CRYONICS

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CRYONICS

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Cryonics as Plan A

By Max More, Ph.D.

Readers of this piece are used to articles by me that convey an encouraging, hopeful, optimistic view of things. This article is not one of those. I will be pressing a point of view that isn't comfortable, reassuring, or fun. Many of you will resist it because of that. If you already have cryonics arrangements, I won't be asking you to do anything different. If you want to live longer and do not have cryonics arrangements, the perspective here makes a major difference – the shift in thinking might even save your life.

Many people speak of cryonics as "plan B," while relying on life extension within their lifetime. They use cryonics as a backup plan in case something unexpectedly fatal happens. Barring such misfortune, they believe that either (a) within their remaining lifetime control of aging will be achieved; or (b) we will make accelerating progress in extending human lifespans so that they will see a time in which technology extends a person's life by more than one year for each year they are alive. The second view has become especially popular and goes by the moniker *longevity escape velocity* (LEV) or *actuarial escape velocity*, a term coined by David Gobel.

Taking someone of my age as an illustration of LEV, right now I'm 58. If life expectancy expands at an accelerating rate, by the time I'm 65 we may be delaying aging by 4 months each year. Each year that passes, I would age only 8 months. At age 70, I might age 6 months each year. At 75, 3 months per year. At 80, we reach LEV and my life expectancy stops decreasing year by year. From that point on, my life expectancy would keep growing indefinitely apart from limits imposed by accidents, homicide, or suicide.

But wait!

Perhaps the life extension curve does not look like the rising exponential curve of LEV. Prior to 2010, life expectancy in the United States rose fairly steadily for decades. Not long before 2010, life expectancy was increasing by about 0.2 years per year. According to the LEV view, life expectancy should now be rising faster than that.

In reality, progress completely stopped. The decade started promisingly. Between 2010 and 2014, life expectancy increased 0.2 years for the total population (less for men, more for women). But from 2014 to 2017, life expectancy *decreased* 0.3 years for the total population. From 2017 to 2018 life there was an increase of 0.1 years. For the decade as a whole (and this is not getting into the pandemic years) the result is a wash.

Health, United States 2019 (cdc.gov)

Life expectancy at birth, USA

1860	39.4
1865	33.1
1890	44.05
1900:	47.3 (men 46.3; women 48.3)
1950	68.2 (men 65.6; women 71.1)
1975:	72.6 (men 68.8; women 76.6)
1980	73.7 (men 70.0; women 78.8)
2000	76.8 (mean 74.1; women 79.3)
2010:	78.7 (men 76.2; women 81.0)
2018:	78.7 (men 76.2; women 81.2)

You *do* see a small increase in life expectancy at later ages after 2010 until the last pre-pandemic year of 2018. The increase is considerably smaller than gain in the 2000-2010 period.

Life expectancy at 65, USA:

1950:	13.9
1975:	16.1
2000:	17.6
2010:	19.1
2018:	19.5

Life expectancy at 75, USA

1980:	10.4
2000:	11.0
2010:	12.1
2018:	12.3

Even if the rise in life expectancy resumes – as I expect it to do – it may not rise exponentially. The rise could be arithmetical, or an S-curve, or a set of fits and starts with periods of no progress interspersed with jumps in lifespan. If you favor the idea that age is caused by the accumulation of damage over time, you might expect gradual progress as we develop ever better and more comprehensive means of halting and reversing that damage. If you believe that aging is primarily programmed into us, perhaps one discovery could lead to a huge boost to lifespan. But when will that boost happen?

Even if we do see exponentially rising lifespans reaching to LEV, how do you know where we are on that curve? In the illustration above, my life expectancy reached LEV at age 80. At that age, what if we are only managing an additional 3 months per year? I might live only a few years longer than you would expect today. In other words, even if progress is exponential, that won't save you if we are too far to the left on the curve or the curve is flatter than advocates believe.

Inventor, visionary, and Alcor member Ray Kurzweil has described cryonics as his "Plan D", the plans A through C being "don't die". Kurzweil has never been reticent about making forecasts. To his credit, he makes these publicly and mostly somewhat specific, and then reviews them over time. Compared to anyone else I know, his forecasts have generally done well. I'm far more doubtful about his forecasts for LEV and the end of aging.

In his 1999 book, *The Age of Spiritual Machines*, Kurzweil's scenario was "Expected lifespan has increased to over 100 by 2019" (p.208). By 2029: "The life expectancy of humans continues to increase and is now around 120 years." (p.223) Clearly, we did not reach an expected lifespan of 100 three years ago. It also seems exceedingly unlikely that lifespan will stretch to 120 in the next 7 years.

Similarly, in a 2017 article, Peter Diamandis quotes Kurzweil as saying: "I predict it's likely just another 10 to 12 years before the general public will hit longevity escape velocity." In 2022, this means 5 to 7 years!" A sneaky way around having to acknowledge the implausibility of the LEV claim would be to argue that such a lifespan had been achieved but we won't know it for decades. This underlines the difficulty in quickly discovering whether a treatment will extend the maximum human lifespan – or even the average life expectancy – without waiting for many years to find out. [Donaldson; de Wolf]

Consider the possibility that we manage to jump onto the LEV curve several times but one or more interventions have expected side effects that have serious health consequences. Given the politics and regulation of the real world, such events could cause a reaction that again drops us below the LEV curve. Even if this never happens, I will show that the LEV idea is far from new – and early advocates would be disappointed with our current state, that agreement is lacking on the nature of aging, and that numerous promising treatments have failed to live up to their promise.

LEV: The launch has been postponed

When you see the same mistake made repeatedly over time, it's reasonable to be doubtful about the idea behind the mistake. The concept of a longevity escape velocity has been around longer than most people realize. I've been following life extension efforts and advocacy since my teens.

One of my favorite magazines when I was 14 was *Future Life.* I still have a few copies. In the November 1978 issue, Robert Anton Wilson wrote an article called "Next Stop, Immortality." He started off by saying that the actuarial tables used by insurance companies were wrong and no one could predict your life expectancy because "Recent advances in gerontology… have led many sober and cautious scientists to believe that human lifespan can be doubled, tripled or even extended indefinitely in this generation."

Wilson went on to express an idea extremely close to that of LEV:

> In short, even if we can only double lifespan in this generation, we will still be around when further breakthroughs will probably triple it, quadruple it or raise it into millenniums. And then some of us will be here when the next quantum jump in lifespan occurs, and the next, until Immortality is achieved.
>
> Expert opinion on longevity has grown steadily more optimistic every time it has been surveyed, because the lab results are better every year. In 1964, a group of scientists was polled on the question and predicted chemical control of aging by the early 21st Century. In 1969, two similar polls found scientific opinion predicting longevity would be achieved between 1993 (low estimate) and 2017 (high estimate.) Dr. Bernard Strehler, one of the nation's leading researchers on aging, predicted more recently that the breakthrough would occur sometime between 1981 and 2001.

Interestingly, Alcor gets a mention at this point: "At the March 1978 Alcor Life Extension conference in Los Angeles, some of the experimental results justifying such forecasts were presented." Wilson also tells us that "an October 1975 McGraw-Hill poll found the majority of experts in the field believed cryonic freezing would be perfected and perfectly safe by 2000."

If there is an LEV curve, it has been shifting away from us for decades, taunting us with our inability to jump onto its upward slope.

Another friend of mine, Jose Cordeiro, mirrors Kurzweil's incredible timetable. In his book, *La Muerte de la Muerte* (*The Death of Death*), Jose says, "By 2029/30, so by the end of this decade we will have reached Longevity Escape Velocity." Since I will be in my late 60s by then, I *really* want to be able to believe Ray and Jose and Peter Diamandis and Aubrey de Grey at his most optimistic. But I cannot. To better understand why, let's take a look back at theories of aging and proposed interventions that seemed promising at the time.

Won't you just tell me what aging is?

In the late 1970s and through the 1980s, I was one of those expecting major advances in life expectancy in the very near future. As reality failed to track the hopeful predictions I had read, my views gradually changed. Over that time, theories of aging have come and most of them have later gone away.

Why do we age and how can we stop it? There is no agreement on this. Across several talks and a panel discussion at the 2012 Alcor Conference, we heard three diverging views from three very smart, very well-informed people: Aubrey de Grey, Michael Rose, and Josh Mitteldorf. Aubrey favors a seven-factor view of

damage as aging; Michael has a genetic view; and Josh favors programmed aging. Some of the past and present theories of aging include:

- Antagonistic pleiotropy theory of aging
- Disposable soma theory of aging
- Free-radical theory
- Glycation theory of aging
- Inflammation theory of aging
- Neuroendocrine theory of aging
- Order to disorder theory of aging
- Rate of living theory
- Reliability theory of aging and longevity
- Somatic mutation theory of aging

Saul Kent provides an admirably thorough overview of the field of life extension in his 1980 book, *The Life Extension Revolution*. There he lays out more than a dozen other theories of aging with only a little overlap with the previous list.

- Random error theory – breakdowns in the genetic machinery.
- Lysosome deterioration. To be treated with membrane stabilizers to repair lysosomal enzymes, e.g., centrophenoxine, Deanol/DMAE.
- The crosslinking of molecules, especially collagen.
- The free radical theory, proposed by Denham Harman. This led to a plethora of antioxidants as ways to quench the free radicals.
- Roy Walford's immunologic theory.
- Programmed aging/the aging clock.
- Regulatory dysfunction of the neuroendocrine system.
- Breakdown in hormonal regulation (Caleb Finch).
- Hormonal regulation of enzyme activity.
- The role of the pituitary gland in the neuroendocrine-controlled rate of aging.
- The aging clock and "unsculptured" hormones (Paul Segall).
- The juvenile hormone (Carroll Williams), which was never found in humans.
- The death hormone. W. Donner Denckla looked for a pituitary hormone.
- The integrated theory of aging, stated by Bernard Strehler emphasizing reduced capacity for cell division in brain, heart, and muscle.

Along with programmed aging, one of the more popular theories (or characterizations) of aging is Aubrey de Grey's with its engineering approach to preventing aging. This aims to tackle seven major categories of aging damage:

1. Cell loss, cell atrophy
2. Junk outside cells
3. Crosslinks outside cells
4. Death-resistant cells
5. Mitochondrial mutations
6. Junk inside cells
7. Nuclear mutations

In 2022, then, we are still far from universal agreement on a theory of aging. We are even further from agreement on how to treat aging.

Where is that elixir?

Time and time again people have excitedly proclaimed a new compound or treatment as a major advance in life extension. In the process of writing this article I recalled some of the old candidates for the "elixir of life", as the alchemists called it. You may remember Gerovital-HC (procaine), an immensely popular treatment since 1951 that was used at least into the 1970s. There was Deanol (DMAE), laetrile therapy for cancer, placental tissue therapy in the Soviet Union, ginseng – which lost popularity as a life extension treatment following a 1970s study in England with a null result, fetal lamb cells and "cellular therapy" in Switzerland, estrogen replacement therapy (not a bad idea but at the time the importance of balancing estrogen with progesterone wasn't well understood), chelation therapy (EDTA), L-Dopa, lergotrile and other ergot derivatives, blood transfusion (newly popular in the form of parabiosis), and nucleic acid therapy.

Saul Kent's book details these and other substances popular in the 1980s. You can find a similar list in Durk Pearson and Sandy Shaw's 1983 book, *Life Extension: A Practical Scientific Approach*. Pearson and Shaw helpfully provide their own regimen of supplements. It includes numerous vitamins in megadoses (but curiously no vitamin D, which has proved to be one of the most worthwhile vitamin supplements), as well as amino acids, inositol, the food additive BHT, thyroid extract, and drugs such as L-Dopa, bromocriptine, Hydergine, and vasopressin. The years since then have found some of these to be helpful for some people in some ways, but not to extend maximum lifespan and with little if any effect on life expectancy.

New supplements periodically capture people's attention and excitement. These include Alpha Lipoic Acid, blueberry extract, carnitine, carnosine, CoQ10 (ubiquinol), DHEA, Ginkgo, Green tea, Melatonin, various minerals and vitamins, N-Acetyl Cysteine, pomegranate extract, SAMe, and Silymarin (milk thistle). More recently: metformin, NAD+, Dasatinib, quercetin, resveratrol, and Rapamycin.

Hunger strike against death

You have probably heard the advice "Eat to live, don't live to eat." Sound advice. Some life extensionists have gone much further and recommended that you *don't* eat to live – or at least eat much less. Perhaps the first paean to caloric restriction was the delightful little book, *The Art of Living Long*, written by Italian nobleman Luigi Cornaro in 1550. Real research began in the 1930s and 1940s with the work of Clive McCay, an American biochemist, nutritionist, and gerontologist.

Caloric restriction research was furthered by my friend, Dr. Roy Walford, also known for being the physician in the first group to inhabit Biosphere II, along with colleague Richard Weindruch, author of *The Retardation of Aging and Disease by Dietary Restriction*. Walford set forth his research and recommendations in *Maximum Life Span* (1985) and *The 120 Year Diet* (1987). Caloric restriction definitely extends mean and maximum life span in many species, with a dramatic extension seen in shorter lived species. However, research on primates has been disappointing. An NIA study did not find calorie restriction to improve survival in rhesus monkeys (Mattison, et. al. 2012), although another study at the Wisconsin National Primate Research Center (WNPRC) reported improved survival associated with 30% CR initiated in adult rhesus monkeys.

Even in the NIA rhesus monkeys, despite no improvement in survival curves, the CR monkeys showed an improved metabolic profile and may have had less oxidative stress. Recent research into intermittent fasting also finds improvements in various measures of health. These improvements seem unlikely to translate into more than a very modest increase in life span in humans. Indeed, theorists as opposed as Michael Rose and Aubrey de Grey agree on one thing: Caloric restriction produces only very modest extension in life span in humans. The downsides of CR include feeling cold, hungry, lacking sex drive, and less resilience in case of infection or accident due to lower stores of metabolic reserves.

I don't mean to be too gloomy here. Recent research may be finding some means of helping to extend life expectancy, if not maximum life span. We have definitely moved on from the days of gland grafting and vasoligation. Although there is much unsupported hype in the area of stem cells, embryonic and pluripotent stem cells may yet yield strong results. Senolytics and senomorphics are under investigation for their potential to clear out senescent cells and improve health. Thymus regeneration needs more research but looks very promising as a means of strengthening the immune system in older individuals and thereby greatly reducing the risk of early infection-related death.

Fatal cryocrastination

Here are some examples, real and hypothetical, of people putting off making cryonics arrangements until it's too late.

Jeremy has said for years that he thinks cryonics has a good chance of working. "I'm definitely going to get around to signing up. I know I'm procrastinating, but I'll get to it soon." Jeremy develops an autoimmune disease. When he applies for life insurance funding for cryonics, he discovers that he's no longer insurable. Lacking other means of funding, Jeremy succumbs to his illness and dies. Permanently.

Joan has been fascinated by cryonics for decades. She's been putting off cryonics arrangements all that time. At 74 years of age, she finally gets moving. When she gets a quote for life insurance to fund her cryopreservation, she gets a nasty shock. She cannot afford the premium payments, and she lacks the means to pre-pay. "If only I'd signed up years ago. I could have easily afforded it then."

Carl reads news stories about cryonics with great interest. "That's a great idea. I think it might actually work," he thinks. One day he checks out the website of a cryonics organization. "Hmm. I should get on with this soon, while I'm still in good health and can afford it comfortably." Carl gets distracted and doesn't follow through by applying for membership. He thinks about it vaguely over the next few months. Before acting, Carl has a fatal heart attack. He is cremated.

Add your own scenario here. There are *many* ways to die, and only one way to make cryonics arrangements.

More reasons for Plan A

Another consideration supports cryonics as Plan A. Suppose we achieve complete control of aging and we are even able to fully rejuvenate people. This does not mean we achieve physical immortality. It does not mean that you cannot die. It does not mean that cryonics will no longer have a purpose.

You may still be prone to some diseases. You may become biologically immortal in the sense that you will never die of old age. But even a biologically immortal person might still be killed by diseases and pathogens that remain without a reliable cure. New pathogens (perhaps engineered to bypass enhanced immune systems) might still kill you. You may have an enhanced immune system but it will not necessarily be able to protect you against all diseases and pathogens.

A biologically immortal or non-aging person is still prone to accidents. Some of the accidents which are fatal today may not be in the future, but some will still kill you. A biologically immortal person can still die by falling from a tall building, plunging down a mountain, or plummeting from a faulty parachute. You can still die from a severe traffic accident (even if these are far less common), be blown up in a aircraft or spaceship, or killed in a homicide, terrorist attack, or war.

A = B = Stay Healthy

Do your best to stay healthy. This is good advice whether you are on Plan A or Plan B. In Plan B, you are primarily working at staying healthy to improve the odds that you will live long enough to reach LEV. Don't die this year because next year may bring a new discovery that gives you more time. In Plan A, you will also want to improve your odds, but you don't think it very likely to make a difference. That leaves you with two other reasons to stay healthy, especially in some specific ways.

One reason is that the cryopreservation process and the capabilities of your cryonics organization may improve over time due to learning and more resources. The other reason is to improve the quality of your cryopreservation. You really want to avoid sudden cardiac arrest, stroke, and aneurysm. These can either directly damage your brain or cause a delay in starting the cryopreservation process. Keeping your vascular system healthy should be a top priority.

Look at your cryonics arrangements as your Plan A. Communicate cryonics to others as Plan A. Don't let them comfortably reassure themselves that cryonics can be Plan B because life extension research will save them in time. If the person you're speaking to is convinced and asks: "Okay, then. So which cryonics organization should I sign up with?" The obvious answer for Plan A is: Plan Alcor! ■

My thanks to Aschwin de Wolf for feedback on a draft of this article.

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ALCOR 50 Conference 2022

CRYONICS

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This year, the Alcor Life Extension Foundation is celebrating its 50th year. To mark the occasion, we are holding a conference on June 3-5, 2022, at the Scottsdale Resort in Scottsdale, Arizona.

The conference itself will be Alcor's **first major in-person gathering in seven years**, so we're going to "go big." We expect members, prospective members, and others interested in life extension and the far future to turn out enthusiastically. We hope not only that our attendees will enjoy hearing from and interacting with you, but also that you may find the experience enjoyable. There is no organization quite like Alcor, after all, and very few opportunities to explore cryonics and its implications for society now and in the far future.

Although many people look at cryonics as their "plan B," our perspective at this event is that cryonics is Plan A. Probably everyone will need cryonics in order to reach a time where aging has been brought under control—and many people will need it sooner than they would like. That will be one of the topics discussed at the conference, along with research in cryonics, research in life extension more generally, financial planning for the very long term, lessons about cultural change from previous movements, and practical life extension.

FOR MORE INFORMATION, GO TO:
https://www.alcor.org/2022-conference/

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SPEAKERS DAY 2 — 06/04

KEYNOTE SPEAKERS


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Prof. David Chalmers

SPEAKERS


Gregory Fahy, PhD


Jason Harrow, JD


Natasha Vita-More, PhD


Max More, PhD


Ashwin de Wolf


Max Marty


Daniel Walters


Michael Korns


Jason Harrow, chFC


Rudi Hoffman, CFP


Mark House, JD


Brian Wowk, PhD

SPEAKERS DAY 2 — 06/04

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Max More, PhD


Dennis Kowalski


Peter Tsolakides


Emil Kendziorra, MD

Break and Networking

Banquet Dinner:
Vista Verde

SPEAKERS DAY 3 — 06/05


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Open Letter from Robert Freitas on the Occasion of Alcor's 50th Birthday Party Celebration

23 February 2022

As you may know, I've recently finished work on a 700-page book called *Cryostasis Revival* that describes how nanorobots can be used to revive cryopreserved patients. I was asked to write a brief personal letter describing how this book came to be, and my purpose in writing it.

I first became interested in cryonics at the age of 14 after watching the famous *Star Trek* episode "Space Seed" that originally aired on February 16, 1967. Alcor began operations almost exactly five years later, on February 23, 1972, promising to actually cryopreserve real human patients in the hopes of their future revival, by means yet unknown. The first glimmerings of how revival might be accomplished using nanotechnology appeared in the 1986 book *Engines of Creation*. But further illumination of this idea had to await subsequent decades of theoretical analysis in medical nanorobotics to determine whether and how it might be feasible.

I became an Alcor member in 2001, but always knew that cryonics revival would be the most challenging application imaginable for nanomedicine. Starting in the early 1990s and continuing to the present day, I've worked full-time to understand and articulate the future capabilities that medical nanorobots will make possible. Cryonics revival initially looked like an extremely daunting task. But over the years, nanorobotic treatment concepts for relatively simple issues such as cancer, heart disease and stroke came into sharper focus, and cures for more complex conditions such as aging and Alzheimer's disease gradually emerged as well. By 2018, after producing ~6000 pages of nanorobotics technical writings citing ~30,000 scientific and medical literature references, there was finally enough technical foundation for me to begin the metaphorical "ascent of Mount Everest."

The project started innocently enough. Aschwin de Wolf asked if I could write a brief paper describing some of the research issues that might be involved in using cryogenic medical nanorobots, or "cryobots", for cryonics revival. The effort need only take a few months. I began to dig into the fascinating details. Aschwin kept encouraging me as the plot thickened. Soon, I was hooked, eventually spending all of my free time over nearly three years to produce, as it says in the introduction, "the first comprehensive conceptual protocol for revival from human cryopreservation, using medical nanorobots." One overall objective of this work has been to help foster the perception of cryopreservation as an acceptable emergency medical procedure within conventional medicine. But there is also a simpler, broader purpose: When someone asks if cryonics revival is possible, or challenges us to show how it might be done, we can just hand them this book and say: "Here's how."

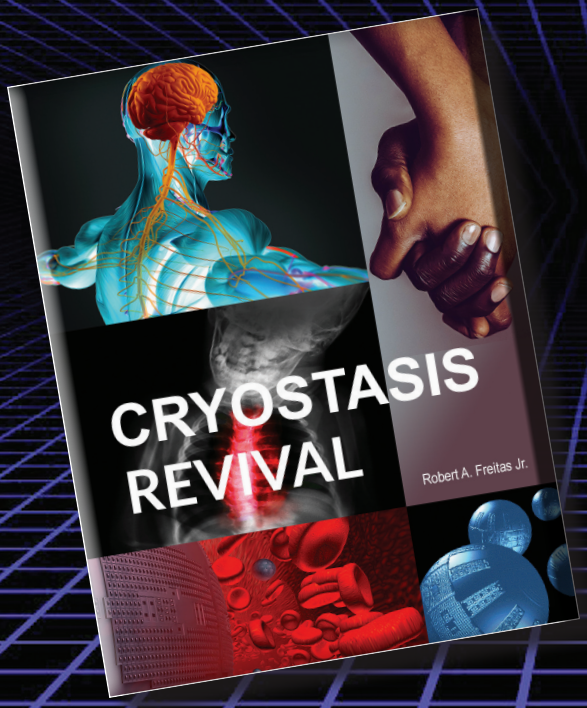
Cryostasis Revival includes suggestions for 304 specific future research projects, many of which could conceivably be funded and pursued now. These items, once completed, would put us at the technical threshold of attempting the first cryonics revivals with maximum recovery of personal identity. I hope this book spurs such research.

I want to thank Alcor for publishing the book and making it available in electronic form on their website on the occasion of the organization's 50th birthday.

Congratulations to my fellow cryonicists for their perseverance and their stalwart dedication to achieving an unbounded healthspan. ■

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., Ambassador, 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

Foreword by Gregory M. Fahy, Ph.D.

Dr. Greg Fahy is a complex systems cryobiologist and the Executive Director and Chief Scientific Officer of the cryobiological biotechnology company, 21st Century Medicine, Inc. His scientific research has been recognized by the Society for Cryobiology, which made him a Fellow in 2014.[1] *His comments are his own and do not reflect the views of any affiliated organization.*

A Glimpse of the Future

This is a book that is ultimately about the technical feasibility of cryonics. Cryonics is the practice of preserving individuals at cryogenic temperatures today for possible revival in the future. Human cryopreservation could in theory have several uses, ranging from the exploration of the cosmos in the distant future to "medical time travel" in the present. Regarding the latter, if medical conditions that are incurable today, including even the "medical condition" of being preserved by today's imperfect methods under often imperfect circumstances, will become curable in the future, then putting the course of today's fatal illnesses on hold by cryopreservation may provide hope for those who are deemed to be beyond hope by today's medicine.[2]

But "if" is a large word in this context. Without a clear answer, cryonics has been inevitably controversial. In the meantime, in the absence of being able to foretell the future, cryonics has historically been defended on the basis of two fundamental empirical observations.[3]

The first observation is the fact that humans have been creating more and more advanced technology, and a deeper and deeper understanding of the world, since our inception as a species, and that this creative process of discovery and improvement is likely to continue. Carried to its logical conclusion, it seems inevitable that, if the species survives and progress is allowed to continue indefinitely, we will eventually acquire the ability to accomplish any goal that does not violate physical and economic law.

The second observation is that cryobiology, the study of the effects of low temperatures on living systems, teaches us that viable mammalian cells can be stored for very long times at cryogenic temperatures and then revived successfully in a distant future. For example, present estimates suggest that it would take 32,000 years for background radiation to kill 90% of cultured cells after freezing to low temperatures.[4] Neurons in the brain are less sensitive to radiation damage than tissue culture cells and so might last longer, and storage times may also be extended by enhanced post-thawing DNA repair alone and by the presence of very high concentrations of cryoprotective agents, which are used in ice-free cryopreservation by vitrification[5] and may be radioprotective.[6] And even longer survival times have been claimed under natural conditions.[7]

Potentially tens of thousands of years is a long time for technological achievements to accumulate. Even today, it seems apparent that advances in all areas of science and technology are proceeding at exponential rates. Some have even projected the arrival of a "singularity,"[8] which is a point in time beyond which progress becomes so transformational that it is impossible to imagine what it will mean for our experience of life, just decades from now.

So it does seem relevant to ask: are the tasks that would be required to revive individuals after previous cryogenic storage with present imperfect techniques forbidden by physical law? The answer depends on two factors: how much and what kind of damage must be repaired, and what repair capabilities are possible in principle?

The first question has been addressed experimentally, as reviewed in depth in this book. From the perspective of cryobiology, there are some positive findings, but also still many unknowns and limitations. When conventional ice crystal damage to whole organs was prevented by vitrification, a rabbit kidney was able to support life indefinitely after cooling to -130 °C, rewarming, and transplantation.[9] Regarding the brain in particular, which is of central importance for the proposition of cryonics, it has been found that, as Freitas reviews in this book, partially frozen animal brains have registered coherent electroencephalograms after thawing from -20 °C,[10] frozen hamsters have recovered despite conversion of more than half of their brain water into ice at -1 °C,[11] and both frozen and vitrified worms have retained memories after rewarming that were instilled before cryopreservation.[12] Hippocampal slices, also, have been vitrified and rewarmed with good retention of viability,[13] ultrastructure,[14] electrical responsiveness,[15] and the ability to generate long-term potentiation.[16] The most direct observations that can be made, however, are those that can be made on the brains of actual human cryonics volunteers. Beyond the macroscopic studies reviewed in this book, there has been one study, whose results are presently being analyzed and prepared for publication, on brain fine structural integrity.[17] Preliminary indications are that brain structure was well preserved on both the histological and electron microscopic level, and was actually preserved much better than in animal brains in past studies. Ice formation was successfully avoided in all brain biopsies examined by differential scanning calorimetry, indicating excellent perfusion of the brain after cardiac arrest and transportation, and whole

brain fracturing was not observed after cooling to -146 °C. These results suggest that, when cryonics is carried out under favorable conditions, and when ice formation is prevented by vitrification, it has every appearance of preserving the structure and the molecular inventory of the brain.

However, cryonics is often attempted under poor conditions, and although the effects of disease and ischemia are reviewed in this book in detail, there is no published information on the effects of these pre-cryopreservation factors on the outcomes of preparation for cryopreservation (although some unpublished studies involving 1 hour of warm ischemia followed by 24 hours of cold storage before cryopreservation have been promising[18]). There are also few[19] published studies of human or other mammalian brain viability after vitrification, and past successful studies involving partial brain freezing[20] did not involve cooling to temperatures low enough for long term storage. Factors that may affect brain viability after vitrification (including brain shrinkage, background hypothermic injury, and possibly protein denaturation by cryoprotective agents[21]) have been individually addressed with success in separate model systems, but whole brain viability studies are lacking. The final reality is that, after all, it is still true that today's methods, if applied to the cooling of either a brain or a whole mammal to cryogenic temperatures, even under good conditions, would not be expected to result in spontaneous recovery, and superimposing variable degrees of cardiac arrest prior to such experiments would make failure even more likely. In addition, preserving the brain is far from being the only problem that must be overcome to restore cryopreserved individuals to life.

Therefore, despite several favorable signs, injury induced by present cryonics procedures cannot be repaired without highly advanced future repair technologies that can be applied to cryopreserved systems. Therefore, the second question, pertaining to the ultimate feasibility of these technologies, remains essential for the evaluation of cryonics, and is fortunately the major issue addressed in this book.

Much has been written previously about the general technical feasibility of what K. Eric Drexler named "nanotechnology" (and later, "molecular nanotechnology"), which is the atomically precise engineering and fabrication of molecular machines and molecularly defined materials. Further, the offspring of nanotechnology, "nanomedicine," has been explored in overwhelming detail in previous works by present author Robert Freitas. Ralph Merkle, too, has contributed much to an understanding of the global feasibility of molecular repair of cryopreserved brains, and other scenarios of repair have been suggested and are reviewed in depth in this volume. However, the present book is the only resource that comprehensively puts together the entire picture of nanomedical repair of cryonics patients as only Rob Freitas can do. "Conventional" nanomedicine must confront modifications to a body that is for the most part already maintaining its own viability. It is an entirely different problem to repair patients who are in a solid state at cryogenic temperatures. For that, new tools must be devised, and in this work, Freitas supplies the closest look we have had so far at what these future tools might include.

Freitas' approach to repair proceeds in a logical fashion. First, survey the damage. Second, gain access to what needs to be repaired by tunneling through inconsequential material, particularly in the vascular system and similar conduits. Third, stabilize structures that must be repaired and install structures necessary for later repair and more detailed surveys. Fourth, figure out what needs to be done based on what has been learned. Fifth, start by stabilizing fractures and then warming sufficiently to enable fracture faces to be fused back together again. And sixth, proceed with the rest of the details (of which there are a great many). It is hard to argue with this staging of events.

Even while attempting to describe as many details of the repair process as possible, however, it must be understood that concepts of repair depend on concepts of the damage that requires repair, and, as noted above, the latter remain incomplete. To his credit, Freitas identifies a myriad of topics worthy of future research throughout these scenarios, an acknowledgement that the present work is not and cannot be the final word, but it does not need to be. Extracting and then replacing molecules like glucose and oxygen, attempting to artificially manipulate osmosis, and artificially resealing membranes with altered semipermeability may all be unnecessary. However, if they are technically possible, then it becomes plausible that lesser capabilities will be able to do lesser tasks that actually are necessary. If the real goal is to plumb the depths of the possible, the present volume accomplishes that goal extraordinarily well.

Will the overall possibilities outlined here someday be realized? Will lives be saved? Will new adventures emerge as the people of the present engage with the entities of the future? Only time will tell. The proposals in this book cannot by themselves prove that cryonics will succeed, or define precisely what conditions of preservation will be required for cryonics to succeed. The totality of the arguments presented does, however, elevate the discussion to an unprecedented level of specificity and detail, and must figure prominently in further scientific evaluation of the proposal of cryonics.

Cryonics, uniquely, is a present practice that is largely based on the possibilities of future technology, but the future has always been hard to see. Now, exactly 60 years after cryonics was first proposed in 1962,[22] Freitas has provided a highly concrete glimpse into a future in which a set of definable and technically defensible future technologies could be equal to the task of repairing virtually any degree of biological injury associated with cryonics. His new comprehensive and falsifiable framework for debate and discussion may well lead to less dismissal and more serious consideration of the proposition of cryonics from this point forward. In that sense, just possibly, cryonics itself, if

not yet those who have undergone it, may be at the threshold of a new awakening. ■

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Cryostasis Revival: The Recovery of Cryonics Patients through Nanomedicine

By Robert A. Freitas Jr.

The technology of cryopreservation has dramatically improved in the 50 years since Alcor's founding in 1972. But in all that time the cryonics community has had only vague answers to the difficult question of revival. Yes, physical structures can be excellently preserved at low temperatures. But exactly how do we plan to breathe life back into our cryopreserved patients? The recently-published[1] 700-page technical book *Cryostasis Revival* was written to provide a detailed answer to this question. The processes proposed in the book make extensive use of a mature nanotechnology and represent "the first comprehensive conceptual protocol for revival from human cryopreservation, using medical nanorobots."

The restorative methods presented in *Cryostasis Revival* generally involve three phases of work: (1) collecting information from preserved structure, (2) computing how to fix damaged structure, and (3) implementing the repair procedure. The first and last of these phases employ sophisticated nanorobots small enough to pass through blood vessels and other microscopic tissue corridors, as well as a nanorobotic support infrastructure called the "vasculoid" that temporarily coats the inner surface of these spaces with atomically precise machinery. The activity in the second phase is primarily computational and takes place outside of the body using an external high-performance computer and specialized software.

Ultimately, it all depends on nanotechnology.

Will Nanotechnology Work?

If a mature nanotechnology is the key to revival, how can we be sure it will exist when we need it, and will actually work when we use it? We know that molecular machines such as nanoscale bearings, ratchets, pumps, motors, conveyors, and the like exist in various forms in biological systems. And they work! Additionally, these basic molecular machines have been assembled into complex micron-scale biological devices called cells, which have many capabilities analogous to those envisioned for medical nanorobots. In turn, these molecular machines and micron-scale biological devices have been assembled into highly-differentiated macroscale systems including large organisms such as human beings. Human beings can manufacture more of themselves, thus increasing total biological productive capacity, much as is envisioned for nanofactories that will someday manufacture more nanofactories, along with medical nanorobots. Because these molecular machines already exist in biological systems, they clearly violate no fundamental physical laws.

It is also important to note that the emergence of biological systems required a continuous chain of incremental evolutionary steps that imposed very stringent design limitations on these systems (e.g., must forage for their own food, defend themselves from predators, not differ markedly from parental systems, carry their own instructions for replication, etc.). Medical nanorobots, on the other hand, can be designed *de novo* at any easier-to-build point in the design space and will have far less stringent design limitations (e.g., can use optimal feedstock materials and energy conveniently supplied externally, can utilize a wider range of building materials, need no defense from predators during fabrication, has no need to self-replicate, etc.), hence can be much simpler systems than biological organisms.

As a result, we have high confidence that medical nanorobots can exist and can be simpler to design and operate than biological systems. How long might it take human technology to fabricate such complex nanosystems? Natural evolution required ~750 million years to evolve the first simple replicating cells via a ponderously slow incremental random walk through a very large design space. In contrast, human scientists can apply intelligence, creativity, selectivity, computer simulations, the physical tools of engineering, and the inspiration of a worked example (i.e., biology) to inform and vastly speed the development process. Human engineers built the first mechanical self-replicating systems in less than 750 years of effort.[2] That's a million times faster than nature required to blindly evolve the first self-replicating cells. So, how long until we have molecular manufacturing? Perhaps centuries? Possibly decades? Opinions on timing differ widely, and the development speed obviously depends on how well the effort is funded, but there are no fundamental scientific or technical reasons why it cannot be done.

Indeed, the earliest parts of this work have already been successfully concluded. Pure mechanosynthesis – the site-specific making and breaking of covalent chemical bonds on specified individual atoms using only mechanical positioning and mechanical forces – was first demonstrated experimentally in 2003.[3] It has been repeatedly confirmed over the years with various chemical elements in numerous experiments,[4] debunking

early objections.[5] The first detailed mechanosynthetic reaction sequences for building small diamondoid structures, validated by 100,000 CPU-hours of computational quantum chemistry simulations, were first published in 2007.[6] This is the gateway to molecular manufacturing.

It's just a question of when, and not if, we'll have medical nanorobots. Cryopatients can afford to wait in their dewars as long as necessary for nanorobotic technology to sufficiently mature.

Recovery of Personal Identity

A crucial aspect of revival from cryostasis is the strong desire to recover the patient's entire memory intact. Do we need to restore the patient perfectly down to the last atom, or will some lesser repair protocol suffice to preserve full personal identity? Each of us believes our mind to be a unique and enormously complex treasure house of knowledge. We might worry that even the tiniest error or omission in scanning or repairing a synaptic structure could result in some significant loss of memory, personality, or personal identity. Such concerns may be grounded in our modern experience with digital computers. In computers, it is often possible for one or a few flipped bits of data, if strategically located on a hard drive or in a software program, to produce disastrous consequences.

But there is a compelling argument that human long-term memory is vastly more robust than this. In 1986, Bell Labs scientist Thomas Landauer estimated that the average rate at which humans accumulate information into long-term memory during the normal activities of life, such as reading text or exposure to visual images, approximates 1-2 bits/sec, asymptotically approaching a stable lifetime total (integrating memory gains with losses) of ~2 x 10^9 bits for adults.[7] This figure includes a generous allowance for motor memory – the information storage required when learning to play a piano, ride a bicycle, or perform gymnastics – and also incorporates an analysis of competing rates of both learning and forgetting. A 2 gigabit human mind is roughly equivalent to the content of a library of ~400 consciously-recallable books of text, each with 250 pages, 400 words per page, 6 characters per word, and 8 bits per character.

These 2 x 10^9 bits should be compared to the best current estimates of ~86 x 10^9 neurons in the average human brain,[8] ~2 x 10^{14} synapses in the adult human neocortex,[9] and ~10^6 protein molecules per synapse.[10] While neurons and their synapses clearly perform many tasks unrelated to long-term memory storage, it would appear that up to ~43 neurons, ~100,000 synapses, and ~10^{11} protein molecules may be associated with each single bit of experienced, recallable, usable human memory. If long-term memory is truly this super-redundant, then it seems highly unlikely that the random loss of a single neuron, or the random corruption or misrepair of thousands of synapses or millions of proteins, could flip the associated single bit from "1" to "0" and destroy the tiniest piece of mind. This apparent robustness of the structures embodying long-term memory is consistent with the observation that human long-term memory persists over periods of decades despite a turnover rate of ~0.7%/hour for synaptic proteins – a half-life of only 2-5 days.[11] Such turnover means that every few days, on average, roughly 1 out of every 20 proteins in every synapse is replaced with a new protein incorporating at least one random peptide sequencing error[12] – yet memory and personal identity persist, in many cases over a lifetime.

As reviewed at length in *Cryostasis Revival*, the physical dimensions of almost all significant dendritic features and synaptic structures seem to be larger than ~100 nanometers (~0.1 micron) in size. Many of the smaller subcomponents composing these features and structures are generic or can be inferred (a) from the patient's DNA; (b) from neuronal connectivity patterns; (c) from synapse type or size and shape,[13] indirectly evidencing relative synaptic strengths; (d) from general knowledge of subcellular structures of specific types; and from other means. Future research will determine if there are any sub-100 nm-scale or molecular-scale structures that might need to be precisely scanned and precisely repaired in order to recover personal identity. This is a key point for revival, since it appears that non-molecular and relatively non-invasive scanning methods can be used to map a cryopreserved body and brain down to ~100 nm resolution.

If research confirms that most or all surviving personal identity-relevant structures can be restored using scans at ~100 nm resolution to plan and execute the repairs, and if a patient receives a "good" (i.e., thoroughly vitrified) cryopreservation, then revival may be successfully accomplished using a relatively less expensive and less complex method called *conventional cell repair* ("Plan A") which is entirely nondestructive and only moderately invasive. This method should recover all of the connectome and most of the synaptome as well.

On the other hand, if the identity, number, and location of structures smaller than ~100 nanometers is determined to be essential to recover personal identity, and if these structures are so damaged by cryopreservation that the repair process requires detailed sub-100-nm knowledge of them in order to infer and restore the correct original state, then conventional cell repair likely will not suffice and a fully invasive molecular scan and *molecular reconstruction* ("Plan B") may be required for the revival of cryonics patients. This process might also be required in cases of extensive damage or extremely poor cryopreservation.

Plan A: Conventional Cell Repair

Conventional cell repair relies on nanorobotic systems that are deployed, first throughout the patient's solid (cryogenic) body, and later throughout the "reliquidified" (~0 °C) body, without disturbing the molecular structure of tissues except to

make repairs. In this process, we scan and record all relevant physical structures to subcellular (~100 nm) resolution from within the vasculature while the patient is still in the solid state. After this information has been obtained and processed into a plan for repair, the patient is warmed sufficiently to allow rapid extraction of all metabolic and degradative molecules as cells reliquidify, quickly establishing complete biological stasis at the higher temperature. Conventional medical nanorobots[14] can then be introduced to comprehensively restore at the subcellular level the cryopatient's previously recorded (and now therapeutically editable) physical structure, over an extended period with reduced time urgency.

Temperature Profile of Various Stages of Revival during Conventional Cell Repair

Temperature	Revival Task
77 K (-195 °C)	Long-term cryogenic storage
77 K (-195 °C)	Steps 1-8 – map, excavate, install vasculoid, prepare plan
223-273 K (-50 to 0 °C)	Step 9 – tissue reliquidification and crackface sealing
273 K (0 °C)	Steps 10-12 – molecular extraction, conventional cell/tissue repair
310 K (37 °C)	Steps 13-15 – molecular instillation, uninstall vasculoid, wakeup

Specifically, this method for cryonics revival involves executing the following 15 operational steps, each of which is described in much greater detail in the book:

Step 1. Millimeter Vascular Scan. In a cryopreserved patient stored at ~77 K (196 °C), noninvasively scan and map all major blood and lymphatic vessels down to 0.1 mm (100 microns) in diameter.

Step 2. Large Vessel Excavation. Employ nanorobots or suitable macroscale technical means to mechanically excavate interior ice or vitrified material from all major blood and lymphatic vessels down to 0.1 mm in diameter.

Step 3. Microvascular Scans. Scan and map the blood and lymphatic microvasculatures, including all arterioles, venules, capillary beds, and lymphatic precollecting ducts, to micron resolution.

Step 4. Microvascular Excavations. Deploy nanorobots to mechanically excavate interior ice or vitrified material from all blood and lymphatic microvasculatures, all void spaces between crackfaces, all exposed perimeter surfaces of organs and other tissues, and some extracellular spaces.

Step 5. Recondition and Map Exposed Ice Surfaces. Clear excavation debris from all exposed ice surfaces, then recondition those surfaces. Geometrically and biochemically map the reconditioned exposed ice surfaces to ~1 nm resolution, locating and identifying all vascular faults and fracture planes in crackfaces throughout the ice.

Step 6. Install Vasculoid. Install the vasculoid appliance, a mechanical ciliary transport system previously proposed[15] as a means for replacing the vascular transport function in a living person. This provides rapid and reliable conveyance of nanorobots and materiel throughout the excavated vasculature of the cryopreserved human body. Vasculoid basic plates cover the lumenal walls of the entire vasculature, bridge any empty gaps across crack voids, and are installed across all major crackfaces using periodically-spaced anchors into the ice to temporarily stabilize the faces.

Step 7. Submicron Tissue Scans. Using sensor components mounted on the ubiquitous vasculoid, all tissues in which the vasculoid is embedded are scanned and mapped to ~100 nm feature resolution in three dimensions, clearly identifying most major organelles in all tissue cells and all other cytoplasmic and extracellular structures down to ~100 nm in size including neuronal synapses and boutons.

Step 8. Compute Whole-Body Repair Plan. Compile existing scan data into detailed whole-body maps covering all exposed cryogenic surfaces, vascular faults, fracture planes, tissue components to 100 nm resolution in 3D, the neural connectome, and cell plasma membrane faults. These maps are used to create data-driven computational models to plan, simulate, and direct repairs.

Step 9. Prethaw and Crackface Fusion. The cryopreserved patient is rapidly warmed to 223-273 K (-50 °C to 0 °C), producing whole-body tissue reliquidification. During the warming process, thermal stresses in the cryogenic tissue are relaxed, allowing separated crackfaces on either side of ice fractures to be drawn together by contraction of vasculoid components, closing all crackface voids.

Step 10. Molecular Extraction. Extraction microprobes equipped with pumps having molecularly specific binding sites at their distal termini (aka. "sorting rotors")[16] are inserted from the vasculoid into reliquidified tissue cells at a 2-5 micron spacing. Tens of thousands of key fuel, metabolic, intermediate, and other molecules are rapidly extracted from the cells, establishing complete biochemical stasis throughout the tissues within ~1 hour of reliquification.[17] The extraction microprobes are then withdrawn from the tissues.

Step 11. Reseal Plasma Membrane Compartments and Rehydrate. Nanorobots are released from the vasculoid to repair all cellular plasma membranes, reseal all compartments against fluid leakage, and rehydrate the cells in part via extracellular water transfers.

Step 12. Conventional Cellular and Tissue Repair. Nanorobots are employed to remove unwanted cells and microbodies,

inspect and repair (or replace) existing cells, and then perform various supplemental repair tasks on tissues and neurons.

Step 13. Patient Warmup and Molecular Instillation. The patient is warmed to normal human body temperature (310 K). Microprobes inserted into cells from the vasculoid instill thousands of essential molecules into intracellular cytoplasm and organelles, omitting only those molecules that could restart active metabolism. The microprobes are then withdrawn from the tissues. Molecules capable of initiating active metabolism are loaded into storage nanorobots that are parked intracellularly, awaiting a future signal to release their cargoes.

Step 14. Uninstall Vasculoid and Finish Repairs. The vasculoid is rapidly withdrawn from the body and replaced with a temporary blood substitute that includes nanorobots capable of supporting normal metabolic and material transport functions, e.g., respirocytes.[18] The patient's metabolism, heartbeat, circulation, and respiration are restarted as key metabolic chemicals are released from the parked storage nanorobots (which are then removed), and final neural repairs are completed. The temporary blood substitute is replaced with manufactured natural blood.

Step 15. Patient Wakeup. Anesthetic agents are removed and the patient awakens to full consciousness.

The serial revival protocol described above for whole-body patients is estimated to require 512 days (~1.4 years) of calendar repair time to complete, using reasonably conservative assumptions. If we can shift cell repair from organelle repair/replacement to exclusively whole-cell replacement operations, and if tolerable whole-body waste heat generation can be increased from 100 watts to 300 watts, then it may be possible to reduce the total calendar time for revival from 512 days to 244 days (~8.1 months). The nominal serial revival protocol for neuro patients is similarly estimated as 66 days (~2.2 months) or 46 days (~1.5 months) under the same two scenarios, and total repair time for both types of patients might be further modestly reduced by parallelizing some or all of these serial operations. The neuro repair estimates exclude the time required to print or regrow an acephalic replacement body and then reattach it to the fully repaired formerly cryopreserved cephalon. These tasks might also be parallelized to some extent.

Note that only lethal damage will be corrected during the revival process. Nonlethal conditions ranging from medical flaws to purely cosmetic issues will not be initially corrected, largely due to lack of informed consent and prioritized limited resources for revivals. Once a patient has been restored to life, a variety of elective procedures including genomic editing, whole-body rejuvenation,[19] or exotic anatomical modifications can be performed at leisure using conventional medical nanorobotics.

Nanostasis. Molecular extraction as summarized above in Step 10 for cryostasis revival is a new concept that also enables true suspended animation for living patients in a process called "nanostasis" or "warm biostasis." One of the nanostatic methods described in the book uses only medical nanorobots injected into the patient's body. To enter nanorobotic suspended animation, the patient would be sedated, cannulated, and cooled to hypothermic temperatures, after which a fleet of ~50 trillion nanorobots would be slowly introduced into all tissues and cells. Intravascular infusion of ~2 liters of compacted empty nanorobots suspended in ~2 liters of carrier fluid would require ~7 hours at a flow rate of ~10 cm^3/minute. Once in their assigned locations inside tissues or cells, and upon receiving the command to proceed, the individual storage nanorobots simultaneously pump all target molecules out of the extracellular or cytosolic spaces in which they are parked and into the robots' internal tankage volume, executing the molecular extraction process in the ideal progressive sequence and placing the patient into a state of reversible suspended animation in ~1 hour or less. While dormant in suspended animation the unconscious nanostatic patient remains susceptible to attack by bacteria and other external parasites. Microbivore-class[20] nanorobots can thwart this invasion both internally and externally to the body using devices that are powered without using metabolically active chemicals (e.g., via acoustic power). The nanostatic patient should be stored in an inert environment (e.g., pure nitrogen) to avoid exposure to oxygen or other metabolically relevant molecules that might enter the body through the skin or elsewhere. The patient should also be kept isothermal by external means since no endogenous heat will be generated other than nanorobot thermal emissions. Revival is accomplished in similar time frames by reversing the molecule intake in a carefully staged manner to redistribute all essential biochemicals to their original locations in the ideal progressive order, then extracting the nanorobots from the body in under an hour via nanorobot washout or by other means, with final revival accompanied by warmup and ACLS[21] or related conventional methods of resuscitation.

Nanotechnology. Of course, the success of the proposed Conventional Cell Repair procedure critically depends on the feasibility of diamondoid nanorobotics. In the unlikely event this technology proves infeasible, then some other method of revival would be required that is beyond the scope of the present work. Finding such other methods appears challenging for reasons enumerated in the book, but it could be a valuable service to the field of cryonics if someone could identify and describe at least one viable non-nanotech path to revival in book-length technical detail.

Plan B: Molecular Reconstruction

If it is determined that individual-unique structures smaller than ~100 nanometers are essential to recover personal identity, then conventional cell repair likely will not suffice and a fully invasive molecular scan, followed by *molecular reconstruction* ("Plan B"), may be required for revival from cryostasis.

Cryopreserved tissue at liquid nitrogen temperatures is literally as hard as solid rock, making nanorobotic locomotion prohibitively energy-intensive. But cryogenic solid materials can be disassembled or reassembled atom by atom using the techniques of mechanosynthesis[22] – the emerging technology of positionally-controlled site-specific mechanically-driven single-atom chemical reactions. In Plan B, subtractive mechanosynthesis can be used to abstract one atom (or one small chemical moiety such as a methyl ($–CH_3$) or amino ($–NH_2$) group) at a time from a specific site on the patient's physical structure. Additive mechanosynthesis can be used to donate one atom (or one small chemical moiety) at a time to a specific site. Recording the identity and precise location of every atom as it is removed or added creates an atomically-precise map of the entire cryopreserved body. The cryopatient's physical structure is then known to a resolution of ~0.1 nm, which is roughly 1000-fold more detailed than the ~100 nm resolution potentially available using Plan A. This is the best resolution that is physically obtainable and virtually guarantees that all available structural information is captured and retained. After the initial scan data has been processed and corrected to eliminate medical flaws, the patient's body can be reconstructed using the corrected scan data.

The first phase of a molecular reconstruction is to extract from the body all non-tissue and other loose matter that can later be replaced with fresh material. These items are not components of the patient's persistent physical structure and make no essential contribution to structural integrity at the molecular scale, or to memory and personal identity, hence there is no need to retain or to map them to atomic precision. Their extraction reduces the total number of molecules that must be precisely mapped and later precisely repaired or replaced. Additionally, the removal process produces a coarse mapping of all interior void spaces that can provide a guide for the more precise atomically-precise mapping yet to come.

As noted, the revival process begins with coarse mapping and bulk extraction, similar to Plan A:

Step 1. Millimeter Vascular Scan. In a cryopreserved patient stored at ~77 K (-196 °C), noninvasively scan and map all major blood and lymphatic vessels down to down to 0.1 mm in diameter.

Step 2. Large Vessel Excavation. Employ nanorobots or other suitable macroscale technical means to mechanically excavate interior ice or vitrified material from all major blood and lymphatic vessels down to 0.1 mm in diameter.

Step 3. Microvascular Scans. Scan and map the blood and lymphatic microvasculatures, including all arterioles, venules, capillary beds, and lymphatic precollecting ducts, to micron resolution.

Step 4. Microvascular Excavations. Nanorobots mechanically excavate interior ice or vitrified material from all blood and lymphatic microvasculatures, and from void spaces between crackfaces.

Step 5. Organ System Excavations. Deploy nanorobots to mechanically excavate ice from the interior gas or fluid volumes of the lungs, gastrointestinal tract, urinary bladder, heart, kidney, spleen, the ventricular system of brain and spine, gallbladder, synovial fluid capsules in joints, and the aqueous humor of the eyes. These excavations are done primarily to avoid the need to process informationally redundant bulk fluids during molecular reconstruction, which would be wasteful of time, energy, and manufacturing resources. All bulk substance removed in this manner can be restored during the whole-body fluid check, either as original or freshly manufactured material according to preference.

Step 6. Clear Excavation Debris. Clear excavation debris from all exposed ice surfaces.

Step 7. Reconstruction. Once nonstructural bulk materials have been extracted from the cryopreserved patient's body, there are two broad pathways to revival that can be followed (as detailed in a 75-page chapter in the book), depending on the philosophical preferences and financial means available to the patient:

(7.1) **Destructive Scan and Molecular Reconstruction of a Replacement Body.** In a destructive molecular scan, the patient's cryopreserved body is disassembled atom by atom, the precise location and type of atom is recorded in a data file, and the atoms are discarded as the process unfolds. After the initial scan file is digitally corrected to incorporate all necessary medical repairs, a new replacement body is manufactured via 3D printing that is a near-exact copy of the original cryopreserved body, but incorporating the specified repairs. This pathway appears to be somewhat faster and less expensive than (7.2).

(7.2) **Nondestructive Scan and Molecular Reconstruction of the Original Body.** In a nondestructive molecular scan, the patient's cryopreserved body is temporarily progressively separated into its constituent atoms or molecules, but only a small piece at a time, during which the precise location and type of each atom is recorded in a data file, after which the same atoms are carefully reassembled back into the original molecules, and the original molecules are reassembled back into their original positions, maintaining the original physical cryopreserved body, completely intact. At any time during the nondestructive scan, fully 99.99999% of the patient's solid body is undisturbed while

only one thin tissue slice ~200 nm thick is being processed over a period of ~10 sec. Successive slices are then scanned in turn, resulting in an estimated 39-month total scan time. Faster processing times are available by adding additional scan slices that are simultaneously processed. The initial scan file that results from this process is then digitally corrected to incorporate all necessary medical repairs. The original cryopreserved body is then repaired by repeating the nondestructive molecular scan, this time inserting the digital corrections incorporating the medical repairs. This pathway appears to be somewhat slower and more expensive than the destructive pathway in (7.1).

A crude cost estimate for cryostasis revival using either conventional cell repair (Plan A) or molecular reconstruction (Plan B) suggests that the key driver of operating expenses is the price of the energy required to power the nanorobots and computers. The total revival cost is estimated as ~$2 million for whole-body patients using Plan A assuming contemporary electricity costs, and similarly using Plan B assuming future energy costs become 100-fold cheaper than today due to widespread commercial atomically precise manufacturing. Revival costs are somewhat reduced for neuro patients compared to whole-body patients because there is much less tissue to process. However, these savings are probably offset by the cost of obtaining and attaching a substitute body to the repaired cephalon.

Validation of the Revival Process

Once we have devised an experimental cryostasis revival protocol that we think will work, how do we test it to be sure? The obvious answer: test it on animals. Cryonics revival protocols can be validated using a variety of animal models including primates. Positive results from these tests should provide sufficient technical validation to warrant approval of the same protocols for the revival of cryopreserved human patients.

The validation tests should seek to confirm the following mental functionalities:

Simple Memory. Vita-More and Barranco[23] conclusively established in 2015 that *C. elegans* nematode worms can survive cooldown to liquid nitrogen temperature and then be warmed back to normal temperature, with their memories of a trained simple behavior intact.

Complex Memory. We can start with rodents such as rats or mice that have learned complex tasks such as how to run a maze,[24] and verify that, like the worms, these small mammals remember whatever they've been taught, demonstrating retention of complex memories after experiencing cryopreservation followed by our revival procedure.

Personality. We then proceed to highly intelligent mammals such as dogs who have learned to recognize their owner or trainer and have been taught a large number of tricks and word associations. One border collie[25] was taught to recognize the labels of over 200 different items. The dog could infer the names of novel things by exclusion learning and could correctly retrieve those new items both immediately and four weeks after the initial exposure to the items. Besides these tests of specific memories and abilities, long-time pet owners know that their canine companions can: (1) express empathy, deception, and imitation; (2) develop demonstrable personalities that reflect how they interact with owners, friends, strangers, and other animals; and (3) display characteristic unique behaviors when confronted with challenges or during play. A dog that replicated its usual idiosyncratic behaviors after experiencing cryopreservation and experimental revival would provide good evidence that the animal's personality had survived intact.[26]

Personal Identity. Chimpanzees and bonobos have cognitive capacities superior to those of dogs in self-consciousness, although dogs do better than chimpanzees at using the behavior of other animals, especially humans, as a cue. The logical animal model for the final phase of cryopreservation revival testing is probably a primate, given their physiological similarities to humans and their clear demonstration of self-awareness. Ideal animal subjects may be trained primates who have been taught language skills using sign language. Kanzi, a bonobo, is believed to understand more human language (after perhaps ~8 years of training) than any other non-human animal in the world.[27] When animals like these are revived from cryopreservation, they can be tested on their memory of words, their ability to perform trained tasks, and their characteristic behaviors to determine the persistence of memory and personality. More importantly, these primates could, in principle, be directly interrogated to obtain answers to questions about their internal mental state – such as "how do you feel?" and "who are you?" to test if their sense of self has survived the revival procedure.

Whole-Brain Emulation (WBE) on Animals. Merkle[28] described a WBE validation procedure that would likely be available in the future era of nanorobotic revivals and could be applied to laboratory animals: "We could record every nerve impulse in the brain by embedding a sufficient number of neurobots….We could then record data from neurobots in the brain of an experimental animal before they were cryopreserved, cryopreserve them, revive them, and then record data from neurobots in the brain of the revived experimental animal, giving us two sets of neuronal data: 'before' and 'after'. Comparing the 'before' and 'after' data would let us tell if we had done a good job in cryopreserving and reviving the experimental animal."

The larger great apes – chimps, orangutans, bonobos, and gorillas – have 30%-40% as many neurons as a human brain.[29] Human, chimp, and rhesus macaque neural tissues show similar adult synaptic number densities at 0.3-0.5 synapses/micron^3, varying slightly with age.[30] There are a few minor neuronal differences between humans and great apes. For

example, prefrontal area 10 has greater spacing among cortical minicolumns in humans than in chimpanzees.[31] The pyramidal neurons of humans have significantly longer and more branched dendritic arbors in all cortical regions than similar neurons in chimpanzees, and the human prefrontal cortex contains a greater proportion of dendrites, axons, synapses, glial cell processes, and microvasculature relative to the space occupied by neuronal and glial somata than in chimpanzees.[32] Post-differentiation, human and primate cultured neurons show slightly different firing rates with time.[33] But these are all relatively minor differences in size, number, spatial distribution, and metabolic rate, not fundamental differences in kind that cell repair nanorobots would likely be able to handle in primates but unable to handle in humans. If we ever discover some exclusively-human physical neurocellular feature that absolutely must be repaired, nanorobots could practice and perfect such rare repair procedures on these specific human-unique features using brain tissue samples taken from fresh human cadavers.

If comparison of a before-cryopreservation WBE with an after-revival WBE of a large primate reveals no significant operating differences when placed in the same simulated environment, and if *in vivo* neurobot scans reveal no fundamental structural differences in the neurons, dendrites, synapses, and connectomes of test primates before and after the revival procedure, then it is difficult to imagine how a human brain subjected to the same recovery process would fare differently, given that the cytoarchitecture, cell type composition, and neurogenic gene expression programs of humans and chimpanzees are remarkably similar.[34]

These results lead to our tentative conclusion that *a successful primate validation of cryonics revival protocols should be sufficient evidence to warrant application of the same protocol to human cryopreservation patients*. This tentative conclusion should be vigorously explored by careful comparison of human and nonhuman primate neurological ultrastructure and brain cytoarchitecture, and should be validated, nuanced, or challenged in future research.

Of course, there are literally hundreds of future research tasks – as enumerated in the book – that must be completed before we can have a reasonable prospect of successfully bringing back the first cryonics patient. My hope is that *Cryostasis Revival* will inspire, focus, and motivate this important work. ■

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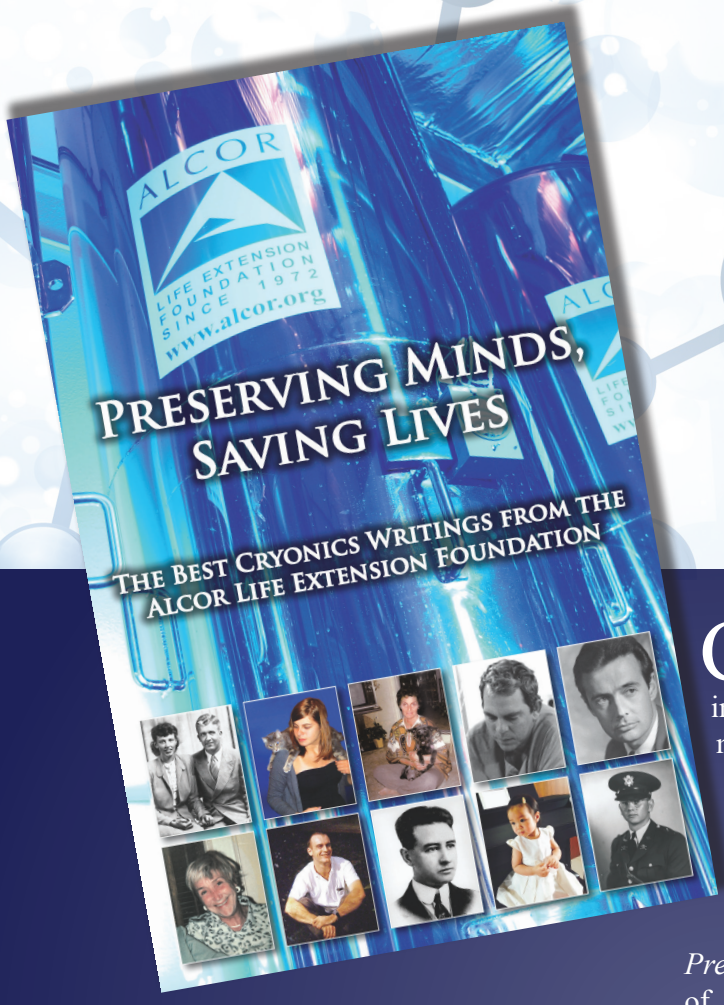

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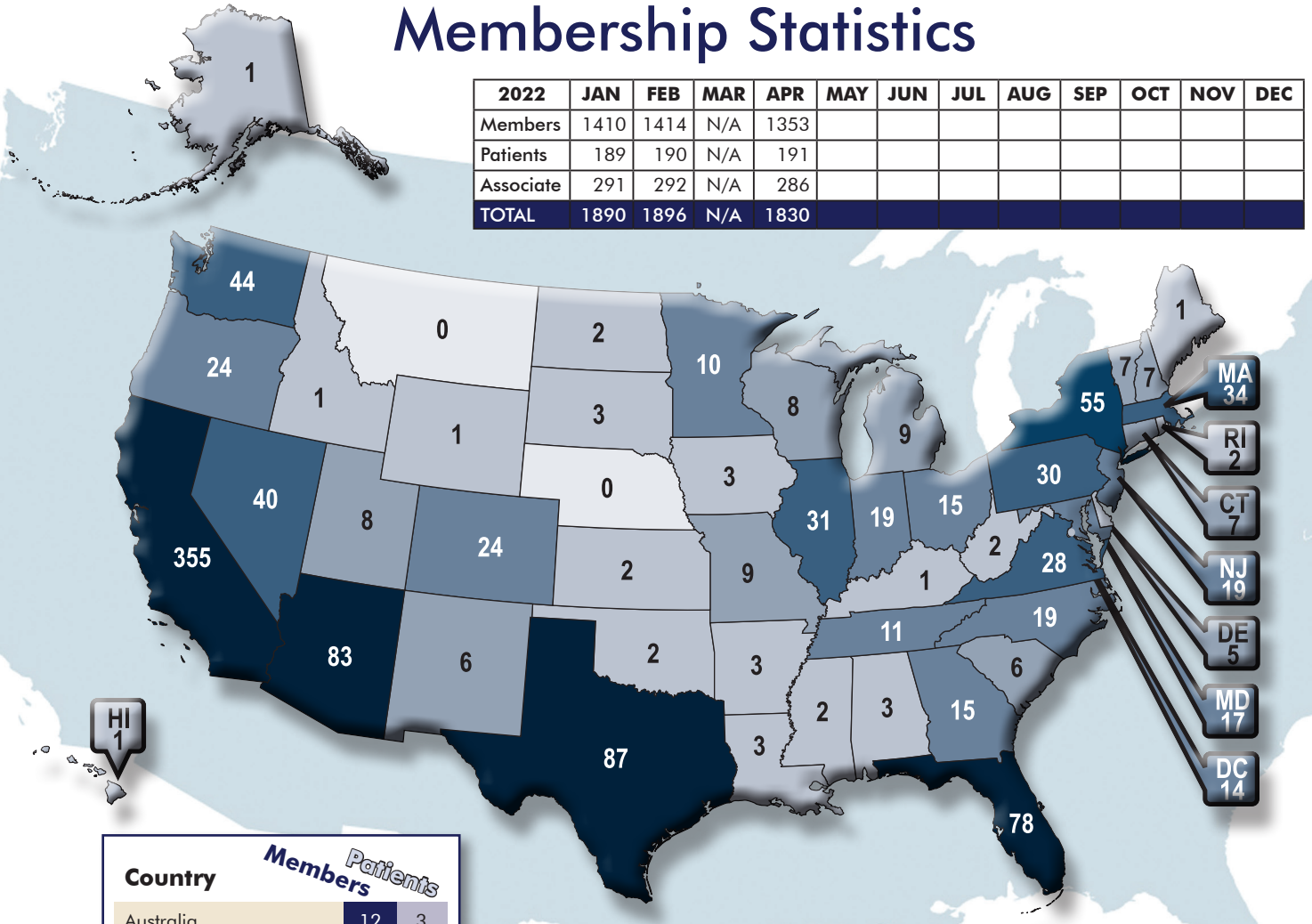
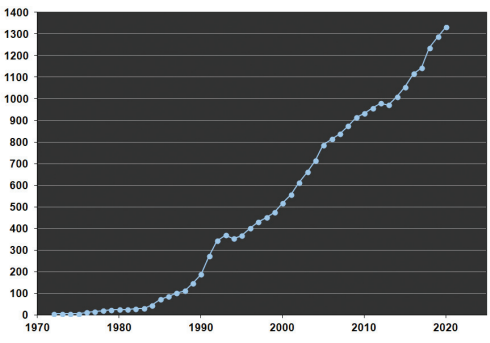
2022	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Members	1410	1414	N/A	1353								
Patients	189	190	N/A	191								
Associate	291	292	N/A	286								
TOTAL	1890	1896	N/A	1830								



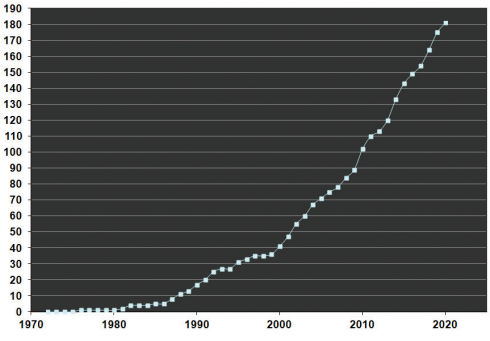
International Members & Patients

Country	Members	Patients
Australia	12	3
Austria	1	0
Belgium	1	0
Brazil	1	0
Bulgaria	1	0
Canada	76	5
China	0	1
Croatia	2	0
Finland	1	0
France	2	1
Germany	18	0
Hong Kong	2	0
Hungary	1	0
Israel	1	1
Italy	1	0
Japan	5	0
Luxembourg	1	0
Mexico	5	0
Monaco	1	0
Netherlands	1	0
New Zealand	1	0
Norway	2	0
Portugal	4	1
Puerto Rico	3	0
Slovenia	1	0
Spain	4	1
Sweden	1	0
Switzerland	3	0
Taiwan	1	0
Thailand	3	1
United Kingdom	39	3
Virgin Islands	1	0
TOTAL	196	17

- 0 Members
- 1–4 Members
- 5–9 Members
- 10–24 Members
- 25–49 Members
- 50–74 Members
- 75+ Members



Number of Alcor members



Number of Alcor patients

Scholar Profile: Robert A. Freitas Jr.

By Aschwin de Wolf

Introduction

Scientific reasoning and creativity are often viewed as two very different realms of reality. On the one hand, we have deductive and inductive reasoning and empirical testing, and on the other we have the "intuitive" realm of imagination. If there is one thing that sets apart the research and writings of Robert Freitas it is the magnitude of ideas that he generates. This, and perhaps a mind-blowing level of productivity that never sacrifices rigor. When working with Freitas on his seminal *Cryostasis* book, I had the unique ability to see both his tremendous work ethic and his creativity in solving formidable challenges. The time has long been ripe to publish a scholar profile of Robert, but after his completion of a massive technical tome on how to revive cryopreserved patients, the present moment seems particularly fit.

Freitas was born in 1952 in Camden, Maine and lived his first five years in Santa Cruz, California, followed by 10 years in the greater Phoenix, Arizona area, to return once more to the sunshine state where he has written most of his academic work in molecular nanotechnology. His father ran various privately held agricultural operations and his mother provided a stable household, allowing Robert to realize his full potential.

Rob at 15, in his last home chemistry lab.

He received his first Gilbert chemistry set at the age of seven. Chemistry turned out to be far more than a transient hobby. In fact, each new Freitas home was equipped with a small lab for him to pursue his interests. His father even facilitated the installation of a makeshift fume hood. Whereas other children occupied themselves with paperbacks, magazines, and comic books between studies, Robert brought a 1962 *Concise Chemical and Technical Dictionary* to middle school. This passion continued into high school, including more practical applications such as "pyrotechnics." He also pursued cross-country running.

His fascination with the design and launch of "home-made rockets, explosives, smoke bombs, and other pyrotechnic and incendiary devices" eventually made its way to the local newspaper after he accidentally blew up the school's chemistry lab. Freitas recalls the event as if it were yesterday:

> The local newspaper article describing the event erroneously reported that I was mixing up a batch of rocket fuel that exploded. I regarded this as an insult to my integrity as a pyrotechnician. The rocket fuel I was using was perfectly safe and could be made to explode only with great difficulty. What actually exploded was a rather large batch of Armstrong's mixture, amped up with powdered aluminum, which served as the explosive payload for my rockets. A simple software program I wrote that balanced chemical equations predicted nonstandard proportions for the various ingredients – which novel proportions, when followed, converted the mixture from a relatively stable primary explosive into a highly sensitive contact explosive. I got distracted with thoughts of my girlfriend that day and became careless, blowing out the windows and earning myself three days in the hospital.

Fortunately, the girlfriend still married him, four years later...

In college, Freitas switched his major from chemistry to physics because it would provide him with the most fundamental knowledge of how the universe worked. Eventually he double majored in physics and psychology. The latter choice was motivated by Asimov's *Foundation* (science fiction book) series and its potential to inform the emerging discipline of "psychohistory." When not climbing or mountain hiking with a friend, Robert completed an (unpublished) 318-page science fiction novel instead of the more traditional senior research thesis for his Physics degree.

While many might have argued in favor of a more advanced degree in physics, Freitas believed that it was not where his greatest talents lay. He wanted to be more than adequate in a chosen field, to "set the world on fire" with the work he pursued. In an effort to tease out that work, he decided to pursue something entirely different from his previous academic pursuits: he attended Santa Clara University of Law where he eventually obtained a Juris Doctor (JD) degree.

However, like physics, law was not the match that lit the fire.

Xenology

"I was never interested in normal stuff: regular physics, regular law," Robert admits. During his law school studies, his interests converged on extraterrestrial life, "weird" legal situations triggered by space travel, and even molecular nanotechnology. Some of the popular articles he published touched on subjects like the legal rights of extraterrestrials (1977, 1979), adoptive fetuses (1980), and robots (1985). It's no surprise that his first comprehensive non-fiction exposition was then concerned with an entirely novel and quite literally alien field that he himself coined: "xenology." Defined as the interdisciplinary study of the planetology, biology, psychology, sociology, technologies, and all other things relating to extraterrestrial life forms, it was the sole subject of a 500,000-word tome that Freitas worked on for five years. Though he was unsuccessful in finding a publisher, he privately distributed the book to researchers in the mid-1990s. It was finally published online in 2008. For such an obscure publication, it touched on several themes that would later find their way into other research and books. Retrospectively, this book might one day be considered a founding text of the field, or, more intriguingly, a practical guide on how to deal with lifeforms very different from our own.

Though it did not strike him until recently, Freitas's evolution from boy wonder raised in an agricultural backdrop to a pioneer in extraterrestrial life and space, bears rather striking resemblance to the literary and cinematic arcs of several popular sci-fi books, movies, and series: consider Cooper, the NASA pilot turned Coloradan farmer of *Interstellar*, James Holden, the son of a Montana family farming cooperative in *The Expanse*, and Graham Hess, the former priest and farmer in Pennsylvania in *Signs*. It seems there is no greater inspiration towards space, than the experience of growing up with vast amounts of it—albeit covered in crops—oneself.

In the early 1980s Robert did 3 SETI (Search for Extraterrestrial Intelligence) telescope searches, which landed him three publications in *Icarus*, a mainstream planetary sciences journal. The optical studies were the first of their kind in the Search for Extraterrestrial Artifacts (SETA), a term he originated in 1983. It should not be surprising that Freitas had no trouble finding his way into NASA, penning the first technical description of a self-replicating interstellar probe, which earned him an invitation to join the 1980 NASA study titled *Advanced Automation for Space Missions*, and later to serve as study Editor. This work culminated in a pioneering chapter-length engineering study of self-replicating factories. This might have been the point where Robert finally found his life calling: the research and development of molecular nanotechnology and its applications to medicine. These interests had to academically slumber for a little bit longer while Freitas published a financial newsletter to communicate the latest results of a complex econometric model of the economy and various investment classes (at some points these topics would come together as we will soon see).

Rob at 18, with his girlfriend Nancy, to whom he's now been married 48 years.

A self-identified late bloomer, his path was arguably more meandering than as the crow flies. But those who seek frequently do find. So too was the case for Freitas who recalls that pivotal moment of knowing in his professional career with great clarity: "Once I realized what nanotechnology was, it just went click. I realized, now *that* is something of magnitude. It's worth spending your life on."

Nanomedicine

Robert published his first Molecular Nanotechnology (MNT) article in *Analog* in 1996. This was a nontechnical article on nanorobots that only briefly touched on medical applications. His first true and rigorous treatment of the idea of nanomedicine was his 1998 paper on "respirocytes," or nanorobots designed to replace red blood cells, published in the journal *Artificial Cells, Blood Substitutes, and Immobilization Biotechnology*, it was titled "Exploratory Design in Medical Nanotechnology: A Mechanical Artificial Red Cell." It was also the first medical nanorobotics paper ever published in a peer-reviewed mainstream medical journal, and the first nanomedicine technical paper listed

in PubMed. In a shorter, accessible, exposition of the respirocyte for *Nanotechnology* magazine Robert writes:

> The artificial respirocyte is a hollow, spherical nanomedical device 1 micron in diameter. The respirocyte is built of 18 billion precisely arranged structural atoms, and holds an additional 9 billion molecules when it is fully loaded. Each main storage tank – one for oxygen, another for carbon dioxide, and a third for ballast water – is constructed of diamondoid honeycomb or a geodesic grid skeletal framework for maximum strength.

The article (and the corresponding paper) then provides a rigorous technical analysis of the requirements and design features of the artificial red blood cell. Respirocytes can carry 236 times as much oxygen to the tissues than natural red blood cells. Artificial red blood cells also have a superior shelf life, can produce superior treatment of anemia, support hypothermic organ preservation / stabilization, and can be administered in conditions where natural oxygen levels are low. Naturally, a human being enhanced with such artificial red blood cells would be more resistant to various ischemic insults and could even produce remarkable feats of personal endurance in sports.

Before delving further into the many applications of nanomedicine that Freitas pioneered, it will be helpful to provide a rigorous definition of "nanomedicine" that distinguishes it from other medical interventions that operate at the molecular level such as gene therapy, nanoscale materials, or the use of micro-electronics in the human body. As a practical application of molecular nanotechnology, nanomedicine concerns the manipulation of matter at the atomic level to treat patients. As further worked out in detail by Freitas in his numerous publications, this usually entails the use of mechanical molecular devices to either treat a specific medical condition or to replace natural human organs, cells, or physiological function altogether. The limits of such nanomedicine are ultimately set by the laws of physics. While many of the treatments that nanomedicine can produce might also be achieved through regular biotechnology, Freitas posits that with a mature mechanical nanotechnology "the range, efficacy, comfort and speed of possible medical treatments further expands enormously." Among the many advantages he lists in *Cryostasis Revival* (pp. 43-48) are the following:

1. Speed of Treatment
2. Control of Treatment
3. Verification of Treatment
4. Minimal Side Effects
5. Faster and More Precise Diagnosis
6. More Sensitive Response Threshold for High-Speed Action.
7. More Reliable Operation
8. Nonbiodegradable Treatment Agents
9. Superior Materials
10. No Replication

A central premise of an advanced nanomedicine is that the difference between disease and health (or even life and death) ultimately reflects the specific organization of molecules (or lack thereof). It should not be surprising then, that writers and scholars who pondered the implications of this kind of ultra-precise medicine recognized that it would profoundly change the way we think about phenomena such as aging or death. Freitas realized that the ability to heal tissue at the molecular level, in conjunction with some kind of low-temperature or chemical stabilization of people pronounced "dead" today, would allow their recovery and revival in the distant future. This idea was conceptually described by Eric Drexler in 1986 but was worked out in great detail by Freitas in his works.

Before Freitas took on the herculean task of thinking through all the conditions that are required to revive a cryopreserved human, he made several landmark contributions to the emerging field of nanomedicine including two book-length general treatments of nanomedicine (Volume I on "Basic Capabilities" and Volume IIA on "Biocompatibility"), and many dozens of technical articles, including comprehensive papers on the treatment of specific medical conditions and nearly a dozen scaling studies for different medical nanorobot designs (a complete list of Freitas's nanotechnology papers is provided with this profile). Technical expositions of other medical nanorobot devices include the microbivore (2005 – artificial white blood cell), the pharmacyte (2006 – a drug delivery vehicle), and the chromallocyte (2007), which constitutes the first technical description of a molecular cell repair device, which is of obvious and fundamental importance to rejuvenation and cryonics revival efforts. This was followed by a 120-page book chapter describing how medical nanorobots could eliminate and reverse aging via "Nanomedically Engineered Negligible Senescence" (2010), then a 433-page technical book proposing how nanorobots could reverse the effects of Alzheimer's disease (2016), and most recently the 700-page *Cryostasis Revival* (2022) that describes the first comprehensive conceptual protocol for revival from human cryopreservation, using medical nanorobots.

Robert's writings are not confined to the "what could a mature nanotechnology do" genre. He has been as prolific in executing theoretical research to make MNT and molecular manufacturing an actual physical reality. In 2004 he published a comprehensive technical book on self-replicating manufacturing systems titled *Kinematic Self-Replicating Machines*, and in 2006 he launched the Nanofactory Collaboration with Ralph Merkle, an early attempt to initiate a serious R&D effort to create the first nanofactory for atomically precise manufacturing. One major output of this effort was their "Minimal Toolset" paper, published in 2008, which provided the first theoretical quantitative systems level

study of a complete suite of reaction sequences for fabricating small atomically precise objects using scanning-probe based ultrahigh-vacuum diamond mechanosynthesis – work for which Robert received the Feynman Prize in Nanotechnology for Theory in 2009. Freitas's first patent, which was also the first patent ever issued on diamond mechanosynthesis, was granted in 2010. Collaborative work continued with quantum chemistry simulation papers examining the stability of various mechanosynthetic tooltips and small diamondoid structures up to ~1800 atoms in size, ideal approach trajectories and operating envelopes for mechanosynthetic tooltips, and theoretical analyses of atomically precise nanoscale computing systems.

Rob at Zyvex in 2002.
Note the nanorobotics designs behind him!

Cryonics

On September 19, 2018, I sent a curious email to Robert inquiring about his interest in writing the first technical paper on "cryobots", nanorobots that can operate at cryogenic temperatures. Intrigued, but pressed for time due to other important projects, he expressed some tentative interest. After some persistent nagging (which Freitas actually welcomed), the initial work for the paper started in March 2019 and writing commenced in August. In January 2020, the size of the "paper" had increased to 176 pages and it became increasingly clear that it was going to be a book-length exposition. A first draft of 841 pages (not a typo) was completed in March 2021. What started out as a modest technical exploration of the operation of nanorobots at ultra-low temperatures had culminated in the most comprehensive technical exposition on cryonics ever written. With support from the *Alcor Life Extension Foundation* and the *Biomedical Research and Longevity Society*, the book was released in an electronic edition and hardback format at Alcor's 50th Anniversary event in New York City on February 23, 2022.

Cryostasis Revival: The Recovery of Cryonics Patients Through Nanomedicine is not just a handbook on how to revive cryonics patients preserved under ideal conditions. It actively engages with the cryobiology and cerebral ischemia literature to outline technical revival options for people cryopreserved after prolonged postmortem delays and/or "straight freezing" (i.e., cryopreservation without cryoprotection). In fact, the foreword of the book was penned by Gregory M. Fahy, noted cryobiologist and pioneer of the use of vitrification in complex organ preservation. One of the attractive features of the book is that it does not impose one favored revival protocol but rather examines a plethora of approaches that have been proposed by human cryopreservation proponents over the years. The work also constitutes the first technical treatment of nanomedical reversal of aldehyde cross-linking, which also makes it relevant to the emerging technology of aldehyde-stabilized cryopreservation (ASC). The book concludes with no fewer than 304 research suggestions to further advance human cryopreservation revival science.

Robert first became enthralled by the concept of cryonics at the age of 14 after watching the famous *Star Trek* episode "Space Seed" that originally aired on February 16, 1967. In 1968 at the age of 15, Freitas wrote the first 55 pages of an unfinished science fiction novel about a teenager who volunteers to be placed in a time capsule and frozen using the new science of "cryobionics." In the novel, the computer-controlled facility was programmed to wake the traveler every century or so, whereupon he would emerge from a hidden high-tech mountain lair and explore first-hand the progress mankind had achieved during his frozen slumber. "Why do it?" the boy was asked. "Curiosity," he replied. "I want to see how man's technology will grow, and how man himself will change, through the years." Today, 54 years later, Freitas is still motivated by this same curiosity about the future but driven even more strongly by the desire to actually create that future – and most importantly, to directly experience it himself. Consequently, Robert became a whole-body member of *Alcor* in 2001. Asked how his personal cryonics arrangements impact his life plans or lifestyle, he answers:

> My Alcor arrangements allow me to feel free to devote my full energies to advancing medical nanotechnologies, secure in the knowledge that if the R&D doesn't go as fast as I hope, and as a result I don't succeed in preventing my own death due to aging or

disease, using medical nanorobots, I have a backup plan (cryonics) that will still get me to the future that I crave to experience.

He recognizes that he might be perceived as somewhat unusual by people close to him. "They accept my cryonics arrangements and are supportive, though they regard my choice (and me) as a bit strange."

Applications

In his book *Nano*, Ed Regis describes a phenomenon in the early nanotechnology community that was called the "Miller point," named after Mark Miller when he realized that a mature nanotechnology would change absolutely everything. To illustrate this point, we conclude this profile with some "strange" features but also profoundly transformative aspects of a society that has adopted MNT, pulled from Robert's extensive work, which includes 233 published items as of March 2022.

The Fine Spirits Synthesizer

> *"Somewhere in the bowels of the cabinet a bartender went into action – a non-human bartender whose electronic soul mixed things not by jiggers but by atom counts, whose ratios were perfect every time, and who could not be matched by all the inspired artistry of anyone merely human."*
>
> – Isaac Asimov, Pebble in the Sky (1950)

Picture yourself with a vintage bottle of Barolo. Held against the light, this Nebbiolo-based wine shows the classic brick color at the rim. Experience its typical tar-rose aroma with complex, fine flavors of red fruits, cedar, and white pepper. The greatest bottles of the greatest years cost a small fortune. The sheer complexity of aroma and taste and silky tannins would be hard to reproduce in a factory. Ultimately, though, as unromantic as this may sound, the greatest alcoholic beverages in the world are distinguished from others by specific concentrations of molecules. There have been several attempts by food scientists and chemists to recreate the classic alcoholic beverages based on chemical analysis of their contents. Such attempts have met with mixed reviews from connoisseurs, although the practice of artificial tinkering (synthetic coloring agents instead of the original herb that imparted the color, artificial flavors etc.) is widespread for mass-produced alcoholic beverages. However, a sufficiently mature molecular nanotechnology would be able to produce an exact molecular recipe from a small sample of the drink in question.

Enter the Freitas Fine Spirits Synthesizer, aka. "Whiskey Machine." ('The Whiskey Machine: Nanofactory-Based Replication of Fine Spirits and Other Alcohol-Based Beverages,' IMM Report No. 47, 2016). The Fine Spirits Synthesizer would be a commercial appliance composed of nanomachinery parts, built by a nanofactory. The Synthesizer incorporates an Assay Unit and a Synthesis Unit. After an exact molecular analysis by the Assay Unit, basic feedstock chemicals are mechanosynthetically combined to create the specific alcoholic beverage of choice by the Synthesis Unit with exact precision, without contaminants, at low cost. This beverage can be an extremely rare vintage or a carefully calibrated new composition by a seasoned drinker. Unlike today's "clumsy" attempts, such drinks will be flawless replicas of the original. One could imagine a point in time where, analogous to the Turing Test, such beverages will pass the, let's call it the "Bacchus Test" (a blind testing of atomically synthesized alcoholic beverages and their originals) and be indistinguishable from the "real" thing as judged by Master Sommeliers and Whiskey experts.

The ability of molecular manufacturing to produce exact replicas of originals has profound consequences for culture as we know it. In principle, it will then be possible to create an exact replica of Johannes Vermeer's "Girl with a Pearl Earring" (perhaps allowing for the different isotopic structure of the atoms – which is not something that affects its visual appearance). This feature of MNT will produce a radical democratization of ownership of unique historical works.

It's not all about top shelf booze and highbrow art either. There are other potential applications that may imbue an otherwise serious and technical subject with a sense of whimsy and fun. Freitas shares a vision of kinematic foods, inspired by the wiggling character of Jell-O, that could turn even the greatest broccoli opponent into a Brassica devotee. He says, "[The food] could walk around on their plate and lay down, or it could split in half, reassemble in a different shape. You could even conceivably talk to it, and it would hear your voice and do different things: turn red, turn blue, sprout its own legs and walk around. All kinds of crazy stuff that you can imagine." The best part? Parents rejoice! All that and it's still edible.

Tangible Nano money

On his website, economist and cryonics advocate Robin Hanson discusses an unfilled niche in economics which he calls the "economics of science fiction" or "economics of future technology." Another modern phrase would be "Singularity economics." Hanson describes the economics of science fiction as the:

> *"economic analysis of the sorts of assumptions typically explored in science fiction. It is distinguished from the typical hard science fiction analysis by using the tools of professional economics, rather than the intuitive social science of the typical engineer. And it is distinguished from most economics by taking seriously the idea that we can now envision the outlines of new technologies which may have dramatic impacts on our society."*

Tangible forms of money may be greatly affected by advanced

molecular technologies because it will enable individuals or organizations to duplicate money at low cost. As Freitas notes in his paper "Tangible Nanomoney," (2000) "any form of physical currency whose value depends solely upon the physical arrangement of common atoms" will fail to meet the traditional criteria that a physical currency needs to satisfy, such as possessing intrinsic value and immunity to counterfeiting. Although counterfeiting of money could remain illegal, the costs of enforcing this may be excessively high. As economist Tyler Cowen observes, "In the very long run, our monetary standard might be determined by what is least susceptible to counterfeiting or alchemy/nanotechnology."

As Freitas notes, a future currency "should be self-validating by its own physical form, and not rely upon any legalistic governmental imprimatur, easily altered surface stamping, or monopoly minting authority to partake of value (e.g., no "fiat" specie)." The most obvious alternative for a government-controlled fiat currency is a commodity-based currency. For such a commodity to be used as money it should be homogeneous, easy to subdivide, and have a high value to weight ratio. The most obvious candidate for such a currency is gold. In his paper, Robert Freitas further discusses ideal candidates for tangible nanomoney such as the superheavy elements (SHE), which could become a part of a new standard, if not part of the physical money itself in case the standard for such a currency and the currency itself would coincide. He also considers land to be a relatively safe investment in the nanofuture. In conversation, he notes that "while you can make more of it, it's not easy to do… because it's huge. You have to move a lot of volume." Clearly, a mature nanotechnology will have effects on both the standard for future money as well as the physical forms of payment that are used in daily economic life.

Atmospheric Carbon Capture and Green Computing

The (hypothesized) potential catastrophic effects of molecular nanotechnology (i.e., the grey goo problem, MNT-enabled weapons) have received substantial discussion. Less recognized is MNT's potential to make substantial, superior contributions to global problems such as pollution. As a more energy-efficient and precise technology, MNT can significantly reduce harm to the environment, even given the same (or even increasing) production. One application of MNT that could be a real "game changer" is its ability to substantially mitigate climate change. In his 2015 paper "The Nanofactory Solution to Global Climate Change: Atmospheric Carbon Capture" (IMM Report No. 45) Robert presents "a molecular manufacturing-based air-scrubbing system called a CO_2 capture plant that is potentially capable of active continuous management of the concentrations of relevant greenhouse gases in the atmosphere. The purpose of a global network of these plants is to maintain the specified greenhouse gas constituents at programmed concentrations that are regarded as ideal for human health, proper ecological maintenance, and human esthetics." Such systems of "molecular filters" or "nano filters" would be significantly more energy-efficient and cheaper than today's 1st generation carbon capture technologies. Detailed proposals for sequestration and storage of CO_2 are proposed but the author also speculates that the "Extracted and sequestered carbon may become a valuable resource in future decades, providing a compact cheap source of carbon to be used as a key building material in the fabrication of diamond-based consumer, commercial, and industrial products that can be manufactured in a worldwide nanofactory-based economy."

Today's microprocessors are almost at a point where circuits cannot get much smaller in size, which puts some hard limits on processing speeds. One potential way forward is through molecular nanotechnology. MNT makes possible a type of mechanical computer that could be 100 billion times more energy efficient than today's green supercomputers. In a paper co-authored with his frequent collaborator Ralph Merkle and others ("Mechanical Computing Systems Using Only Links and Rotary Joints", *Journal of Mechanisms and Robotics*, 2018) a new model for mechanical computing is presented that requires only two basic parts, links and rotary joints, "to create all necessary combinatorial and sequential logic required for a Turing-complete computational system."

From his initial dabbling in pyrotechnics, to his first detailed exposition of the field of xenology, to his pioneering theoretical work in molecular nanotechnology and its medical applications, culminating in novel solutions for precise manufacturing, computing, and even climate change, Robert Freitas has been a formidable force of technical rigor and creativity, whose influence will only be growing in the decades to come. The longevity community is grateful for his immense contributions to life extension and cryostasis research. ■

Rob smiling at Singularity University in 2011.

Nanomedicine, Nanorobotics, Nanofactories, Molecular Assemblers and Machine-Phase Nanotechnology Publications of Robert A. Freitas Jr.

A detailed up-to-date list with links to online abstracts, papers, books, and translations can be found here: https://www.rfreitas.com/NanoPubls.htm

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Revival of Cryonics Patients: Some Thoughts on Robustness of Memories

By R. Michael Perry, Ph.D.

Basic to the cryonics premise is the property that cryopreserved tissue would undergo very little change over substantial amounts of time stretching to centuries or more. This view is generally accepted by the scientific mainstream,[1] even though there is widespread skepticism that such preservation will eventually lead to the healthy revival of those who are so preserved.[2] The optimism of cryonicists regarding the prospects of revival depends on recognizing an information-theoretic criterion of death: death has not happened, and revival can occur in principle, so long as there is enough identity-critical information in the preserved remains that the basic personality elements can still be inferred.[3]

Of central importance in this thinking is the presence or absence of structures or configurations in the brain encoding memories that delineate the life experience of the patient. If these structures are well-enough preserved the memories can be recovered. Apart from memories there should be ample information (through DNA for instance) to reconstruct a functioning body for the preserved individual, or to assist as needed in the repair and restoration of the preserved, original body to a healthy functioning state, so the patient truly "comes back." Restoring the patient in his/her original, biological body, possibly with extensive repairs or replacement of missing parts (especially in the case of neuropatients) is but one possible approach to the problem of revival. Another consists of "uploading" where identity-critical information is transferred to an advanced computational device of the future. After suitable processing which could be very extensive but informed by advanced knowledge, the patient with personality elements restored would "wake up" as a kind of program running in a virtual reality. (This condition is known as "whole brain emulation" or WBE but an entire surrounding world and virtual body for the patient could also be emulated, along with others who would share this world.) In this way biological and other limitations might be completely bypassed and the revival setting itself might be optimized in ways difficult or impossible with the more straightforward revival in a standalone body. (Some might prefer the standalone body for philosophical or other reasons, even if the uploading scenario proves workable and reliable. In any case it would be good to have different options.)

In either case all relevant information that can be extracted from the remains or other sources would reasonably be utilized. (Or at any rate, an amount of information deemed sufficient for revival must be extracted.) It seems a safe bet that in any reasonable cryonics case the worst deficit the revived patient would suffer is some amount of amnesia regarding episodic memories, which in turn could be at least partly alleviated through use of information extraneous to the patient's remains such as written notes, photographs, historical records, and the like. A patient with even very poor preservation might thus emerge with the basic knowledge and skills they had before, including language proficiency, math and reading skills, motor skills and the like. They might also have considerable knowledge about themselves and others with whom they were acquainted, places they lived or attended school, jobs they had, organizations they were part of, and so on, all based on surviving information from one source or another.

Here the main focus will not be on how revival might be handled in the more compromised cases (including possibilities that go beyond the survival of relevant information in any form[18]). Instead, we explore the prospect that memory information will likely survive in the brain if the latter is not too damaged in passing from near clinical death to cryogenic temperature. The formation and storage of memories in the brain has been the focus of decades of intensive research yet much is still unknown.[19,20] Here we do not try to penetrate very far into this vast thicket of partially-understood complexity, but instead offer some basic, dimensional considerations that suggest that at least the storage of brain memories should be fairly robust.

Our starting point is the recently-completed, massively comprehensive study by Robert Freitas, *Cryostasis Revival*.[4] There he notes how in computer programs the information may be not at all robustly stored. "In computers, it is often possible that even a single flipped bit of data, if strategically located on a hard drive or in a software program, can produce disastrous consequences." However: "There is an argument that human long-term memory is vastly more robust than this." His argument starts with research in the 1980s to determine how much information a person can be expected to accumulate over a lifetime. (For completeness I include this material here though it largely repeats Freitas's own summary elsewhere in this issue.)

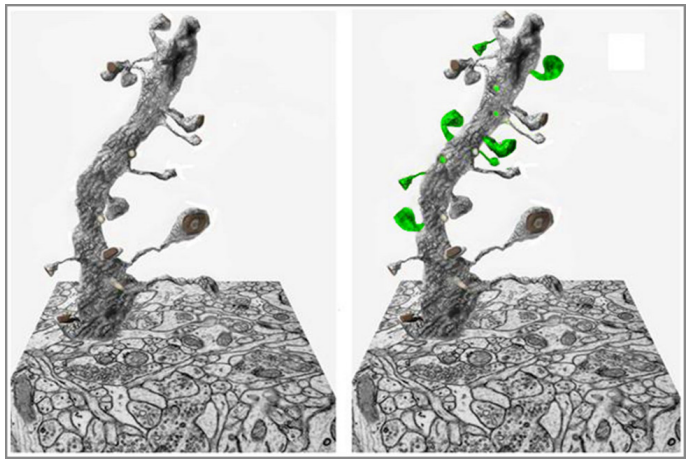
"In 1986, Thomas Landauer estimated that the average rate at which humans accumulate information into long-term

memory during the normal activities of life, such as reading text or exposure to visual images, approximates 1-2 bits/sec, asymptotically approaching a stable lifetime total (integrating memory gains with losses) of ~2 x 10^9 bits for adults.[5] This figure should be compared to the best current estimates of ~86 x 10^9 neurons in the average human brain,[6] ~2 x 10^{14} synapses in the adult human neocortex,[7] and ~10^6 protein molecules per synapse.[8] While neurons and their synapses clearly perform many tasks unrelated to long-term memory storage, it would appear that up to ~43 neurons, ~100,000 synapses, and ~10^{11} protein molecules may be associated with each single bit of experienced, recallable, usable human memory. If long-term memory is truly this super-redundant, then it seems highly unlikely that the random loss of a single neuron, or the random corruption or misrepair of thousands of synapses or millions of proteins, could flip the associated single bit from '1' to '0' and destroy the tiniest piece of memory. This apparent robustness of the structures embodying long-term memory is consistent with the observation that human long-term memory persists over periods of many decades despite a turnover rate of ~0.7%/hour for synaptic proteins – a half-life of only 2-5 days.[9] Such turnover means that every few days, roughly 1 out of every 20 proteins in every synapse is replaced with a new protein incorporating at least one random peptide sequencing error[10] – yet memory and personal identity persist, in many cases over a lifetime."

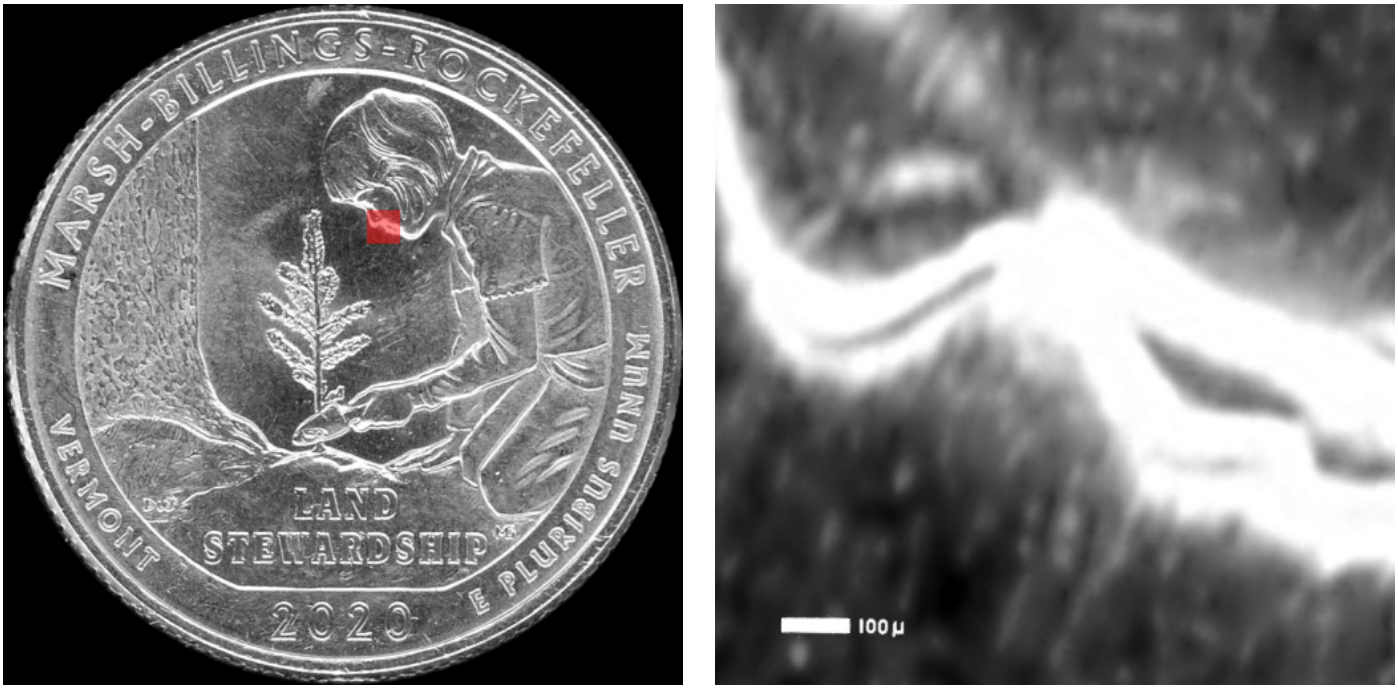
Some additional data about the human brain will lead to estimates of expected volume-per-bit on a micrometer, not nanometer scale. Weight of cortex: 1,233 g; number of cortical neurons: 16 billion; weight of cerebellum: 154 g; number of cerebellar neurons: 69 billion; density of brain tissue: about 1.045 g/cc.[11,12] From this we obtain in addition: volume of cortex: 1,180 cc; volume of cerebellum: 147 cc, total: 1,327 cc. Dividing the latter by the estimated 2 x10^9 bits for long-term memory in adults gives about 6.6 x 10^{-7} cc/bit or 660,000 cubic micrometers per bit, corresponding to a cube about 87 micrometers in height. (By comparison, the unaided human eye can see objects down to about 100 micrometers or 0.1 mm in size.[13]) This is what we would expect if the memory material were spread more-or-less uniformly over the entire total of cerebral cortex and cerebellum. Restricting to just the cerebral cortex would not change the cube height much (reducing it to 84 micrometers). As a more drastic restriction, suppose we assume that only .1% of the cerebral cortex or other brain volume stores all the 2 x 10^9 bits. This would reduce the cube height by an additional factor of 10 to 8.4 micrometers, still well above the nanometer size range of ultrastructural details in the brain, further reinforcing the impression of the robustness of long-term memories, whatever the details of how they are stored.

The brain in fact is a fantastic storage medium. One estimate pegs the total capacity of the cerebral cortex at about 74 TB or 600 trillion bits,[21] dwarfing the above estimated memory size by a factor of 300,000. However, I don't interpret this as indicating the actual human memory is much larger than the figure arrived at by Landauer. Instead, more likely the extra bits of the cortex (and presumably other areas that may store memory information such as the cerebellum), to the extent they are used at all, are put to use to strengthen the encoding of the relatively few bits that are actually stored.

In much the same way a printed page in a book uses the molecular details of ink particles, wood fibers and the like to reliably capture the relatively modest contents of the visible text, that is to say, a few hundred words or (at most) a few thousand bits. If the brain functions analogously it could account for both the relative modesty of the memory as found by Landauer, and its noted durability over time. If so, it could also work much in our favor for the revival of cryonics patients. In such a process it still may be necessary to do a full molecular scan of the preserved tissue, to best judge what particular bits in the memory are encoded, particularly when substantial damage occurred prior to cryopreservation. The information retrieval, on the other hand, would arguably be the principal step in the whole revival process, other details such as whether particular cells which are damaged by freezing can be restored to functioning being less important or insignificant.



Possible mechanism for storage of memories in the brain. Left: three-dimensional reconstruction of dendrite of rat brain hippocampus, isolated from the surrounding tissue block. The dendrite, in the image resembling a gnarled tree trunk, has branching, bulb-tipped processes called dendritic spines that connect to axons or other processes via synapses and also store information including, it is thought, long-term memories. Right: same dendrite with additional dendritic spines imaginatively added (green, "new growth") to illustrate expected appearance after storage of additional memory information. Height of dendrites is ~10 micrometers.[14-17]



Visualizing the microscale. Left: U. S. 25c piece of 2020, diameter 24,300µ or micrometers (also known as microns). Right: image shows enlargement of small detail highlighted in red in the left image, with scale bar indicating 100µ, which is about the limit of resolution of the human eye. According to the arguments presented here, the structures that encode bits of memory in the brain may be not much smaller than this, raising hopes that memories might be recoverable even from highly damaged neural tissue.

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Alcor Longevity Circle of Distinguished Donors

The Alcor Board of Directors is pleased to announce the formation of the **Alcor Longevity Circle of Distinguished Donors**. This new organization will honor those members and their foundations that have donated in excess of $100,000 over the past few years to support Alcor and its affiliated organizations. In addition to being recognized in Alcor publications and at conferences and other events, members will also be entitled to:

- Exclusive access and a quarterly conference call with Alcor Directors, officers, and officials to get in-depth briefings and ask questions and make suggestions.
- Special recognition, seating, and access to officials at Alcor conferences.
- An exclusive yearly, hosted in-person event honoring members with face-to-face interaction with Alcor Directors, officers, and officials.
- A unique, professionally designed and engraved memento of their membership.

These benefits are, of course, overshadowed by the immense gratitude members' and patients' families will always have for these especially generous individuals. New levels of membership (higher and lower levels of participation) may also be announced in the future. ■

Support Alcor's **RAPID** Research

Readiness **A**nd **P**rocedure **I**nnovation/**D**eployment **(RAPID)**

In order to advance the science and reputation of cryonics, Alcor plans to conduct ongoing research to develop novel and near-future products related to cryopreservation procedures and protocols. The RAPID team is developing relationships and contracts to procure recently deceased human cadavers, which are not Alcor members or patients, but are already earmarked for medical research. The idea is to procure one to two cadavers per month to conduct research. We would go on a "light standby" to enable fast access to cadavers.

The RAPID initiative will support cryonics research in multiple ways. Most immediately, it will help advance research into liquid ventilation – using a patient's lungs as a heat exchanger to induce very rapid hypothermia. Animal studies alone cannot take LV development to the next level due to different chest anatomy. LV research will include cooling rate control; chest compression studies; and timing and sensor feedback.

RAPID will also enable research comparing chemical fixation to cryoprotection and will support rewarming studies. Another benefit will be a great improvement in cryonics-specific surgical training. That includes raising and cannulating the carotids; cephalic isolation; raising and cannulating the femoral arteries; field neuro procedure training; median sternotomy training; and alternate surgical approaches.

Alcor is requesting donations through GoFundMe. All donors will receive quarterly reports from Alcor regarding the progress with fundraising and milestone achievements rising from the RAPID program! Please donate today to support Alcor's RAPID initiative. Alcor is a non-profit, federally tax-exempt, 501(c)(3) corporation and your donation may be tax deductible. ■

Donate here: https://charity.gofundme.com/o/en/campaign/rapid-research/alcorlifeextensionfo

For more information, see the presentation here: https://www.youtube.com/watch?v=BUaVcVMuFWQ&feature=youtu.be

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.

Epigenetic Age Acceleration Is Not Associated with Age-Related Macular Degeneration

January, 2022

Researchers here show that present epigenetic clocks perform poorly in the context of retinal aging and the dysfunction of age-related macular degeneration. Epigenetic age acceleration is the difference between epigenetic age as assessed by the clock algorithm and chronological age. In the more established clocks, a higher epigenetic age correlates with risk of mortality and many age-related conditions. It remains largely unknown as to how specific forms of age-related damage and dysfunction lead to specific epigenetic changes, however, and therefore poor performance in any given use case can only be discovered, not predicted in advance. This makes it a challenge to use epigenetic clocks in their most desired capacity, as a low-cost, fast alternative to life span studies in the assessment of potential rejuvenation therapies.

This is the first study to our knowledge formally evaluating whether epigenetic age acceleration (EAA) in Horvath-multi tissue, Hannum, and Skin and Blood epigenetic clocks is associated with age-related macular degeneration (AMD) and important risk factor covariates including smoking status. We sought to address whether EAA is observed in the retinal pigment epithelium (RPE), as it is a primary site of AMD pathogenesis, and in whole blood, as the epigenetic clocks have been widely applied and validated in blood-derived genomic DNA.

EAA was not observed in AMD. However, we observe positive EAA in blood of smokers, and in smokers with AMD. In the RPE, we observed a marked negative EAA across all groups with no significant differences in EAA between AMD and normal samples using all three clocks. This result cannot be characterised as true negative age acceleration because of poor performance of the epigenetic clocks in RPE. The consistent poor correlation of predicted DNAm age with chronological age observed in the RPE markedly improved when analysing whole blood-derived genomic DNA data, explained by the datasets used to train each respective epigenetic clock.

Reasonable performance of each respective epigenetic clock in whole blood strengthens the observation of no association of EAA with AMD in blood, though this remains open to further investigation in the RPE, which can be addressed using a bespoke RPE epigenetic clock with greater predictive accuracy. Construction of a tissue-specific RPE clock is necessary for future studies to capture the specific epigenetic ageing processes in the RPE.

Link: https://doi.org/10.3390/ijms222413457

Altos Labs Officially Launches with $3 Billion in Funding to Tackle In Vivo Reprogramming

January, 2022

Altos Labs was formed to develop in vivo reprogramming into a viable class of therapies to treat aging. Reprogramming occurs during embryonic development, and the discovery of the Yamanaka factors allows this process to be enacted in any cell. To date this has largely been used in the development of induced pluripotent stem cells, a source of cells for research and therapy. The other effects of reprogramming are coming to be just as interesting, however: a resetting of the epigenetic marks characteristic of cells in old tissues, and a restoration of mitochondrial function. Studies in mice show that partial reprogramming, reversing epigenetic aging while not converting cells into stem cells, produces benefits. Can this be made safe enough for use in humans? Therein lies the question.

As the launch announcement indicates, Altos Labs is shaping up to be a sizable project, populated by luminaries from academia and industry. It may have more committed funding at this point than the whole of the rest of the nascent longevity industry. It is likely an interesting story, yet to be told, as to how exactly in vivo reprogramming, of all of the possible approaches to the treatment of aging, gained so much support among high net worth individuals interested in aging as a field of development. If these funds are spent well, the next decade will see all of the immediate questions answered regarding the use of in vivo reprogramming as a therapy.

The present big picture understanding of reprogramming is an interesting one. It may be the case that cycles of DNA damage and repair lead, via the usual indirect routes of cellular biochemistry, to much of the characteristic epigenetic change that occurs with age. In which case resetting those epigenetic marks is indeed a form of repair and rejuvenation, of a similar scope as senolytic therapies that remove senescent cells and their negative impact on metabolism. Reprogramming cannot repair DNA damage, it cannot do much for accumulations of metabolic waste that even young cells cannot break down, such as persistent cross-links and lysosomal aggregates. But it may well achieve enough to be worth the effort to develop a safe implementation for human medicine.

Altos Labs launches with the goal to transform medicine through cellular rejuvenation programming

Altos Labs (Altos) launched today as a new biotechnology company dedicated to unraveling the deep biology of cellular rejuvenation programming. Altos' mission is to restore cell health and resilience to reverse disease, injury, and the disabilities that can occur throughout life. The company launches with a community of leading scientists, clinicians, and leaders from both academia and industry working together towards this common mission. Altos launches with $3B fully committed from renowned company builders and investors.

The Altos executive team will be composed of Hal Barron, MD (incoming CEO), Rick Klausner, MD (Chief Scientist and Founder), Hans Bishop (President and Founder), and Ann Lee-Karlon, PhD (Chief Operating Officer). Hal Barron is currently President of R&D and Chief Scientific Officer at GSK and will join Altos as CEO and Board co-chair effective August 1, 2022. Klausner was former director of the National Cancer Institute and entrepreneur, Bishop was former CEO of GRAIL and Juno Therapeutics, and Lee-Karlon was former Senior Vice President at Genentech.

Altos will be initially based in the US in the San Francisco Bay Area and San Diego, and in the UK in Cambridge. The company will also have significant collaborations in Japan. Set within these geographies, activity will be organized across the Institutes of Science and the Institute of Medicine. The Altos Institutes of Science will pursue deep scientific questions and integrate their findings into one collaborative research effort. The Altos Institute of Medicine will capture knowledge generated about cell health and programming to develop transformative medicines.

"Altos seeks to decipher the pathways of cellular rejuvenation programming to create a completely new approach to medicine, one based on the emerging concepts of cellular health. Remarkable work over the last few years beginning to quantify cellular health and the mechanisms behind that, coupled with the ability to effectively and safely reprogram cells and tissues via rejuvenation pathways, opens this new vista into the medicine of the future. Altos begins with many of the leading scientists who are creating this new science. Together, we are building a company where many of the world's best scientists can collaborate internally and externally and develop their research with the speed, mission, and focus of private enterprise. Our success will depend upon a culture of intense collaboration, enthusiasm, and openness."

Does NAD+ In Fact Decline With Age Sufficiently to be a Useful Target for Interventions?

January, 2022

Nicotinamide adenine dinucleotide (NAD) is an important part of the mechanisms by which mitochondria produce chemical energy-storing molecules to power cellular processes. NAD levels fall with age, concurrent with growing mitochondrial dysfunction. There is some enthusiasm for approaches - such as supplementation with vitamin B3 derivatives - that might compensate for this issue and thereby improve mitochondrial function in later life.

Researchers here suggest that in fact the quality and quantity of evidence for NAD+ levels to decline with age doesn't rise to the level that the scientific community should be using as a basis to proceed towards the development of interventions. I think it most likely that more rigorous work will confirm the existing evidence. More pertinent objections to sizable investment in NAD upregulation are that (a) exercise increases NAD levels to a greater degree than any of the other approaches assessed to date, and (b) the results of clinical trials of NAD upregulation are decidedly mediocre.

Nicotinamide adenine dinucleotide (NAD+) is an essential molecule involved in various metabolic reactions, acting as an electron donor in the electron transport chain and as a co-factor for NAD+-dependent enzymes. In the early 2000s, reports that NAD+ declines with aging introduced the notion that NAD+

metabolism is globally and progressively impaired with age. Since then, NAD+ became an attractive target for potential pharmacological therapies aiming to increase NAD+ levels to promote vitality and protect against age-related diseases.

This review summarizes and discusses a collection of studies that report the levels of NAD+ with aging in different species (i.e., yeast, C. elegans, rat, mouse, monkey, and human), to determine whether the notion that overall NAD+ levels decrease with aging stands true. We find that, despite systematic claims of overall changes in NAD+ levels with aging, the evidence to support such claims is very limited and often restricted to a single tissue or cell type. This is particularly true in humans, where the development of NAD+ levels during aging is still poorly characterized. There is a need for much larger, preferably longitudinal, studies to assess how NAD+ levels develop with aging in various tissues. This will strengthen our conclusions on NAD metabolism during aging and should provide a foundation for better pharmacological targeting of relevant tissues.

Link: https://doi.org/10.3390/nu14010101

More Funding for the Dog Aging Project

January, 2022

There is a growing enthusiasm for aging research and the development of interventions aimed at slowing or reversing aging. This has reached the point at which people with significant resources are becoming involved, and thus the more prominent projects in the research and development communities are gaining support that would have been hard to find just a few short years ago. This new funding for the Dog Aging Project is a good example of the growing level of support for work on aging, undertaken by people who have bought into the vision of a future in which medical technology allows for much longer, healthier lives for all.

The Dog Aging Project, a scientific initiative to help companion dogs and people live longer, healthier lives together, has received a $2.5 million pledge from a consortium of tech entrepreneurs. The Dog Aging Project brings together a community of dogs, owners, veterinarians, researchers, and volunteers to carry out the largest canine health study in the world. The donation will expand this research into longevity science. The donors include Brian Armstrong, Coinbase founder and CEO; Peter Attia, physician; Juan Benet, Protocol Labs founder and CEO; Fred Erhsam, co-founder of Paradigm and Coinbase; Adam Fisher of Bessemer Venture Partners; author Tim Ferriss and the Saisei Foundation; Jed McCaleb, Stellar co-founder and CTO and founder of the Astera Institute; and food author Darya Rose and internet entrepreneur Kevin Rose.

The Dog Aging Project has two fundamental goals: first, to understand how genes, lifestyle, and environment influence aging; and second, to intervene to increase healthspan, the period of life spent free from disease. Discoveries made by the Dog Aging Project could be translatable to people. More than 32,000 companion dogs and their owners are already part of the Dog Aging Project. All the dogs live and play at home with their families. Most of these dogs participate in the observational Longitudinal Study of Aging. Each dog owner completes extensive surveys about the health and life experience of their dog through a secure research portal. This information is paired with comprehensive environmental, genetic, and biochemical data to yield insights about aging.

In addition, the Dog Aging Project is conducting a double-blind, placebo controlled, veterinary clinical trial of the medicine rapamycin, which at low doses has been shown to extend lifespan in laboratory animals. The trial is called TRIAD, an acronym for Test of Rapamycin in Aging Dogs. The $2.5 million in new funding provided by the consortium of donors will go directly to scientific research. This support will allow the Dog Aging Project to expand the TRIAD Trial to include more study locations and to increase the number of dogs enrolled in TRIAD.

Link: https://newsroom.uw.edu/news/tech-entrepreneurs-pledge-25-million-dog-aging-project

Two Years of Calorie Restriction Produces Thymic Regrowth in Humans

February, 2022

The thymus is responsible for turning thymocytes produced in the bone marrow into T cells of the adaptive immune system, in a complicated process of selection. This system is highly productive in youth, but active thymic tissue atrophies with age. This occurs for reasons that are far from fully explored, but may involve complex systemic issues related to rising inflammation and ongoing exposure to pathogens. As the thymus atrophies, the supply of T cells diminishes, and this loss of reinforcements is one of the major causes of immune aging. The T cell component becomes ever more full of exhausted, damaged, misconfigured, and senescent cells.

In this context, the following research materials are very interesting indeed. The authors report on their demonstration that a couple of years of mild calorie restriction in humans (a 14% reduction in calorie intake) can produce regrowth of the atrophied thymus. A very striking cross-sectional MRI image is provided in the publicity materials. The researchers go into some detail as to which of the countless metabolic changes produced in response to a reduced calorie intake are responsible for these effects. They point to PLA2G7 downregulation, which may be a target for future therapies to mimic this outcome. That

PA2G7 downregulation suppresses inflammation is a point of support for inflammation-centric hypotheses of age-related thymic atrophy.

The study includes imaging and metrics for the thymus, but looks to be light on important details regarding the T cell output of the thymus and related immune system parameters. Unfortunately, this is par for the course in studies of thymus regrowth and resulting restoration of more youthful T cell production. Researchers either measure the size and structure of the thymus, or the relevant immune system parameters, and almost never both of these items in the same study.

Calorie restriction trial reveals key factors in extending human health

New research is based on results from the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) clinical trial, the first controlled study of calorie restriction in healthy humans. For the trial, researchers first established baseline calorie intake among more than 200 study participants. The researchers then asked a share of those participants to reduce their calorie intake by 14% while the rest continued to eat as usual, and analyzed the long-term health effects of calorie restriction over the next two years.

The team started by analyzing the thymus, a gland that sits above the heart and produces T cells, a type of white blood cell and an essential part of the immune system. The thymus ages at a faster rate than other organs. By the time healthy adults reach the age of 40, 70% of the thymus is already fatty and nonfunctional. And as it ages, the thymus produces fewer T cells.

The research team used magnetic resonance imaging (MRI) to determine if there were functional differences between the thymus glands of those who were restricting calories and those who were not. They found that the thymus glands in participants with limited calorie intake had less fat and greater functional volume after two years of calorie restriction, meaning they were producing more T cells than they were at the start of the study. But participants who weren't restricting their calories had no change in functional volume.

The researchers then honed in on the gene for PLA2G7, which was one of the genes significantly inhibited following calorie restriction. PLA2G7 is a protein produced by immune cells known as macrophages. This change in PLA2G7 gene expression observed in participants who were limiting their calorie intake suggested the protein might be linked to the effects of calorie restriction. To better understand if PLA2G7 caused some of the effects observed with calorie restriction, the researchers also tracked what happened when the protein was reduced in mice in a laboratory experiment.

Reducing PLA2G7 in mice yielded benefits that were similar to what we saw with calorie restriction in humans. Specifically, the thymus glands of these mice were functional for a longer time, the mice were protected from diet-induced weight gain, and they were protected from age-related inflammation. These effects occurred because PLA2G7 targets a specific mechanism of inflammation called the NLRP3 inflammasome. Lowering PLA2G7 protected aged mice from inflammation.

Link: https://news.yale.edu/2022/02/10/calorie-restriction-trial-reveals-key-factors-enhancing-human-health

Caloric restriction in humans reveals immunometabolic regulators of health span

The extension of life span driven by 40% caloric restriction (CR) in rodents causes trade-offs in growth, reproduction, and immune defense that make it difficult to identify therapeutically relevant CR-mimetic targets. We report that about 14% CR for 2 years in healthy humans improved thymopoiesis and was correlated with mobilization of intrathymic ectopic lipid. CR-induced transcriptional reprogramming in adipose tissue implicated pathways regulating mitochondrial bioenergetics, anti-inflammatory responses, and longevity. Expression of the gene Pla2g7 is inhibited in humans undergoing CR. Deletion of Pla2g7 in mice showed decreased thymic lipoatrophy, protection against age-related inflammation, lowered NLRP3 inflammasome activation, and improved metabolic health. Therefore, the reduction of PLA2G7 may mediate the immunometabolic effects of CR and could potentially be harnessed to lower inflammation and extend the health span.

Link: https://www.science.org/doi/10.1126/science.abg7292

A Hypothetical Project: the Fast Track to Partial Reprogramming in Human Volunteers

February, 2022

In the recent past, I have suggested that it is practical and useful for small organizations to run low-cost clinical trials in large numbers in order to build physician support for treatments for aging that should, by rights, already be in the clinic. The senolytic treatment of dasatinib and quercetin is the most obvious candidate, given its low cost, availability for off-label use, broad, large, and reliable benefits in animal models of aging and age-related disease, and human evidence for efficacy in clearing senescent cells to a similar degree as it does in mice.

Today I'll propose a different angle on early, small trials. In this case the goal is to fast-track access for human volunteers to whole-body partial reprogramming. In partial reprogramming, cells are exposed to Yamanaka factors for a limited time, long enough to reset epigenetic marks to a youthful configuration, but (hopefully!) not long enough for any significant number of cells

to lose their differentiated state and become induced pluripotent stem cells capable of forming tumors. In mice, a variety of gene therapy approaches have been used to introduce expression of reprogramming factors, and in the short term the benefits appear interesting enough to follow.

As long-term readers might recall, I've long been dismissive of attempts to adjust epigenetic changes characteristic of aging, as (a) these changes were, in my eyes, a long way downstream from root causes, and (b) the research community was likely to try to make these changes one at a time, with limited individual benefit resulting from any given intervention. What changed my mind on this was the discovery that cycles of DNA damage and repair cause characteristic age-related epigenetic changes. That work needs expansion and replication, but it places some sizable fraction of epigenetic change very much closer to the root causes of aging than previously thought, and makes reversal of those changes a good point of intervention if there is a cost-effective way of doing it. Which there is, in principle, in the form of partial reprogramming.

A great deal of funding is now devoted to the matter of developing partial reprogramming into therapies. NewLimit will be much more nimble than the behemoth that Altos Labs has become, and Turn.bio nimbler still, but I'd still expect a decade to pass between where we are now and the first partial reprogramming therapies becoming available in the clinic in any meaningful sense. These entities will conduct a significant amount of preclinical research, and will be following the standard regulatory playbook thereafter. That takes a long time. Even then, there is a strong chance that the first therapies will be very cautious implementations, such as by being limited to the treatment of retinal diseases and only introduced into the eye.

As an alternative, I believe it would be feasible for a smaller, more agile, directed group to put together a gene therapy for most-of-the-body expression of reprogramming factors and administer it in a small trial of volunteers outside the US, accomplishing that goal in two years or so. The important challenges in reaching that milestone in just a few short years, likely consuming most of that time, are people matters rather than technical matters.

A good approach for a gene therapy capable of only short-term expression appropriate to partial reprogramming would be lipid nanoparticles (LNPs) carrying mRNA encoding the Yamanaka factors, to be injected intravenously in initially low and then ascending doses in human volunteers. The LNPs would be one of the later generation of low immunogenicity variants, while the mRNA would be optimized to reduce immunogenicity in the ways that are presently standard practice in the industry. These are existing technologies, a known sequence for expression of the reprogramming factors, and a matter of running a simple but multi-step manufacturing process that involves two distinct companies and some shipping back and forth.

This gene therapy really doesn't have to be produced using highly expensive, slow Good Manufacturing Practices (GMP) methods in order to be reasonably safe. While some medical technologies do require great care in their manufacture, in this case low-cost research grade materials will do just fine. To ensure correct manufacture at reasonable cost, one runs a quality control study for each batch in cell cultures and in mice, looking for expression of proteins, LNP size, correct sequence of mRNA, and a few other items. That data should be enough to convince anyone that the result is as expected. When injecting into humans, doses should start very low in order to assuage concerns about unexpected immunogenicity.

From a technical perspective, good options for manufacturing of the LNPs are Entos Pharmaceuticals and Acuitas Therapeutics, given what is known of the biodistribution (e.g. not passing the blood-brain barrier, so excluding brain tissue from reprogramming) and safety profiles of their products. For the mRNA there are more companies on the table, but TriLink Biotech is the leading manufacturer, owning some important process patents. The first people matter is to convince the LNP and mRNA companies to act as hands-off manufacturers for a group intending to perform human trials with research grade materials, likely outside the US. There will probably be reputational concerns amongst the leadership of companies that must work closely with the FDA.

All of the other people matters revolve around regulatory approval to perform these trials: which jurisdictions, how the regulatory bodies work in those regions, finding willing clinic owners, and so forth. The Bahamas is a favorable location for a number of groups that are presently setting up clinics for potential anti-aging therapies and would likely be interested in enabling a fast track to partial reprogramming trials. That said, given the good relationship between Bahamas regulators and the FDA I suspect they would require some form of GMP or GMP-like manufacture, significantly increasing costs.

Healthy volunteers in middle age would be a better choice at the outset of this project than those who are very old or very ill, as they will be more resilient in the case of, for example, unexpected immunogenicity. When looking for efficacy, outcomes to measure include epigenetic age, all the omics data that is shown to be rejuvenated by partial reprogramming in mice, and physical function: kidney and liver function, immune function, blood pressure, aerobic capacity, and so forth. The most important question is that of cancer risk, and regardless of how much is spent on clinical trials, or whether they are conducted by large or small organizations, that data will only emerge many years later.

Conducting this project seems to me largely an exercise in organization and finding the funding, with no major technical roadblocks. The big unknown, cancer risk, will remain a big unknown for a long time yet.

Comment by Aubrey de Grey

First let me say that David's insight concerning the epigenetic consequences of cycles of DNA repair is very smart and almost certainly correct... qualitatively. However, when it comes to the magnitude of the effect, I am hesitant about the extrapolation to humans from David's findings in yeast. I know he is assiduously working to answer that question.

But that's not actually what I want to focus on here, because (as is my wont) I am more interested in how to fix damage than in how it arises.

The main thing that makes me skeptical about partial reprogramming as a useful modality for human rejuvenation is its risk of tumorigenesis. It is well known that tumour cells typically have a more "undifferentiated" gene expression profile than the cells from which they arose, which says that dedifferentiation can in some circumstances be tumorigenic. But of course the Yamanaka factors are precisely what naturally turn gametes into a zygote and beyond, i.e. not into tumours, so there must be ways around that risk. But... can indiscriminate application of those factors to an adult get around it? My main concern here is telomerase, which:

– is turned on by the Yamanaka factors

– is (as was shown decades ago by Shay and Wright) typically the LAST thing to change during tumorigenesis (simply because basically everything else that needs to change entails INactivating a gene, which mutationally is far easier)

– is necessary (unless ALT happens) for a tumour to become big enough to be clinically detectable, let alone metastatic

– is typically turned on in cancers by an accumulation of epigenetic changes to its promoter region, rather than by a single mutation, hence is statistically sure to be nearly turned on in a great many not-yet-full-blown-tumour cells before it gets properly turned on in any such cell.

Thus, until such time as we have cancer totally licked (and here, as usual, I will highlight the amazing drug 6-thiodG, which was also discovered by Shay and is being taken forward by MAIA - look it/them up), I strongly believe that any partial reprogramming approach that can potentially activate telomerase must be very painstakingly accompanied by the absolute best possible technology for early detection of cancer, such as high-sensitivity detection of circulating tumour cells. Even then there is a big risk, because shedding of cells by the primary tumour may often NOT precede telomerase activation (the Shay/Wright study only looked at the primary tumour).

So I'm strongly in favour of the exploration of dedifferentiation factors that (even when expressed constitutively) take cells less far back: that make them more regenerative but do not activate telomerase. Full disclosure – as is well known, I worked for some time at AgeX, which is looking at exactly that – but I have no financial stake there.

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

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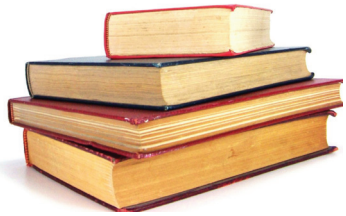

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Revival Update

Scientific Developments Supporting Revival Technologies

Reported by R. Michael Perry, Ph.D.

Asymptotically Good Quantum and Locally Testable Classical LDPC Codes

Pavel Panteleev, Gleb Kalachev

https://arxiv.org/abs/2111.03654, 21 Jan. 2022 (latest version), accessed 1 Feb 2022.

Abstract

We study classical and quantum LDPC codes of constant rate obtained by the lifted product construction over non-abelian groups. We show that the obtained families of quantum LDPC codes are asymptotically good, which proves the qLDPC conjecture. Moreover, we show that the produced classical LDPC codes are also asymptotically good and locally testable with constant query and soundness parameters, which proves a well-known conjecture in the field of locally testable codes.

From: Qubits Can Be as Safe as Bits, Researchers Show

Mordechai Rorvig, *Quanta* Magazine, 06 Jan 2022, https://www.quantamagazine.org/qubits-can-be-as-safe-as-bits-researchers-show-20220106/, accessed 1 Feb. 2022.

Over the centuries, we have learned to put information into increasingly durable and useful form, from stone tablets to paper to digital media. Beginning in the 1980s, researchers began theorizing about how to store the information inside a quantum computer, where it is subject to all sorts of atomic-scale errors. By the 1990s they had found a few methods, but these methods fell short of their rivals from classical (regular) computers, which provided an incredible combination of reliability and efficiency.

Now, in a preprint posted on November 5, Pavel Panteleev and Gleb Kalachev of Moscow State University have shown that – at least, in theory – quantum information can be protected from errors just as well as classical information can. They did it by combining two exceptionally compatible classical methods and inventing new techniques to prove their properties.

"It's a huge achievement by Pavel and Gleb," said Jens Eberhardt of the University of Wuppertal in Germany.

Today, quantum computers can use only around 100 qubits, the quantum equivalent of classical bits. They will need thousands or millions more to become truly useful. The new method for quantum data maintains constant performance as the number of qubits scales up, so it should help keep the size and complexity of future quantum computers to a minimum.

The authors also showed how their quantum method could play a long-sought after role in making classical information testable for errors – at the same time that another group discovered the same capability in a classical method. "It is amazing how a problem that was open for 30 years was solved essentially at the same time by two different groups," said Alex Lubotzky of the Weizmann Institute of Science in Israel.

University of Maryland School of Medicine Faculty Scientists and Clinicians Perform Historic First Successful Transplant of Porcine Heart into Adult Human with End-Stage Heart Disease

Debora Kotz, University of Maryland School of Medicine, 10 Jan 2022, https://www.medschool.umaryland.edu/news/2022/, accessed 1 Feb 2022.

Opening Paragraph

In a first-of-its-kind surgery, a 57-year-old patient with terminal heart disease received a successful transplant of a genetically-modified pig heart and is still doing well three days later. It was the only currently available option for the patient. The historic surgery was conducted by University of Maryland School of Medicine (UMSOM) faculty at the University of Maryland Medical Center (UMMC), together known as the University of Maryland Medicine.

From: Surgeons Transplant Pig's Heart into Dying Human Patient in a First

Tom Metcalfe, *LiveScience*, 11 Jan 2022, https://www.livescience.com/first-pig-heart-transplant-to-human, accessed 1 Feb 2022.

Doctors have transplanted the heart from a genetically modified pig into the chest of a man from Maryland in a last-ditch effort

to save his life. The first-of-its-kind surgery is being hailed as a major step forward in the decades-long effort to successfully transplant animal organs into humans.

Although it's been tried before – one of the earliest subjects, known as Baby Fae, survived 21 days with a baboon's heart in 1984, according to Time – the practice has fallen into disuse because the animal organs are usually quickly rejected by their human host.

But doctors say this new transplant is a breakthrough because the donor pig had undergone gene-editing to remove a specific type of sugar from its cells that's thought to be responsible for previous organ rejections in patients.

The recipient of the pig's heart transplant, 57-year-old Maryland handyman David Bennett, was ineligible for a transplant from a human donor.

Bartley P. Griffith, MD and patient, David Bennett
Photo: University of Maryland School of Medicine

The transplant heart was surgically removed from the donor pig before the surgery on the human patient; pig organs are considered suitable for transplant to humans because they are about the same size and shape.

The surgery to transplant a heart from a genetically-modified pig into a human patient was carried out at the University of Maryland Medical Center four days ago. So far the patient is doing well.

The method of genetically modifying the pigs' organs so they are less likely to be rejected by the human immune system has been pioneered by Muhammad Mohiuddin, a professor of surgery at the University of Maryland School of Medicine.

The donor pig underwent gene editing to "knock out" three genes that could trigger an immune system response in humans, and six human genes to aid its acceptance by a human patient were added.

The surgery took place on Friday (Jan. 7), and after four days the human patient is breathing on his own, although he is still connected to a heart-lung machine to strengthen his blood circulation, according to a statement from the University of Maryland Medical Center (UMMC). The next days and weeks will be critical to whether he survives the operation.

The man, 57-year-old David Bennett from Maryland, has terminal heart disease, but several medical centers had determined that he was ineligible for a human transplant, the statement said.

"It was either die or do this transplant. I want to live. I know it's a shot in the dark but it's my last choice," Bennett said the day before his surgery. "I look forward to getting out of bed after I recover."

From: In Memoriam: David Bennett

Unattributed, University of Maryland Medical Center, 9 March, 2022, https://www.umms.org/ummc/news/2022/in-memoriam-david-bennett, accessed 16 May 2022.

David Bennett, the 57-year old patient with terminal heart disease who made history as the first person to receive a genetically modified pig's heart, passed away yesterday afternoon on March 8. Mr. Bennett received the transplant on January 7 and lived for two months following the surgery. His condition began deteriorating several days ago. After it became clear that he would not recover, he was given compassionate palliative care. He was able to communicate with his family during his final hours.

"We are devastated by the loss of Mr. Bennett. He proved to be a brave and noble patient who fought all the way to the end. We extend our sincerest condolences to his family," said Bartley P. Griffith, MD, who surgically transplanted the pig heart into the patient at the University of Maryland Medical Center (UMMC). … "Mr. Bennett became known by millions of people around the world for his courage and steadfast will to live." … Muhammad M. Mohiuddin, MD, Professor of Surgery and Scientific Director of the Cardiac Xenotransplantation Program at UMSOM, added: "We are grateful to Mr. Bennett for his unique and historic role in helping to contribute to a vast array of knowledge to the field of xenotransplantation."

Mr. Bennett first came to UMMC as a patient in October 2021, where he was bedridden and placed on a heart-lung bypass

machine, called extracorporeal membrane oxygenation (ECMO), to remain alive. He was deemed ineligible for a conventional heart transplant. Before consenting to receive the transplant, Mr. Bennett was fully informed of the procedure's risks, and that the procedure was experimental with unknown risks and benefits. On December 31, the US Food and Drug Administration granted an emergency authorization for the surgery in the hope of saving his life.

Following surgery, the transplanted heart performed very well for several weeks without any signs of rejection. The patient was able to spend time with his family and participate in physical therapy to help regain strength. He watched the Super Bowl with his physical therapist and spoke often about wanting to get home to his dog Lucky.

"We have gained invaluable insights learning that the genetically modified pig heart can function well within the human body while the immune system is adequately suppressed," said Dr. Mohiuddin. "We remain optimistic and plan on continuing our work in future clinical trials."

Acute multidrug delivery via a wearable bioreactor facilitates long-term limb regeneration and functional recovery in adult Xenopus laevis

Nirosha J. Murugan, Hannah J. Vigran, Kelsie A. Miller, Annie Golding, Quang L. Pham, Megan M. Sperry, Cody Rasmussen-Ivey, Anna W. Kane, David L. Kaplan, Michael Levin

SCIENCE ADVANCES • 26 Jan 2022 • Vol 8, Issue 4 • DOI: 10.1126/sciadv.abj2164, https://www.science.org/doi/10.1126/sciadv.abj2164, accessed 1 Feb 2022.

Abstract

Limb regeneration is a frontier in biomedical science. Identifying triggers of innate morphogenetic responses in vivo to induce the growth of healthy patterned tissue would address the needs of millions of patients, from diabetics to victims of trauma. Organisms such as Xenopus laevis – whose limited regenerative capacities in adulthood mirror those of humans – are important models with which to test interventions that can restore form and function. Here, we demonstrate long-term (18 months) regrowth, marked tissue repatterning, and functional restoration of an amputated X. laevis hindlimb following a 24-hour exposure to a multidrug, pro-regenerative treatment delivered by a wearable bioreactor. Regenerated tissues composed of skin, bone, vasculature, and nerves significantly exceeded the complexity and sensorimotor capacities of untreated and control animals' hypomorphic spikes. RNA sequencing of early tissue buds revealed activation of developmental pathways such as Wnt/β-catenin, TGF-β, hedgehog, and Notch. These data demonstrate the successful "kickstarting" of endogenous regenerative pathways in a vertebrate model.

From: Scientists Regrow Frog's Lost Leg

Mike Silver, TuftsNow, 26 Jan 2022, https://now.tufts.edu/articles/scientists-regrow-frog-s-lost-leg, accessed 1 Feb 2022.

A normal African clawed frog.
Photo: Pouzin Olivier, via Creative Commons

For millions of patients who have lost limbs for reasons ranging from diabetes to trauma, the possibility of regaining function through natural regeneration remains out of reach. Regrowth of legs and arms is the province of salamanders and superheroes.

But in a study published in the journal *Science Advances*, scientists at Tufts and Harvard University's Wyss Institute have brought us a step closer to the goal of regenerative medicine.

On adult frogs [the African clawed frog, *Xenopus laevis*], which are naturally unable to regenerate limbs, the researchers were able to trigger regrowth of a lost leg using a five-drug cocktail applied in a silicone wearable bioreactor dome that seals in the elixir over the stump for just 24 hours. That brief treatment sets in motion an 18-month period of regrowth that restores a functional leg.

Many creatures have the capability of full regeneration of at least some limbs, including salamanders, starfish, crabs, and lizards. Flatworms can even be cut up into pieces, with each piece reconstructing an entire organism. Humans are capable of closing wounds with new tissue growth, and our livers have a remarkable, almost flatworm-like capability of regenerating to full size after a 50% loss.

But loss of a large and structurally complex limb – an arm or leg – cannot be restored by any natural process of regeneration in humans or mammals. In fact, we tend to cover major injuries with an amorphous mass of scar tissue, protecting it from further

blood loss and infection and preventing further growth.

"Using the BioDome cap in the first 24 hours helps mimic an amniotic-like environment which, along with the right drugs, allows the rebuilding process to proceed without the interference of scar tissue," said David Kaplan.

Each drug fulfilled a different purpose, including tamping down inflammation, inhibiting the production of collagen which would lead to scarring, and encouraging the new growth of nerve fibers, blood vessels, and muscle. The combination and the bioreactor provided a local environment and signals that tipped the scales away from the natural tendency to close off the stump, and toward the regenerative process.

The researchers observed dramatic growth of tissue in many of the treated frogs, re-creating an almost fully functional leg. The new limbs had bone structure extended with features similar to a natural limb's bone structure, a richer complement of internal tissues, including neurons, and several "toes" grew from the end of the limb, although without the support of underlying bone.

An Autonomous Chemically Fueled Artificial Protein Muscle

Matthias C. Huber, Uwe Jonas, Stefan M. Schiller

https://doi.org/10.1002/aisy.202100189, 13 January 2022, accessed 1 Feb 2022

Abstract

Complex multimaterial networks of the human body, for example, muscles, enable dynamic autonomous movements. Bioinspired mimicry of muscular systems is of great interest in soft robotics and biomedicine. Currently a broad range of synthetic macromolecules and natural or modified biomacromolecules imitate muscular systems, but no protein muscles with mechanoactive protein components are realized. Biomimetic bio-based muscle systems allow to combine the potential of nature's high-performance proteins, for example, silk, resilin, elastin, or titin, with novel adaptive and functional properties and sustainable biotechnological production. While biological protein motors and muscles are powered by the hydrolysis of adenosine triphosphate, no synthetic bio-based muscles are described, operating autonomously using chemical energy to exert directional movements. Herein, an artificial protein muscle is introduced, exerting rhythmic autonomous movements via nonequilibrium states driven by chemically fueled pH oscillation reactions. Key to the design are recombinantly produced human matrix proteins selectively reengineered to respond to different stimuli. The results also show how directional movements can be independently triggered by changes in pH and temperature including a selective on-switch and a combination of nonequilibrium states enabling "learning and oblivion"-like material effects. This paves the road for the next generation of autonomous materials in pharmacy, soft robotics and living matter.

From: Artificial Muscles Made of Proteins

Anonymous, https://www.sciencedaily.com/releases/2022/01/22 0128141254.htm, 28 Jan 2022, accessed 1 Feb 2022

Dr. Stefan Schiller and Dr. Matthias Huber from the University of Freiburg's livMatS Cluster of Excellence have succeeded in developing a muscle solely on the basis of natural proteins. The autonomous contractions of the material, which the researchers presented in the journal *Advanced Intelligent Systems*, can be controlled with the help of pH and temperature changes. The movements are driven by a chemical reaction that consumes molecular energy for this purpose. "Our artificial muscle is still a prototype," says Schiller. "However, the high biocompatibility of the material and the possibility of adjusting its composition to match particular tissue could pave the way for future applications in reconstructive medicine, prosthetics, pharmaceutics, or soft robotics."

In the past, scientists have already taken natural proteins as a basis for developing artificial muscle systems and built them into miniscule molecular machines or into polymers. However, it has not yet been possible to develop synthetic muscle materials that are entirely bio-based and move autonomously with the help of chemical energy.

The material used by the Freiburg team is based on elastin, a natural fibrous protein that also occurs in humans, for instance giving elasticity to the skin and blood vessels. Following the model of this protein, the researchers developed two elastin-like proteins, one of which responds, for example, to fluctuations in pH, the other to changes in temperature. The scientists combined the two proteins by means of photochemical cross-linking to form a bilayered material. It is possible in this process to flexibly shape the material and set the direction of its movement.

The researchers succeeded in inducing the rhythmic contractions by using a chemical energy source as fuel, in this case sodium sulfite. In an oscillating chemical reaction in which the pH changes in cycles due to a special linkage of several reactions, the added energy was converted into mechanical energy via non-equilibrium states of the material. In this way, the researchers induced the material to contract autonomously in a cyclical manner. They were also able to switch the contractions on and off with the help of temperature changes: The oscillating chemical reaction started at a temperature of around 20 degrees Celsius, and the material began to make rhythmic movements. In the process, it was possible to program certain states for the

material to assume and to reset them again with another stimulus. The scientists thus achieved a simple system for implementing learning and forgetting at the material level.

"Since it is derived from the naturally occurring protein elastin and is produced by us through biotechnological means, our material is marked by a high sustainability that is also relevant for technical applications," explains Schiller. "In the future, the material could be developed further to respond to other stimuli, such as the salt concentration in the environment, and to consume other energy sources, such as malate derived from biomass."

Exercise-Induced Piezoelectric Stimulation for Cartilage Regeneration in Rabbits

Yang Liu, Godwin Dzidotor, Thinh T. Le, Tra Vinikoor, Kristin Morgan, Eli J. Curry, Ritopa Das, Aneesah McClinton, Ellen Eisenberg, Lorraine N. Apuzzo, Khanh T. M. Tran, Pooja Prasad, Tyler J. Flanagan, Seok-Woo Lee, Ho-Man Kan, Meysam T. Chorsi, Kevin W. H. Lo, Cato T. Laurencin, Thanh D. Nguyen

Science Translational Medicine Jan 2022 • Vol 14, Issue 627 • DOI: 10.1126/scitranslmed.abi7282, accessed 1 Feb 2022

Abstract

More than 32.5 million American adults suffer from osteoarthritis, and current treatments including pain medicines and anti-inflammatory drugs only alleviate symptoms but do not cure the disease. Here, we have demonstrated that a biodegradable piezoelectric poly(L-lactic acid) (PLLA) nanofiber scaffold under applied force or joint load could act as a battery-less electrical stimulator to promote chondrogenesis and cartilage regeneration. The PLLA scaffold under applied force or joint load generated a controllable piezoelectric charge, which promoted extracellular protein adsorption, facilitated cell migration or recruitment, induced endogenous TGF-β via calcium signaling pathway, and improved chondrogenesis and cartilage regeneration both in vitro and in vivo. Rabbits with critical-sized osteochondral defects receiving the piezoelectric scaffold and exercise treatment experienced hyaline-cartilage regeneration and completely healed cartilage with abundant chondrocytes and type II collagen after 1 to 2 months of exercise (2 to 3 months after surgery including 1 month of recovery before exercise), whereas rabbits treated with nonpiezoelectric scaffold and exercise treatment had unfilled defect and limited healing. The approach of combining biodegradable piezoelectric tissue scaffolds with controlled mechanical activation (via physical exercise) may therefore be useful for the treatment of osteoarthritis and is potentially applicable to regenerating other injured tissues.

From: Electric Knee Implants Could Help Treat Pain of Osteoarthritis

Clare Wilson, *New Scientist: Health*, 12 Jan 2022, https://www.newscientist.com/article/2304357-electric-knee-implants-could-help-treat-pain-of-osteoarthritis/?utm_source=sciencedaily&utm_medium=partner&utm_campaign=190122_sciencedaily_editorial, accessed 1 Feb 2022.

Knee implants that generate a tiny electrical current may be able to stimulate cartilage regrowth as a treatment for arthritis. Rabbits given the implants, which generate electricity from mechanical forces as the animals move around, experienced more healing after cartilage damage than those given a placebo device.

Osteoarthritis is a common cause of knee pain as people get older. It involves the wear and tear of cartilage, a rubbery layer capping the ends of bones that normally stops them rubbing together.

Many experimental treatments are in development, such as new drugs and implants of stem cells, immature cells that have the ability to develop into any cell type. Some research suggests that a mild electric current can encourage cartilage cells in the knee to multiply and repair damage.

To avoid having to put batteries inside the body, Thanh Nguyen at the University of Connecticut in Storrs and his colleagues have developed a biodegradable membrane, about half a millimetre thick, which generates electricity when it is compressed and stretched. The material has a scaffold-like structure to encourage cells to migrate into it.

Nguyen's group tested the current idea by creating holes in the knee cartilage of rabbits and patching them up with the material. After a month of rest, the researchers encouraged the rabbits to hop around for 20 minutes a day by putting them on slowly moving treadmills, to exercise their legs and generate the electric current.

Two months later, the team took tissue samples from the joints and scored them on how intact and healthy they appeared under the microscope. The team found that cartilage cells had moved into the patches and the joints appeared more intact. "Stem cells from bone marrow are recruited to the scaffold," says Nguyen.

Cartilage from these rabbits scored 15 out of 18 on average, while a group of rabbits given patches of a similar material that didn't generate electricity scored about 5. If used in people, the material used to make the implant would dissolve after about two months – although it could be tweaked to make it last longer, says Nguyen.

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.

Chana Phaedra, "**Reconstructive Connectomics**," *Cryonics* 34(7) (July 2013): 26-28.

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

Ralph C Merkle, "**Revival of Alcor Patients**," *Cryonics*, 39(4) & 39(5) (May-June & July-August 2018): 10-19, 10-15.

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

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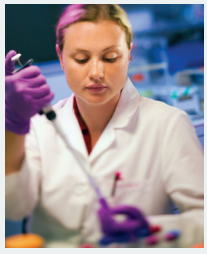

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