CRYONICS

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CRYONICS

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Deliverance versus Doomsday: The Perspectives of Cryonics

Today we stand at a crossroads of time, more staggeringly magnificent, more alive with promise but also peril, more challenging and more thrilling than ever before in our history. On one hand we could attain to a status of near divinity, with diseases and aging things of the past, an enduring existence in a world of happiness, harmony, freedom from want, and a reassuring stability. The transition from today's limited life to such a joyful and meaningful outcome might rightly be called our Deliverance. Such a goal, long fantasized, has been an impossible dream, but with the progress now in many scientific fields, it can at least be taken seriously, and, I think, approached with optimism and hope. For it surely is a natural and proper outcome of our progress, like the butterfly emerging from its chrysalis. Quite reasonably, it *must* happen—in order that all shall go as it should.

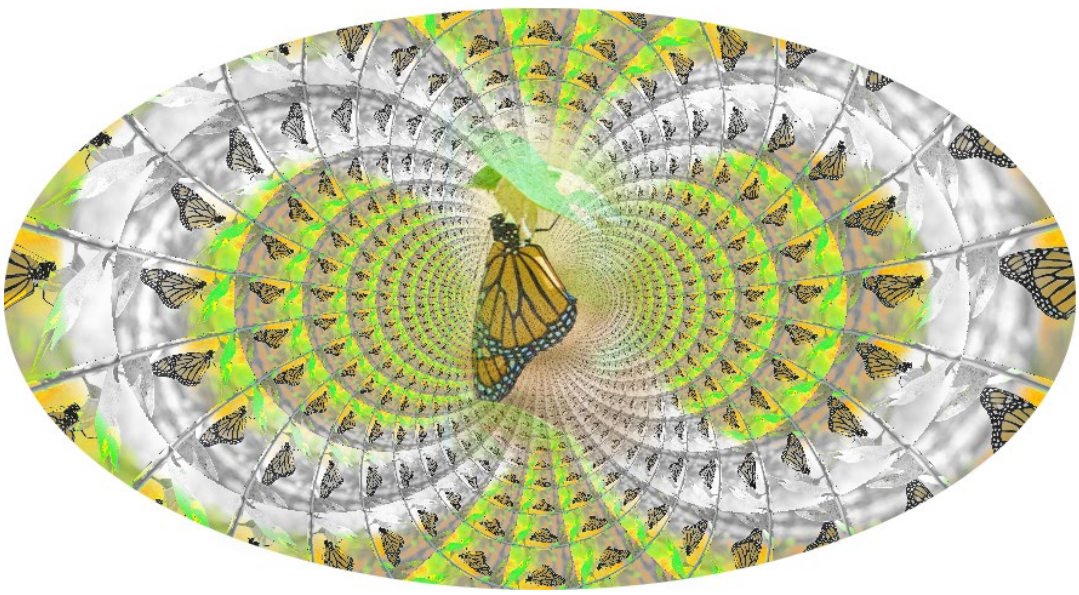
But a very real alternative is almost too terrible to contemplate: the human race and possibly all life on earth could be destroyed. Today there is much violence in the world. Competing militaries devise better and better weapons to strike and mangle each other, and are actively doing so. Nuclear weapons are not being used yet, but the horrid possibility is raised. Even if belligerent nations manage to settle their differences and avoid catastrophe, terrorists or other misguided individuals with access to advanced technology could still finish the job. Other Doomsday possibilities that some worry over include catastrophic climate change over use of fossil fuels, or the possibility that the human race may go extinct as fewer and fewer people want to have children. It may be that some of these bad outcomes are unlikely. But between Deliverance and, in some form, Doomsday, it may be that no third, enduring alternative is very likely either.

At any rate, clearly civilization is not simply going to stand still. Whether we like it or not, great and sweeping changes are happening and are sure to continue and grow.

In cryonics we have a special stake in the future, one that is not negated if we must also suffer clinical death like everybody else up to now. That is, we hope to be revived someday from our cryopreserved remains. If we are revived, we expect that Deliverance, or definitely "getting there," not Doomsday, must have occurred, else who would be both present and motivated to take the trouble to revive us?

Meanwhile we proceed as best we can, offering cryonics services to those who are interested, and trying to promote our cause, which brings us to this newsletter. In this issue there is something especially significant. Greg Fahy reports on work showing good human brain preservation using Alcor's main cryopreservation protocol. Journal publication of the results is expected soon, when more confirming results are obtained. Cryonics has aroused a lot of skepticism over the years; here a blow is being struck to favor the practice on scientific grounds. On a less cheerful but still hopeful note, we report the Alcor cryopreservation of Steve Harris, M.D., long a mainstay of cryonics who contributed much, both in research activities and in reaching out to the cryonics community to help those in need. We must take care of our own when they experience a supreme need, as did Dr. Harris – and we hope, of course, to see them happy and healthy someday.

On that note, dear reader, we hope you will also find this issue, with other articles besides those just mentioned, worth your while!



Based on public domain photo at rawpixel.com/image/4028226/first-day-monarch-butterfly

Steve Harris in Remembrance

by R. Michael Perry

It was with shock and sadness that I learned of Steve Harris's passing from a heart attack last November (2023), and subsequent cryopreservation at Alcor. I still remember him much as you see in the picture above from 1991. Steve was in his mid-thirties, looking really younger than that, a fresh, eager kid, but also an M.D., with knowledge and interests well beyond any ordinary M.D. Steve was interested in the deep questions of life in a profound way. It was not sufficient to merely note and lament or stoically accept and rationalize certain "verities." One must instead confront the seemingly unbreachable limitations of our existence with serious intent to do some work-arounds.

Steve was not happy with the normal course of human life, ending as it does in aging and death (or death by other causes earlier). Among other things, he was a gerontologist who studied aging with an eye to how it might be delayed or reversed. He was also a geriatrician, concerned about real people now suffering and dying from this "natural" malady, just as he was also concerned and trying to help those who could benefit from conventional medicine.

Aging is still with us, despite any advances we may have made in understanding or mitigating it, and it may be with us for some time yet. Steve recognized that and faced it squarely and bravely. People are dying, and you reach a point where existing medicine can do no more. The thought of giving up on these people and committing their remains to one or another process of destruction he found repugnant. He wanted to do better. The answer was, of course, cryonics. As with his other endeavors, Steve's interest in cryonics was not merely passive or even limited to getting signed up with funding in place and staying that way, but he made some major contributions to the field. These are summarized under such headings as (1) brain resuscitation, (2) quantification of post-arrest ischemic injury, (3) liquid ventilation, (4) novel cryoprotectants, and (5) ice blockers. Brian Wowk in his excellent article[1] has summarized these and Steve's many other contributions in and outside the broad field of life extension. Here I offer an addendum to help round out the picture and extend it in certain directions. Neither article, it

is fair to say, does full justice to its subject which deserves a much longer treatment, but as usual we have to respect limitations of time and circumstance.

Steve was, by turns, both fun-loving and serious. He was generous in his contributions and not much demanding when it came to being recognized or compensated for what he did. As one case in point, he gave financial help to others though not being particularly wealthy himself. He helped with expenses so one cryonicist I know could get their pet frozen at Alcor, and helped another one I know with their rent.

For the main part of my article, I'll start with a little incident I remember from when Alcor was in Riverside, California, I think it was about 1988.

Setting Water on Fire

As one of Steve's many interests, he had a collection of chemical elements. I still have somewhere a sample of gallium he sent me in a small vial. Gallium is a metal that melts from the heat of your hand, that is, at about 85°F. Otherwise, it's pretty inert and you can do what you want with it. Another metal, sodium, is not so inert but has so much affinity for oxygen that if you put it in water, an explosion may occur as the sodium atoms rip oxygen and some hydrogen out of the water molecules. Other, reactive hydrogen atoms are left behind that combine vigorously and produce hot hydrogen gas, which is then free to ignite with oxygen in the atmosphere and generally does. In effect, you are setting water on fire.

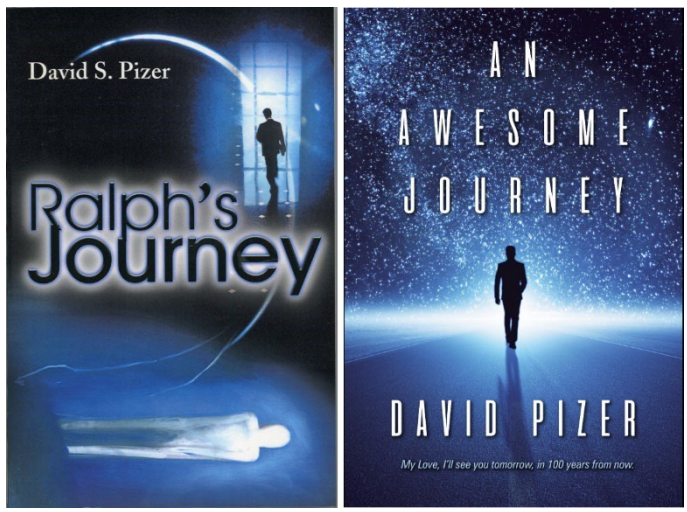
So, one evening at the Riverside facility, Steve and Hugh Hixon were out in Alcor's parking lot, playing like two truant schoolboys with this metal that Steve supplied. I remember hearing popping sounds as pea- sized pellets of sodium hit the water. I didn't follow all they were doing, having other things to do, but no doubt it was entertaining.[2]

Ralph's Journey

The next incident is more involved and more serious, though still relatively light-hearted. David Pizer wrote a novel, *Ralph's Journey*. Ralph Dombrowsky, fresh out of high school, starts his career as an errand runner at an auto paint shop and ends up one of the richest people in the state of Arizona. Early on he encounters something weird. His boss's wife succumbs to a heart attack, only there isn't any funeral. Instead, she is frozen, in hopes of getting her back some day. The Phoenix Cryopreservation Society is a secret organization in this primitive time (mid-to-late 1950s, anticipating real-life cryonics organizations by a decade or so). Then, after many adventures stretching over decades, Ralph finally has terminal cancer and is himself cryopreserved. He takes his place by his fiancée who tragically was fatally injured in a car accident when the two were still teenagers. (And Ralph stayed true to her, despite temptations, during all the extra years of his life until his own preservation.) More decades pass. The two then are revived and both restored to youthful fitness, along with old friends, and all are living happily when the story ends.

David Pizer was an Arizona businessman who had never written a novel before, but then he encountered cryonics, got involved, and, like Steve, wanted to do more than just be signed up with funding in place. In addition to writing the novel, he started a promotional organization, the Society for Venturism. They published a newsletter, held conferences and conventions, and carried out other activities including fundraising events for needy, terminally ill people who wanted the expensive cryopreservation but couldn't afford it. He was also, for several years, vice president of Alcor, and played a crucial role in its move from California to its present location in Scottsdale, Arizona, in 1994. (Now in his eighties, David lives near Alcor, and still has arrangements with them for cryopreservation. The Venturist organization is no longer active like it once was, but is still issuing no-autopsy cards with photo ID.[3])

As for the novel, David was a good storyteller, but many passages needed editing. I took a hand in this, but Steve got interested and did his own edit, further improving many passages with his medical knowledge, writing skills, and sensitivities to human drama in its different forms. This was no trivial task – the novel is hundreds of pages long – but Steve did it all without asking any compensation. (The novel was published by an online company and is still available, along with a rewrite David did some years later.[4])



David's novel (2000), and rewrite (2020).

Estimating Ischemic Exposure

The third topic I'll address is more technical and more directly related to cryonics: the effort to quantitatively estimate ischemic exposure as a cryonics patient, starting with cardiac arrest at body temperature, is cooled down to cryogenic temperatures. Brian Wowk in his article has summarized Steve's efforts with this problem, but I was also involved, and will add a bit.

The need to deal with ischemia – an oxygen deficiency that occurs following cardiac arrest (or possibly from other causes) – is an unavoidable consequence of the process of cryopreservation. The passage from body temperature to the cryogenic range is far from instantaneous, no matter how it's done, and cells deprived of oxygen very long under warm conditions experience injury and may deteriorate. The effects can be mitigated somewhat if oxygen is supplied to the tissues during cooling – under the best conditions this is routinely done – but serious stress and damage are still very likely. While we don't fully understand the nature of ischemic injury and probably won't for some time, we can agree that it's something we want to minimize. A good quantitative measure of ischemic exposure could be very

valuable in assessing how well we are doing in reducing possible cell damage and how we might do better.

For the approach developed by Steve, Aschwin de Wolf and me, we start at body temperature, approximately 37°C. One hour exposure at this temperature becomes our unit, and we try to arrive at an equivalent rating for exposures at other temperatures. An approximate rule for this is called the Q_{10} rule.[5] In one commonly used version a ten-degree Celsius drop in temperature cuts the rate of activity – including the injury we want to avoid – by a factor of 2. So, for instance, one hour exposure of tissue at 27°C would, by this reckoning, be equivalent to only half an hour at 37°, ten degrees warmer. A tissue exposed at body temperature for one hour, followed by a one-hour exposure at ten degrees cooler, would thus experience 1½ total hours equivalent ischemic time. More generally, an equivalent ischemic exposure is obtained by adding up many, generally small contributions as the sample reaches one temperature or another briefly during its descent. (The limit of this fine subdivision is to be using integral calculus for a quantity that varies continuously with time.)

In 1996 I did a preliminary, theoretical study of this idea, calling the resulting quantity the "measure of ischemic exposure" (MIX).[6] Steve Harris in 2003 did a much deeper study, with application to experimental data, renaming the quantity the "equivalent homeothermic ischemic time" or E-HIT This comprehensive and massive work was never quite finished but updated in 2020 .[7] Quoting from the abstract:

> In [this] essay, heat transfer problems and inferences of temperature time-constants in cryonics are discussed, as well as the critical importance of supplying oxygen to the brain while metabolic rate is still high, during the first phase of cryonics treatment. Data from three real and contrasting cryonics cases are discussed, with abstraction of the kinds of information which the author would like to see calculated or estimated for all cryonics cases, where possible. Studies of postmortem conductive head cooling in the forensic literature are discussed, as they apply to cryonics. An appendix gives equations, mathematical approaches, and numerical computational methods. Some theoretical and experimental results are also given, showing a fair match from known human forensic and cryonics data.

In particular he studied a type of cooling called Newtonian after Isaac Newton who first elucidated it. This, to a first approximation, is the sort of cooling a mass of tissue would experience if placed in a colder, fixed-temperature environment and left to cool on its own. (Though this is far from ideal, it occurs very frequently when cryoprotection procedures cannot be started immediately after pronouncement.) Finally, in 2020, Aschwin de Wolf and I reworked some of Steve's ideas and developed a practical procedure that includes an allowance for partial oxygenation of tissue during cooling.[8] Aschwin renamed the quantity the S-MIX or "standardized measure of ischemic exposure" and it is now routinely used in Alcor's cases.

A Future Challenge

The work on measuring ischemic exposure was only one of many important contributions Steve Harris made in his long involvement in cryonics. It is with no intent to slight these other contributions that I quote again from his paper on ischemic exposure:

> [I]t so happens that the process of getting freshly-declared dead people rapidly frozen, not to mention vitrified, is very, very difficult. People do not die on schedule, even when they know they have a terminal problem. Even if they are cryonicists, they do not like to plan for the event, or even think about it. Their families, even less so. Because of unpredictability, arranging to have a team of cryonicists standing by at a cryonicist's death, which may occur far from any major cryonics facility, is a logistics nightmare. No matter how much planning has been done, there are almost inevitable legal and social problems in gaining physical control over a human body in the first minutes, or even hours, after death has been legally declared. It all costs a lot of money, it is emotionally and physically draining, and (even worse) the immediately tangible payoff for managing it well, is almost nil. A superbly-preserved cryonics patient looks much the same (and sometimes cosmetically even worse) as one who didn't get nearly so good a job. The differences, such as there are, might only be findable on electron microscopy which is expensive and difficult to do, and which isn't routinely done. And which would not tell the whole story, even if it were done.

It is a sad irony just how well the above assessment fit Steve's own case when it came up unexpectedly. For him the E-HIT/S-MIX rating he worked so hard to perfect (while not available yet, as I write this) cannot be favorable. To give some grim details: Steve was unattended an estimated more than 13 hours after his fatal heart attack, became a medical examiner's case, and was finally straight frozen[9] (as a neuro[10]). Straight freezing is used as a last resort when perfusion of cryoprotectant to reduce freezing damage cannot be carried out due to massive clotting from ischemia.

Steve deserved better than that. But this outcome is all too common. Our friends of the future are going to have some challenging cases when it's time to attempt revival. Meanwhile *we must do better* with our aging population and other members who may suddenly arrest and not be found for a while. (Alcor does have resources to help prevent post-mortem cases, such as the Alcor Check-in Service for members who live alone. If you would like to improve your chances for a good cryopreservation, please contact Alcor for assistance.[11])

References:

1. Brian Wowk, "A Man for All Ages," https://biostasis.substack.com/p/a-man-for-all-ages-dr-steven-b-harris, accessed 23 Jan. 2024.

2. Hugh Hixon, private communication, 13 Jan. 2024.

3. Author's personal knowledge.

4. Books by David Pizer: *Ralph's Journey*, iUniverse, 2000; *An Awesome Journey*, BookBaby, 2020.

5. https://en.wikipedia.org/wiki/Q10_(temperature_coefficient), accessed 23 Jan. 2024.

6. R. Michael Perry, "Toward a Measure of Ischemic Exposure," *Cryonics* 17(2) (2Q 1996) 21.

7. Steven B. Harris, “Initial Cooling in Cryonics,” 2020 version: https://e.pcloud.link/publink/show?code=XZ5gneZDQhapcwznpzGTNAllp9gQB2UEtcV, accessed 20 Jan, 2024; 2003 version: https://www.biostasis.com/pdfs/steveharris_ehit.pdf, accessed 20 Jan. 2024. Quotations are from 2020 version.

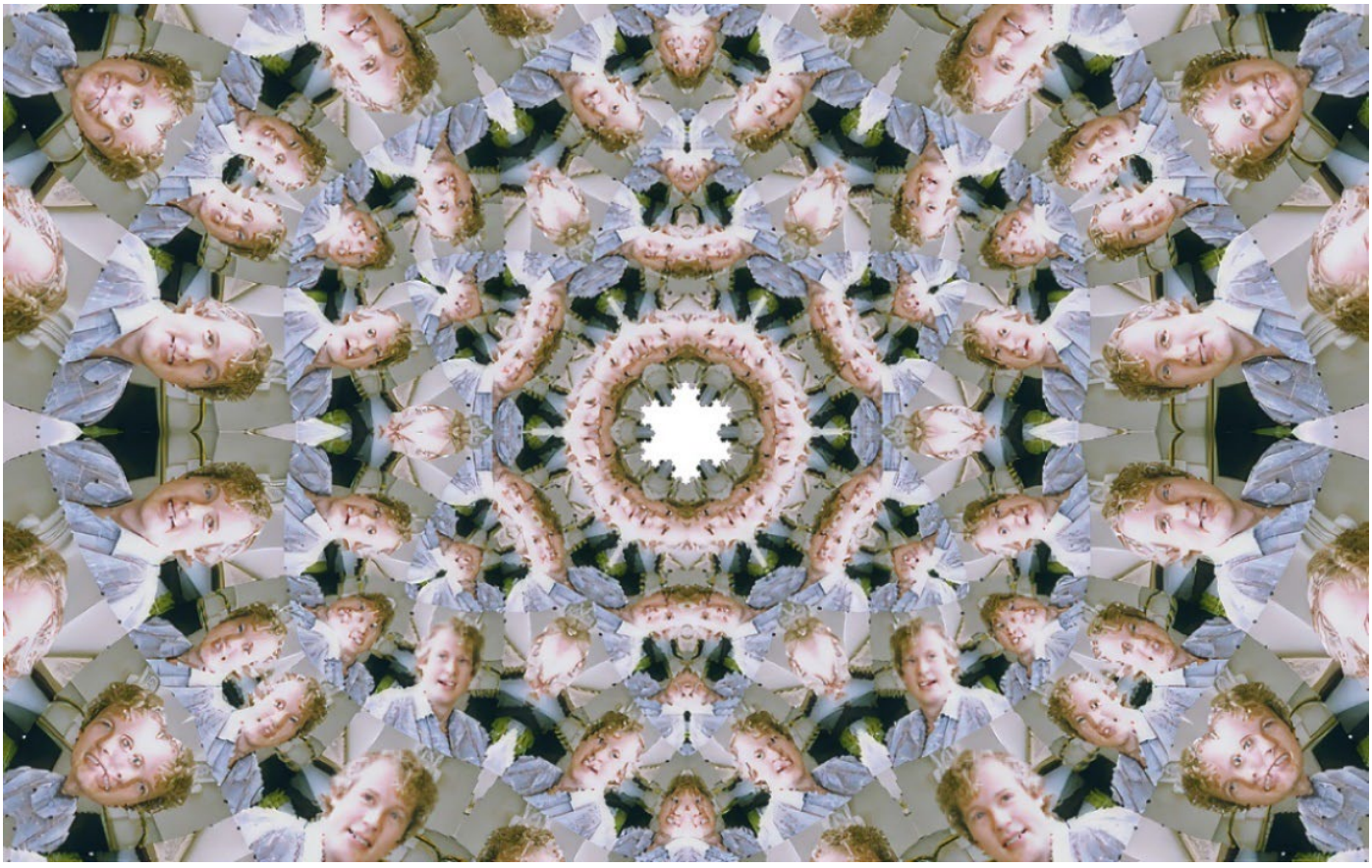
8. R. Michael Perry and Aschwin De Wolf, “The S-MIX: A Measure of Ischemic Exposure,” *Cryonics* 41(4) (4Q 2020) 12-15.

9. https://www.youtube.com/watch?v=_S1LXlt6nbM (video), 46:14, accessed 22 Jan. 2024.

10. https://www.alcor.org/complete-list-of-non-confidential-cryopreserved-alcor-patients/, accessed 22 Jan. 2024.

11. Sentences in parentheses quoted from https://www.alcor.org/library/case-announcements/, case A-1130, accessed 23 Jan. 2024.

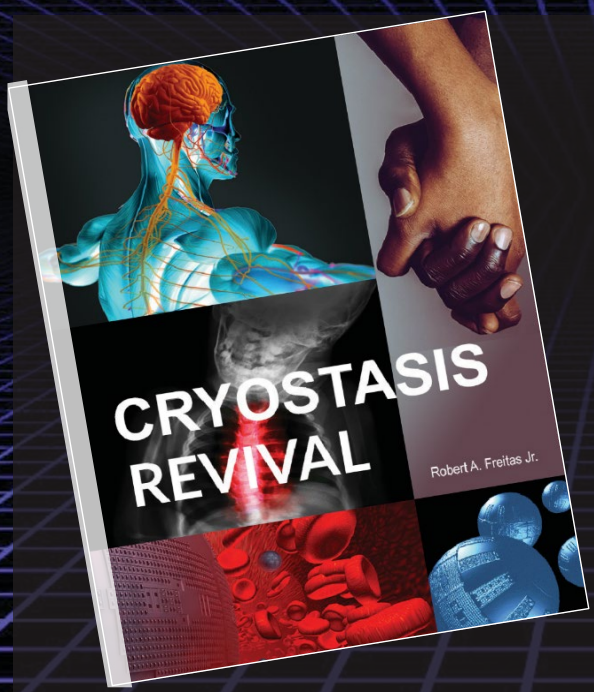
Picture credit: cropping of picture used in ([1]), sharpened by author (further cropped version used on cover).



I’m betting that Steve with his bubbly sense of humor would appreciate this rather wacky kaleidoscope image, based on the photo beginning this article, with snowflake (actually a Koch curve) in the center representing – why not? – cryonics! – RMP.

New Book by Robert A. Freitas Jr.

Cryostasis Revival: The Recovery of Cryonics Patients through Nanomedicine



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

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

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

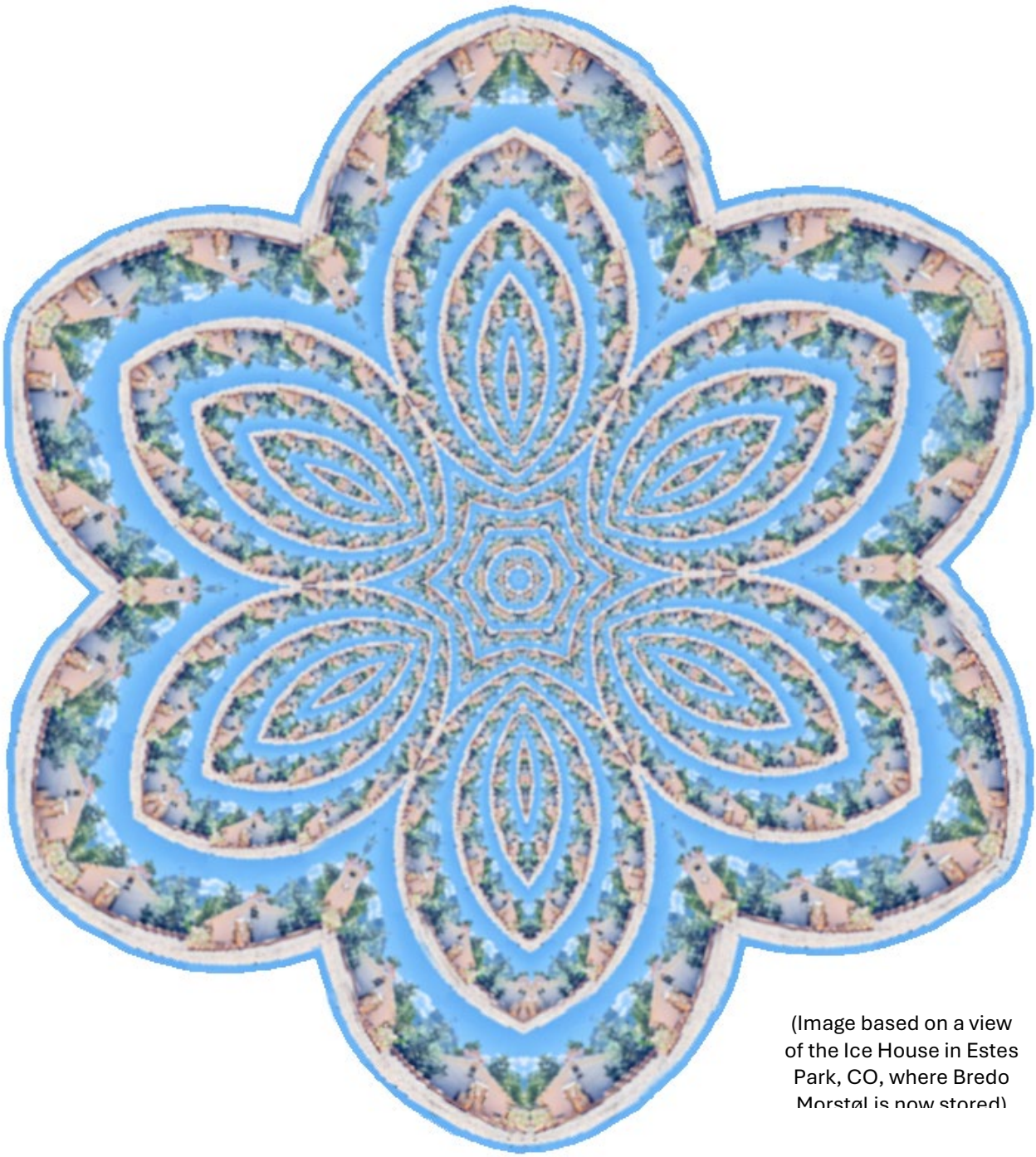
"We now have considerable evidence that cryopreserved patients retain the physical structures encoding memory and personality. For most people, the difficulty lies in understanding how it could ever be possible to repair and revive patients. Leading nanomedicine expert Robert Freitas fills in that gap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

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

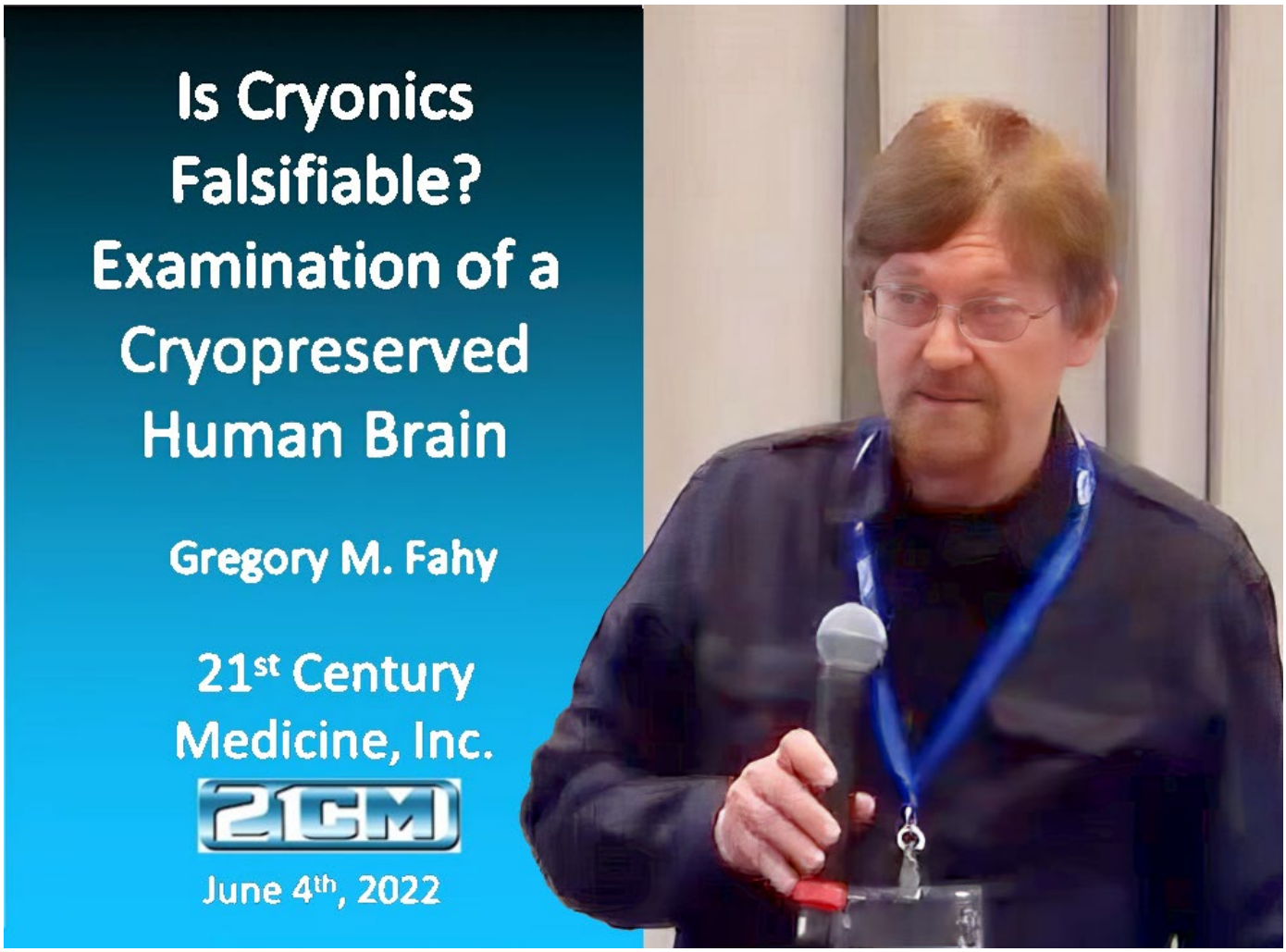
Free electronic book and hardback copies for sale at:
https://www.alcor.org/cryostasis-revival or Amazon.com

Membership Statistics

2023-24	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
Cryo Members	1417	1415	1415	1417	1424	1419	1422	1423	1418	1424	1425	1430
Basic Members	36	34	35	35	35	35	36	38	39	40	43	46
Patients	205	206	208	212	212	217	218	222	224	225	226	227
Assoc./Apps	218	223	217	218	219	228	238	245	249	247	248	241
Total	1876	1878	1875	1882	1890	1899	1914	1928	1930	1936	1942	1944



(Image based on a view of the Ice House in Estes Park, CO, where Bredo Morstøl is now stored)



Gregory M. Fahy *is a California-based cryobiologist, biogerontologist, and businessman. He is Vice President and Chief Scientific Officer at Twenty-First Century Medicine, Inc, from whom Alcor licenses its cryoprotection solution, and has co-founded Intervene Immune, a company developing clinical methods to reverse immune system aging. He is the world's leading expert in organ cryopreservation by vitrification, and was the 2021-2022 President of the Society for Cryobiology.*[1][2] *In reproducing Greg's talk I have, as usual, edited lightly for clarity and conciseness, and also abridged slightly at the end, omitting one question not relevant to the results presented. Of the more than forty slides shown in the original presentation, I've omitted text-only material that was repeated word-for-word by the speaker. The full presentation is viewable at [1] – RMP.*

Good morning, everybody. It's great to be here. I'm going to touch on a subject that's important to me as a cryobiologist and also has significance for cryonics as viewed by a non-cryonicist, and that's the concept of falsifiability, connected with science. We're gonna discuss that topic by relating it to an experiment that was done a few years ago and is still actually ongoing, involving the examination of a cryopreserved human brain. So, I just want to start off making a couple of comments about the relationship between cryonics and science. There's this syllogism that's of significance now, in the way cryobiologists view cryonics, and it goes like this: Science is a method for discovering truth. Cryonics is an act of speculation. Speculation is not the discovery of truth, and therefore cryonics is not science.

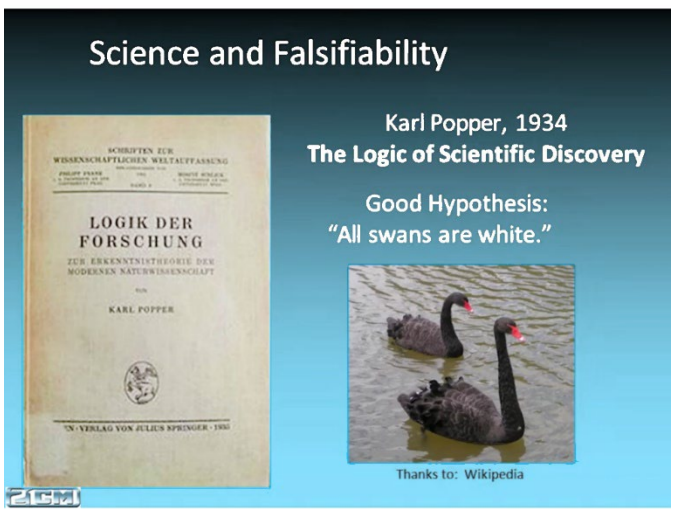
The reason that I bring this up is that, thanks in part to some ruckus that was raised at the 1981 meeting of [the Society for Cryobiology], the Society instituted a policy statement about cryonics and that reads in part as follows: "Preferences regarding disposition of the dead are clearly a matter of personal choice and therefore inspppropriate subjects of Society policy. The Society does, however, take the position that cadaver freezing is not science. The act of freezing a dead body and storing it indefinitely on the chance that some future generations may restore it to life is an act of faith, not science." [Laughter].

There were some changes in leadership in the Society recently, and as part of the result of that, the segment was updated in 2018, and it now reads a little bit better and it goes like this: "Preferences regarding the disposition of post mortem human bodies or brains are clearly a matter of personal choice, therefore inappropriate subjects of Society policy. The Society does, however, take the position that the act of preserving a body, head or brain after clinical death and storing it indefinitely on the chance that some future generations may restore it to life, is an act of speculation or hope not science, and as such is outside the purview of the Society."

Now, that last line about being outside the purview of the Society, that's at least a little bit of an improvement because these policy statements have underlain the expulsion of cryonicists for membership in the Society and inhibition of discussion between proponents and opponents of cryonics. Cryobiologists who are interested in cryonics are basically lepers within the society. So we'd like to examine how these issues could be improved upon.

Let's talk about the issue of the difference between cryonics and science. Science proceeds by constant testing of hypotheses. And cryonics claims to be a scientific experiment. We cryopreserve you now, we wake you up 200 years from now and see if it works or not. That's the experiment. The problem is that it takes decades or hundreds of years to get to the end of that experiment. So, for the time being, any scientist looking at this proposition is going to regard this as useless from the scientific point of view. You cannot evaluate this idea because we can't do the experiment now.

Carl Popper in 1934 wrote a book called *The Logic of Scientific Discovery* and he put forward the idea that the reason that science is good and works is that in science, you can define a good hypothesis versus a bad hypothesis. A good hypothesis is one that theoretically can be challenged and falsified, if it's wrong. A good hypothesis might be that all swans are white. You can challenge that and disprove that hypothesis if you can find a single black swan, for example. If you never find a black swan, however, then the hypothesis stands until it's later falsified. [Slide 1].



Slide 1

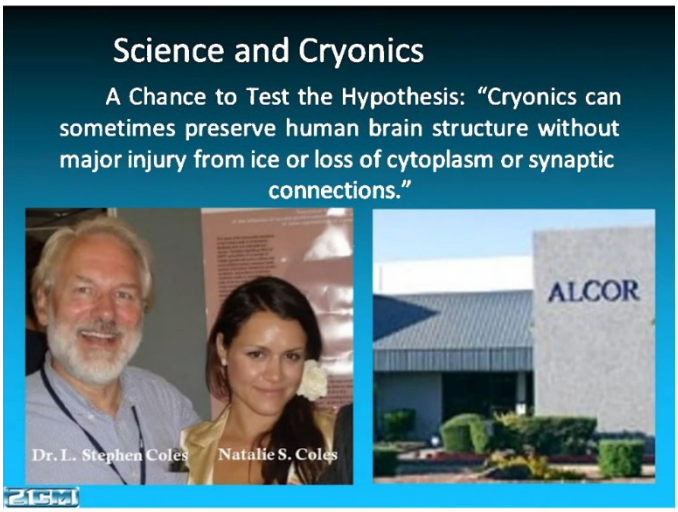
So, in cryonics, you might say, well, our hypothesis is that some cryonicists will survive or there's hope of survival or something like that. That's a bad hypothesis because you can't do the experiment now to test it, because that premise depends upon technology that doesn't exist now, molecular medical nanotechnology, and we don't have that yet. So this hypothesis is worthless from a scientific point of view because you can't test it, you can't falsify it, it's impossible. [Slide 1]. But there are good hypotheses that can be created within the realm of cryonics. These can be constructively used to build the case for cryonics gradually over time, incrementally. One example is the hypothesis that Robert McIntyre had some time back, and we tested it in our lab at 21st Century Medicine, that aldehyde stabilized cryopreservation [ASC, sometimes pronounced "ask"] can preserve brains well. So that hypothesis was not falsified. It was proven to be correct from what we can see. Another one is that human brains could be mostly vitrified. And this was actually taken on by Alcor. It decided to do CT scanning of their cryopatients and examine and quantify the amount of vitrification that actually takes place in the human brain in real world cryonics cases.[3] And then you all remember another cryonics hypothesis that was put forward, which is that memory can survive after either freezing or vitrification. And that hypothesis was not falsified either, but was upheld by the scientific method.[4]

And so these hypotheses begin to construct a case for cryonics. We're starting from the point where no viability is possible, which has questionable validity in some domains. We go to a very practical demonstration that at least we can get to the vitrification part of this process. We establish the principle that the goal of revival is not intrinsically impossible, because there's at least one example in which memory can survive, opening the possibility that memory could survive in people as well. But we'd still like something a bit more direct if we could get it. So that comes to the hypothesis that I'm going to spend the rest of this talk talking about, which is the hypothesis that cryonics can sometimes preserve human brain structure without major injury from ice or loss of cytoplasm per synaptic connections. Because if you don't preserve brain substance and brain structure, it's unlikely that cryonics is going to work. But if you can, it opens the door to cryonics possibly working. So we want to at least establish that much.

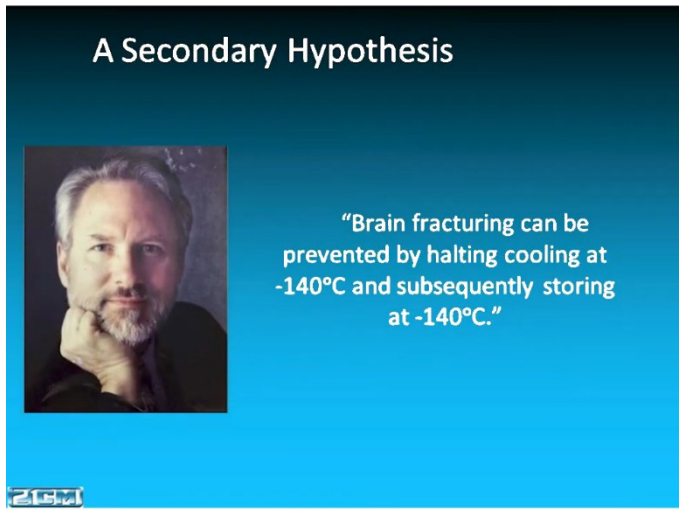
Fortunately for us, and unfortunately for one particular individual, Doctor Steven Coles, we had a chance to test that hypothesis a number of years ago. Dr Coles was the leader of a gerontology research group. He developed a fatal pancreatic cancer and had to be cryopreserved. He had not planned for it in advance and had no money available to pay for it. But fortunately, he did have a wonderful wife who supported him. So he was able to do whatever was necessary to get the process done provided that there was some mechanism to accomplish it. Alcor, on the other hand, played an incredibly significant role here as well because Alcor consented to do an experiment that would allow Dr Coles to be cryopreserved without having him pay for it in exchange for investigating that particular hypothesis as well as a secondary hypothesis. [Slide 2].

Dr Coles had not signed up for cryonics partly because he regarded fracturing as the equivalent of cremation. He did not think that fracturing injury would be reversible. So he was just skeptical, but the proposition was put to him, Dr Coles, suppose you become the person that answers that question once and for all. We can design an experiment that will hopefully not fracture your brain but still allow you to be cryopreserved and stored for geologic time periods. Are you interested? So he said yes. So the secondary hypothesis is that brain fracturing could be prevented by halting cooling at -140° Celsius and subsequently storing the brain indefinitely at that temperature.

So, here's the proposition: all of the cost of cryopreservation will be covered by Alcor, the Alcor research budget, as a charity



Slide 2



Slide 3

case. But the conditions are that the brain must be removed, so it can be inspected for cracks after vitrification. This is feasible because in research done at 21st Century Medicine on vitrifying whole pigs, we could demonstrate that every time we saw a fracture in an organ, it started at the surface of the organ and propagated in. So we didn't have to dice up Doctor Cole's brain into little pieces to look for fractures. All we had to do is look at the surface of the brain and preserve the great majority of the brain to get that done.

The second sacrifice that Doctor Coles had to have, in just having his brain removed from its skull so it could be photographed all the way around for cracks, is that it had to be biopsied several times. This was so we could test for the ice formation tendency of the brain and for the ability of his brain to take up cryoprotective agents. But also, perhaps most critically, it was so we could look, for the first time, at the structure of a human cryopatient's brain after preparation for cryonics, both at the light and the electron microscopic level. Our ultimate goal was publishing the results in a scientific journal. Now, there's an interesting wrinkle to that last part because Dr Coles wanted to be a co-author on the paper. [Laughter.] So I promised him that would happen.[Slide 3]

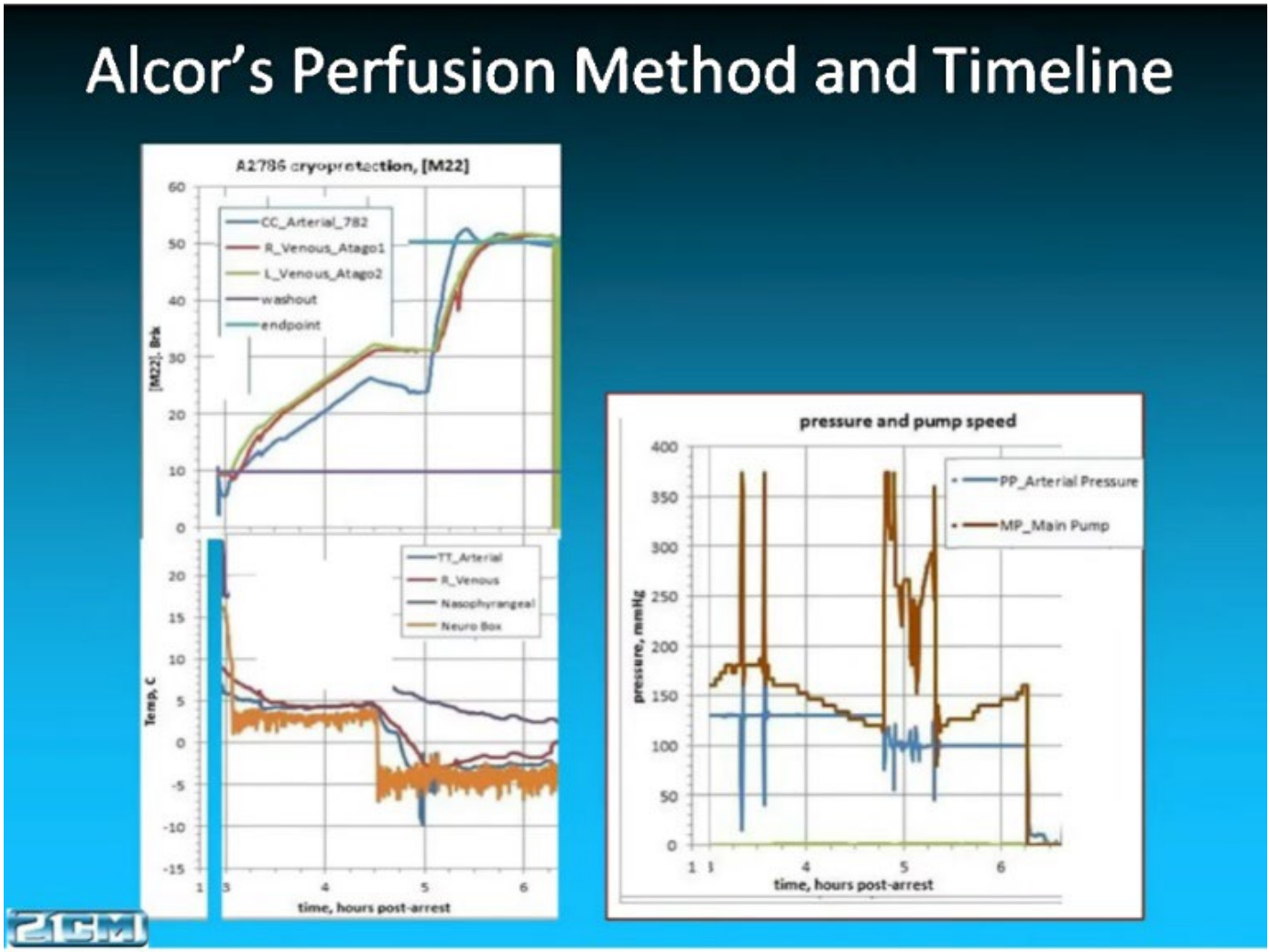
So here's how this case went. And I have to say that the case did not go perfectly. It went the way cases usually do with lots of imperfections, questionable events and problems and that's good in this case because that's the kind of situation we want to test. On the other hand, it was not a basket case either. He didn't wait, you know, and get discovered two weeks after he died. He was very prudent, he knew he had less time than people were telling him, so he moved to Arizona, checked into a hospice near Alcor, and proceeded to decline over several days. The manuscript about this will go into great detail about his physical state during those agonal days and which were not always pleasant or wonderful.

But Alcor was able to arrange a standby and transport to their facility after deanimation. The transport actually was accomplished one hour and 24 minutes after arrest. So it's not like he was instantly whisked out of the hospice and into Alcor, it did take some time. And then his cephalon was isolated for perfusion; that isolation took an hour and eight minutes after he arrived at Alcor. more time passing, more cold ischemia, more chances for things to go wrong.

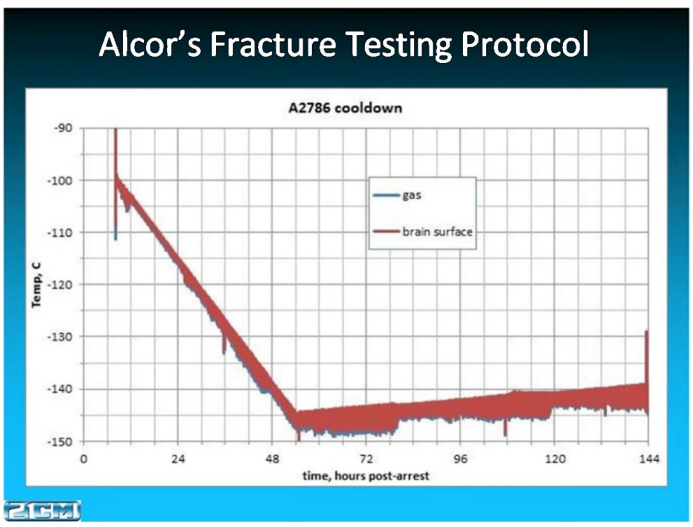
Then the cryoprotective perfusion was started, a total of three hours and 16 minutes after cardiac arrest. And that's significant because there was a big cardiovascular surgeon in Madrid that I had met at one time who said he was not interested in cryonics as he was sure the human brain cannot be reperfused three hours after clinical death. This case actually puts the lie to that hypothesis.

In any case, then the brain had to be removed. Ironically, the usual surgeon who was on hand to do procedures for Alcor at the time was not available. But Alcor found somebody at the last minute who had never done a cryonics case before. This guy actually had to remove Dr Cole's brain, but he did it successfully. Then the brain had to be sampled using methods that Alcor never had tried before, which were conveyed to Alcor by email like five minutes before they had to be done. And so everybody was going crazy and feeling very much under pressure and under the gun. But they managed to do it correctly, right at the last minute, mercifully. And then we had to do a controlled cool to -140 and not below. So Hugh [Hixon, Alcor's facility engineer] had to rig that up at the last minute to make it possible, which he very successfully did. Then we had to do the photography of the vitrified brain to see if it fractured or not. That required more jury rigging at the end there after a fairly short amount of time, but that was accomplished as well. And then the last part is just long term storage and that part is underway.

So this just shows the time course of the procedure and some of the warts in Alcor's data tracking system. [Slide 4]. The dark line that you see in the upper [left] panel is the arterial concentration. You see it's reading lower than the venous concentration, which is impossible. So they had a problem with their refractometers, but you can see that the introduction of cryoprotectant [CPA] went smoothly and fairly linearly for a while.



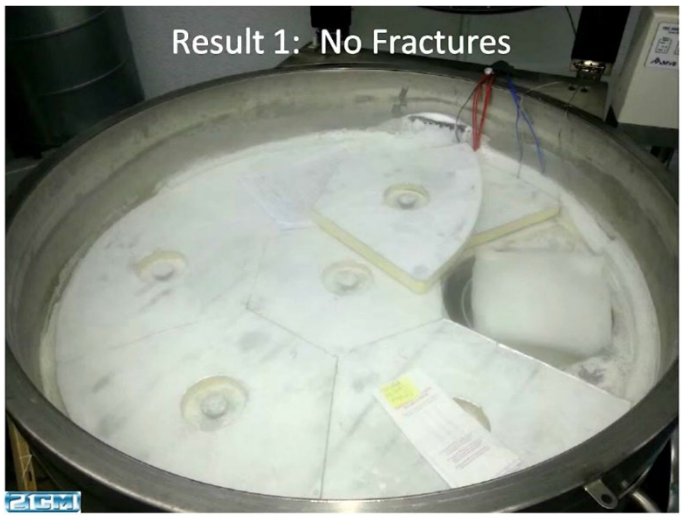
Slide 4



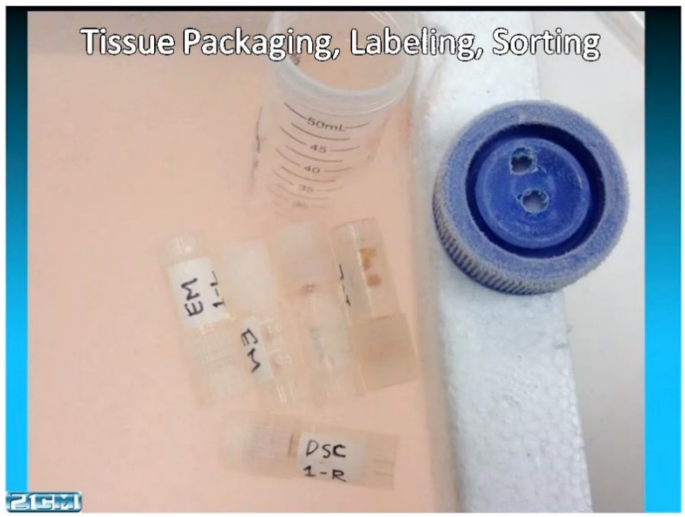
Slide 5

There was a pause to allow CPA uptake. And then there was a final jump to the final M22 vitrification solution. You can see in the lower left panel, the initial perfusion was done around 3° Celsius in the environment of the cephalon, a little bit colder than that afterwards. And the perfusion, as you see it on the right with the blue line, was done at 130 millimeters of mercury during the early stages of cryoprotection and 100 millimeters of mercury later.

So here's the fracturing experiment. [Slide 5]. Hugh did a beautiful job of putting this together. There's a nice linear cooling rate here of the environment and the brain surface temperature. There were no internal probes, we don't know quite what the brain internal temperature was, but I can tell you it probably caught up to this by the end. But unfortunately, despite the beautiful job that Hugh did, he was kind of asleep at the switch when you actually got to -140, and he left the brain unattended for a few more hours and it went down to -147. Obviously, the farther you go down in temperature, the larger the risk is that there may be fracturing, so this could have easily messed up the experiment. So when I chastised Hugh, he very gingerly brought the brain back to -140, and we all hoped for the best. And the answer was there were no fractures. [Applause.]

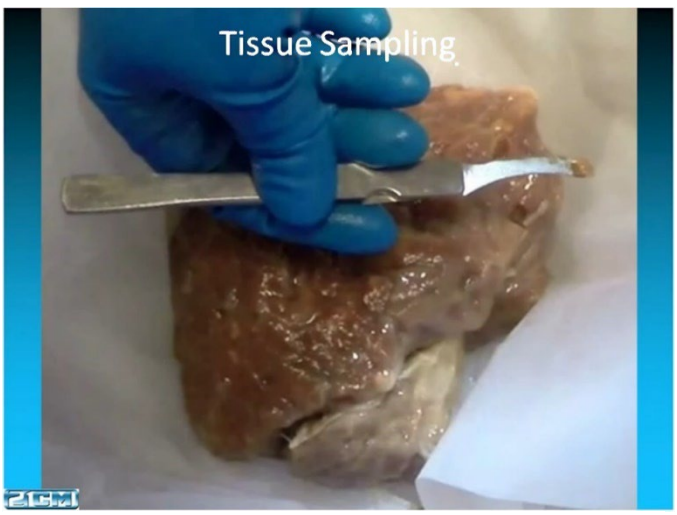


Slide 6



Slide 8

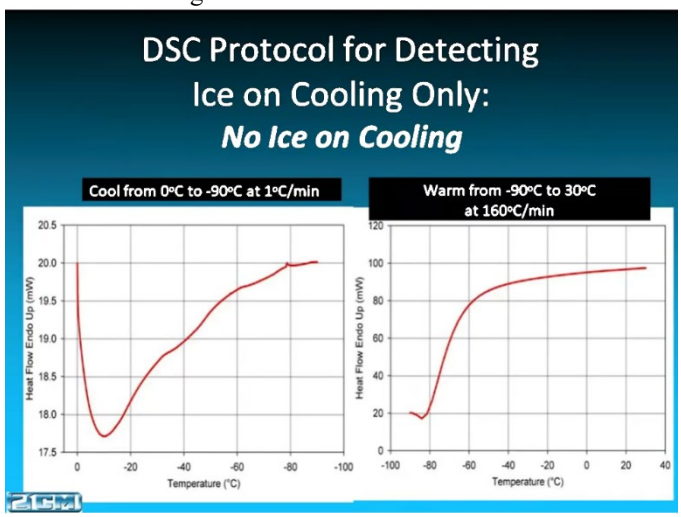
So, the reason that I'm showing you this image [Slide 6] rather than the image of the brain is that the image of the brain was electronically captured and the electronic file was accidentally erased. So, that's terrible, but eye-witness accounts are unanimous in saying there were no cracks. And this is the kind of environment that had to be set up. You can spray liquid nitrogen into an environment like this and maintain the temperature around -140 with not a lot of vapor. You can actually do the photography long enough to determine the answer to your question without changing the brain temperature, and then store the brain in this long-term storage container.



Slide 7

So now let's go to the more intense aspects of this test tissue sampling. This is a typical example of the surgeon retaining a fairly hefty-sized biopsy from Doctor Cole's brain. [Slide 7]. The biopsies were taken bilaterally and from the top and the bottom aspects of the brain. When I received them, they looked kind of like this. [Slide 8]' They're in Nunc tubes and they're labeled for either EM [electron microscopy] or DSC [differential scanning calorimetry, for ice content]. And as you can see, they're all kind of amber colored, which means that there's no visible ice in them. If ice had formed in these things at a macro scale, you would have seen white spots or lightness. There's no such thing. I organized all these things in these 50 milliliter tubes so we could then process them. You have to figure out how to handle these tissues so that you can preserve their properties faithfully.

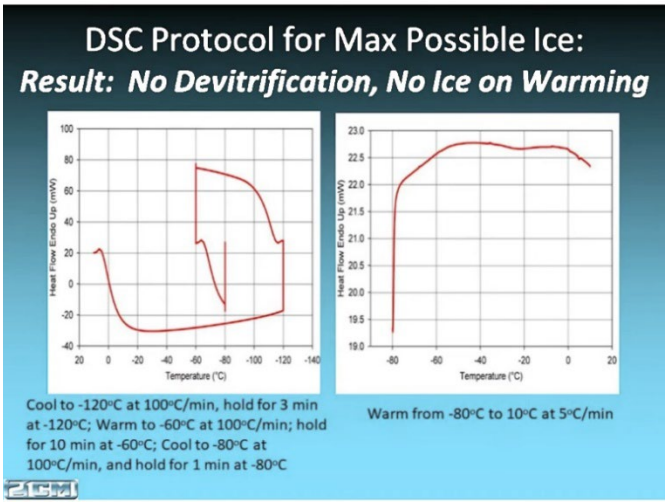
So, in terms of determining how much CPA they had in them and how resistant they were to ice formation, I decided to just take these biopsies, drop them into M22 at room temperature so we could warm them quickly, and then, immediately, as soon as they warmed, in a few seconds blot them. This way the M22 they would have dropped into, would not penetrate into the tissue and screw up the results. And by doing it this way, there was no frost condensation on the samples which would have diluted them and given us a false result..



Slide 9

So then, after you take this biopsy and warm it up and cut it in two you use one half of the sample for ice formation tendency by DSC and the other half for cryoprotective agent content by

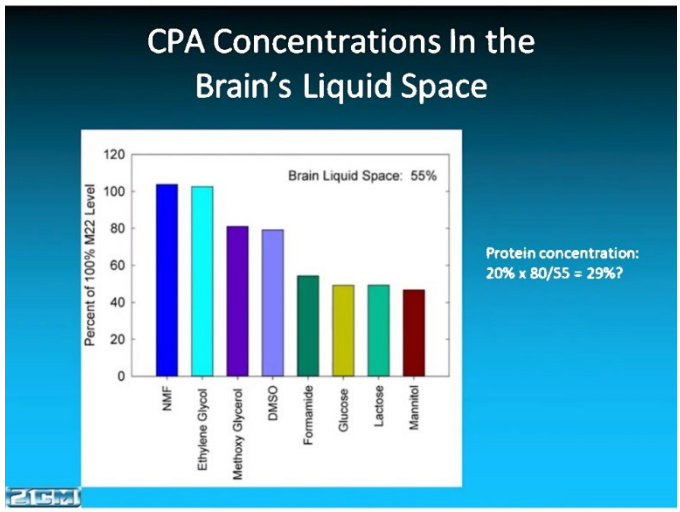
HPLC [high performance liquid chromatography]. So, without belaboring this too much, these are the kind of protocols we looked at. [Slide 9]. We wanted to know if Dr Coles' brain was susceptible to ice formation on slow cooling. But to do this, you do a slow cool to about -90 then you do a fast warm, back up to above zero. And if ice is going to form during slow cooling, it will, and then when you warm it up quickly, you're gonna see a spike, you're gonna see a melting peak. And as you see on the right side, there's no melting peak at all. So there was no ice formed during cooling. You see this temperature excursion on the left, but that's just the DSC sort of figuring out what to do, that's actually not any sort of freezing event.



Slide 10

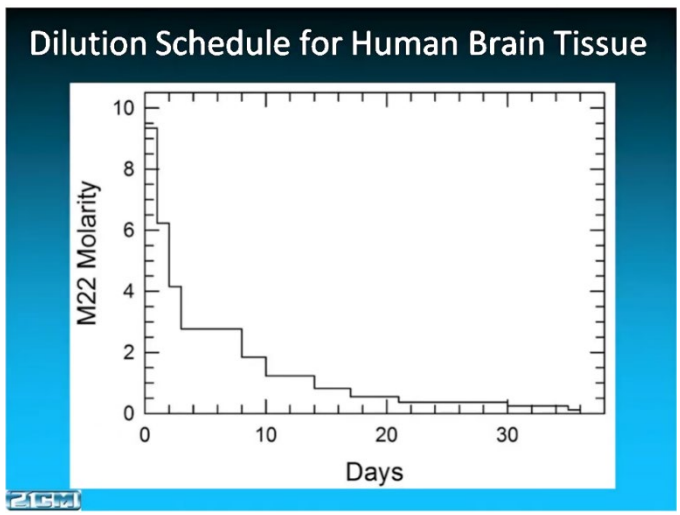
And then the stringent test is: okay, if there's no ice formed on cooling, *could* there be ice? Maybe if there was a slower cooling event, there could have been ice formation on cooling. So let's see what the maximum possible ice content would be in Dr Coles' brain if it had been subjected to bad conditions during cooling. So it's kind of an elaborate procedure, but basically you cool to -120, and so it's nucleated, you warm up to -60 to allow those crystals to grow to substantial size, then you cool back down. [Slide 10]. You can get a clean record when you warm it slowly, so you cannot escape any possible ice formation by outrunning it. And what you see on the right is that there's actually no ice formation, even in warming. There's a couple of bumps, but that's again, just the machine getting its bearings and you can tell that because there's no melting peak. So we were not able to form ice in Doctor Cole's brain no matter how hard we tried – that's good. [Applause]

The next challenge is how much of our M22 formula actually got in Dr Coles' brain cells and into the brain in general. [Slide 11]. So we determined that the liquid content in Dr Coles' brain, based on the biopsy samples, was about 55% of its total volume. And of that, you can determine that some of the cryoprotective components of M22 fully permeated 100% of the concentration in doctor's brain compared to what they were in the perfusate.



Slide 11

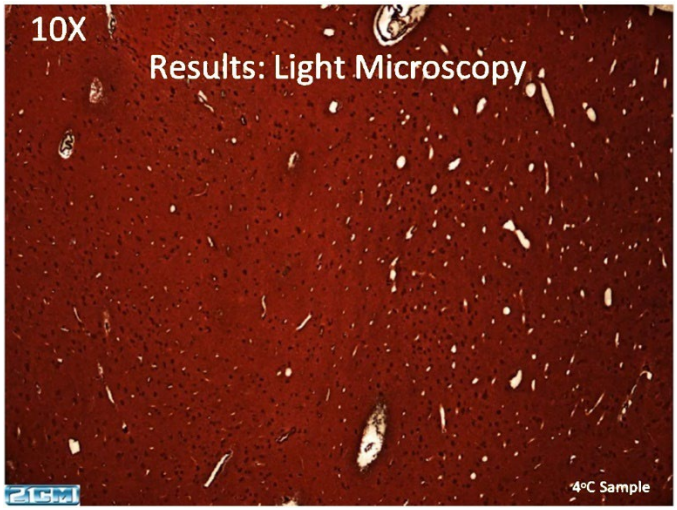
A couple of components were about 80% of full strength and one component was down at the same level as extracellular sugars. But, you have to remember that the brain was shrunken and that means that the protein concentration in those brain cells might have been as high as 29%. You have to add the protein concentration to the CPA concentration, and when you do that, I think that accounts for why Dr Cole's brain was so amazingly stable against ice formation. So we have to consider this experimental test a success as well.



Slide 12

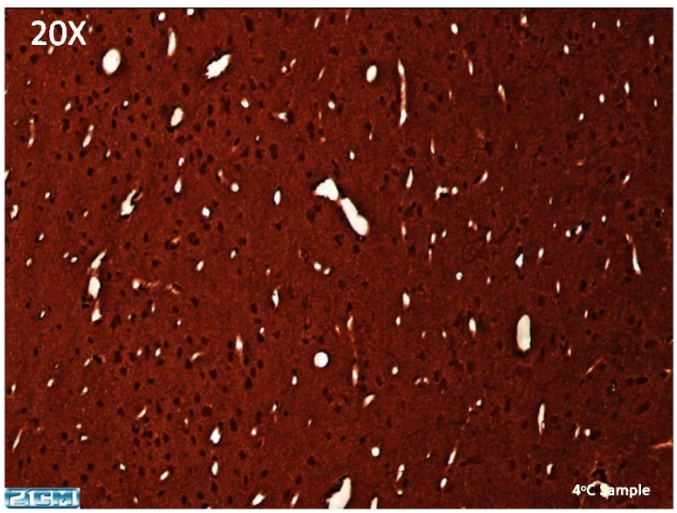
But now we come down to the real nitty gritty. This is really the question we're all most interested in and that is the structural preservation of Doctor Coles' brain. So we dropped the brain samples into M22 fixative either at room temperature to speed up the warming process or at 4° Celsius to avoid deterioration at room temperature while each sample was fixed. We let them fix for a while and then washed them free of CPA. Before warming, they were amber colored, therefore, seemed to be devoid of ice and they stayed that way during warming and fixation. This shows the dilution of the brain samples [Slide 12]. In

order to look at them, you have to get rid of the M22, or reduce it by about one third every so often until we got 0% of the CPA.



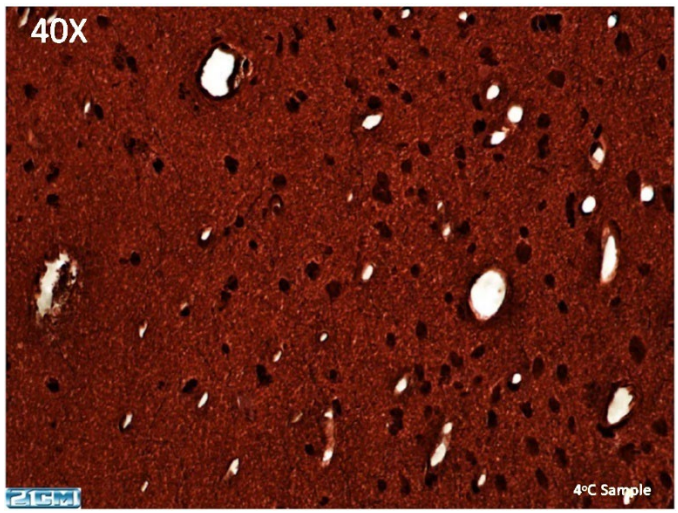
Slide 13

So, what are the results? This is the first light microscopy ever done on an actual human cryopatient [Slide 13]. And what it shows is that all of the structure is still there, at least from what we can see at this level of magnification. But what you're seeing is a lot of white spots. What are those white spots? Those white spots are capillaries, they're normal, they're intact, and there's nothing about them that's really showing much damage. Above the headline you see a little bit of shrinkage space between the capillary and the brain tissue, but there's no debris in that space. So this is 10X. Let's go to 20X. [Slide 14].



Slide 14

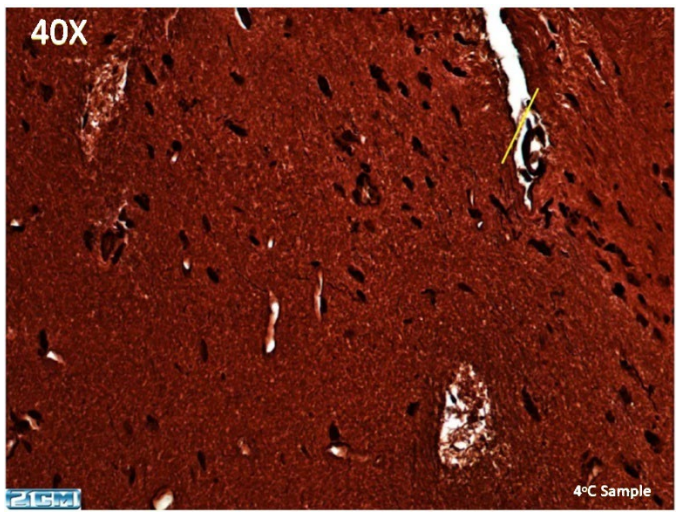
And you can sometimes see damage at higher mags that you don't see at lower mags, but no, we see the same pattern over and over again, and I could show you a million of these images. These are not the only images that we took, everywhere you look over and over again, without exception, you see the same thing. [Slide 15]. There are no ice cavities in the tissue. There's



Slide 15

no loss of ground substance, there's no loss of mass. The tissue remains densely stained with the histological stains that we were using at the time, and the capillaries for the most part look intact.

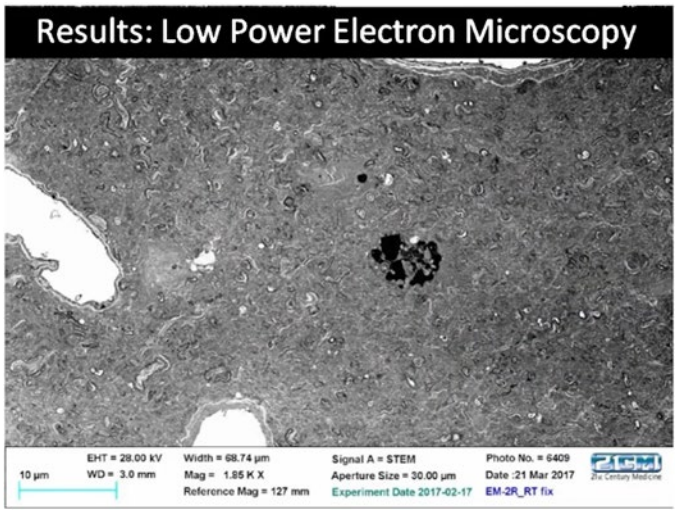
Now I'll show you some examples of things that might be questionable when this happened, but I don't think they actually are. So that's one example on the left, you see this thing that looks a little questionable. I don't think that that's actually, damage to the brain itself as I'll explain in a second.



Slide 16

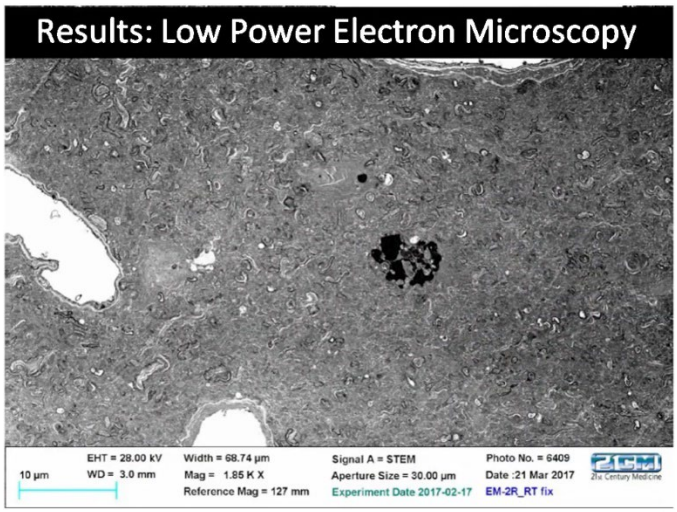
So, here's another 40X [Slide 16] and you see a couple more of these questionable spaces, one over here and one over here. But if you look at this area up here, you can see that I've drawn a line through an area that shows this thin tendril of cells next to a shrunken capillary. And if you were to cut through that, you'd see exactly what you see in those other two areas and you can see that those areas are overlying a capillary and you can see the capillary wall. I don't believe that's actual brain damage. I think that's just an artifact of the way the sample happened to be cut in that exact area. So, the bottom line is that everything

we can see on the light microscope level indicates all the structure's there. Yes, it's dense, it's compacted. We get shrinkage with M22. But that doesn't mean the structure is gone. The structure is definitely there. If we have doubts about it, we have to look at the tissue more closely with the electron microscope.



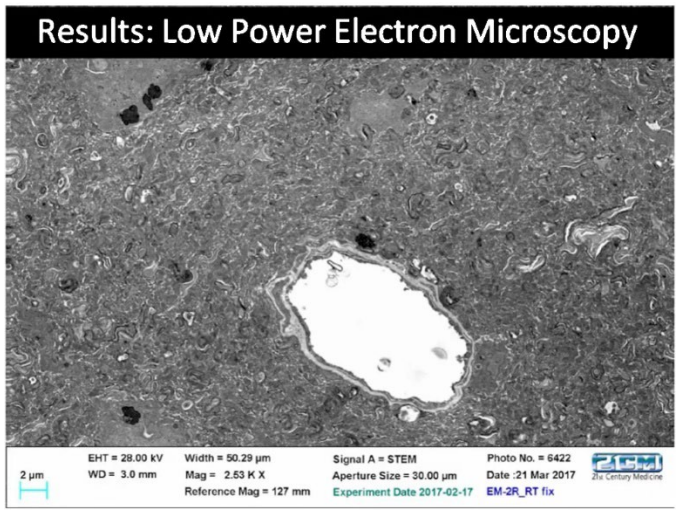
Slide 17

We know what the overall lay of the land is from light microscopy. With electron microscopy, we see the details. [Slide 17]. The details are the same on the electron microscopic level. The tissue is all there. It's condensed. The capillaries are intact, the brain tissue is not missing, there are no holes in it. There's varied shrinkage spaces, but that's about it. Now, there is something weird going on in this sample and that's this funny looking thing in the middle here [dark area]. And that is I think Dr Coles' unique tissue there. Dr Coles' mentation was perfect when he got cryopreserved. He didn't have any symptoms, but he seems to have had something going on up there that led to this because I've never seen anything like this in any animal experiment that I've ever done on brain cryoprotection or in any human normal case. So I think that that is an artifact of Dr Coles himself.



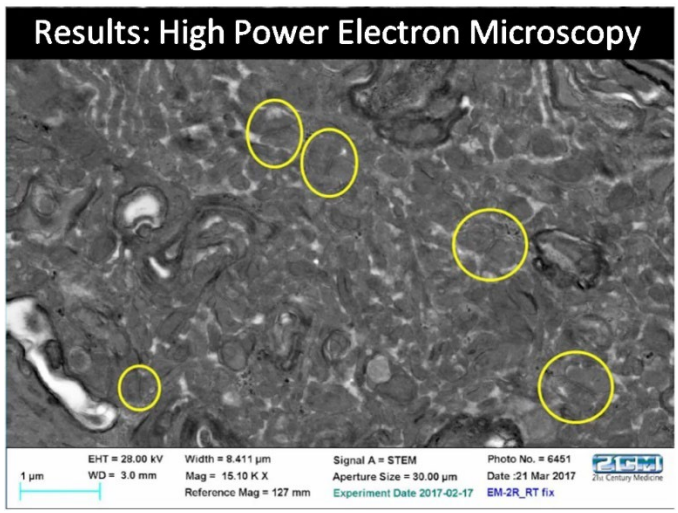
Slide 18

So once again, if you look around the brain at this low power electron microscope level, you see the same thing over and over again. [Slide 18]. You see intact capillaries.You see some shrunken axons, but they're still perfectly intact. They're just shrunken with a little shrinkage space around them, but they're perfectly fine. There's nothing non-inferable about them. And [Slide 19] you see the same thing over and over again, maybe a little debris inside the capillaries; the capillaries are in good shape. For the most part, we don't see a lot of shrinkage spaces around the capillaries, which is actually better than we sometimes see in animal models. So we need to now look at a higher power of electron microscopy to pull out the details because the tissue is shrunken, which makes it hard to see the intimatedetails of the structure to make sure it's all there.



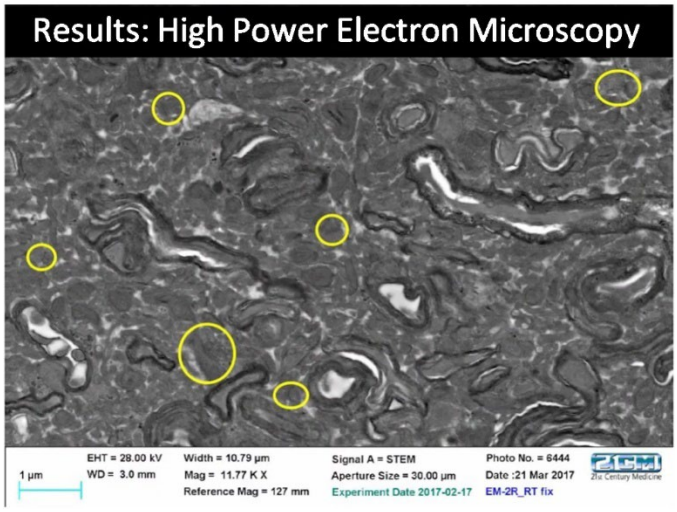
Slide 19

So this is high power electron microscopy and what you see is basically the same thing. [Slide 20]. I've actually circled some synapses in this figure, so you can see them, down here, you can see the post synaptic density pretty well. And you just see



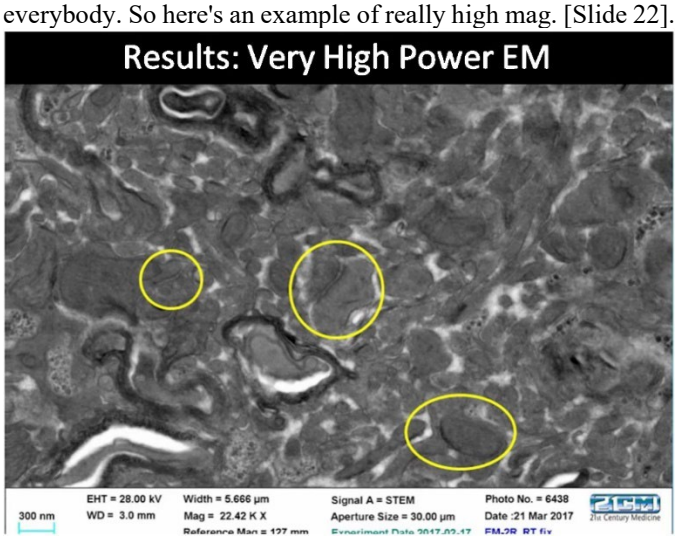
Slide 20

the same thing over again and you see some shrinkage spaces over here, but there's actually no brain damage associated with that, at least structural damage. This is another example showing this actually really beautifully preserved axoplasm within the myelin sheath here. [Slide 21]. So we used to worry that cryoprotectant couldn't get through here and protect these things, but it looks like they can get detected anyway; lots more synapses that seem to be intact.



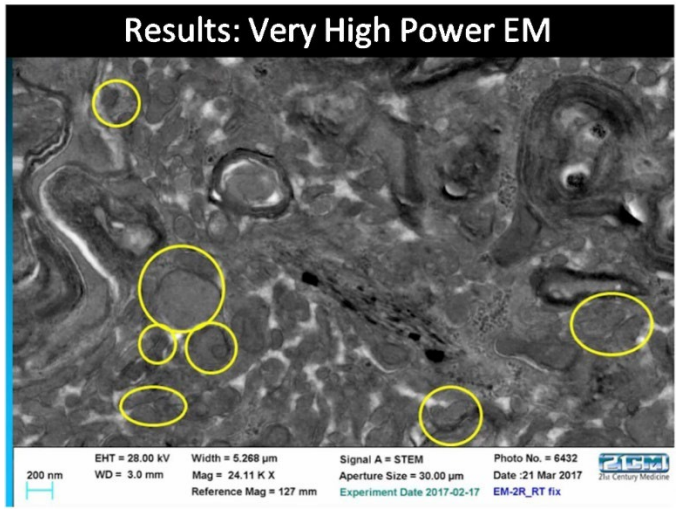
Slide 21

But to really look, you have to look at really high mag to satisfy everybody. So here's an example of really high mag. [Slide 22].



Slide 22

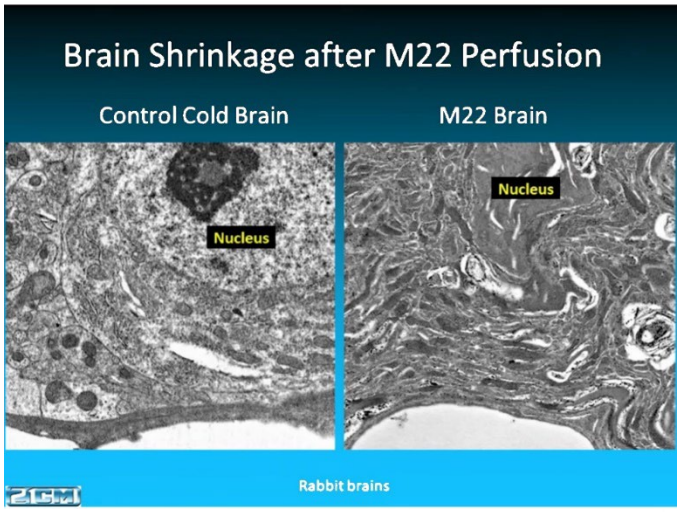
Again, you can see postsynaptic density, and if you look a little bit hard over here, you can see, hence, even presynaptic neurotransmitter vesicles. And it's not like these are only found only in one or two micrographs, you see these all over the place, you see the synaptic clefts, you see shrinkage spaces. [Slide 23]. This means that the spaces are created by osmosis here, which means that the membranes here surrounding the shrinkage spaces have to be intact so that they can respond osmotically to create those spaces. It means the membranes are intact.



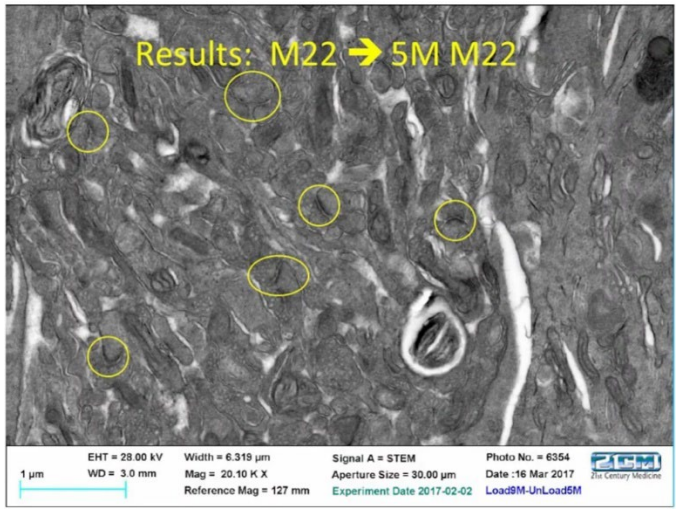
Slide 23

So, in summary, the first ever evaluation of an actual Alcor case showed no detectable fracturing, no ice crystal formation or damage, acceptable preservation of histology, good preservation of ultrastructure, a very likely connectome preservation, and I have to add, also, a lack of fracturing. I would say it was better structure than I often see with rabbit brains which have been a gold standard up to this point. So the conclusion is that the cryonics hypotheses can be falsifiable. But the good news is that the present hypothesis was not falsified, it was actually supported. And that goes along with previous cryonics hypotheses, about ASC, and human brain vitrification, and the survival of memory after vitrification and freezing, which also survived potentially falsifying challenges. So, cryonics is opening itself to scientific scrutiny of at least some of the premises, some of the hypotheses around it. But there is one last issue and that is that the hypothesis we're testing here, that cryonics can sometimes preserve human brain structure, needs to be qualified, in that one case does not prove "sometimes." It means it happened once; you have to do it at least one more time to prove the point. But that's a minor bar compared to where we are already. So, this is a tremendous advance in the history of the science behind cryonics. But there's more coming.

There is a scientific publication in preparation that will describe these results to the scientific community for the first time and hopefully begin to change these scientific debates about cryonics. [Applause]. Thank you. But it will also contain more than just this human case. It will contain some animal data that supports it. And this slide just shows the fundamental problem that we had with this case, which is brain shrinkage. [Slide 24]. As you can see the structure of the normal rabbit brain on the left looks quite different than what you see on the right. The structures are distorted. You can still recognize things like nuclei but they look nothing like they do in normal situations. So we did some experiments that prove that even though the structures are shrunken, they're not obliterated, they're still there. They're just hard to see. The way you do this is by partially washing out the cryoprotective agent. [Slide 25]. If you wash it all out, then you can get into osmotic damage as indicated by the black X there. But if you wash it part of the way out and the brain is



Slide 24



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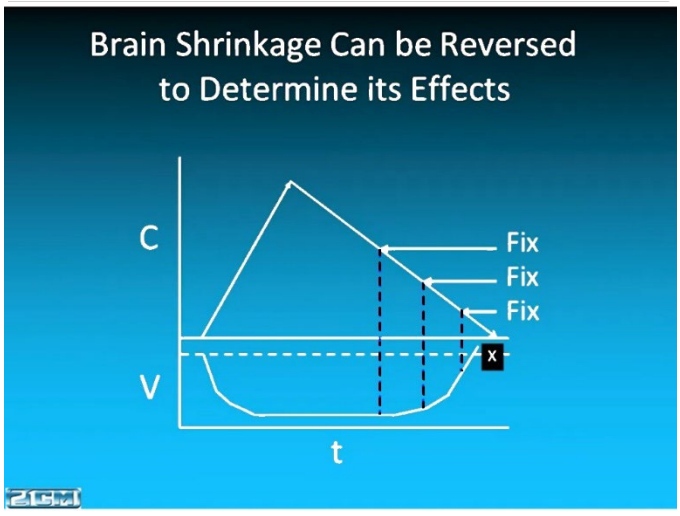

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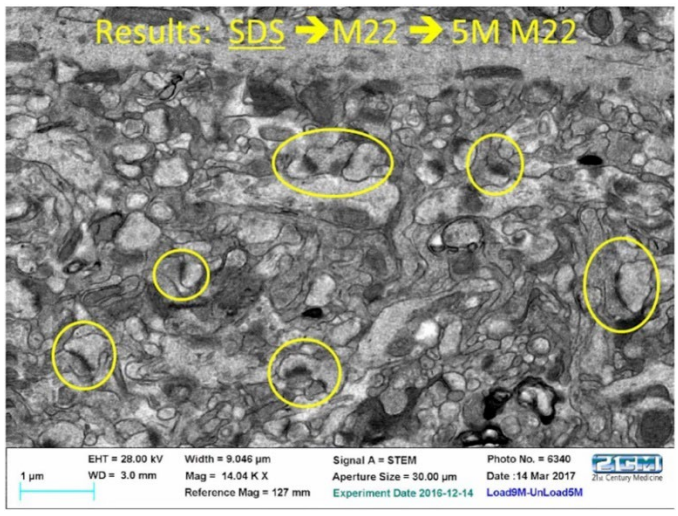


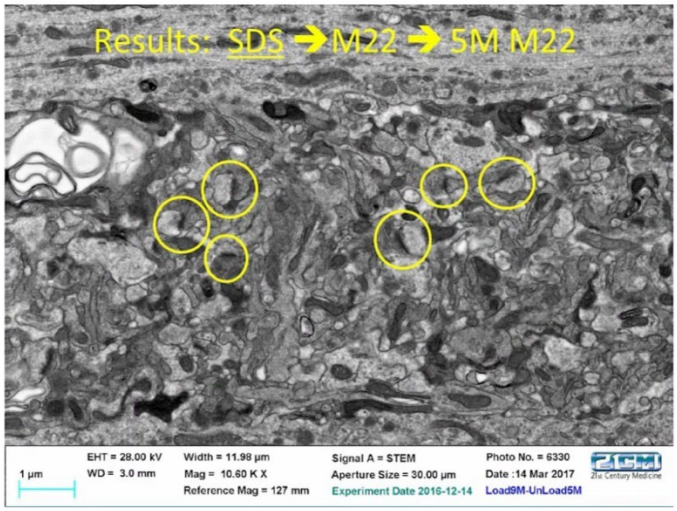
Slide 27

rehydrated, the structures are less compact and thus more easily visible and more recognizable to your traditional neurobiologist, therefore more convincing, and you don't get into osmotic damage.

So this is what you get when you do that kind of an experiment. This is a rabbit brain that was loaded up with full strength M22 and diluted out to about half strength M22, about five molar M22. [Slide 26]. And what you see is the beautifully preserved ultrastructure with crisp cell membranes, very crisp synapses, many of which have been circled and you do see weird things like this occasionally, but whatever this is, it's shrunken, it's compact, there's no debris in the area. It's not damaged, just shrunken.

And you can get even better results going to the next level by using Yuri Pichugin's trick of exposing the brain to sodium dodecyl sulfate before you do the experiment. [Slide 27]. That opens up the blood-brain barrier, you load this brain with M22, you wash it up to five molar, and you get a result so beautiful, it looks like an artist actually drew it for us. There's just beautiful preservation of snapses, very clear preservation of presynaptic vesicles and postsynaptic densities, all over the place wherever you look. And this is another example, the same thing again, we saw this all over the place and up at the top of the screen, covered up by the headline, is this lovely nonmyelinated axon looking quite beautiful. [Slide 28]. Now, we do see these little blank areas over here on the side, you know, in which things are shrunken. But again, we don't really see that so much with human brains. So the human brain is actually better than this.

I want to thank Dr Steven Coles for making this presentation. I want to thank Dr Steven Coles for making this presentation possible. And I want to thank Natalie Coles who's here with us today for making this experiment possible. [Applause]. [Slide 29]. It would not have been possible without you, Natalie. Thank you so much. And I want to thank Alcor, because Alcor was very brave to enable this experiment. This experiment could have led to terrible results. It could have led to embarrassment. It could have set back cryonics. But it had to be done



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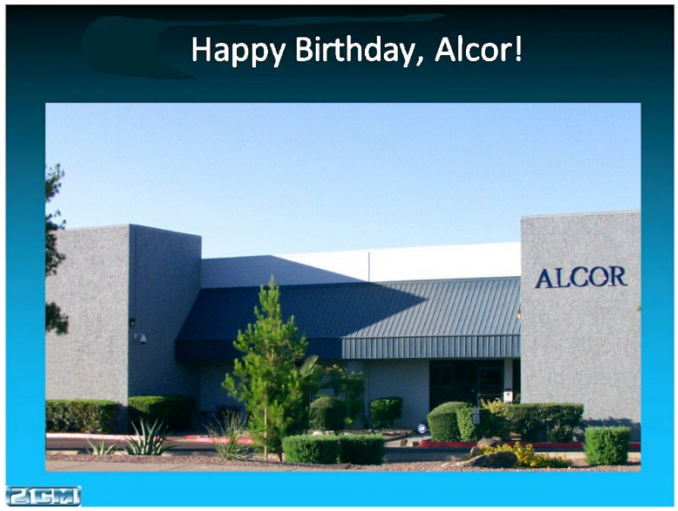

Slide 30

Slide 29

because we're not just doing this for the fun of it. You know, we're doing this because we want it to work. We have to see if it's gonna work or not. And the only way to do it is to examine it, and look at it with unblinking eyes. So congratulations to Alcor for being brave enough to enable this to work, for paying for this out of its own research budget. I think this is the best research money Alcor has ever spent. And we'd like to see more of this happen in the future. So I just wanted to say happy birthday, Alcor. Thanks everybody, for coming. [Applause]. [Slide 30]. And, there's time for questions.

Max More: Thank you Greg, we have some time for questions. Actually, I have a first request. First of all, next time we do this, can we please not get the protocol at the last minute? We'll be writing things down off the phone and trying to convey ... [laughter].

Greg Fahy: That's another compliment I have to give Alcor though, for being able to really stretch under very difficult conditions to get this critical experiment done correctly. Everybody, I think that Alcor needs to be congratulated for their role in this landmark experiment.

Rudi Hoffman: I've heard about the fracturing issue all my cryonics career, and people talk about that, but I'm not sure most of us really understand it. What sizes are we dealing with? And obviously, this is all a protocol that does is not at -196 [the normal, liquid-nitrogen temperature of cryopreservation, but above it]. This is intermediate temperature storage. It's not yet quite available. Would you address those two questions?

Greg Fahy: Sure. So, the size of a fracture varies depending upon the conditions under which it's formed. So, in organs that we've looked at so far, and that Alcor has looked at in autopsy cases on non-brain structures, the fracture can actually cleave an organ all the way in half, in the worst case scenario. Usually they cleave the organ part of the way. So you see the fracture on the surface of the organ, but it doesn't penetrate all the way through. In the case of brains it may break up the brain into pieces, and that would be a problem because then if the pieces shift, your nano repair technology is gonna have to not only match up structures on the two sides of the fracture, but also move the pieces into the position to do the healing. You would really rather avoid fracturing if you can. You're absolutely right. It's not possible for most people right now because Alcor and in fact, no other cryonics organization that I know of, although maybe the Europeans are ahead of us on this, has intermediate temperature and long term storage available for most people. But Alcor does actually have a dewar that operates at -140 that has room in it for a few more people. Only neuros but not whole bodies yet. But 21st Century Medicine is actually actively engaged in a design for whole body intermediate temperature storage for the Europeans, I believe. So that may be coming online at least over there. And depending upon demand, it may become available in the United States. It's merely a matter of economics. It's more expensive to store at higher temperatures because you have to maintain those temperatures by feeding energy in which boils a little bit more liquid nitrogen, but may double the cost. But I personally would rather pay the extra money and not be fractured because that's just one more obstacle between now and coming back and that would be best avoided if possible.

Max More: Do we know if brain shrinkage is a concern?

Greg Fahy: That's the reason that we did the rabbit experiments to follow up on the Dr Coles' results. People who advocate Xenon as an alternative to cryoprotection claim that it's obvious that M22 would just dissolve the brain. Therefore, there's nothing left. Therefore, all these images that we're showing of shrunken brains are just showing soup, basically. In order to overcome that objection, we diluted the the CPA down to rehydrate the brain, so you can actually see the structure. When you do that, it's obvious all of the structure is still there. And we haven't done a molecular inventory of the brain, but I would wager all the molecular inventory of the brain is still there. So I don't think that the shrinkage is fatal, let's put it that way. On the other hand, it would be nicer to avoid it if we can. So that's the next way. I mean, there are complications of doing that in clinical cases because after prolonged cold ischemia, the blood-brain barrier starts to become leaky. And so you can't use specific agents to open it. On the other hand, maybe you don't need them anymore. Maybe you can avoid some of the brain shrinkage as a bonus of some of this other damage that takes place. So we like to capture everybody under conditions as good as Doctor Coles and then be able to add on to that, blood-brain barrier opening technology to avoid brain shrinkage. We're not there yet. But even though we're not there yet, I'm very confident that other people preserved the way Dr Coles was preserved will have very well-preserved brain structure.

Max: Was this experiment done with the control eg your brain cooled and warmed without cryoprotectant?

Greg Fahy: Well, that would not be a very good control. [Light laughter.] If you do that kind of thing, you may see some signs of preservation, especially on the histological level. But if you look at it at the electron-microscopic level, it would look terrible. I've done infinite numbers of experiments in which I was trying to freeze brains using every cryoprotectant in the book and every concentration in the book. And you don't want to go that way. That's all I can tell you. The results are not pretty. If you don't want your brain to be reduced to hash, it's much better to be vitrified. Now, having said that, we did do an experiment in which we perfused rabbit brains with 3.72 molar glycerol and froze them and freeze-substituted them to see what they look like before you thaw. There's a lot of the damage that you see take place during thawing. And what we saw is that the brain was shot through with these veins of ice that seemed to course through it, sort of like a basket weave that seemed to sort of be pushing through it indiscriminately regardless of what sort of brain structures might be there. It looks very nasty on a histological level. But when you look at it by transmission or scanning electron microscopy, you find that the ice spaces have smooth walls, they compress the tissue very neatly and compactly between them and they have not ripped up the tissue. That would be part of that paper that we're gonna publish as well. But there's hope for people whose brains are frozen also, I would say, but the preference would be to do it well.

Max More: You're saying Michio Kaku is wrong, that the cells don't blow up or explode ... [Laughter.]

Greg: Yeah, Michio needs to revise his science a bit there.

Max: So, the straight frozen brains are not necessarily hopeless, but for revival would require something like advanced medical nanotechnology getting in there at cryogenic temperatures to fix them. So we don't want to give up on those, but also it's not the desirable condition.

Greg: If you want to make hypotheses about the revivability of straight frozen brains, you're gonna have a much harder time finding a reasonable hypothesis, but you can't rule it out yet either.

Max: So, very quick answer, if you know it, what day was Dr Cole's procedure done? 2014?

Greg: I think it was circa 2014 or so. It's ridiculous. It took us a long time to get the samples out of Alcor and to 21st Century Medicine, and it took me a long time to get them analyzed. But the beauty of cryonics is that you can afford to wait, so we could do the experiment.

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Dr. More (*left*) with Prof. Chalmers at the Alcor conference

Philosophical Aspects of Cryonics, Life extension, and Virtual Worlds

Prof. David Chalmers in conversation with Dr. Max More

Alcor 50th Anniversary Conference, Scottsdale, Arizona, June 4, 2022

David Chalmers *is one of the most famous contemporary philosophers and cognitive scientists. His most recent book,* Reality+*, is the first serious philosophical treatment of what is real, and what is valuable, in virtual worlds. This is a topic of special interest to cryonicists, especially those of us who hope we may live through this type of technology, one day in the far (or maybe not so far) future.*

Max More *is a former Alcor President, and, at the time of this talk, was Alcor's Ambassador and host of the Conference*

Max More: I met [Dr. Chalmers] once a few years ago rather briefly. But I've been following his work. He is a philosopher and cognitive scientist specializing in the areas of philosophy of mind and philosophy of language. He is a Professor of Philosophy and Neuroscience at New York University, as well as Director of the NYU Center for Mind, Brain and Consciousness. He is best known for formulating the Hard Problem of Consciousness. His most recent book, which I can recommend having read all 520 pages of it, is *Reality+: Virtual Worlds and the Problems of Philosophy*. I'm sure we'll be talking about some of those today, some of those issues. So please welcome David Chalmers. [Applause, Dr. Chalmers acknowledges, Max continues].

MM: Now I can ask you questions or you can just offer some observations on what you've already heard today. You know, we can just launch into that.

David Chalmers: OK. Well, thanks. Great pleasure to be here. I'm really a newcomer to the world of cryonics or at least an outsider. I've not thought about it in depth before this time, although I've certainly read a few things here and there and issues about cryonics are very adjacent to some of the issues on which I work, issues of consciousness and identity, not to mention, wow! [Lights start to flicker.]

MM: The simulation is malfunctioning. [Laughter].

DC: Okay! You just mentioned consciousness and the lights flicker. But yeah, why don't you go ahead?

MM: Your book is a really detailed examination, takes you step by step really for thoughts about virtual worlds, all kinds of errors like deep fakes as well, how we can know things but really a very philosophical discussion starting off with the simulation argument, and how we can know, or can we know that we aren't in a simulation. It's really the best discussion I've seen of that to this point. I'm not gonna give you [the audience] the surprise conclusions or anything like that. You need to read it for yourself. There was also a lot of discussions about not full-blown simulations but, you know, virtual reality, virtual worlds of various kinds. I wonder, whether when we're revived or rehabilitated, there might be a role for some kind of virtual training sphere because, you know, when we first come back, we will probably not have much of a clue about things. So what do you think would be the benefits of using virtual worlds for cryonics rehabilitation?

DC: Yeah, I mean, it certainly seems very likely that there'd be room for a lot of use of the virtual worlds on revival from cryonics. I guess this is probably most obvious in the case of the neuros where you preserve the head only. Then you know, if there's not actually a physical body waiting for them, I presume that revival from cryonics is gonna be an extremely difficult and perhaps traumatic process for people who go through it. There's gonna have to be a very long period of readjusting to things like control of a body.

That process may be actually much more straightforward in a virtual world where one has a kind of control over a virtual body, at least in the initial stages, I think it's very easy to imagine. But at least for the purpose of say, a physical calibration, getting this on board with a virtual body would at least be a predecessor to connecting up to a physical body. Furthermore, there's also social risk. I imagine waking up from cryonics immediately, into a whole new world full of chaos and new people, it's gonna be a rather difficult process. If one can wake up in a world and stay with one's family or friends who were themselves cryopreserved, then okay, maybe that's a lot less traumatic. Also it's possible though that maybe Alcor, for example, will have its own virtual world into which people who are revived from cryopreservation naturally enter.

Hey, maybe this is actually one function for this conference. You know, when you wake up from cryopreservation and you don't know anybody there, that's kind of a drag. But if you wake up from cryopreservation, and here are all these people you met at the Alcor conferences hanging out in the Alcor virtual world,

MM: Alcorland.

DC: Alcorland. You've got the trademark? Okay. So I think those are very natural functions for virtual worlds, at least in the early stages. So it's entirely possible that at various stages in the future, many, many people are going to be full-time living in virtual worlds. Perhaps, you know, if population growth continues and the earth is extremely crowded, there may be all kinds of incentives for non-cryopreserved people already to be living in virtual worlds. And if suddenly you guys are super successful and there are a billion people cryopreserved, waiting to be revived, then maybe revival into a virtual world is gonna be a very real possibility.

MM: There's a concern some people might have. I know at least one person in the audience has this concern. And I don't think you addressed it in the book as far as I remember. Have you seen the Black Mirror episode, White Christmas?

DC: Um-hm.

MM: Yes. So what about that kind of scenario that the fear that if you come back in a virtual world, you're completely at someone else's mercy and they could flip the dial and make you suffer through millennia of silence and drive you insane. What kind of safeguards do you think there are likely to be or should we be thinking about?

DC: Well, virtual worlds right now are largely constructed by corporations. Meta has their own virtual worlds that they're trying to create. Many of the video game worlds are owned by one corporation or another. The popular virtual reality spaces like alt-space is owned by Microsoft. So it's true that insofar as you come back into a virtual world under the control of some corporation, you have to worry about their incentives. I suspect that, you know, elite people, privileged people will have access to virtual worlds where they've got some significant degree of autonomy. On the other hand, the virtual worlds for the masses, which may end up being free or low cost to entry, you know what they say: when something is free, then you're probably the product being sold.

The kinds of manipulation you see on social media are very real for a virtual world. So I very much hope that there are gonna be virtual worlds controlled by many entities in the future: state controlled, user controlled, decentralized on the Blockchain. Indeed, foundation controlled. I think it would be very, very natural for Alcor to have its own virtual worlds governed by the Alcor Board according to certain ethical principles to make sure people are not overly manipulated.

MM: Maybe you should put that in your paperwork that you want to be brought back in an Alcorland or one that's controlled by a good group of people who you trust. It's kind of a tricky issue, really. What information about the brain do you think will be sufficient to recreate consciousness in your understanding of how consciousness functions? Do you have any concerns about preservation of, like Penrose's view of these weird little structures that he thinks are not preserved? Do you think that matters? Do you think the current processes as you understand them are likely to preserve consciousness if done well?

DC: This is, to a large extent, a biological question and also a question about theories of consciousness. I do believe that if

you preserve the brain well enough, then you ought to be able to preserve consciousness and indeed identity. There are really two questions with respect to any future version of ourselves. At least, say, three things that we care about. First, there's just behavior. Is this going to at least have the cognitive capacities to behave the way that I was behaving? Will I have my capacities for perception or reasoning or memory or emotion and so on? From the outside, will that at least look like me? That's a major question. And the question is to some extent biological. But beyond that, there are questions about consciousness. We want that being in the future to be genuinely conscious, to have a state of subjective experience. Beyond that, we care about identity. We care that that person who is revived is actually me and not somebody else.

You know, in the case of some technologies like say uploading, which I think we'll talk about, some of these questions are very real. Will a silicon a digital upload of our brains genuinely be conscious, and indeed will it genuinely be me?

Where cryopreservation is concerned and where if we assume the technology of an accurate enough revivals of the brain, then I would expect that we ought to be able to get all three of those things: behavior, consciousness, and indeed, identity. I think we've got pretty good reason to believe that a system with a brain enough like ours is going to be conscious. That's fairly uncontroversial. [Lights flicker, laughter]. Wow.

MM: ... Consciousness! Every time! [Laughter].

DC: It's like they're trying to turn us into philosophical zombies. [Laughter].

MM: [There was] a point raised about microtubules [tiny brain structures studied by Roger Penrose and Stewart Hameroff, thought by some to be important in consciousness]...

DC: There are biological questions about what is required. What kind of fine grained information in the brain is relevant for consciousness? It seems, like, say, at the very least the connectome structure is going to be relevant. Get that connectome!

I saw the talk this morning [Greg Fahy's talk, elsewhere in this issue] where it looked like an awful lot of synaptic structure seems to be preserved. That's heartening. And you know, if that's true across the board, then it looks like at least say the connectome structure, the structure by which neurons are connected to neurons, will be preserved. Now is preserving the connectome structure enough to actually get any of those three things, you know, full scale human behavior, consciousness or identity? I think even when it comes to behavior, we don't know, maybe fine-grained information is gonna matter, maybe the connection strengths are gonna matter. Maybe there are gonna be cells other than neurons which are going to matter. So to some extent, there are biological questions there. The extent to which current cryopreservation techniques actually preserve the relevant structure is probably beyond my pay grade, in this sense.

That said, as a philosopher, I'd say, well, there are the biological questions about what's going to be required to preserve brain function well enough. That's largely a biological question. Are there further philosophical worries beyond preserving the behavior, about preserving consciousness and identity? In the case of uploading, there certainly are. In the case required, I think most philosophical theories would predict that if you preserve our brain structure well enough, you will also replicate our consciousness.

Maybe there are some religious views that bring in a soul. I gotta say that under certain circumstances, the soul will leave the body and then perhaps upon reanimation, either we'll find it impossible to reanimate because the soul is no longer around, or worse, we'll reanimate a philosophical zombie, a behavioral duplicate of us without consciousness. I would think of that as a fairly marginal view in this context, not taken that seriously by philosophers and scientists who think about this topic.

Setting aside that kind of view, I would think, philosophically, preserve the brain well enough, and revive the brain well enough, and you will provide consciousness and likewise for identity. Again, the soul question comes up. I mean, if the soul leaves the brain on cessation of brain function, then what happens when you revive? You have to get a new soul off the shelf? [Laughter].

MM: What good is the soul anyway? I'm always puzzled by what the soul is supposed to do, to carry identity around until you reincarnate, in some views, but certainly you have the same personality with the same soul. But I don't really know of what use the soul is.

DC: I think it's precisely a vehicle for identity. That's what souls are for, for reidentifying you over time. And reincarnation, well, that's what is really distinctive about it. You get to be this new being. You don't remember the old being, but that's the plan.

MM: There's no continuity. If you take the continuity view of identity, it's not good that you have this route to continue. I'll just make a comment on the soul point. Rather than argue that there is no soul, I'll point out to you, people who need the soul generally seem to believe that the soul enters the body at the point of conception. I would point out that there are millions of people walking around who were cryopreserved who were just embryos at the time, and they don't report any kind of a problem with being reborn, or a psychic event, nor do people who were under anesthesia or people in unconscious states, who have very little activity in the neural centers. So it doesn't seem to be a problem and if there is a soul, apparently it's gone before we become animate, so it presumbably passes in space and time, so it shouldn't really get ambition for hanging around. There shouldn't really be a problem.

DC: If your soul, on the other hand, has already been reincarnated long ago, when you get revived, do you guys grab that old soul back? Do you get a new soul off the rack, or do you just turn it into a souless zombie? Given the appropriate religious views, it's going to be a real question. I'm skeptical myself about that, the background, playing without a soul. But if you believe in a soul, you have to have to at least worry about it.

MM: Well, I was wondering if people who believe in souls are not fledged. Whenever I used to teach all religion, I would always ask my students to describe what it's like in heaven. And I would always get these blank looks. "Huh? I never thought about it." What do you mean you never thought about it? "I have no clue whether you have a body to enjoy ..." I mean, no clue at all. It was kind of puzzling.

DC: And the next question's gonna be, what is it like in Alcorland?

MM: Yeah. [Laughter].

DC. That's a new, technofuturist heaven.

MM: We'll get an advisory committee working on it right away. There we go, Steve [Graber], there's a new job for us. What do you think about the possibility of that, rather than being revived entirely biologically? There's a range of scenarios. Let's take a fairly modest one to begin with. What if it turns out that the work of Ted Berger and such people with synthetic neurons works out, and it turns out for some reason to be easier just to replace some neurons with these, you know, field effect transistors or mechanical parts. Do you think that would be a threat to continuity of consciousness, and if so why and if not, why not?

DC: I think the safest case is when you do have some kind of strong physical continuity with the original physical organism. So let's take a case even not involving cryopreservation. Let's take a case of gradual replacement, say of my biological neurons. My neurons are wearing out and they can be replaced by synthetic neurons. And maybe my neurons get replaced one at a time, or one brain area at a time by synthetic neurons. So I start out 100% biological. Then after a while I'm 90% biological, 10% synthetic, 50-50, all the way and maybe eventually 100% synthetic. I guess in that case, I'm reasonably confident that consciousness and identity would be preserved, at least assuming again, that the synthetic neurons can replicate brain function well enough to give you the original kinds of behavior without a massive breakdown in cognitive capacities.

You could actually go through this process yourself gradually over a period of weeks or years even. And I think we'd all be very naturally inclined to think that you'd still be the same person at the end. So at least in that case, gradual uploading or gradual replacement of biology by synthetic neurons seems okay to me for preserving consciousness and identity. And I've used that in some other work and argue for the possibility at least of synthetic consciousness. My own view is consciousness doesn't have to be biological. It can also be present in digital systems in a silicon basis and so on. As long as the right information structures are present.

Then, moving to your case, this is a case of revival from cryopreservation where perhaps we replace some of the neurons in advance by synthetic neurons. We look at our cryopreserved brain and we say, okay, well, these neurons seem to be healthy, but these seem to have somehow been damaged, we better replace some of them with synthetic neurons. You know, again, to me, if it's five or ten percent of the brain, I'm inclined to think that looks a bit like getting a neural prosthesis. I'd be inclined to think that clearly can preserve consciousness and identity, if it preserves enough of the brain functioning. If you did it all at once, then if you use the biological brain as a guide to a new wholly synthetic organism you're creating, well, that's much closer to what people normally think of as uploading. And which is the controversial case, maybe we can get to that.

MM: Before we get to that, I'll kind of hand-wave a little bit about replacing biological neurons and replacing sufficient brain function. Do you have any thoughts on how deep we need to basically emulate that level? Do we just need to emulate the connectome with the firirings of the neurons? Do we need to emulate what's going on with the biology of the cell itself, simulate the mitochondria and all those functions? What do you think we need to get down to?

DC: My default here, the conservative view, is that it's neural processing that matters, but we really don't know. Certainly there are people like Stuart Hameroff who thinks it's the processing in the microtubules in cell walls; there are various theorists who think that quantum properties are what matter. It is kind of at the very least interesting that in C. elegans where we've mapped out 302 neurons in their connectome, their connecting structure, no one's been able to actually use that to produce a good simulation of C. elegans' functioning. Is that because something other than the connectome structure matters? So I think this is actually right now an empirically open question, to guess what level of brain functioning we need to preserve.

MM. We can try it in like five percent of the brain or one percent at a time and try it with different people and see what happens if you start zupping zombified. So, okay, let's go to the uploading, head in that direction. So, given what you've already said, under what conditions or what, because of different kinds of uploading, different ways of getting uploaded, destructive versus copying and multiple copies and so on, do you think that could preserve identity? So someone's cryopreserved, maybe it might be possible, it might be easier to scan the brain and create a software version. Does it matter if you keep the original or not? And so on.

DC: These are very difficult questions, questions about preservation of consciousness and especially preservation of identity in uploading. Again, I think the safest case is gradual uploading where you know, the neurons get replaced one at a time by something synthetic. I think there's a pretty reasonable case that after replacing just a small portion of the brain with a synthetic substitute, identity will be preserved, and then you kind of chain that step by step. There's a pretty good case for consciousness and identity being preserved at the end. I think if there's no consciousness at the end, then I guess the thought is well, either there's a breakdown of functioning which is gonna come back to the more biological scientific question and what's required for functioning or you'll say what's left at the end is all that brain functioning, but with no consciousness. This is the philosophical zombie. You might think at the end of uploading, we'd be left with an unconscious zombie. Despite being an advocate that the idea of a philosophical zombie is coherent, I do find it extremely implausible that this would happen in practice. But at least because you have to think, okay, what happens to consciousness during the uploading process? If it's found gradually, does it suddenly disappear at a certain point? 100% to 0? That seems like an extremely implausible continuity or does it gradually fade out? Well, maybe these lights were trying to illustrate that gradual fadeout for us. So in the middle, you're actually conscious but only half conscious and you say you're fully conscious, that leads to all kinds of difficulties too. So for those unphilosophical analyses, I'm inclined to think gradual uploading is likely to preserve our consciousness and identity.

The hard case, the hardest case is – here's a case that many people would think would go the other way. This is nondestructive

uploading. Nondestructive uploading is when you keep the original biological organism around and you create an upload, a digital duplicate, you know, based on, say, that person's brain. So maybe while this has been going on, someone's been scanning my brain using the secret brain scanners you have in the back of Alcor somewhere and creating a duplicate of me in the next room, and that duplicate is now waking up.

"Duplicates" – R.M.P.; face is AI-generated.

I guess you have that many people's intuition about that would be okay, well that person, they could be intelligent, they could be conscious. But would they be me? That's the question of identity. There I think many people's intuition is no, that wouldn't be me, that would be somebody else. When questions of self interest are concerned, I I'd be concerned with this being and not with that being.

So in nondestructive uploading, many people start to worry about identity. And then there's the medium case of destructive uploading. What if we create a silicon duplicate while destroying the original brain? In the gradual uploading case that happens. Let's just say now it happens all at once. We create a duplicate in the next room and we destroy the original brain. I mean something like this happens in the [Derek] Parfit teleporter, right, you kill the original. But in that case, you create a biological copy. The same issue comes up even there, of identity. Is that me or is that not me? That's, the philosophical hard case, I think.

So I do think that if you want to do this safely, the best case is gradual uploading the biological original. Versions of this case are gonna come up, in cryonics I think, potentially in cryonic revival. It's very likely, at least entirely possible, I think, that there could be a period in which brain revival is very difficult and risky. And maybe the technology of the day will be such that if you revive a brain, then you're likely to have some quite serious damage. So the conservative people will choose not to have their brain revived for at least until maybe decades later when the technology is perfected.

MM. You were conservative in that context.

DC. Right. [Light chuckle]. But actually this is interesting in this context, the the cryopreservationist can come out looking conservative in certain ways. The alternative: in the meantime, say, uploading technology has actually really been perfected because for various reasons, uploading technology, you know, requires really good imaging technology far beyond what we have now for brain imaging. But one can imagine a point in the future where it's possible to gather all the relevant information about the brain by imaging it, and using maybe advanced artificial intelligence to create a digital upload. Digital technologies in general are easier than biotechnology, I take it, so I think it's a very real possibility.

There could be a period say of some decades where cryo revival is at least extremely risky, but cryo uploading, uploading a digital, synthetic being based on the cryopreserved brain is feasible. And then the question is what do you want to have? Maybe uploading at this point in society has become actually quite common. Many people are being uploaded and they seem to be fine. They even say their memories are preserved. Yeah, I'm here. Being uploaded is great. You live forever and so on then. So it could even become quite common.

And then the question is what does the cryonics advocate say to this? We say okay, well now this is a great form of survival. So do we at least encourage all of our cryoreserved patients to be uploaded or do we say, oh no, it's too risky We don't know whether uploading actually preserves the original being. And therefore we're going to wait it out for some decades until brain revival is possible. So this is the context in which the cryonics advocates can start to look like the bioconservatives. "Yeah, that whole digital uploading thing, it's a little bit dodgy, a little bit dangerous. You need the original brain, dammit.

MM. We are conservative in that, you know, we don't throw away the body or burn it or bury it. We keep it, we conserve it. So we are pretty conservative.

There are some interesting scenarios in your book kind of drawing on [Daniel] Dennett's "Where am I?" and Greg Egan with the dual, that kind of replicates the brain function. Also, I thought of surrogates. I don't think you mentioned it in the book but in the graphic novel and in the movie *Surrogates* people are kind of in their closets and then they're in these not virtual bodies but a kind of android bodies. But I'm gonna mention the virtual ones. So that's an interesting scenario there where you keep your brain. But perhaps the functioning of your virtual self, really, maybe a different physical self, could be kept in lockstep with it. And then where are you? Are you here? Are you there? Does it really matter?

DC. This question comes up actually. If you think about a movie like *The Matrix*, you know, Neo inside the matrix, he's got this this body and presumably there's a brain. If Neo undergoes brain surgery in the matrix, we find that we're gonna find a brain in his head. But there's also outside the matrix, another brain, a biological one which is inside his body connected to a pod in this VR. So there's two brains here, there's a biological brain out there in the pod and a digital brain here inside the matrix. Which one of them is actually running Neo? Are there actually two Neos? The biological Neo who is outside the matrix

and the digital Neo who is within the matrix? You know, in *The Matrix*, there's this thing where if you die in the matrix, you die in the in the outside world. That always seems kind of crazy. This could actually explain that. It turns out that to avoid getting two different Neos, you've always got to keep those two brains totally in sync with each other. Whatever happens to the digital Neo also happens to the biological Neo's brain and so on. So brain death in the matrix world will automatically lead to brain death in the biological world. That can at least explain that rather otherwise surprising plot point.

MM. I [imagine, if] revived from cryopreservation, that I come back and say, "I know Kung Fu," and also, something that would be very handy, [would be to] just bring back the knowledge of everything. So, I didn't get to read all the material forwarded to us, there's a lot of it, I've been busy. But I don't know if you got to the discussion of death. In my own dissertation, I spent like a quarter of my dissertation on a chapter called The Terminus of the Self because obviously, if you're just an identity and continuity, then at some occasion it ends. So, do you have thoughts about our current conceptions of death? Do you think they are accurate, partially accurate? Do you think we've replaced them? And if so, under what criteria?

DC. I haven't thought about this deeply, but there does seem to be a lot of motivation for splitting different concepts and conceptions of death. I think this is actually almost across the board. I'm a philosophical pluralist about almost everything. Is there one notion of a gene? No, you can understand a gene this way or that way or that way. Is there more than one notion of consciousness? Well, there's phenomenal consciousness and there's access consciousness. Is there more than one notion of free will? I think, absolutely.

And there's got to be more than one notion of death. And it's already begun to split in debates over brain death and organismic death. I think cryonics just gives one very obvious need for a split. After standard cessation of brain activity, but cryonic preservation, then according to one notion of death, standard notions of brain death, this counts as death. But according to another more intuitive notion of death, if there's the possibility of revival, it's not death.

Your work makes that distinction very nicely, I cannot remember what you call them, there's like ...

MM: Permanent and irreversible, or ...

DC: Yeah, so I think actually there could turn out to be even more notions here. Just say your biological body has been entirely destroyed. But we kept really good records, brain scans, very detailed, maybe along with a lot of information about your biological body and so on. By the way, you should all be getting regular brain images and be regularly videoed and put yourself in all kinds of unusual circumstances and record your reactions because the more information we have about you whether for cryonics or not the better.

So maybe there'll be a situation where there's no possibility of biological reactivation, but there's the possibility of uploading. Then you might say, okay, well, then we're going to need to split off a third notion of death, which is, it's biological. The biological death process is irreversible, however, this uploading reactivation remains a possibility. And then if that becomes common enough, especially if uploading becomes a common thing, then we may be very naturally inclined to say, okay, you don't die even when the biological organism is entirely destroyed as long as there are records which permit some kind of reanimation.

By the way, one logical consequence of this is it may turn out there are individuals now dead in the standard sense, but about whom we have many records, I mean, even, you know, some of the great philosophers and scientists of the past. For Einstein we've got a lot of writings and a lot of records, is it possible that some artificial general intelligence of the future might be able to reconstruct Einstein based on the information that we have? I mean, there's already been little things like this happening now with GPT-3 and other large language models which take data about people and try and reconstruct them. The extreme version of this might be that, say a writer or a politician about whom there's a lot of audio and video evidence, they could in principle be reconstructed from the evidence we have in the future. That raises the question is Einstein actually now dead if there's the possibility of a reanimated uploaded Einstein reconstructed from records in the future? So I think it could well be that in light of all these technologies, the notion of death is just gonna split multiple ways.

MM: And if you cannot really agree on identity and continuity, you know, exact conditions, I guess we could go with something like Robert Nozick's closest continuer view. So if you did produce someone who you weren't really sure if they're actually literally identically your continuer, they're the closest continuer. So maybe then they adopt the property or the rights or get the fame and glory or something like that.

DC: Like by the way, you know, this guy did his PhD in philosophy based all about personal identity, right? This very issue of personal identity. Was it *The Diachronic Self* in the early nineties?

MM: Yeah. [Max More's Ph.D. thesis.]

DC: You find it online. It's a very deep treatise on notions of death and notions of identity. And yet there are all these different philosophical theories of personal identity. Is it the brain, is it the biological organism that matters? Is it the memories that matter? Is it the personality that matters? Is it the computer program your brain is running that matters? Is it the closest continuer that matters? You might think this is a very abstruse philosophical debate. But I do think that once we actually find ourselves in this technological future with all these options confronting us, upload or not, cryopreserved or upload, this kind of uploading or that kind of uploading. These philosophical questions are going to become extremely practical questions. The people who accept, say, the memory theory on which uploading guarantees identity, well, they will be happy to upload and maybe they won't need to go for the original organism. People who accept the brain view of personal identity, on the other hand, are going to resist any form of uploading. So these philosophical debates are going to become extremely practical debates and hopefully philosophers won't be out of a job in this future.

MM: I have the last jobs here. It raises a lot of interesting practical issues actually, for Alcor thinking well into the future when

we actually hopefully do start reviving people because if people have left wishes, which they can do, we can't enforce them legally because they're not legally recognized today, but you can certainly leave wishes. What if you leave wishes that mean that you will have to wait another 50 years or something? Like maybe the uploading is easy now, but biologically it will be another 50 years. Do we then wait because that's what you ask for? Does that get overridden under certain circumstances? Because people will say, well, that was 100 years ago, they had no clue what the options were. It raises a lot of kind of tricky questions.

DC: Yeah, these are very tough questions for you guys to be thinking about because it may depend on the time of the day. It may well depend on the philosophy of the day. Well, back in the 21st century, they knew nothing about personal identity and consciousness. Now that we really understand how it works. And we fully understand that, you know, uploading preserves it all. Therefore, there's no need actually to keep the brain around. Or maybe Alcor is gonna turn out to have three options. You know, right now there's the body or the brain. And maybe in the future there will be body or brain or just a whole lot of records, you know, a whole lot of brain scans and so on. And, and you know, a lot of people here, I take it think preserving the brain is good enough because the rest of the body, although important is not crucial to your being revived, not crucial to your personal identity. And likewise, many people could decide in the future that actually the biology is not crucial either as long as we have the algorithm, as long as we have the record, that will be good enough. If it turns out that in the future, we have consensus on one of those years, then the question is yes, what happens to people who have chosen cryonics? Should that be determined by the best science and philosophy of the future or should it be determined by their decisions right now? Maybe we're gonna have to have another little metabox to check on the cryonics forms where you say I want to go with what I say now, whatever they discover in the future versus I defer to the Alcor board of directors.

MM: Some people are absolutely opposed to uploading and absolutely convinced that would not be them. And so they're probably gonna say under any circumstances do not do that. Although I guess they haven't got a thing to lose there, really. They're not there. Here's a question that's probably unfair because you spend quite a few chapters establishing this in your book, so I don't know if you can do an elevated picture-version. Given that whether we upload or whether we stay in physical bodies but use virtual reality a lot of the time because it's more convenient and so on, what about the objection that well, virtuals aren't real, things you do in virtuals are not real. Maybe a lot of the people might not be real. you don't know. So none of it really matters. Those objects and visuals are not real objects and so on.

DC: Yeah, I'm very much opposed to that view, which is a very common and popular view. I think it's gradually changing. But yeah, there's a traditional notion, IRL – in real life – the real world [view] is that a digital world is not a real world and the real world is the physical world. I think already this view is getting to be a little bit old fashioned and so much of our lives these days is digital. And especially like the younger generation it just grows out of the so nearly fully digital environment. It's very clear that digital worlds are just as real and just as meaningful as digital environments are just as real as the physical world. I mean, right now, people spend a lot of time in virtual worlds, but it's mostly for video games and especially on two dimensional screens and so on.

But it's easy to imagine a future where we're hanging out in immersive virtual realities. And for much more than just video game purposes – for real social interaction, the kind of thing that already happens now with worlds like second life where people build communities, build relationships, they work, they play in these virtual worlds. And then, you know, one view says all that is not real and can only ever be escapism. I think that's increasingly clearly the wrong view. I think we can have meaningful interactions with other people. And so much of the meaning in our lives comes from relations with other people. You have meaningful friendships, meaningful communities in virtual worlds – people already have some of those and they're just gonna get more central in the future. You can have meaningful projects in virtual worlds. I'm inclined to think there's no principal distinction between virtual worlds and the physical world when it comes to meaningfulness. There may be some differences here and there. If you're really into nature, obviously, you're not gonna find genuine nature in a virtual world, you have to find genuine nature in the physical world. And there are questions about whether there's genuine birth and death in a virtual world. So there are differences, but it's not differences of the kind that says, this kind of life is meaningful and this kind of life is meaningless. And this may actually matter when it comes to thinking about it if, in the future, when upon being, for example, revived from cryopreservation, we're all hanging out in these virtual worlds. And maybe people are gonna have to have a little check box for their philosophical views on this too.

If you think virtual realities are not genuine realities, then you're gonna say, do not revive me into a virtual world or at least don't keep me there for long. Whereas if you're okay with being in a virtual world, then you might say, yeah, put me into a virtual world.

It may be that in many respects, virtual worlds are much better than nonvirtual worlds, maybe they'll be faster, more powerful, allow all kinds of new forms of embodiment. But yeah, that may need to be another checkbox.

MM: Maybe the conservative thing will be assumed. We haven't done the uploading just to wake the person up enough to say, hey, we've got this great new uploading technology. Is that okay? And the person says, okay, maybe or NO!, in which case, we can at least ask them that. So how much time do we have here? Okay. Five minutes. Okay, good. Let's take some questions from the audience.

Aschwin de Wolf: Thank you so much. It was very fascinating. A brief observation and a question for you. The observation is actually the Albert Einstein situation, even more intriguing because he was neither buried nor cremated after his death.

DC: We still have his brain.

AdW: It was heavily fixed. But then they partitioned it in many, many pieces they sent to all kinds of universities. So maybe even by information theoretic criteria, he's distributed and still

there in one way or another. We wrote a blog entry about it a little while ago. I actually didn't know that about Einstein.

DC: There's a whole book about this called *Who Got Einstein's Brain*?

Aschwin (*right*) addresses David Chalmers

AdW: Oh Yeah, all right. The one thing I think you've also done work on and I'm not sure if I'm using the phrase correctly, but the extended self. Because of course, in cryonics, you know, some people are neuro, some people like whole body like myself. But when I talk to some people outside of cryonics what you often see is that it's still too reductionist for them because to them, identity is about the relationships they have, the assets they own. And so, unless they feel they can take that with them, they don't feel like they're preserving enough, you know, to take with them, if they only do their brain or their whole body. They want to take more with them. So what's your take on that perspective?

DC: There's a way of thinking about identity where it's kind of very basic and no matter what happens to you, you're still the same person. There's a way of thinking about identity, which is more fine-grained where you know, the person you are can change from time to time with big developments and on which in fact, you may have different identities, for example, at work and at home with your family and with your friends. In that sense of identity, I do think it's very likely that identity could change upon reanimation. In fact, there's a notion of a transformative experience which kind of changes the person you are in that sense, and things like that happen. I don't have much doubt that revival from cryopreservation would certainly be a transformative experience in that sense. It would be a massive event in one's life that would in some sense change the person one is. But maybe there's just an ambiguity in the notion of identity here. I've undergone some transformative experiences in my time that have changed the person I am. But still, in some sense, I have survived that process. The same person, David Chalmers is still here, even though the persona the personality has changed. So I guess I'd be inclined to think that, at the very least this would be like moving to a wholly new country and a wholly new community and with wholly new technologies and it would be transformational in that sense. But I'd like to think that's consistent with survival.

Aubrey de Gray: You made a very sharp distinction between the case of incremental brain replacement versus destructive uploading. To be honest, what worries me about it is that there seems to be a continuum between the two.

Aubrey de Grey

DC: And you say you are *something*, basically.

AdG: I'm basically on your side with that, but what worries me about it is that there seems to be a continuum between the two in the sense that you know, how is it,100 and 21% or 30% and 50%? It's worse than that. You could say, okay, you could do it in two steps, but the steps might not equal, you might do 75% and then 25 for example. So the fact that there's a continuum seems to me to have a problem with the end of the continuum being sharply different in terms of the outcome.

DC: Yeah, I mean, this is part of why the case of destructive uploading is such a hard case because I think there's a really good argument for thinking it is survival and a pretty good argument for thinking it's not. The best argument for thinking it is survival is pretty much the one you just gave. Gradual uploading seems to be a form of survival. Speed up gradual uploading, fast enough, and it basically turns into a destructive uploading, you know, brain to synthetic brain in a year, in a week, in a second, in one step. So that's a pretty good argument, one you just made, for saying destructive uploading is a form of personal survival. On the other hand, there's the argument from thinking about nondestructive uploading where you create me in the next room. And very many of us are very inclined to say that is not me surviving there, that's not identity, and then, you know, gradually get rid of the original. So there's an argument that goes the other way.

I think at the end of the day, I'm with you. My own view, if I had to guess is that destructive uploading is actually a form of identity and survival. But it's these two conflicting arguments that make it so hard.

MM: We could squeeze in a couple more.

Denisa Rensen: Thank you. This discussion makes me think about what we can do. Let's say you sign up for neuropreservation and what can you do right now in this consciousness time? Continuing from dualism, most dualism has you versus self, really hard identity versus identity you feel changing as you spend time in nature, the whole bionic theory anyway, and then the

experience of identity you have, let's say in 5-MeO-DMT experiences where that sense of self completely dissolves yet you return. Do you feel like anyone about to sign up for cryonics should cultivate these experiences, so there isn't a shock potentially? Like should we all be full-spectrum experienced instead of hypo?

Denisa Rensen with Max More

DC: Yeah, that's really interesting. I guess I think my own view is that, you know, you find meaning in life where you want to find it. I think the meaning of our existence is ultimately grounded in the fact that we are conscious beings having conscious experiences and in virtue of being conscious, we find different things meaningful to us. That said, I think different people find meaning in entirely different places and different kinds of experiences. Some people find it in nature and some people find it in psychedelic experiences. Some people find it in intellectual experiences. Some people even find it in philosophy. So I guess I would like to think that all of these sources of experience or at least many of them will still be possible after cryonic revival, after uploading and so on. Some of them may not be like maybe nature will be harder. Here's one interesting thought: many of us academics get a lot of meaning from being at the forefront of our fields, if only in a tiny little niche, you know, a scientist is actually advancing knowledge. However, what if we get revived into a world where like artificial general intelligence has long since taken over, advancing the forefront of knowledge. So we can no longer get meaning in our lives from doing that. You're probably right that at that point, you'd want to cultivate finding meaning in a much broader class of experiences. Perhaps you're right, there's a case for being full spectrum in advance of all this to make sure that we'll be able to find meaning in a bunch of new places.

MM: Last question.

Natasha Vita-More: I've been thinking about whole brain emulation in a binary tone. It's one or the other, it's either destructive or it's the brain and the computation. I never see it as binary, and I wanted your view on this. You can upload to be sure with whole brain emulation, with the Randall Koene effect. But you can also download and you can go back and forth. And that's always been my conception of what whole brain emulation really concerns, that it's an experiential matter or nonmatter that goes through the consciousness and identity. And then you might like it, you might not, you go back down to the biosphere maybe inspired, you cross over to different environments much like Denisa mentioned. So I think that looking outside the binary spectrum, how would you address that?

Natasha Vita-More

DC: Yeah, it's interesting. A lot of people around here always say, well, you've got to get beyond dualisms, go for non-duality, gotta get beyond the binary. I've always quite liked dualisms myself. I find myself drawn to them and then there are always interesting points on the spectrum. But yeah, you said downloading. So it's the idea, there's always one of you here, but sometimes you'll take a biological form and sometimes you'll upload and the biological one will be gone. But now you'll be here in a digital form and sometimes you'll download again to biology. It's really interesting. I mean, one thing we seem to be finding now is that your digital technology is ultimately so much more powerful than or at least advances in ways so much faster than biological technology that it's easy to imagine a future where the digital versions of you had such amazing capacities. It would be harder for biological systems to replicate [this]. Brains, for example, seem to be fundamentally very slow in the way they process. They use chemical transmission at synapses. Maybe in the end we're going to have digital versions that are so much faster. That's not to say you won't still be able to download into biology, but maybe at the moments when you download into biology you'll find yourself 1000 times slower than all your friends. Okay, okay, good. [Chuckles]. Don't meditate for too long because 100 years will pass in the digital world. Yeah. But, but I think you're right. There ought to be room for both.

MM: Well, I'm sure we can go on forever and we probably will in the future. But for now, thank you very much, David.

DC: Thanks.

MM: Pleasure. [Applause].

Assembly theory explains and quantifies selection and evolution

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Abstract

Scientists have grappled with reconciling biological evolution[1,2] with the immutable laws of the Universe defined by physics. These laws underpin life's origin, evolution and the development of human culture and technology, yet they do not predict the emergence of these phenomena. Evolutionary theory explains why some things exist and others do not through the lens of selection. To comprehend how diverse, open-ended forms can emerge from physics without an inherent design blueprint, a new approach to understanding and quantifying selection is necessary[3,4,5]. We present assembly theory (AT) as a framework that does not alter the laws of physics, but redefines the concept of an 'object' on which these laws act. AT conceptualizes objects not as point particles, but as entities defined by their possible formation histories. This allows objects to show evidence of selection, within well-defined boundaries of individuals or selected units. We introduce a measure called assembly (*A*), capturing the degree of causation required to produce a given ensemble of objects. This approach enables us to incorporate novelty generation and selection into the physics of complex objects. It explains how these objects can be characterized through a forward dynamical process considering their assembly. By reimagining the concept of matter within assembly spaces, AT provides a powerful interface between physics and biology. It discloses a new aspect of physics emerging at the chemical scale, whereby history and causal contingency influence what exists.

From: Physics has long failed to explain life—but researchers are testing a groundbreaking new theory in the lab

Lee Cronin, *The Conversation*, 25 Oct. 2023, https://phys.org/news/2023-10-physics-lifebut-groundbreaking-theory-lab.html, accessed 26 Oct. 2023.

Modern physics can explain everything from the spin of the tiniest particle to the behavior of entire galaxy clusters. But it can't explain life. There's simply no formula to explain the difference between a living lump of matter and a dead one. Life seems to just mysteriously "emerge" from non-living parts, such as elementary particles.

Assembly theory is a bold new approach to explaining life on a fundamental scale, with its framework recently published in *Nature*. It assumes that complexity and information (such as DNA) are at the heart of it. The theory provides a a way to understand how these concepts emerge in chemical systems.

Emergence is a word physicists use to explain something that is bigger than the sum of its parts—such as how water can feel wet when individual water molecules don't. Wetness is an emergent property.

While the mathematics is elegant, the theory can ultimately only be reliable if it is tested in the lab. Carefully designed experiments, such as the one my colleagues and I are carrying out right now, will be essential to ground the abstractions of assembly theory in chemical reality.

At the core of assembly theory is the idea that objects can be defined not as immutable entities, but by the history of how they formed. This shifts focus to the processes by which complex configurations are constructed from simpler building blocks.

The theory proposes an "assembly index" which quantifies the minimal steps, or shortest path, required to build an object. This measure tracks the degree of "selection" necessary to yield an ensemble of objects—referring to the memory, such as DNA, required to create living things.

Living things, after all, don't just occur spontaneously, such as helium in stars. They require DNA as a blueprint for creating new versions.

Characterizing the regulatory Fas (CD95) epitope critical for agonist antibody targeting and CAR-T bystander function in ovarian cancer

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Abstract

Receptor clustering is the most critical step to activate extrinsic apoptosis by death receptors belonging to the TNF superfamily. Although clinically unsuccessful, using agonist antibodies, the death receptors-5 remains extensively studied from a cancer therapeutics perspective. However, despite its regulatory role and elevated function in ovarian and other solid tumors, another tumor-enriched death receptor called Fas (CD95) remained undervalued in cancer immunotherapy until recently, when its role in off-target tumor killing by CAR-T therapies was imperative. By comprehensively analyzing structure studies in the context

of the binding epitope of FasL and various preclinical Fas agonist antibodies, we characterize a highly significant patch of positively charged residue epitope (PPCR) in its cysteine-rich domain 2 of Fas. PPCR engagement is indispensable for superior Fas agonist signaling and CAR-T bystander function in ovarian tumor models. A single-point mutation in FasL or Fas that interferes with the PPCR engagement inhibited apoptotic signaling in tumor cells and T cells. Furthermore, considering that clinical and immunological features of the autoimmune lymphoproliferative syndrome (ALPS) are directly attributed to homozygous mutations in FasL, we reveal differential mechanistic details of FasL/Fas clustering at the PPCR interface compared to described ALPS mutations. As Fas-mediated bystander killing remains vital to the success of CAR-T therapies in tumors, our findings highlight the therapeutic analytical design for potentially effective Fas-targeting strategies using death agonism to improve cancer immunotherapy in ovarian and other solid tumors.

From: Scientists Find 'Kill Switch' That Activates Cancer Cell Death in The Lab

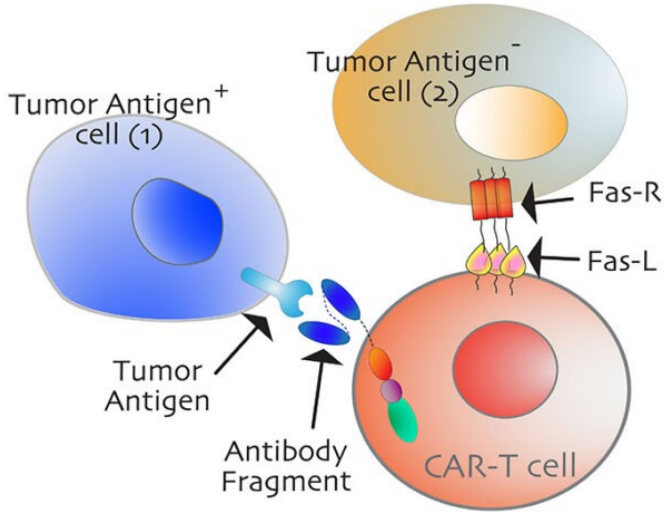
Carly Cassella, *Health*, 23 Nov. 2023, https://www.sciencealert.com/scientists-find-kill-switch-that-activates-cancer-cell-death-in-the-lab, accessed 24 Nov. 2023.

Scientists have figured out a way to detonate the 'doors' that lead to the heart of cancerous tumors, blowing them wide open for drug treatments. The strategy works by triggering a 'timer bomb' on the cells that line a tumor's associated blood vessels. These vessels control access to the tumor tissue, and until they are opened, engineered immune cells can't easily gain entry to the cancer to fight it off. The timer bomb on these cells is actually a 'death' receptor, called Fas (or CD95). When activated by the right antibody, it triggers the programmed death of that cell.

Scientists at the University of California, Davis (UCD) and Indiana University argue that until recently, Fas has been "undervalued in cancer immunotherapy". To date, not one Fas antibody has made it to clinical trials. In recent experiments using mouse models and human cell lines, scientists at UCD have at last identified specific antibodies that, when attached to Fas receptors, effectively trigger self-implosion.

"Previous efforts to target this receptor have been unsuccessful. But now that we've identified this epitope, there could be a therapeutic path forward to target Fas in tumors," explains immunologist and senior author of the study Jogender Tushir-Singh.

The antibody that binds to this epitope (a specific part of the death receptor), essentially represents the kill switch for the cell. Once this immune checkpoint is blown open, other cancer therapies, like CAR-T therapy, can gain access to more of their targets, which are often clumped together and hidden within the tumor. CAR-T therapy works by programming a person's own white blood cells, called T-cells, to bind to and attack specific types of cancerous cells.



A bystander tumor cell (gold) is killed by the Fas-mediated CAR-T cell (red), which can also attack other cancer cells (blue)

Human microglia show unique transcriptional changes in Alzheimer's disease

Katherine E. Prater, Kevin J. Green, Sainath Mamde, Wei Sun, Alexandra Cochoit, Carole L. Smith, Kenneth L. Chiou, Laura Heath, Shannon E. Rose, Jesse Wiley, C. Dirk Keene, Ronald Y. Kwon, Noah Snyder-Mackler, Elizabeth E. Blue, Benjamin Logsdon, Jessica E. Young, Ali Shojaie, Gwenn A. Garden, Suman Jayadev

Nature Aging volume 3, pages894–907 (01 Jul. 2023), https://www.nature.com/articles/s43587-023-00424-y

Abstract

Microglia, the innate immune cells of the brain, influence Alzheimer's disease (AD) progression and are potential therapeutic targets. However, microglia exhibit diverse functions, the regulation of which is not fully understood, complicating therapeutics development. To better define the transcriptomic phenotypes and gene regulatory networks associated with AD, we enriched for microglia nuclei from 12 AD and 10 control human dorsolateral prefrontal cortices (7 males and 15 females, all aged >60 years) before single-nucleus RNA sequencing. Here we describe both established and previously unrecognized microglial molecular phenotypes, the inferred gene networks driving observed transcriptomic change, and apply trajectory analysis to reveal the putative relationships between microglial phenotypes. We identify microglial phenotypes more prevalent in AD cases compared with controls. Further, we describe the heterogeneity in microglia subclusters expressing homeostatic markers. Our study demonstrates that deep profiling of microglia in human AD brain can provide insight into microglial transcriptional changes associated with AD.

From: Brain autopsies suggest a new culprit behind Alzheimer's disease

Rebecca Dyer, *Health*, 19 Dec. 2023, https://www.sciencealert.com/brain-autopsies-suggest-a-new-culprit-behind-alzheimers-disease, accessed 20 Dec. 2023.

University of Washington-led research, published in [July], discovered microglia in the brains of people with Alzheimer's disease were in a pre-inflammatory state more frequently, making them less likely to be protective. Microglia are immune cells that help keep our brains healthy by clearing waste and preserving normal brain function.

In response to infection or to clear out dead cells, these nifty shape-shifters can become less spindly and more mobile to engulf invaders and rubbish. They also 'prune' synapses during development, which helps shape the circuitry for our brains to function well. It's less certain what part they play in Alzheimer's, but in people with the devastating neurodegenerative disease, some microglia respond too strongly and may cause inflammation that contributes to the death of brain cells. Unfortunately, clinical trials of anti-inflammatory medications for Alzheimer's haven't shown significant effects.

To delve into the role of microglia in Alzheimer's disease, University of Washington neuroscientists Katherine Prater and Kevin Green, along with colleagues from multiple US institutions, used brain autopsy samples from research donors – 12 who had Alzheimer's and 10 healthy controls – to study the gene activity of microglia.

Using a new method to enhance single-nucleus RNA sequencing, the team was able to identify in depth 10 different clusters of microglia in the brain tissue based on their unique set of gene expression, which tells the cells what to do. Three of the clusters hadn't been seen before, and one of them was more common in people with Alzheimer's disease. This type of microglia has genes turned on that are involved in inflammation and cell death. Overall, the researchers found that microglia clusters in the brains of people with Alzheimer's disease were more likely to be those in a pre-inflammatory state. The microglia types in the brains of people with Alzheimer's disease were less likely to be protective, compromising their ability to pull their weight in cleaning up dead cells and waste and promoting healthy brain aging.

The scientists also think microglia can change types over time. So we can't just look at a person's brain and say for sure what type of microglia they have; keeping track of how microglia change over time could help us understand how they contribute to Alzheimer's disease.

Master regulators of biological systems in higher dimensions

Holger Eble, Michael Joswig, Lisa Lamberti, William B. Ludington; ed. Eugene I. Shakhnovich

PNAS, 14 Dec. 2023, https://www.pnas.org/doi/10.1073/pnas.2300634120

Significance

Some parts of biological networks exert more regulatory control than others. Identifying these is essential to understanding biology. For instance, master regulator genes control essential cellular processes in metabolism and development, and keystone species control ecosystem stability. These key regulators have more direct, pairwise interactions with other genes or species than average, but this approach misses interactions that change in different contexts. Because context-dependent effects are prevalent in biology, we developed an approach that identifies regulators of interactions in the entire network. The approach uses the mathematical concept of epistasis on fitness landscapes. This approach reveals master regulator genes and keystone microbiome species that affect evolutionary trajectories and lifespan of the host, respectively.

Abstract

A longstanding goal of biology is to identify the key genes and species that critically impact evolution, ecology, and health. Network analysis has revealed keystone species that regulate ecosystems and master regulators that regulate cellular genetic networks. Yet these studies have focused on pairwise biological interactions, which can be affected by the context of genetic background and other species present, generating higher-order interactions. The important regulators of higher-order interactions are unstudied. To address this, we applied a high-dimensional geometry approach that quantifies epistasis in a fitness landscape to ask how individual genes and species influence the interactions in the rest of the biological network. We then generated and also reanalyzed 5-dimensional datasets (two genetic, two microbiome). We identified key genes (e.g., the rbs locus and pykF) and species (e.g., Lactobacilli) that control the interactions of many other genes and species. These higher-order master regulators can induce or suppress evolutionary and ecological diversification by controlling the topography of the fitness landscape. Thus, we provide a method and mathematical justification for exploration of biological networks in higher dimensions.

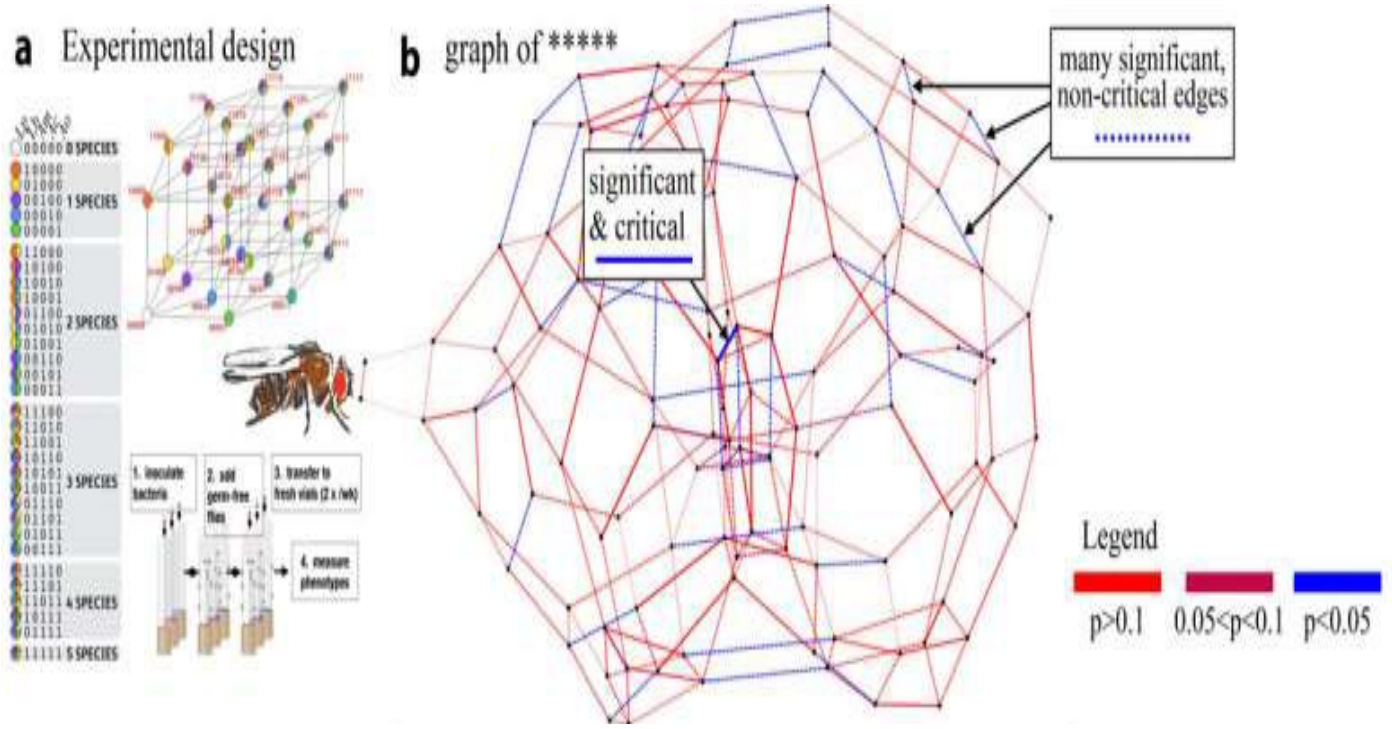
From: A new mathematical language for biological networks

Jana Gregor, *Phys.org*, 18 Dec. 2023, https://phys.org/news/2023-12-mathematical-language-biological-networks.html, accessed 21 Dec. 2023.

A team of researchers around Berlin mathematics professor Michael Joswig is presenting a novel concept for the mathematical modeling of genetic interactions in biological systems. Collaborating with biologists from ETH Zurich and Carnegy Science (U.S.), the team has successfully identified master regulators within the context of an entire genetic network.

The research results provide a coherent theoretical framework for analyzing biological networks and have been published in the *Proceedings of the National Academy of Sciences*.

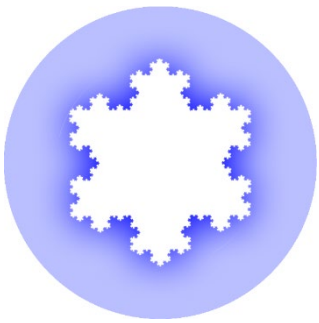
It is a longstanding goal of biologists to determine the key genes and species that have a decisive impact on evolution, ecology, and health. Researchers have now succeeded in identifying certain genes as master regulators in biological networks. These key regulators exert greater control within the system and steer essential cellular processes. Previous studies have mainly focused on pairwise interactions within the system, which can be strongly affected by genetic background or biological context.



Graphical representation of microbiome manipulations in fruit flies. The loss of lactobacilli causes a global distortion of the epistastic landscape of the microbiome. Credit: Michael Joswig

"Context-dependent effects are widespread in biology but have not been sufficiently investigated. A major challenge with biological networks is that they are high dimensional. Therefore, for the first time, our team is pursuing a more far-reaching approach that includes higher-order interactions and thus identifies key regulators in the context of the entire network," explains Joswig, who is a Professor for Discrete Mathematics and Geometry at the Technische Universität Berlin, a Distinguished Fellow of the Berlin Cluster of Excellence MATH+, as well as a group leader at the Max Planck Institute for Mathematics in the Sciences in Leipzig.

The scientists examined real data sets provided by biologists who analyzed the life expectancy of the fruit fly Drosophila based on the presence of certain combinations of bacteria in the gut. In order to describe these processes mathematically, the team applied a high-dimensional approach from geometry, reinterpreting the well-known biological concept of epistasis. Epistasis refers to an interaction phenomenon between different genes, wherein one gene may influence the appearance of another.

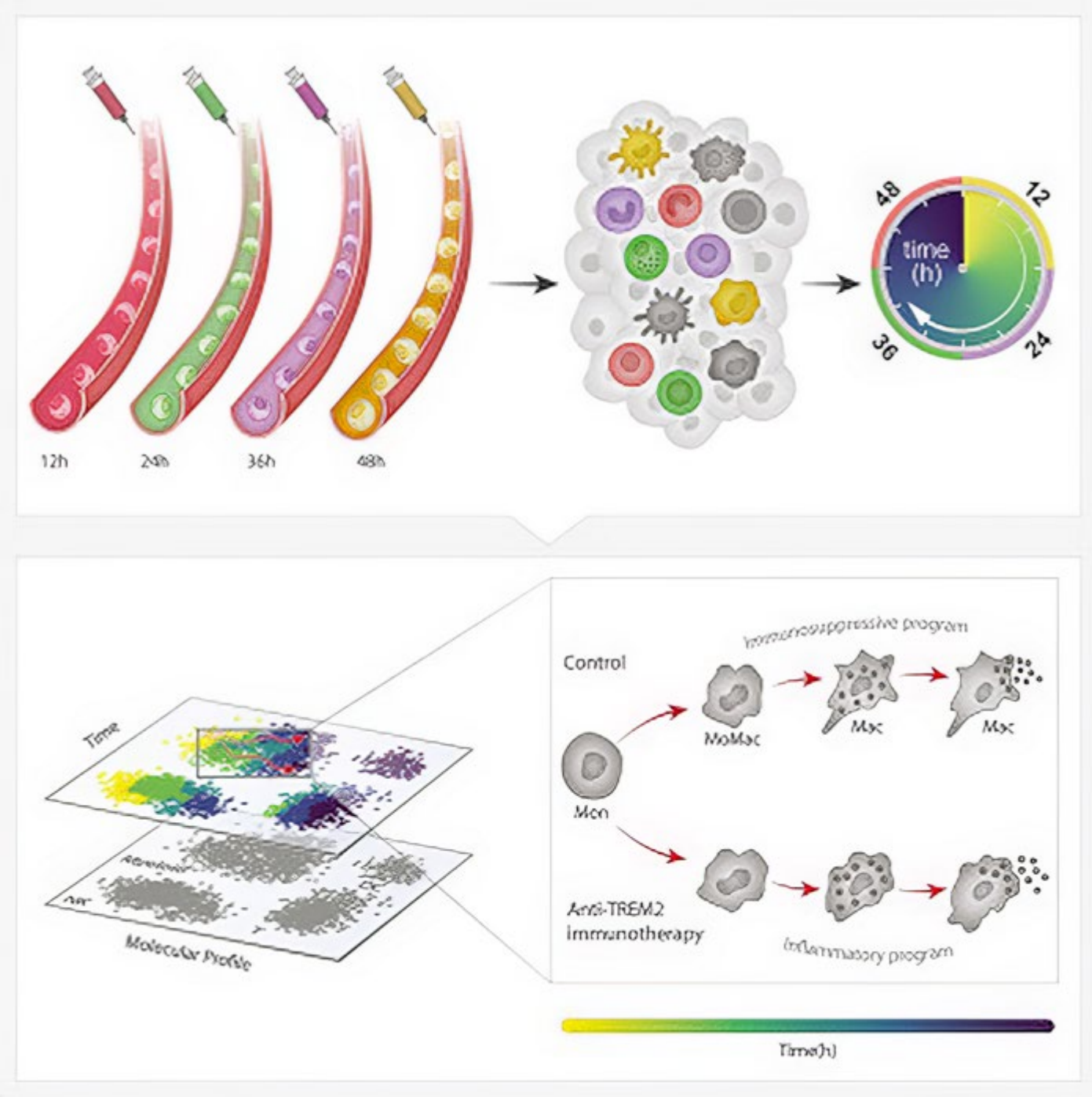


Time-resolved single-cell transcriptomics defines immune trajectories in glioblastoma

Daniel Kirschenbaum, Ken Xie, Florian Ingelfinger, Tobias Weiss, Assaf Weiner, Ido Amit et al, *Cell* online 21 Dec. 2023, https://www.cell.com/cell/abstract/S0092-8674(23)01317-X

Summary

Deciphering the cell-state transitions underlying immune adaptation across time is fundamental for advancing biology. Empirical *in vivo* genomic technologies that capture cellular dynamics are currently lacking. We present Zman-seq, a single-cell technology recording transcriptomic dynamics across time by introducing time stamps into circulating immune cells, tracking them in tissues for days. Applying Zman-seq resolved cell-state and molecular trajectories of the dysfunctional immune microenvironment in glioblastoma. Within 24 hours of tumor infiltration, cytotoxic natural killer cells transitioned to a dysfunctional program regulated by TGFB1 signaling. Infiltrating monocytes differentiated into immunosuppressive macrophages, characterized by the upregulation of suppressive myeloid checkpoints *Trem2*, *Il18bp*, and *Arg1*, over 36 to 48 hours. Treatment with an antagonistic anti-TREM2 antibody reshaped the tumor microenvironment by redirecting the monocyte trajectory toward pro-inflammatory macrophages. Zman-seq is a broadly applicable technology, enabling empirical measurements of differentiation trajectories, which can enhance the development of more efficacious immunotherapies.



Graphical Abstract

From: Back to the future: Scientists develop the first method to measure cellular changes in the body over time

Weizmann Institute of Science, 21 Dec. 2023, https://phys.org/news/2023-12-future-scientists-method-cellular-body.html, accessed 26 Dec. 2023

While physicists continue to argue about whether time is indeed an illusion, as Albert Einstein claimed, biologists have no doubt about its significance for understanding life as a dynamic system.

In recent years, they have been gaining an increasingly deeper understanding of complex biological systems using tools enabling the simultaneous analysis of vast amounts of cellular and molecular data and the probing of cellular circuitry that drives disease. However, these in-depth investigations of how cells behave and interact have provided only separate snapshots of what happens inside complex organisms, without accounting for the dimension of time and revealing the sequence of cellular events.

Now, in a new study published in *Cell*, researchers from Prof. Ido Amit's lab at the Weizmann Institute of Science have managed for the first time to develop a method for tracking and measuring changes over time in single cells inside the body.

It is now possible to obtain high-resolution images of how diseases develop and how the body responds to different medications, to identify rare cell populations, decipher which cells interact with one other and how they are spatially distributed in a tissue.

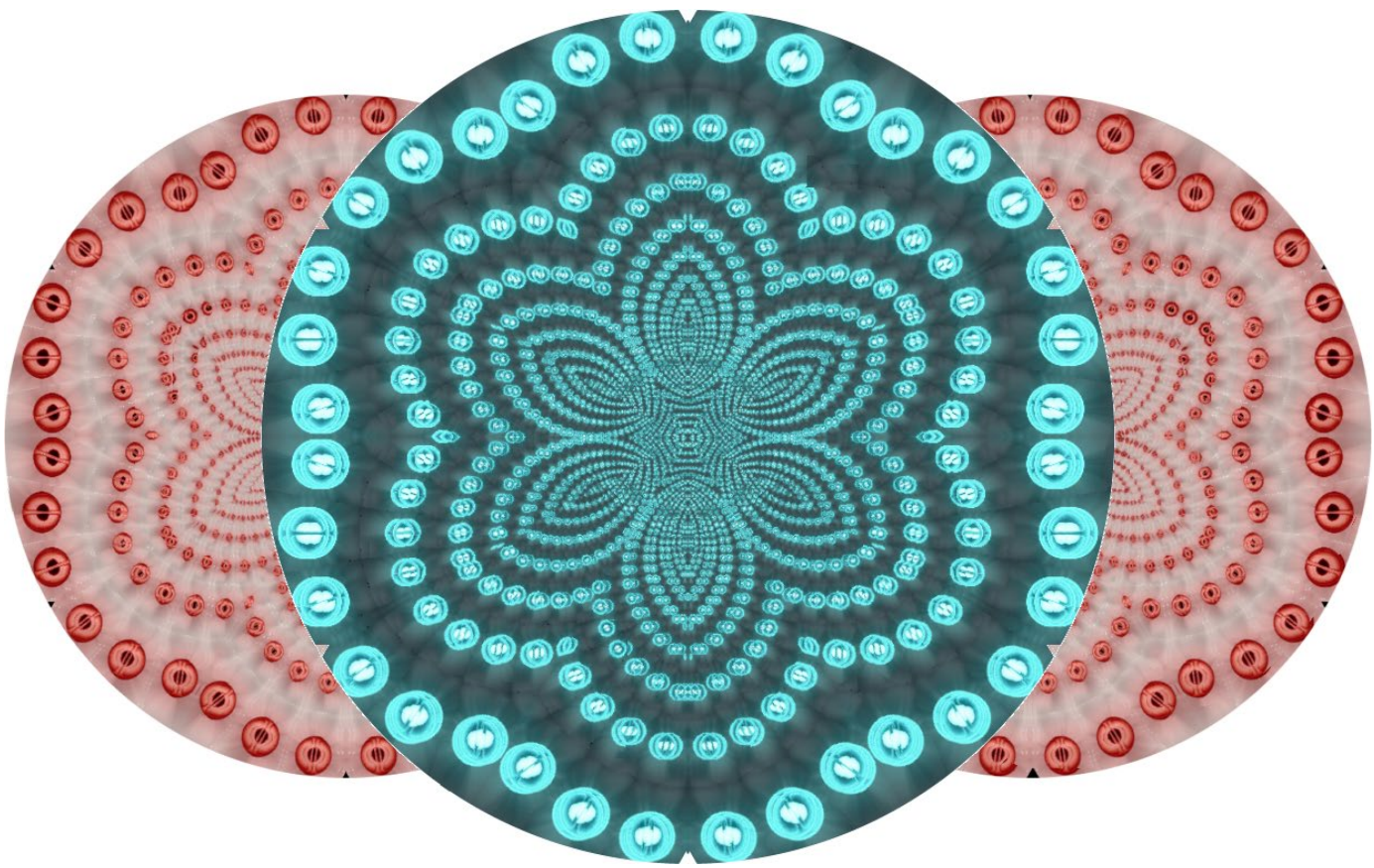
However, all these important insights are equivalent to getting many still-frame images from a movie and trying to understand the plot. "Knowing what preceded what is not enough to deduce causality, but without this knowledge, we don't really have a chance of understanding what the cause is and what is the effect," Amit says.

The development of the groundbreaking new technology started with the research of Dr. Daniel Kirschenbaum, a postdoctoral researcher in Amit's lab. Kirschenbaum was born in Hungary and did his Ph.D. in neuropathology in Switzerland, where he studied glioblastoma, the most common and aggressive brain tumor.

"We usually think of cancer as cells growing out of control, but in fact, cancer is also the loss of the ability of the body, and specifically of its immune system, to control this growth," he says. "And when you look at tumors, large parts of them are composed of dysfunctional immune cells, which sometimes make up one third or even half of all the cells in a tumor."

Glioblastoma is one of the most immune-suppressive types of tumors. "To understand how to defeat this cancer, we need to understand what happens to the immune cells as they enter the tumor and why they lose the capacity to fight the tumor and become dysfunctional," Kirschenbaum explains. "Ideally, we'd want to have a little clock on each cell telling us when it entered the tumor and when the signals and checkpoints that instruct it to become incompetent are activated. This back to the future time machine was thought to be impossible to develop."

The breakthrough came when Kirschenbaum decided to take an uncanny approach. "Instead of trying to measure time in cells within the tumor tissue, we decided to try to mark the cells while they are still in the blood—before they enter the tumor. By using different fluorescent dyes at different time points, we are later able to know exactly when each cell entered the tissue and how long it had been there, and this reveals the dynamic changes that happened to the cells in the tissue, for example, what are the different stages at which immune cells become dysfunctional inside the tumor."



(Started with Pixabay /CC0 Public Domain image.)

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/).

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

What is Cryonics?

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

How do I find out more?

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

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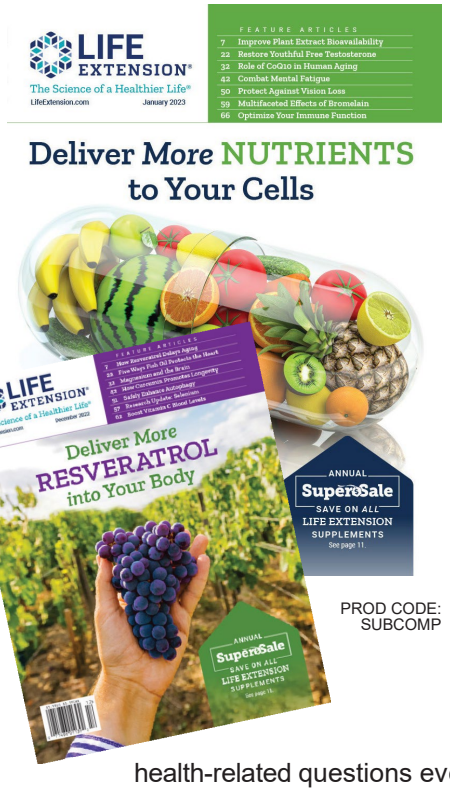

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