons why ALT is an attractive target is that it does not operate in normal, non-cancerous cells, which removes many of the normal issues regarding off-target effects in the inhibition of cellular mechanisms. There is room here for a group to perform a broad screen for ALT inhibitor small molecules, in search of a useful lead for a preclinical development program.

**Safely Replace the Hematopoietic System**

The generation of immune cells occurs in the bone marrow, the responsibility of hematopoietic stem cells and descendant progenitor cell populations. While the mechanisms of aging, particularly chronic inflammation, are disruptive of the niche structures that support hematopoietic cells, there is also damage to the cells themselves. It has long been possible to replace hematopoietic cells, but this is a procedure that requires aggressive chemotherapy to clear existing populations and comes with a non-trivial degree of risk. To introduce a new population of engineered hematopoietic stem cells into most old people, an entirely new, safer, and more gentle strategy will be needed. Consider the production of universal or patient-matched hematopoietic stem cells that are changed in ways that allows them to outcompete native cells and take over stem cell pools in the bone marrow, for example.

Link: https://www.fightaging.org/archives/2023/02/request-for-startups-in-the-rejuvenation-biotechnology-space-2023-edition/

February 21st, 2023

**Thoughts on How to Help Advance Work on the Treatment of Aging**

This article lists a variety of types of activity and projects that might be undertaken to help to speed up the development of ways to treat aging as a medical condition. If you don't have a background in the life sciences, but nonetheless find human longevity a compelling topic, and would like to work in the field, what can you do? That is a good question, and often asked. There are many options that don't involve working as a scientist in a laboratory, though educating yourself about the science helps a great deal when it comes to picking the better options from the array of choices on the table.

Aging is a set of molecular and cellular processes that affects us all, but what if we could extend our healthy lifespan and live longer, healthier lives? This is the goal of the rapidly growing field of longevity. And after my last post about leaving my CTO job to work on longevity a lot of people have reached out asking what I'm working on actually? What I'm building for longevity? The short answer is... nothing. Yet. The long answer is... well, this post. I believe that anyone can work on anything they put their mind to if they are willing to put in the time and effort to learn the necessary skills. Whether it's research, funding, talent, media, practical longevity, aging therapeutics, or infrastructure, there are numerous opportunities to make a significant impact in this field.

$6.96 billion was raised across 96 funding rounds in 2022. This may seem like a lot but it's actually nothing. Remember that Instagram was acquired for $1 billion. So trying to bring more funding to the longevity field is very much needed. Someone needs to help talented people transition into the field. And believe me, we need far, far more people working on longevity. Recruiting and community building are important. The narrative around longevity is changing towards a more strategic conservatism which is proving to have better adoption. But it's far away from reaching a mainstream level. We need more communicators designing and evolving new narratives for different people.

The first drug targeted to extend healthy lifespan by 10-20 years could be developed and commercialized this decade. Aging therapeutics usually means getting the science out of the lab. So most often than not, someone with biology background will try to start or join a startup around their expertise. But what about people who are not coming from academia? The reality is that it may take anything from 6 months to 1 year (maybe even more) of full dedication to gain enough context, map the gaps, understand low hanging fruits, understand which technologies are the most promising, and get in love with a strong hypothesis to join or build a startup around it. This is the hardest part: in an ocean of possibilities, which one to choose? Which one is the most interesting? What technology is the most promising? What are the low hanging fruits?

Link: https://www.stanete.com/work-on-longevity/

March 2nd, 2023

**Risk of Death Due to Heart Attack Has Fallen Considerably Over The Past 20 Years**

Atherosclerosis leading to heart attack is one of the more amenable issues in aging to control through lifestyle choice and available medications. A very rigorous commitment to diet, exercise, and lowering LDL cholesterol will greatly reduce the odds of developing atherosclerotic plaque sufficient to produce heart attack or stroke. A combination of better treatment and better lifestyle choices has led to a sizable reduction in mortality due to heart attack in recent decades. Eliminating atherosclerosis entirely is going to require new developments in medical science, however, as lowering LDL cholesterol doesn't do much to help those people who have already developed significant atherosclerotic plaque.

New findings, based on an analysis of data from the Centers for Disease Control and Prevention (CDC) from 1999-2020, indicate that age-adjusted rates of death attributed to acute myocardial infarction (the medical term for heart attack) fell by an average of over 4% per year across all racial groups over the two-decade period. "Researchers often highlight the bad news, but people should know that even if we're not there yet, we're making progress in the right direction. I think the reasons are multifactorial, spanning all the way from health-promoting and prevention activities through treatment during and after a heart attack."

Researchers found the overall rate of death from heart attack, adjusted for age, fell from about 87 deaths per 100,000 people in 1999 to about 38 deaths per 100,000 people in 2020. It is difficult to definitively determine whether the decline is the result of fewer heart attacks occurring or better rates of survival when they do occur because of new diagnostic strategies and treatment options, researchers said. For example, hospitals now frequently test for troponin in the blood when a heart attack is suspected, which can help clinicians diagnose a heart attack at an earlier stage than was possible with previous diagnostic strategies. This change has led to earlier and more sensitive heart attack detection but also makes it challenging to compare data on heart attacks over time.

On the prevention side, the public has become more aware of the need to reduce cardiovascular risk factors through steps such as quitting smoking and managing cholesterol. Clinicians also have a better understanding of the signs of a heart attack and improved tools to quickly diagnose and treat them when they occur. More hospitals are also equipped with mechanical support devices to assist with heart attack treatment and new medications such as potent antiplatelet drugs have become available, which may have improved survival rates and reduced the likelihood of a second heart attack.

Link: https://www.acc.org/About-ACC/Press-Releases/2023/02/22/21/30/Heart-Attack-Deaths-Drop-Over-Past-Two-Decades

March 2nd, 2023

**Improving 3D Printing of Fine Structures in Artificial Tissue**

The biggest challenge in tissue printing is the achievement of sufficient control over small scale structure to produce a vasculature that can supply the tissue as it develops. Without that capacity, tissue growth is limited to thin sheets and tiny organoids. Advances have been made in recent years, such as the work of Volumetric, but there is still a way to go before large tissue sections are regularly generated for use in medicine. This is in large part why work on decellularization continues to proceed apace, taking donor tissue and stripping the cells from it to leave the extracellular matrix structure, with all of its fine-scale detail and chemical cues to guide new, patient-matched cells into the correct locations and development activities.

Bioprinting is based on 3D-printing technology, using cells and biopolymer to create biological structures and tissues. One of the most promising types of 3D-bioprinting is called digital light processing (DLP) bioprinting. Within this branch of 3D-bioprinting, progress has been impeded by practical and technical impediments. It has proven difficult to print tissues with high cell densities and finely resolved structures.

DLP-based 3D bioprinting uses a digital micromirror device (DMD) to project a 2D cross-section of the 3D model to the photo-crosslinkable bioink. When exposed to light, the photocrosslinkable bioink, which can be either synthetic or natural, solidifies. Then, a motorized stage lifts up the bioink by a few tens microns to 200 microns, which allows uncured bioink to refill the gap. When the next cross-section is projected to the bioink, a new layer solidifies and the process repeats.

When all goes well, a newly formed layer precisely matches the shape of the projected cross-section. However, with existing methods, the incorporation of cells in the bioink can cause severe light scattering, which blurs the projected light in the bioink. As a result, the newly formed layers cannot replicate the fine details of the projected cross-sections. The researchers reduced this light-scattering effect by tenfold, allowing them to print with high cell densities and high resolution thanks to the contrast agent iodixanol, a new ingredient in the bioink.

Tuning the refractive index of the bioink minimizes the scattering effect and significantly improves the fabrication. The new research shows that a ~50 μm feature size can be achieved in a refractive-index-matched gelatin methacrylate (GelMA) bioink with a cell density as high as 0.1 billion/mL. This approach introduces a few novel technical innovations, including a hollow organic vascular network embedded in a cell-laden thick tissue, enabling it for perfused and long-term culture, and a snow-flake and spoke shape to showcase the high resolution for both positive and negative features.

Link: https://today.ucsd.edu/story/a-new-technique-creates-greater-fidelity-in-bioprinting-functional-human-tissues

March 22nd, 2023

**George Church on Reprogramming as a Treatment for Aging**

In a recent interview, George Church offers opinions on partial reprogramming as an approach to rejuvenation. In the last few years this has moved from popular topic to becoming a sizable

fraction of the longevity industry, given the large-scale funding that is now devoted to partial reprogramming groups. Short-term exposure to the Yamanaka factors can be used to reset the epigenetic patterns of a cell in old tissue to be more like those of a cell in young tissue, with corresponding gains in function. There are potentially serious issues to be worked out, such as how to eliminate the possibility of cancer due to the few cells that might fully reprogram into pluripotency in a short time, but this is nonetheless an exciting area of medical science that is now heavily funded. We should expect to see significant progress in the years ahead.

**Do we understand how cellular reprogramming improves health and longevity?**

"There have been two major camps in aging since long ago. One says that aging happens due to damage, to proteins, lipids, RNA, and DNA, and that you have to go in there with your repair kit and fix it as a therapist. The other camp says that it's all epigenetic, and that if you convince the cell that it's young, it will get its own toolkit out and start repairing as much as it can. Some things are beyond repair. If you delete all copies of a tumor suppressor, that's not something a young cell can repair. But most things are fixable with epigenetics - at least, that's how the second hypothesis goes.

"I believe in a hybrid model. I think most of the work can be done epigenetically. A surprising amount of it can be done via the bloodstream, but probably not all of it. Then, there's a residual amount that you can fix with the Yamanaka factors and another residual amount that you can fix by restoring genes. Since we do the epigenetic reprogramming by adding in genes, it's not that fundamental a difference between adding in genes that will go into the blood, adding genes that will reprogram the nucleus, and adding genes that are missing, like tumor suppressors. In a certain sense, they are all addressable by multiplex gene therapy. That's why being able to either use multiple rounds of dosing or to have bigger vectors will become increasingly important."

**Given the rising popularity of partial reprogramming, what is its overall place in the longevity landscape?**

"I think there are subtle but important differences between anti-aging drugs and drugs that improve biomarkers in the way that statins improve cholesterol. That doesn't mean such drugs increase longevity, just that they improve this one biochemical. It could actually hurt you; for instance, it could improve cardiovascular chances for some subset of the population, but for another subset, it could hasten muscle pain. So, affecting biomarkers is one thing. Reversing diseases of aging is different. You could do it just by addressing that particular disease, or you could do it more broadly, affecting multiple diseases. You might get FDA approval for one of them, but it's actually affecting multiple ones, and maybe acting preventatively. Say, there might be a cure for muscle wasting that helps prevent a variety of diseases. Finally, you're really at the core of aging when you reprogram shared elements - with good feedback systems that already exist in the body or with feedback systems that you introduce as part of the therapy."

**Are you bullish about longevity biotech?**

"I think the whole field is very healthy economically and scientifically. We have passed through multiple "valleys of death". We're now in the solid science phase, and this field is going to be very impactful, maybe more impactful than any other pharmaceuticals in history, including even antibiotics, because our very ability to fight off diseases is age-related. Almost every single form of human morbidity and mortality has an age-related component to it. If you want to have a pleiotropic effect on many different diseases, this is the way to go."

Link: https://www.lifespan.io/news/prof-george-church-on-cellular-reprogramming-and-longevity/

March 29th, 2023

**The Tradeoff of Working with Short-Lived Laboratory Species**

It is cheaper and faster to study aging - and potential approaches to treat aging - in short-lived species. The disadvantage is that much of what is learned and achieved will be irrelevant to aging as it occurs in longer-lived species such as our own. The response to calorie restriction, an upregulation of cellular housekeeping mechanisms that lengthens life, fortunately evolved early on in the development of life, and the biochemistry is surprisingly consistent even across widely divergent species. Thus much can be learned of it in lower animals with short life spans. Unfortunately, it turns out that this class of intervention doesn't affect life span in longer-lived species like our own to anywhere near the degree it does in short-lived species. This is the tradeoff of working with short-lived models, in a nutshell: more can be done, but all of that work may turn out to be of very limited utility.

Wouldn't it actually accelerate progress if we instead did most testing in far shorter-lived animals, like the roundworm C.

elegans or the fruit fly Drosophila? On its face, that's a totally reasonable question: time is ticking for all of us, and we want to get longevity therapeutics into people's hands as quickly as possible! And certainly these short-lived animals have taught us a lot about the roles of different biological signaling pathways.

Some interventions that work in C. elegans act by altering the worms' early developmental processes, which isn't terribly helpful to those of us who "have the misfortune of already being alive." That's also becoming increasingly evident in mice. We've known for about twenty years now that mutations that block IGF-1/growth hormone signaling in mice slow down their aging and extend lifespan. But those mutations dampen down signaling through these pathways throughout the animals' entire lives. To take advantage of that discovery and develop a longevity therapeutic that would work in middle-aged and older adults, a large part of the anti-aging effect would have to be due to the hormone still being low during adulthood. Instead, studies have shown that almost all the benefit of IGF-1 signaling inhibition goes away if growth hormone production is brought back to normal during the very earliest period of life.

The preceding examples apply to studies based on trying to usurp the regulation of metabolism to slow the aging process down. SENS Research Foundation is instead grounded in the direct "damage-repair" strategy of SENS. If we're going to use an organism as a test animal for rejuvenation biotechnology, it has to accumulate similar kinds of aging damage as we do, and it must do so in similar tissues and with similar pathological results. And here C. elegans and Drosophila just aren't qualified for the job. For instance, C. elegans don't live long enough to accumulate cells overtaken by mitochondrial DNA deletions, and there is no clear link between other kinds of mitochondrial DNA damage and the rate of aging in these worms. C. elegans also have no bones, so no osteoarthritis or osteoporosis either. And they lack any of the cells dedicated to the immune system.

Link: https://www.sens.org/sens-why-not-worms-flies/

April 7th, 2023

**Analysis of Historical Data Shows Periods of Increasing Human Maximum Life Span**

Remaining life expectancy at 65 has increased by a year with every passing decade since at least the middle of the 20th century, an improvement that has occurred without deliberate targeting of the mechanisms of aging. To what degree is this observed trend in human life expectancy due to (a) a general slowing of aging that will carry on throughout the entire life span, and thus lengthen maximum observed life span, or (b) a more selective slowing of processes of aging that does not meaningfully impact lifespan-limiting mechanisms that operate in late life, and thus does not lengthen maximum life span?

For example, we know that supercentenarians (the tiny fraction of people who live to be age 110 and older) exhibit significant degrees of transthyretin amyloidosis, and this may be the majority cause of death in that age category. Much earlier in old age, this form of amyloidosis is present but probably not a major killer in comparison to other mechanisms of aging. It is entirely plausible that positive effects on life span resulting from past improvements in medical technology and changing lifestyle choices could have limited effects on this one specific issue, and thus would have a limited effect on maximum human lifespan.

Whether or not this is the case or is an open question, however. This is an interesting area of scientific inquiry, and today's open access paper is a worthy and novel addition to the literature regarding historical trends in life expectancy, but this work is of limited relevance to efforts to extend human life. We have a list of causative mechanisms of aging to target for repair, and a biotechnology community advanced enough to undertake that work. The best approach to the treatment of aging as a medical condition is to start fixing issues and see how it goes: clearance of senescent cells, for example, is performing exceptionally well in animal models, and will hopefully see greater progress into human use in the years ahead.

**Mortality Postponement and Compression at Older Ages in Human Cohorts**

*A key but unresolved issue in the study of human mortality at older ages is whether mortality is being compressed (which implies that we may be approaching a maximum limit to the length of life) or postponed (which would imply that we are not). We summarize historical mortality data in 19 currently-industrialized countries by birth cohort using a variant of the Gompertz mortality law, and find that it fits cohort mortality data extremely well. Using this law, we identify the youngest age at which individuals in each cohort reach an assumed mortality plateau, which we call the Gompertzian Maximum Age (GMA). We find that over much of the period covered by our data, there was no increase in the GMA. Historical improvements in life expectancy were therefore largely the result of mortality compression. We demonstrate, however, that there have been episodes where the GMA increased. The presence of these episodes of mortality postponement suggests that the maximum length of a human life is not, in fact, fixed.*

*The first episode of mortality postponement that we identify occurred for cohorts born in the early part of the second half of the 19th century, and was more pronounced for females than for males. Over this period, the GMA increased by around 5 years. We can only speculate as to the causes of this increase, but as the first of these cohorts reached age 50 just after 1900 and the last reached age 100 in 1980, this may be related to a first wave of improvements in public health and medical technology. We identify a second, and much more significant, episode of mortality postponement, which is affecting cohorts born between 1910 and 1950 (so those currently aged between 70 and 110). We estimate that the GMA for these cohorts may increase by as much as 10 years, and remaining life expectancy at age 50 by as much as 8 years, depending on the country.*

*The timing of these episodes of mortality postponement explain why longevity records have been so slow to increase in recent years - cohorts old enough to have broken longevity records were too old to experience the current bout of postponement - and identifies significant potential for longevity records to rise by the year 2060 as younger cohorts, who did experience it, reach advanced old age. Our results on the division of changes in remaining life expectancy at age 50 across cohorts between*

*compression and postponement are robust to our modelling choices. Likewise, our conclusion that longevity records will likely be broken in the coming decades is also robust to a wide range of possible assumptions. But our predictions of precisely by how much these records will rise, and when, depend on our modelling assumptions, in particular on the maximum mortality rate we assume.*

*We emphasise further that cohorts born before 1950 will only have the potential to break existing longevity records if policy choices continue to support the health and welfare of the elderly, and the political, environmental and economic environment remains stable. The emergence of Covid-19 and its outsize effect on the mortality of the elderly provides a salutary warning that none of this is certain. If, however, the GMA does increase as the current mortality experience of incomplete cohorts suggests is likely, the implications for human societies, national economies, and individual lives will be profound.*

Link:
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0281752

April 12th, 2023

**Demographic Aging is Absent in Naked Mole Rats**

Naked mole rats are an extreme example of compression of morbidity in mammals, in that individuals show few signs of aging until very late in life. Their biochemistry is peculiar in a number of ways when compared with other mammals. Their senescent cells do little harm to surrounding tissues; their protein synthesis is highly efficient; the are better at repairing DNA damage; they exhibit impressive cancer suppression mechanisms; and so forth. Will it be possible to build human enhancements or medical technologies from what is learned of naked mole rat metabolism? It is plausible that this is a very complicated extremely long-term project; equally any part of naked mole rat biochemistry could turn out to inform a comparatively simple, targeted intervention. It is too early to say.

The species Heterocephalus glaber, commonly known as the naked mole-rat, is a eusocial mammal endemic to the arid and semi-arid regions of northeast Africa. In the wild, naked mole-rats live an almost completely subterranean lifestyle, in colonies of up to 295 animals (average size is 60 animals/colony) that cohabitate a network of tunnels that the mole-rats dig themselves with their large, ever-growing incisors. Naked mole-rats are notable for their extreme lifespans, living longer than any other documented rodent, with the longest previously-reported lifespan of 37 years and many animals living beyond 30 years. These values are notable in the context of this species' small body size due to the strong correlation across species between that value and mammalian lifespan: maximum lifespan potential (MLSP) increases by 16% for each doubling of average species body mass.

For most mammalian species, lifespan is limited by an exponential increase in the per-day risk of death (i.e. mortality hazard) with age in accord with a statistical distribution first defined by Gompertz based on human mortality. The increase in mortality hazard with age is referred to as "demographic aging". We have previously shown H. glaber to achieve its exceptional longevity through defiance of this trend, exhibiting near constant mortality hazard across the full spectrum of observed lifespans, with no hazard increase evident even many-fold beyond their expected MLSP. For naked mole-rats, the lack of demographic aging is accompanied by seemingly-indefinite maintenance of many physiological characteristics that typically change with age. Naked mole-rats are resistant to age-related diseases such as cancer, neurodegeneration, and cardiovascular disease and show signs of tissue regeneration and remodeling preventing the deterioration of age-associated physiological function.

Here, we re-visited the demographic analysis of our naked mole-rat collection, with husbandry data now extended by five years across an expanded set of animals. We found our original conclusions of naked mole-rat mortality hazard being age-independent to be reproduced, using either the total sum of all historical data or only those data collected after our previous study - the latter qualifying as a replication study.

Link: https://doi.org/10.1101/2023.03.27.534424

April 13th, 2023

**A Narrow Review on Progress Towards Gene Therapies to Treat Aging**

There are a great many genes that one might target with gene therapies to treat aspects of aging. The review here is quite narrow in scope, and only looks at a few approaches to gene therapy, and a few of the genes that might be targeted, those that have arguably received more attention in this context and are either the subjects of small clinical trials or might be entering trials in the near future. It even omits follistatin and myostatin in favor of telomerase, klotho, VEGF, and APOE. The latter is probably not all that interesting as a target, but it is very well researched as a result of the strong focus on funding Alzheimer's disease programs over the past few decades.

The telomerase reverse transcriptase (TERT) gene encodes the rate-limiting catalytic TERT protein, a subunit of telomerase. Studies on telomeres and telomerase have been conducted since the start of research on aging. Many studies have shown that defects in telomeres or telomerase exert a substantial influence on the development of aging-related diseases. Some in vivo experiments have already reported that TERT gene therapy exhibits exciting efficacy for treating diverse diseases. Researchers tentatively introduced AAV-mouse Tert into 12- and 24-month-old mice, and they found noticeable improvements in various aging-related molecular biomarkers. Interestingly, an increase in median lifespan was also observed. Later, researchers designed an AAV9 vector that expressed Tert in heart tissue to treat heart failure after myocardial infarction (MI). Intravenous injection of this vector into mouse models of myocardial infarction showed that mice with the vector expressing TERT had less damage to the cardiac indices of both structure and function, decreased mortality and improved biomarkers.

KL, another classic aging-related gene, has a much shorter research history than that of the TERT gene, just over twenty years. Exploring concrete mammalian models (mostly mouse models) of aging-related diseases has revealed the therapeutic effect of enhancing KL expression in neurodegenerative diseases, chronic kidney diseases, cardiovascular diseases, etc. Preclinical evidence has demonstrated that KL has broad therapeutic promise for treating various aging-related diseases. However, no interventional clinical trials have been conducted to assess the clinical potential of KL.

The entire human body is widely affected by vascular endothelial growth factor (VEGF), and the formation and function of blood vessels are highly reliant on VEGF. VEGF is negatively associated with aging, and its high VEGF expression has a protective effect on the cardiovascular system. However, many studies have identified it as a potential target in malignant tumors and it is regarded as a promoting factor. Therefore, it remains a concern whether it will induce cancer when applied in anti-aging gene therapy. Researchers conducted an experiment based on the hypothesis that vascular aging is a founding factor in organismal aging. Over an experimental period of more than 30 months, they reported increased lifespans and physiological function after applying the gain-of-function system of transgenic VEGF and AAV-assisted VEGF transduction. Thus, VEGF seems to play a paradoxical role in aging similar to the telomerase gene, which inspires further systematic and careful exploration of potential treatments.

Gene therapies, especially in the field of aging provide new hopes for treating diseases. However, not all aging-related genes have the potential to be the targets. Satisfactory efficacy is only achieved by combining them with an adaptive operational strategy and efficient carriers. Additionally, some genes may simply be predictors of prognosis or capable of screening out effective medications for diseases. To be a therapeutic target, the candidate gene should have a relatively distinct and clear role.

Link: https://doi.org/10.14336/AD.2022.00725

April 19th, 2023

**Changes in Synaptic Ultrastructure Connected to Age-Related Impairment of Working Memory**

In today's open access paper, researchers report the discovery of differences in the synaptic ultrastructure of aging primates, differences that are connected to loss of memory function. The working hypothesis is that faltering mitochondrial activity inhibits correct formation of synapses, and that this issue is one of the important factors to distinguish individuals that go on to develop worse memory performance in later life.

Every cell contains hundreds of mitochondria, descendants of ancient symbiotic bacteria. Mitochondria are responsible for generating the chemical energy store molecules, adenosine triphosphate, that power cellular processes. It is well known that this activity declines with age, perhaps largely due to failing quality control of damaged mitochondria. Autophagy targeted to mitochondria, known as mitophagy, recycles worn and damaged mitochondria, but is shown to become less effective with age. This occurs for a variety of proximate causes that include changes to mitochondria themselves, as well as failures in parts of the complex autophagy mechanisms.

In energy-hungry tissues like the brain and muscles, loss of mitochondrial activity likely produces a sizable contribution to age-related dysfunction. Many different cellular processes will be affected, and the example in today's paper is but one of these. Restoration of mitochondrial function in older individuals is an important goal for the research community, but so far the range of available interventions have struggled to outperform the effects of exercise and calorie restriction. This includes mTOR inhibition, mitochondrially targeted antioxidants, NAD+ precursor supplements, and so forth. One might hope that the next generation of interventions, including transplantation of functional mitochondria, will produce more impressive outcomes.

Link:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10132463/

**Mitochondria Power-Supply Failure May Cause Age-Related Cognitive Impairment**

Brains are like puzzles, requiring many nested and codependent pieces to function well. The brain is divided into areas, each containing many millions of neurons connected across thousands of synapses. These synapses, which enable communication between neurons, depend on even smaller structures: message-sending boutons (swollen bulbs at the branch-like tips of neurons), message-receiving dendrites (complementary branch-like structures for receiving bouton messages), and power-generating mitochondria. To create a cohesive brain, all these pieces must be accounted for.

Prior studies had found that brains lose synapses as they age, and the researchers saw this pattern in their non-human primate model, too. But when they looked at the synapses that remained, they found evidence of a breakdown in coordination between the size of boutons and the mitochondria they contained. A fundamental neuroscientific principle, the ultrastructural size principle, explains that whenever one part of the synaptic complex changes in size, so too must all the other parts. The

synapse, the mitochondria, the boutons - all these parts must scale in accordance with one another. The team found that adherence to the ultrastructural size principle was essential for avoiding working memory impairment with age. By viewing violation of the ultrastructural size principle and mitochondria-related failures as the key to age-related cognitive impairment, the study ushers in a new era for aging research.

Link: https://www.salk.edu/news-release/mitochondria-power-supply-failure-may-cause-age-related-cognitive-impairment/

**Violation of the Ultrastructural Size Principle in the Dorsolateral Prefrontal Cortex Underlies Working Memory Impairment in the Aged Common Marmoset**

*Here, we tested the hypothesis that changes to synaptic ultrastructure that affect synaptic efficacy stratify marmosets that age with cognitive impairment from those that age without cognitive impairment. We utilized electron microscopy to visualize synapses in the marmoset dorsolateral prefrontal cortex (dlPFC) and measured the sizes of boutons, presynaptic mitochondria, and synapses. We found that coordinated scaling of the sizes of synapses and mitochondria with their associated boutons is essential for intact working memory performance in aged marmosets. Further, lack of synaptic scaling, due to a remarkable failure of synaptic mitochondria to scale with presynaptic boutons, selectively underlies age-related working memory impairment.*

*We posit that this decoupling results in mismatched energy supply and demand, leading to impaired synaptic transmission. We also found that aged marmosets have fewer synapses in dlPFC than young, though the severity of synapse loss did not predict whether aging occurred with or without cognitive impairment. This work identifies a novel mechanism of synapse dysfunction that stratifies marmosets that age with cognitive impairment from those that age without cognitive impairment. The process by which synaptic scaling is regulated is yet unknown and warrants future investigation.*

Link:
https://www.frontiersin.org/articles/10.3389/fnagi.2023.1146245/full

May 9th, 2023

**The Relationship Between Telomere Length and Replicative Senescence is Quite Different in Blind Mole Rats**

In mammalian tissues, cells become senescent constantly as a result of reaching the Hayflick limit on cell replication. Telomeres, lengths of repeated DNA sequences at the ends of chromosomes, are reduced in length with each cell division. When too short, or otherwise damaged, cellular senescence or programmed cell death is the outcome. In youth, senescent cells don't tend to last long: they secrete a potent mix of pro-inflammatory signals that attracts the attention of the immune system and are consequently destroyed by immune cells. With advancing age, this clearance slows down, and senescent cells accumulate to cause harm.

Matters are somewhat different in the exceptionally long-lived naked mole-rat and blind mole-rat species, however, both species in which individuals exhibit very little age-related decline until very late in life. Their senescent cells are nowhere near as active and pro-inflammatory as is the case in other mammals, for one thing, and thus senescent cell accumulation has nowhere near the same detrimental contribution to long-term health. Secondly, as noted in today's open access paper, the relationship between telomeres and replicative senescence appears to be quite different, and their version of the Hayflick limit may function in ways that have yet to be explored.

The existence of the Hayflick limit on cell replication is fundamental to multicellular life. We are made up of (a) a tiny number of stem cells are are privileged, maintaining long telomeres via the use of telomerase and capable of continued replication, and (b) a vastly greater number of somatic cells that are limited in their ability to replicate. This arrangement is how the risk of cancer is kept low enough for evolutionary success; most potentially cancerous mutational damage has no lasting impact because it occurs in somatic cells that will soon enough be replaced, and cannot spread the mutation to many descendants.

In this context, it is worth recalling that mole-rats exhibit minimal cancer incidence, for reasons still under investigation, but which certainly include highly efficient cancer suppression mechanisms. It may well be the case that this cancer suppression has allowed evolution to take the use of telomeres and the Hayflick limit in a different direction than is the norm for mammals.

**Damage-Free Shortening of Telomeres Is a Potential Strategy Supporting Blind Mole-Rat Longevity**

*In this study, we examined the average telomere length and telomerase activity, as well as the formation of telomere associated foci (TAFs) and the mRNA expression levels of the shelterin components in cultured primary cells of Spalax, a long-lived, hypoxia-tolerant, and cancer-resistant blind mole-rat species.*

*We showed that with cell passages, Spalax fibroblasts demonstrated significant shortening in telomere length, similar to rat cells, and in line with the processes observed earlier in tissues. We also demonstrated that the average telomere length in Spalax fibroblasts was significantly higher than the average length in rats, similar to previously reported results in Spalax muscles. Long telomeres are controversially described in the literature by their association with cancer risk, aging, or longevity. Extremely long telomeres in mice were reported to produce beneficial metabolic effects, low cancer risks, and longevity. Whether the long, seemingly guarded telomeres are one of the driving forces in Spalax longevity and healthy aging remains unclear.*

*It may be speculated that longer telomeres are attributed to telomerase overexpression, which presumably prolongs cell survival; however, we found that Spalax fibroblast telomerase activity was, in fact, lower than that of its counterpart in rats, which further supports our hypothesis that integrity maintenance of the telomeres (such as via shelterin activity), rather than telomere elongation, is characteristic of Spalax cells as a strategy that contributes to its long lifespan and supports its unique mode of cellular senescence.*

*It was suggested that long-lived animals have adopted a mechanism whereby the pace of telomere attrition and the activity of the telomerase is the same as that in other, short-lived animals. However, since initially, Spalax exhibits longer and potentially safeguarded telomeres, it seems tempting to speculate that the time it takes to reach critical length/damage that ignites the senescence machinery is longer and therefore, may contribute to their profoundly unique mode of replicative senescence lacking the canonical inflammatory response known to accompany the senescent phenotype in all studied species.*

*In summary, our results support that Spalax have evolved strategies for genome protection that apparently include telomere maintenance machinery, together contributing to its longevity and healthy aging. These strategies include a unique mode of senescence not induced by persistent DNA damage response (DDR) or telomere attrition, but which rather seems to be an independent cell program driven by other types of 'clocks'. The precise mechanisms of telomere maintenance and the apparently 'non-canonical senescence clock' require further investigation in Spalax and other long-lived species as possible requisites for long lifespan and healthy aging.*

Link: https://www.mdpi.com/2073-4425/14/4/845

May 24th, 2023

**Innate Immune Regulation in Life Extension via Calorie Restriction**

The primary challenge in understanding how calorie restriction slows aging and extends life is that it changes near everything in the operation of cellular metabolism. Finding the important differences is a matter of searching for the needle in the haystack. The most compelling evidence to date points to increased autophagy as the important determinant, greater effort made by cells to repair damage, maintain function, and recycle components. It remains likely that other mechanisms are also important, however. Here, researchers focus on regulation of the innate immune system in response to a reduced calorie intake; they are working with nematodes, but many of the noteworthy aspects of calorie restriction are much the same across all species.

Dietary restriction (DR) is a practically effective and reproducible nutritional intervention that extends lifespan in many organisms. Many studies have shown that DR improves immune function, and immune signaling components are required for DR-induced lifespan extension. These results support the idea that the immune system acts as an important mechanism for DR-induced longevity. Recently, analysis of genes that regulate aging or immune response in animal models, including C. elegans, Drosophila, mice, and even humans, has revealed that aging and immunity are controlled by the same signaling pathways, such as TOR/S6K signaling pathway, pleiotropically. DR-induced longevity is also associated with the modulation of the TOR/S6K signaling pathway. Thus, these results suggest that the immune function may be closely associated with aging regulation through DR.

**The Innate Immune Signaling Component FBXC-58 Mediates Dietary Restriction Effects on Healthy Aging in *Caenorhabditis elegans***

*In this study, we found that the F-box gene fbxc-58 is a downstream effector of the S6K signaling pathway, and that it regulates both pathogen resistance and aging in C. elegans. Furthermore, fbxc-58 is necessary for the effects of DR on lifespan extension. F-box protein acts as a modular E3 ubiquitin ligase adaptor protein, and the ubiquitin-dependent mechanisms have been shown to determine lifespan in response to DR or modulate the innate immune response. Therefore, we suggest that gaining insights into the detailed mechanistic aspects of fbxc-58 signaling pathway could elucidate the conserved signaling mechanism that links innate immunity and DR-induced healthy aging in animals.*

*Further, DR prevents or reduces the burden of age-related diseases or disabilities. Especially, in an aging and sedentary society, sarcopenia, an age-associated muscle disease, is beginning to be recognized as an acute disease condition. Although an effective sarcopenia treatment regime has not yet been identified, nutritional intervention is considered an effective method of preventing sarcopenia. In this study, we found that DR prevents muscle aging via fbxc-58 in C. elegans. fbxc-58 is essential for DR-mediated alleviation of the age-associated decline in muscle activity and protection of mitochondrial network in body wall muscle. Thus, we propose that investigating the molecular mechanism of action of F-box proteins, including fbxc-58, in DR will shed light on means to prevent sarcopenia and offer a potentially practical means of encouraging healthy aging via DR.*

Link: https://doi.org/10.18632/aging.204477

May 24th, 2023

**Less Sleep and a Longer Life, a Desirable Mutation**

A person who sleeps six hours rather than eight hours every day, give or take, is effectively gaining a bonus 12.5% additional time spent alive and active. From that perspective, there isn't all that much difference between being able to sleep two hours less every night throughout life, without consequences, and being able to live for the better part of an additional decade in good health. There are mutations that produce this effect in humans, other mammals, and lower animals such as flies, and at least one of them does so without any apparent negative side-effects.

Today's open access paper offers an exploration of one of these mutations, a small alteration in DEC2, which not only reduces the need for sleep, thereby granting additional subjective life span, but is also found to extend actual life span in flies. The size of the effect is larger than many of the calorie restriction mimetic compounds explored in recent years. Interestingly, the authors here argue that reduced need for sleep is more a reflection of increased robustness and health resulting from this mutation than any independent, top-down alteration of the regulation of sleep.

**A familial natural short sleep mutation promotes healthy aging and extends lifespan in *Drosophila***

*One of the most well-studied examples of natural short sleepers in the human population are individuals with rare genetic mutations in the dec2 gene. Dec2 is a transcriptional repressor that, in mammals, is recruited to the prepro-orexin promoter and represses the expression of orexin, a neuropeptide that promotes wakefulness. A single point mutation in dec2 (dec2P384R) inhibits the ability of Dec2 to bind the prepro-orexin promoter, resulting in increased orexin expression. Consequently, wakefulness increases, and individuals sleep on average 6hrs/day instead of 8hrs/day.*

*Intriguingly, these natural short sleepers do not appear to exhibit any phenotypes typically associated with chronic sleep deprivation, and expression of the dec2P384R mutation in mice suppresses neurodegeneration. Thus, it has been suggested that individuals harboring the dec2P384R mutation may employ compensatory mechanisms that allow them to thrive with chronic sleep loss. However, whether the dec2P384R mutation directly confers global health benefits has not yet been tested experimentally in any system.*

*In this study, we used a Drosophila model to understand the role of the dec2P384R mutation on animal health and elucidate the mechanisms driving these physiological changes. We found that the expression of the mammalian dec2P384R transgene in fly sleep neurons was sufficient to mimic the short sleep phenotype observed in mammals. Remarkably, dec2P384Rmutants lived significantly longer with improved health despite sleeping less. In particular, dec2P384R mutants were more stress resistant and displayed improved mitochondrial fitness in flight muscles. Differential gene expression analyses further revealed several altered transcriptional pathways related to stress response, including detoxification and xenobiotic stress pathways, that we demonstrate collectively contribute to the increased lifespan and improved health of dec2P384R mutants.*

*Finally, we provide evidence that the short sleep phenotype observed in dec2P384R mutants may be a result of their improved health rather than altered core sleep programs. Taken together, our results highlight the dec2P384R mutation as a novel pro-longevity factor and suggest a link between pro-health pathways and reduced sleep pressure.*

Link:
https://www.biorxiv.org/content/10.1101/2023.04.25.538137v1.full

May 29th, 2023

**Self-Reported Data From Several Hundred Rapamycin Self-Experimenters**

Rapamycin is arguably the best of the many calorie restriction mimetic small molecules, treatments that can provoke some of the sweeping, favorable metabolic and cellular changes produced by a reduction in calorie intake. The data showing a modest slowing of aging in mice with rapamycin treatment is robust and well replicated, albeit only producing a 5-10% extension of life span, much less than has been shown to be possible via forms of calorie restriction. Like calorie restriction, rapamycin upregulates the cellular housekeeping process of autophagy, but there is much more going on under the hood for both of these interventions.

Is rapamycin better than exercise for longevity? In mice, yes. In humans, who knows? No-one has yet devoted the time and funding to completing a robust clinical trial of rapamycin aimed at evaluating late life health and life expectancy, though the PEARL trial, funded by philanthropic donations, is a step in the right direction. Another step one can take at lesser cost than a clinical trial is to survey some of the many people who are taking rapamycin in the hopes that it will slow aging. Thus, we have today's open access paper. While self-reported data is of generally poor quality, for all the obvious reasons (and perhaps especially so in this context!), it is sometimes possible to learn from it, given a large enough study population. The one thing I'd be inclined to take at face value is the reporting on side-effects, for example.

**Evaluation of Off-Label Rapamycin Use to Promote Healthspan in 333 Adults**

*Rapamycin (sirolimus) is an FDA-approved drug with immune-modulating and growth-inhibitory properties. Preclinical studies have shown that rapamycin extends lifespan and healthspan metrics in yeast, invertebrates, and rodents. Several physicians are now prescribing rapamycin off-label as a preventative therapy to maintain healthspan. Thus far, however, there is limited data available on side effects or efficacy associated with use of rapamycin in this context. To begin to address this gap in knowledge, we collected data from 333 adults with a history of off-label use of rapamycin by survey. Similar data were also collected from 172 adults who had never used rapamycin.*

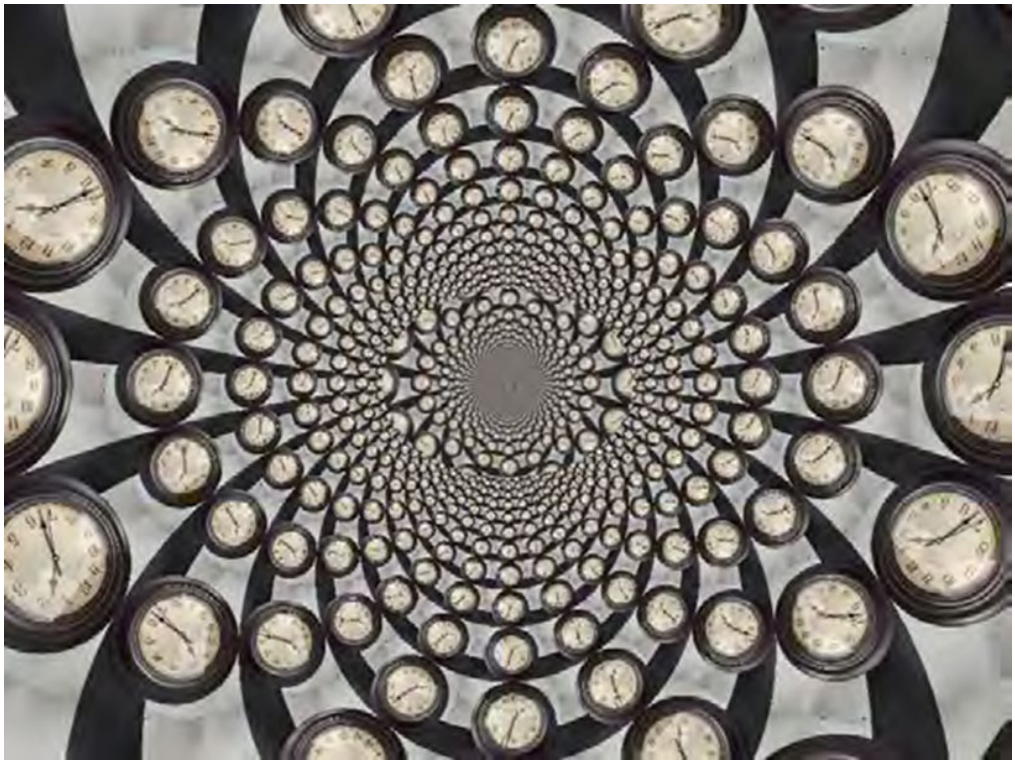
*Rapamycin users generally reported perceived improvements in quality of life since beginning off-label use of rapamycin. Ratios of greater than 3:1 in agreement were observed for self-reported improvements in health, happiness, brain function, feelings of youthfulness, confidence, calmness, anxiety, and generalized aches and pains. Interestingly, greater than fivefold more rapamycin users agreed with the comment that "family/friends have commented that I look good" than disagreed, suggesting that these perceived self-benefits may also be apparent to others.*

*Rapamycin use by organ transplant patients is associated with a long list of potential side effects. Interestingly, among survey respondents, only mouth sores was significantly more prevalent in rapamycin users compared to non-users. The lack of apparent side effects associated with off-label rapamycin use here is also consistent with prior reports that once weekly administration of 5mg of the rapamycin derivative everolimus has side effects comparable to placebo among healthy older adultsThis study has several limitations that make the data less reliable than what would be obtained from a double-blind, randomized clinical trial. The self-reported nature of the data and the possibility of unintended bias in the participant pool reduce confidence that these results would be recapitulated in a larger, more heterogenous population. In particular, we cannot rule out the possibility that the population of rapamycin users is self-selected against people who started taking rapamycin and stopped because of negative experiences; however, we attempted to recruit as broadly as possible to include such individuals both through social media and through direct recruitment of prior patients who had been prescribed rapamycin in the past.*

*It is also possible that individuals taking rapamycin off-label are more likely to practice healthy lifestyle habits or take other substances that could confound this analysis. We attempted to evaluate this and found no major differences between groups. Indeed, both rapamycin users and non-users in this study appear to be atypical in that they report higher rates of exercise and healthy dietary habits, lower body mass index, and lower rates of alcohol consumption and tobacco use, relative to the general population. It is possible that potential benefits and side effects from off-label rapamycin use would be different in a less healthy population.*

Link: https://link.springer.com/article/10.1007/s11357-023-00818-1

*Send email to Reason at Fight Aging!: reason@fightaging.org*



"More Time, Please!" – graphic by R. M. Perry

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**Want to learn more? Contact Linda Chamberlain at linda.chamberlain@alcor.org**

# Revival Update

## Scientific Developments Supporting Revival Technologies

Reported by R. Michael Perry, Ph.D.

## Vitrification and Nanowarming Enable Long-Term Organ Cryopreservation and Life-Sustaining Kidney Transplantation in a Rat Model

Zonghu Han, Joseph Sushil Rao, Lakshya Gangwar, Bat-Erdene Namsrai, Jacqueline L. Pasek-Allen, Michael L. Etheridge, Susan M. Wolf, Timothy L. Pruett, John C. Bischof, Erik B. Finger

*Nature Communications* **14**, Article number: 3407 (2023), https://rdcu.be/dkZkx, accessed 1 Sep. 2023.


**Abstract**

Banking cryopreserved organs could transform transplantation into a planned procedure that more equitably reaches patients regardless of geographical and time constraints. Previous organ cryopreservation attempts have failed primarily due to ice formation, but a promising alternative is vitrification, or the rapid cooling of organs to a stable, ice-free, glass-like state. However, rewarming of vitrified organs can similarly fail due to ice crystallization ifrewarming is too slow or cracking from thermal stress if rewarming is not uniform. Here we use "nanowarming," which employs alternating magnetic fields to heat nanoparticles within the organ vasculature, to achieve both rapid and uniform warming, after which the nanoparticles are removed by perfusion. We show that vitrified kidneys can be cryogenically stored (up to 100 days) and successfully recovered by nanowarming to allow transplantation and restore life-sustaining full renal function in nephrectomized recipients in a male rat model. Scaling this technology may one day enable organ banking for improved transplantation.


**From: Researchers Perform First Successful Transplant of Functional Cryopreserved Rat Kidney**

Univ. of Minn. *News and Events*, 22 Jun. 2023, https://twin-cities.umn.edu/news-events/first-successful-transplant-functional-cryopreserved-rat-kidney, accessed 1 Sep. 2023.

U Mechanical engineering postdoctoral researcher Zonghu Han is a co-first author of a new study showing how rat kidneys can be cryogenically stored for up to 100 days, successfully rewarmed using the group's innovative nanowarming approach, cleared of cryoprotective fluids and nanoparticles and then successfully transplanted into rats to restore full kidney function. Credit: Rebecca Slater.

In a groundbreaking new study, engineers and medical researchers at the University of Minnesota Twin Cities have proven the life-saving potential of long-term organ preservation at ultra-low temperatures by successfully transplanting a rewarmed kidney in a rat and restoring full kidney function.

The research, published in Nature Communications, has the potential to save thousands of human lives by enabling long-term storage of organs for transplantation.

"This is the first time anyone has published a robust protocol for long-term storage, rewarming, and successful transplantation of a functional preserved organ in an animal," said the study's co-senior author John Bischof, a mechanical engineering professor and director of the University of Minnesota Institute for Engineering in Medicine. "All of our research over more than a decade and that of our colleagues in the field has shown that this process should work, then that it could work, but now we've shown that it actually does work."

Currently, about 20% of kidneys donated for transplantation each year can't be used, often because these organs cannot be kept on ice for longer than a few hours and do not reach recipients in time. Long-term cryopreservation methods like vitrification — cooling an organ in cryoprotective chemicals so fast it avoids forming ice — have been around for decades. However, the biggest problem has been the inability to rewarm

them without major damage from ice or cracking.

The University of Minnesota team developed a specialized nanowarming process that warms the organ rapidly and uniformly from within rather than just at its surface. Their revolutionary method uses iron oxide nanoparticles dispersed throughout a cryoprotectant solution which is flushed through the organ's blood vessels. The iron oxide nanoparticles act as tiny heaters throughout the organ when activated using noninvasive electromagnetic waves. Importantly, the iron oxide nanoparticles can be washed out after rewarming.

In this study, authored by postdoctoral researchers Zonghu Han (mechanical engineering) and Joseph Sushil Rao (surgery), the team showed that rat kidneys can be cryogenically stored for up to 100 days, successfully rewarmed, cleared of cryoprotective fluids and nanoparticles, and transplanted into rats. When the kidneys were transplanted, the five rat recipients were able to restore full kidney function within 30 days without additional interventions.

"We have been working on this process for years to make sure everything was in place before we transplanted into a rat," said Michael Etheridge, a principal research engineer in the University's mechanical engineering department. "Still, it is a very complicated process. We weren't surprised this worked, but we weren't going to be surprised if it didn't work. I'm very proud of our team."

Long-term organ banking could increase donor organ utilization, improve donor/recipient matching, enable immune tolerance protocols (reducing the need for immunosuppression drugs), and improve procedure preparation and scheduling. Importantly, while demonstrated in the kidney, this approach may one day be applied across transplant organs and also enable long-term storage of organs and tissue for biomedical and pharmacological research.

The researchers have shown that all aspects of this approach can be scaled to larger organs and will next look to demonstrate the process using pig kidneys. While it will take several years before a cryopreserved organ will be transplanted into humans, the team is confident that it could successfully be done in the future.

## Brain Structure and Phenotypic Profile of Superagers Compared with Age-Matched Older Adults: a Longitudinal Analysis from the Vallecas Project

Marta Garo-Pascual, MS; Christian Gaser, PhD; Linda Zhang, PhD; Jussi Tohka, PhD; Miguel Medina, PhD; Bryan A Strange, MBBS

The Lancet Healthy Longevity, 13 Jul. 2023,

https://www.thelancet.com/journals/lanhl/article/PIIS2666-7568(23)00079-X/fulltext, accessed 17 Aug. 2023.

**Summary**

*Background*

Cognitive abilities, particularly memory, normally decline with age. However, some individuals, often designated as superagers, can reach late life with the memory function of individuals 30 years younger. We aimed to characterise the brain structure of superagers and identify demographic, lifestyle, and clinical factors associated with this phenotype.

*Methods*

We selected cognitively healthy participants from the Vallecas Project longitudinal cohort recruited between Oct 10, 2011, and Jan 14, 2014, aged 79.5 years or older, on the basis of their delayed verbal episodic memory score. Participants were assessed with the Free and Cued Selective Reminding Test and with three non-memory tests (the 15-item version of the Boston Naming Test, the Digit Symbol Substitution Test, and the Animal Fluency Test). Participants were classified as superagers if they scored at or above the mean values for a 50–56-year-old in the Free and Cued Selective Reminding Test and within one standard deviation of the mean or above for their age and education level in the three non-memory tests, or as typical older adults if they scored within one standard deviation of the mean for their age and education level in the Free and Cued Selective Reminding Test. Data acquired as per protocol from up to six yearly follow-ups were used for longitudinal analyses.

*Findings*

We included 64 superagers (mean age 81.9 years; 38 [59%] women and 26 [41%] men) and 55 typical older adults (82.4 years; 35 [64%] women and 20 [36%] men). The median number of follow-up visits was 5.0 (IQR 5.0–6.0) for superagers and 5.0 (4.5–6.0) for typical older adults. Superagers exhibited higher grey matter volume cross-sectionally in the medial temporal lobe, cholinergic forebrain, and motor thalamus. Longitudinally, superagers also showed slower total grey matter atrophy, particularly within the medial temporal lobe, than did typical older adults. A machine learning classification including 89 demographic, lifestyle, and clinical predictors showed that faster movement speed (despite no group differences in exercise frequency) and better mental health were the most differentiating factors for superagers. Similar concentrations of dementia blood biomarkers in superager and typical older adult groups suggest that group differences reflect inherent superager resistance to typical age-related memory loss.

*Interpretation*

Factors associated with dementia prevention are also relevant for resistance to age-related memory decline and brain atrophy, and the association between superageing and movement speed could provide potential novel insights into how to preserve memory function into the ninth decade.

*Funding*

Queen Sofia Foundation, CIEN Foundation, Spanish Ministry of Science and Innovation, Alzheimer's Association, European Research Council, MAPFRE Foundation, Carl Zeiss Foundation, and the EU Comission for Horizon 2020.

**From: Science Shows 'SuperAgers' Have These 3 Lifestyle Factors in Common**

Kells McPhillips, *Well and Good*, 30 Jul. 2023, https://www.wellandgood.com/super-agers/, accessed 17 Aug. 2023.

If life were a video game and you could choose your player, you'd probably want to select a SuperAger, or someone set to live 80-plus years with the mental acuteness of someone decades younger. In the real world, we don't get to choose an avatar, but new research suggests that we may be able to improve our chances of super-aging with a few key behaviors. A July study published in *The Lancet* indicates that advanced agers share three significant things in common regarding movement, sleep, and mental health.

Past research has shown that SuperAgers have more gray matter, essential tissue that aids in daily functions, in their brains. For this study, researchers chose 55 cognitively healthy participants aged 79 years or older, plus 64 SuperAgers (including 38 women and 26 men over 81 years of age) based on their scores on the Free and Cued Selective Reminding Test, a memory test that evaluates learning abilities.

"The study compared SuperAgers with typical folks, both in their 80s, in order to understand which differences in lifestyle, clinical factors, and brain structure exist between them," says Diogo Barardo, PhD, from Novos, a longevity solutions company. "This can be a starting point to explore if any, or a combination of these differences, is 'causal' in the future. That is, if these factors are the source of the SuperAgers' superpower of having almost no memory decline."

Scientists employed an artificial intelligence (AI) model to distinguish between SuperAgers and typical older adults. Ultimately, researchers discovered a correlation, or a scientific connection, between SuperAgers and three of the 89 demographic, lifestyle, and clinical predictors scraped by the AI.

First, SuperAgers displayed faster movement speed. "There was no difference in the amount of exercise, but there could be a difference in the amount/intensity of physical activities not identified by subjects as exercise per se, such as climbing stairs and gardening, that is contributing to the difference in movement speed," says Trinna Cuellar, PhD, head of research and development and vice president of biology at Tally Health. SuperAgers were also seen to have better mental health, and didn't complain as often about sleep (even though there was no markable difference in actual sleep duration between SuperAgers and typical folks).

However, what this study *didn't* find is just as interesting, according to Dr. Barardo. "There was no gender or genetic difference between the groups," he says. The AI model also defied earlier research that has showed that those with life partners are likely to live longer. "At least in this cohort, SuperAgers were more likely to be separated and divorced than typical old adults," says Dr. Barardo.

## Direct Speech Reconstruction from Sensorimotor Brain Activity with Optimized Deep Learning Models

Julia Berezutskaya, Zachary V Freudenburg, Mariska J Vansteensel, Erik J Aarnoutse, Nick F. Ramsey, Marcel A.J. van Gerven

*Journal of Neural Engineering*, 19 July 2023, https://iopscience.iop.org/article/10.1088/1741-2552/ace8be, accessed 2 Sep. 2023

**Abstract**

Development of brain-computer interface (BCI) technology is key for enabling communication in individuals who have lost the faculty of speech due to severe motor paralysis. A BCI control strategy that is gaining attention employs speech decoding from neural data. Recent studies have shown that a combination of direct neural recordings and advanced computational models can provide promising results. Understanding which decoding strategies deliver best and directly applicable results is crucial for advancing the field. In this paper, we optimized and validated a decoding approach based on speech reconstruction directly from high-density electrocorticography recordings from sensorimotor cortex during a speech production task. We show that 1) dedicated machine learning optimization of reconstruction models is key for achieving the best reconstruction performance; 2) individual word decoding in reconstructed speech achieves 92-100% accuracy (chance level is 8%); 3) direct reconstruction from sensorimotor brain activity produces intelligible speech. These results underline the need for model optimization in achieving best speech decoding results and highlight the potential that reconstruction-based speech decoding from sensorimotor cortex can offer for development of next-generation BCI technology for communication.

**From: Brain Signals Transformed into Speech through Implants and AI**

(unattributed), Radboud University, 29 Aug. 2023, https://www.ru.nl/en/research/research-news/brain-signals-transformed-into-speech-through-implants-and-ai, accessed 2 Sep. 2023.

Researchers from Radboud University and the UMC Utrecht have succeeded in transforming brain signals into audible speech. By decoding signals from the brain through a combination of implants and AI, they were able to predict the words people wanted to say with an accuracy of 92 to 100%. Their findings are published in the Journal of Neural Engineering this month.

The research indicates a promising development in the field of Brain-Computer Interfaces, according to lead author Julia Berezutskaya, researcher at Radboud University's Donders Institute for Brain, Cognition and Behaviour and UMC Utrecht. Berezutskaya and colleagues at the UMC Utrecht and Radboud University used brain implants in patients with epilepsy to infer what people were saying.

"Ultimately, we hope to make this technology available to patients in a locked-in state, who are paralyzed and unable to communicate," says Berezutskaya. "These people lose the ability to move their muscles, and thus to speak. By developing a brain-computer interface, we can analyse brain activity and give them a voice again."

For the experiment in their new paper, the researchers asked non-paralyzed people with temporary brain implants to speak a number of words out loud while their brain activity was being measured. Berezutskaya: "We were then able to establish direct mapping between brain activity on the one hand, and speech on the other hand.

We also used advanced artificial intelligence models to translate that brain activity directly into audible speech. That means we weren't just able to guess what people were saying, but we could immediately transform those words into intelligible, understandable sounds. In addition, the reconstructed speech even sounded like the original speaker in their tone of voice and manner of speaking."

Researchers around the world are working on ways to recognize words and sentences in brain patterns. The researchers were able to reconstruct intelligible speech with relatively small datasets, showing their models can uncover the complex mapping between brain activity and speech with limited data. Crucially, they also conducted listening tests with volunteers to evaluate how identifiable the synthesized words were. The positive results from those tests indicate the technology isn't just succeeding at identifying words correctly, but also at getting those words across audibly and understandably, just like a real voice.

"For now, there's still a number of limitations," warns Berezutskaya. "In these experiments, we asked participants to say twelve words out loud, and those were the words we tried to detect. In general, predicting individual words is less complicated than predicting entire sentences. In the future, large language models that are used in AI research can be beneficial. Our goal is to predict full sentences and paragraphs of what people are trying to say based on their brain activity alone. To get there, we'll need more experiments, more advanced implants, larger datasets and advanced AI models. All these processes will still take a number of years, but it looks like we're heading in the right direction."

## A Novel Nematode Species from the Siberian Permafrost Shares Adaptive Mechanisms for Cryptobiotic Survival with *C. elegans* Dauerlarva

Anastasia Shatilovich, Vamshidhar R. Gade, Martin Pippel, Tarja T. Hoffmeyer, Alexei V. Tchesunov, Lewis Stevens, Sylke Winkler, Graham M. Hughes, Sofia Traikov, Michael Hiller, Elizaveta Rivkina, Philipp H. Schiffer, Eugene W. Myers, Teymuras V. Kurzchalia

*PLOS Genetics*, 27 Jul. 2023,

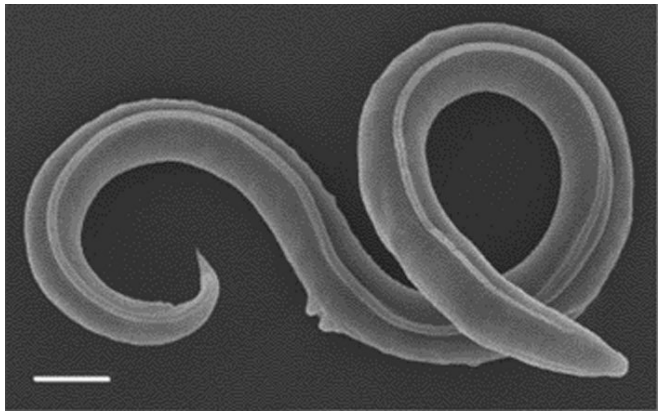
https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1010798, accessed 2 Sep. 2023.

**Abstract**

Some organisms in nature have developed the ability to enter a state of suspended metabolism called cryptobiosis when environmental conditions are unfavorable. This state-transition requires execution of a combination of genetic and biochemical pathways that enable the organism to survive for prolonged periods. Recently, nematode individuals have been reanimated from Siberian permafrost after remaining in cryptobiosis. Preliminary analysis indicates that these nematodes belong to the genera *Panagrolaimus* and *Plectus*. Here, we present precise radiocarbon dating indicating that the *Panagrolaimus* individuals have remained in cryptobiosis since the late Pleistocene (~46,000 years). Phylogenetic inference based on our genome assembly and a detailed morphological analysis demonstrate that they belong to an undescribed species, which we named *Panagrolaimus kolymaensis*. Comparative genome analysis revealed that the molecular toolkit for cryptobiosis in *P. kolymaensis* and in *C. elegans* is partly orthologous. We show that biochemical mechanisms employed by these two species to survive desiccation and freezing under laboratory conditions are similar. Our experimental evidence also reveals that *C. elegans* dauer larvae can remain viable for longer periods in suspended animation than previously reported. Altogether, our findings demonstrate that nematodes evolved mechanisms potentially allowing them to suspend life over geological time scales.

**From: A Worm Has Been Revived after 46,000 Years in the Siberian Permafrost**

Issy Ronald, *CNN*, 28 Jul. 2023, https://www.cnn.com/2023/07/28/world/worm-resurrected-frozen-siberian-permafrost-intl-scli-scn/index.html, accessed 2 Sep. 2023.



The worm had not been thawed in about 46,000 years. Alexei V. Tchesunov and Anastasia Shatilovich/Institute of Physicochemical and Biological Problems in Soil Science RAS

Scientists have revived a worm that was frozen 46,000 years ago — at a time when woolly mammoths, sabre-toothed tigers and giant elks still roamed the Earth.

The roundworm, of a previously unknown species, survived 40 meters (131.2 feet) below the surface in the Siberian permafrost in a dormant state known as cryptobiosis, according to Teymuras Kurzchalia, professor emeritus at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden and one of the scientists involved in the research.

Organisms in a cryptobiotic state can endure the complete absence of water or oxygen and withstand high temperatures, as well as freezing or extremely salty conditions. They remain in a state "between death and life," in which their metabolic rates decrease to an undetectable level, Kurzchalia explained.

"One can halt life and then start it from the beginning. This a major finding," he said, adding that other organisms previously revived from this state had survived for decades rather than millennia.

Five years ago, scientists from the Institute of Physicochemical and Biological Problems in Soil Science in Russia found two roundworm species in the Siberian permafrost.

One of the researchers, Anastasia Shatilovich, revived two of the worms at the institute by simply rehydrating them with water, before taking around 100 worms to labs in Germany for further analysis, transporting them in her pocket.

After thawing the worms, the scientists used radiocarbon analysis of the plant material in the sample to establish that the deposits had not been thawed since between 45,839 and 47,769 years ago.

But still, they didn't know whether the worm was a known species. Eventually, genetic analysis conducted by scientists in Dresden and Cologne showed that these worms belonged to a novel species, which researchers named Panagrolaimus kolymaenis.

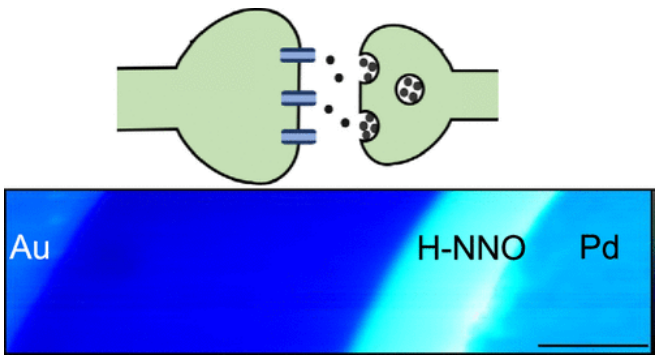
Researchers also found that the P. kolymaenis shared with C. elegans — another organism often used in scientific studies — "a molecular toolkit" that could allow it to survive cryptobiosis. Both organisms produce a sugar called trehalose, possibly enabling them to endure freezing and dehydration.

## Spatial Interactions in Hydrogenated Perovskite Nickelate Synaptic Networks

Ravindra Singh Bisht, Jaeseoung Park, Haoming Yu, Chen Wu, Nikhil Tilak, Sylvie Rangan, Tae J. Park, Yifan Yuan, Sarmistha Das, Uday Goteti, Hee Taek Yi, Hussein Hijazi, Abdullah Al-Mahboob, Jerzy T. Sadowski, Hua Zhou, Seongshik Oh, Eva Y. Andrei, Monica T. Allen, Duygu Kuzum, Alex Frano, Robert C. Dynes, Shriram Ramanathan

*Nano Lett.* 2023, 23, 15, 7166–7173, 28 Jul. 2023, https://pubs.acs.org/doi/10.1021/acs.nanolett.3c02076, accessed 3 Sep. 2023.

**Abstract**




A key aspect of how the brain learns and enables decision-making processes is through synaptic interactions. Electrical transmission and communication in a network of synapses are modulated by extracellular fields generated by ionic chemical gradients. Emulating such spatial interactions in synthetic networks can be of potential use for neuromorphic learning and the hardware implementation of artificial intelligence. Here, we demonstrate that in a network of hydrogen-doped perovskite nickelate devices, electric bias across a single junction can tune the coupling strength between the neighboring cells. Electrical transport measurements and spatially resolved diffraction and nanoprobe X-ray and scanning microwave impedance spectroscopic studies suggest that graded proton distribution in the inhomogeneous medium of hydrogen-doped nickelate film enables this behavior. We further demonstrate signal integration through the coupling of various junctions.

**From: Mimicking the Mind: Quantum Material Exhibits Brain-Like "Non-Local" Behavior**

(unattributed) University of California – San Diego 16 Aug. 2023, https://scitechdaily.com/mimicking-the-mind-quantum-material-exhibits-brain-like-non-local-behavior/, accessed 3 Sep. 2023

We often believe that computers are more efficient than humans. After all, computers can solve complex math equations in an instant and recall names that we might forget. However, human brains can process intricate layers of information rapidly, accurately, and with almost no energy input. Recognizing a face after seeing it only once or distinguishing a mountain from an ocean are examples of such tasks. These seemingly simple human functions require considerable processing and energy from computers, and even then, the results may vary in accuracy.

Creating brain-like computers with minimal energy requirements would revolutionize nearly every aspect of modern life. Funded by the Department of Energy, Quantum Materials for Energy Efficient Neuromorphic Computing (Q-MEEN-C) — a nationwide consortium led by the University of California San Diego — has been at the forefront of this research.

UC San Diego Assistant Professor of Physics Alex Frañó is co-director of Q-MEEN-C and thinks of the center's work in phases. In the first phase, he worked closely with President Emeritus of University of California and Professor of Physics Robert Dynes, as well as Rutgers Professor of Engineering Shriram Ramanathan. Together, their teams were successful in finding ways to create or mimic the properties of a single brain element (such as a neuron or synapse) in a quantum material.

Now, in phase two, new research from Q-MEEN-C, published in *Nano Letters*, shows that electrical stimuli passed between neighboring electrodes can also affect non-neighboring electrodes. Known as non-locality, this discovery is a crucial milestone in the journey toward new types of devices that mimic brain functions known as neuromorphic computing.

"In the brain it's understood that these non-local interactions are nominal — they happen frequently and with minimal exertion," stated Frañó, one of the paper's co-authors. "It's a crucial part of how the brain operates, but similar behaviors replicated in synthetic materials are scarce."

Like many research projects now bearing fruit, the idea to test whether non-locality in quantum materials was possible came about during the pandemic. Physical lab spaces were shuttered, so the team ran calculations on arrays that contained multiple devices to mimic the multiple neurons and synapses in the brain. In running these tests, they found that non-locality was theoretically possible.

When labs reopened, they refined this idea further and enlisted UC San Diego Jacobs School of Engineering Associate Professor Duygu Kuzum, whose work in electrical and computer engineering helped them turn a simulation into an actual device.

This involved taking a thin film of nickelate — a "quantum material" ceramic that displays rich electronic properties — inserting hydrogen ions, and then placing a metal conductor on top. A wire is attached to the metal so that an electrical signal can be sent to the nickelate. The signal causes the gel-like hydrogen atoms to move into a certain configuration and when the signal is removed, the new configuration remains.

"This is essentially what a memory looks like," stated Frañó. "The device remembers that you perturbed the material. Now you can fine-tune where those ions go to create pathways that are more conductive and easier for electricity to flow through."

Traditionally, creating networks that transport sufficient electricity to power something like a laptop requires complicated circuits with continuous connection points, which is both inefficient and expensive. The design concept from Q-MEEN-C is much simpler because the non-local behavior in the experiment means all the wires in a circuit do not have to be connected to each other. Think of a spider web, where movement in one part can be felt across the entire web.

## Proteomics Analysis of plasma from middle-aged adults identifies protein markers of dementia risk in later life

Keenan A. Walker, Jingsha Chen, Liu Shi, Yunju Yang, Myriam Fornage, Linda Zhou, Pascal Schlosser, Aditya Surapaneni, Morgan E, Grams, Michael R. Duggan, Zhongsheng Peng, Gabriela T. Gomez, Adrienne Tin, Ron C. Hoogeveen, Kevin J. Sullivan, Peter Ganz, Joni V. Lindbohm, Mika Kivimaki, Alejo J. Nevado-Holgado, Noel Buckley, Rebecca F. Gottesman, Thomas H. Mosley, Eric Boerwinkle, Christie M. Ballantyne, Josef Coresh

*Science Translational Medicine,* 15(705), 19 Jul. 2023

**Abstract**

A diverse set of biological processes have been implicated in the pathophysiology of Alzheimer's disease (AD) and related dementias. However, there is limited understanding of the peripheral biological mechanisms relevant in the earliest phases of the disease. Here, we used a large-scale proteomics platform to examine the association of 4877 plasma proteins with 25-year dementia risk in 10,981 middle-aged adults. We found 32 dementia-associated plasma proteins that were involved in proteostasis, immunity, synaptic function, and extracellular matrix organization. We then replicated the association between 15 of these proteins and clinically relevant neurocognitive outcomes in two independent cohorts. We demonstrated that 12 of these 32 dementia-associated proteins were associated with cerebrospinal fluid (CSF) biomarkers of AD, neurodegeneration, or neuroinflammation. We found that eight of these candidate protein markers were abnormally expressed in human postmortem brain tissue from patients with AD, although some of the proteins that were most strongly associated with dementia risk, such as GDF15, were not detected in these brain tissue samples. Using network analyses, we found a protein signature for dementia risk that was characterized by dysregulation of specific immune and proteostasis/autophagy pathways in adults in midlife ~20 years before dementia onset, as well as abnormal coagulation and complement signaling ~10 years before dementia onset. Bidirectional two-sample Mendelian randomization genetically validated nine of our candidate proteins as markers of AD in midlife and inferred causality of SERPINA3 in AD pathogenesis. Last, we prioritized a set of candidate markers for AD and dementia risk prediction in midlife.

**From: A Signal Hidden in Your Blood Predicts Dementia Risk Decades in Advance**

David Nield, *Health*, 25 Jul. 2023, https://www.sciencealert.com/a-signal-hidden-in-your-blood-predicts-dementia-risk-decades-in-advance, accessed 3 Sep. 2023

The earlier that Alzheimer's disease and other similar conditions can be spotted, the better the treatment options are, and scientists have discovered a blood biomarker that could signal the risk of dementia many years in advance.

A team from the National Institute on Aging, the University of Texas, and the Johns Hopkins Bloomberg School of Public Health in the US, as well as other institutions across the world, looked at data on 10,981 individuals collected across the course of 25 years.

In particular, the researchers analyzed the proteome of these individuals: the complete set of proteins expressed in a body, driving all kinds of biological processes from cell communication to hormone levels.

The analysis revealed 32 proteins that, when found at unusually high or low levels in the blood in people aged 45 to 60, were associated with an increased risk of developing dementia later in life.

"The present study leveraged data from multiple cohorts to identify and characterize 32 proteins and 4 protein networks in plasma of middle-aged adults that were strongly associated with dementia risk in subsequent decades," write the researchers in their published paper.

This study doesn't go as far as to look at why these protein imbalances are linked to dementia risk, but they could help scientists more accurately assess dementia risk in older adults.

Interestingly, many of the proteins weren't directly involved in the functioning of the brain. That backs up previous research showing that the onset of dementia and its underlying triggers aren't something that happens exclusively in the brain.

Several of the identified proteins were linked to proteostasis, or the healthy regulation of the proteome. This process helps prevent the protein clumps that are found in the brains of people who have developed Alzheimer's.

Other proteins played key roles in the immune system, perhaps showing that there's something about an immune system reaction or failure that increases the chances of dementia starting to take hold in the brain.

There's still a long way to go with this research, but eventually we may get to the stage where blood can be tested for signs of dementia risk. If those signs are caught earlier, personalized treatments can be put in place.

# A Roadmap to Revival

Successful revival of cryonics patients will require three distinct technologies: (1) A cure for the disease that put the patient in a critical condition prior to cryopreservation; (2) biological or mechanical cell repair technologies that can reverse any injury associated with the cryopreservation process and long-term care at low temperatures; (3) rejuvenation biotechnologies that restore the patient to good health prior to resuscitation. OR it will require some entirely new approach such as (1) mapping the ultrastructure of cryopreserved brain tissue using nanotechnology, and (2) using this information to deduce the original structure and repairing, replicating or simulating tissue or structure in some viable form so the person "comes back."

The following is a list of landmark papers and books that reflect ongoing progress towards the revival of cryonics patients:


Jerome B. White, "**Viral-Induced Repair of Damaged Neurons with Preservation of Long-Term Information Content**," Second Annual Conference of the Cryonics Societies of America, University of Michigan at Ann Arbor, April 11-12, 1969, by J. B. White. Reprinted in *Cryonics* 35(10) (October 2014): 8-17.

Michael G. Darwin, "**The Anabolocyte: A Biological Approach to Repairing Cryoinjury**," *Life Extension Magazine* (July-August 1977):80-83. Reprinted in *Cryonics* 29(4) (4th Quarter 2008):14-17.

Gregory M. Fahy, "**A 'Realistic' Scenario for Nanotechnological Repair of the Frozen Human Brain**," in Brian Wowk, Michael Darwin, eds., *Cryonics: Reaching for Tomorrow*, Alcor Life Extension Foundation, 1991.

Ralph C. Merkle, "**The Molecular Repair of the Brain**," *Cryonics* 15(1) (January 1994):16-31 (Part I) & *Cryonics* 15(2) (April 1994):20-32 (Part II).

Ralph C. Merkle, "**Cryonics, Cryptography, and Maximum Likelihood Estimation**," First Extropy Institute Conference, Sunnyvale CA, 1994, updated version at http://www.merkle.com/cryo/cryptoCryo.html.

Aubrey de Grey & Michael Rae, "**Ending Aging: The Rejuvenation Breakthroughs That Could Reverse Human Aging in Our Lifetime**." St. Martin's Press, 2007.

Robert A. Freitas Jr., "**Comprehensive Nanorobotic Control of Human Morbidity and Aging**," in Gregory M. Fahy, Michael D. West, L. Stephen Coles, and Steven B. Harris, eds, *The Future of Aging: Pathways to Human Life Extension*, Springer, New York, 2010, 685-805.

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Robert A. Freitas Jr., "**The Alzheimer Protocols: A Nanorobotic Cure for Alzheimer's Disease and Related Neurodegenerative Conditions**," *IMM Report* No. 48, June 2016.

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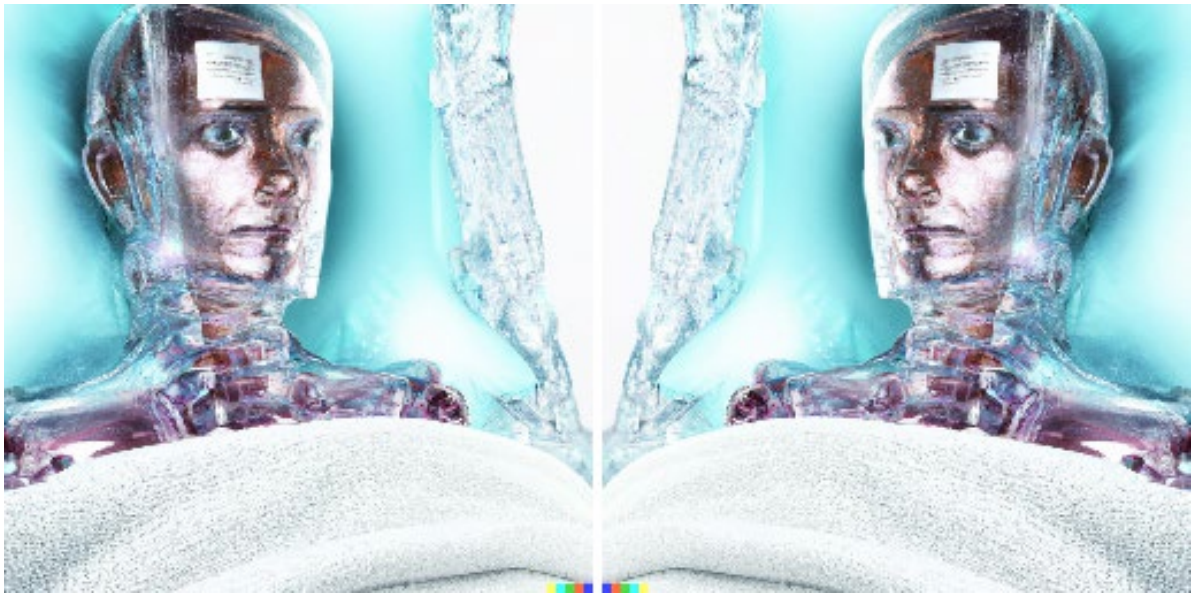
Robert A. Freitas Jr., "**Cryostasis Revival: The Recovery of Cryonics Patients through Nanomedicine**," Alcor Life Extension Foundation, 2022 (https://www.alcor.org/cryostasis-revival/).

"Revival of Frozen patients in the future," *left* image Dall-E 2, Feb. 2023.

# What is Cryonics?

Cryonics is an attempt to preserve and protect human life, not reverse death. It is the practice of using extreme cold to attempt to preserve the life of a person who can no longer be supported by today's medicine. Will future medicine, including mature nanotechnology, have the ability to heal at the cellular and molecular levels? Can cryonics successfully carry the cryopreserved person forward through time, for however many decades or centuries might be necessary, until the cryopreservation process can be reversed and the person restored to full health? While cryonics may sound like science fiction, there is a basis for it in real science. The complete scientific story of cryonics is seldom told in media reports, leaving cryonics widely misunderstood. We invite you to reach your own conclusions.

# How do I find out more?

The Alcor Life Extension Foundation is the world leader in cryonics research and technology. Alcor is a non-profit organization located in Scottsdale, Arizona, founded in 1972. Our website is one of the best sources of detailed introductory information about Alcor and cryopreservation (www.alcor.org).

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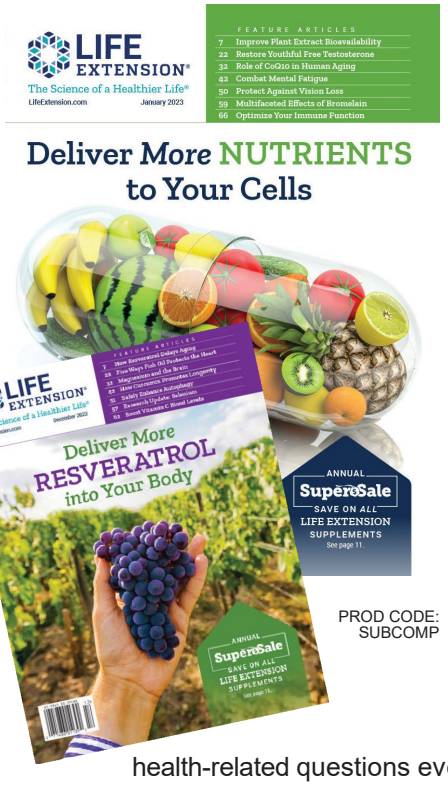


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