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Scholar Profile: Randal Koene

page 3

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Contents

Scholar Profile: Randal Koene

By Nicole Weinstock

Bay Area neuroscientist and whole brain emulation pioneer, Randal Koene, is working hard to bring unprecedented diversity to the human race.

"When I finally got around to being way more systematic about choosing what to do and why to do certain things, the reason why I decided to focus on building whole brain emulation is because I felt like that kind of mastery over who we are, that's the sort of thing that opens up so many more doors. That's what creates this potential for what I would call a 'Cambrian explosion' of different directions for development."

Founder and chairman of 501(c)(3) nonprofit, Carboncopies Foundation, Koene is at the forefront of research and development for whole brain emulation, a term that he himself coined many years ago. It describes the technological capability that would support mind uploading, a more popular (albeit generic) phrase conceptualized in science fiction movies and literature dating back to the 1950s. Several decades later, it forms the premise for some arguably mainstream sci-fi productions, such as Netflix's series adaptation of Richard K. Morgan's book, *Altered Carbon* (2002) and Disney's memorable blockbuster, *Avatar* (2009). Needless to say, the growing representation of mind uploading in popular culture is no coincidence. Behind the silver screen, scientists like Koene have been advancing the hard science making theory reality.

Dr. Koene holds a Ph.D. in Neuroscience from McGill University and an M.Sc. in Electrical Engineering from Delft University. His resume boasts an array of experiences in academia, as well as the for profit and nonprofit arenas. Koene's unwavering commitment to whole brain emulation across two decades has earned him global recognition, from Silicon Valley startups to audiences of TedXTallinn. As his nonprofit closes in on its tenth anniversary in 2020, Koene shares more on the evolution of his career and his role in the emerging field of whole brain emulation.

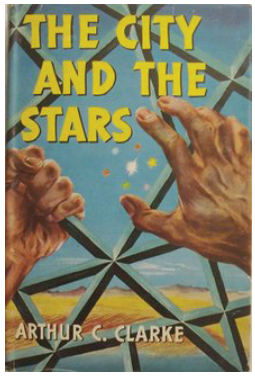
Randal Koene at the Foresight Summit in 2017. Image courtesy of JoshuaLee@SunyataStudios.com.

A life without limits

Were it not for the oft-corrected pronunciation of his surname (COON-uh), one might be easily convinced that Dr. Koene was born and raised in a university town somewhere in Boston. For those better acquainted with the Dutch however, his judicious and eloquent use of language is rather confirmation of his roots in the culturally tolerant and trade-dependent nation of the Netherlands. Born to a German artist and a Dutch particle physicist, Koene's parentage encouraged a balance of vision and logic that well-equipped him to pioneer a brand-new field. His was a home where his early (and still persistent) interests in science fiction and space exploration could run free.

From Koene's description, his passion for what was then referred to as mind uploading, slowly developed across years, prompted by growing cognizance of his own constraints.

"It was this bumping into realizations over time, like, 'Okay, so I can only work this many hours in a day on these wonderful hobby projects that I have because I need sleep. That's a weird thing. Why do we need sleep?' Or, 'Why is it that I can't think faster than I do? Why is it that computers can calculate much faster and better than people can?'



The cover of the first edition of Arthur C. Clarke's novel, The City and the Stars.

Young Koene was not just preoccupied by the mental and physical limitations of humans. He was also struck by the surprising brevity of the human lifespan from a historical frame of mind, "especially compared with the enormous amount of time that the Earth has already been here and all of that. It's just so tiny, and that seemed kind of a shame."

His concerns found a possible solution in the fictional city of Diaspar, the setting of Arthur C. Clarke's 1956 novel, *The City and the Stars*. Koene came across it when he was 13 years old. Set a billion years into the future, Diaspar is run by machines connected to a central computer that loads a rotating selection of its inhabitants' minds into manufactured human bodies. This early exposure to a vision of mind uploading, legitimized by a respectable author such as Clark (who eventually co-wrote the screenplay for *2001: A Space Odyssey*), signaled a change in Koene that allowed him to seriously pursue the means to solve humanity's biological limitations.

From physics to neuroscience

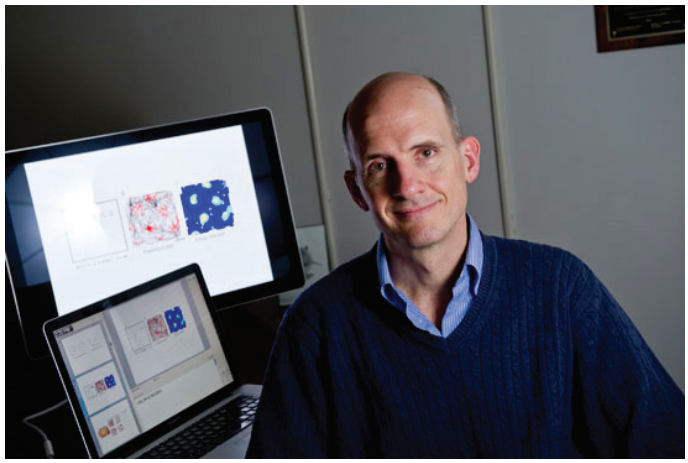
"Of all the sciences that I knew as a teenager, [physics] was the one that was most clear to me as a path where you get to understand the world around you and then work with the world around you." Following in his father's footsteps, Koene enrolled in the University of Amsterdam's Physics program, studying thermodynamics, electromagnetism, and even astronomy. While it may seem like a detour from his calling in whole brain emulation, Koene attributes his versatility and interdisciplinarity to his initial studies.

"...[Physics] is a good basic foundation to build on, especially if you're working on something that is so unknown for which you may have to borrow from a lot of different disciplines. You need to be able to tie into all these other things that you wouldn't normally think had anything to do with biology or with neuroscience, especially if you're doing technology development."

After graduation, he began his Master of Science in Electrical Engineering at the Delft University of Technology (TU Delft), an hour's train ride to the south and west of Amsterdam. While TU Delft is the oldest public technological university in the country, its electrical engineering program was cutting edge, advancing research in AI, neural networks, and information theory.

"It still wasn't neuroscience, but it was a connector because neural networks in their more, I guess, idealized version that you see in artificial intelligence, are a step where you can try to understand structure and function without having to immediately deal with all of the complexity of this underlying patchwork that evolution has built for the brain. Plus, information theory was really important to try to understand what's going on when we think, so what we're actually doing. What are these networks doing? How are they manipulating sensory data signals that are coming into the brain?"

After completing his thesis on the extraction of rules sets from trained neural networks in 1996, Koene crossed the Atlantic to embark on his Ph.D. in Computational Neuroscience at McGill University in Montreal, Canada. Following his defense in 2001, he began his postdoc at Boston University's Center for Brain &



One of Koene's greatest mentors, Michael Hasselmo, of Boston University's Center for Brain & Memory.

Memory under Michael Hasselmo's leadership. Looking back, Koene considers Hasselmo to be one of the strongest mentors of his career.

"On the one hand, he's smart because in his lab he always pairs experiment and theory. He has some people building models—computer models—and he has other people testing those models by running experiments. Then they iterate back and forth very quickly." While many labs may have adopted this practice in the years since, it was far from standard at the time.

In Koene's estimation, Hasselmo was also an exemplar of integrity and optimism in the scientific community. "He was just someone who could have his own personal theories, write papers about it, have disagreements with other scientists, but never get into this acrimonious kind of stuff that you often read about in academia...He kept and maintained extremely positive relationships with a huge network of other scientists."

A new field emerges

While Koene was finishing up at Delft, the first World Wide Web conference opened, the World Wide Web Consortium was established, and supposedly, the first ever online purchase was made (a large Pizza Hut pizza as fate would have it). The nature and accessibility of the web facilitated the growth of cyber communities centered around fringe interests, like mind uploading. Mind uploading enthusiast and then neuroscience Ph.D. candidate Joe Strout took full advantage of this.

From his home in San Diego, an ocean and a continent away, he created the first website about mind uploading focused on the technical elements. He also started a mailing list to unite others with similar interests: the Mind Uploading Research Group. Koene joined the list, as did many others who continue to advance the field today. With Strout's blessing, Koene eventually took over administration of the mailing list, creating a new platform, www.minduploading.org, to house related research.

The list encouraged greater exchange and inquiry amongst its recipients. Around the year 2000, it had become clear that the term "mind uploading" needed a counterpart. It was descriptive of an end goal capability, but did little to address the scientific and technological aspects that would give rise to it. After some back and forth, Koene suggested the nomenclature that stuck: whole brain emulation. The newly minted term married two important concepts, "emulation" and "whole brain." Koene borrows from electronic gaming to explain the first:

> If you have a Nintendo emulator that you're running on your Mac, then you should be able to play Mario Brothers on that Nintendo emulator on your Mac the same way as you would if you had an actual Nintendo machine right there. That's what an emulator is. The idea here is, okay, if you're going to try to achieve something like mind uploading, then what you need is something that is the emulator, something that is going to emulate what the biological brain is normally doing for you so that you experience the behavior that's emerging from that as as indistinguishable from the original as possible.

Koene discusses Substrate Independent Minds with Stuart Mason Dambrot on Critical Thought TV in 2012.

While the idea of emulators and emulation might require some mental exercise for the unanointed to computer programming, "whole brain" is somewhat self-explanatory...or is it? As Koene explains, this concept has ample room for interpretation:

> We purposefully didn't make it too clear what 'whole' meant, because at the time, and even now, we're not really sure which parts of the brain are absolutely essential if you want to have that experience that things feel the same and that you can control your behavior in the same way. It's not clear if that means that you just need the higher brain functions, so everything from, say, the limbic system up, or if you need to include, say, your spinal column or other parts of your peripheral nervous system.

The same conversation about mind uploading that gave way to whole brain emulation, also led to the origination of a third term: substrate-independent mind (SIM). Rather than describe the technological approach to mind uploading, substrate-independent mind was intended to describe the outcome of whole brain emulation.

"...Substrate-independent means that it doesn't need to run in biology. It doesn't necessarily need to run in a digital computer. It doesn't need to run in an analog computer. It doesn't need to run on...some futuristic computer that we can't even imagine yet. It could be any type of system on which you could implement this emulator." The term isn't perfect, says Koene, but it's more precise than mind uploading, which invites broad interpretation, even today.

A different kind of roadmap

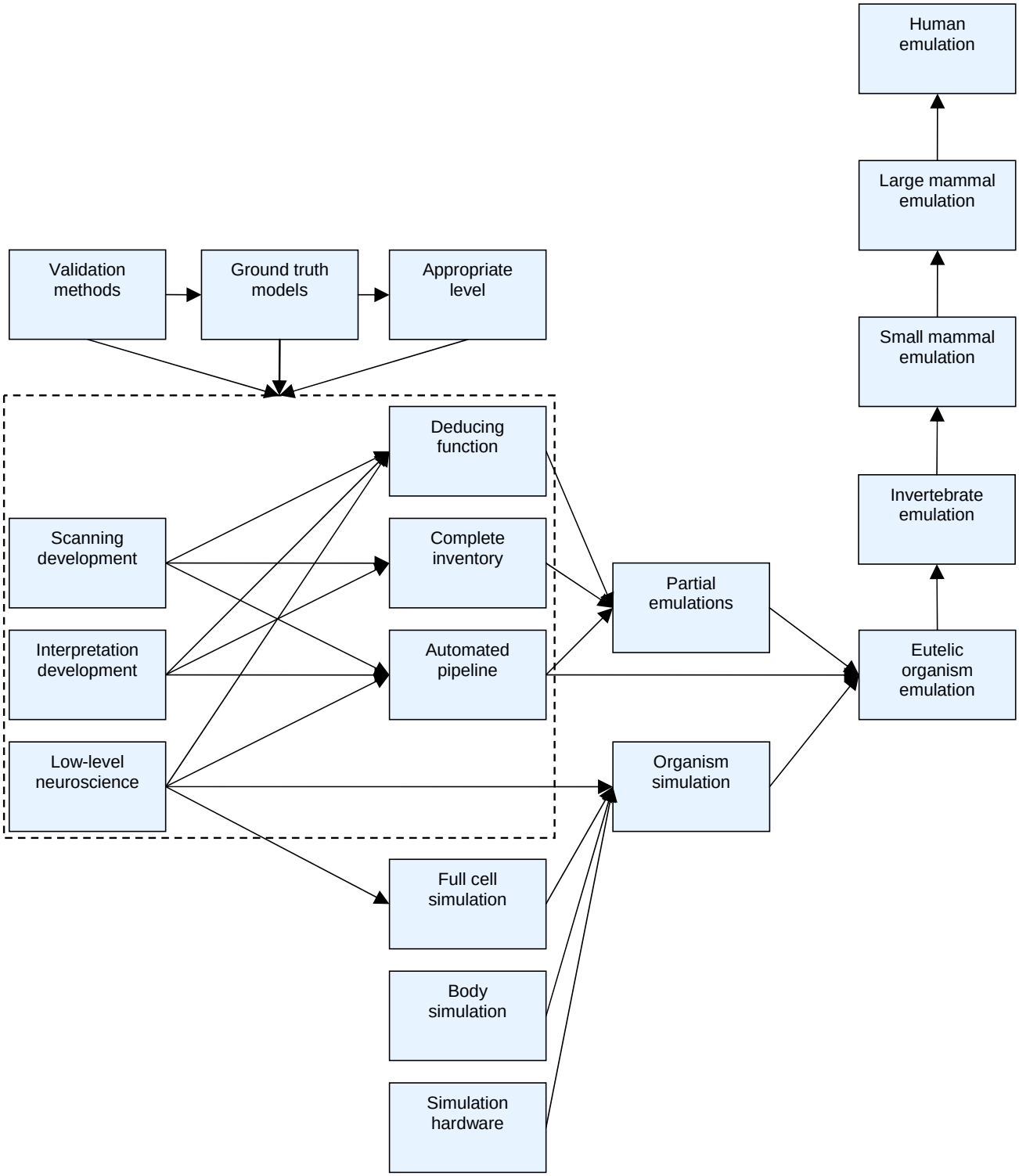
Koene continued his postdoctoral research for five years at Boston University's Center for Brain & Memory, after which time he accepted a position as a Research Assistant Professor. That same year, 2007, he attended a small but focused whole brain emulation workshop hosted by the University of Oxford's Future of Humanity Institute. Koene and his fellow attendees set out to contribute their various expertise to the design of a step-by-step strategy to achieving whole brain emulation.

The workshop proceedings were summarized in the 2008 white paper published by Anders Sandberg and Nick Bostrom, *Whole Brain Emulation: A Roadmap*. A formal introduction to the field, the roadmap outlined the three major technological capabilities deemed necessary to its success: 1) the ability to scan the brain, 2) the ability to translate information from the scanned imagery into a software model, and 3) the ability to simulate that same software model. The paper broke down each of these major areas into a series of smaller steps, and some of those smaller steps into even smaller steps. The roadmap that grew out of these considerations, in addition to important uncertainties and external technology interactions had two phases, as illustrated in the paper's diagrams.

The publication of this first roadmap was a watershed moment for Koene and his cohorts. It was the proverbial bible that formally introduced the field of whole brain emulation to the science arena, lending credence to their efforts, and a source of shared focus moving forward.

A departure from academia

While Koene was still teaching at Boston University, the financial crisis hit. It altered the landscape of academia, prompting Koene to consider alternate paths towards whole brain emulation research. His shift in mindset was met with interest by Tecnalia, a very large organization based in northern Spain that was pursuing research and technological advancement in an array of emerging industries, from solar to robotics to neurotechnology.



The original whole brain emulation roadmap, as illustrated in the 2008 white paper by Sanders and Bostrom, Whole Brain Emulation: A Roadmap.

Koene was the obvious choice to spearhead the development of this last department.

Tecnalia's funding platform was unique. Their strategy relied heavily on tax incentives, which were motivational in a profitable

economy, but quite mutable in the recession that belatedly hit Spain in 2009. Faced with a new financial reality, Tecnalia's support shifted interest away from pure research, and with it, the core of Koene's vision. Staring down the tunnel of inevitable reorgs, layoffs, and other typicalities of a waning fund base, he prepared for another move.

In the coming months, Koene doubled down on networking as he began to investigate other professional potentialities. He eventually planned a trip along the (U.S.) West Coast to scout out a number of promising ventures. During that time, he met William and Michael Andregg, the sibling founders of Halcyon Molecular in Silicon Valley. Founded in 2008, Halcyon Molecular was a whole genome sequencing startup on its way to launching the fastest, cheapest method of DNA sequencing to date. The leadership of Halcyon was keen to advance efforts in whole brain emulation, as soon as their bread and butter product took off. Koene decided the wait would be worthwhile. He accepted their offer, overseeing the development of their image analysis lab where a special electron microscope would read hundreds of DNA images per second.

Koene was eventually given full rein to explore whole brain emulation at Halcyon. It was a dream, however brief in duration. Reports of a competitor finalizing a similar product persuaded leadership to change direction, a decision which ultimately led to the startup's dissolution. Koene, who remains good friends with the Andreggs, took it as a comprehensive introduction to Silicon Valley: "The secret [to Silicon Valley] is that failing isn't a bad thing. Failing is considered a good thing because then you've learned something and you'll do better the next time around."

While the Andregg brothers regrouped to eventually launch the startup, Fathom Computing, Koene immediately began directing scientific strategy and collaborations for the nonprofit 2045 Strategic Social Initiative. He was also deeply involved in their Global Futures 2045 Congress, a 2013 event focused on discussing new evolutionary strategies for some of the 21st century's greatest challenges.

The birth of Carboncopies

On top of his work with the 2045 Initiative, Koene was also knee-deep in developing Carboncopies, an organization dedicated to the support of scientists focused on solving the challenges critical to the success of whole brain emulation. Its launch and subsequent progress was one of the reasons why the Andregg brothers gave Koene so much flexibility back at Halcyon. It generated a lot of enthusiasm and interest.

"I felt it was time to do more, as far as creating a field rather than just a community," says Koene. "If you want to create a scientific field, you need more. You need publications. You need something of a whatever the bible is that everyone returns to in order to know what's going on in that field...You need to have a network of scientists who know each other so that they can create projects together."

Dr. Koene represents Carboncopies at his 2012 TedXTallinn presentation, "Machines in minds to reverse engineer the machine that is mind."

Since its inception in 2010, Carboncopies has grown to become a full-fledged 501(c)(3). Koene believes that this designation encourages a greater sense of trust in the organization's mission and its unyielding dedication to research over profit. Though Carboncopies is still largely volunteer-run and working off a modest budget, he considers it one of his proudest achievements. Across its nearly ten years in existence, it has been effective in maintaining good standing in both the scientific community and the general public, through an enduring transparency and factual bedrock. Randal explains:

> We're in it for the real science and to talk to scientists, but also to communicate to the general public the scientific vision and approach to whole brain emulation, not just the hype version. I'm always emphasizing that this isn't about hype. This isn't about saying anything about, 'Oh, we're going to have this tomorrow,' or anything like that. It's just focusing on the pure problem itself. That really has worked. It's something that doesn't chase people away.

A hippocampal neural prosthesis

A collaboration between the University of Southern California (USC) and the Wake Forest Baptist Medical Center made impressive headlines in 2011. The team had succeeded in a proof-of-concept hippocampal prosthesis in live rats. In 2013, they moved on to live monkeys, and in 2018, to humans, demonstrating its remarkable promise in improving episodic memory. Human participants were epilepsy patients who already had surgically implanted electrodes in different parts of their brains. Researchers recorded brain activity in response to a memory test, analyzing the recordings and creating a mathematical model to predict neuron activity during successful memory formation. During a second memory test, they used the model to stimulate the indicated areas of the hippocampus, improving patient memory by a whopping 37%.

Koene has long-valued the advances of the USC-Wake Forest team as a way to experience a very partial kind of brain emulation. For whole brain emulation that can be made available to the masses however, he finds the methodology to reflect some serious challenges. Implanting electrodes in various parts of the brain is inherently risky, and the number required to measure all neuron activity in the brain is significant, to say the least.

"If it turns out that the studies that we do by building prostheses show that you only need to record from 20% of the neurons to be able to replicate the function in a way where it's indistinguishable for the patient, that'd still be 20% of 86 billion neurons...It would be much easier if you could create these whole brain emulations not from the recordings, but from the structure of the brain."

He suggests an alternative approach that applies the lessons of these studies in neural prosthetics to the mapping of well-preserved brain tissue. In this scenario, structural information can be used almost exclusively to create a whole brain emulation. This of course, makes the ability to preserve brain tissue without degradation paramount.

Common ground in cryonics

Koene's first exposure to cryonics was at the whole brain emulation workshop in Oxford back in 2007. Though he is disinterested in revival into a necessarily human form, he is certainly very supportive of any advances in brain preservation. After all, a brain that can be cryopreserved is also a brain with the potential to be scanned for whole brain emulation.

Koene is also very sympathetic to many of the social challenges that surround cryonics, as they are frequently mirrored in his field as well. Medical acceptance in what is otherwise perceived as end-of-life circumstances is one area where he hopes to see more acceptance. He describes a scenario that is at the forefront of many an aging cryonicist's mind:

> You would see something where regulations can be changed so that you have [cryopreservation] as a standard at any hospital where, if something happens, you can be preserved rather than being shipped to the coroner. If that were an option that was just generally available, then it would make the outcome so much better because then everybody would be treated quickly and you wouldn't have a lot of deterioration before a team can get in there and do something.

Moving Carboncopies forward

As Koene looks to the next decade of Carboncopies, he is eager to bolster symbiotic partnerships, especially that which the organization shares with Kenneth Hayworth's nonprofit, the Brain Preservation Foundation. Promoting scientific research and services development of whole brain research for long-term static storage, the foundation is most known for its past preservation competitions involving first a mouse brain (or similar) and then a large mammalian brain. The foundation's current competition, the Aspirational Neuroscience Prize, will award a total of one million dollars to forty neuroscientists across ten years. Each recipient will be nominated for their efforts to uncover the physical coding of long-term memory, and/or the structural and molecular basis of memory.

In addition to this work, Koene is focused on keeping Carboncopies at the cutting edge of trends in education and communications. In the past year, for example, the nonprofit began to record live workshop interviews with different scientists, such as the AI Safety interview with Estonian theoretical physicist and co-founder of Skype, Jaan Tallinn. Koene believes this has been successful in garnering more public involvement as well as greater focus amongst the scientific community.

A third and equally important priority for Carboncopies is the refresh of the original whole brain emulation roadmap from the 2008 white paper. Koene's updated roadmap will reflect advances from the last several years and the many disciplines that impact the success of the field. "When the original roadmap was conceived back in 2007, there were only a few people at the workshop, so we didn't have representatives for each one of these problems. Also, many of the problems weren't that well understood."

Koene's new vision of the roadmap presents four or five major challenges that need to be surmounted, rather than the original three. It is focused on more than connectomics, and operates on the assumption that a digital computer may not be the only and/or principal platform involved in the end product. Together with Anders Sandberg, who continues his work at the University of Oxford, Koene hopes to secure funding for a second workshop in 2020 from which a roadmap version 2.0 may be officially released. ■

To read more about Randal Koene, you may visit his personal website www.randalkoene.com. To find out more about whole brain emulation and/or to support research efforts therein, Dr. Koene directs you to the 501(c)(3) nonprofit website, www.carboncopies.org. You can contact Dr. Koene directly with any questions or comments at rkoene@carboncopies.org.

Q&A

What do you see as some of the greatest benefits of whole brain emulation?

The greatest benefit to human society of whole brain emulation is opening up the blueprint of human experience to maximum adaptability. Consider, human brains, like human bodies, are a result of natural selection. They have demonstrated an ability to serve the survival of human society, human individuals, and human DNA, through the challenges posed by the natural environment during our evolution. Those challenges are rather specific, they are certainly not universal.

Creativity and inventiveness, our ability to devise new ways and new tools to help us survive different environments and challenges and consequently to thrive, those are characteristics we point to as uniquely human. In a sense, taking charge of the further development of our brains and bodies is the next step.

We are unable to think at the speeds of computers, unable to experience and interact at sub-millisecond time intervals, a temporal scale of the universe that has been inaccessible to us, even though our machines live there. We are unable to survive in the vacuum of space or on the lifeless surfaces of most planets. Naturally, our machines take those journeys and inhabit those places.

We are unable to experience interstellar travel, because the journey exceeds our lifespan. Again, machines can do this.

We cannot, individually, tackle problems or challenges that demand attention or persistence longer than our lifespan, which certainly affects our ability to care about or deal with problems such as environmental breakdown or climate change that are multi-generational.

We don't even have real memory of events, conversations, scenes, etc. Our memory fades, is easily corrupted, can only be recalled through triggering cues, and is largely constructed on the spot. By contrast, our recording devices and machines can retain honest records almost indefinitely.

There are many more examples of constraints or quirks of human cognition that we could deal with and that did not greatly impact our experience of the Pleistocene, but which do stand in our way now.

In short, whole brain emulation allows us to overcome the capabilities and experience gap between human and machine, to reinvent ourselves through self-directed evolution. Accomplishing whole brain emulation, as well as making that available as a method for mind uploading to anyone willing is about making the choice to join in the exploration of the greater future of space and time, beyond an exclusive focus on the constrained existence of our ancestors.

Ultimately, whole brain emulation may also be about the survival of humanity, of the human experience, as a part of an ecosystem of intelligences.

What are some of the most important ethical considerations in a future with whole brain emulation?

It is very difficult to predict the most important ethical considerations in a future with so many new possibilities. I'm trying to imagine if researchers working on ARPANET in 1969 could have foreseen any of the main ethical considerations that we now worry about with regards to the Internet. They had no idea that the Internet would lead to social media with all of its pros and cons. Then again, even Aldous Huxley's *Brave New World* was able to foresee some of the problematic trends that would arise, based on an understanding of human motivations.

In that sense, some things that I think will always need care and defense are freedom of thought, freedom of choice, and self-determination. Each of those three are already in constant need of active defense, because there are motivating forces that tend to encroach on them. For example, the drive to acquire power in all its forms (e.g. capital) tends to motivate people to seek to impose their will on others. To have such influence, can involve pushing for specific laws, or injecting misinformation, or collecting personal information to push advertising, etc.

It stands to reason that further increasing the ability to acquire personal data (brain scanning), and to influence thought and action, presents positive opportunity, but also adds risk factors that originate in competitive motivations mentioned above.

I know that all sounds rather abstract, not as explicit and concrete as listing specific ethical concerns that we might think of today, e.g. the right to choose whether to use whole brain emulation technology or not, the human rights of uploaded individuals, equal access for all to whole brain emulation and related technologies, the right to your own personal data, not infringing on the rights of others as you make your own choices. I just think it's more honest not to claim that I can at this point foresee the specific ethical issues that will concern us the most.

In his 2018 book, The Age of Em, ***Robin Hanson described a future in which (brain) emulations or "ems" rule the earth. Have you read it? If so, what were your thoughts?***

I read the book, and Robin is a friend of mine. I thought it was a fair exercise of a very specific formula applied to just one thread of technology and its possible effects on society. You can quickly tell that it was a limited exploration and should not be taken as

an actual prediction of what society would be like. For example, Robin chose not to include AI at all. In his future society, copies of emulated human brains are used to carry out all sorts of tasks that we would typically predict might soon be accomplished by AI of various sorts.

What would the vision have looked like if it had been attempted for a more realistic mix, an ecosystem of intelligences, as it were, in which emulated human brains exist alongside enhanced emulated human brains, and alongside non-human AI of various kinds? It was probably much too complicated to attempt sincere futurism for that much more realistic outcome than for the artificially limited clean-room version Robin decided to attempt. I think that's fair, and it's to be expected. Making good futurist predictions is extremely difficult beyond very short time frames such as 5-10 years, because there are innumerable strands of technology and social change that interact with one another as they develop over the years.

I would love to see many more attempts made by many authors to describe their visions of a future with whole brain emulation and mind uploading.

How do you envision notions of birth and death in a future of substrate-independent minds? How will this affect population? Will the fluctuation of population continue to be relevant?

I know I keep repeating myself when I say that predictions are very hard to make, but I have to add that caveat anyway. Here are a few things that I think should be taken into account as anyone tries to predict "population" in a future with whole brain emulation:

1. Persons who are substrate-independent do not need to depend on the same resources as default homo sapiens. Their embodiment (artificial body /virtual body/etc) will demand a source of energy, but not a "carbon-footprint" on Earth, as it were.

2. It is entirely possible/plausible that there will always be a (large?) population of persons who prefer to live as biological homo sapiens, and who will continue to have babies as usual.

3. There may be new forms of birth and death that we don't presently know. For example, a new person may come about by combining characteristic features of existing persons (and their emulated brains), or by raising a new person from a "tabula-rasa" blueprint of a human brain/body. There may also be new persons who are a combination of human and AI. There may be forms of "death" that are unlike death today. For example, a person may cease to exist as an individual by fully merging into a group mind of sorts. Or a person may temporarily cease to exist by pausing experience for decades or centuries. A person may go through such a range of individual developments or enhancements that the resulting person is no longer recognizable as the one at the outset (of course the same might be said for the person one becomes after decades of experience compared with one's infant self).

The fluctuation of population will probably continue to be relevant in the sense that the density of a type of population and the distribution of resources will always need to be properly balanced in any one place and time. This is true for any species of animal today, and it is also true for automobiles and gasoline, or light bulbs and electricity. In that sense, good management of densities and resources will always be important.

For example, the notion that space travel would somehow alleviate population and resource concerns has always seemed rather silly to me. Unless you squeeze everyone on Earth onto a spaceship and travel elsewhere, any number of persons leaving Earth to head elsewhere will have almost no effect at all on the local issues of population and resources on Earth. Sending pilgrims to America had no effect on population and resources in Europe at the time either.

Will advances like neural prosthesis and whole brain emulation impact lifestyle habits? For example, recent studies suggest a connection between Alzheimers and sugar consumption.

That's an interesting connection between Alzheimer's and sugar consumption. Yes, I'm sure that lifestyle habits will be affected by neural prosthesis and whole brain emulation. Our lifestyle habits included no time spent on social media before we had the Internet, so clearly, the introduction of new technology has an impact on our habits. We will probably be doing a lot of things that we cannot imagine right now.

Do you think the emerging field of VR (Virtual Reality) is any indication of receptivity to mind uploading?

Yes, it provides some confirmation that there is a path for the human mind to adapt to new circumstances. We saw some of this already, in that we can adapt to driving a car and being so accustomed to it that the vehicle almost feels like a body. I'm sure kayakers out there can relate to this as well. VR allows us to experiment and explore with even more unusual pseudo-embodiment and environments, to see how we respond to that, and what it takes to acclimate.

Are there environmental factors that affect the chances that whole brain emulation will become possible?

Yes, I think there are. Any circumstance that dramatically affects worldwide capabilities in terms of science, economy and infrastructure will affect the chances (and the timeline) for achieving whole brain emulation. The science and engineering needed for WBE would have been impossible in the world of the 18th century. If the world economy and infrastructure

breaks down, or if our scientific and economic output has to be directed exclusively at another major problem (e.g. environmental cataclysm) then that would delay achieving whole brain emulation, and possibly even keep it from ever happening.

Achieving whole brain emulation is not a foregone conclusion. It is not just a matter of time. There can be economic, social, legal, and other reasons why we might never do that. That said, and looking at it from the other end, I find it hard to believe that any truly sophisticated species, a species that has expanded beyond its solar system or that has a written history and society older than a few thousand years, would have done so without something like whole brain emulation or an alternative approach to taking full control of their own design and development.

How can whole brain emulation assist in the biological revival of cryonics patients?

I imagine that one avenue for biological revival of cryonics patients would be to produce an entirely new (young, healthy) body for the patient, and to also produce a brand-new biological brain for the patient. That brain would need to be grown/tuned so that its connectome and operations produce the same personal experience of being as before cryopreservation. It might be possible to carry out an upload to a whole brain emulation from the cryopreserved brain first, to ensure in that emulation that everything is working as desired, and to then use that to impose the right development/tuning on the fresh biological brain (i.e. to "download" into that brain).

To be honest, this is not something that I often carefully think about, because I don't regard the "download" back to a biological brain as presenting any useful benefit that I would be personally interested in. Perhaps there is though, and I certainly acknowledge that this is a process path that some people will be interested in.

Do you think personal identity entails more information than the "connectome?"

I don't think I'm an expert on this topic, and at the Carboncopies Foundation we have just begun to publicly explore the topics of theories of consciousness and personal identity as part of an effort to update the roadmap to whole brain emulation.

Let me first use a literal interpretation of your question, namely whether there is "more information" needed than the connectome to generate a mental experience with identical characteristics: I think there is more to it than the connectome, where the connectome is just a list of which neuron is connected to which other neuron. Clearly, it will matter how they are connected, i.e. how the synaptic receptors involved respond, how the neurons involved respond to changes in their membrane potential caused by changes at synaptic sites somewhere along their somatic or dendritic structures. Such responses will be caused both by direct transmission of activity from neuron to neuron, but also by more diffuse pathways where cells in one location release chemicals that are subsequently received by neurons in various locations reached by those chemicals. There may even be subtle effects of electromagnetic fields, although we would have to determine if those rise beyond the brain's noise threshold. It might even be that we need some model of the modulatory effects of certain glial cell populations. In short, a good model of a specific brain that will faithfully produce desired functional responses will have to be more detailed than the mere connectome can probably provide.

At least, I think this will be true for the first good neural prostheses and for the first attempts at a whole brain emulation of some small animal (e.g. the fruit-fly Drosophila). Perhaps, as we learn more about the large-scale mechanisms employed in the brain, those that ensure robust operation and guaranteed communication between brain regions, we may be able to abstract further. We may end up caring more about neural population dynamics and the activity of groups of neurons than about the delicate details of activity at individual cells. It's hard to predict this with any amount of certainty, because we haven't experimented and played with any advanced neural prosthesis or small-animal whole brain emulations yet.

Beyond this, when people ask about personal identity, they often mean subjective experiences such as a "stream of consciousness." I am still learning about this side of things, but you can keep track of my up-to-date questions and comments by following our most recent online workshops and by watching the video recordings thereof. For the record, at the moment I'm fairly convinced by arguments, such as those of Susan Blackmore, that stream of consciousness is as illusory as our sense of perceiving a true "visual scene."

Is there a particular experience that you've always dreamt about that could made possible by a substrate-independent mind? What is your dream substrate?

I think what I would love is to be able to experience many things at once and to then merge those experiences into one personal set of memories, and also to be able to experience things that I could normally never live to experience. That includes an ability to choose my embodiment freely each day. Perhaps today I wish to be a space-probe on Pluto, tomorrow a swarm of micro-bots in the Mariana Trench, and the day after to be weightless and disembodied in a virtual reality environment. I would love to have reliable, real memory, and I would love to be able to sense, think and respond so quickly, that a second seems like an hour.

My dream substrate is, I guess, what today would be called "the cloud," so that my mind is generated by operations happening somewhere but not having to care where, knowing that there is plenty of robust redundancy in the underlying devices, regular synchronization with backups, and that my senses and actions can take place through myriad forms of input/output and embodiments.

Pattern Survival Versus Gene Survival

By Randal A. Koene

Originally published on February 11, 2011 at www.kurzweilai.net

I decided to write this article after I found that many colleagues and participants whom I spoke with at the recent Humanity+ (*ref. R.A. Koene, 2010b*) and Transvision (*ref. R.A. Koene, 2010a*) conferences were struggling with personal and strategic decisions when they considered what sort of future to strive for.

We are hampered by a historical dearth of attention to the very fundamentals that could support choosing a technological objective, such as cryonics, the elimination of biological aging, artificial general intelligence, or mind uploading to a whole brain emulation or other implementation of substrate-independent minds.

There is a brewing debate about whether it is truly possible to enhance the human experience, or whether the way we experience being is in fact already the most that we can aspire to. In general, we can ask: How well-considered are the different goals espoused by transhumanist thinkers? Which ones are supported by a sound rationale?

None of us want our efforts to go to waste, or to chase down lesser and near-sighted ends. Very specifically and very personally, we can ask:

> *What does a self-consistent, intelligent and capable person do? Which goals are so sound, so promising and so exciting that you can allow those goals to fully motivate you? Which goals can you embrace in the knowledge that you stand on a firm foundation, that your thinking is clear, and that you can be a pioneer to excel in a significant part of a vast new future?*

This is very important, because each of us has to choose where to dedicate our time and our effort. Similarly, solid foundations should inform decision making about all kinds of support that can be given to specific types of projects.

In my work, I have reached this point twice, from different angles. I arrived at it once by daring to ask myself the deeper questions behind the search for greater longevity. I arrived at it the second time by questioning basic expectations proclaimed by researchers in the field now known as artificial general intelligence (AGI). I began to address the problem from the latter angle when I spoke at the recent Winter Intelligence Conference at Oxford University (*ref. R.A. Koene, 2011*). In this article, I will therefore address the problem of solid foundations, with an emphasis on the matter of longevity… or more crucially: emphasizing the matter of survival.

Solid context for your quest

Well, what do you aim for? We will need to better understand the context of the question first. Let us establish some of the bedrock rules of our universe. There is no universal purpose. Let go of all of the flimsy constructs that rely on notions of what should be. What we do observe and can build on is causation. One perspective that is built on causation is the concept of Universal Darwinism (*ref. D. Dennet, 2005*). We will discuss Universal Darwinism in a moment.

Above, we have the universal, objective context of the question. What is the subjective context? Of course, you are not aware of the entire universal context. In fact, the only context you are aware of, contemplate and care about is the one generated by the confluence of retrieved memory, processed perception and executive processing within your own mind. That is as much of reality as there ever is to any one of us. Within that reality, that context, you choose goals, because you have interests, wishes or desires that are directly related to further possible experiences within that subjective context. Some future experiences you want to have, some you want to avoid[1].

Having established those two contexts essential to our question, I commence with a simple examination of the differences between "Gene Survival" and "Pattern Survival," their place in Universal Darwinism, and their place in our subjective interests. As I will show, the differences increasingly give us reason to drive a change in focus from the former to the latter.

Universal Darwinism and being aware

Universal Darwinism (*ref. D. Dennet, 2005*) is a useful way to look at the results of competition throughout the universe. This extends beyond the realm of the animate, as in the biosphere of Earth. Inanimate aspects of the universe likewise experience the consequences of interactions that can be deemed competitions. When we apply this perspective, we see a tendency everywhere for some structures, some discernible components of the universe to prevail over others and, thereby to occupy a larger niche in space and time.

Likewise, it is useful to recognize that the organization of the universe, down to its quantum level, can be thought of as an

arrangement that is describable, that is information (*ref. S. Lloyd, 2006*). This information universe determines all the relationships of its constituent parts, its various incarnations at different times, even the many possibilities represented by the concepts of the "multiverse" (*ref. D. Deutsch, 1997*).

When we combine both of these realizations, then we can describe the effects of Universal Darwinism in the Information Universe as a competition for "Pattern Survival." A pattern is some specific packet of information, which when put to use will achieve certain interactions and consequences.

There is a pattern that is very dear to us. This pattern is the information content of our minds. By the information content, I mean both the parameter settings (e.g., memory), as well as the ways in which the parameters are used, the functions carried out by the mind (e.g., learned behavior, characteristics) (*ref. C. Eliasmith & C.H. Anderson, 2003*). Why is this pattern so very dear to us? Well, that is based on the subjective context we identified earlier. *That pattern is all that we are aware of being*.

Self, conscious existence, is a matter of mental processes. They are the combination of perceptual processing, recall and use of memories and learning, and decision-making that is affected by the mind functions that were instantiated and shaped in accordance with intrinsic drives. All of what we know, sense and experience takes place within our minds. It is these patterns that define our awareness.

Those patterns are, of course, themselves the result of ongoing competition between patterns within the mind, patterns that are established, reshaped, outgrown, etc. And they are the result of evolutionary pressures that led to the development of the hardware that runs the mind. The intrinsic drives are intimately connected with those evolutionary pressures, with the survival of the genes that describe a human being.

Having long-term interests and surviving to see them through

Our experience, therefore, leads us to place great value on the patterns that are our minds, and on the survival of those patterns, both personally and in terms of the memes we support. Our identities seek Pattern Survival. We also recognize the connection through our intrinsic drives with the "Gene Survival" that played such an important role in our native environment, the biosphere of Earth.

There are significant differences between the pursuit of gene survival and the pursuit of pattern survival. Here is an example of how these differences affect personal decisions and actions in practical terms. Do you consider yourself a hard-nosed realist? A person of practical values, of business, someone who dedicates the majority of their time to the widely accepted ideals and goals of personal and business accomplishment? Do you specialize in attaining success among your peers in terms of wealth and status?

Those qualities make sense as part of a strategy with the ultimate objective of improving the odds that your **children** — or the children in another genetic line that you are a guardian of — will be able to **procreate** in the future. A focus on social and business success, aimed at wealth and status, but *without transhumanist objectives*, is a sensible and self-consistent strategy for gene survival — even though you and your pattern of personal characteristics will terminate at your death regardless of wealth or status.

Are you, on the other hand, more concerned with the ideas, the memes, that you continually champion through your very behavior, your characteristic responses and interactions? Perhaps you do not plan to have children, and you are not primarily in charge of guaranteeing the procreation of another genetic line? Is your main interest instead drawn to the pattern of developments that you would like to see in the future, what you would consider **improvements beyond the species' status quo**?

If you are a transhumanist, it is sensible to seek a strategy optimized for such pattern survival and competition. If that is your chosen objective, then, rationally, such a strategy must include work towards the transhumanist goal that can enable your pattern survival; otherwise, it is not self-consistent. Seeking strategies optimized for pattern survival of mind functions is, not coincidentally, the very definition of the objective to achieve substrate-independent minds (SIM).

We need not ask if a transhumanist would prefer to continue to exist as the same pattern or be greater than it; it is simply a fact that patterns will compete and those that best modify, adapt, and expand the domain influenced by their characteristic interactions win. To be clear, I am not talking about static pattern survival, but **pattern competition**.

Pattern competition favors the personal characteristics of some, and their characteristic interactions support memes that influence future developments. A simple example: There are certain ways in which you would like to see the future be different from the present, which is probably distinct in some ways from how anyone else would like to see it.

A little knowledge is a dangerous thing, but a little exploration goes a long way

But how can we understand the original or re-implemented mind sufficiently to enable it to grow? How can you cautiously escape the human "catchment" area — the precarious balance, where, to attain greater mental capabilities, we reach insights that remove hard-wired delusions and thereby modify our finely-tuned intrinsic reward mechanisms in a way that leads to behavior that is unfavorable to survival?

The concept of a "catchment" area (*ref. S. Gildert, 2010*) has been described as the result of evolutionary optimization of human

intelligence. Our intrinsic drives are geared to seek reward that is directly linked to gene survival. All of our actions, all of our decisions, even the way we interpret our experiences are subject to reward mechanisms that were selected in accordance with gene survival. The optimization can be considered a local maximum, surrounded by alternative modes of behavior that were not selected for and may be less suitable guides for survival. If most of the alternatives bear detrimental risks then we can consider ourselves in many ways confined to this catchment area. It may be, that the catchment area is delicate, that it resembles a small island surrounded by a rocky landscape of possibilities, some of which could endanger our survival.

Reward mechanisms tuned by natural selection are beneficial within the existing set of goals and requirements in the human environment. As we acquire insight into our own reward mechanisms, perceive their limitations and gain the ability to modify them, there is the risk that we may promote behaviors that put our survival in jeopardy.

One example would be the realization that we can maximize our ability to experience reward by setting simple goals and high rewards ("wireheading"), not unlike the lab-rat caught in a pleasure-loop by continually pressing a lever that delivers dopamine to its brain.

Another example would be to modify the sense of reward that we experience when we receive the agreeable judgment of our peers in matters of social cohesion and moral values. It is true that accepted notions of right and wrong have undergone changes throughout human history, but an outright elimination of some of our basic, unquestioned drives could be more perilous if carried out without extraordinary precautions.

Here we turn to exploration and safeguards. Whole brain emulation (WBE) (*ref. R.A. Koene, 2006; A. Sandberg & N. Bostrom, 2008*) is a tool that gives you the ability to explore, such as when astronomers could first use telescopes to explore the universe. And by emulating all the relevant functions as implemented in the brain you minimize any initial differences and their potential hazards. WBE is a useful way — though not the only one — by which to move mind functions to another substrate, because it solves at least the problem of Access. You can carry out finely-tuned experiments, which is an opportunity that goes beyond what telescopes give astronomers.

For example, we may explore what happens if you run everything in the cortex twice as fast. Or we explore what happens if you plug in flawless memory. Whole brain emulation gives you all the basics of substrate-independent pattern survival for the mind: Continuation of the set of characteristic functions and parameters that determine how a person's interactions with the environment deploy and support memes — characteristic interactions that affect the future.

This is an *experimental approach* by which to move from the set of constraints within one Darwinian survivor arrangement to a different set of constraints within another Darwinian survivor arrangement. Skill at doing this, at hacking minds and finding the shifts or hops required, will increase as we learn. From an art, it can become a science. We may even learn how to pre-compute the values, according to a Darwinian metric, that correspond to each of the steps of some development plan aimed at modifications of mind functions.

Some of this experimentation may be carried out through brain-computer interfaces, without whole brain emulation. *Even so, advancing substrate-independent minds (ASIM) is ultimately the only way to develop the means for human minds to escape out of and make significant strides beyond their catchment area.* ASIM is not just about making thinking things. It is not simply about longevity. It is not about remaining the same. ASIM specifically addresses the search for a feasible route and a fighting chance to play a role in the future of a Darwinian universe (*http://carboncopies.org*).

Knowing the cause is half the cure

Pattern survival in humans is currently being driven by gene-survival, even though the evolution of humans is itself merely a byproduct of the competition for gene survival (ref. R. Dawkins, 1976). So how can one motivate pattern survival without gene survival? How can one separate the desire to procreate thought characteristics that support specific memes from the desire to procreate genes in humans?

We will not debate competition and Darwinism here any more than we would debate gravity. These are given. We begin with the **end-result perspective**, considering that which will exist: Those things that compete successfully occupy more of space-time; the patterns of information representative of those successful things that excel at competing and developing have a great impact on the universe. Gene survival is a more narrow subset of competing patterns.

An individual may choose not to play the Darwinism game, either by not aiming at any type of pattern survival or through outright suicide. That individual is simply removed by natural selection from the pool of surviving patterns. It does not change the Darwinian outcome from the larger perspective. I posit that, finally, in terms of domains in space-time inhabited by developing patterns, the greatest part of those patterns that resulted from thinking entities will belong to those entities that transcended their equivalent of highly localized gene-survival.

We are not debating good, bad, morality, or purpose. We assume only Darwinian outcomes and try to understand the properties of those evolving, thinking entities that dominate the future. There is no universal purpose by which it would be deemed intrinsically better or worse to play this Darwinian game or to opt out.

That choice already depends on **your personal characteristics**, from which a corresponding degree of competitiveness and survival may follow. For the purposes of this exercise, we do not need to concern ourselves further with the opt-outs, and instead consider the routes that belong to those likely to predominate.

It is true that from a purely practical standpoint, at present, pattern survival and gene survival are linked. But there is a shift in balance that will shortly unlink them.

Compilers and emulators incorporate the knowledge of material things

Can a perceiving entity that is not based on the self-replicating properties of genetic material survive over a long period of time?

When it comes to Universal Darwinism and adaptation, it is a specific set of information, a specific piece of knowledge that is adapted to a certain niche. Adapted knowledge tends to survive within its niche in some embodiment, i.e., in some "substrate." Every time a replicator replicates, it uses non-replicating physical material to build another copy. And non-replicating knowledge can be embodied in different physical substrates each time. This way, even better survival may be achieved by consistently moving to safer substrates.

The material is not crucial. Life is about knowledge. Intelligence — whatever it means — is about knowledge or its use and survival. It is also about an interaction with the environment. A well-adapted entity's knowledge causes its niche to maintain that knowledge or pattern.

Self-replicating properties of genetic material can be arranged in the substrate that is used to compile and emulate functions based on a pattern, even if the substrate is not (human) DNA. Genetic material carries within it the ability to enact the creation of environmental conditions that favor the replication and spread of its self-same code. The body is such an environment, aiding the genetic replicators.

Substrate-independent existence implies that one can devise compilers and emulators in various available resources to operate using the relevant patterns in a manner that includes properties of replication, propagation, and adaptation.

We can appreciate that similar patterns may appear embodied in waves in water, in electromagnetic radiation, etc. A computer virus exists in a different substrate from ours and carries out some of the replicator functions, though it is rather parasitic and makes a home for itself in resources largely arranged for its use by others. SIM seeks not only how to extract and store patterns, but also how to engineer these flexibly implementable compilers and emulators.

Gene survival is easily annihilated due to its extreme dependence on the local environment (*ref. N. Bostrom & M.M. Cirkovic, 2008*). *Gene replication by itself will not survive for significant portions of universal time.* The major thinking survivors of the space-time envelope are the descendants of thinking entities from which substrate-independent forms emerge.

Competition will emerge at some point in which the successful party will be the one that has a focus on pattern survival, and that most successfully imprints its developing patterns of thought and interaction on the future. We can be Darwinian survivors if we are adaptable and up to the admittedly great challenge of moving beyond the current limitations to our thought in terms of **access**, **interpretability**, and **capability**.

Humans have been moving towards an interest in pattern survival ever since they began to think about thinking, and since they began to explore the experience of self-awareness. We see the early consequences of this shift in the remembrance of those who have contributed memes in science, art, and the history of our species. The shift is accentuated today by organized efforts aiming specifically to accomplish the necessary transition.

Beyond an indefensible status quo, our rational expectations and true interests beckon

What if a human SIM contains no information about genes, the prerequisites for survival of the pattern of the brain? The program we are currently running was evolved to and is dedicated to effective gene survival and propagation. Memes are just another tool to ensure that. Gene survival seems the very foundation of everything we are and drives us to do everything we do. What if we cannot separate from gene survival without a change dangerous to the SIM's motivation for survival? What if there is no smooth way to make the cut and escape catchment?

An unsubstantiated worry about not being able to change with adequate caution and tentativeness is not sufficient to argue against the possibility. Until there is further cause to give substance to the specifics of these separation concerns, they express something like the uneasiness that the gods of "purpose" might strike back if we dare to change the focus in terms of which thing is being perpetuated: genes vs. minds.

Therein lies the specter of the old "don't tamper with nature" argument — and yet all progress is a function of doing exactly that. Uneasiness about re-purposing that which has emerged from gene survival (namely, our minds, our perception, our sense of personal identity and self-awareness) is not in itself a practical argument against the possibility of re-instantiating a human mind on different hardware — and then to be able to make gradual changes.

To run the first SIM, and experimentally escape catchment, it may be necessary to glean information from DNA, body simulation, or more. Matters of *scope and resolution* remain to be solved for mind uploading, whole brain emulation, and substrate-independent minds. It is evident, though, that there

is a severely finite combination of resolution and scope that is relevant to the human experience.

Consequently, that experience can be emulated as a first step toward gradual change. As the possibility exists in principle and in practice, we must determine what the minimal scope and resolution requirements are for the most feasible technique.

To understand just how finite the scope and resolution requirements probably are, simply consider the brain as a black box with processes that relate I/O data (chemical, electromagnetic, etc.) that are not drowned in noise. It quickly becomes apparent that while the amount and rate of discernible I/O is significant by today's computing standards, it is not frightfully large.

There is no reason why we should defend the survival of characteristic genes as if they had greater purpose than the survival of our characteristic thinking. Remember: There is no universal purpose. There is no reason to be more attached to the sequence of nucleotides that defines the human form than to the one that defines the form of an ant. The part that is interesting to us is the emergent world of thought and perception.

The winds of change

Are there signs of a changing emphasis in humans from gene survival to pattern survival? There is reason to believe so.

There are competitive, Darwinian pressures among thinking entities. A shift from gene survival to pattern survival is a necessary preparation for the competition between our own emergent intelligence and intelligence of another origin. That other origin could be machine intelligence without the same set of intrinsic drives, or intelligence emergent in thinking entities elsewhere in the cosmos.

Greater capabilities in this competition are based on a greater understanding of one's own thinking processes, and the ability to make adaptations therein. At some point, this will demand that we move beyond the captivity within boundaries of our specific drives optimized for gene survival, our primordial reward functions. That escape can be sought through a careful transition during which competitive motivation is sustained.

Look again from the perspective of the end result: Universal Darwinism applied to thinking entities; whatever adapts and survives well. Whatever you end up creating should suit that selection. A kind of SIM will fare better in many more domains than our good old flesh and bone. In the long run, *we escape doom only by seeking to escape the catchment.*

To tackle this, do not look from past to future and think that genetic survival is the current drive and therefore we can have no route to another form that can survive. Rather, think of the future first. With reason as a guide, deduce the overall qualities of the predominant outcome. Look at what would thrive, and turn us into that. The next successful step will also have something that drives its survival for some period of time, even if it is not Homo sapiens' DNA. Gradual and tentative changes are the safest way to move there from what we are now, if we do not know a better approach.

In other words, advance substrate-independent minds. Start with what we have: The human brain (body too, if you like), and work from there.

Of all the transhumanist strategies, ASIM is both imbued with its originating human interests and also it most directly embraces and plays the game of competitive natural selection. We aim to base its objectives on properties that can be reasonably supposed to be those of successful competing patterns from the point of view of the end result. ■

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Insightful review of the early drafts of this article, as well as deeper insight into matters of possible limitations on AGI and human enhancement were graciously provided by Dr. Suzanne Gildert. Additional review was provided by Michael Andregg.

Footnotes

[1]This realization does not imply hedonism, because I make no claim that all the experiences you want to have are pleasurable or that all the experiences you want to avoid are painful.

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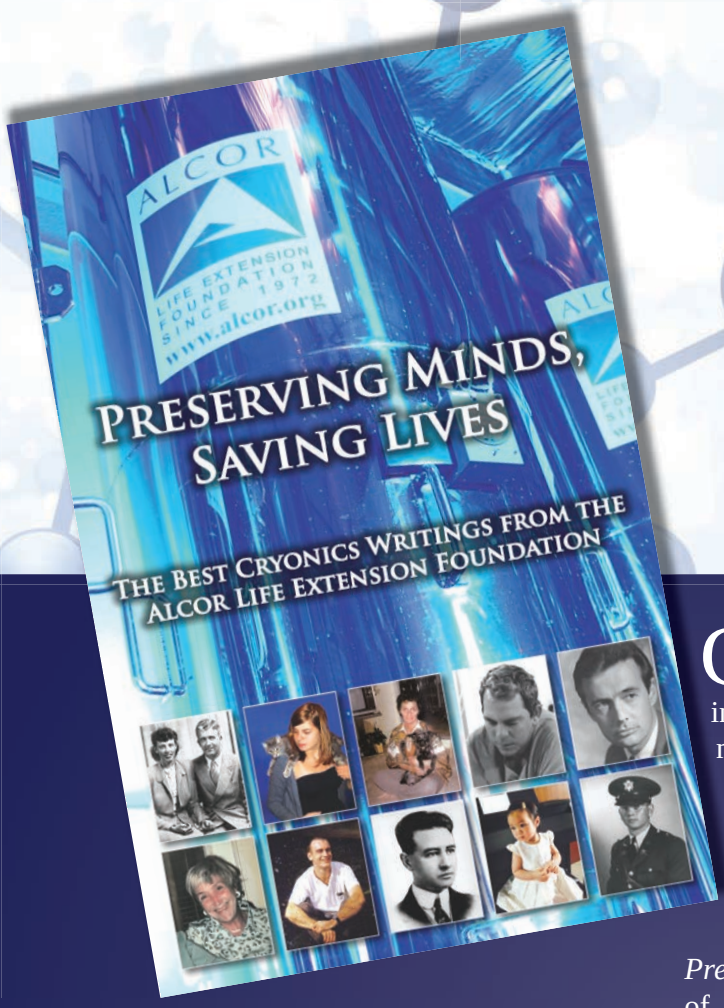

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– Max More, Ph.D.
President and CEO of Alcor

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Yinfeng Cryonics Services in China

By Ben Best

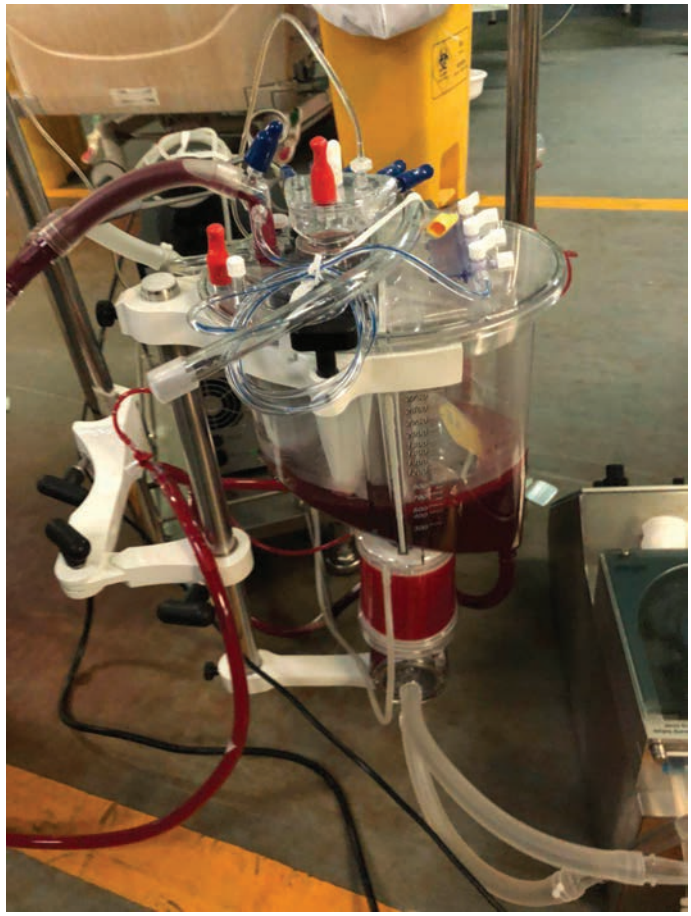
Early in 2016 Alcor's Medical Response Director Aaron Drake left his position to go to China to help Yinfeng Biological create a full-service, whole-body cryopreservation facility. Aaron became a consultant for Alcor for five months of the year when he is not in China.

Taken at Yinfeng in September 2016. Luguan Yan is in the center, flanked on the right by Aaron Drake, and flanked on the left by me (Ben Best). Aaron is flanked on the right of the photo by the Director of the Cryomedicine program, and I am flanked on the left side of the photo by the cardiothoracic surgeon.

The Yinfeng Group is a 7,000-employee corporation located in the city of Jinan, Shandong, China. Yinfeng Biological is a 1,100-employee division of the Yinfeng Group. Yinfeng Biological stores cord blood stem cells in liquid nitrogen, currently storing over 400,000 samples. With Aaron Drake's assistance, Yinfeng Biological sought to create a Cryomedicine subdivision capable of providing whole body cryopreservation services, including standby, stabilization, transport, vitrification perfusion, cool-down to liquid nitrogen temperature, and long-term storage in liquid nitrogen.

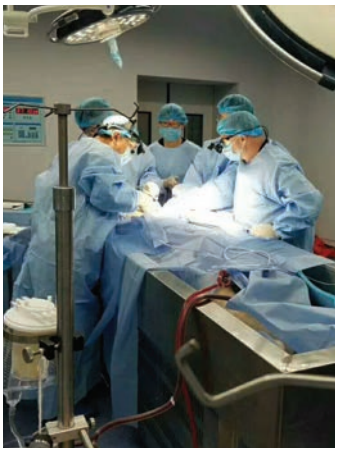
Yinfeng cryonically preserved its first patient in May 2017. By July 1, 2019 Yinfeng had cryonically preserved six patients, all whole-body (neuropreservation is not a currently offered service). Especially in large cities, nearly all native Chinese are cremated upon death, unless they are willing to pay $100,000 per year for burial (with mandated cremation if yearly payments are missed). Native (born in China) Chinese who have not worked in the United States cannot make arrangements with an American cryonics company to be shipped to the United States upon death, rather than be cremated.

Yinfeng is able to offer cryonics services by classifying cryonics patients as research subjects (rather than corpses). The cost of cryopreservation by Yinfeng is two million Yuan (about USD$290,000) as a one-time payment for all cryonics services, including unlimited storage time in liquid nitrogen. As life insurance is not common in China, it has not been used as a funding mechanism to pay for Yinfeng cryopreservation yet.



Apparatus being used for ECMO (Extra-Corporeal Membrane Oxygenation) on a cryonics patient.

Yinfeng has committed a large amount of money to developing its cryomedicine services. Aaron Drake was hired as a foreign expert under China's Thousand Talents Plan and works for roughly seven months per year in China. Aaron works along with 21 other full or part-time employees in the Cryomedicine



Surgery being performed to access central blood vessels for vitrification perfusion

Patient in cool-down box being cooled to liquid nitrogen temperature prior to being placed in a dewar for long-term storage

Cooled-down patient in a metal container being lowered into a dewar for long-term storage in liquid nitrogen

subdivision, including surgeons, anesthesiologists and perfusion physicians. Yinfeng is planning to relocate to a 900,000 square foot facility (fifty times the size of Alcor), which is scheduled for completion in July, 2020. The new facility will not only provide cryonics services but will also conduct research on cryopreservation of body tissues and organs. By July 1, 2019 Yinfeng was already banking 76 different tissues or organs.

Standby for a Yinfeng cryonics patient is attended by six standby members, plus four surgical members. Whether the patient is pronounced dead locally or at a remote location in China, stabilization begins by placing the patient on ECMO (ExtraCorporeal Membrane Oxygenation), a technique for replacing the functions of the heart and lung by mechanically circulating blood outside the body for oxygenation and removal of carbon dioxide. The patient is on a thumper and surrounded by bags of ice (not in an ice bath) during the ECMO-installing surgery, but the surgeons are expert enough that extracorporeal circulation can begin within 15-20 minutes. A remote patient remains on ECMO during transport until arriving at the Yinfeng facility in Jinan.

ECMO can then be used for blood washout and circulatory system cooling down to 15°C, at which temperature vitrification perfusion begins. (Yinfeng uses a vitrification solution developed by a Chinese cryobiologist.) The patient is then placed in a cool-down box until cooled to liquid nitrogen temperature, at which time the patient is transferred to a dewar containing liquid nitrogen for long-term storage.

Currently there is only one dewar per patient, but family dewars are expected in the future. The family unit is powerful in China, and families must approve the cryopreservation of their relative, before it is allowed. Families often have a ceremony honoring the life of the patient near the dewar holding the patient.

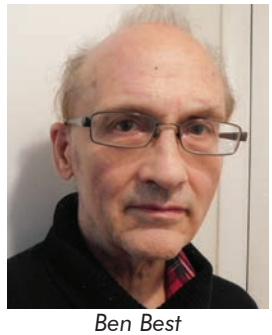
Yinfeng has a membership program for future cryonics patients. As of July 1, 2019, there were 51 Yinfeng cryonics members.

Family members of a cryonics patient in a dewar, ceremoniously bowing and offering flowers in honor of the patient

A video was made of the cryopreservation of the first Yinfeng cryonics patient in May, 2017 (vimeo.com/243966672). The video was shown at the Cryonics Symposium International hosted by Rudi Hoffman at the Church of Perpetual Life in Hollywood, Florida on July 27, 2019. The video was introduced by Luguan ("Jeremy") Yan, a Chinese businessman who translated Robert Ettinger's PROSPECT OF IMMORTALITY into Chinese, as part of his efforts to promote cryonics in China. ■

Australian Cryonicists and Cryonics Organizations

By Ben Best



Ben Best

On Sunday, September 1, 2019 I attended a dinner near Sydney, Australia airport with some Australian cryonicists (people interested in cryonics), specifically: Mark Milton, James Newton-Thomas, Gavin Smith, and Russel Fawcett. I alternated between providing information about cryonics events, organizations, and activities—and asking questions about the status of cryonics in Australia. Concerning the latter, my current understanding (based on the meeting and subsequent emails) follows.

James Newton-Thomas and Gavin Smith

Philip Rhoades seems to be the person with the longest history of promoting cryonics in Australia. Philip is the Executive Officer of the Cryonics Association of Australasia (CAA, http://cryonics.org.au/). Based on the "asia" part of the name, I thought Australasia included India and China, but Philip pointed me to the Wikipedia page https://en.wikipedia.org/wiki/Australasia, indicating the term only includes Australia, New Zealand, and Melanesia. CAA provides emergency support for transporting cryonics patients to cryonics facilities in the United States: http://cryonics.org.au/membership/

In 2004 Philip purchased land he intended to be used as an Australian cryonics facility, but the project did not go very far. In recent years, Philip has been very occupied with creating a Life Extension Village (http://lev.com.au/).

In 2009, Mark Milton and Peter Tsolakides began working to create an Australian cryonics organization under the name of Stasis Systems Australia (SSA), which was incorporated in May 2012. Land was purchased for the facility in Holbrook, New South Wales in 2016. The building is to be completed in 2020.

Mark Milton

Four independent organizations are to manage cryopreservation services: (1) Cryonics Services Australia (http://cryonicsservicesaustralia.com/csa/) charges a $600 fee for assisting Australians in sign-in up for cryopreservation (with SSA, Alcor, CI, etc.). (2) Cryopath (http://www.cryopath.org/cryopath/) will handle SST (Standby, Stabilization, and Transport) for SSA or to cryonics organizations outside of Australia (3) SSA operating under the business name Southern Cryonics (https://southerncryonics.com/, https://www.facebook.com/StaSysAus/) will offer long-term liquid nitrogen patient storage, zoned as a cemetery, but operating as a research facility. (4) CryoPrime, an invitation-only (no website) trustee company offering individual trusts that can last for hundreds of years which can be used by cryonicists for reanimation or by anyone else for any other purpose.

SSA would be initially financed by Founding Members who each contributed AUS$50,000 to pay for their own cryopreservation and finance the facility. Founding Members also had some responsibility for management, but most management would be done by the 3-member SSA Board, which would be Founding Member controlled.

Russel Fawcett

Gavin Smith taking a selfie of the dinner group

Until 2018 the SSA Board consisted of Mark Milton, Peter Tsolakides, and Marta Sandberg. Mark and Peter were Founding Members, but Marta is not, being a Cryonics Institute (CI) Director, and committed to being cryopreserved at CI where her husband is currently in liquid nitrogen. Marta was included because of her extensive cryonics activism and knowledge.

Peter's plans for SSA were different from those of Marta or Mark. Peter decided that once the Southern Cryonics facility was built and operational, the cost of cryopreservation would increase from AUS$50,000 to AUS$150,000, possibly with further price increases indexed to inflation. Founding Members (aka Investors) can buy more than one cryopreservation for themselves, and sell them at a profit after the price increases. Founding Members would continue to have ultimate control over SSA.

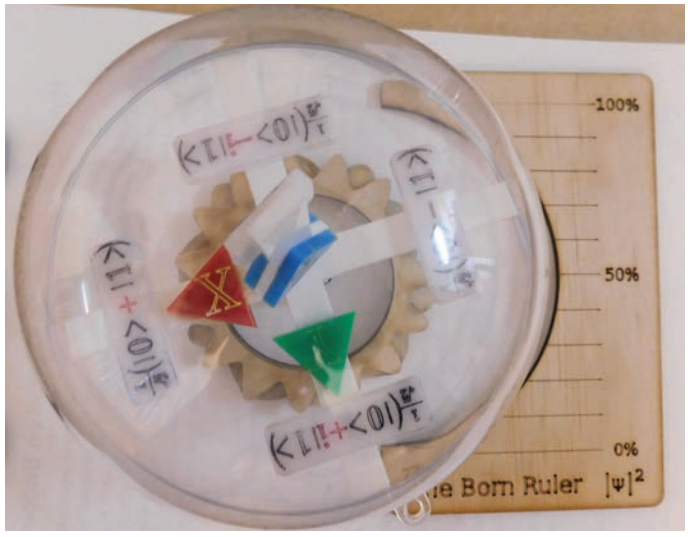
Peter also wanted to spend a large amount of money on architectural plans. There would be no provisions for SSA operating costs to be covered by anything other than Founding Member funds until SSA was operating, with non-Founding Members paying for SSA services (which could take years).

Marta and Mark disagreed with these and other plans of Peter. Because Marta was not a Founding Member, she was forced off the SSA Board by a majority vote of Founding Members. Mark soon thereafter resigned from the Board, and sold his Founding Membership to Peter's brother George, who became an SSA Board Member (https://southerncryonics.com/the-team/). George is a professional mechanical engineer who has developed a technical interest (at least) in cryonics, helping with establishing CryoPath technical capabilities.

James Newton-Thomas, along with Philip Rhoades, is very active in CAA, but is not involved with SSA. James and Philip have modified the constitution of CAA to certify and validate cryonics organizations in Australia, requiring periodic financial audits, and other evidence that the organizations do what they say they will do. SSA has been regularly qualifying for certification. Philip remains the most high-profile cryonicist in Australia, despite not currently being associated with SSA (https://www.abc.net.au/news/2017-02-14/holbrook-australias-cryonics-capital-frozen-bodies/8265416)

Philip has indicated that he may join SSA in the near future. SSA currently has about twenty Founding Members, which means that there should be at least one million Australian dollars to proceed with the construction of the Southern Cryonics cryonic storage facility, scheduled for completion in 2020. With Marta and Mark off the SSA Board of Directors, Peter Tsolakides should be able to implement his plans without interference.

Gavin Smith currently has no cryonics arrangements, and has not been following Australian cryonics activities. I met Gavin at an Alcor conference several years ago. Gavin is preoccupied with his DIY ("Maker") projects, but imagines that he may eventually sign-up with a cryonics organization. He takes great interest in cryonics technology, and took detailed notes during the meeting.



Gavin Smith's fabricated model of a Bloch qubit

At the end of the meeting, Gavin presented me with his "Maker" model of what looks to me to be a Bloch sphere representation of a qubit https://en.wikipedia.org/wiki/Qubit#Bloch_sphere_representation, where a qubit is superposition of probability amplitudes between zero and one, the basis of quantum computers. This led to a discussion of means for crypto-currencies to avoid vulnerability to quantum computers. This is very relevant for me, because I have been making presentations to the Cryonics Asset Preservation Group about use of crypto-currencies for post-reanimation asset preservation: https://cryonicssociety.org/wp-content/uploads/BBest-QSSLAP-Crypto_5-Tampa.ppt

Not only crypto-currencies would be vulnerable to the hypothesized powers of quantum computers, but so would billions of dollars of e-commerce. Hence there is a great interest in protecting against such vulnerabilities. https://en.wikipedia.org/wiki/Post-quantum_cryptography, https://www.ncbi.nlm.nih.gov/pubmed/31439770 ■

Hal Finney Cryonics Research Fund

The Hal Finney Cryonics Research Fund aims to advance the technology behind cryopreservation for future revival. The fund was established in 2018 through a generous donation by Brad Armstrong, a successful cryoptocurrency entrepreneur, Alcor member, and admirer of cryoptocurrency pioneer Hal Finney.

The fund is currently focused on research with the potential to:

- Advance the cryopreservation of brain tissue or whole brains, or
- Advance the clinical practice of cryonics, including patient stabilization, transport, and cryopreservation practices.

Project proposals of all sizes will be considered. For examples of the kinds of projects that will be considered for funding, you can read about past and ongoing Alcor-funded projects at https://alcor.org/AboutAlcor/researchcenter.html. These should be taken as indicative of topics relevant to Alcor's mission, but should not be considered exhaustive.

To be considered for funding, please submit a short (1/2 to 1 page) letter of interest to info@alcor.org that includes:

1. Principal investigator and key research personnel
2. A brief summary of the project goals, approaches employed
3. Estimated budgetary needs
4. Overall significance if the project succeeds
5. Any other information you deem worth including

Letters of interest are reviewed on a rolling basis by Alcor's research committee, and if the project is of interest you will be contacted to submit a full application. The length of a full grant application varies according to the size of the request, but it is typically shorter than government research grant proposals (e.g. NIH, NSF, CIHR) of the same scope. ■

FOR THE RECORD

Cryonics and Public Skepticism: Meeting the Challenges to Our Credibility

By R. Michael Perry, Ph.D.

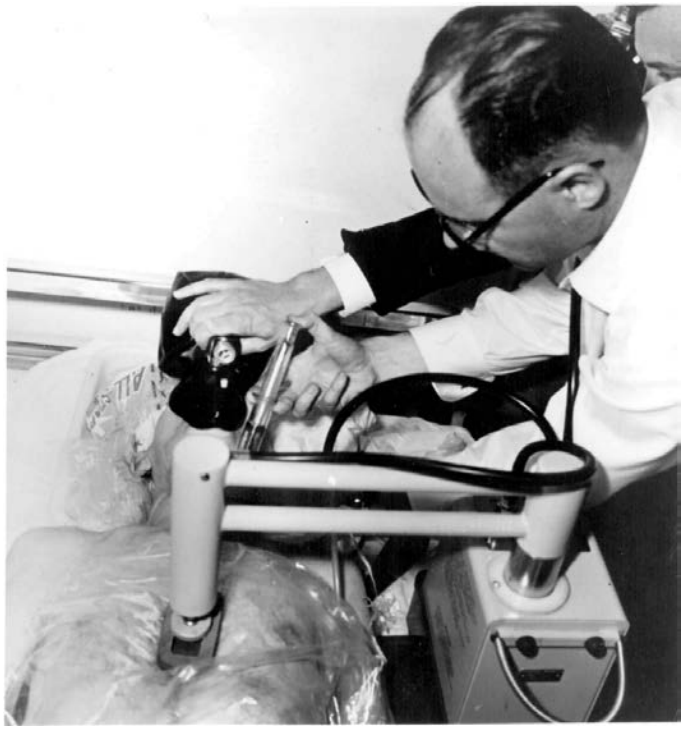
Introduction

Cryonics is a science-based attempt to provide a pathway to future medicine for persons who can no longer be helped through conventional medicine. Extreme cold is used to preserve the patient's remains, especially the brain, at legal death, in hopes that it will one day be possible to restore this person to healthy consciousness, with diseases cured and aging reversed. Such an outcome is not guaranteed yet there are technical arguments that suggest it may be achieved someday. Presently, however, a portion of the scientific mainstream is skeptical about this potential and cryonics is not widely endorsed.

The scientific skepticism has been addressed in these pages more than once—most recently about four years ago.[1] Now seemed a good time for a reexamination, in view of some recent hostility, and the present article will take a closer look at some of the expressed opposition, with coverage and conclusions not anticipated in the earlier articles. One conclusion will be that probably, for the foreseeable future, we must live with the various common beliefs that distinguish us from the mainstream, including claims that cryonics is a scam, impossible, infeasible, pseudoscientific, or simply undesirable. These are not likely to go away until scientists better understand the conceptual basis of cryonics and new evidence is obtained that supports its workability. We should not despair. Rational arguments favoring cryonics, notably repair scenarios suggested by K. Eric Drexler and elaborated and endorsed by Ralph Merkle and Robert Freitas, lend confidence that can support our efforts until more direct evidence is obtained.

To maintain our confidence and carry forward our efforts presents some challenges. Our convictions require that we persevere in our approach to saving lives, even in the absence of the kind of scientific validation we would like to have, and the scientific mainstream would like to witness. Such validation might consist of demonstrated, reversible suspended animation for a mammal, or other return to functionality of a preserved organism of high neural complexity. On the other hand, the absence of full validation is no license for shoddy practices, and we must do our best in what we do, with whatever tools we have.

Opposition to cryonics, of course, is nothing new. When the practice started in the 1960s there was optimism among its proponents that it would soon become widespread. This did not happen, but instead the general public remained indifferent or turned hostile. Some of the opposition came from scientists who doubted that any future technology, however advanced, would be able to carry out the desired revivals. One such critic was chemist and reduced metabolism expert Robert Prehoda. Prehoda's position was that any then-available, long-term preservation using deep cold, if applied to a human brain, would cause damage "beyond any conceptual means of future repair and restoration to original function."[2] The then-fledgling cryonics movement was condemned as "a pseudo-scientific cult which is presenting a completely distorted picture of the prospects for suspended animation to the general public."[3] Only, he thought, with more research and perfecting of techniques could one dare hope that preservation would be adequate for eventual revival, even making allowance for any future advances while the subjects remained essentially unchanging in cold storage.



Robert Prehoda participating in the Bedford Freezing, Jan. 1967, despite his opposition to "cryonics now."

Yet in a certain way Prehoda was overly optimistic in his forecasting, predicting that reversible suspended animation might occur within 30 years of the 1969 publication of his book on the subject—again, though, only with more research. Meanwhile a public which had been mesmerized by the promise of cryonics might underestimate the tremendous difficulties remaining before the process could ever be made workable, and accordingly soft-pedal support for the necessary research, including funding. Prehoda offers his own scenario for revival, using yet-to-be-developed preservation techniques. These methods would follow, and relatively soon, if his proposed research program could be launched. Hoped-for advances would allow both human hibernation and true suspended animation in the form of indefinite, reversible long-term storage at low temperature.

Prehoda's optimistic forecast went unrealized, and cryonics endured hard times in which most of the early patients were lost, but a small group of dedicated advocates persisted, and the practice endured. As for scientific credibility, matters took a turn for the better with the 1986 publication of *Engines of Creation* by K. Eric Drexler. Taking cues from a 1959 lecture, "There's Plenty of Room at the Bottom," by Richard Feynman, *Engines* explores the idea that machines able to manipulate matter at the atomic scale should be technologically possible and not in violation of any physics. Operations should be feasible at low temperature. Among the many possible applications would be to address the problem of cryonics revival; a "conceptual means of future repair and restoration to original function" could indeed be envisioned. The future repair option would be open, not merely to patients preserved by superior methods yet to be developed, but by those preserved, under relatively good conditions, using currently available or previously available techniques. A further elaboration of details for possible mechanisms of revival, again vindicating "freeze now" over objectors like Prehoda, was offered by Ralph Merkle in speculative essays on brain repair after cryopreservation.

The work of Drexler and Merkle, supplemented by others, was important for its scientific support of cryonics, as something worth practicing today. Still skepticism persisted, a notable confrontation being the debate between Nobel chemist Richard Smalley, and Eric Drexler, 2001-03. Though an advocate of nanotechnology himself, Smalley took a dim view of the sort of advances Drexler was proposing and doubted such progress could ever be made.

Drexler ably defended his position, but doubts continued, and today cryonics is still being dismissed as pseudoscientific by some scientists and others. One such dismissal is in the online encyclopedia Wikipedia, which has recently been edited to reflect a decidedly hostile attitude. Many fine, well-researched articles are to be found in Wikipedia, and it is troubling to see our practice denigrated in such terms there.

On the other hand, though, this sort of thing is to be expected, and again we must not become discouraged. Cryonics revival, by indications, will not happen for a long time. The claims made about how it will happen are not presently falsifiable, which is one of the hallmarks used in attaching the label of "pseudoscience." (That we in cryonics think the claims will *eventually* be falsifiable, that is, we will be able to determine objectively whether they are valid or not, does not carry much weight with determined skeptics. Indeed, they will tell us that *that claim too* is not falsifiable, at least not until some nebulous future that may never happen. It is also worth noting that *choosing* cryonics for the possible benefits it may offer is a form of decision making under uncertainty, thus not inherently falsifiable.)

In this article we first summarize Prehoda's arguments against "cryonics now" and then consider his revival scenario, which he imagined would follow when (and only when) research had demonstrated its efficacy. The Drexler-Merkle-Freitas revival scenario is outlined, with its implication that "cryonics now" should instead be pursued, in anticipation of successful revival techniques, though none exist today. We then consider the Smalley-Drexler debate, with its bearing on whether the projected revival according to Drexler et al. will ever be possible. Next, we summarize some relatively recent, hostile reactions. Michael Hendricks, *MIT Technology Review*, deplores the "false science" (= pseudoscience) "of cryonics." Ken Hayworth, rebutting Hendricks, nevertheless finds current cryonics practices unsatisfactory, and calls for not offering cryonics to the public until better evidence of efficacy is obtained. Aschwin de Wolf offers a powerful rebuttal to the anti-cryonics stance of both responders. Wikipedia, however, now characterizes cryonics as a pseudoscience; this is taken up in its own section. Some final thoughts follow, starting with the Scientists' Open Letter on Cryonics, where dozens of Ph.D. scientists express support for the practice. Suggestions are made for some simple research initiatives that could help our credibility with the scientific mainstream and the public at large, along with cash prizes for those who succeed.

Prehoda's Arguments against "Cryonics Now," and His Revival Scenario

Prehoda, as we have noted, was opposed to cryopreserving people at clinical death, until a method of revival had been demonstrated. Instead, he considered the contemporary practice that had developed of freezing people to be pseudo-scientific. In Prehoda's words, a "pseudo-scientific proposal or idea" is "a hypothesis or combination of hypotheses which cannot be accepted by any of the leading specialists in the field."[4] The proponents of a pseudoscience, then, are not "leading specialists in the field," but something else. For cryonics the "field" was (simplistically, more later) cryobiology. No prominent cryobiologist in Prehoda's time had endorsed cryonics, though in a rebuttal Robert Ettinger noted that also none would say it

had no chance of working. Prehoda's objections, however, do not stop with simple labeling, nor are they particularly dependent on specialists, beyond noting their lack of support.

Prehoda's objections, and his own scenario for revival of cryopreserved patients, are detailed in his 1969 book, *Suspended Animation*. Arguments against "cryonics now" start with a discussion of pseudoscientific movements in general and why they flourish in the absence of confirming scientific evidence or even in the face of contrary evidence. Many people gain an important sense of meaning and purpose from certain beliefs, which may then override objections that others find compelling. Such beliefs are often connected with religion. A case in point (not noted by Prehoda but still representative) concerns the presence of living creatures on Earth. How did life get here? Creationism, or intelligent design, is favored by those wishing to uphold the biblical account in Genesis. Darwinian evolution without intelligent design or intervention is the mainstream scientific view, backed by what is seen as compelling evidence from the fossil record and other sources.

Prehoda then considers the specifics of cryonics. Certainly, cryonicists resemble others he deems pseudoscientific, in holding certain beliefs or hopes in connection with what they perceive as attainable goals, even though others differ. Prehoda himself, as one of the dissenters, reiterates his position that cryopreservation by then-current methods is not likely to be reversible by any future technology. It should only occur when (if ever) there is general agreement, among those scientists who can be considered "leading specialists in the field," that prospects are good for revival. At this point it would no longer be a pseudoscience by his criteria, thus acceptable scientifically and respectable, granted that anyone dying before this time must be abandoned to destruction. (Prehoda's position too, that cryonics as then practiced would never prove reversible by any future technology, was not falsifiable.)

Aside from the reluctance to try to save the dying now, Prehoda was highly positive about the prospect of suspended animation through cold storage. A chapter of *Suspended Animation* offers an imaginative scenario for a man who has serious medical issues: a combination of cancer and heart disease.[5] Starting in 1989, the patient is put "on hold" through recent, reduced-metabolism breakthroughs—human hibernation and a stronger variant, chemical stasis or anabiosis—which stop short of true suspended animation but extend his life for ten years. His life is still endangered, however, and will be lost unless there is further intervention of a different order than what has been tried.

Fortunately, by 1999 something more radical is now available: full, suspended animation (reversible cryopreservation). "The freezing barrier had been overcome the previous year. Animals have been frozen and revived with no apparent damage. You can now be held in the frozen state until science can guarantee reliable cures for your diseases and also restore you to youthful vigor. …" Revival, then, is a given due to the protocol which has been developed and verified scientifically.

Prehoda then details an imagined scenario for reversible cryopreservation which uses hyperbaric pressure and an unusual combination of perfusates. The process, somewhat like a modern cryonics protocol, is in two stages consisting of (1) cryoprotective perfusion (cryoprotection), and (2) cooldown and freezing, an involved operation whereby the perfused patient is frozen in stages and finally chilled to cryogenic temperature.

Step (1), cryoprotection, starts with a "machine that first perfuses an oxygenated cell-free plasma through [the] body at 45 psi." The body temperature is then lowered to 0°C and most of the water in the (now bloodless) body is replaced with heavy water (D_2O). "A 5-percent-by-volume addition of fluorinated DMSO is now added to the perfusate. This chemical will partially protect the cells during freezing, but its main function is to act as a biological carrier, insuring that the powerful metabolic inhibitors will reach adequate levels within all the cells." To help reduce the level of dissolved salts within the cells, salt-free albumin and ATP are added to the perfusate, then the pressure is greatly increased, "and large quantities of dissolved xenon gas begin to be circulated through the body." Separate perfusion systems protect the fluid-filled cavities around the brain and spinal cord, and in the eyes.

Step (2), cooldown and freezing, is now ready to begin. The heavy water is replaced "with a liquid fluorocarbon which can hold large quantities of xenon." The pressure is slowly increased as the temperature is lowered, until, at 5,000 psi, "an optimum quantity of xenon can be perfused through the body, thoroughly penetrating every cell." The pressure is increased to 30,062 psi while the temperature, now -24°C, is held constant to dissipate the heat of fusion induced by the pressure increase. Then the pressure is lowered again to 5,000 psi, an action which causes freezing of a large mass of tissue. During this freezing the tissue is protected from damage by the prevalence of xenon hydrate. By repeating the pressure increase-decrease cycle at ever lower temperatures the entire body is frozen without injury, and the temperature is finally reduced to 4.2°K (-268°C), the temperature of liquid helium. (It is worth remarking here that this protocol seems oblivious of any costs that might be involved, such as for use of expensive xenon or storage at liquid helium temperature when much cheaper liquid nitrogen storage should suffice. Prehoda was understandably focused on "proof of concept" not practical details of implementation.) The patient is "now in a state of complete suspended animation." The frozen body is removed from the pressure chamber and storage continues at the low temperature.

There matters rest until finally, in 2069, all the patient's ailments are curable, including aging. (Prehoda was not bothered by assuming this, though such cures were unavailable in his own time.) Given the sophistication of the cryopreservation seventy

years before, revival is a relatively straightforward reversal, coupled with reconditioning as needed. For example, "cells removed from different parts of the body have been stimulated into growing into complete replacement organs." The patient is returned to the pressure chamber, and first warmed from liquid helium temperature to -80°C, while the pressure is again increased to 30,062 psi. Then: "Precisely controlled microwaves and ultrasonic waves quickly raise the temperature to -24°C, where all the tissues are again in the liquid state." The tissue is then reconditioned, as the temperature is slowly raised, and the pressure lowered. "Perfusion fluids circulate through the body, removing the xenon and fluorinated DMSO. Chemicals are introduced to counteract the metabolic inhibitors." Any remaining heavy water is replaced by the normal variety, and the salt content of the cells is restored to normal levels. When the temperature reaches 25°C, natural blood replaces the perfusate and atmospheric pressure is restored. Finally, as body temperature (37°C) is approached, "the EEG brain wave monitoring shows that there has been no neural damage during the long interval of suspended animation. Slowly, the first thought begins to form deep in the subconscious. …"

With the patient revived, any preexisting ailments can be treated. Prehoda's scenario, we have seen, assumes that reversibility of the cryopreservation process will have been demonstrated beforehand. The purpose of cryopreservation is only to buy time to perfect methods of curing diseases and other disorders, not perfect methods of revival.

The Drexler-Merkle-Freitas Revival Scenario

It has been half a century since Prehoda penned his thoughts in *Suspended Animation*. His imagined scenarios of human hibernation and chemical anabiosis by 1989 and reversible human cryopreservation by 1999 did not materialize. Prehoda was no dogmatist in his optimism, however, but acknowledges in his book that a much longer time interval might pass before these breakthroughs, or they might never occur.

In any case, with the appearance of K. Eric Drexler's *Engines of Creation* (1986) we are offered a new current of scientific thought about the feasibility of cryogenic storage for later revival. Drexler's ideas were further developed and refined in his Ph.D. dissertation at MIT, which in turn was enlarged and appeared in 1992 as the book, *Nanosystems*.[6] Drexler's ideas in turn trace back to a 1959 lecture by Nobel physicist Richard Feynman, "There's Plenty of Room at the Bottom," where Feynman says: "The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom."[7] Feynman notes that incredible feats of miniaturization, such as writing the entire *Encyclopaedia Britannica* (all 24 volumes) on the head of a pin ought to be possible and suggests some ways (focusing metallic ion beams and the like) this might be accomplished.

Going further, Feynman notes that, in the world of biology, nature has engineered many marvelous devices that do very complicated things at very fine scales going down to the level of molecules and atoms and offers that we should be able to do the same. Life is chemistry, of a certain sort (emphasizing the element carbon and the many complicated things it does in chemical interactions), so it might be said that chemistry offers a well-demonstrated approach to the fine manipulations Feynman is forecasting. However, much of his thinking is not toward further refinements of chemical interactions but mechanical processes that might also achieve the desired, fine scale manipulations, an important distinction, as we shall see.

Richard Feynman

Drexler builds on Feynman's ideas in *Engines* and *Nanosystems*, reiterating that we could usefully harness the potential of manipulating matter at molecular and atomic scales, a field that has come to be known as nanotechnology. Today Drexler's original nanotechnology is called "molecular nanotechnology" or MNT, while "nanotechnology" is given a broader meaning. Here we shall be mainly concerned with MNT. Among the possibilities would be an "assembler"—a device that could make any of a wide variety of other devices, including copies of itself, so that production of devices with particular, desired functions could proceed rapidly. (For this device Drexler also borrows ideas from John von Neuman's theoretical work on self-reproducing automata going back to the 1940s, seconded by a colleague, Stanislaw Ulam.[8]) Drexler notes Prehoda's saying "Almost all reduced metabolism experts … believe that cellular damage caused by current freezing techniques could never be corrected." He responds: "Of course, these were the wrong experts to ask."[9] Instead, physicists, computation theorists and materials scientists have deep insights that ought to be relevant.

This would particularly follow if, following Feynman, we imagine that MNT encompassed the possibility of mechanical systems that could work at a fine scale, bypassing the need for biological or other chemical processes that have narrow requirements in a watery environment (temperature range in particular). No longer is the argument so forceful that revival must be demonstrated in animal models before cryopreservation can be reasonably applied to humans. One must only have confidence that the necessary structure that would define the person is still present in some, inferable form, and that MNT as envisioned can be developed. Among the possibilities might be armies of tiny devices and tiny computers to control them, assisted by mainframe computing as needed, able to work in

coordinated fashion to accomplish many desired goals. A system of such devices, or other system able to function at a molecular scale, could be equipped with its own, internal power supply and operate in a vacuum on material at low temperature. It then might be especially effective in operations on a preserved human body, that otherwise has rocklike hardness and stability.

We could then imagine proceeding in three stages. (1) First would be just a fact-gathering task, mainly, to obtain a detailed map of the brain structure at the necessary resolution, perhaps at the level of molecules, to judge what repairs or reconditioning would be needed. (2) Informed by computations from this starting database, repairs would be made and reconditioning of the tissue to remove effects of injury, diseases, and aging. The reconditioning would extend to other structures in the body, less critical than the brain but still important. Missing parts would be restored, as in the case of "neuro" or head-only or brain-only patients, who could be fitted with manufactured bodies similar to the original, based on DNA. Conditioning could also modify, replace or remove any substances, cryoprotectants or fixation chemicals, for example, not wanted or needed later. (3) In the latter stages of the conditioning process the patient would be restored to body temperature and consciousness in a state of good health.

This is only one possible revival scenario, another commonly imagined one being, after step (1), to transfer the brain information to an advanced computer which could then do an emulation of the original person. In this way the patient would become a "software being," different but equivalent in essential ways to what was formerly resident in a biological brain, which could be viewed in turn as just another sort of computational venue in which to house and "run" a personality. (The best "housing" devices of the future might be decidedly superior to nature's product that has served our needs for so long, albeit imperfectly.) The patient could then wake up in an inspiring virtual setting, including portals to the "real" world outside, with aging and diseases eliminated. This is the "uploading" scenario, for those not bothered that such an upload would be "only a copy," not the "original." The emulation might then be "downloaded," if so wished, to an individual body, either biological, artificial, or with a combination of both features.

Such thoughts as the preceding, and others supporting the likely feasibility of recovery of persons from cryopreservation via different routes, are offered in a series of articles by Ralph Merkle and Robert Freitas. A landmark Merkle's 1992 speculative essay, "The Technical Feasibility of Cryonics," revised and elaborated as "The Molecular Repair of the Brain." Merkle concludes: "Given the life-saving nature of cryonics, it would be tragic if it were to prove feasible but was little used."[10]

Step (1), mapping the brain, arguably the most crucial to the whole operation (at least with cryopreservation methods available today, which generally induce fracturing), might be approached in several different ways. Merkle suggests "divide and conquer," where the brain might be broken in pieces, carefully, with insignificant loss of information, and the pieces broken further and further, until obtaining pieces small enough to map without further breakup. This is mainly a "brute force" argument intended to suggest that some type of process to attain the desired result is feasible, not to find an optimal process. Merkle and Freitas note also that the brain's own vasculature might be exploited. By clearing out solidified material in arteries, veins, and capillaries it should be possible to approach within 20 micrometers or so of any point in the neural structure, which could facilitate a mapping strategy (with, of course, many further details to be worked out).[11]

By now there is extensive literature on MNT, including several books by Drexler himself[12], and a massive study by Freitas relating to future medicine.[13] What is missing is implementation, and this provides an entry point for skeptics.

Skepticism about MNT

Nature has clearly developed MNT but in a limited way, using aqueous chemistry in a narrow temperature range. Can we do better, as we will likely have to do if we are going to restore cryonics patients? Can we develop mechanical MNT, able to operate at low temperature, to do the fine-scale mapping of the brain's interior and (if bodily revival rather than uploading is desired) repair and rebuilding?

Skeptics have said that nothing approaching Drexler's general-purpose assembler is possible, thus we cannot expect to do what would be necessary to carry out cryonics revival (nor many other things we would like to do). Three important kinds of alleged barriers to what we would like to do concern the "manipulator arm" and "fingers" of the putative assembler, also referred to as a nanobot. These are: (1) the "shaky fingers" problem, (2) the "fat fingers" problem, and (3) "sticky fingers" problem, to which, in each case, Drexler and others have provided answers.

The "shaky fingers" problem concerns the fact that at small scales things are not steady but vibrate. The vibration, a thermal effect, becomes larger with increasing temperature and more serious, at any temperature, with decreasing distances. Yet it is not enough to prevent biological systems from working, so arguably more general MNT could be made to work too.

The argument that this should be so is greatly strengthened by considering details, as Ralph Merkle and others have done. Ray Kurzweil, in reference mainly to Merkle's work, notes that "conceptual designers of [MNT] have emphasized building structural components from diamondoid or carbon nanotubes. … Analysis of these designs [has] shown them to be thousands of times more stable in the presence of thermal effects than biological systems, so they can operate in a far wider temperature range. … Similar challenges were made regarding

positional uncertainty from quantum effects. … A nanobot will be constructed from hundreds of thousands to millions of carbon atoms, so a nanobot will be billions of times more massive than an electron. Plugging this ratio in the fundamental equation for quantum positional uncertainty shows this to be an insignificant factor."[14]

The "shaky fingers" problem, then, is arguably not an insurmountable barrier. Two other problems, the "fat fingers" and "sticky fingers" problems, were addressed in a celebrated series of exchanges between Eric Drexler and Richard Smalley, 2001-03.[15] Smalley shared the 1996 Nobel Prize in chemistry for the 1985 discovery of buckminsterfullerene (the "buckyball") and other "carbon cages."[16] An advocate of nanotechnology, including molecular-scale electronics, he nonetheless stopped short of endorsing Drexler's more radical ideas, particularly the feasibility of the assembler, also referred to as a "self-replicating nanobot." In an article in *Scientific American* he summarized his arguments that such a device is not possible:[17]

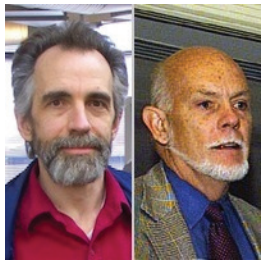
> "Because the fingers of a manipulator arm must themselves be made out of atoms, they have a certain irreducible size. There just isn't enough room in the nanometer-size reaction region to accommodate all the fingers of all the manipulators necessary to have complete control of the chemistry.... [Also,] the atoms of the manipulator hands will adhere to the atom that is being moved. So it will often be impossible to release this minuscule building block in precisely the right spot. Both these problems are fundamental, and neither can be avoided. Self-replicating, mechanical nanobots are simply not possible in our world."

A rebuttal to Smalley, co-authored by Drexler, Merkle, Freitas, J. Storrs Hall, and others, was published through the Institute for Molecular Manufacturing. The biological ribosome is a molecular machine designed by nature which builds protein molecules subject to instructions provided by RNA:

> "This ubiquitous biological molecular assembler suffers from neither the 'fat finger' nor the 'sticky finger' problem. If, as Smalley argues, both problems are 'fundamental,' then why would they prevent the development of mechanical assemblers and not biological assemblers? If the class of molecular structures known as proteins can be synthesized using positional techniques, then why would we expect there to be no other classes of molecular structures that can be synthesized using positional techniques?"[18]

As the debate continued, Drexler offered an appeal to Feynman's ideas in the 1959 lecture: "although inspired by biology... Feynman's vision of nanotechnology is fundamentally mechanical, not biological." He concluded:

> "Positional control naturally avoids most side reactions by preventing unwanted encounters between potential reactants. Transition-state theory indicates that, for suitably chosen reactants, positional control will enable synthetic steps at megahertz frequencies with the reliability of digital switching operations in a computer. The supporting analysis for this conclusion appears in *Nanosystems* and has withstood a decade of scientific scrutiny."[19]



K. Eric Drexler (left), Richard Smalley

Drexler then makes an appeal to Smalley to reconsider his objections, in the interests of advancing progress in nanotechnology and "achieving the grand vision articulated by Richard Feynman." Smalley did not relent, but instead offered further arguments for his own position, with a warning:

> "You and people around you have scared our children. I don't expect you to stop, but I hope others in the chemical community will join with me in turning on the light, and showing our children that, while our future in the real world will be challenging and there are real risks, there will be no such monster as the self-replicating mechanical nanobot of your dreams."[20]

Smalley died in 2005, of leukemia. Long an agnostic, Smalley had by then embraced Christianity and expressed a favorable viewpoint about Intelligent Design: "The burden of proof is on those who don't believe that Genesis was right, and there was a creation, and that the Creator is still involved. … [The fact is] this planet was built specifically for us. …"[21] This is not noted with any intent of disparagement of a dying man's search for hope and meaning as options dwindle. Religious conversions or intensifications are well-known to occur as people get older and sense the end of life approaching,[22] though naturally this does not always happen, others finding solace in a scientific outlook. However the point is worth making that some, for whatever reasons, attribute any "natural" nanotechnology to the workings of God thus perhaps "off limits" to the sort of interventions and enhancements proposed by Drexler and others.

Critical responses to the debate showed the expected variations. For Steven A. Edwards in *The Nanotech Pioneers* the evaluation of the arguments was difficult because of ambiguities in the specifications and even the definition of a molecular assembler. Speaking of Drexler's magnum opus on the subject, "nowhere in it does *Nanosystems* contain a blueprint for a molecular assembler… We are told, for instance, that a manipulator arm would involve 4,000,000 atoms, but we are not told which atoms, or how they would be put together." The debate he dismisses as "mainly an entertaining academic diversion to most nanotechnologists."[23]

Futurist Ray Kurzweil in *The Singularity is Near* is more positive toward Drexler, declaring him the winner of the debate, and accusing Smalley of distorting his opponent's ideas with responses that were "short on specific citations and current research and long on imprecise metaphors." Smalley, moreover, "is ignoring the past decade of research on alternative means of positioning molecular fragments using precisely guided molecular reactions… [which have] been extensively studied."[24]

We have seen that Smalley accuses Drexler of having "scared our children" and takes solace that no such "monster" as the fancied nanobot could become a reality. Kurzweil responds:

> "I would point out to Smalley that earlier critics also expressed skepticism that either world-wide communication networks or software viruses that would spread across them were feasible. Today, we have both the benefits and the damage from both of these capabilities. However, along with the danger of software viruses has also emerged a technological immune system. While it does not completely protect us, few people would advocate eliminating the Internet in order to eliminate software viruses. We are obtaining far more benefit than damage from this latest example of intertwined promise and peril."[25]

Kurzweil is not oblivious to the possible dangers of MNT should it be realized. To address this very problem a nonprofit organization, the Foresight Institute, was cofounded by Drexler in 1986. Kurzweil notes: "Drexler and his colleagues at the Foresight Institute have been in the forefront of developing the ethical guidelines and design considerations needed to guide the technology in a safe and constructive direction."[26]

MNT, however, has still not been realized, nor have revivals from cryopreservation, and just as with MNT, skepticism about cryonics continues. Some interesting developments a few years ago raised the concerns of Prehoda in a new guise, and a recent, widely consulted reference has been revised with a decidedly hostile tone.

Back to Cryonics: Hendricks and Hayworth Weigh In, then de Wolf

The story we resume here starts with a New York *Times* article about the cryopreservation of 23-year-old Kim Suozzi (at Alcor) in January 2013.[27] Kim (ironically) had herself been a neuroscience major and doing well in college (Truman State University, Kirksville, Mo.) when she started experiencing headaches, and finally was diagnosed with inoperable brain cancer.

Michael Hendricks was a neuroscientist and assistant professor of biology at McGill University (Montreal, Quebec, Canada). Though sympathetic to the plight of the young cancer victim, Hendricks nonetheless offered a determined, hostile response to the *Times* article ("The False Science of Cryonics," MIT Review, 15 Sep. 2015[28]). Cryonics is seen as "a cottage industry spurred by 'transhumanist' principles that offers to preserve people in liquid nitrogen immediately after death and store their bodies (or at least their heads) in hopes that they can be reanimated or digitally replicated in a technologically advanced future." The perceived promise of recent work in "connectomics"—dealing with mapping the connections between neurons in the brain—has empowered proponents to "add a patina of scientific plausibility to this idea." He warns us, however, that "a map of connections is not sufficient to simulate, let alone replicate, a nervous system…"

As evidence he notes that the small roundworm he studies, *Caenorhabditis elegans*, had its complete pattern of synaptic connectivity—its connectome—mapped thirty years before. "Yet even with the full connectome in hand, a static model of this network of connections lacks most of the information necessary to simulate the mind of the worm." Brain activity, he concludes, "cannot be inferred from synaptic neuroanatomy."

He then (sensibly) asks three questions. "First, what information is required to replicate a human mind? Second, do current or foreseeable freezing methods preserve the necessary information, and how will this information be recovered? Third, and most confounding to our intuition, would a simulation really be 'you'?"

Hendricks after some discussion then decides that, on one hand, it is unlikely that current or previously available cryopreservation methods preserve the necessary information to carry out a restoration of the individual to consciousness, either in the original biological form or as a simulation. (Basically, this is Prehoda's old argument, oblivious of the possibilities of future MNT.) Moreover, he concludes, a simulation of you, supposing one is possible in the future after all, just could not be "you"—intuition speaks too strongly against it.

The article closes on a note of severity and condemnation: "reanimation or simulation is an abjectly false hope that is beyond the promise of technology and is certainly impossible with the frozen, dead tissue offered by the 'cryonics' industry. Those who profit from this hope deserve our anger and contempt."

(A comment regarding "profits" that are earned in the "cryonics industry": Cryonics organizations generally do have a paid staff. It's very hard to get by on just volunteer help alone, as cryonics history shows, when pioneering organizations failed and nearly all the patients from these early times were lost.[29] Generally, these organizations had no paid staff, and little money to pay a staff. But today, most if not all cryonics organizations are not-for-profit, and salaries and worker compensation are relatively modest. People are mainly involved in cryonics not to earn income or make "lucrative career choices" but to try to save lives, including but not limited to their own.)

A rebuttal to Hendricks's arguments is offered by Ken Hayworth.[30] Though it is unfriendly to cryonics as it is currently practiced, it is encouraging overall. Hayworth is a Ph.D. neuroscientist and is president of the Brain Preservation Foundation (BPF) which he cofounded. He is a coinventor of a tape-to-SEM process for rapid imaging of volumes of brain tissue by splitting the tissue into many very thin slices, and he designed and built several automated machines to implement this process. As he says: "The BPF has offered a challenge prize for the development of a medical procedure which can preserve a human brain so that people today can potentially take advantage of mind uploading technology [more than] 100 years in the future." (The prize has been awarded in two forms, for aldehyde-stabilized cryopreservation of small and larger mammalian brains.)[31]

Early in his rebuttal Hayworth takes organizations like Alcor to task: "I started the Brain Preservation Prize as a challenge to Alcor and other such companies to 'put up or shut up', challenging them to show that their methods preserve the synaptic circuitry of the brain. After five years they have been unable to meet our prize requirements even when their methods were tested (by a third party) under ideal laboratory conditions. Out of respect for loved ones I will not comment on any particular case, but it is clear from online case reports that their actual results are often far worse than the laboratory prepared tissue we imaged. Speaking personally, I wish that all such companies would stop offering services until, at a minimum, they demonstrate in an animal model that their methods and procedures are effective at preserving ultrastructure across the entire brain. By offering unproven brain preservation methods for a fee they are effectively making it impossible for mainstream scientists to engage in civil discussion on the topic."

Ken Hayworth

(Comment: The main problem here seems to be that current cryonics protocols produce substantial brain dehydration in the course of cryoprotective perfusion. Such dehydrated tissue is difficult to image by the methods Dr. Hayworth is using. A study that was done recently showed, apparently, that the synaptic and other information that should have met Dr. Hayworth's criteria is preserved by the sort of protocols that are used, when applied under good conditions. The paper, according to a confidential source, is still in preparation.—R.M.P.).

Otherwise, Dr. Hayworth is more positive than his opponent: "Unlike you … I do think that cryonics and other brain preservation methods are worthy of serious scientific research today." Hayworth offers that while early cryonics methods turned the brain to "mush," recent results by 21st Century medicine offer a more encouraging outlook. "… it looks like as of 2015 we may finally have a method (Aldehyde Stabilized Cryopreservation) that can demonstrably preserve synaptic connectivity of a brain over centuries of storage. … And we are beginning to see a plausible path for how such a brain's connectome might be mapped in the future."

But Dr. Hendricks made a point of saying that knowing just the connectome could not be sufficient for reviving the patient—too much other critical information would have been lost. Science tells us (he tells us) that such revival, or equivalent simulation, is "impossible" even for the small roundworm (C. elegans) Hendricks studies. Hayworth responds: "Really? Science tells you this is 'impossible' because you have failed to do so in your worm studies so far?"

Hayworth then discusses details of what is known and not known about the functioning of synapses in various brain structures, among other results mentioning that "we know enough to have had 'simulations' of retinas for two decades." He continues: "I am certainly not saying that we now know everything about how the brain works, but I am saying that there is more than enough reason to suspect that the structural connectome may be sufficient to successfully simulate a brain given the depth of neuroscience knowledge we should possess by the year 2100 or 2200. Dismissing that as even a possibility hundreds of years in the future based on your failed attempts at understanding some particulars of *C. elegans* nervous system today seems very shortsighted. If you have real theoretical arguments then present them."

On the issue that "a simulation of you could not be 'you'," often referred to as the "copy problem," he offers a spirited counterargument extending over several paragraphs. As a sample: "We are evolved biological robots, period. That is what science really has told us unequivocally. Do you seriously disagree with this? There are no magic molecules in the brain that define us, just computation. Our consciousness is just another type of computation, one that computes a 'self model' to assist in intelligently planning our future actions. Such computationalism is the foundational assumption of cognitive science and I would argue of neuroscience as well. There is no room for magic in neuroscience."

(Much has been written about the copy problem, with fierce opinions on both sides of the issue. Some recent articles in *Cryonics* offer reasons for accepting that one would survive in a copy[32], which would reduce and likely simplify the requirements for revival. Here however the focus is on how cryonics should be regarded in terms of scientific plausibility and respectability, not this other interesting topic.)

A little more should be said about Hayworth's negative assessment of current cryonics practices. As noted, Hayworth

thinks cryonics companies should "stop offering services" until they can demonstrate better ultrastructural preservation of brain tissue. Here he seems like Prehoda in calling for a halt to cryonics practice until procedures are better validated, which would require more research. An intelligent response, I think, would be a close parallel to the case of Prehoda. There we had a procedure, freezing with some efforts at cryoprotection, that arguably would prove workable, even though no demonstration of workability had yet occurred. (Though the procedure may have reduced the brain to "mush" as Hayworth has insisted, he has also not confronted the issue of whether the brain information necessary for revival could still be extracted through future MNT, which arguably is still a likely possibility.) There it seemed appropriate to continue "cryonics now" and so it appears today, and arguably all the more so, since procedures have improved, and ice damage is much reduced. The dehydration of brain tissue that current protocols produce does not appear, on the face of it, to produce destruction of fine structure (why should it?), and one can hope an adequate validation can be obtained (or has been obtained already) from methods other than Hayworth used.

Finally, I note that Aschwin De Wolf, editor of *Cryonics* and longtime Alcor member, issued a strong rebuttal to Hendricks and a plea for cryonics to be considered respectable.[33] that appeared in *Cryonics* in 2015, incorporating some responses to a reporter who asked about Alcor's position. Hendricks' article "rests on several mistaken assumptions," a major one being that cryonics appears to require or imply mind uploading.

> "…While some of our individual members are interested in this topic, the default resuscitation scenario for cryonics patients involves molecular repair of the patient's biological brain (and body). While we are encouraged by the rise of connectomics, the aim at Alcor is to cryopreserve all the fine details of the brain and even secure viability of the brain as well as we can. In fact, in our stabilization procedures we aim to keep the brain viable by contemporary medical criteria and collect data to evaluate the efficacy of our procedures."

The article further notes that cryonics organizations are not-for-profit and that members often fund their cryopreservations through life insurance. Finally, there is a spirited defense of the practice of cryonics even though no revivals have yet been achieved:

> "We strongly disagree that without proof of human suspended animation or flawless ultrastructural preservation it is not ethical to practice cryonics. Our organization challenges the mainstream definitions of death, and we believe that perfected cryopreservation is a sufficient but not necessary condition for cryonics to succeed. As long as we have good reasons to believe that the original state of the brain can be inferred from the damaged state, making cryonics arrangements can be a rational choice to make. To our knowledge, there are no rigorous, scientific, studies that demonstrate that today's cryonics procedures produce irreversible destruction of identity-critical information."

Recent Hostility from Wikipedia

I will say here that, overall, I consider Wikipedia, the free online encyclopedia, to be one of the most useful references for just about any topic I care to look up. Especially if I want an introduction to some esoteric subject, say, in higher mathematics, so often Wikipedia comes through brilliantly. Their articles in general are well-researched and well-referenced. Their policy of letting general users edit means that a lot of material comes in from a lot of sources. (I've even made a few contributions myself.) Their editorial board is there to catch any obvious improper postings, and generally appear to do a good job. (They also from time to time make it known that they need at least some financial wherewithal to operate and ask for donations; I have made some modest donations and expect to make more.) One further indication of respect I have is that I have used Wikipedia references extensively and approvingly in articles I have written for *Cryonics*, including this one. That said, even Wikipedia is run by human beings who are subject to human foibles. So, as one might expect, not everything is perfect according to one's own standards (themselves subject to shortcomings), especially when it comes to a highly controversial subject like cryonics.

Anyway, looking back over the history of versions of the Wikipedia article "Cryonics" with the Wayback Machine, there is a wealth of information which time and space do not permit doing justice to (and this is not the only source of relevant information, far from it). But, to skim just a very few highlights, I find the following starting paragraph for Feb. 4, 2004, the earliest date I could find:

> "Cryonics is the practice of preserving organisms, or at least their brains, for possible future revival by storing them at cryogenic temperatures where metabolism and decay almost completely stop. A person held in such a state (either frozen or vitrified) is said to be cryopreserved. Barring social disruptions of their cryopreservation, a perfectly vitrified person is expected to remain physically viable for a period of about 10,000 years, after which time cosmic ray damage has been thought to be irreparable. Many scientists in the field, most notably Ralph Merkle and Brian Wowk, hold that Molecular Nanotechnology has the potential to extend even this limit many times over."[34]

The rest of the article is positive and upbeat, while not overlooking difficulties with cryonics; and criticism and skepticism are given their due. I would rate it a good article, worthy of Wikipedia's usual standards. As of early this year (2019), the article on cryonics is still reasonably even-handed if

more reserved and more graphic in its language.[35] Over the past few months, though, things have changed. Here are the present opening paragraphs of the same article (referencing omitted):

> "**Cryonics** (from Greek: κρύος *kryos* meaning 'cold') is the low-temperature freezing (usually at −196 °C or −320.8 °F or 77.1 K) and storage of a human corpse or severed head, with the speculative hope that resurrection may be possible in the future. Cryonics is regarded with skepticism within the mainstream scientific community. It is a pseudoscience, and its practice has been characterized as quackery.
>
> "Cryonics procedures can begin only after clinical death, and cryonics 'patients' are legally dead. Cryonics procedures ideally begin within minutes of death, and use cryoprotectants to prevent ice formation during cryopreservation. It is however not possible for a corpse to be reanimated after undergoing vitrification, as this causes damage to the brain including its neural networks. The first corpse to be frozen was that of Dr. James Bedford in 1967. As of 2014, about 250 dead bodies had been cryopreserved in the United States, and 1,500 people had made arrangements for cryopreservation of their corpses.
>
> "Economic reality means it is highly improbable that any cryonics corporation could continue in business long enough to take advantage of the claimed long-term benefits offered. As of 2018 most of the early cryonics companies had gone out of business, and their stored corpses thawed and disposed of."[36]

Well, it isn't hard to see the unmistakable progression toward greater intolerance and hostility. And, there is no shortage of hostile articles to draw on as the "references" that Wikipedia insists must liberally accompany its articles. (It is, of course, right and proper to insist on this; references in turn should be of high quality, as well as used with appropriate discretion.)

One of the more vitriolic of the cited references, which is used to support the suggestion of cryonics being "quackery," is Corey Pein's "Everybody Freeze!" from *The Baffler*, March 2016. Like Michael Hendricks' anti-cryonics article in *MIT Review*, it is a response to the New York *Times* article (by science reporter Amy Harmon) about the Kim Suozzi case. Ungently it begins, and ungently it ends. Cryonics is "the decades-old quack procedure, which involves freezing corpse parts for later resuscitation …" On the other hand: "Narratives are made by the artful omission of facts." This in fact is the opening sentence of the whole article, and Pein makes its relevance clear later: "Science reporter Amy Harmon's narrative depended upon the artful omission of the single most pertinent fact: that cryonics is an utter crock, has always been a crock, and will continue to be a crock for the foreseeable future, no matter what a handful of contrarian university-affiliated researchers with a financial stake in the corpse-freezing racket may claim."[37]

(After a blast like this, I omit further comment for now – readers can look up the article and draw their own conclusions.) The third quoted paragraph from the Wikipedia article also bears some comment. Apparently, cryonics companies are necessarily rickety affairs that are unlikely to last long enough to bear the fruit of resuscitating their patients if such an unlikely prospect were to be possible after all. This conclusion seems to rest on two studies, one on the future prospects of companies like the ones now doing cryonics, the other on organizations that started up in the 1960s and had ceased operations by 1980, with loss of most of their patents.

David Stodolsky

The study of future prospects is "The Growth and Decline of Cryonics" by the psychologist David Stodolsky, PhD, a longtime cryonics activist that many will be familiar with for his determined pursuit of his own vision of how the cryonics movement should be implemented.[38] It is an ambitious investigation which addresses economic, political, and religious issues over a projected time scale of centuries. It draws pessimistic conclusions about the likelihood of U.S. cryonics organizations surviving until their patients can be reanimated, *as long as their present policies continue*. It does, however, also outline approaches for addressing the difficulties, something that is overlooked by Wikipedia in its reference to the study. Quoting from the abstract: "Two alternative strategies are suggested that could minimize failure risk by reversing the stagnation of the industry. A 'repackaging' of cryonics could accelerate growth and improve services, as well as the political position of the industry. This repackaging includes a restructuring of the channels for funding cryonics. Integration with the mainstream assumes using the funeral industry as a sales channel."

As further evidence of negative prospects, Wikipedia cites the record of early organizations which failed and lost most of their patients. However, this is a small number (less than two dozen is a likely estimate[39]) compared to those preserved today, which number in the hundreds.[40] Lessons were learned from these early failures and succeeding organizations have established a much better track record, with a fierce determination to meet any challenges as future decades unfold. Again, the failures are noted, but the positive aspects are ignored.

It is worth reporting that much of the Wikipedia article still seems reasonably factual and informative—those who want

David Gerard

the negative reminders should be satisfied, while others can tune them out. The question comes up of who at Wikipedia might be responsible for the badmouthing, that is to say, for both making the negative edits and making sure they stay in place in case anyone else tries to undo them (which has happened). Study shows a similarity of the (unattributed) negative wording to the writings elsewhere of David Gerard,[41] who in some recent private emails was named as the "main saboteur of the cryonics Wikipedia entry." (Gerard, for the record, has also the authored a critical, irreverent book on cryptocurrency, *Attack of the 50 Foot Blockchain*. Is there a connection between this evident peeve of his and his other one on cryonics?)

Where Do We Go from Here? Some Thoughts

Corey Pein, in his cryo-bashing extravaganza above, referred to "claims," presumably in support of cryonics, of "a handful of contrarian university-affiliated researchers with a financial stake in the corpse-freezing racket." If we try to sort this out, it develops that indeed there are "university-affiliated researchers" and others in academia who have expressed support for cryonics. (A few, it's true, are employed by or otherwise derive a substantial part of their income from cryonics organizations; less than ten, I'd say, and certainly far from the majority, nor are there many others in academia who derive income from cryonics.) But a group of them has signed a "Scientists' Open Letter on Cryonics,"[42] worth quoting from here:

> "Cryonics is a legitimate science-based endeavor that seeks to preserve human beings, especially the human brain, by the best technology available. Future technologies for resuscitation can be envisioned that involve molecular repair by nanomedicine, highly advanced computation, detailed control of cell growth, and tissue regeneration.
>
> "With a view toward these developments, there is a credible possibility that cryonics performed under the best conditions achievable today can preserve sufficient neurological information to permit eventual restoration of a person to full health.
>
> "The rights of people who choose cryonics are important, and should be respected."

Among the 68 signatories are Eric Drexler, Robert Freitas, Ken Hayworth, Ralph Merkle, and David Stodolsky. (None of these are employed in cryonics, though Merkle is on the board of directors of Alcor; I also signed it. It is also ironic that this letter is not a "primary source" thus cannot be referenced directly in a Wikipedia article, but hostile quotes from scientists in the tabloid press can.)

Ralph Merkle

Meanwhile, we have to live with the fact that we are not a mainstream enterprise. What we are trying for, to restore clinically and legally dead people to healthy consciousness someday, is a disturbing thought to many people for various reasons, but it should not deter our quest nor diminish our efforts. Efforts should continue in the more conventional areas such as perfecting better cryopreservation protocols and showing that brains can be preserved in viable form for extended periods postmortem. We must make the best use of the protocols we now have for cryopreservation, review our mistakes, and try our utmost to do better.

Beyond the more usual things, we should make appeals for more scientists to sign the Open Letter above. With enough scientists showing support, it will be more difficult to sustain the "pseudoscience" labeling. References like Wikipedia which do this could be pressured harder to change. In addition, there are some initiatives that might be pursued immediately (if not already being researched, as some certainly are) and might relatively quickly produce results that would help us:

1. Complete the study to show that present cryopreservation methods preserve the brain's connection architecture as well or nearly as well as the aldehyde-stabilized cryopreservation that satisfied Ken Hayworth. Hayworth would hopefully, publicly tone down his opposition to current cryonics practices and we would benefit. (This is not to suggest that the aldehyde-stabilized cryopreservation that Hayworth favors is necessarily a bad idea, but only that current practices that do not use this method at least are also preserving the brain's ultrastructure at comparable levels.)

2. Find out more about the physical basis of memory in the brain.

3. Carry out studies to demonstrate post-cryopreservation survival with memories for more advanced creatures than *C. elegans*.

4. More studies to show persistence of mammalian brain structure and functions postmortem. (This research carries the caveat that success might provoke a negative mainstream reaction relating to brains formerly thought "dead" now being seen as "still alive"—this would have to be managed.)

5. More theoretical work showing how MNT might be implemented, with emphasis on application to cryonics revival. This would especially put focus on systems that would operate at low temperature and would be able to do "readouts" of objects, to determine the internal structure down to molecular levels.

6. Make any kind of tangible progress toward actual implementation of Drexlerian nanosystems. With such progress it might be but a short step to showing how general-purpose devices could be built, including those capable of low-temperature operations.

Projects like the above have something in common beyond furthering technology that might physically assist us in cryonics operations, whether at the preservation or at the revival end. That is, they are potentially *disruptive*, challenging mainstream attitudes at a deep level. It might be said that challenging attitudes in this way has importance at least comparable to the direct seeking of physical benefits. When attitudes change, progress accelerates due to a cascade effect: less opposition all around means existing research can proceed with less hindrance, researchers who might otherwise remain sidelined will join the effort, and more funding resources will become available. In this way rates of progress could vastly increase.

So where, we might ask, would the funding come from for projects like the above? Recently Alcor was gifted $5 million for research, most of which I understand is not yet committed. Could some of that funding be used in such efforts as these? In light of this I will make one more suggestion:

7. Offer cash prizes for major accomplishments in the above. A "nonpartisan" organization could be set up to judge and administer the awards, and organizations like Alcor would be invited to make donations for the purpose. (A $50,000 donation would only be 1% of the amount Alcor was recently gifted, and might, as one example, be awarded for any of several advances.)

The above suggestion is nothing new but can be taken as urging for "more of the same." The Foresight Institute has for many years offered prizes for both theoretical and experimental work in nanotechnology (the "Feynman Prize," $5,000 in each of the two categories annually). It also offers a challenge Grand Prize ($250,000) "to the first persons to create both a nanoscale robotic arm capable of precise positional control, and a nanoscale 8-bit adder, conforming to given specifications."[43] Closer to home, cryonicist Joe Kowalsky (Cryonics Institute board member) has established a $50,000 Organ Cryopreservation Prize for successfully, cryogenically preserving a mammalian organ and reimplanting it, with long-term survival.[44]

So – let there be more prizes and more results to follow from them! And let there be more dialogue and less confrontation between partisans on different sides of the cryonics issue! ■

The author thanks Blake Delaney, Aschwin de Wolf, and David Stodolsky for helpful comments in the preparation of this article

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33 ADW.
34 WC1.
35 WC2.
36 WC3.
37 CP.
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40 WC3.
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"For the Record" Bibliography

By R. Michael Perry

This is a list of the "For the Record" columns I've done over the years since the series started in 1990. Each article's title is given, together with reference to its appearance in *Cryonics*. Also included are articles that deal with matters long before cryonics was started in the 1960s, but with the theme of in some way addressing the problem of mortality or thinking about it. (A case in point is Benjamin Franklin who envisioned being preserved and revived at a later time when he expected that lifespan would be greatly lengthened.) I've also included a few articles which were not actually under the "For the Record" banner but, I thought, enough "the same type" to also deserve inclusion. Finally, a few of the "For the Record" articles themselves were not really about cryonics history or prehistory but other matters of interest and are omitted.

In retrospect it is clear that the early articles were often written to different standards and with a different mindset than the later ones. When then-magazine editor Ralph Whelan wanted me to start this column back in 1990, he suggested just "a couple of paragraphs" on some topic related to past developments in some way. The first article I did, for the November 1990 *Cryonics*, was titled "John Hunter, Cryonics Forerunner", and consisted of one page of 3-column fine print, its main part three paragraphs. (By comparison, some of the later articles are more than ten times this size. Hunter, by the way, was a researcher who froze some fish in 1766 hoping they would revive on thawing; unfortunately, they did not.) In addition is an opener that sets the tone for the series as a whole:

"This is the first installment of what is planned to become a regular monthly feature on cryonics history. I am planning these as more-or-less self-contained vignettes, to make the information more accessible (though of course I hope readers will find it worthwhile to read them consecutively, too). Although I do not intend to adhere to strict chronological order, the opening installments will emphasize the origins of the cryonics movement and its earlier history."

This I've followed more-or-less throughout. Cryonics history was sometimes turbulent and sometimes controversial, even among cryonicists. Caught up in this drama, and relying on then-available sources, I sometimes expressed views that differ from what I hold today, particularly with the early cryonics failures, where I am now inclined to be more forgiving of the mistakes and misjudgments made by earnest if naïve practitioners. (In particular, on Robert Nelson and his involvement in cryonics, I recommend the Nov.-Dec. 2018 article, which has information that has come to light since the earliest articles were written.) This is not to claim that the early activists were faultless but to give greater weight to the magnitude and difficulty of what they were trying to accomplish and did somewhat accomplish, alongside the human failings and shortcomings that did inevitably occur.

CRYONICS ISSUE	PAGES	TITLE
Nov. 1990	12	John Hunter, Cryonics Forerunner
Dec. 1990	10-11	The First Cryonics Newsletter
Jan. 1991	10-11	Franklin as Pioneering Immortalist
Feb. 1991	4-5	Cryonics Precursor [Bedbug, Mayakovsky]
Mar. 1991	4-5	Some Early Thoughts about Neuro
Apr. 1991	3-4	John locke and Personal Identity
May 1991	12-13	The Penultimate Trump (Ettinger SF story)
Jun. 1991	14-16	The Second "Certainty" and Similar Constraints
Jul. 1991	11-14	First Suspension No "Blue Sky" Event
Aug. 1991	8-9	The Decline and Fall of LES Part 1 of 2
Sep. 1991	24-25	The Decline and Fall of LES 2
Oct. 1991	7-8	Fyodorov — the Grandfather of Immortalism
Nov. 1991	5-6	Riding the Jameson Satellite
Dec. 1991	6-8	Cryobiologists versus Cryonicists: Roots of the Cold War

Jan. 1992	6-8	Lucretius: Immortalist Glimmerings from an Ancient Skeptic
Feb. 1992	5-8	Suspension Failures: The Dark Side of Cryonics History
Mar. 1992	4-7	Nelson, Nisco, and the “Cryotorium”
Apr. 1992	4-7	Why Cryonics Probably Will Work
May 1992	4-6	Gilgamesh and the Transhuman Condition
Jun. 1992	4-6	Gerald Feinberg, Scientific Cryonics Advocate
Jul. 1992	4-8	Cryonic Suspensions: Cumulative Listing and Some Unusual Highlights
Aug. 1992	4-6	Unity and Disunity in Cryonics
Sep. 1992	4-7	Our Finest Hours: Notes on the Dora Kent Crisis, Part 1 of 3
Oct. 1992	4-7	Our Finest Hours: Notes on the Dora Kent Crisis, Part 2 of 3
Nov. 1992	6-7	Our Finest Hours: Notes on the Dora Kent Crisis, Part 3 of 3
Dec. 1992	3-4	Winwood Reade’s Martyrdom
Jan. 1993	4-6	Gold from Dross
Mar. 1993	3-6	Marie Phelps-Sweet
Apr. 1993	3-6	They Froze the First Man
May 1993	4-7	Cryonics and the Encyclopedia of Death
Jun. 1993	5-7	Religion and Cryonics
Jul.-Aug. 1993	7-10	The First Cryonics Operation
Sep. 1993	9-11	Cryonics and Armand Karow, Jr.
Nov. 1993	5-9	Glimpses of a Lost Immortalist
Dec. 1993	6-8	The First Recorded Meeting
Jan.-Mar. 1994	9-11	Trials of a Hopeful Immortal: The Life and Times of Origen
Apr.-Jun. 1994	8-10	The Realities of Patient Storage
Jul.-Sep. 1994	4-6	30 Years of Immortality
Oct.-Dec. 1994	5-9	A Brief History of Alcor Research
Jan.-Mar. 1995	12-14	Nanotechnology, Cryonics and Bronze Restoration
Apr.-Jun. 1995	10-12	William Godwin as Pioneering Futurist
Jul.-Sep. 1995	24-26	The First Cross-Country Cryotrip
Oct.-Dec. 1995	3-5	The Man with the Broken Ear
Jan.-Mar. 1996	4-7	IABS: the Institute for Advanced Biological Studies
Apr.-Jun. 1996	3-7	The Fedorov File: Glimpses of an Elusive Immortalist
Jan.-Mar. 1997	16-19	Frances Bacon, Shaper of the Future
Jan.-Mar. 1998	36-39	Death at the Edge of Forever: the Story of a Child
Apr.-Jun. 1998	41-44	Remembering Beverly Greenberg
Jul.-Sep. 1998	29-31	In the Name of Liberty: the Thomas Donaldson Case
Oct.-Dec. 1998	35-39	The Seekers of Immortality [list of cryopatients as of writing]
Jan.-Mar. 1999	36-40	Alcor’s Legal Battles
Apr.-Jun. 1999	33-37	Dick Jones
Jul.-Sep. 1999	26-32	In Search of the Spike
Oct.-Dec. 1999	55-58	The Making of Cold
Apr.-Jun. 2000	12-15	Remembering Mae Ettinger
Apr.-Jun. 2001	40-46	Cryonicist Authors and their Books
Oct.-Dec. 2001	35-38	Alcor Then and Again: Twenty-Five and Ten Years Ago
Jan.-Mar. 2002	29-31	Robert Prehoda and Suspended Animation
Jul.-Sep. 2002	28-31, 33	Prehoda’s Challenge to Cryonics

Oct.-Dec. 2002	41-42, 54	Remembering Allen McDaniels
Jan.-Mar. 2003	29-32	Alcor Then and Again: Twenty-Five and Ten Years Ago
Apr.-Jun. 2003	26-29	The Immortalist Vision of J. D. Bernal
Jan.-Feb. 2004	17-21	1988 — a Year to Remember
Nov.-Dec. 2004	8-11	Alcor's First Newsletter
Jan.-Feb. 2005	17-21	Suspension Failures: Lessons From the Early Years
Mar.-Apr. 2005	22-25	In and Around Alcor: Twenty-Five and Ten Years Ago
May-Jun. 2005	22-25	Last Early Hurrah: The Cryonics Conference of 1971
Sep.-Oct. 2005	23, 25	Cryonics and Science Fiction Theatre
Oct.-Dec. 2006	19	Remembering Joe and Terri Cannon
Feb. 2013	20-23	John Adolphus Etzler: Pioneer Prophet of Radical Abundance
Mar. 2013	18-19	Jean Finot: Prolongevity Advocate of the Early Twentieth Century
Apr. 2013	16-18	Cryonics in New York: How it Started
May 2013	18-20	Daoist Roots of Immortalism: A Protoscience of Prolongevity
Jun. 2013	14-16	Cryonics in New York: Optimism before the First Freezing, 1966-68
Jul. 2013	29-33	Cryonics in New York: Human Freezings and Other Events, 1968-1969
Aug. 2013	18-22	Cryonics in New York: Decline, Tragedy, and Twilight: 1969-1974 and Later
Sep. 2013	32-37	Protocols in Cryonics: Prehistory and Early History
Oct. 2013	20-24	Carrel and Lindbergh: Why Not Immortality?
Nov. 2013	6-10	The High Price of Life on Hold: Sheskin's Study and Other Reflections on Cryonics in New York
Dec. 2013	14-20	Carrying On: The Aftermath and Legacy of Early New York Cryonics
Feb. 2014	10-15	Notes on the Cryopreservation of James Bedford
Mar. 2014	9-14	Russian Scientific Cosmism: A Prelude to Modern Immortalism
Apr. 2014	6-7	Remembering John Bull
May 2014	12-15	Companion Animals at Alcor: Some Lessons from the Early Years
Jun. 2014	6-9	The Prospect of Immortality at Age Fifty
Sep. 2014	6-11	Cryonics Patient Storage: A Brief History
Nov. 2014	11-15	Quintessence: Remembering Jerry White
Jan. 2015	6-14	Why Not? Cryopreservations That Might Have Been
May 2015	6-11	What Did Brunol Say? Notes from the Architect of the First Controlled Human Cryonics Preservations
Jan.-Feb. 2016	8-15	Cryonics Under Fire: Meeting the Challenges of Hostile Scientists Then and Now
Mar.-Apr. 2016	22-31	Charity Cases in Cryonics
May-Jun. 2016	14-26	Ev Cooper and the Conference that Didn't Happen: Trials of an Early Freezing
Sep.-Oct. 2016	28-38	The Cinematic Cryonicist: Four Documentary Videos, Early and Later
Nov-Dec. 2016	24-37	Cryonics in Europe: Some Historical Highlights
May-Jun. 2017	34-41	A Year of Jubilees: Some Important Cryonics Anniversaries
Nov-Dec. 2017	28-35	The Price of Life: Isaac Asimov, Cryonics, and Human Death Extension
Jan.-Feb. 2018	30-39	Cryonics Newsletters: Some Historical Highlights [LES Newsletters]
May-Jun. 2018	26-33	Cryonics Newsletters: Some Historical Highlights, Part 2a [CSNY Newsletters]
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Revival Update

Scientific Developments Supporting Revival Technologies

Reported by R. Michael Perry, Ph.D.

Programmable Bacteria Induce Durable Tumor Regression and Systemic Antitumor Immunity

Sreyan Chowdhury, Samuel Castro, Courtney Coker, Taylor E. Hinchliffe, Nicholas Arpaia, and Tal Danino

***Nature Medicine* 25, 1057–63, 3 Jul 2019, https://www.nature.com/articles/s41591-019-0498-z, accessed 4 Dec 2019**

Abstract

Synthetic biology is driving a new era of medicine through the genetic programming of living cells. This transformative approach allows for the creation of engineered systems that intelligently sense and respond to diverse environments, ultimately adding specificity and efficacy that extends beyond the capabilities of molecular-based therapeutics. One particular area of focus has been the engineering of bacteria as therapeutic delivery systems to selectively release therapeutic payloads in vivo. Here we engineered a non-pathogenic *Escherichia coli* strain to specifically lyse within the tumor microenvironment and release an encoded nanobody antagonist of CD47 (CD47nb), an anti-phagocytic receptor that is commonly overexpressed in several human cancer types. We show that delivery of CD47nb by tumor-colonizing bacteria increases activation of tumor-infiltrating T cells, stimulates rapid tumor regression, prevents metastasis and leads to long-term survival in a syngeneic tumor model in mice. Moreover, we report that local injection of CD47nb-expressing bacteria stimulates systemic tumor-antigen-specific immune responses that reduce the growth of untreated tumors, providing proof-of-concept for an abscopal effect induced by an engineered bacterial immunotherapy. Thus, engineered bacteria may be used for safe and local delivery of immunotherapeutic payloads leading to systemic antitumor immunity.

From: Bacteria Engineered as Trojan Horse for Cancer Immunotherapy by Holly Evarts, Columbia University Engineering, 3 Jul 2019, https://engineering.columbia.edu/press-releases/trojan-horse-cancer-immunotherapy, accessed 4 Dec 2019

The emerging field of synthetic biology—designing new biological components and systems—is revolutionizing medicine. Through the genetic programming of living cells, researchers are creating engineered systems that intelligently sense and respond to diverse environments, leading to more specific and effective solutions in comparison to current molecular-based therapeutics.

At the same time, cancer immunotherapy—using the body's immune defenses to fight cancer—has transformed cancer treatment over the past decade, but only a handful of solid tumors have responded, and systemic therapy often results in significant side effects. Designing therapies that can induce a potent, anti-tumor immune response within a solid tumor without triggering systemic toxicity has posed a significant challenge.

Researchers at Columbia Engineering and Columbia University Irving Medical Center (CUIMC) announced today that they are addressing this challenge by engineering a strain of non-pathogenic bacteria that can colonize solid tumors in mice and safely deliver potent immunotherapies, acting as a Trojan horse that treats tumors from within. The therapy led not only to complete tumor regression in a mouse model of lymphoma, but also significant control of distant, uninjected tumor lesions. Their findings are published today in *Nature Medicine*.

"Seeing untreated tumors respond alongside treatment of primary lesions was an unexpected discovery. It is the first demonstration following a bacterial cancer therapy of what is termed an 'abscopal' effect," says Tal Danino, assistant professor of biomedical engineering. "This means that we'll be able to engineer bacteria to prime tumors locally, and then stimulate the immune system to seek out tumors and metastases that are too small to be detected with imaging or other approaches."

Regulation of Lifespan by Neural Excitation and REST

Joseph M. Zullo, Derek Drake, Liviu Aron, Patrick O'Hern, Sameer C. Dhamne, Noah Davidsohn, Chai-An Mao, William H. Klein, Alexander Rotenberg, David A. Bennett, George M. Church, Monica P. Colaiácovo, and Bruce A. Yankner

***Nature* 574, 359–64, 16 Oct 2019, https://www.nature.com/articles/s41586-019-1647-8#article-info, accessed 5 Dec 2019**

Abstract

The mechanisms that extend lifespan in humans are poorly understood. Here we show that extended longevity in humans is associated with a distinct transcriptome signature in the cerebral cortex that is characterized by downregulation of genes related to neural excitation and synaptic function. In *Caenorhabditis elegans*, neural excitation increases with age and inhibition of excitation globally, or in glutamatergic or cholinergic neurons, increases longevity. Furthermore, longevity is dynamically regulated by the excitatory–inhibitory balance of neural circuits. The transcription factor REST is upregulated in humans with extended longevity and represses excitation-related genes. Notably, REST-deficient mice exhibit increased cortical activity and neuronal excitability during ageing. Similarly, loss-of-function mutations in the *C. elegans* REST orthologue genes *spr-3* and *spr-4* elevate neural excitation and reduce the lifespan of long-lived *daf-2* mutants. In wild-type worms, overexpression of *spr-4* suppresses excitation and extends lifespan. REST, SPR-3, SPR-4 and reduced excitation activate the longevity-associated transcription factors FOXO1 and DAF-16 in mammals and worms, respectively. These findings reveal a conserved mechanism of ageing that is mediated by neural circuit activity and regulated by REST.

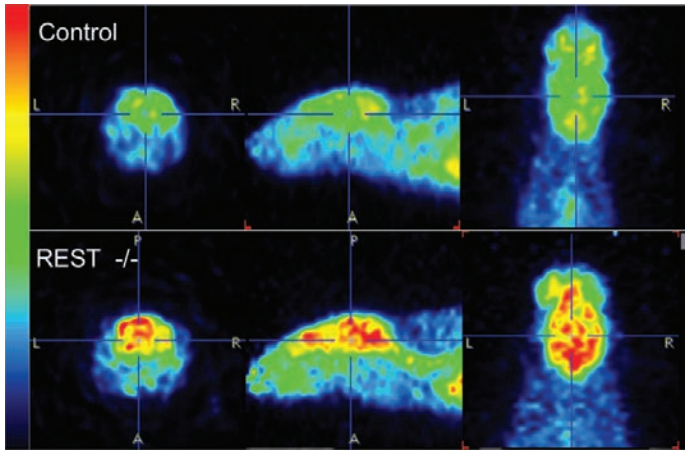
From: New Player in Human Aging by Stephanie Dutchen, Harvard Medical School, 16 Oct 2019, https://hms.harvard.edu/news/new-player-human-aging, accessed 6 Dec 2019

A new character has stepped onstage in the story of human aging: neural excitation. The brain's neural activity, long implicated in disorders ranging from dementia to epilepsy, plays a role in human aging and life span, according to research led by scientists in the Blavatnik Institute at Harvard Medical School. The study, published Oct. 16 in *Nature*, is based on findings from human brains, mice and worms and suggests that excessive activity in the brain is linked to shorter life spans, while suppressing such overactivity extends life. The findings offer the first evidence that the activity of the nervous system affects human longevity. Although previous studies had suggested that parts of the nervous system influence aging in animals, the role of neural activity in aging, especially in humans, remained murky.

"An intriguing aspect of our findings is that something as transient as the activity state of neural circuits could have such far-ranging consequences for physiology and life span," said study senior author Bruce Yankner, professor of genetics at HMS and co-director of the Paul F. Glenn Center for the Biology of Aging.

Neural excitation appears to act along a chain of molecular events famously known to influence longevity: the insulin and insulin-like growth factor (IGF) signaling pathway. The key in this signaling cascade appears to be a protein called REST, previously shown by the Yankner Lab to protect aging brains from dementia and other stresses. Neural activity refers to the constant flicker of electrical currents and transmissions in the brain. Excessive activity, or excitation, could manifest in numerous ways, from a muscle twitch to a change in mood or thought, the authors said.

It's not yet clear from the study whether or how a person's thoughts, personality or behavior affect their longevity. "An exciting future area of research will be to determine how these findings relate to such higher-order human brain functions," said Yankner. The study could inform the design of new therapies for conditions that involve neural overactivity, such as Alzheimer's disease and bipolar disorder, the researchers said. The findings raise the possibility that certain medicines, such as drugs that target REST, or certain behaviors, such as meditation, could extend life span by modulating neural activity.



Mice lacking the protein REST (bottom) showed much higher neural activity in the brain (red) than normal mice (top). Image: Yankner Lab/Nature

A Single Combination Gene Therapy Treats Multiple Age-Related Diseases

Noah Davidsohn, Matthew Pezzone, Andyna Vernet, Amanda Graveline, Daniel Oliver, Shimyn Slomovic, Sukanya Punthambaker, Xiaoming Sun, Ronglih Liao, Joseph V. Bonventre, and George M. Church

PNAS 116 (47) 23505-11, 19 Nov. 2019, first published 4 Nov 2019, https://www.pnas.org/content/116/47/23505, accessed 6 Dec. 2019

Abstract

Comorbidity is common as age increases, and currently prescribed treatments often ignore the interconnectedness of the involved age-related diseases. The presence of any one such disease usually increases the risk of having others, and new

approaches will be more effective at increasing an individual's health span by taking this systems-level view into account. In this study, we developed gene therapies based on 3 longevity associated genes (fibroblast growth factor 21 [FGF21], αKlotho, soluble form of mouse transforming growth factor-β receptor 2 [sTGFβR2]) delivered using adeno-associated viruses and explored their ability to mitigate 4 age-related diseases: obesity, type II diabetes, heart failure, and renal failure. Individually and combinatorially, we applied these therapies to disease-specific mouse models and found that this set of diverse pathologies could be effectively treated and in some cases, even reversed with a single dose. We observed a 58% increase in heart function in ascending aortic constriction ensuing heart failure, a 38% reduction in α-smooth muscle actin (αSMA) expression, and a 75% reduction in renal medullary atrophy in mice subjected to unilateral ureteral obstruction and a complete reversal of obesity and diabetes phenotypes in mice fed a constant high-fat diet. Crucially, we discovered that a single formulation combining 2 separate therapies into 1 was able to treat all 4 diseases. These results emphasize the promise of gene therapy for treating diverse age-related ailments and demonstrate the potential of combination gene therapy that may improve health span and longevity by addressing multiple diseases at once.

From: One Fell Swoop by Lindsay Brownell, 6 Nov 2019, https://hms.harvard.edu/news/one-fell-swoop, accessed 6 Dec 2019

As we age, our bodies tend to develop diseases such as heart failure, kidney failure and diabetes, and the presence of any one disease increases the risk of developing others. A drug usually targets only one condition, largely ignoring the interconnectedness of age-related diseases and requiring patients to take multiple drugs, which increases the risk of negative side effects.

A new study from Harvard Medical School and the Wyss Institute for Biologically Inspired Engineering at Harvard University reports that a single administration of an adeno-associated virus (AAV)-based gene therapy delivering combinations of three longevity-associated genes to mice dramatically improved or completely reversed multiple age-related diseases, suggesting that a systems-level approach to treating such diseases could improve overall health and extend life span.

"The results we saw were stunning and suggest that holistically addressing aging via gene therapy could be more effective than the piecemeal approach that currently exists," said first author Noah Davidsohn, a former research scientist at HMS and the Wyss, who is now the chief technology officer of Rejuvenate Bio. "Everyone wants to stay as healthy as possible for as long as possible, and this study is a first step toward reducing the suffering caused by debilitating diseases."

The study was conducted in the lab of senior author George Church, the Robert Winthrop Professor of Genetics in the Blavatnik Institute at HMS and a Wyss core faculty member, as part of Davidsohn's postdoctoral research into the genetics of aging. Davidsohn, Church and their co-authors homed in on three genes previously shown to confer increased health and life span benefits in mice genetically engineered to overexpress them: FGF21, sTGFβR2 and αKlotho. They hypothesized that providing extra copies of those genes to nonengineered mice via gene therapy would similarly combat age-related diseases and confer health benefits.

To test this hypothesis, the team created separate gene therapy constructs for each gene using the AAV8 serotype as a delivery vehicle, injecting them into mouse models of obesity, type II diabetes, heart failure and renal failure, both individually and in combination with the other genes to see if there was a synergistic beneficial effect.

FGF21 alone caused complete reversal of weight gain and type II diabetes in obese, diabetic mice following a single gene therapy administration, and its combination with sTGFβR2 reduced kidney atrophy by 75 percent in mice with renal fibrosis.

Heart function in mice with heart failure improved by 58 percent when given sTGFβR2 alone or in combination with either of the other two genes, showing that a combined therapeutic treatment of FGF21 and sTGFβR2 could successfully treat all four age-related conditions, therefore improving health and survival.

Administering all three genes together resulted in slightly worse outcomes, likely from an adverse interaction between FGF21 and αKlotho, which remains to be studied.

It is important to note that the injected genes remained separate from the animals' native genomes, did not modify their natural DNA and could not be passed to future generations or between living animals.

"Achieving these results in nontransgenic mice is a major step toward being able to develop this treatment into a therapy, and co-administering multiple disease-addressing genes could help alleviate the immune issues that could arise from the alternative of delivering multiple, separate gene therapies for each disease," said Church. "This research marks a milestone in being able to effectively treat the many diseases associated with aging, and perhaps could lead to a means of addressing aging itself."

Memory Retrieval Modulates Spatial Tuning of Single Neurons in the Human Entorhinal Cortex

Salman E. Qasim, Jonathan Miller, and Joshua Jacobs (Biomedical Engineering, Columbia Engineering; Cory S. Inman, Robert E. Gross, and Jon T. Willie (Neurological Surgery, Emory University); Bradley Lega and Jui-Jui Lin (Neurological Surgery, University of Texas Southwestern, Dallas); Ashwini Sharan and Chengyuan Wu (Neurological Surgery, Thomas Jefferson University, Philadelphia); 4, Michael R. Sperling (Neurology, Thomas Jefferson University); Sameer A. Sheth (Neurological Surgery, Baylor College of Medicine, Houston), Guy M. McKhann (Neurological Surgery, Columbia University); Elliot H. Smith (Neurosurgery, University of Utah); Catherine Schevon (Neurology, Columbia University); and Joel Stein (Radiology, University of Pennsylvania).

https://www.nature.com/articles/s41593-019-0523-z#Sec19. 11 Nov 2019, accessed 2 Dec 2019

Abstract

The medial temporal lobe is critical for both spatial navigation and memory. Although single neurons in the medial temporal lobe activate to represent locations in the environment during navigation, how this spatial tuning relates to memory for events involving those locations remains unclear. We examined memory-related changes in spatial tuning by recording single-neuron activity from neurosurgical patients performing a virtual-reality object–location memory task. We identified 'memory-trace cells' with activity that was spatially tuned to the retrieved location of the specific object that participants were cued to remember. Memory-trace cells in the entorhinal cortex, in particular, encoded discriminable representations of different memories through a memory-specific rate code. These findings indicate that single neurons in the human entorhinal cortex change their spatial tuning to target relevant memories for retrieval.

From: Specific Neurons that Map Memories Now Identified in the Human Brain by Holly Evarts, Columbia University, 11 Nov 2019, https://engineering.columbia.edu/press-releases/joshua-jacobs-neurons-map-memories, accessed 4 Dec 2019

An important aspect of human memory is our ability to conjure specific moments from the vast array of experiences that have occurred in any given setting. For example, if asked to recommend a tourist itinerary for a city you have visited many times, your brain somehow enables you to selectively recall and distinguish specific memories from your different trips to provide an answer.

Studies have shown that declarative memory—the kind of memory you can consciously recall like your home address or your mother's name—relies on healthy medial temporal lobe structures in the brain, including the hippocampus and entorhinal cortex (EC). These regions are also important for spatial cognition, demonstrated by the Nobel-Prize-winning discovery of "place cells" and "grid cells" in these regions—neurons that activate to represent specific locations in the environment during navigation (akin to a GPS). However, it has not been clear if or how this "spatial map" in the brain relates to a person's memory of events at those locations, and how neuronal activity in these regions enables us to target a particular memory for retrieval among related experiences.

A team led by neuroengineers at Columbia Engineering has found the first evidence that individual neurons in the human brain target specific memories during recall. They studied recordings in neurosurgical patients who had electrodes implanted in their brains and examined how the patients' brain signals corresponded to their behavior while performing a virtual-reality (VR) object–location memory task. The researchers identified "memory-trace cells" whose activity was spatially tuned to the location where subjects remembered encountering specific objects. The study is published today in Nature Neuroscience.

The team was able to measure the activity of single neurons by taking advantage of a rare opportunity: invasively recording from the brains of 19 neurosurgical patients at several hospitals, including the Columbia University Irving Medical Center. The patients had drug-resistant epilepsy and so had already had recording electrodes implanted in their brains for their clinical treatment.

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.

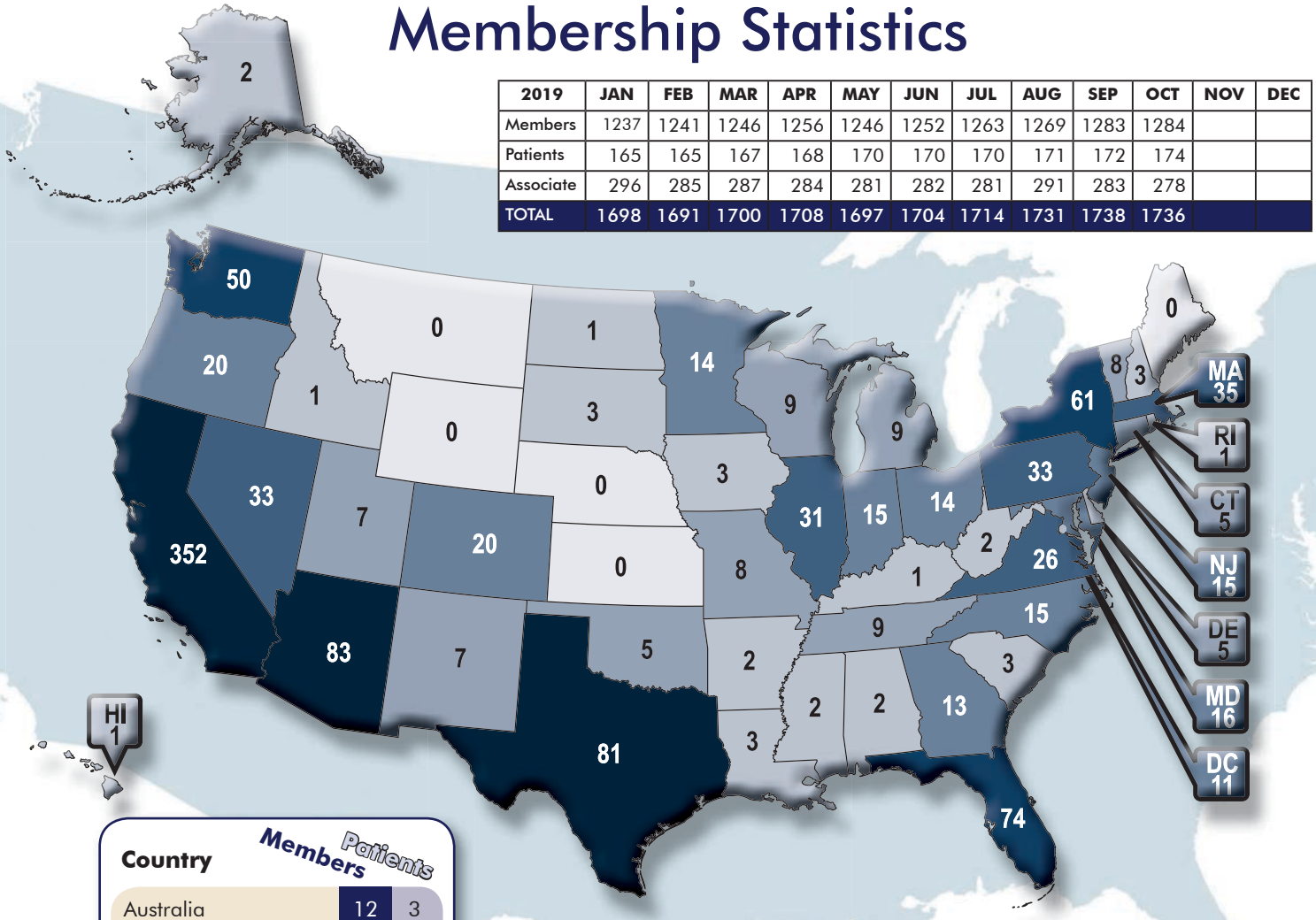
Chana Phaedra, "**Reconstructive Connectomics**," *Cryonics* 34(7) (July 2013): 26-28.

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.

Membership Statistics

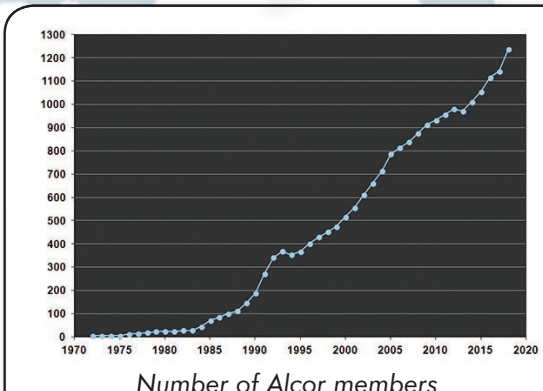
2019	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Members	1237	1241	1246	1256	1246	1252	1263	1269	1283	1284		
Patients	165	165	167	168	170	170	170	171	172	174		
Associate	296	285	287	284	281	282	281	291	283	278		
TOTAL	1698	1691	1700	1708	1697	1704	1714	1731	1738	1736		



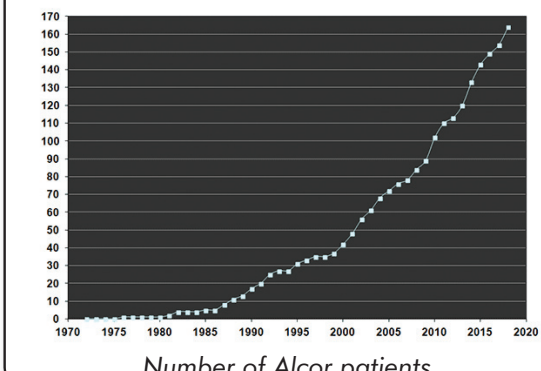
International Members & Patients

Country	Members	Patients
Australia	12	3
Austria	1	0
Belgium	1	0
Brazil	1	0
Bulgaria	1	0
Canada	62	4
China	0	1
Finland	1	0
France	0	1
Germany	18	0
Hong Kong	1	0
Israel	1	1
Italy	2	0
Japan	5	0
Luxembourg	1	0
Mexico	5	0
Monaco	1	0
Netherlands	1	0
New Zealand	1	0
Norway	2	0
Portugal	4	1
Puerto Rico	1	0
South Korea	1	0
Spain	5	1
Taiwan	1	0
Thailand	2	1
United Kingdom	40	3
TOTAL	170	16

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



Number of Alcor members



Number of Alcor patients

Alcor Associate Membership

Supporters of Alcor who are not yet ready to make cryopreservation arrangements can become an Associate Member for $5/month (or $15/quarter or $60 annually). Associate Members are members of the Alcor Life Extension Foundation who have not made cryonics arrangements but financially support the organization.

Associate Members will receive:

- ***Cryonics* magazine by mail**
- **Discounts on Alcor conferences**
- **Access to post in the Alcor Member Forums**
- **Access to local Alcor meetings and training events**

ALCOR
LIFE EXTENSION FOUNDATION
The World's Leader in Cryonics
www.alcor.org

To become an Associate Member send a check or money order ($5/month or $15/quarter or $60 annually) to Alcor Life Extension Foundation, 7895 E. Acoma Dr., Suite 110, Scottsdale, Arizona 85260, or call Marji Klima at (480) 905-1906 ext. 101 with your credit card information.

Or you can pay online via PayPal using the following link:

http://www.alcor.org/BecomeMember/associate.html *(quarterly option is not available this way)*.

Associate Members can improve their chances of being cryo-preserved in an emergency if they complete and provide us with a Declaration of Intent to be Cryopreserved (http://www.alcor.org/Library/html/declarationofintent.html). Financial provisions would still have to be made by you or someone acting for you, but the combination of Associate Membership and Declaration of Intent meets the informed consent requirement and makes it much more likely that we could move ahead in a critical situation.

Fight Aging!

Reports From the Front Line in the Fight Against Aging

Reported by Reason

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

Amyloid-β is not Merely Molecular Waste

April, 2019

Alzheimer's disease begins with the accumulation of amyloid-β in the brain, but this doesn't mean that amyloid-β is purely molecular waste. Yes, it is harmful given the presence of too much of it in the central nervous system, but that is true of most of our biochemistry. There is good evidence for amyloid-β to act as an antimicrobial system, for example, which is the basis for considering persistent infection as a potential contributing cause of Alzheimer's disease, in which infectious agents drive the generation of ever increasing amounts of amyloid-β. Even setting aside that and other evidence, however, it is quite possible to argue that amyloid-β must have some important function, based on evolutionary theory and the fact that the molecule exists at all.

The argument is frequently made that the amyloid-β protein (Aβ) persists in the human genome because Alzheimer's disease (AD) primarily afflicts individuals over reproductive age and, therefore, there is low selective pressure for the peptide's elimination or modification. This argument is an important premise for AD amyloidosis models and therapeutic strategies that characterize Aβ as a functionless and intrinsically pathological protein. Here, we review whether evolutionary theory and data on the genetics and biology of Aβ are consistent with low selective pressure for the peptide's expression in senescence.

Aβ is an ancient neuropeptide expressed across vertebrates. Consistent with unusually high evolutionary selection constraint, the human Aβ sequence is shared by a majority of vertebrate species and has been conserved across at least 400 million years. Unlike humans, the overwhelming majority of vertebrate species do not cease reproduction in senescence and selection pressure is maintained into old age. Hence, low selective pressure in senescence does not explain the persistence of Aβ across the vertebrate genome.

The Grandmother hypothesis (GMH) is the prevailing model explaining the unusual extended postfertile period of humans. In the GMH, high risk associated with birthing in old age has led to early cessation of reproduction and a shift to intergenerational care of descendants. The rechanneling of resources to grandchildren by postreproductive individuals increases reproductive success of descendants. In the GMH model, selection pressure does not end following menopause. Thus, evolutionary models and phylogenetic data are not consistent with the absence of reproductive selection pressure for Aβ among aged vertebrates, including humans.

Our analysis suggests an alternative evolutionary model for the persistence of Aβ in the vertebrate genome. Aβ has recently been identified as an antimicrobial effector molecule of innate immunity. High conservation across the Chordata phylum is consistent with strong positive selection pressure driving human Aβ's remarkable evolutionary longevity. Ancient origins and widespread conservation suggest the human Aβ sequence is highly optimized for its immune role.

Link: https://doi.org/10.3389/fnagi.2019.00070

Boosting Levels of NAD+ May Make Senescent Cells More Aggressively Inflammatory

May, 2019

Enhancing levels of NAD+ in mitochondria via delivery of various precursor compounds as supplements is growing in popularity as an approach to boost faltering mitochondrial function and thus modestly slow the progression of aging. A human trial demonstrated improved vascular function as a result of nicotinamide riboside supplementation, for example. Researchers here show that increased NAD+ will likely make worse the inflammatory signaling of senescent cells, however.

Senescent cells accumulate with age, and are an important cause of the chronic inflammation of aging that drives the progression of many age-related diseases.

The results here suggest that efficient senolytic treatments to selectively destroy senescent cells should precede any of the current approaches to raising levels of NAD+ in older individuals - and it is an open question as to whether any of the existing available options are efficient enough to make NAD+ enhancement safe in the longer term. Those people self-experimenting with NAD+ precursor supplementation should consider keeping a close eye on markers of inflammation.

Cellular senescence is a stable growth arrest that is implicated in tissue ageing and cancer. Senescent cells are characterized by an upregulation of proinflammatory cytokines, which is termed the senescence-associated secretory phenotype (SASP). NAD+ metabolism influences both tissue ageing and cancer. However, the role of NAD+ metabolism in regulating the SASP is poorly understood. Here, we show that nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme of the NAD+ salvage pathway, governs the proinflammatory SASP independent of senescence-associated growth arrest.

NAMPT expression is regulated by high mobility group A (HMGA) proteins during senescence. The HMGA-NAMPT-NAD+ signalling axis promotes the proinflammatory SASP by enhancing glycolysis and mitochondrial respiration. HMGA proteins and NAMPT promote the proinflammatory SASP through NAD+-mediated suppression of AMPK kinase, which suppresses the p53-mediated inhibition of p38 MAPK to enhance NF-κB activity. We conclude that NAD+ metabolism governs the proinflammatory SASP. Given the tumour-promoting effects of the proinflammatory SASP, our results suggest that anti-ageing dietary NAD+ augmentation should be administered with precision.

Link: https://doi.org/10.1038/s41556-019-0287-4

Rejuvenation Therapies Will Also Have Cycles of Hope and Disillusionment

May, 2019

Every new class of rejuvenation therapy, and there will be many of them in the decades ahead, will follow a cycle consisting of a few years of rapidly growing hype, followed by a sharp crash of disappointment, and then, ultimately, long years of slow and steady success. People attach great hopes to the early stages of every new technology, unrealistic expectations for sweeping, immediate change and benefit. Those expectations are usually possible to realize in the long term, but they can only be met in the later stages of development, perhaps several decades after the advent of the new approach to rejuvenation. Producing a mature product that meets the early visions needs the participation of an entire industry, much of which typically does not exist at the start of the process.

Every new technology goes through this cycle, lasting decades from start to finish. The life span of a technology is perhaps fifty years, depending on where one wants to draw the line between a given technology and its next generation, and the first decade can be quite the wild ride when it comes to raised expectations and sudden disillusionment. Human beings are just built this way, the incentives operating at every step of the development process produce this outcome regardless of the fact that we've all seen it before.

Nothing happens quickly, even when the course of action is obvious, even when proof of principle exists for a new medical technology. This is the result of the way in which investment and commercial development works in practice, as it is based on a great deal of happenstance in the percolation of new information through communities, as well as the process of finding, organizing, and persuading groups of people. It takes a few years for a potential entrepreneur to move from exposure to concept to launching a startup company. It takes a few years for a company to succeed or fail. It takes a few years for those lessons to percolate through the research and development communities. Similar cycles play out in the grant writing and publish or perish world of research. Several of these cycles may be needed for any new technology to launch in a useful form. This is why even comparatively straightforward advances can take a decade to make their way out of the labs. Nothing is really all that simple in practice, and regulation slows down these cycles of progress in medicine in comparison to other industries.

Why do the early years of development, those leading in to the first clinical therapies for a new medical technology, inevitably involve an excess of hype? Well, firstly it is sufficiently challenging to raise funds for research in the early stages that advocates tend to sell the vision of the complete industry, the end product rather than the first versions. Further, in the world of biotech startups and venture capital, near all investors are looking for the seeds of enormous, industry-changing companies, the big wins that will provide enormous returns on investment. All venture funds provide their investors with returns that are largely derived from a couple of big wins amidst the failures and the mere successes, and the financial model for such funds is predicated on finding those few big wins. This cultivates, directly and indirectly, a culture of public relations and industry commentary that is prone to hype, to emphasizing the facts in ways that are attractive to investors. Lastly, the people who would benefit from rejuvenation therapies, or indeed any radical new advance in the capabilities of medical science, rarely have a good understanding of the realities and the underlying science, and can muster an enormous degree of hope on that basis.

It is worth considering that the development of therapies is in fact

a difficult and challenging process in its details. It involves a great deal of discovery as matters move from cells to mice to human trials. The early stem cell therapies of fifteen to twenty years ago were an example of the type, in that the simple transplantation of stem cells did not lead to the reliable regenerative therapies that were hoped for at the outset, cures that would reverse heart disease and numerous other age-related conditions. These hopes led to the establishment of countless clinics and a sizable medical tourism industry. Obstacles were discovered, in the form of the sizable logistical costs, the difficulties in standardizing cells for therapy, the unreliable benefits when it comes to regeneration. Transplanted stem cells do not survive for long, and it is their temporary signaling that produces benefits, changing for a time the behavior of native cells and tissues. After the initial years of work, the results consist of a few standardized approaches that fairly reliably reduce chronic inflammation for a time, a considerable benefit, but that fail to reliably improve tissue function and structure. This is a lesser outcome by far than the goals aimed at by the early advocates and developers.

The development catches up to the early hype, however. It just takes time. Presently the field of stem cell research and development is well on the way towards approaches that are in principle capable of reliably producing regeneration. Some of those are quite similar to the early visions, the transplantation of cells that survive in large numbers to integrate with tissues and improve their function. They result from incremental, steady advances in capabilities, rather than any profound new approach to the problem. Others are indeed entirely novel lines of work that didn't exist, even in concept, at the turn of the century, such as the use of full or partial reprogramming to produce patient-specific or universal cell lines, or even to alter cells in vivo.

The world turns, and we live in an age of change, a revolution in progress in the capabilities of biotechnology and its application to medicine. It just doesn't happen quite as rapidly as everyone would like it to.

Repair Biotechnologies Raises a $2.15M Seed Round to Fight Age-Related Diseases

May, 2019

As many of you know, Bill Cherman and I founded Repair Biotechnologies in 2018 with the intent of developing promising lines of rejuvenation research into clinical therapies. There are many opportunities given the present state of the science and far too few people working on them. This remains true even as large amounts of venture funding are entering the space; our field needs more entrepreneurs. I'm pleased to note that we're making progress in our pipeline at Repair Biotechnologies, and have recently closed a seed round from notable investors in order to power us through to the next phase of our work.

What does the Repair Biotechnologies team work on? When we initially set out, after a survey of the field, we settled upon regeneration of the thymus via FOXN1 upregulation as the lowest of low-hanging fruit, a project with good evidence in the literature and the potential of a sizable upside to health in later life when realized. The thymus atrophies with age, and this is a major factor in the age-related decline of the immune system, as the thymus is where T cells mature. Reductions in the supply of new T cells eventually lead to an immune system packed with malfunctioning, senescent, and overspecialized cells that are incapable of defending effectively against pathogens and errant cells.

A little later we picked up development of a fascinating line of research relating to the vulnerability of macrophages to cholesterol. The pathologies of atherosclerosis are caused when macrophage cells become ineffective at clearing out cholesterol from blood vessel walls. They are overwhelmed by oxidized cholesterol in particular, but too much cholesterol in general will also do the trick. Macrophages become inflammatory or senescent, and die, adding their debris to a growing fatty plaque that will eventually rupture or block the blood vessel. By giving macrophages the ability to degrade cholesterol, we can in principle reverse atherosclerosis by making macrophages invulnerable to the cause of the condition. This is, we believe, a much better approach than that of trying to reduce cholesterol in the bloodstream.

Repair Biotechnologies, Inc. announced today $2.15 million in seed venture funding, to accelerate the preclinical development of its pipeline of drugs targeting thymus regeneration, cancer, and atherosclerosis. The $2.15 million in funding was led by Jim Mellon, the billionaire investor and chairman of Juvenescence Ltd. Also participating in the round are Emerging Longevity Ventures, Thynk Capital, and SENS Research Foundation.

"We are committed to developing treatments for the root causes of aging and its associated diseases through the damage repair approach," said Reason, co-founder and CEO. "With this funding round, we will be able to further develop our therapies and validate them in animal models, bringing them closer to the clinic and patients."

The thymus gland is vital to the adaptive immune system, but with age, the thymus shrinks, leading to a decreased immune cell production and a compromised immune system. Repair Biotechnologies is developing a therapy with the aim of reverting this atrophy of the thymus, which the company believes can be an effective treatment against some forms of cancer. Repair Biotechnologies' second major project relates to atherosclerosis, which is caused by the accumulation of intracellular waste in arteries. While present therapies focus on reducing cholesterol,

Repair Biotechnologies has licensed a technology to make the macrophage cells responsible for repairing arteries resilient to excess cholesterol, and thus able to repair atherosclerotic damage.

"SENS Research Foundation was founded to push forward proof-of-concept work demonstrating the validity of the SENS paradigm to the point at which people can actually do something with it. Now we're seeing some of these technologies getting the recognition from investors that they deserve, which in turn is driving critical growth in the private-sector side of the field," said Aubrey de Grey, co-founder and Chief Science Officer of SENS Research Foundation. "I'm thrilled to see Repair Biotechnologies taking things in this area to the next level."

Evidence for the Mutation Accumulation Hypothesis of the Origin of Aging

May, 2019

Researchers here examine the growing vaults of genomic data for evidence to support the theory that aging evolves because evolutionary selection is inefficient when it comes to gene variants that have harmful effects in later life. Selection acts most readily on variants that aid reproductive success in early life. Thus variants that are damaging in late life accumulate, reinforcing an age-related decline of health and robustness. This is closely related to the concept of antagonistic pleiotropy, which refers to genes and biological systems that are beneficial in youth but become harmful in later life. These will tend to be selected for, with all of the attendant unpleasant consequences for individual members of the species.

Medawar's mutation accumulation hypothesis explains aging by the declining force of natural selection with age: Slightly deleterious germline mutations expressed in old age can drift to fixation and thereby lead to aging-related phenotypes. Although widely cited, empirical evidence for this hypothesis has remained limited. Here, we test one of its predictions that genes relatively highly expressed in old adults should be under weaker purifying selection than genes relatively highly expressed in young adults.

Combining 66 transcriptome datasets (including 16 tissues from five mammalian species) with sequence conservation estimates across mammals, here we report that the overall conservation level of expressed genes is lower at old age compared to young adulthood. This age-related decrease in transcriptome conservation (ADICT) is systematically observed in diverse mammalian tissues, including the brain, liver, lung, and artery, but not in others, most notably in the muscle and heart. Where observed, ADICT is driven partly by poorly conserved genes being up-regulated during aging. In general, the more often a gene is found up-regulated with age among tissues and species, the lower its evolutionary conservation. Poorly conserved and up-regulated genes have overlapping functional properties that include responses to age-associated tissue damage, such as apoptosis and inflammation. Meanwhile, these genes do not appear to be under positive selection.

Hence, genes contributing to old age phenotypes are found to harbor an excess of slightly deleterious alleles, at least in certain tissues. This supports the notion that genetic drift shapes aging in multicellular organisms, consistent with Medawar's mutation accumulation hypothesis.

Link: https://doi.org/10.1111/acel.12965

Reporting on Efforts to Design an XPRIZE for Longevity

May, 2019

The principals of the XPRIZE Foundation have been contemplating a longevity-focused research prize for many years now, but the process of design and set up never quite managed to make it all that far. By the look of things, that state of affairs might be changing. That the first working rejuvenation therapies are in clinical trials is something of a prompt for many organizations that needed either a little more supporting evidence or public approval to move forward with their plans relating to aging. Thus the XPRIZE Foundation held a gathering earlier this year in which members of the longevity science community came together to design a suitable research prize structure to encourage work on extending healthy longevity.

For those unfamiliar, the XPRIZE Foundation is famous for designing multi-million-dollar, global competitions to incentivize the development of technological breakthroughs. On April 29th and 30th, the XPRIZE Foundation hosted an event at its headquarters in Culver City, California that could have a profound effect on the evolving landscape of biorejuvenation research: the Future of Longevity Impact Roadmap Lab. With this event, the purpose of which was to gather subject matter experts to brainstorm a potential longevity-research prize, XPRIZE has turned its focus towards solving the critical problem of age-related diseases on society and extending healthy human lifespan for all.

The attendees were a diverse crowd, a veritable who's who of the broader pro-longevity movement: researchers such as Steve Horvath and Greg Fahy, investors such as Sergey Young (board member of XPRIZE and creator of the $100 million Longevity Vision Fund), long-time advocates such as myself, Aubrey de Grey, and Jim Strole, global policy makers, journalists, cryonicists such as Max More, transhumanists such as Zoltan

Istvan and Natasha Vita-More, and of course XPRIZE founder Peter Diamandis.

To facilitate this, the attendees, numbering approximately 70, were divided into tables of four or five - each person tasked with generating a preliminary idea for a longevity-focused XPRIZE and further charged with convincing the rest of their table that their proposed idea should be the one put forth by their table to the rest of the group for consideration. My table happened to include Aubrey de Grey, and thus I knew that a lively discussion was all but assured.

The idea I personally put forth was a conceptually simple one: meaningful physiological remediation of dementia (not just proxy diagnostics or biomarkers) by 2030. I thought this was well suited to the the XPRIZE qualities of "bold, but feasible" and "define the problem, not the solution", and it has several other factors in its favor, namely that dementia is by far the most damaging aspect of aging in terms of protracted emotional suffering and large-scale socioeconomic effects, it is the one aspect of aging that everyone already unequivocally believes is horrific and needs solving, the existing system has failed to solve it for decades, many promising therapy angles have no traditional profit motive and thus will not come to market without additional incentive, success would be clear to validate, and curing it would create an amazing and hopeful narrative with which to enlist the entire world in overcoming all of the diseases of aging.

Aubrey apparently agreed, and with his vote of confidence, this idea became one of the prize concepts pitched to the entire group for consideration. Ideas arising from the other tables' groups covered a wide range of topics as well, included growing fully functional organs from stem cells, demonstrating the arrest of epigenetic markers of aging, successful brain transplantation, creation of an ageless mouse, and restoration of homeostatic and damage repair mechanisms in the elderly.

In terms of an ideal XPRIZE contest, the sought-after configuration was maximal impact and audacity, a proof-of-concept expected date achievable within 10 or 15 years, and with the shortest possible time period between proof-of-concept and widespread adoption. When all was said and done, two concepts stood out. These were the aforementioned proposals put forth by Aubrey and myself: limited but specifically measured human rejuvenation by 2032 and meaningful physiological remediation of dementia by 2030. Of course, with the current exercise completed and the attendees now back to their respective homes and workplaces, it remains to be seen just how the outcome will inform the immediate plans of the XPRIZE Foundation.

Link: https://www.leafscience.org/success-at-the-xprize-foundation/

Evidence for Adult Neurogenesis in Humans Even in Very Late Life

May, 2019

The past year or so has seen an energetic debate over whether or not new neurons are generated in the adult human brain, a process known as neurogenesis. This process is well known and well studied in mice, and thought to be very important in the resilience and maintenance of brain tissue. The human data has always been limited, however, due to the challenges inherent in working with brain tissue in living people, and it was assumed that the mouse data was representative of the state of neurogenesis in other mammals. In this environment, the publication of a careful study that seemed to rule out the existence of neurogenesis in adult humans produced some upheaval, and spurred many other teams to assess the human brain with greater rigor than was previously the case.

So far, all of the following published studies do in fact show evidence of adult neurogenesis in humans. This is the better of the two outcomes, as the regenerative medicine community has based a great deal of work on the prospect of being able to upregulate neurogenesis in order to better repair injuries to the central nervous system, or partially reverse the decline of cognitive function in the aging brain. The study here is particularly reassuring, as it shows that even in very late life there are signs that new neurons are being generated in the brain.

The idea that new neurons continue to form into middle age, let alone past adolescence, is controversial, as previous studies have shown conflicting results. A new study is the first to find evidence of significant numbers of neural stem cells and newly developing neurons present in the hippocampal tissue of older adults, including those with disorders that affect the hippocampus, which is involved in the formation of memories and in learning. Researchers also found that people who scored better on measures of cognitive function had more newly developing neurons in the hippocampus compared to those who scored lower on these tests, regardless of levels of brain pathology.

The researchers think that lower levels of neurogenesis in the hippocampus are associated with symptoms of cognitive decline and reduced synaptic plasticity rather than with the degree of pathology in the brain. For patients with Alzheimer's disease, pathological hallmarks include deposits of neurotoxic proteins in the brain. "In brains from people with no cognitive decline who scored well on tests of cognitive function, these people tended to have higher levels of new neural development at the time of their death, regardless of their level of pathology. The mix of the effects of pathology and neurogenesis is complex and we don't understand exactly how the two interconnect, but there is clearly a lot of variation from individual to individual. The fact that we

found that neural stem cells and new neurons are present in the hippocampus of older adults means that if we can find a way to enhance neurogenesis, through a small molecule, for example, we may be able to slow or prevent cognitive decline in older adults, especially when it starts, which is when interventions can be most effective."

The researchers looked at post-mortem hippocampal tissue from 18 people with an average age of 90.6 years. They stained the tissue for neural stem cells and also for newly developing neurons. They found, on average, approximately 2,000 neural progenitor cells per brain. They also found an average of 150,000 developing neurons. Analysis of a subset of these developing neurons revealed that the number of proliferating developing neurons is significantly lower in people with cognitive impairment and Alzheimer's disease. The scientists are now interested in finding out whether the new neurons discovered in the brains of older adults are behaving the way new neurons do in younger brains.

Link: https://today.uic.edu/new-neurons-form-in-the-brain-into-the-tenth-decade-of-life-even-in-people-with-alzheimers

Extremely Long Lived Cells are Found in Many Tissues, Not Just the Brain

June, 2019

Researchers here report that the brain is not the only organ to exhibit cells that are as long-lived as the animal containing them. A number of other organs contain at least some long-lived cells, even for tissues thought to be highly regenerative and in which tissue turnover is comparatively rapid, such as the liver. It remains to be seen as to how this new information interacts with present thinking on the damage of aging, in which there is a central role for a reduction in stem cell activity and consequent loss of new cells generated to replace old tissue populations.

Scientists once thought that neurons, or possibly heart cells, were the oldest cells in the body. Now, researchers have discovered that the mouse brain, liver, and pancreas contain populations of cells and proteins with extremely long lifespans - some as old as neurons. "We were quite surprised to find cellular structures that are essentially as old as the organism they reside in. This suggests even greater cellular complexity than we previously imagined and has intriguing implications for how we think about the aging of organs, such as the brain, heart, and pancreas."

Since the researchers knew that most neurons are not replaced during the lifespan, they used them as an "age baseline" to compare other non-dividing cells. The team combined electron isotope labeling with a hybrid imaging method (MIMS-EM) to visualize and quantify cell and protein age and turnover in the brain, pancreas and liver in young and old rodent models. To validate their method, the scientists first determined the age of the neurons, and found that - as suspected - they were as old as the organism. Yet, surprisingly, the cells that line blood vessels, called endothelial cells, were also as old as neurons. This means that some non-neuronal cells do not replicate or replace themselves throughout the lifespan.

The pancreas, an organ responsible for maintaining blood sugar levels and secreting digestive enzymes, also showed cells of varying ages. A small portion of the pancreas, known as the islets of Langerhans, appeared to the researchers as a puzzle of interconnected young and old cells. Some beta cells, which release insulin, replicated throughout the lifetime and were relatively young, while some did not divide and were long-lived, similar to neurons. Yet another type of cell, called delta cells, did not divide at all. The pancreas was a striking example of age mosaicism, i.e., a population of identical cells that are distinguished by their lifespans.

Prior studies have suggested that the liver has the capacity to regenerate during adulthood, so the researchers selected this organ expecting to observe relatively young liver cells. To their surprise, the vast majority of liver cells in healthy adult mice were found to be as old as the animal, while cells that line blood vessels, and stellate-like cells, another liver cell type, were much shorter lived. Thus, unexpectedly, the liver also demonstrated age mosaicism.

Link: https://www.salk.edu/news-release/how-old-are-your-organs-to-scientists-surprise-organs-are-a-mix-of-young-and-old-cells/

Infection Induced Systemic Inflammation as a Contributing Cause of Alzheimer's Disease

June, 2019

The big question regarding Alzheimer's disease has always been why only some people suffer this form of dementia. While being overweight clearly increases the risk of dementia, and it is easy to argue that this is because of the chronic inflammation generated by visceral fat tissue, not every overweight individual progresses to the point of Alzheimer's disease. Some people who are not overweight suffer Alzheimer's disease. The condition starts with rising levels of amyloid-β aggregates forming in the brain, thought to be a progressive process occurring over a decade or more prior to any clinical symptoms, but why does this only happen to some people?

The attractive nature of the various infection hypotheses of Alzheimer's disease is that they can answer this question. Only

some people with the relevant risk factors suffer Alzheimer's disease because exposure to infectious agents over a lifetime, particularly those that persist in the body, such as various herpesviruses, or lyme spirochetes, is a matter of chance, only loosely related to physical characteristics. In recent years, researchers have identified amyloid-β as an antimicrobial peptide, a part of the innate immune response to pathogens. In this context it makes sense for infection, particularly persistent infection, to be driving the raised levels of amyloid-β necessary to develop Alzheimer's disease.

In this open access paper, the authors have a different emphasis on infection, suggesting that it is the raised inflammation resulting from infection that drives the progression of Alzheimer's disease. It is quite true that Alzheimer's has a strong inflammatory component. One interpretation of this is that high enough levels of amyloid-β cause dysfunction and cellular senescence in the immune cells of the brain, producing a state of chronic inflammation that in turn encourages the formation of damaging tau aggregates and the onset of the final, severe stage of the condition. But perhaps that inflammation is also a consequence of the infections that drive amyloid-β aggregation.

Among the different risk factors underlying Alzheimer's disease (AD), infection might play a role in late-onset AD. Over the past three decades, infectious agents such as bacteria, viruses, fungi, and protozoa have been reported to trigger the development of AD. The infection hypothesis is not a recent idea. In the 1990s, three laboratories from different countries associated the infection with the etiology of AD. Elderly patients infected with herpes simplex virus (HSV)-1 developed toxic accumulation of amyloid β (Aβ) and phosphorylated (p)-tau protein in the brain. In autopsy cases with histopathologically confirmed AD, spirochetes were found in blood, cerebrospinal fluid, and brain tissue. A national representative survey of US residents involving 1,194 patients with 1,520 hospitalizations for infection with severe sepsis revealed that sepsis survivors were independently associated with substantial and persistent new cognitive impairment and functional disability. All of these studies support the notion that infectious etiology might be a causative factor for the inflammatory pathway associated with AD progression.

The accumulation of misfolded amyloid-β (Aβ) in the brain has been proposed to be the critical triggering event in a complex pathophysiological cascade that leads to AD pathology. The additional physiological role of Aβ as an antimicrobial agent in in vitro and in vivo models has been shown. Studies suggested that Aβ oligomerization, which is considered a pathological development in the context of neurodegeneration, may be a necessary step to potentiate the antimicrobial activity of the peptide. These results raised some important questions about the association between AD and microbial infection. The authors also unveiled the mechanism by which Aβ elicits its antimicrobial property. Aβ binds to a microbe and entraps it by forming amyloid fibrils. The presence of microbes serves as an efficient surface for nucleation of amyloid aggregates, thereby raising the possibility of amyloid deposition.

Even so, the findings raise the question of how the protective function of Aβ fails. The possible answer is microglial dysfunction; accumulation of biologically active peptides following an infection might have not been effectively cleared by microglia in the brain of patients with AD. Additionally, Aβ accumulation in the brain may act as an early toxic event in the pathogenesis of AD. The Aβ monomers, soluble and probably nontoxic, would aggregate into different complex assemblies, including soluble oligomers and protofibrils, with various degrees of toxicity. That may spread throughout the brain, and eventually develop into insoluble amyloid fibrils further assembled into amyloid plaques, which are one of the characteristic histological lesions on AD brains.

Recently, the results from three different groups of investigators demonstrated that sepsis, a life-threatening acute organ dysfunction due to a dysregulated host immune response after infection, induces systemic inflammation that exacerbates the accumulation of Aβ and triggers AD progression. These reports suggest that inflammation is a cardinal component of the pathophysiology of sepsis. Thus, the role of inflammation might be associated with the long-term cognitive impairment observed in sepsis survivors.

Although the molecular cascade that links systemic inflammation and neuroinflammation is still enigmatic, the possible modules that occur after infection, which lead to long-term impairment and brain dysfunction that ultimately trigger AD pathology, may include the following: Invading microorganisms escalate the peripheral Aβ load, a necessary step to neutralize and eliminate the pathogen from the peripheral environment. The peripherally produced Aβ and cytokines enter the central nervous system as systemic inflammation is able to increase blood-brain barrier permeability. An increase in RAGE expression during systemic inflammation also facilitates the transport of Aβ to the central compartment. Finally, the entry of foreign substances triggers brain-immune system crosstalk, which in turn leads to activation of microglia / astrocytes and local production of inflammatory mediators and reactive species. Further comprehension of these mechanisms with newer insights is warranted to develop a strategy for the potential advancement of therapeutics for infection-induced AD progression.

Link: https://www.frontiersin.org/articles/10.3389/fnagi.2019.00122/full

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.

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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). We also invite you to request our FREE information package on the "Free Information" section of our website. It includes:

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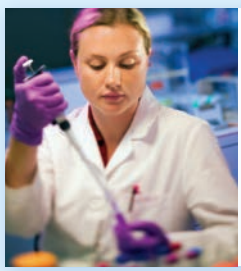

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