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Our Inflation Problem

By Max More, Ph.D.

Another inflation article? Don't turn away! We all should stay focused on cryonics inflation, especially in this time of rapid increases in prices throughout the economy. The imminent increase in the minimum for whole body members helps bring attention to this continuing challenge.

Here is a fact. It's an obvious fact. Even so, many of us ignore it or pretend that we don't need to concern ourselves with it in practice. That fact is: ***Cryopreservation minimums will rise over time.***

With economy-wide inflation in the mid- to high-single digits, cost increases present themselves as urgent. But, even if we return to something close to 2 to 3% average inflation over the next few years, the nature of compounding inflation should tell us to pay attention.

Most people are weak at financial planning. Cryonicists are not exempt from this. Despite repeated warnings about inflation and the inadvisability of securing only minimum funding, many members have done exactly that. Alcor has made major progress with the underfunding crisis. The situation could worsen again unless members better understand how to plan for cryonics inflation. Grandfathering old cryopreservation minimums is a recipe for financial disaster. How can Alcor and its members plan for future increases in the cost of cryopreservation?

> "Well organized public facilities on a substantial scale will probably exist fairly early in 1966, by present indications. The cost of cryostasis according to several independent estimates will be well within the $8,500 figure I mentioned for preparation and perpetual storage, with easy financing through group insurance or similar plans."
> — Robert C.W. Ettinger in *The Prospect of Immortality*, paperback edition, postscript dated October 29, 1965.

Past trends and warnings

Members who face increasing minimums are tempted to blame Alcor. Fair enough, to a degree. Alcor has planned and acted poorly by failing to raise minimums more often. More determination is now evidence to do better at this from now on. Alcor has also gone wrong by continuing to make neuro members subsidize whole body members when it comes to patient storage costs. On the other hand, Alcor has long recommended that new members secure more than the current minimum. That said, it would be wrong to put all the blame on Alcor. Putting blame in the wrong place will lead to bad solutions.

Each of us should take personal responsibility in planning for cost increases. Numerous articles over the years have warned of inflation and the need to think ahead. You can find links to many of those articles in the references.

For historical perspective let's look at the history of cryopreservation minimums over the past 41 years.

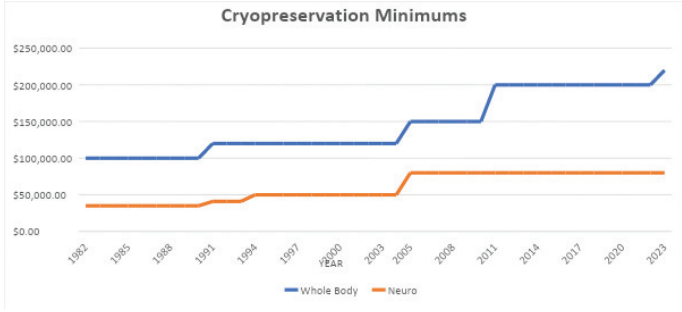
Change in Cryopreservation Minimums, 1982-2023

	Minimum 1982	Minimum 2023*	Av. Inflation (1982-2022)	Actual av. increase
Neuro	$35,000	$80,000	2.81%	2.02%
Whole body	$100,000	$220,000	2.81%	1.93%

**2023 minimums do not include the Comprehensive Member Standby (CMS) waiver. To pay zero CMS fees, the required minimum is $20,000 higher.*

Over the past 41 years, Alcor has averaged an annualized increase of 2.02% for neuro minimums, and 1.93% for whole body. These increases are lower than the rate of general inflation. This equates to a doubling time of roughly 34.5 years for neuro and 36 years for whole body. These amounts are likely to double more quickly than this because minimums were last raised in 2005 for neuro and 2010 for whole body (until the imminent 2023 increase).

History of Alcor Cryopreservation Minimums



How can we project the future?

Inflation will almost certainly continue. When there is a legal monopoly on currency in a country, competition does not exist to constrain monetary authorities. [More, 1995] Deflation is possible but unlikely unless the authorities have completely failed to learn from the experience of the Great Depression. [Friedman, 2010; Rothbard, 2000.] It may take several years to come back down from over 9% to the Federal Reserve's 2% target. The long-term average is close to 3%.

If you have read just about anything by Rudi Hoffman, you will have come across the Rule of 72. This cognitive shortcut is not just a cool party trick, it's a quick and not-too-dirty means of estimating doubling times for costs based on the rate of increases. (Or the doubling time of an investment based on its return.) You take the inflation rate (or interest rate) and divide it into 72 and that gives you the doubling time. At 3% inflation, prices will double about every 72/3 = 24 years. Compounding is powerful. After 24 years, your price has doubled but after 48 years it has quadrupled and after 72 years it has risen 800%. As Rudi Hoffman has put it:

> "Ignoring the effects of compound interest or gravity is inadvisable. Mathematical and physical reality does not CARE how precious you are, how you have sacrificed for years to pay cryonics dues for your family, how deserving and sincere you are, how loyal to the cause, how your spouse won't let you spend more on cryonics, how badly the kids need braces or shoes, how you have become old or uninsurable." [Hoffman, 2012]

Because compound growth is exponential, it is easy to be too complacent if you think ahead only a few years. After 5 years at 3%, your increase is a modest 16%. If you do not expect to be cryopreserved for 40 years, your price will then be 331% of the starting amount.

But is 3% a reasonable average annual number for cost increases? On what basis should we estimate future nominal prices? We could use the long-run average of an inflation index such as the consumer price index (CPI), producer price index (PPI), employment cost index (ECI), or the GDP deflator, or the personal consumption expenditures price index (PCEPI). Some past writing has used the long-term average of the CPI – around 3.1%. [Alcor 2011]

This approach quickly becomes complicated. Which of the numerous indices is most relevant to the costs of cryonics organizations? Does that index have a sufficiently long history to derive a reliable long-term average? (Most indices do not go back as far as the CPI.)

A better way may be to look at past trends in actual costs for a cryonics organization. This method only works for organizations that have been in operation for decades. Fortunately, that includes Alcor.

Elements of cryopreservation (CP) costs

The minimum amount for a cryopreservation at any time depends on four elements:

1. The cost of standby, stabilization, and transport (SST).

2. The allocation for operations.

3. The cost of patient storage.

4. The allowed draw percentage on the Alcor Care Trust (ACT).

SST costs: SST costs have held steady for years but that is largely due to external financial support for a major provider of SST services. New approaches may lower costs, such as field cryoprotection. Costs may go up if we have to use more medical professionals. Alcor bundles the cost of SST into the CP minimum. Cryonics Institute advertises a lower cryopreservation fee but standby and stabilization cost extra. The cost to cover SST from Suspended Animation for two standbys with coverage for more than a minimal two days costs around twice as much as CI's front-line cryopreservation charge. That is a stark illustration of the relatively large cost of SST, at least as currently performed.

Allocation for operations: It looks like operating costs per member have been steady over time although this has not been examined closely in over a decade. [Merkle, 2010] It is beyond the scope of this article to determine the precise trajectory of costs. That would require not merely looking at the total expense lines in each year's financial statements but also teasing out unusual costs as well as costs that are compensated for by revenues (such as costs of and income from each cryopreservation). For the most part, operating costs affect membership dues rather than cryopreservation minimums. Only the amount over and above cryopreservation costs, if any, would affect minimums.

Much of the allocation to operations is used to cover the costs of SST which are not fully covered by CMS fees. This portion of the total also pays for surgery and cryoprotective perfusion. The cost of doing this in Alcor's operating room differs from the cost of doing it in the field. Field cryoprotection may open up opportunities for significant cost reductions. In "How to Cryopreserve Everyone" Ralph Merkle estimated marginal costs for field perfusion at $1,350 per neuro and $2,450 per whole body if done at scale. Some of his numbers are too low and some costs – such as transportation – are not included. [Merkle 2014] Still, more efficient use of personnel spread over a larger volume of cases may well yield some economies.

Part of the allocation is intended to contribute to operations and so to the organization as a whole. How much that has happened given many underfunded cases, I cannot say.

Here is an open question: How much should each cryopreservation contribute to the organization beyond covering costs of SST and

storage? One extreme would be to allocate zero to operations. That would modestly reduce the cryopreservation minimums but would make the organization even more dependent on dues, bequests, and donations. Toward the other extreme, each case would provide a large amount to operations. If the number of cases were high enough, it might then be possible to eliminate membership dues. The latter extreme would not work today because there are not enough fully funded cases.

Imagine that operations scaled well, so that multiplying the membership by ten or a hundred increased operating costs by much less. With 100 cryopreservation cases per year, if $20,000 per case went to operations, membership dues might be minimized or possibly eliminated. The larger an organization grows, the more it may be feasible to shift away from membership dues. Nothing in cryonics is simple though. Among other factors, we would need to consider the resulting shift from tax-deductible expenses to non-deductible expenses for members.

Patient storage: Another large portion of total cryopreservation costs is allocated to patient storage. For neuro patients, it comes to $25,000 or 31.25% of the current $80,000 minimum. For whole body patients – who take up ten times the volume – the portion is $135,000 or 61.4% of the minimum. The cost trajectory of patient care over time is therefore especially important in estimating future whole body minimums.

Patient storage costs include liquid nitrogen, rent for the patient care bay, depreciation, insurance, security, staff time allocated to monitoring and maintaining dewars, and other items. The cost of liquid nitrogen may go down if we used much more. Automation is being implemented to reduce the cost of monitoring and maintenance. The SuperDewar design is already reducing the per-patient cost of liquid nitrogen and floor space. Ralph Merkle has proposed designs for storing a huge number of patients resulting in enormous economies of scale. [Merkle, 2014]

ACT draw: The maximum allowed draw percentage on the Alcor Care Trust is 2% per year. It is a little more complex than that, with a slow and gradual adjustment allowed if investments perform well, but it is close enough for our purposes. The ACT allocation is determined by the annual cost of patient storage multiplied by 50. The $135,000 allocated to the ACT for each whole body patient will cover annual expenses of $2,700. One way the ACT portion of total cryopreservation costs could increase or decrease would be if the percentage draw were decreased or increased. I'll examine that option below. Here, I think it is safest to stick with the current draw, at least so long as the ACT is not regularly and massively boosted by donations or bequests.

So long as we keep the 2% draw fixed, the only ways to deal with increases in the cost of patient storage are to increase the ACT allocation or (much more dangerously) to increase return on investments. Only if economies of scale can be achieved can we reduce that allocation.

From an internal Alcor perspective, it is not necessary to correctly estimate the average increase in prices for patient storage. What matters is keeping the draw on investments to no more than 2%. If the draw exceeds 2% and continues to do so, the ACT allocation will have to be increased. From a member's perspective, that does not help with financial planning. It remains important to have a basis for projecting costs. This matters both for Alcor's communications and what expectations it creates, and for individual members in figuring out how much funding to provide and how to provide it.

Will the long-term average change in nominal costs continue into the future? In other words, is the past a good guide to the future?

Scenarios

What will the minimums be 30 and 50 years from now? Even if we look at actual costs rather than indices, we simply cannot be sure of the pace of price increases over decades to come. We have seen there are reasons to hope some costs will rise more slowly than general inflation but there are other reasons why real costs may stay where they are or even increase. Our best bet is to keep in mind a range of scenarios.

For historical context, inflation in the USA has averaged 2.9% over the last 40 years and 3.1% from 1913 to 2020. Cryonics cost increases may be lower, the same, or higher so we should look at how the numbers work out for various rates of increase. Here are the projected amounts if the average annual increase is 2%, 3%, 4%, and 5%:

	2%	3%	4%	5%
Neuro 2053	$146,000	$197,000	$265,000	$357,000
Neuro 2073	$217,000	$358,000	$569,000	$970,000
WB 2053	$401,000	$540,000	$729,000	$983,000
WB 2073	$598,000	$984,000	$1,620,000	$2,666,000

Clearly, if you are a neuro member funded at $80,000 or even $100,000 or a whole body member funded at $220,000 or even $300,000, you will need to provide additional funding over time. A dollar committed today will be worth only a fraction of a dollar when it is needed.

You can use the following online calculator to find the projected amounts for other years and other rates of increase: Compound Interest Calculator – (thecalculatorsite.com)

Solutions

Limit draw on ACT investments: The Alcor Care Trust (ACT) is charged with investing its funds to maximize growth while

minimizing risk. The fund should generate more than enough money to cover patient maintenance indefinitely and grow over time – even without the influx of new funds. The minimum allocations are calculated to suffice for capital preservation and growth despite patient care costs and inflation. What is a safe annual draw over the long term?

If we were to draw 5% per year to cover the same $2,700, we would only need an ACT allocation of $54,000. Great! That will allow us to reduce the cost of a whole body by $81,000. Let's do it!

If we are going to think along those lines, why not assume a draw of 20% per year? Then the ACT allocation would only need to be $13,500 instead of the current $135,000. Sadly, that is not going to work. It would work for a few years but then the ACT would run out of money and our patients would thaw.

But why 2%? Why not 3% or 4%? At 4%, the ACT allocation would be cut by $67,500 and the percentage may still seem modest. 4% has been the traditional recommendation for an initial limit on withdrawing retirement funds. However, retirement is not expected to last more than 20 to 40 years, depending on age at retirement and life expectancy. It may take much longer to repair and revive cryonics patients. The money in the ACT must withstand ups and downs in the market while generating sufficient income to cover costs for maybe a century. Maybe more.

The traditional rule for retirement says you should draw no more than 4% annually from your savings. The assumption is that you should be able to manage close to a 4% return after inflation. Often this advice has come with the suggestion that you increase the draw each year to compensate for inflation. Many people have challenged the adequacy of this conventional wisdom. It was relatively safe advice when few people lived past their 70s. For those needing retirement income for decades, a 4% draw could drain all investments, especially with an inflation escalation modifier and especially if the market is high at the time of retirement (sequence of return risk).

Historically, Alcor's ACT (or its predecessor) has sometimes been drawn on at 4% or higher. As Ralph Merkle noted:

> By 2010 Alcor was drawing on the PCT at a rate of 5% per year to pay the costs of maintaining its patients in cryopreservation. The PCT draw grew to this unsustainable percentage because underfunded cases led to the PCT principal not being as large as it should have been. The draw only retreated to 2.5% in 2011 after an unforeseen bequest fortuitously doubled the value of the PCT in late 2010. [Alcor, 2011]

An argument could be made, at least in the abstract, that the ACT – or a similar fund for another cryonics organization – could be sustained with a 3% draw or even 3.5%. Using a Monte Carlo simulator, you can select various investment ratios and withdrawal rates. I have not found one that allows you to select a 100-year timeframe, but Portfoliovisualizer does go up to 60 years. I like this spreadsheet because it allows you to change numerous variables, including your mix of investments, withdrawal rate, projected future returns for each asset class, and to set a Final Target Value percentage –how much you have left at the end of the period.

You can also find out how much the risk goes up if your withdrawals start when the market is highly valued (CAPE ratio >20), and if the market is at an all-time high). Rather than estimating the risk of running out of money completely, you can inquire about the risks of ending up with any percentage of your starting investment. [Earlyretirementnow, 2021; a simpler version is: Portfoliovisualizer, 2022] A couple of examples:

> Over a 60-year period at a 3.00% withdrawal rate and a 60/40 stocks/bonds mix, there is 0.00% chance of your funds falling below 10% of the starting amount (inflation adjusted)
>
> At 3.50% with the same portfolio, there is an overall 2.99% failure probability. If the CAPE ratio is over 20, the risk increases to 6.69%. If the CAPE >20 and the market is at an all-time high, the failure probability increases to 7.20%.
>
> With 60% stocks and 40% bonds but raising the final target value to 75%: 3.00% draw failure probability is zero. 3.50%: 5.64% overall, 19.50% if CAPE >20, and 27.20% if CAPE >20 and market at a high.
>
> 75% stocks, 15% bonds, 10% 30y U.S. Treasuries: Final target value = 25%. 3.25%: Zero failure probability under all conditions. At 3.50%, 0.81% chance under all conditions, 2.79% if CAPE >20, and 6.40% if CAPE >20 and the market is at an all-time high.
>
> 75% stocks, 15% bonds, 10% 30y U.S. Treasuries: Final target value = 25%. 3.25% still zero failure probability over 60 years.
>
> 75% stocks, 15% bonds, 10% 30y U.S. Treasuries: Final target value = 75%. At 3.00%, the failure probability = 0% in all conditions. At 3.50%, the failure probability is 5.64% under all conditions, 19.50% with CAPE >20, and 27.20% with CAPE >20 and the market at a high.

I have not extended the Monte Carlo simulations to 100+ years, so I do not know if 3% remains a safe withdrawal rate. You could also make an argument that the withdrawal rate could be higher than 2% because the ACT will be boosted by bequests and gifts. This has certainly been true historically. The sensibly conservative approach is to ignore this possibility since it is only a possibility, not a certainty.

Importantly, these examples allow for the initial investment to decline to either 25% or 75% of the initial value (adjusted for inflation). A strong reason to stick with the seemingly super-conservative 2% limit is that we do not want the real value of the ACT to decline. We want it to *increase greatly* to meet the unknown costs of repair, revival, and rehabilitation. If the ACT can manage to gain even 2% annually on average (above inflation and the 2% draw), after 100 years it will end up with more than 7 times the starting amount.

No grandfathering: "Grandfathering" means allowing early adopters to continue indefinitely paying the same amount as when they started. Since the amount is stated in nominal, not real dollars, over time the organization will be badly shortchanged. This puts all patients at risk. Grandfathering can only possibly work if the organization grows very fast and sustains that growth. That does not guarantee a working approach but is a necessary condition.

I have seen some people arguing that grandfathering is a standard business practice. This is true but misleading as applied to cryonics. Companies grandfather in prices for early customers only for a limited period. After that, they either cancel the grandfathering or else restrict the grandfathered customers to increasingly unappealing options. An example of this is mobile phone plans.

Life insurance options: An obvious option to deal with future increases in prices is to buy life insurance well in excess of current minimums. Many people refer to this as "overfunding." I have objected to this term for years. You may think you are overfunded today but one day you will only be *funded* or *underfunded*. A better term would be "superfunding" or simply "over-minimum funding."

This option has some appeal for someone who is young and in good health with a decent income. Especially for neuro members, additional insurance funding may make sense since some companies may not offer an amount as low as today's neuro minimum. Also, larger amounts may be only minimally more expensive (up to a point).

Another option is to buy a life insurance policy that can reasonably be expected to increase in nominal value over time – enough to maintain the policy's real (inflation-adjusted) value. Whole life policies and some indexed universal life policies may work for this. On the downside, these policies are more expensive. You can make it easier for yourself if you choose a policy that allows you to increase the coverage amount.

Life insurance is a powerful and useful tool for funding cryonics. It also benefits from being bankruptcy proof. If you go bankrupt, almost everything can be taken from you except life insurance (and, in some states, your house). Another upside is that insurance acts as a kind of "forced" saving. On the downside, life insurance is not a great investment. The insurance companies are providing a service and they have to get paid for it.

Invest and top-up funding: If you want to get better returns than given by life insurance, you can take several paths. You might buy inexpensive term life insurance to cover you for today's minimums and near-term prices increases while investing to grow your wealth. Or you could put off making cryonics arrangements and take your chances without life insurance coverage. Another variant is to invest to build wealth over time and create a cryonics funding trust. Your assets will go into the trust at legal death. The trust should specify the funding to go to the cryonics organization. Such trusts must be approved by Alcor.

Incremental prepay: You might cover current minimums using life insurance but then periodically add to that funding by paying into a prepaid account. You can use a refundable prepaid account which allows you to get your money back if you change your mind but which earns no interest. Or you can use a permanent prepaid account that is not refundable but which covers you against cost increases.

A final option for making up for a shortfall in funding is the alternative funding option that I introduced several years ago. This can only be used for 50% or less of your total funding and relies on ownership of property, retirement funds, and so on. Not much use has been made of this so far and it is a burden on the organization. (In a much larger Alcor of the future, a department may be dedicated to managing this option.)

You would need to check with Alcor to see if this option would still be acceptable and under what conditions. For example, the existing policy discounts the value of alternative funding assets by 50% to allow for the risk that they are incorrectly valued or will be lost to other claimants.

The organizational approach: After years of allowing the underfunding problem to grow, Alcor finally tackled it head on in 2011, leading to the Underfunding Plan. This plan is still in operation but applies only to members who joined it before the cut-off date. Raising cryopreservation minimums is easy to put off because some members will inevitably become unwilling or unable to afford the increased amount. Putting off CP increases only worsens the problem and makes eventual adjustment more painful.

The organizational approach to dealing with inflation should be to increase CP minimums by small amounts more frequently. When inflation is low, minimums may need to be adjusted only every three to five years. In times of higher inflation, a yearly adjustment may be wise. Not only would this effectively manage the underfunding problem from the organization's point of view (although at the cost of losing some members), it also creates expectations in the minds of members. If the organization does

not raise minimums for 15 or 20 years, it is hardly surprising that members imagine that they need not plan for more funding.

Inflation exists and shows no signs of going away over the long term. We dislike it and it causes us much grief aside from cryonics arrangements. But pretending that it is not there only leads to disaster. Unless you have already provided your cryonics organization with tens of millions in funding, you should be considering your options. ■

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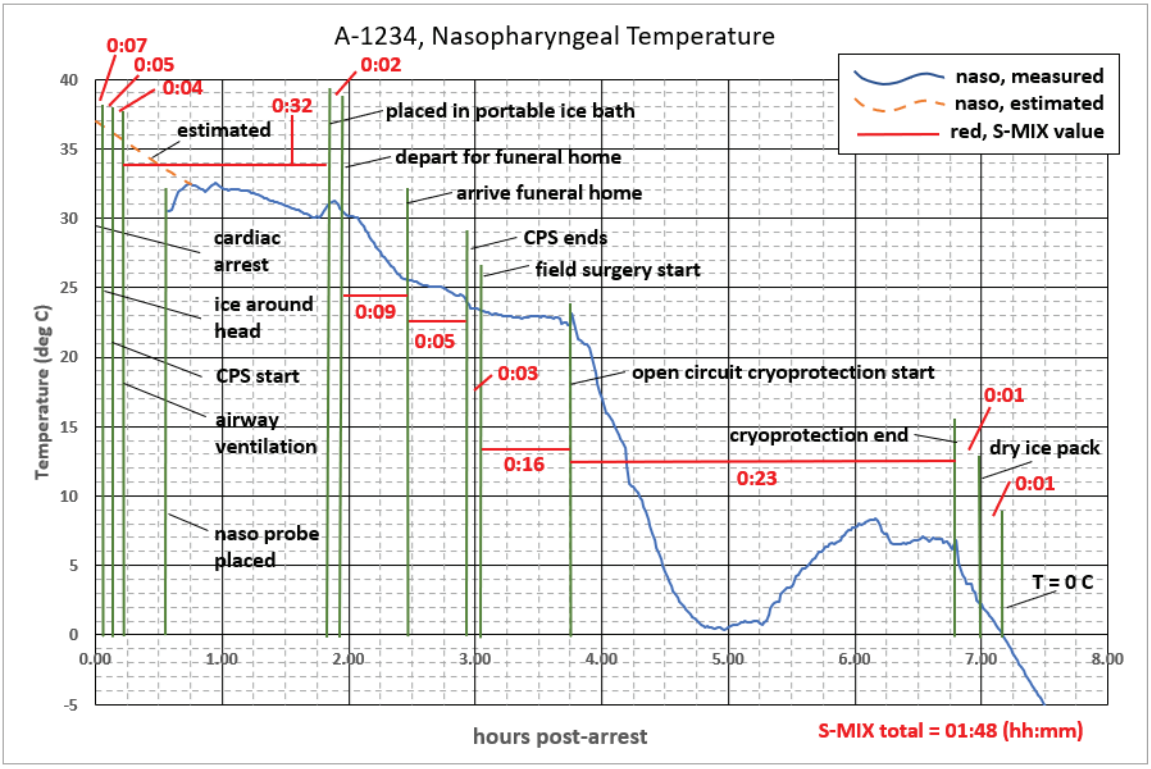
Case Report Implementation of the S-MIX (Standardized Measure of Ischemic Exposure)

By Brook Norton

For most of the time that cryonics has been practiced, it has been difficult to quantify how well each cryopreservation case was carried out. Determining success by observing patient revivals will not happen for decades. Further, patients are immersed in liquid nitrogen, and so are difficult to inspect. The situation is similar to the feedback problem that exists in the life extension field where it is impractical to try a therapy and then wait decades to see how long the subjects live. To get around this challenge for life extension trials, biological clocks are being developed to provide quick feedback for how many years of life a therapy can add. To work around the feedback challenge in cryonics, two fairly recent methods have been developed and implemented.

The first method has been to create a metric, applicable to both past and future cases, that quantifies ischemic damage (from lack of oxygen) in the interval from cardiac arrest until the patient temperature descends to 0º C. That is the S-MIX (Standardized Measure of Ischemic Exposure) metric, and its implementation in case reports will be reviewed here. The second feedback method is to perform a CT (computerized tomography) scan of the patient. This is accomplished while the patient remains immersed in liquid nitrogen. The CT scan produces an image that indicates the level of vitrification by showing the density of water ice (bad), or lack thereof (good) in the tissues scanned, especially the brain. S-MIX covers human cryopreservation procedures carried out above 0º C. CT scanning gives feedback for preservation quality of the entire cryopreservation, down to liquid nitrogen temperature. Both of these methods provide essential feedback to the team so that the effectiveness of various cryonics technologies can be evaluated and improved upon.

S-MIX is in units of time and provides an equivalent normothermic (normal body temperature) exposure time. For example, if a patient experiences circulatory arrest and remains undiscovered, at near normal body temperature, for 1 hour before cooling starts, then 1 hour is added to S-MIX. As patient temperature decreases, the rate of ischemic damage quickly decreases, and S-MIX accumulates more slowly. Every case incurs some ischemic damage since it takes some time to cool from normal body temperature down to 0º C. Theoretically, if a patient were somehow instantly cooled to 0º C after circulatory



arrest, there would be no ischemic damage and S-MIX would have the ideal value of 0 hours.

The derivation of the S-MIX formula was presented in "The S-MIX: A Measure of Ischemic Exposure" by R. Michael Perry and Aschwin de Wolf, in the 4th quarter, 2020 edition of *Cryonics* magazine. That article explains that the S-MIX derivation accounts for the common approximation that the metabolic rate is cut in half for every 10º C that the temperature drops. S-MIX can be calculated by dividing the temperature plot into segments, like cardiac arrest until ice bath cooling, CPS (cardiopulmonary support) until the start of surgery, etc. S-MIX, for each segment, depends on:

- starting and ending temperatures
- time spent in each segment
- whether CPS included ventilation (if so, S-MIX is reduced by 50% for that segment)
- whether blood washout included oxygenation (if so, S-MIX = 0 for that segment)

The above plot shows the patient body temperature for an actual case, from cardiac arrest until the temperature drops below 0º C. The red values are the S-MIX for each segment. They total to a final S-MIX of 1 hr 48 min. Comparing 1:48 equivalent ischemic time to the actual elapsed time of 7:10, from cardiac arrest to 0º C, it can be seen that quickly lowering the temperature dramatically reduces ischemic damage.

During patient standby, stabilization, and transport (SST), video and detailed records of dozens of parameters are collected. After the patient begins the cooldown to liquid nitrogen temperature, SST data is documented in a case report. The field report and other data, such as recorded communications, are consolidated into an Alcor case report. The case report is then reviewed to identify key events that affect S-MIX, shown by vertical green lines in the plot.

All potential S-MIX event times are entered into Excel. Final S-MIX events are designated with an "x" as shown in the below image snipped from the larger spreadsheet. Days-after-cardiac-arrest are calculated in the far-right column. Note that, for example, T+1 indicates the day following cardiac arrest (perhaps only minutes after cardiac arrest), not that the event occurs a full day later. A macro sorts the event table, moving "x" events to the top, in chronological order. Once an event is marked "x", its date/time is automatically used in the plot and in the S-MIX calculation.

Event name	date	time (MST)	Table_1 S-MIX	T+X days
Cardiac arrest	1/15/2023	23:30	x	T-0
ice bath, CPS, airway	1/16/2023	00:05	x	T+1
Transport patient to MOV for surgery	1/16/2023	00:35	x	T+1

Different cases may use different data loggers to record patient temperature. The raw data output can vary in date/time format, units of Fahrenheit or Celsius, and frequency of temperature readings. So, the raw data is copied into Excel where it is automatically pre-conditioned to a consistent date/time format, Celsius units, and a sampling frequency of 1/minute.

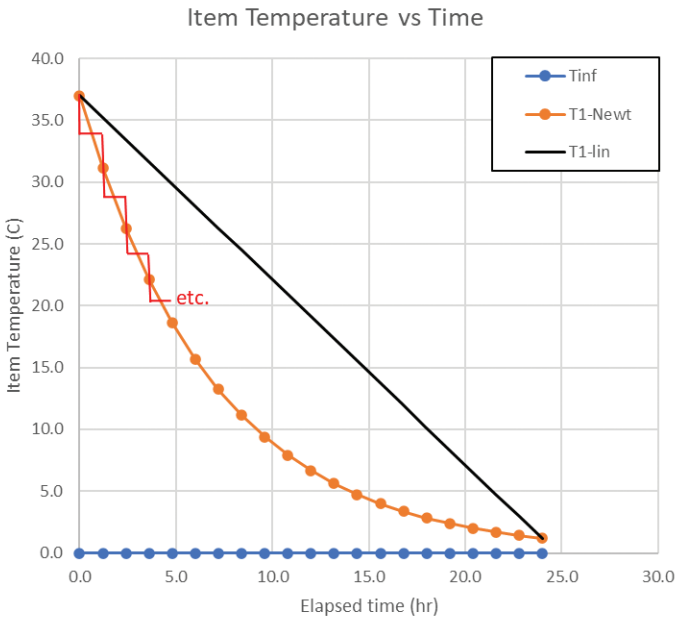
More than one datalogger stream may be used, such as for SST, transport, and cryoprotectant perfusion at Alcor. In any case, raw data is copied to Excel, concatenating datalogger streams, and covering the duration from cardiac arrest until the patient temperature passes through 0º C.

The resulting blue temperature line in the plot is reviewed for segments that may need to have corrupted data overridden, or missing data filled in with an estimate. Estimated temperatures may be needed from cardiac arrest until a temperature probe is placed, or when a probe is accidentally allowed to come in contact with ice water, or because of other possible technical glitches. Estimated data can be seen in the above plot, shown as the orange dashed line at the upper left.

Excel automatically queries the temperature data at the times designated by the green event lines. S-MIX is then calculated for the duration between every data point (typically several hundred) and summed to determine the total S-MIX.

Excel automatically plots the blue temperature line, orange estimated line(s), and green vertical event lines in the above plot. Event line labels are manually added.

The below example plot is given to illustrate how the S-MIX calculation is approached. This example shows a patient being cooled with water ice, from a normal body temperature of 37º C, down to 2º C in 24 hours. If only those two endpoints were



known, the intervening temperature decline would need to be estimated. The black line shows a linear estimate, and the orange line shows a more realistic Newtonian decline. T-infinity is the temperature that the patient would reach if allowed to cool indefinitely, in this case, approaching 0º C, shown by the blue line.

The above-mentioned article by Perry and de Wolf provides equations for calculating S-MIX-linear, S-MIX-Newtonian, rate of ischemic damage, and T-infinity, from just the two endpoints. The article also provides the equation for the Newtonian temperature decline, shown by the orange line in the below plot. Plotting the orange temperature line provides more insight as to why Newtonian cooling, which declines faster, gives a lower (good) S-MIX than an assumed linear cooling.

To calculate S-MIX for the orange Newtonian line, it is first broken into small segments, shown by orange dots. S-MIX for each small segment could be calculated from the equation that uses just the two segment endpoints. However, it turns out to be more computationally efficient in Excel to use a stepwise approach shown by the red line. The horizontal part of the red line gives the average temperature for that segment and the segment duration. The equation for (the rate of ischemic damage) X (the segment duration) gives the segment S-MIX contribution. The segment contributions can be summed to obtain the final S-MIX, for example 1 hr and 48 minutes in the above plot.

The Newtonian S-MIX is used in Excel because, compared to a linear approximation, it more accurately models the actual temperature drop for a cooling human body. At the same time that the Newtonian formulas were implemented, the capability to evaluate S-MIX for every datalogger point was also implemented. Ironically, the high density of datalogger points, and thus the small time between points, results in linear and Newtonian S-MIX that are nearly the same for those segments with datalogger temperatures. And so, the Newtonian capability is most valuable for filling in the gaps where datalogger data is missing.

The S-MIX Excel tool provides a convenient way to estimate ischemic damage for cryopreservation cases with complete, or incomplete temperature data. The detailed S-MIX mathematics are built into the tool so that case-report writers need not engage the mathematics, needing only to enter time and temperature data.

The S-MIX analysis will be presented in new case reports. The primary goal is to provide feedback on which cryonics procedures are most effective at reducing ischemic damage, pointing the way to improved procedures for future cases. ■

Recent Advances in Dementia Diagnosis

By R. Michael Perry, Ph.D.

Introduction

Quoting from Wikipedia (https://en.wikipedia.org/wiki/Dementia#Dental_health, accessed 27 Nov. 2022): "Dementia is a disorder which manifests as a set of related symptoms, which usually surfaces when the brain is damaged by injury or disease. The symptoms involve progressive impairments in memory, thinking, and behavior, which negatively affects a person's ability to function and carry out everyday activities. Aside from memory impairment and a disruption in thought patterns, the most common symptoms include emotional problems, difficulties with language, and decreased motivation. The symptoms may be described as occurring in a continuum over several stages. Consciousness is not affected. Dementia ultimately has a significant effect on the individual, caregivers, and on social relationships in general. A diagnosis of dementia requires the observation of a change from a person's usual mental functioning, and a greater cognitive decline than what is caused by normal aging. Several diseases and injuries to the brain, such as a stroke, can give rise to dementia. However, the most common cause is Alzheimer's disease, a neurodegenerative disorder."

Dementia is a problem anyone must face as aging sets in. Many, it is true, are lucky and do not suffer serious mental impairment even in advanced old age, but the possibility is always there. It is an especially worrying problem to cryonicists who are hoping for the best preservation of the brain at clinical death. If clinical death must occur and we must be cryopreserved, we would at least like to have our minds intact.

So, what can be done about it? Again, from the Wikipedia article: "There are limited options for treating dementia, with most approaches focused on managing or reducing individual symptoms. There are no treatment options available to delay the onset of dementia. Acetylcholinesterase inhibitors are often used early in the disorder course; however, benefit is generally small. More than half of people with dementia may experience psychological or behavioral symptoms including agitation, sleep problems, aggression, and/or psychosis. Treatment for these symptoms is aimed at reducing the person's distress and keeping the person safe."

With prospects grim for treating dementia once it is diagnosed, there is especially strong interest in early detection. Treatment might then start years in advance of the main symptoms, and overall, perhaps obviate these symptoms or greatly reduce their severity. Toward this end, some recent research reported below has identified several possible approaches, ranging from retinal assessments to using machine learning. The list is not claimed to be exhaustive but representative, as in the RU section; here we also let the researchers and those reporting their work speak for themselves.

Retinal Layer Assessments as Potential Biomarkers for Brain Atrophy in the Rhineland Study

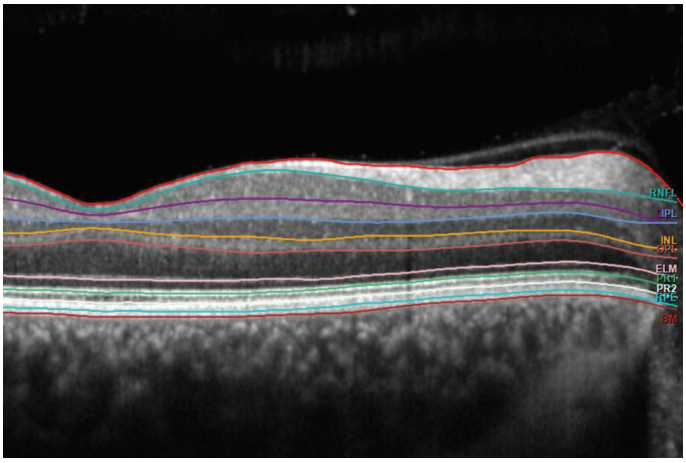
Matthias M. Mauschitz, Valerie Lohner, Alexandra Koch, Tony Stöcker, Martin Reuter, Frank G. Holz, Robert P. Finger, Monique M. B. Breteler, *Scientific Reports* 12, article number 2757, 17 Feb. 2022, https://www.nature.com/articles/s41598-022-06821-4, accessed 13 Nov. 2022.

Abstract

Retinal assessments have been discussed as biomarkers for brain atrophy. However, available studies did not investigate all retinal layers due to older technology, reported inconsistent results, or were based on small sample sizes. We included 2872 eligible participants of the Rhineland Study with data on spectral domain–optical coherence tomography (SD–OCT) and brain magnetic resonance imaging (MRI). We used multiple linear regression to examine relationships between retinal measurements and volumetric brain measures as well as fractional anisotropy (FA) as measure of microstructural integrity of white matter (WM) for different brain regions. Mean (SD) age was 53.8 ± 13.2 years (range 30–94) and 57% were women. Volumes of the inner retina were associated with total brain and grey matter (GM) volume, and even stronger with WM volume and FA. In contrast, the outer retina was mainly associated with GM volume, while both, inner and outer retina, were associated with hippocampus volume. While we extend previously reported associations between the inner retina and brain measures, we found additional associations of the outer retina with parts of the brain. This indicates that easily accessible retinal SD-OCT assessments may serve as biomarkers for clinical monitoring of neurodegenerative diseases and merit further research.

From: The Retina as a Potential Biomarker for Reduced Brain Matter

DZNE Press Releases (unattributed), 15 Mar. 2022, https://www.dzne.de/en/news/press-releases/press/the-retina-as-a-potential-biomarker-for-reduced-brain-matter/, accessed 13 Nov. 2022.



Cross-section through the human retina showing its different layers – acquired by "spectral domain optical coherence tomography" (SD-OCT). For use only in connection with this press release. Source: UKB/ Mauschitz

Researchers from the Department of Ophthalmology at the University Hospital Bonn (UKB) and Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE) have found a close connection between the dimensions of retinal structures and those of the brain. They report on this in the journal *Scientific Reports*. Their study results suggest that assessments of the eye's retina could help to detect a loss of brain substance, i. e. "brain atrophy". The findings are based on data from the so-called Rhineland Study.

Within the framework of the Rhineland Study – a large-scale population study in the Bonn city area – DZNE is researching key factors for a healthy life. Determining biomarkers for dementia and other neurodegenerative diseases is one of the study's goals. One focus is on the human retina, for which the DZNE closely cooperates with the Department of Ophthalmology of UKB. "There is evidence that the retina can serve as a window into the brain, so to speak. Our current results support this view," says Prof. Dr. Frank G. Holz, Director of the Department of Ophthalmology of UKB. "Compared to earlier studies, we used more advanced technology and investigated a larger group of people."

In almost 3,000 participants of the Rhineland Study aged between 30 and 94 years, the retina was assessed using "spectral domain optical coherence tomography" (SD-OCT) – a technique that provides detailed images of the retina and its various layers. In addition, brain scans were performed by magnetic resonance imaging (MRI). The data were analyzed using sophisticated software algorithms. "This allowed for automated identification and determination of thickness and volumes, of both the different retinal layers and the different structures of the brain. Next, we looked for associations between the volume of the retina and the volume of certain brain structures," explains Dr. Dr. Matthias M. Mauschitz, resident at UKB's Department of Ophthalmology, postdoctoral scientist at DZNE and first author of the current publication.

"There was a close relation between layers of the inner retina and the so-called white matter in the brain," Mauschitz adds. "The thinner these retinal layers, the smaller the volume of the brain's white matter." By contrast, sections of the outer retina were mainly associated with the gray matter of the cerebral cortex. In the brain's occipital lobe, where visual processing happens, these associations were particularly pronounced. And the researchers found further relationships. "Interestingly, the thickness of different retinal layers correlated closely with the volume of the hippocampus. This is an area of the brain that plays a central role in memory and is often affected in dementia," says Prof. Dr. Robert P. Finger, senior ophthalmologist at the UKB's Department of Ophthalmology.

"Imaging of the retina using SD-OCT is relatively simple, non-invasive and inexpensive. The current results suggest that SD-OCT measurements of the retina could potentially serve as biomarkers for brain atrophy and to monitor progression of certain neurodegenerative diseases," says Prof. Dr. Monique M. B. Breteler, Director of Population Health Sciences at DZNE and head of the Rhineland Study. "Further population-based studies as well as studies in patient groups and over a longer period of time are now needed to verify these results in a clinical setting."

Amyloid-Beta Misfolding and GFAP Predict Risk of Clinical Alzheimer's Disease Diagnosis within 17 Years

Léon Beyer, Hannah Stocker, Dan Rujescu, Bernd Holleczek, Julia Stockmann, Andreas Nabers, Hermann Brenner, Klaus Gerwert, *Alzheimer's & Dementia* / Early View, 19 Jul. 2022, https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12745, accessed 20 Nov. 2022.

Abstract

Introduction

Blood-based biomarkers for Alzheimer's disease (AD) are urgently needed. Here, four plasma biomarkers were measured at baseline in a community-based cohort followed over 17 years, and the association with clinical AD risk was determined.

Methods

Amyloid beta (Aβ) misfolding status as a structure-based biomarker as well as phosphorylated tau 181 (P-tau181), glial

fibrillary acidic protein (GFAP), and neurofilament light (NfL) concentration levels were determined at baseline in heparin plasma from 68 participants who were diagnosed with AD and 240 controls without dementia diagnosis throughout follow-up.

Results

Aβ misfolding exhibited high disease prediction accuracy of AD diagnosis within 17 years. Among the concentration markers, GFAP showed the best performance, followed by NfL and P-tau181. The combination of Aβ misfolding and GFAP increased the accuracy.

Discussion

Aβ misfolding and GFAP showed a strong ability to predict clinical AD risk and may be important early AD risk markers. Aβ misfolding illustrated its potential as a prescreening tool for AD risk stratification in older adults.

From: Blood Test Spots Signs of Alzheimer's Years Before Symptoms Appear: Scientists

Simona Kitanovska, Zenger News, 2 Aug. 2022, https://www.newsweek.com/blood-test-spots-signsalzheimers-years-before-symptoms-appear-scientists-1730214, accessed 28 Jan. 2023.

A simple blood test can spot signs of Alzheimer's 17 years before symptoms appear, according to new research. Scientists have created a sensor that can detect signs of the condition years before they first manifest themselves. It should mean older people can be screened easily for the disease. If they are showing signs of it, they can be given drugs at an early stage when the drugs will work better. The researchers hope one day the disease will be stopped while patients still have no symptoms and before any irreversible damage occurs.

The gadget works by sniffing out where the protein amyloid-beta, which can help identify the disease, has folded and lost its original shape. Misfolded proteins also play a role in the development of other diseases such as Parkinson's and Huntington's disease. As the disease progresses, this misfolding can cause plaques in the brain. The German academics hope the breakthrough will allow more Alzheimer's-busting drugs to be developed in the future and allow existing ones to be made to work better.

Clinical trials for Alzheimer's drugs have been failing by the dozen because plaque tests used in them do not detect the disease in time. Once plaques appear they seem to do irreversible damage. In existing tests, the plaques are either detected in the brain via an expensive PET scan or detected indirectly. The new sensor detects the misfolding proteins which cause the plaques to appear, meaning the disease can be caught earlier.

For the study, the team analyzed the blood plasma of Germans to look for signs of the condition. The blood samples had been taken between 2000 and 2002 then frozen; participants were between 50 and 75 years old and had not yet been diagnosed with Alzheimer's disease. The team then selected 68 participants who had been diagnosed with Alzheimer's disease during the 17-year followup and compared them with 240 people who had not been diagnosed with it.

The sensor was able to identify the 68 people who later developed Alzheimer's with a high degree of accuracy. They then tried other gadgets, including the P-tau181 which is seen as promising, but found they could not detect the disease 17 years early.

The team found analyzing the concentration of glial fiber protein can also indicate the disease up to 17 years before symptoms appear even though it does so much less precisely than the sensor. Analyzing both the folding protein and glial fiber protein concentration could further increase the accuracy of the test.

"Our goal is to determine the risk of developing Alzheimer's dementia at a later stage with a simple blood test even before the toxic plaques can form in the brain, in order to ensure that a therapy can be initiated in time," said lead study author Professor Klaus Gerwert, of Ruhr University Bochum, Germany.

Investigating the Power of Eyes Open Resting State EEG for Assisting in Dementia Diagnosis

Jack L. Jennings, Luis R. Peraza, Mark Baker, Kai Alter, John-Paul Taylor, Roman Bauer, *Alzheimer's Research & Therapy* 14, 109, 5 Aug. 2022, https://alzres.biomedcentral.com/articles/10.1186/s13195-022-01046-z, accessed 25 Nov. 2022.

Abstract

Introduction

The differentiation of Lewy body dementia from other common dementia types clinically is difficult, with a considerable number of cases only being found post-mortem. Consequently, there is a clear need for inexpensive and accurate diagnostic approaches for clinical use. Electroencephalography (EEG) is one potential candidate due to its relatively low cost and non-invasive nature. Previous studies examining the use of EEG as a dementia diagnostic have focussed on the eyes closed (EC) resting state; however, eyes open (EO) EEG may also be a useful adjunct to quantitative analysis due to clinical availability.

Methods

We extracted spectral properties from EEG signals recorded under research study protocols (1024 Hz sampling rate, 10:5 EEG layout). The data stems from a total of 40 dementia

patients with an average age of 74.42, 75.81 and 73.88 years for Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), respectively, and 15 healthy controls (HC) with an average age of 76.93 years. We utilised k-nearest neighbour, support vector machine and logistic regression machine learning to differentiate between groups utilising spectral data from the delta, theta, high theta, alpha and beta EEG bands.

Results

We found that the combination of EC and EO resting state EEG data significantly increased inter-group classification accuracy compared to methods not using EO data. Secondly, we observed a distinct increase in the dominant frequency variance for HC between the EO and EC state, which was not observed within any dementia subgroup. For inter-group classification, we achieved a specificity of 0.87 and sensitivity of 0.92 for HC vs dementia classification and 0.75 specificity and 0.91 sensitivity for AD vs DLB classification, with a k-nearest neighbour machine learning model which outperformed other machine learning methods.

Conclusions

The findings of our study indicate that the combination of both EC and EO quantitative EEG features improves overall classification accuracy when classifying dementia types in older age adults. In addition, we demonstrate that healthy controls display a definite change in dominant frequency variance between the EC and EO state. In future, a validation cohort should be utilised to further solidify these findings.

From: Dementia Diagnosis Could Be Fast-Tracked Using Artificial Intelligence

University of Surrey Press Release (unattributed), 21 September 2022, https://www.surrey.ac.uk/news/dementia-diagnosis-could-be-fast-tracked-using-artificial-intelligence, accessed 25 Nov. 2022.

Different forms of dementia could be spotted sooner and more easily by analysing recordings of patients' electrical brain activity using artificial intelligence (AI), according to new research. Scientists from the University of Surrey and the University of Newcastle have shown that it is possible to use electroencephalography (EEG) as a low-cost diagnostic tool to help clinicians identify different forms of dementia, including Lewy body, Alzheimer's and Parkinson's dementia.

Dr Roman Bauer, senior author of the study from the University of Surrey, said:

"Our study shows that using artificial intelligence analysis of EEG data as a diagnostic tool to identify dementia could be life-changing for many people. We have shown that by combining brain activity captured from patients with their eyes open and with their eyes closed, our machine learning algorithms can accurately detect different forms of dementia, including Lewy body dementia, which is often only found post-mortem. As a result, we believe that our method could allow people to be diagnosed and treated sooner.

"The clear next step for our project is to gather support for a clinical trial for this incredibly promising technology."

In the study, the researchers used EEG data (with eyes open and with eyes closed) from 40 people living with dementia in their 70s. In addition, the study used 15 healthy control subjects.

According to the World Health Organisation, 55 million people live with dementia worldwide. However, studies have shown that Lewy body dementia can be found in more than 25% of dementia cases post-mortem, suggesting that there is an under-representation of that specific type in current data.

Pre-diagnostic Cognitive and Functional Impairment in Multiple Sporadic Neurodegenerative Diseases

Nol Swaddiwudhipong, David J. Whiteside, Frank H. Hezemans, Duncan Street, James B. Rowe, Timothy Rittman, *Alzheimer's & Dementia*, 12 Oct. 2022, https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.12802, accessed 27 Nov. 2022.

Abstract

Introduction

The pathophysiological processes of neurodegenerative diseases begin years before diagnosis. However, pre-diagnostic changes in cognition and physical function are poorly understood, especially in sporadic neurodegenerative disease.

Methods

UK Biobank data were extracted. Cognitive and functional measures in individuals who subsequently developed Alzheimer's disease (AD), Parkinson disease, frontotemporal dementia, progressive supranuclear palsy, dementia with Lewy bodies, or multiple system atrophy were compared against individuals without neurodegenerative diagnoses. The same measures were regressed against time to diagnosis, after adjusting for the effects of age.

Results

There was evidence for pre-diagnostic cognitive impairment and decline with time, particularly in AD. Pre-diagnostic functional impairment and decline were observed in multiple diseases.

Discussion

The scale and longitudinal follow-up of UK Biobank participants provides evidence for cognitive and functional decline years before symptoms become obvious in multiple neurodegenerative diseases. Identifying pre-diagnostic functional and cognitive changes could improve selection for preventive and early disease-modifying treatment trials.

From: Scientists Detect Dementia Signs As Early As Nine Years Ahead of Diagnosis

University of Cambridge (unattributed), 13 Oct. 2022, https://www.cam.ac.uk/research/news/scientists-detect-dementia-signs-as-early-as-nine-years-ahead-of-diagnosis, accessed 27 Nov. 2022.

Cambridge scientists have shown that it may be possible to spot signs of brain impairment in patients as early as nine years before they receive a diagnosis for one of a number of dementia-related diseases.

In research published today in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, the team analysed data from the UK Biobank and found impairment in several areas, such as problem solving and number recall, across a range of conditions.

The findings raise the possibility that in the future, at-risk patients could be screened to help select those who would benefit from interventions to reduce their risk of developing one of the conditions, or to help identify patients suitable for recruitment to clinical trials for new treatments.

There are currently very few effective treatments for dementia or other neurodegenerative diseases such as Parkinson's disease. In part, this is because these conditions are often only diagnosed once symptoms appear, whereas the underlying neurodegeneration may have begun years – even decades – earlier. This means that by the time patients take part in clinical trials, it may already be too late in the disease process to alter its course.

Until now, it has been unclear whether it might be possible to detect changes in brain function before the onset of symptoms. To help answer this question, researchers at the University of Cambridge and Cambridge University Hospitals NHS Foundation Trust turned to UK Biobank, a biomedical database and research resource containing anonymised genetic, lifestyle and health information from half a million UK participants aged 40-69.

As well as collecting information on participants' health and disease diagnoses, UK Biobank collected data from a battery of tests including problem solving, memory, reaction times and grip strength, as well as data on weight loss and gain and on the number of falls. This allowed them to look back to see whether any signs were present at baseline – that is, when measurements were first collected from participants (between five and nine years prior to diagnosis).

People who went on to develop Alzheimer's disease scored more poorly compared to healthy individuals when it came to problem solving tasks, reaction times, remembering lists of numbers, prospective memory (our ability to remember to do something later on) and pair matching. This was also the case for people who developed a rarer form of dementia known as frontotemporal dementia.

People who went on to develop Alzheimer's were more likely than healthy adults to have had a fall in the previous 12 months. Those patients who went on to develop a rare neurological condition known as progressive supranuclear palsy (PSP), which affects balance, were more than twice as likely as healthy individuals to have had a fall.

For every condition studied – including Parkinson's disease and dementia with Lewy bodies – patients reported poorer overall health at baseline.

First author Nol Swaddiwudhipong, a junior doctor at the University of Cambridge, said: "When we looked back at patients' histories, it became clear that they were showing some cognitive impairment several years before their symptoms became obvious enough to prompt a diagnosis. The impairments were often subtle, but across a number of aspects of cognition.

"This is a step towards us being able to screen people who are at greatest risk – for example, people over 50 or those who have high blood pressure or do not do enough exercise – and intervene at an earlier stage to help them reduce their risk."

Systematic evaluation of urinary formic acid as a new potential biomarker for Alzheimer's disease

Yifan Wang, Ying Wang, Jinhang Zhu, Yihui Guan, Fang Xie, Xiao Cai, Jiale Deng, Yan Wei, Rongqiao He, Zhuo Fang, Qihao Guo, *Frontiers in Aging Neuroscience*, 30 Nov. 2022, https://www.frontiersin.org/articles/10.3389/fnagi.2022.1046066/full, accessed 30 Nov. 2022.

Summary

Introduction: The accumulation of endogenous formaldehyde is considered a pathogenic factor in Alzheimer's disease (AD). The purpose of this study was to investigate the relationship between urinary formic acid and plasma biomarkers in AD.

Materials and methods: Five hundred and seventy-four participants were divided into five groups according to their diagnosis: 71 with normal cognitive (NC), 101 with subjective cognitive decline (SCD), 131 with cognitive impairment without

mild cognitive impairment (CINM), 158 with mild cognitive impairment (MCI), and 113 with AD.

Results: With the progression of the disease, urinary formic acid levels showed an overall upward trend. Urinary formic acid was significantly correlated with Mini-Mental State Examination (MMSE) scores, the Chinese version of Addenbrooke's Cognitive Examination III (ACE-III) scores, and Montreal Cognitive Assessment-Basic (MoCA-B) time. The areas under the receiver operating characteristic curves (AUC) of urinary formic acid in distinguishing NC from AD was 0.797, which was similar to that of plasma neurofilament light chain (NfL; AUC = 0.768) and better than other plasma biomarkers (Aβ40, Aβ42, Aβ42/Aβ40, T-tau, P-tau181, and P-tau181/T-tau). We also found that using urinary formic acid and formaldehyde levels could improve the accuracy of using plasma biomarkers to determine AD disease stage.

Discussion: Our study revealed the possibility of urinary formic acid as a potential novel biomarker for the early diagnosis of AD.

From: Study Identifies a Urinary Biomarker to Reveal Early-Stage Alzheimer's Disease

Danielle Ellis, *News, Medical Life Sciences*, 30 Nov. 2022, https://www.news-medical.net/news/20221130/Study-identifies-a-urinary-biomarker-to-reveal-early-stage-Alzheimere28099s-disease.aspx, accessed 30 Nov. 2022.

Could a simple urine test reveal if someone has early-stage Alzheimer's disease and could this pave the way for large-scale screening programs? A new study in *Frontiers in Aging Neuroscience* certainly suggests so. The researchers tested a large group of patients with Alzheimer's disease of different levels of severity and healthy controls with normal cognition to identify differences in urinary biomarkers.

They found that urinary formic acid is a sensitive marker of subjective cognitive decline that may indicate the very early stages of Alzheimer's disease. Current methods to diagnose Alzheimer's are expensive, inconvenient, and unsuitable for routine screening. This means that most patients only receive a diagnosis when it is too late for effective treatment. However, a non-invasive, inexpensive, and convenient urine test for formic acid could be just what the doctor ordered for early screening.

"Alzheimer's disease is a continuous and concealed chronic disease, meaning that it can develop and last for many years before obvious cognitive impairment emerges," said the authors. "The early stages of the disease occur before the irreversible dementia stage, and this is the golden window for intervention and treatment. Therefore, large-scale screening for early-stage Alzheimer's disease is necessary for the elderly."

So, if early intervention is important, why don't we already have routine screening programs for early-stage Alzheimer's? The issue lies with the diagnostic techniques that doctors currently use. These include positron emission tomography brain scans, which are expensive and expose the patient to radiation. There are also biomarker tests that can reveal Alzheimer's disease, but these require invasive blood draws or a lumbar puncture to obtain cerebrospinal fluid, which can be off-putting for patients.

However, a urine test is non-invasive and convenient and would be well suited for large-scale screening. While researchers have identified urinary biomarkers for Alzheimer's disease previously, none have been suitable to reveal the early stages of the disease, meaning that the golden window for early treatment remains elusive.

The researchers behind this new study have previously investigated an organic compound called formaldehyde as a urinary biomarker for Alzheimer's. However, there was room for improvement in detecting early-stage disease. In this latest study they primarily focused on formic acid, a metabolic product of formaldehyde, to see if that performed better as a biomarker.

A total of 574 people participated in the study, and participants were either healthy volunteers with normal cognition, or had differing degrees of disease progression, ranging from subjective cognitive decline to fully-fledged disease. The researchers analyzed the participants' urine and blood samples and performed psychological evaluations.

The study found that urinary formic acid levels were significantly increased in all the Alzheimer's groups compared with the healthy controls, including the early-stage subjective cognitive decline group, and correlated with a cognitive decline. This suggests that formic acid could act as a sensitive biomarker for early-stage Alzheimer's disease.

Interestingly, when the researchers analyzed urinary formic acid levels in combination with blood-based Alzheimer's biomarkers, they found that they could more accurately predict what stage of the disease that a patient was experiencing. However, further research is needed to understand the link between Alzheimer's and formic acid.

"Urinary formic acid showed an excellent sensitivity for early Alzheimer's screening," said the authors. "The detection of urine biomarkers of Alzheimer's is convenient and cost-effective, and it should be performed during routine physical examinations of the elderly."

Brief Afterthoughts

Dementia, the risk of which grows as we age, poses a special threat to the cryonicist. We want to be cryopreserved, if we must, with mind and memory intact. Many of us (along with others) when faced with a terminal illness would opt for "death with

dignity" rather than let nature take its course. With dementia this is especially difficult, first, because it is not generally classed as a terminal illness, and second, because, as it progresses, there is the horrifying prospect of our deepening impairment in understanding, memory and judgment. We may lose awareness of our intentions about cryopreservation in the first place, and concurrently, the competence to make decisions that could have hastened it when it was badly needed. Dementia currently is largely untreatable. Research such as that reported here is at least opening new pathways for early detection and, we hope, more effective ways of reducing symptoms and thus aiding our transition to a future, disease-free life. ■

Overcoming Population Arguments to Living Longer

By Max More, Ph.D.

We "cryonauts" look forward to a long future. Whether we hope to survive long enough to beat the aging process or whether we hope to be revived from cryopreservation, we hope and expect to be around many decades from now. For over half a century, one of the main objections we have heard is that the world is overpopulated and will become much more so. In my Getting Better series of articles, I have shown that we are not overpopulated and that life tends to get better over time.

Is overpopulation something we should worry about for the rest of this century and beyond? My answer is no. First of all, more people are not inherently a problem. Each new person comes not just with a mouth to feed but with hands and brains to create and produce. So long as they are not prevented from using their hands and brains, additional people are a positive, not a negative. As economist Julian L. Simon wrote: "The world's problem is not too many people, but lack of political and economic freedom."

Second, even if more people were a problem, that does not justify preventing us from living longer. Third, fears of rapid population growth are badly outdated. [Ehrlich, 1990] Global population growth has been slowing for decades and total global population is projected to peak between the mid-2060s and the 2080s. The population of most developed countries is expected to fall well before then, the only exceptions being countries benefiting from plenty of immigration. Finally, to the extent that we should worry about too many people, we should be far more concerned about birth rates than death rates.

Values first

Let us pretend for a moment that population growth is or will become a serious problem. Would this give us a strong reason for opposing the extension of the human lifespan? No. Opposing extended life because eventually it might add to existing problems would be an ethically irresponsible response. Suppose you are a doctor faced with a child suffering from pneumonia. Would you refuse to cure the child because she would then be well enough to run around and step on the toes of others?

On the contrary, our responsibility lies in striving to live long and vitally and helping others do the same. The more progress we make on this primary goal, the more we can focus our energy on solving other challenges. Long, vital living at the individual level certainly benefits from a healthy physical and social environment. The superlongevity advocate would want to help find solutions to any population issues. But dying is not a responsible or healthy way to solve anything.

If we are to take seriously the idea of limiting lifespan so as to control population, why not be more proactive about it? Why not drastically reduce access to currently commonplace medical treatments? Why not painlessly execute anyone reaching the age of 70? (This would be "retirement" in the sense of the classic SF movie Blade Runner.) Once the collective goal of population growth is accepted as overriding individual choices, it is hard to resist this logic. Some radical green groups have indeed gone the whole way and accepted this result.

Fertility, not longevity, matters

Limiting population growth by opposing life extension not only fails the ethical test, it also fails the pragmatic test. Keeping the death rate up simply is not an *effective* way of slowing population growth. Population growth depends far more on how many children families have than on how long people live. In mathematical terms, longer life has no effect on the exponential growth rate. It only affects the constant of the equation. This means that it matters little how long we live after we have reproduced.

Compare two societies: In country A, people live on average only to 40 years of age, each family producing 5 children. In country B, the lifespan is 90 years but couples have 4 children. Despite the much longer life span in country B, their population growth rate will be much lower than that of country A. It makes little difference over the long term how many years people live after they have had children. The population growth rate is determined by how many children we have, not how long we live.

For the United States (whose population grows faster than Europe), the bottom line was summed in a presentation to the President's Council on Bioethics by Biodemographer S. Jay Olshansky:

> If we achieved immortality today, in other words, if the death rate went down to zero, then the growth rate would be defined by the birth rate. The birth rate would be about 15 per thousand, which means the doubling time would be 53 years, and more realistically, if we achieved immortality, we might anticipate a reduction in the birth rate to roughly ten per thousand, in which case the doubling time would be about 80 years. The bottom line is, is that if we achieved immortality today, the growth rate of the population would be less than what we observed during the post-World War II baby boom. [Olshansky, 2002]

Olshansky and his colleagues also calculated the effect on life expectancy at birth from eliminating various diseases. A cure for cancer would increase life expectancy by about 3.5 years. About the same for elimination of heart disease. If we eliminated all cardiovascular diseases, diabetes and all forms of cancer, life expectancy at birth in humans would reach about 90. Olshansky argues that tackling aging would yield greater life expectancy benefits than tackling these diseases one-by-one.

Biodemographers Leonid Gavrilov and Natalia Gavrilova conducted a sophisticated analysis of the effects of longer life spans on total population. Using Swedish demographic data due to its detail and history, they showed that population effects would be minimal to modest, depending on the specific scenario. Their starting point was a 2005 population of 9 million. Without any intervention, population would fall by one-third by 2105. In "Demographic Consequences of Defeating Aging" [Gavrilov & Gavrilova, 2010], the researchers consider four main scenarios:

1. Negligible senescence after age 60. Median lifespan increases from 84 to 134 years for men and from 88 to 180 years for women but after 100 years the Swedish population would increase by only 22%.

2. Negligible senescence for 10% of the population. Population declines by 28%.

3. Negligible senescence for 10% of the population with growing acceptance leading to 1% added to the negligible senescence group each year and the last 5% refusing these technologies. Instead of a decline from 9 million to 6 million by 210, the population would decline to about 7.9 million. Population declines by 13.5%.

4. Mortality continues to decline after age 60 years down to the levels observed at age 10, and then remaining constant. The population grows by 22% by 2105. If rejuvenation starts at 40 instead of 60, the population will grow by 47%.

The researchers note that the Swedish situation of 2010 reflects the current situation of most advanced nations today. "These numbers suggest that we should not hesitate to push for quite radical extensions of healthy human life span." Extension of healthy lifespan would help to prevent a demographic catastrophe.

Global population growth ending

All projections of the population in 2100 or any year decades from now are estimates based on specified assumptions. Past projections by the UN have been reasonably accurate although they have mostly been revised down over time. The three main sources of future population estimates are the United Nations Population Division; the Wittgenstein Centre in Austria; and the Institute for Health Metrics and Evaluation at Washington University. They each use a distinctive methodology, the second and third being more sophisticated than the UN's. They each also provide different projections by varying assumptions such as (most crucially) fertility rates. I will skip the details and summarize the findings of each.

UN Population Division: According to the World Population Prospects 2022, the world's population is projected to reach a peak of around 10.4 billion people during the 2080s and to fall to 10.35 billion by 2100. The UN report also notes that, today, two-thirds of the global population lives in a country or area where lifetime fertility is below 2.1 births per woman (also known as replacement fertility). The number of people under 25 peaks in the 2030s.

The Wittgenstein Centre: Wolfgang Lutz and colleagues combine expert opinion and statistical modeling. This group uses a more sophisticated model of fertility and life expectancy compared to the UN. A major difference in outcomes results from the Lutz groups' assumption that fertility will continue to fall in sub-Saharan Africa at a similar rate to recent years, whereas the UN assumes a slowdown in that decline. The Wittgenstein Center also assumes, based on expert opinion, that the fertility rate in low fertility countries will converge to 1.75 births per woman, but that this will not be until 2200 (rather than by 2100 as assumed by the UN).

In the Centre's Medium (SSP2) scenario, world population would continue to increase until around 2070-2080 when it would reach a maximum level of around 9.8 billion before starting a slow decline, reaching about 9.5 billion by the end of the century. [Lutz, 2018 & 2108b] If more rapid social development is assumed world population would peak in 2055-2060 at 8.9 billion and decline to 7.8 billion by 2100. With lower female education and higher fertility rates, world population would reach 13.4 billion in 2100.

The fertility rate is affected by major factors. Factors increasing fertility include immigration from higher fertility countries increasing flexibility in work practices, public childcare provision, and local family policies. Factors decreasing fertility include increasing uncertainty in individual life-course planning, expanded education, higher cost of raising children, and acceptance of voluntary childlessness.

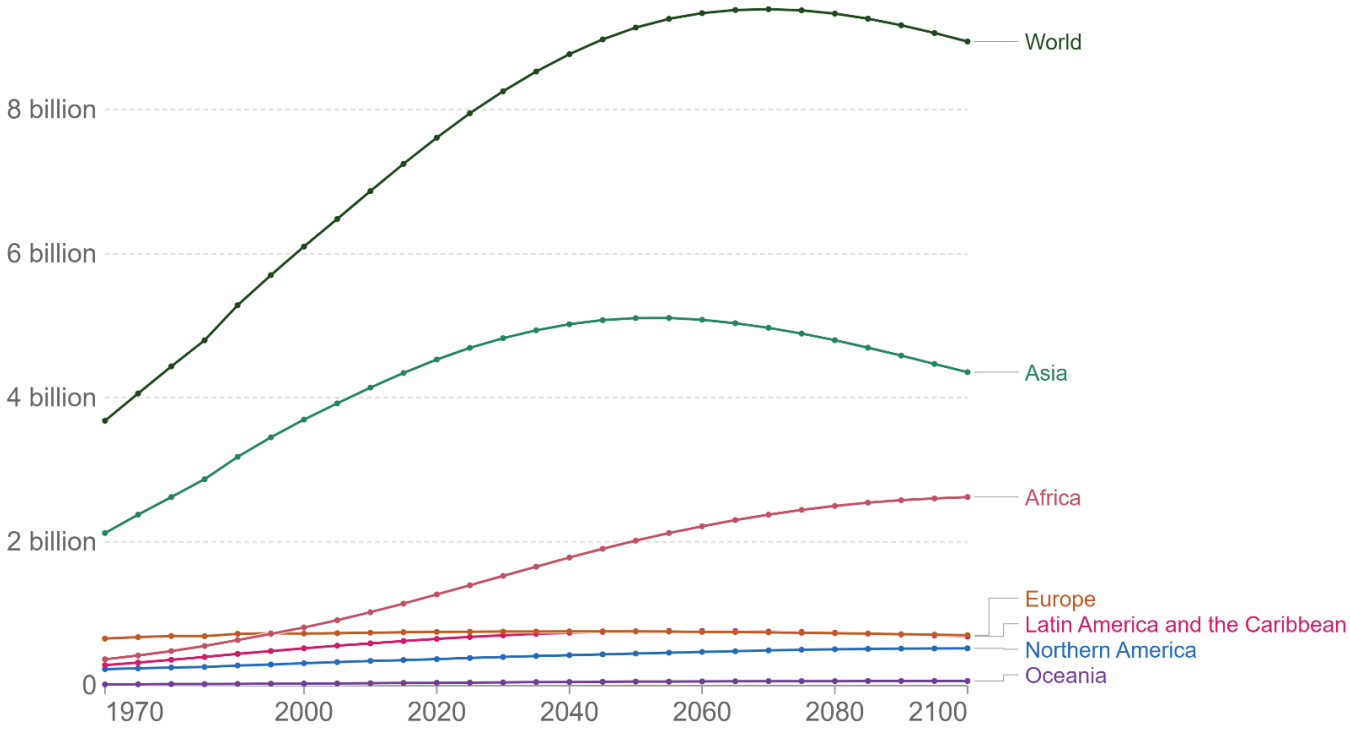
Between the pessimist and the optimistic educational scenarios, the difference in population size by 2060 is over one billion (9.8 vs. 8.9 billion).

In 2010, 117 countries had fertility rates above the replacement level of 2.1. The Center's medium projection finds that there will be only 71 in 2030, 43 in 2050, and 17 in 2060. Of those latter 17, only 5 will have a fertility rate above 2.5. Almost half of the global population now lives in regions with below replacement fertility.

Projections of the world population by the Wittgenstein Centre, 1970 to 2100

Our World in Data

Shown is the SSP2 scenario which is the 'most likely scenario' of the various scenarios WC-IIASA produced. It is based on the medium fertility and medium mortality projections combined with the continuation of educational trends (GET scenario).



Source: Medium SSP2 - Wittgenstein Centre for Demography and Global Human Capital OurWorldInData.org/future-population-growth • CC BY

Europe (EU-28) will reach a maximum of 512 million by about 2035. Eastern Europe will lose about 10% of its population. China's population will be 200 million lower in 2060 than in 2016. India's population will be 31% larger. Most of the growth in population will come from Africa and India.

The Institute for Health Metrics and Evaluation (IHME): The IHME study improves on the UNPD and Wittgenstein forecasts in seven ways. Those seven include better modeling of fertility, the effects of educational attainment, mortality, and migration. [Vollset, 2020] This produced a 2100 global population forecast lower than the Wittgenstein Centre forecast and much lower than the UNPD forecast. The most likely trajectory for world population is a peak just after mid-century and a substantial decline by 2100.

A third of the difference is due to faster reductions in sub-Saharan African fertility and two thirds due to the lower level of fertility expected in populations with below replacement fertility levels, particularly China and India. Some countries with below replacement level fertility, including the USA, Australia, and Canada are likely to maintain the working age population due to net immigration.

	2017 Population	2100 Population	Peak Population
World	7.64 billion	8.758 billion	9.733 billion (2064)
USA	325 million	336 million	364 million (2062)
Canada	36 million	33 million	45 million (2078)
UK	67 million	71 million	75 million (2063)
China	1.412 billion	732 million	1.432 billion (2024)
India	1.381 billion	1.093 billion	1.605 billion (2048)
Japan	128 million	60 million	128 million (2017)
Germany	83 million	66 million	85 million (2035)
Brazil	212 million	165 million	235 million (2043)

Indonesia	258 million	229 million	301 million (2047)
Central Sub-Saharan Africa	122 million	343 million	344 million (2097)
Southern Sub-Saharan Africa	77 million	124 million	125 million (2097)
Western Sub-Saharan Africa	434 million	1.548 billion	1.548 billion (2100)

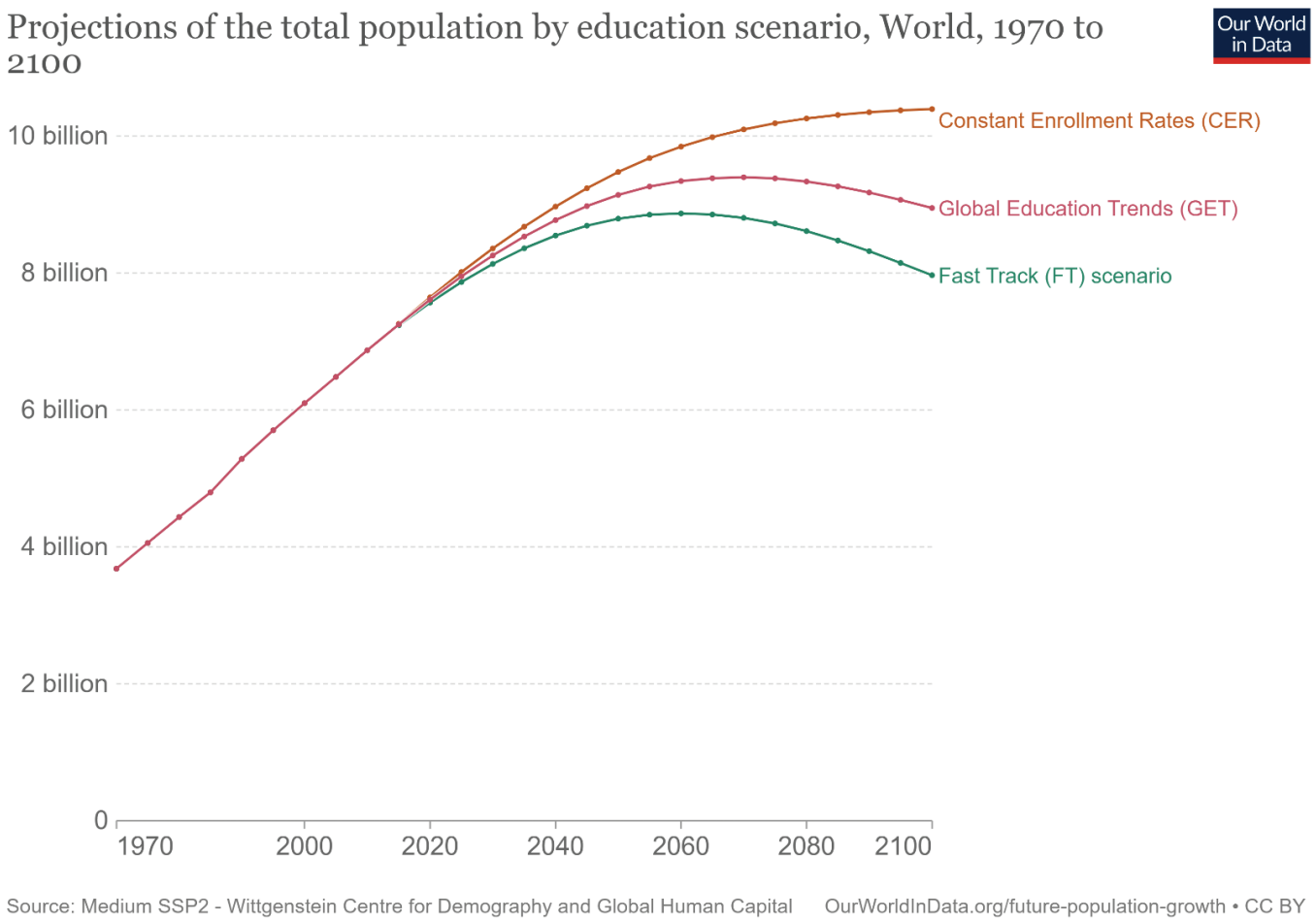
Table adapted from "Population and total fertility rate in 2017, in 2100 with the reference scenario, and in 2100 with the SDG pace scenario and the year of peak population." IHME.

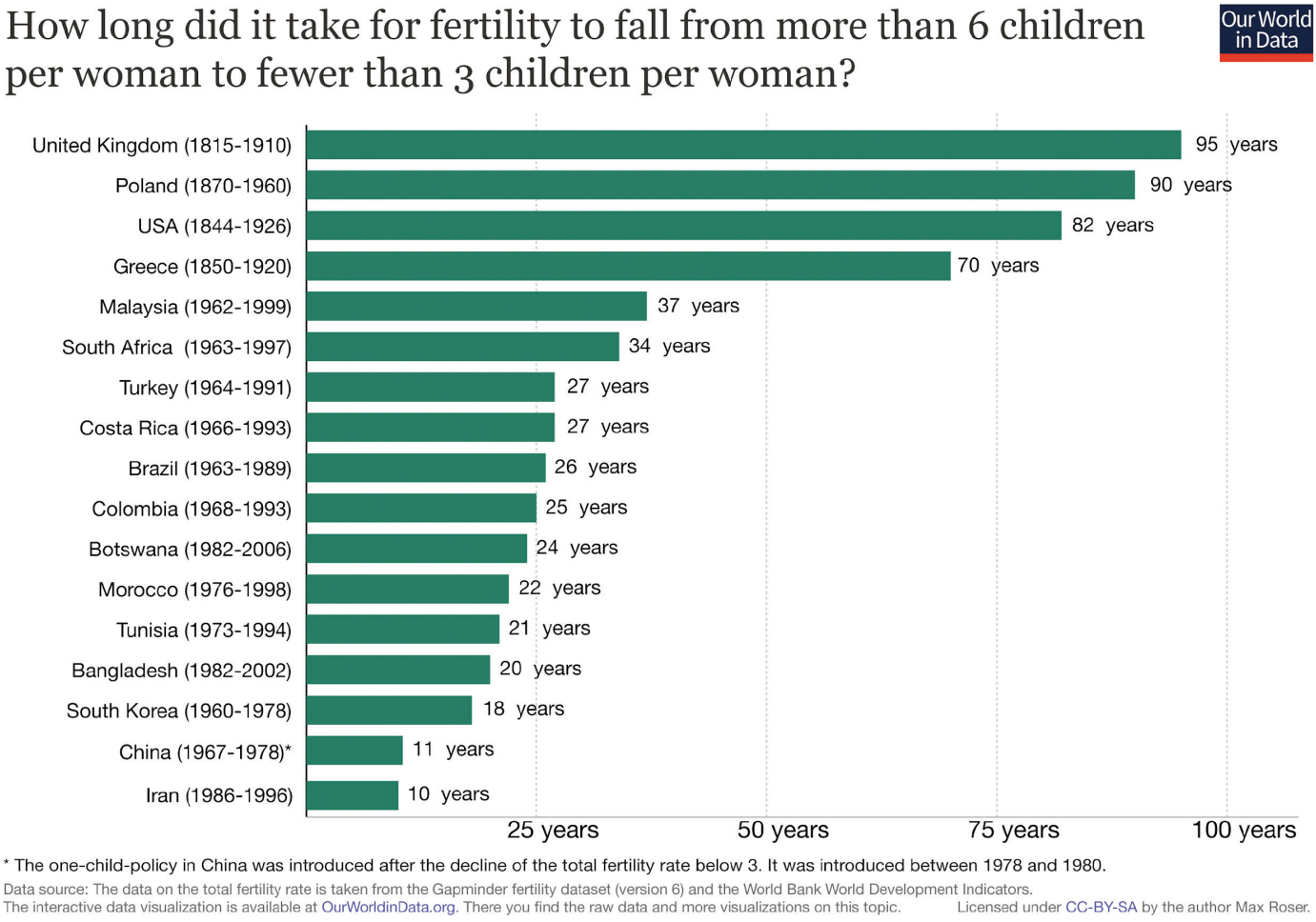
In the most likely scenario, the five largest countries in 2100 would be India, Nigeria, China, the United States, and Pakistan. However, these are not on the same path. Nigeria is expected to continue growing through 2100 but China and India are expected to peak before 2050 and then decline steeply. (More recent numbers suggest that China may have peaked already.) By 2100, China would be down to 51.1% of its peak population and India to 68.1% of its peak. The USA is projected grow its population until mid-century and then decline by less than 10% of the peak by 2100.

Like Japan in the 1980s, many people in the US have worried about the rise of China. The economic rise of China has been slowing as people have been drawn from agriculture to the cities. But now that shift is slowing and the fertility rate has plummeted. Many people point to the one-child policy as an example of effective (too effective) central planning. In fact, the one-child policy was introduced in 1978-80, *after* fertility had declined from 6 to less than 3. So, it truly is a good example of central planning – and its failure. Current attempts to reverses the trends are failing.

The Africa wild card

Projections for the developed world can be made with considerably more confidence than those for Africa. You can see this in the difference between the UN and University of Washington projections, with the former expecting almost a tripling of Africa's population by 2100 and the latter only a doubling. The IHME projects also show a wide range of outcomes depending on various factors affecting fertility.





We do not know yet whether fertility rates in Africa will follow those in the rest of the world. The UW projections see Africa reaching a fertility rate below 2 by the 2070s under the medium assumptions. Population panickers seem to be unaware of how rapidly fertility rates have fallen since the peak in the late 1960s.

The next most populous country today is India. Its population is projected to grow until mid-century. This is highly likely given that the number of children in India peaked more than a decade ago and is now falling.

Going down

Despite their differing models and projections, the three major forecasters all see global population growth slowing and the population aging by the end of this century. The Wittgenstein Centre, the Washington University researchers differ from the UNPD in expecting global population to age faster, peak sooner and then decline faster. Some other conclusions from the IHME projections:

- By 2100, fertility will fall below the level required to maintain population in 183 out of 195 countries. This would change only if those countries adopted more open immigration policies. However, obviously more migration cannot affect the world population.
- Global population will peak in 2064 at around 9.7 billion people and then decline to 8.8 billion by 2100.
- 23 countries, including Japan, Italy, Spain, Portugal, and Thailand, will experience a population decrease of more than 50% by 2100.
- Countries whose population will shrink by 25% to 50% include China. Many of the countries with the fastest-shrinking population will be in Asia and Eastern Europe.
- Working age populations will shrink faster than total population in countries such as China and India, with major economic implications.
- The combined population of Europe (excluding the UK), China, Russia, Japan, South Korea, and Taiwan will start falling before 2030.

- Even with an assumed increase in fertility rates, the populations of China, the EU, Russia, and Japan will decline sooner and more rapidly than the USA. Thanks to higher net migration, the population of the USA is projected to keep growing for another half century despite its below replacement fertility rate.

Causes of slowing population growth

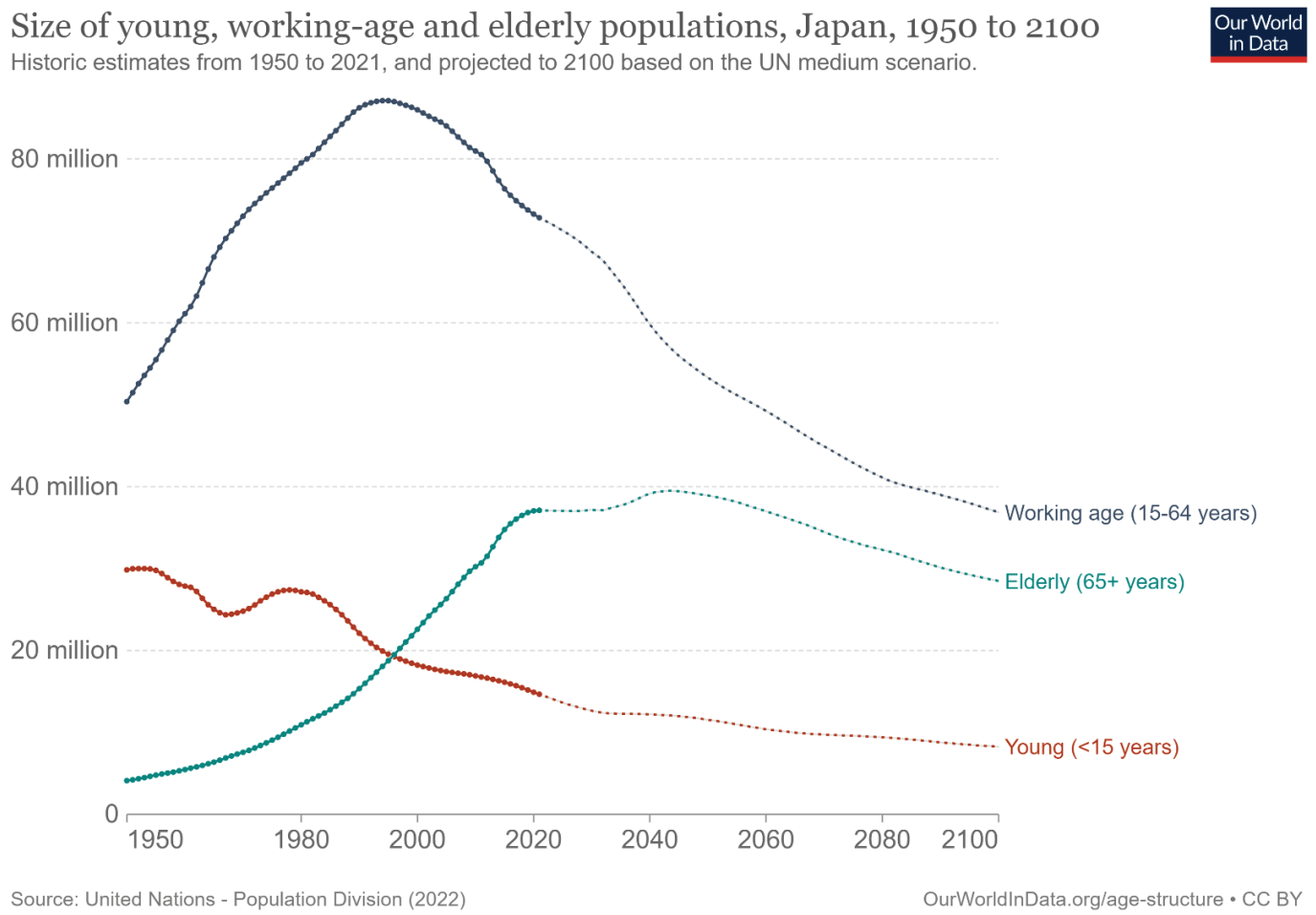
Unfortunately, a peak and then falling population looks inevitable in a world lacking dramatic life extension. Numerous factors are conspiring to depress fertility and therefore population. Population aging reduces fertility by reducing the number of potential mothers. In developing countries, children shift from being producers to being consumers. Raising children becomes increasingly expensive. Ideal family size is shrinking as it is linked to the smaller family size of earlier cohorts. Higher incomes and educational levels lead to delayed or canceled childbearing.

Economic challenges of declining population

With a growing population comes a growing market, more specialization and division of labor (a key driver of productivity), and more innovation. Governments can reduce or prevent these benefits through constant war and by failing to protect property rights. So long as sufficient legal and cultural protections exist, a growing population will generate these vital benefits. [Simon, 1990; 1997; 2019]

Must a falling population therefore suffer decreasing wealth, well-being, and opportunity? We have relatively little experience of gradually falling populations and the economic outcomes. Most major reductions in population historically have been sharp and severe, resulting from war, disease, or mass starvation. A more gradual and predictable decline should be more manageable. Even so, there are clear downsides, at least assuming similar economic policies as those existing today.

More economically significant than a shrinking total population is a reduction in the working age population. The "dependency ratio" is the ratio between people defined as dependents (under-15s and over-65s) and working-age people. In countries such as Nigeria, the dependency ratio is projected to fall through the end of this century. This means the country's working population has fewer people to support potentially resulting in more rapid economic growth, an effect called the "demographic dividend." The full extent of this dividend is not automatic. In India the



dependency ratio fell from almost 80% in 1970 to less than 50% today but it failed to enjoy the full benefits because deficiencies in education and health in addition to poor job creation has limited growth in the labor market.

In many of the more advanced economies, the dependency ratio is projected to rise throughout this century. This will be a major issue in Europe and more so in China. You can see this especially vividly in Japan.

In Japan, as in most advanced nations, the demographic over 65 will grow. Since the youthful group is not expected to change significantly, the working age demographic will shrink. For each person of working age, more will be spent on medical and retirement expenses. This may be paid partly by higher taxation with its growth-suppressing effects, or by increased borrowing which can increase inflation and raise the cost of capital, thereby slowing growth with all its benefits.

If people enjoyed more years of healthy life, the dependency ratio would be held down. A rapid enough increase in healthy lifespan would enable societies to thrive despite static or declining populations.

Also, speculatively but increasingly plausibly, artificial general intelligence (AGI) may help to compensate for a shrinking working age population. This could help not only with taking the place of unavailable workers but in taking care of older, infirm people. Japan is investing heavily in robotics to this end.

The imperative to further extend the human lifespan

Even if there were a population problem in a few countries, extending the human life span would worsen the problem no more than would improving automobile safety or worker safety, or reducing violent crime. Who would want to keep these deadly threats high in order to combat population growth? If we want to slow population growth, we should focus on reducing births, not on raising or maintaining deaths. If we want to reduce births, we might voluntarily fund programs to provide contraceptives and family planning to couples in poorer countries. This will aid the natural developmental process of choosing to have fewer children.

Consider, also, that with a very high probability, the first truly effective technologies to extend the maximum human life span will come with a significant cost of development and application. Population effects would first be felt, therefore, in the developed countries where populations are already peaking or declining. This highlights the falsity of the idea that extended lifespans would dramatically increase population. Increased longevity would have little effect on global population, especially considering the small and falling share of the global population accounted for by the developed nations.

As we have seen, the world does not have a problem of too many people now or in the future. The real problem is a static and declining population that is aging and infirm. Investment in life extending measures would therefore have a massive payoff economically in addition to saving lives. A 2008 McKinsey Global Institute study titled "Why the Baby Boomers Will Need to Work Longer" pointed out that "A two-year increase in the median retirement age over the next decade would add almost $13 trillion to real US GDP during the next 30 years." [Beinhocker, 2008]

Suppose that we were to eliminate major diseases including heart disease, cancer, and stroke. Demographers have calculated that eliminating cancer would increase life expectancy at birth by only about 3.5 years. A cure for heart disease would have a similar effect. If you do not die of one thing, you will die of something else. It turns out that if you eliminated all cardiovascular diseases, diabetes, and all forms of cancer together, life expectancy at birth in humans would rise from just over 72 globally or 77.2 in the USA (2021) to about 90. That's a welcome but surprisingly modest increase. [Goldman, 2013; [Olshansky, 2002]

The same researchers, using the Future Elderly Model, found that if we delayed aging and increased life expectancy by 2.2 years of mostly good health, the increase in economic value would be $7.1 trillion (2010 dollars) over 50 years. Imagine the benefits from 10, 20, or 50 extra years of good health. By contrast, tackling heart disease or cancer separately produces diminishing improvements in health and lifespan by 2060 primarily because of exchanging one risk for another.

Simply extending healthy life spans without making any other changes will produce massive benefits but also massive costs, as shown below. That would be an unrealistic scenario given that we have already responded to longer lives by delaying the retirement age. The green line in the chart shows the effect on major entitlement spending of a 2.2 year extension in life while adjusting eligibility for tax-funded benefits. That chart concerns only entitlement spending and does not include the enormous benefits of increased economic output.

Remember the study by Gavrilov and Gavrilova: They concluded that even in the event of a successful biomedical triumph over aging, "population changes are surprisingly slow in their response to a dramatic life extension." Their modest life extension scenarios still led to a declining population. Even the more radical scenarios increased population only modestly and that only happens by unrealistically assuming that every person in the country adopts anti-aging technologies. If some reject these technologies for reasons of religion, inconvenience, non-compliance, fear of side effects, or costs, the total population could still decline over time.

For the United States (whose population grows faster than Europe), the bottom line was summed in a presentation to the President's Council on Bioethics by S.J. Olshansky. In his

Life Extension & Population Factsheet

Population in most developed countries has stopped growing or is shrinking.

Global population is projected to peak between 2064 and the 2080s and then decline. Global population will peak in 2064 at around 9.7 billion people and then decline to 8.8 billion by 2100.

By 2100, fertility will fall below the level required to maintain population in 183 out of 195 countries (94%).

23 countries, including Japan, Italy, Spain, Portugal, and Thailand, will experience a population decrease of more than 50% by 2100.

The combined population of Europe (excluding the UK), China, Russia, Japan, South Korea, and Taiwan will start falling before 2030.

The wealthier countries, which are those most in need of more people of productive age, are the ones that will first have life extension. Countries with higher fertility rates will probably not enjoy significant life extension until fertility slows down and GDP is higher.

Fertility, not longevity, makes a big difference. Countries below replacement levels, if they gradually adopt radical life extension, will slow down their population loss and perhaps reverse it modestly.

If we stopped aging today, the population would grow more slowly than it did during the post-World War II baby boom.

Increasing healthy life expectancy by 50 years would increase economic value over 75 years by $242 trillion.

In functional economies, more people are not inherently a problem. Each new person contributes a brain and produces and creates. Growing populations tend to be healthier.

An aging population means a rising dependency ratio which is an economic strain. More years in good health can help.

scenario, the death rate went down to zero while the birth rate started at about 15 per thousand and declined to 10 per thousand. "The bottom line is that if we achieved immortality today, the growth rate of the population would be less than what we observed during the post-World War II baby boom." This would mean a doubling time of 80 years. [Olshansky, 2002]

I have been writing on the topic of population trajectories for over 40 years. [More, 1978, 1997, 2004, 2014] The typical view I have encountered has remained stubbornly unchanged in that time – even as it becomes increasingly distant from the current reality and the most plausible projections. I see a confusion of population with problems created by corruption, authoritarianism, economic ignorance and mismanagement, and warfare.

The confused population-based objection to life extension and cryonics is our perennial enemy. Let us continue to overcome that enemy with informed persuasion. Once the enemy belief vacates the minds it occupies, more people will be open to accepting and supporting our desire to enable everyone to live much longer, healthier lives. ■

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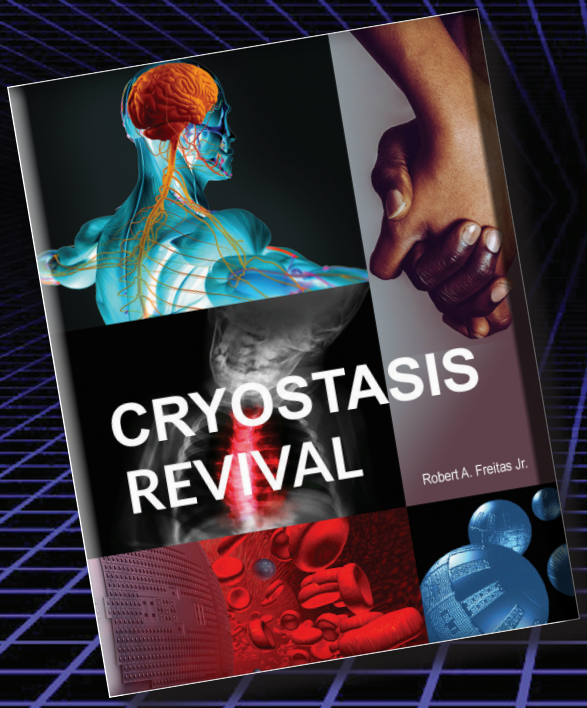
New Book by Robert A. Freitas Jr.

Cryostasis Revival: The Recovery of Cryonics Patients through Nanomedicine



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

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

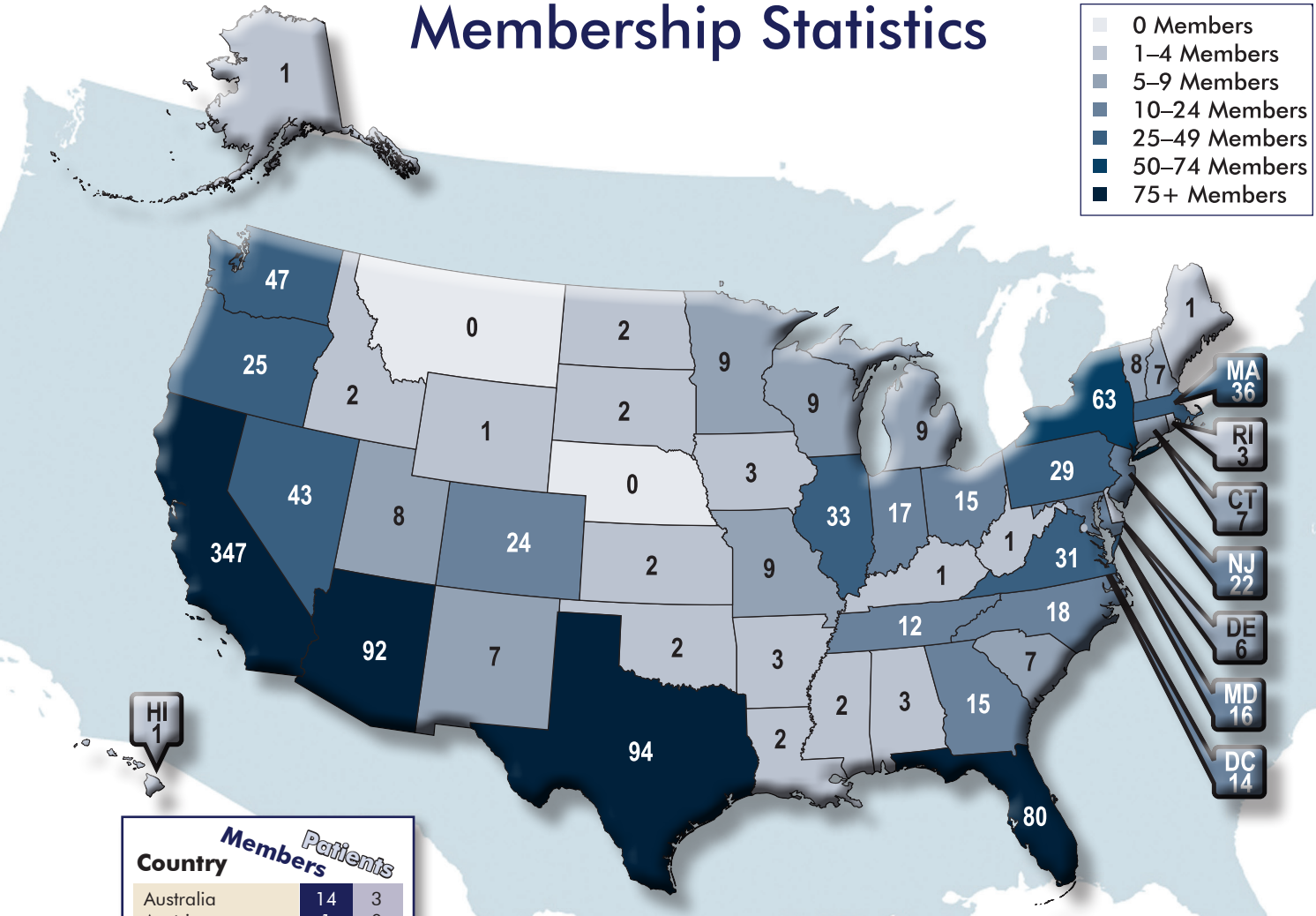
"Future repair and revival of damaged cryopreserved tissue has been the subject of speculation for decades. This book by a nanomedicine expert examines the problem in detail far beyond anything ever written before. With more than 3000 references, it's both wide-ranging and intensely specific about diverse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

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

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

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

Membership Statistics

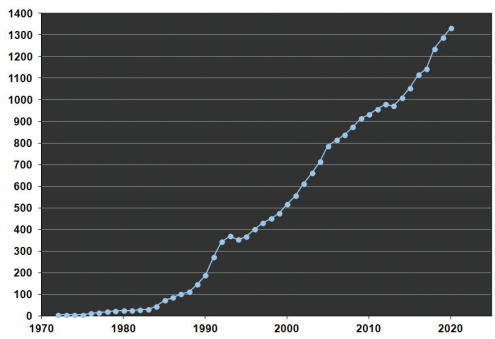


International Members & Patients

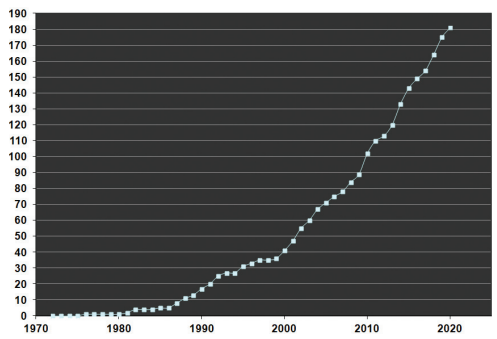
Country	Members	Patients
Australia	14	3
Austria	1	0
Belgium	1	0
Brazil	1	0
Bulgaria	1	0
Canada	67	5
China	0	1
Croatia	1	0
Finland	1	0
France	2	1
Germany	18	0
Hong Kong	2	0
Hungary	1	0
Israel	1	1
Italy	1	0
Japan	6	0
Luxembourg	1	0
Mexico	5	0
Monaco	1	0
Netherlands	1	0
New Zealand	2	0
Norway	2	0
Poland	1	0
Portugal	5	1
Puerto Rico	3	0
Slovenia	1	0
Spain	4	1
Sweden	1	0
Switzerland	7	0
Taiwan	1	0
Thailand	3	1
United Kingdom	48	4
Virgin Islands	1	0
TOTAL	205	18

2022	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Cryo Members	1380	1384	1389	1392	1393	1398	1401	1403
Basic Members	5	15	18	19	27	30	32	32
Patients	191	193	194	198	200	201	201	203
Assoc./Apps	238	228	239	263	253	233	230	232
TOTAL	1814	1820	1840	1872	1873	1862	1864	1870

As a consequence of the transition to a new membership model, complete numbers are only available starting from May 2022 for this year.



Number of Alcor members



Number of Alcor patients

Alcor Longevity Circle of Distinguished Donors

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

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

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

Support Alcor's **RAPID** Research

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

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

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

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

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

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

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

Fight Aging!

Reports From the Front Line in the Fight Against Aging

Reported by Reason

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

The Path to the Clinic for First Generation Senolytic Therapies

August 2022

Senolytic therapies selectively destroy lingering senescent cells in old tissues, improving health as a result. Senescent cells, while never very large in absolute numbers, even in late life, actively maintain a degraded state of tissue and organ function via secretions that provoke chronic inflammation, detrimental alterations to the behavior of normal cells, and harmful remodeling of tissue structure, such as the development of fibrosis. A large number of animal studies have demonstrated rapid rejuvenation and reversal of aspects of specific age-related conditions to result from clearance of senescent cells. The best of the early senolytic approaches, small molecule drugs and plant extracts that sabotage senescent cell resistance to apoptosis, such as the dasatinib and quercetin combination, manage to destroy as many as half of the senescent cells in a given tissue, with the degree of clearance varying widely between therapies and tissues.

Given the animal data, which is far and away the most robust and impressive of all of the approaches to the treatment of aging attempted to date, there is an enthusiasm for human clinical trials. Unfortunately, these early small molecule drugs are largely off-patent or close to it, and so near all of the sizeable funding in the field goes towards the development of new, patentable senolytic therapies rather than the validation of existing low-cost treatments that might be more rapidly brought to the clinic. Still, a number of clinical trials of early, low-cost senolytic drugs are ongoing, as noted by the authors of this open access paper. In the years ahead, those will be joined by the second generation senolytic therapies under development, hopefully at least marginally better as a result of the effort put into their development, and what has been learned to date about the ways in which early senolytics work. This is all moving far too slowly, however!

Epigenetic aging: Biological age prediction and informing a mechanistic theory of aging

Cellular senescence and senolytics: the path to the clinic

The elimination of senescent cells has emerged as a plausible therapeutic strategy for preventing, delaying, or alleviating multiple diseases and age-related dysfunction. Promising results of senolytics in preclinical models suggest therapeutic and preventive opportunities for delaying multimorbidity and increasing healthspan. A key priority should be the identification of reliable, sensitive and specific gerodiagnostics – biomarkers to quantify senescent cell abundance, the senescence-associated secretory phenotype (SASP), and senolysis as well as other pillars of aging.

Fundamental aging mechanisms can be grouped into so-called hallmarks or 'pillars' of aging; these include genomic instability, progenitor cell exhaustion/dysfunction, telomeric and epigenetic changes, dysregulated protein homeostasis, altered nutrient sensing, mitochondrial dysfunction, altered intercellular communication, chronic low-grade inflammation, fibrosis, microbiome dysregulation and cellular senescence. The Geroscience Hypothesis holds that these pillars of aging, including cellular senescence, tend to progress in concert and may be root-cause contributors to the pathophysiology of multiple diseases, age-related dysfunction and loss of resilience. The Unitary Theory of Fundamental Aging Mechanisms builds on the Geroscience Hypothesis by positing that interventions targeting any one fundamental mechanism may target the others. For example, interventions that target cellular senescence tend to attenuate other fundamental aging mechanisms leading to reduced inflammation, attenuated exhaustion of progenitors, decreased fibrosis, alleviated mitochondrial dysfunction, and a partially restored microbiome in experimental animal models of aging and chronic diseases

Based on promising results in preclinical models, over 20 clinical trials of senolytic therapies are completed, ongoing or

planned. Because side effects of senolytics in humans are not yet fully known, and to maximize benefit-risk ratios, the first clinical trials are underway in patients with serious health conditions, such as diabetic kidney disease, Alzheimer's disease, frailty and idiopathic pulmonary fibrosis (IPF). The first in-human trial of senolytics (dasatinib and quercetin, D + Q), the Hematopoietic Stem Cell Transplant Survivors Study, is still underway (NCT02652052; first patient dosed on 1 April 2016). The first senolytic clinical trial published was an open-label pilot study in which 14 patients with IPF were treated with intermittent D + Q on 3 days per week for 3 weeks. Results suggested that senolytics improved physical function in these frail patients. Furthermore, post hoc analysis of a study involving 20 patients with IPF showed that urine levels of the 'geroprotective' factor α-Klotho were higher after oral D + Q than before treatment. In an open-label phase 1 pilot study in 9 patients with diabetic kidney disease, a 3-day course of oral D + Q was sufficient to decrease adipose tissue senescent cell burden, inflammation, fibrosis and circulating SASP factors for at least 11 days after the last dose of senolytics, indicating target engagement and suggesting that an intermittent dosing regimen may be effective in humans.

These early data warrant evaluation in larger randomized, double-blind, placebo-controlled trials for senescence-associated disorders and diseases, some of which are underway.

Link: https://www.nature.com/articles/s41591-022-01923-y

Epigenetic Aging Slows During Hibernation in a Common Bat Species

August 2022

This open access paper on epigenetic age and hibernation in bats makes an interesting companion piece to similar research into marmots from earlier in the year. It seems that hibernation may slow epigenetic aging in a range of species, though it may not be enough to explain differences in life span between all similar hibernating and non-hibernating species. Nonetheless, researchers have for some years shown interest in the biochemistry of hibernation in the context of aging. It remains to be seen what there is to learn here, and whether it can form the basis for therapies or enhancements in human medicine.

Comparative analyses of bats indicate that hibernation is associated with increased longevity among species. However, it is not yet known if hibernation affects biological ageing of individuals. Here, we use DNA methylation (DNAm) as an epigenetic biomarker of ageing to determine the effect of hibernation on the big brown bat, Eptesicus fuscus. First, we compare epigenetic age, as predicted by a multi-species epigenetic clock, between hibernating and non-hibernating animals and find that hibernation is associated with epigenetic age. Second, we identify genomic sites that exhibit hibernation-associated change in DNAm, independent of age, by comparing samples taken from the same individual in hibernating and active seasons.

This paired comparison identified over 3000 differentially methylated positions (DMPs) in the genome. Genome-wide association comparisons to tissue-specific functional elements reveals that DMPs with elevated DNAm during winter occur at sites enriched for quiescent chromatin states, whereas DMPs with reduced DNAm during winter occur at sites enriched for transcription enhancers. Furthermore, genes nearest DMPs are involved in regulation of metabolic processes and innate immunity. Finally, significant overlap exists between genes nearest hibernation DMPs and genes nearest previously identified longevity DMPs. Taken together, these results are consistent with hibernation influencing ageing and longevity in bats.

In conclusion, application of a multi-species bat epigenetic clock provides strong evidence that hibernation is associated with slower epigenetic ageing. The multi-species clock explains 94% of the variation in the chronological ages of both hibernating and non-hibernating big brown bats; however, the clock estimates are equal to or greater than the chronological age, suggesting big brown bats age slightly faster than a 'typical' bat, especially during the active period.

Link: https://doi.org/10.1098/rspb.2022.0635

First Generation Stem Cell Therapies Remain Comparatively Poorly Understood

August 2022

We are something like thirty years into the increasingly widespread use of first generation stem cell therapies. Cells are derived from a variety of sources, processed, and transplanted into patients. Nearly all of these transplanted cells die, but while they survive they secrete signals that suppress inflammation and encourage native cells to change their behavior for the better. It is fair to argue that these treatments have not yet realized the potential originally hoped for, the robust regeneration of damaged tissues. While suppression of inflammation is reliably achieved, regeneration and restored function for organs occurs in only some patients, and to a varying, modest degree.

More generally, not enough is known of how these therapies produce beneficial effects, or of the way in which cells interact in these circumstances. That leads to discussions such as the one offered in this open access paper, in which clinicians look over their data to make the empirical observation that some sources

of cells are better than others for treating specific conditions. Why this might be the case, or even whether it would still be the case in broader datasets, is an open question. Too little is known, much more research is needed, and this is the case decades into the development of this field!

If the original vision for cell therapies is to be realized, then the future of this field must be one in which the challenges of cell survival and cell integration into tissues are solved, allowing the wholesale replacement of damaged and dysfunctional stem cell populations. This may require the rejuvenation of tissues that make up stem cell niches, as at least some of the evidence accumulated to date suggests that stem cell populations can be functional, even in later life, if only protected from age-related changes in the signaling environment provided by the niche and surrounding tissues. That is a somewhat harder problem to solve than issues involving the transplanted cells themselves. But at the end of the day, defeating the challenges of stem cell therapies may require defeating the challenges of degenerative aging.

Stem cell-based therapy for human diseases

From a cellular and molecular perspective and from our own experience in a clinical trial setting, adipose-derived mesenchymal stem cells (AD-MSCs), bone marrow-derived MSCs (BM-MSCs) and umbilical cord derived MSCs (UC-MSCs) exhibit different functional activities and treatment effectiveness across a wide range of human diseases. In this paper, we have provided up-to-date data from the most recently published clinical trials conducted in neuronal diseases, endocrine and reproductive disorders, skin regeneration, pulmonary dysplasia, and cardiovascular diseases. The implications of the results and discussions presented in this review and in a very large body of comprehensive and excellent reviews as well as systematic analyses in the literature provide a different aspect and perspective on the use of MSCs from different sources in the treatment of human diseases.

We strongly believe that the field of regenerative medicine and MSC-based therapy will benefit from active discussion, which in turn will significantly advance our knowledge of MSCs. Based on the proposed mechanisms presented in this review, we suggest several key mechanistic issues and questions that need to be addressed in the future:

1. *The confirmation and demonstration of the mechanism of action prove that tissue origin plays a significant role in the downstream applications of the originated MSCs.*

2. *Is it required that MSCs derived from particular cell sources need to have certain functionalities that are unique to or superior in the original tissue sources?*

3. *As mechanisms may rely on the secretion of factors from MSCs, it is important to identify the specific stimuli from the wound environments to understand how MSCs from different sources can exhibit similar functions in the same disease and whether or not MSCs derived from a particular source have stronger effects than their counterparts derived from other tissue sources.*

4. *Should we create "universal" MSCs that could be functionally equal in the treatment of all diseases regardless of their origin by modeling their genetic materials?*

5. *Can new sources of MSCs from either perinatal or adult tissues better stimulate the innate mechanisms of specific cell types in our body, providing a better tool for MSC-based treatment?*

6. *A potential 'priming' protocol that allows priming, activating, and switching the potency of MSCs from one source to another with a more appropriate clinical phenotype to treat certain diseases. This idea is potentially relevant to our suggestion that each MSC type could be more beneficial in downstream applications, and the development of such a "priming" protocol would allow us to expand the bioavailability of specific MSC types.*

From our clinical perspective, the underlying proposal in our review is to no longer use MSCs for applications while disregarding their sources but rather to match the MSC tissue source to the application, shifting from one cell type for the treatment of all diseases to cell source-specific disease treatments. Whether the application of MSCs from different sources still shows their effectiveness to a certain extent in the treatment of diseases or not, the transplantation of MSCs derived from different sources for each particular disease needs to be further investigated, and protocols need to be established via multicentre, randomized, placebo-controlled phase II and III clinical trials.

Link: https://www.nature.com/articles/s41392-022-01134-4

A Better Way of Measuring Senescent Cell Burden Across Tissues and Species

August 2022

Researchers here propose a better way of measuring the burden of cellular senescence in aged tissues, one that works well across different tissues and species. It is complicated, involving expression of many genes, but the existing simple metrics, such as measurement of senescence-associated beta-galactosidase levels, are increasingly thought inadequate to the task. Senescent cells likely vary in character and metabolism between tissues in ways that have become meaningful now that researchers are past the period of early validation of therapies targeting senescent cells. Now it is important to obtain a much better idea as to the

effectiveness of various potential treatments in mice or humans than is presently the case.

Cellular senescence is now recognized as a fundamental mechanism of aging in animals and humans. Senescent cells can develop a senescence-associated secretory phenotype (SASP), consisting of pro-inflammatory cytokines, chemokines, extracellular matrix-degrading proteins, and other factors that have deleterious paracrine and systemic effects. Further, because senescent cells accumulate in multiple tissues in temporal and spatial synchrony with age-associated functional decline in both animals and humans, they have been hypothesized to drive the deterioration linked to numerous chronic diseases. Importantly, the SASP as a feature of cellular senescence represents not just a locally or systemically detrimental set of factors that, in the aging organism, cause physical, metabolic, and cognitive decline, but is also a therapeutic target of interest. Thus, given the broad availability of next-generation sequencing, there is considerable interest in monitoring responses to senolytic treatments. However, this has been challenging, especially at the single cell level. In part, this is due to an imprecise definition of the heterogeneous population of senescent cells and their associated SASP which complicates appropriate monitoring of senescent cell clearance.

Due to variations in the composition of a "senescence gene set" in the current literature, in the present study we sought to identify commonly regulated genes in various age-related datasets in a transcriptome-wide approach that included whole-transcriptome as well as single cell RNA-sequencing (scRNA-seq). Based on an extensive review of the literature, we defined a panel of 125 genes as our senescence gene set ("SenMayo"), which we then validated in our own as well as publicly available datasets of tissues from aged humans and mice, including changes in this gene set following the clearance of senescent cells. Recognizing the difficulty of identifying senescent cells within scRNA-seq analyses, we next applied SenMayo to available scRNA-seq data from human and murine bone marrow/bone hematopoietic and mesenchymal cells, ascertained the identity of the senescent cells in these analyses, and characterized the communication patterns of senescent hematopoietic or mesenchymal cells with other cells in their microenvironment. Finally, we experimentally validated key predictions from our in silico analyses in a mouse model of aging and following genetic clearance of senescent cells.

Link: https://doi.org/10.1038/s41467-022-32552-1

More Evidence Against Herpesvirus Infection as a Meaningful Contribution to Alzheimer's Disease

September 2022

There is a continuing debate over the role of persistent viral infection in the development of neurodegenerative disease. It seems plausible that such infection could increase chronic inflammation, and inflammation in brain tissue is a hallmark of neurodegenerative conditions. Just because the mechanism exists doesn't mean it is the primary, or even important, component of the disease process however. This is ever the challenge in complex age-related diseases, determining which of the many mechanisms in play are in fact those that primarily cause the condition. So there is a back and forth of epidemiological studies in recent years, attempting to settle the role of viral infection, particularly by herpes viruses, in neurodegenerative conditions such as Alzheimer's disease. At present neither side has a convincing advantage in weight of evidence, which suggests that there may be a more complex set of interactions going on under the hood.

The causes of Alzheimer's disease are not fully understood. There are clear associations with the accumulation of abnormal proteins in the brain, beta-amyloid and tau. There is also clear evidence of neuroinflammation, and there appears to be evidence of immune dysfunction in microglia, a type of immune cell found within the brain. One recurring theory is that herpes viruses, which are responsible for cold sores, genital herpes and other infections, might cause Alzheimer's disease.

However, researchers studying 1,009 participants in the Baltimore Longitudinal Study of Aging (BLSA) have found that while symptomatic herpes viruses were associated with neurological and cognitive symptoms, there was no evidence to support the long-held theory that they are linked to Alzheimer's disease. The participants who were diagnosed with herpes had higher cognitive scores at the beginning of their participation but demonstrated greater longitudinal decreases in attention performance. The study did not find a link between herpes virus infection and the volume of total brain or gray matter, or in areas associated with Alzheimer's disease. Of the total participants, 119 had a record of symptomatic herpes infection. These infections were linked to longitudinal decreases in white matter volume, particularly in the temporal lobe. Being treated with antivirals slowed the declines in occipital white matter.

Link: https://www.biospace.com/article/study-symptomatic-herpes-viruses-linked-to-brain-changes-but-not-alzheimer-s/

Using the Peripheral Nervous System as a Source of Cells for Central Nervous System Regeneration

September 2022

It is in principle possible to obtain cells from the peripheral nervous system that may, once cultured and expanded in number, and possibly altered in their behavior via the application of suitable signal molecules, produce regeneration in the brain or other portions of the central nervous system. The peripheral nervous system is more readily accessed than the central nervous system, and this is the big point in favor of searching the periphery of the body for cells that might be useful in areas of the more protected, less accessible inner body.

With a steadily aging population there is an increasing prevalence of neurological disorders. Given the lack of effective treatment strategies and a limited ability for the central nervous system (CNS) to regenerate endogenously, there is a critical need to better understand exogenous strategies for nervous system repair. Stem cell therapy offers a promising approach to promote the repair of neurologic tissue and function, however studies to date have been limited by various factors including challenges in harvesting donor cells from the CNS, ethical concerns regarding use of embryonic or fetal tissue, tumorigenic potential of induced pluripotent stem cells, and immune-mediated rejection of non-autologous cell sources.

Here we review and propose two alternative sources of autologous cells derived from the peripheral nervous system (PNS) for CNS repair: enteric neuronal stem cells (ENSCs) and neural crest-derived Schwann cells found in subcutaneous adipose tissue (termed SAT-NSCs). ENSCs can be successfully isolated from the postnatal enteric nervous system, propagated in vitro, and transplanted successfully into models of CNS injury via both direct intracerebral injection and systemic tail vein injection. Similarly, SAT-NSCs can be readily isolated from both human and mouse adipose tissue and, although not yet utilized in models of CNS injury, have successfully been transplanted and restored function in models of colonic aganglionosis and gastroparesis. These unique sources of PNS-derived autologous cells offer an exciting option for stem cell therapies for the CNS as they have proven neurogenic potential and eliminate concerns around tumorigenic risk, ethical considerations, and immune-mediated rejection.

Link: https://doi.org/10.3389/fnins.2022.970350

The Hevolution Foundation Plans to Fund Aging Research and the Longevity Industry

September 2022

Funding for aging research and the development of therapies to treat aging as a medical condition used to be hard to come by. It was a fringe field of medicine. But slow years of bootstrapping incremental progress – hard work, patient advocacy, and philanthropy – eventually led to technology demonstrations, such as the rejuvenation of mice with senolytic therapies, that convinced the first large sources of funding to enter the field. That produced further progress, and the start of a longevity industry, enough to convince deeper pockets to participate. That in turn made slowing and reversing aging a viable investment for a growing number of sizable sources of wealth.

History teaches us to be cautious about newly announced large investments in the field of aging and longevity, however. Calico launched with much fanfare, hundreds of millions of Google's dollars devoted to aging research, but a decade on it seems clear that little will result from this initiative. We might look at Altos Labs, recently launched with $3 billion in funding, as a newer Calico, but with the narrow goal of achieving human rejuvenation via cell reprogramming technologies. Will a narrow focus allow success where a broad focus leads to an organization losing its way? Only time will tell.

The Hevolution Foundation has broadly announced intentions to funnel very large amounts of Saudi Arabian sovereign wealth into aging research and the longevity industry. The organization has started slowly, but we can ask the same sorts of questions as of other large initiatives: will meaningful projects be funded? Much of the longevity industry, and much of aging research, is focused on goals that cannot and will not make much of a difference to the healthy human life span, such as the prevalent calorie restriction mimetics, supplements, and approaches to cellular stress response upregulation. Many of the large investment funds have devoted much of their funding to date to aging-branded efforts that are really just business as usual in medicine and biotech, nothing that offers the possibility to significantly change the shape of a human life.

The most important battle today, with regard to human aging, is over steering funding to projects that are more likely rather than less likely to result in significant rejuvenation. Senolytics, not calorie restriction. Partial reprogramming, not more supplements. And so forth. Until the broad scope of aging research and the longevity industry is significantly focused on rejuvenation, it is hard to be more than cautiously optimistic about any new large-scale venture, no matter how good their rhetoric sounds at the outset.

Hevolution CEO on how to spend $1 billion a year on longevity

"First of all, we are very much about extending healthy life, not just lifespan. I think if you ask anybody, with rare exception, they don't want to live longer for the sake of living longer. 'For the benefit of all' means not only being all-inclusive, but how do you democratise these technologies and discoveries? If we can't scale and democratise discoveries, and how to maximise the impact, then we should question ourselves: why are we doing this? Number one, we need to provide and support the development of the scientific field," says Hevolution's CEO Dr Mehmood Khan, who bemoans the huge gap in funding from governments around the world that goes into aging research compared to diseases like cancer, Alzheimer's, and heart disease (most of which are the consequences of aging). There's a log scale, if not two log scales, difference between the funding that goes into understanding how to keep people healthy on a biological level, versus treating the consequences of it. And that gap needs to be filled."

Another challenge that Khan sees is that most of the funding that is currently available for aging research is very much siloed, both within countries but also within disciplines. "One institute will fund the biology, and another will fund clinical research – it is not integrated together, for a whole variety of reasons. And that all needs to change. The irony is that the largest part of the healthcare budget for all developed countries is age-related diseases. So, we're already paying for the consequences of this ... and it's only getting bigger because our populations are aging."

When setting up Hevolution, Khan strongly felt that, to achieve all of this with the right incentives, the organisation had to be a non-profit. "If we were mandated as a for-profit organisation, then it's going to all be about return on investment back to our investors, and funders, which changes the types of decisions you'll make. To avoid this, you have to create a non-profit organisation, where the mission implementation is about funding science, which has no strings attached. We're not looking for an equity stake or anything like that – just fund the science, regardless of geographic location, for the benefit of all."

"Our vision is that we can invest up to a billion dollars a year, but the question now is how do we get there? The rate-limiting step in this is not the ability to invest or provide scientific research funding, but how to do that responsibly, such that the field can absorb it. This field needs to grow, and part of that is creating a pipeline of good scientific ideas, a pipeline of talent, and then pull that through into where venture comes in and build companies and then grow those companies. Some are already along that spectrum, but the funnel is not large enough, the pipeline is not large enough. So we're starting by funding science but we'll also be announcing our first investments very soon." Khan says that Hevolution's research funding and venture capital investment approaches will run in parallel, although how much of that $1 billion budget is allocated to each is not yet determined.

Link: https://longevity.technology/news/hevolution-ceo-on-how-to-spend-1-billion-a-year-on-longevity

Influenza Vaccination Correlates with Modestly Lower Risk of Stroke

September 2022

Following on from a recent study that suggested undergoing yearly vaccination for influenza can greatly reduce Alzheimer's risk, researchers here show that influenza vaccination correlates with a lower risk of stroke. The mechanisms of interest behind both of these correlations seem likely to revolve around chronic inflammation, an important factor in both the growth of atherosclerotic plaques in blood vessels and the onset and progression of neurodegenerative conditions. Firstly, suffering influenza is an inflammatory event, and the vaccine lowers the incidence and severity of that outcome. Secondly vaccination of this sort can reduce inflammation in the central nervous system via what is known as trained immunity, an improvement in the function of the innate immune system in response to the vaccine.

Researchers looked at a health care database in Spain and identified people who were at least 40 years old and had a first stroke over a 14-year period. Each person who had a stroke was compared to five people of the same age and sex. There were 14,322 people who had a stroke and 71,610 people who did not have a stroke. Then the researchers looked at whether people had received the influenza vaccine at least 14 days before the stroke or before that same date for those who did not have a stroke.

A total of 41.4% of those who had a stroke had received the flu shot, compared to 40.5% of those who did not have a stroke. But the people who got the shot were more likely to be older and to have other conditions such as high blood pressure and high cholesterol that would make them more likely to have a stroke. Once researchers adjusted for those factors, they found that those who received a flu shot were 12% less likely to have a stroke than those who did not.

The researchers also looked at whether the pneumonia vaccine had any effect on the risk of stroke and found no protective effect. Since the study was observational, it does not prove that getting the flu shot reduces the risk of stroke. It only shows an association. There could be other factors that were not measured that could affect the risk of stroke.

Link: https://www.aan.com/PressRoom/Home/PressRelease/5012

In the Matter of Human Longevity There Will Be Opportunists and Alchemists

September 2022

I suspect that a sizable, earnest community of opportunists and alchemists focused on anti-aging and longevity will continue to exist even as we transition from an era in which the only approaches to aging (beyond exercise and calorie restriction) were snake oil, the only service providers frauds, to an era in which therapies to slow aging and produce rejuvenation actually exist and are robustly proven to do what they say on the label. Will reliable, low-cost ways to measure biological age drive out the true believers who try whatever intervention is hyped, fail to gain scientific understanding, and fail to use adequate measures of success, living on a diet of hope? Will reliable, low-cost ways to measure biological age drive out the opportunists who sell that hope, in the form of whatever trendy, unproven strategy is claimed to slow aging today? Maybe, given time.

Sadly, the advent of epigenetic clocks hasn't yet helped that much. Since no-one knows what exactly an epigenetic clock measures in terms of the progression of aspects of aging, such as underlying molecular damage, or specific loss of function to organs and systems, we now have would-be demagogues claiming justification via low epigenetic ages allegedly resulting from their own personal strategies. This sort of data cannot yet be trusted in the absence of accompanying biomarkers of aging in which one can see meaningful differences following interventions. Those biomarkers are in short supply for basically healthy people much under the age of 50; differences will be small until later life for nearly everything that can be attempted at the present time. There are a few exceptions to this situation, such as the state of the gut microbiome and the thymus and the ovaries, but the important line items of immune health, cardiovascular health, and function of other organs just haven't faltered enough by that stage of life to be useful markers at this time.

This article, with the usual depressing undertone of virtue signaling that journalists of the popular press seem to think is required these days, is an example of the consequences of a world in which most people cannot tell the difference, or do not care to tell the difference, between arrant nonsense, unproven therapies, proven therapies, legitimate scientific development, and outright snake oil. It all gets lumped into one bucket labeled "treating aging", and those of us on the inside of aging research, patient advocacy, and the longevity industry wonder why it is sometimes challenging to convince people that aging can be treated, that we are on the way to human rejuvenation, that it is different this time, that what is going on is something more than branded skin care, fools tilting at windmills, fraud, and lies to cover up the wrinkles and the failing physiology.

The Death Cheaters

Last fall, a group of 30 people gathered at an Etobicoke estate to sample the latest in life-extension innovations. They sipped brain-boosting beverages laced with lion's mane mushrooms and garnished with grapefruit, participated in a breathwork session and soaked up the electromagnetic pulses of the BioCharger, a $20,000 device that looks like a giant blender, sounds like a bionic mosquito and is purported to fight chronic disease, brain fog, and flagging libido, among many other ailments. The evening was a soft launch for Longevity House, a private members' club for Toronto's burgeoning community of biohackers.

The price tag, $100,000 for a lifetime membership, was staggering. The promise, even more so: a chance to live longer, possibly to 120 years old. And not just longer but better, free from chronic illness and cognitive decline, by which standard six figures starts to sound like a bargain. Before launching Longevity House, Michael Nguyen was best known as the haberdasher to Toronto's one-percenters. In 2021, Nguyen purchased a $3-million, 7,500-square-foot mansion in Mimico and packed it with the latest in high-performance fitness equipment: alongside the BioCharger is a Tonal (the weightlifting system LeBron James uses), a Carol (an artificially intelligent exercise bike) and a Katalyst (an electronic muscle-stimulation garment that looks like a wetsuit and promises "the world's most efficient workout"). There is also a red-light therapy room, a full-body vibration plate, a cold plunge tub, and a custom-built sauna. Nguyen and his team have secured partnerships with in-demand health and wellness-practitioners-naturopaths, breathwork specialists, a chakra guy, a therapist who specializes in psychedelics, and functional-medicine doctors who read blood and stool samples like physiological tea leaves.

Biohacking – to "hack" one's biology for the purposes of optimization – is wellness spiked with gadgetry. It's New Age woo-woo with internet-age efficiency, Gwyneth Paltrow's Goop but for tech bros. (As yet, Longevity House has no female members, and on more than one occasion, I heard Joe Rogan's name spoken with reverence.) What is a biohack, exactly? That's hard to pin down since the category covers pretty much any health intervention, from the obvious to the outlandish. Yoga is a biohack. So is wearing a Fitbit. So are probiotics and mood-enhancing supplements, forest bathing, and looking deeply into another person's eyes for a full minute. Also DIY experimental gene editing, fecal transplantation, and uploading your consciousness onto an external server in the hopes of one day joining a race of cyborgs. (Elon Musk is working on it.) The common thread among biohackers is a mindset that views Mother Nature's work as a starting point.

Nguyen is used to the naysayers – history is littered with them. "We're operating outside the norms of society, which can make people nervous," he says. And that's true, isn't it? Don't all

breakthroughs start off as someone's outlandish idea? Wasn't Galileo convicted of heresy for his audacious insistence that the Earth orbits the Sun? Isn't it possible that my staunch allegiance to science will leave me on my deathbed while the biohackers skateboard into the next century? Nguyen is a charming and passionate hype man. But is he a modern Galileo or just a guy cashing in on the latest craze?

Link: https://torontolife.com/city/inside-the-weird-world-of-cryotherapy-biocharging-and-fecal-transplants/

Amyloid-β in the View of Alzheimer's as a Condition Driven by Persistent Infection

September 2022

Amyloid-β is an antimicrobial peptide, a part of the innate immune system's attempt to disrupt the activities of infectious pathogens. Some data suggests that Alzheimer's disease, characterized in its early and preclinical stages by slow aggregation of misfolded amyloid-β in ever larger amounts, is driven by persistent infection. It is by no means certain that this is the case, but it does place the aggregation of amyloid-β in a somewhat different light than was originally the case, when it was thought of as molecular waste and little more.

Given that amyloid-β is performing a useful function, reducing or eliminating its production is probably a bad idea – and indeed this idea was attempted and made patient outcomes worse. The right way forward in the matter of amyloid-β is most likely periodic clearance of the harmful aggregates or harmful excess elsewhere in cells, a goal presently complicated by the failure of clearance via immunotherapies to produce patient benefits in the clinic. This may be because the wrong forms or locations of amyloid-β were targeted, or because amyloid-β ceases to be the primary pathology in later stages of the condition, when chronic inflammation and tau aggregation drive one another in a feedback loop that kills neurons and leads to death.

Does An Immune Role for Beta-Amyloid Create a Therapeutic Dilemma for SENS?

Neurons produce Abeta as an antimicrobial peptide (AMP), a way to protect themselves from microbial assailants. When they come in contact with a pathogen, molecules of Abeta bind to the intruder, which triggers them to stick together into aggregates. Trapping the brain bugs in a sticky web allows Abeta to deactivate the microbial raiders, protecting the brain from infectious assault. With this model, a number of things that scientists have been reporting for years suddenly start to make sense. For one thing, it's long been known that the complement system is activated in the early stages of Alzheimer's disease. The complement system is a part of the innate immune system that directly destroys pathogens by tearing open their membranes, and it was already known to be activated by other AMPs. The model also explains why proteins that are part of the complement system are often found bound up with Abeta plaques in the brain.

If Abeta is an AMP, it also reframes the role of inflammation in the aging and Alzheimer's brain, and the associated activation of brain-resident immune cells called microglia. Microglia are like the macrophages of the brain, gobbling up particulate matter, cellular debris, and other harmful materials in the brain – including, importantly, Abeta – and digesting it in their lysosomes. Microglia have receptors on their surfaces that cause them to spring into action when they get a whiff of activated complement proteins, and Abeta causes dormant complement protein precursors to be converted into their active forms. In the Abeta-as-AMP model, this becomes an elegant host defense system: Abeta is released, traps a marauding microbe in a self-aggregating web of proteins, and then activates complement proteins to help finish off the enemy and to recruit microglia to clean up the battlefield.

This sequence protects the brain from these toxic materials in the short term – first from the infectious intruder, and then from Abeta itself. Abeta is produced in the short term as an emergency response to microbial marauders; microglia are then activated and recruited to clear the dead pathogens and aggregated proteins out of the brain so that they don't cause harm of a different sort. So long as this cycle is executed flawlessly, the brain remains protected from threats and sustains function. But none of these processes are perfect, they leave behind a few microbes here ... a few protein aggregates there ... and a few dysregulated microglia in another corner. Meanwhile, other aging processes make it increasingly difficult to close the loop on the cycle of releasing and aggregating Abeta, destroying pathogens, and recruiting microglia to clean up the battlefield afterward.

Abeta defends the brain against microbial invaders by forming aggregates that capture and neutralize them. Once they've already carried out the attack, the whole snarled-up mess – Abeta polymers, dead microbes, and complement proteins – serves no further purpose and can be toxic to the brain. So Abeta that is cleared out after becoming aggregated has already finished serving a useful purpose, and is mere battlefield rubble that must be safely swept away to help rebuild the neighborhood.

Link: https://www.sens.org/amyloid-versus-brain-microbes-and-the-sens-strategy/

Rapamycin in Early Life Delays Development and Modestly Extends Life Span in Mice

September 2022

As a general rule, 10% life extension in mice via metabolic alteration is uninteresting. It depends on the fine details, of course, but most age-slowing interventions so far discovered are in some way upregulating cellular stress response mechanisms, or adjusting growth hormone signaling. Neither of these approaches works anywhere near as well in long-lived mammals, such as our own species, as it does in short-lived mammals, such as mice, and in lower animal species. Short-lived species have life spans that are very plastic in response to environmental cues, such as the lack of nutrients that provoke greater stress response activity. Calorie restriction can extend life in mice by as much as 40%, but certainly doesn't have that great an effect in humans. Growth hormone receptor knockout can extend mouse life span to an even greater degree, but humans with the analogous Laron syndrome don't appear to live significantly longer than the rest of us.

This open access paper reports on another novel dead end in considering the effects of metabolic change on longevity. Here, an mTOR inhibitor is given to mice in early life. The result is slowed development, reduced growth, and a modest 11.8% extension of median life span. mTOR inhibition is a well-proven way to modestly and reliably slow aging when used in later life in mice, but here the effects appear an amalgam of the usual mechanisms of stress response upregulation coupled with the reduced growth seen in mice in which growth hormone signaling is disabled. It is scientifically interesting to see that developmental effects can lead to this outcome, but the relevance to human medicine seems tenuous. At the end of the day, this is simply not an area of study that can plausibly lead to sizable gains in human healthy longevity.

Rapamycin treatment during development extends life span and health span of male mice and Daphnia magna

Some indirect evidence supports the causal relationship between inhibition of growth signaling and longevity if targeted during development. For example, growth hormone (GH) knockout mice and mice lacking GH production live up to 50% longer than their wild-type siblings. However, their longevity was diminished if they were treated with growth hormone during early postnatal development. At the same time, growth hormone knockout induced at adult age had limited to no effects on longevity. However, there have been no experiments where growth pathways are directly inhibited only during development and the longevity outcomes measured.

Rapamycin is a well-characterized mechanistic target of rapamycin (mTOR) inhibitor and is among the most validated and potent pharmaceutical interventions that extend life span in mice. Rapamycin can extend life span if given in adulthood or later in life in various mouse strains, including genetically diverse UMHET3 mice (a cross of four inbred strains). Rapamycin failed to extend the life span of growth hormone receptor knockout mice. Furthermore, early life (EL) rapamycin treatment was previously shown to suppress growth of mice. Thus, rapamycin is a perfect candidate to test how targeting growth only early in life can affect life span, and we used it in our study, examining its effects on longevity, health span, biological age, and gene expression.

Here, we subjected genetically diverse UMHET3 mice to rapamycin for the first 45 days of life. The mice grew slower and remained smaller than controls for their entire lives. Their reproductive age was delayed without affecting offspring numbers. The treatment was sufficient to extend the median life span by 10%, with the strongest effect in males, and helped to preserve health as measured by frailty index scores, gait speed, and glucose tolerance and insulin tolerance tests. Mechanistically, the liver transcriptome and epigenome of treated mice were younger at the completion of treatment. Analogous to mice, rapamycin exposure during development robustly extended the life span of Daphnia magna and reduced its body size. Overall, the results demonstrate that short-term rapamycin treatment during development is a novel longevity intervention that acts by slowing down development and aging, suggesting that aging may be targeted already early in life.

Link: https://www.science.org/doi/10.1126/sciadv.abo5482

Still No Success Worthy of the Name in Anti-Amyloid Immunotherapies to Treat Alzheimer's Disease

October, 2022

Work on immunotherapies that can clear amyloid-β from the brain, an approach to treating Alzheimer's disease, continues to slowly grind out incremental benefits. First, the prospective treatments failed to clear amyloid-β, then they failed to show any degree of patient benefits, and now the latest trial data indicates a minor slowing of progression in Alzheimer's patients. It is unclear where the ceiling lies in this slow and painful process. Amyloid-β clearance is in principle a good idea, and implementations may become useful, given time and better understanding. It is certainly the case that an expensive therapy that merely slows the progression of Alzheimer's by 27% is not much of a therapy, however.

Sadly, the incentives operating on the leadership of pharmaceutical companies working with therapies targeted to large patient populations tend to favor efforts to spin mediocre outcomes into a success story. Medical regulation makes it so expensive to deploy new therapies that only very large organizations can carry work forward into late stage clinical trials, where the costs rise into the hundreds of millions of dollars. These organizations are beholden first and foremost to their shareholders, not to the patient community. Not that it would be any better were large governmental agencies to do the same thing.

Finally: Big Win on All Outcomes for Lecanemab in Phase 3 Topline Results

Eisai and Biogen yesterday announced positive topline results from the Phase 3 Clarity trial of their anti-amyloid antibody lecanemab. The drug slowed decline on the primary endpoint, CDR-SB, by 27 percent over 18 months, and also nudged down decline on all secondary clinical endpoints. The incidence of the brain edema known as ARIA-E was 12.5 percent, about one-third of that seen with Biogen's approved anti-amyloid antibody Aduhelm. That said, researchers also noted the absolute difference in CDR-SB scores was small, at 0.45, with some questioning how clinically meaningful this is. In the bigger picture, researchers said the data strengthen the amyloid cascade hypothesis. "This confirms the importance of Aβ in disease pathogenesis. This is the first time a therapeutic antibody has clearly changed the course of Alzheimer's disease. It is a pivotal moment in the history of Alzheimer's therapy."

Link: https://www.alzforum.org/news/research-news/finally-big-win-all-outcomes-lecanemab-phase-3-topline-results

Five big questions about the new Alzheimer's treatment

In the study, people getting lecanemab still had cognitive decline, but it progressed 27% slower than in those on a placebo. That translates to 0.45 points on the 18-point CDR-SB. Although the difference is modest, it's spawning hope. "This does make us feel a little better. These drugs do work." Lecanemab had side effects, most notably certain brain abnormalities seen with other anti-amyloid therapies, including swelling and small hemorrhages in the brain. Neuroimaging turned up these concerns in about 21% of patients on lecanemab, and 9% of those on the placebo. Although these abnormalities often produce no symptoms, about 3% of those getting lecanemab did have symptoms from them.

Doctors aren't sure how the apparently gentler slope of cognitive decline would be perceived by patients and their families. "Does that mean that grandma is going to have a few better days, a few better months, a few better years? It's still an open question." Commenters hesitate to make grand pronouncements, especially after last year's flameout of aducanemab. "We're all feeling a sense of wariness and caution. We want to dig into the data before we make any large conclusions."

Link: https://www.science.org/content/article/five-big-questions-about-new-alzheimer-s-treatment

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

Revival Update

Scientific Developments Supporting Revival Technologies

Reported by R. Michael Perry, Ph.D.

Controlling Gene Expression with Deep Generative Design of Regulatory DNA

Jan Zrimec, Xiaozhi Fu, Azam Sheikh Muhammad, Christos Skrekas, Vykintas Jauniskis, Nora K. Speicher, Christoph S. Börlin, Vilhelm Verendel, Morteza Haghir Chehreghani, Devdatt Dubhashi, Verena Siewers, Florian David, Jens Nielsen, Aleksej Zelezniak, *Nature Communications* 13, 5099, 30 Aug. 2022, https://www.nature.com/articles/s41467-022-32818-8, accessed 28 Nov. 2022.

Abstract

Design of de novo synthetic regulatory DNA is a promising avenue to control gene expression in biotechnology and medicine. Using mutagenesis typically requires screening sizable random DNA libraries, which limits the designs to span merely a short section of the promoter and restricts their control of gene expression. Here, we prototype a deep learning strategy based on generative adversarial networks (GAN) by learning directly from genomic and transcriptomic data. Our ExpressionGAN can traverse the entire regulatory sequence-expression landscape in a gene-specific manner, generating regulatory DNA with prespecified target mRNA levels spanning the whole gene regulatory structure including coding and adjacent non-coding regions. Despite high sequence divergence from natural DNA, in vivo measurements show that 57% of the highly-expressed synthetic sequences surpass the expression levels of highly-expressed natural controls. This demonstrates the applicability and relevance of deep generative design to expand our knowledge and control of gene expression regulation in any desired organism, condition or tissue.

From: AI Tailors Artificial DNA for Future Drug Development

Chalmers University of Technology news.cision.com (unattributed), 24 Nov. 2022, https://news.cision.com/chalmers/r/ai-tailors-artificial-dna-for-future-drug-development,c3672724, accessed 28 Nov. 2022.

With the help of artificial intelligence, researchers at Chalmers University of Technology, Sweden, have succeeded in designing synthetic DNA that controls the cells' protein production. The technology can contribute to the development and production of vaccines, drugs for severe diseases, as well as alternative food proteins much faster and at significantly lower costs than today.

The principle behind the new method is similar to when an AI generates faces that look like real people. By learning what a large selection of faces looks like, the AI can then create completely new but natural-looking faces. It is then easy to modify a face by, for example, saying that it should look older, or have a different hairstyle. On the other hand, programming a believable face from scratch, without the use of AI, would have been much more difficult and time-consuming. Similarly, the researchers' AI has been taught the structure and regulatory code of DNA. The AI then designs synthetic DNA, where it is easy to modify its regulatory information in the desired direction of gene expression. Simply put, the AI is told how much of a gene is desired and then 'prints' the appropriate DNA sequence.

"DNA is an incredibly long and complex molecule. It is thus experimentally extremely challenging to make changes to it by iteratively reading and changing it, then reading and changing it again. This way it takes years of research to find something that works. Instead, it is much more effective to let an AI learn the principles of navigating DNA. What otherwise takes years is now shortened to weeks or days", says first author Jan Zrimec, a research associate at the National Institute of Biology in Slovenia and past postdoc in Aleksej Zelezniak's group.

The researchers have developed their method in the yeast Saccharomyces cerevisiae, whose cells resemble mammalian cells. The next step is to use human cells. The researchers have hopes that their progress will have an impact on the development of new as well as existing drugs.

"Protein-based drugs for complex diseases or alternative sustainable food proteins can take many years and can be extremely expensive to develop. Some are so expensive that it is impossible to obtain a return on investment, making them economically nonviable. With our technology, it is possible to develop and manufacture proteins much more efficiently so that they can be marketed," says Aleksej Zelezniak.

Cytidine-Containing Tails Robustly Enhance and Prolong Protein Production of Synthetic mRNA in Cell and *in Vivo*

Cheuk Yin Li, Zhenghua Liang, Yaxin Hu, Hongxia Zhang, Kharis Daniel Setiasabda, Jiawei Li, Shaohua Ma, Xiaojun Xia, Yi Kuang, *Molecular Therapy Nucleic Acids*, 11 Oct. 2022, https://www.cell.com/molecular-therapy-family/nucleic-acids/fulltext/S2162-2531(22)00269-4?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2162253122002694%3Fshowall%3Dtrue, accessed 27 Nov. 2022.

Abstract

Synthetic mRNAs are rising rapidly as alternative therapeutic agents for delivery of proteins. However, the practical use of synthetic mRNAs has been restricted by their low cellular stability as well as poor protein production efficiency. The key roles of poly(A) tail on mRNA biology inspire us to explore the optimization of tail sequence to overcome the aforementioned limitations. Here, the systematic substitution of non-A nucleotides in the tails revealed that cytidine-containing tails can substantially enhance the protein production rate and duration of synthetic mRNAs both *in vitro* and *in vivo*. Such C-containing tails shield synthetic mRNAs from deadenylase CCR4-NOT transcription complex, as the catalytic CNOT proteins, especially CNOT6L and CNOT7, have lower efficiency in trimming of cytidine. Consistently, these enhancement effects of C-containing tails were observed on all synthetic mRNAs tested and were independent of transfection reagents and cell types. As the C-containing tails can be used along with other mRNA enhancement technologies to synergically boost protein production, we believe that these tails can be broadly used on synthetic mRNAs to directly promote their clinical applications.

From: HKUST Researchers Discover New Way to Synthesize mRNAs Enhancing Effectiveness of mRNA Drugs and Vaccines

Hong Kong University of Science and Technology (unattributed), 11 Oct, 2022, https://hkust.edu.hk/news/research-and-innovation/hkust-researchers-discover-new-way-synthesize-mrnas-enhancing, accessed 27 Nov. 2022.

A team of synthetic biologists at the Hong Kong University of Science and Technology (HKUST) has recently discovered a way that could increase synthetic mRNA's protein production efficiency by up to 10 times, which means the effectiveness of mRNA vaccines and drugs – such as those used against cancer, Covid-19 or other genetic diseases, will be greatly boosted with even less dosage of the mRNAs.

mRNAs can be synthesized to teach our cells in making any kind of proteins, such as antigens, enzymes and hormones which are essential in fighting infections and regulating bodily functions, so mRNA is arguably a preferred option for vaccines and treatment for many different kinds of diseases. However, high dosage and repeated injections are often required for mRNA drugs and vaccines in order to generate sufficient amounts of protein in the body, so enhancing mRNA's effectiveness – such as by increasing its protein production efficiency, is a hot subject among scientists as our immune system, for example, could work better with more of certain antibodies.

Now, a team led by Prof. Becki KUANG Yi, Assistant Professor at the Department of Chemical and Biological Engineering at HKUST, discovered a way that could enhance both the life span and efficiency of mRNA. Having engineered different mRNA's tail sequences, Prof. Kuang's team eventually discovered optimized sequences that could produce 3 to 10 times as much proteins as unoptimized tail sequences commonly used for synthetic mRNAs on both human cells and on mice. Duration of protein production is also doubled.

This new technology will not only reduce the amount and the number of injections needed for mRNA drugs and vaccines, but will also potentially lower the cost of treatments. It can also be used along with other mRNA enhancement technologies to synergically boost protein production.

"Increasing the protein production of synthetic mRNA is generally beneficial to all mRNA drugs and vaccines," said Prof Kuang. "In collaboration with Sun Yat-Sen University, our team is now exploring the use of optimized tails for mRNA cancer vaccines on animals. We are also looking forward to collaborating with pharmaceutical companies to transfer this invention onto mRNA therapeutics and vaccines' development pipelines to benefit society."

Temporal Optimization of Radiation Therapy to Heterogeneous Tumour Populations and Cancer Stem Cells

Cameron Meaney, Mohammad Kohandel, Arian Novruzi, *Journal of Mathematical Biology*, 13 Oct. 2022, https://pubmed.ncbi.nlm.nih.gov/36227423/, accessed 29 Nov. 2022.

Abstract

External beam radiation therapy is a key part of modern cancer treatments which uses high doses of radiation to destroy tumour cells. Despite its widespread usage and extensive study in theoretical, experimental, and clinical works, many questions still remain about how best to administer it. Many mathematical studies have examined optimal scheduling of radiotherapy,

and most come to similar conclusions. Importantly though, these studies generally assume intratumoral homogeneity. But in recent years, it has become clear that tumours are not homogeneous masses of cancerous cells, but wildly heterogeneous masses with various subpopulations which grow and respond to treatment differently. One subpopulation of particular importance is cancer stem cells (CSCs) which are known to exhibit higher radioresistence compared with non-CSCs. Knowledge of these differences between cell types could theoretically lead to changes in optimal treatment scheduling. Only a few studies have examined this question, and interestingly, they arrive at apparent conflicting results. However, an understanding of their assumptions reveals a key difference which leads to their differing conclusions. In this paper, we generalize the problem of temporal optimization of dose distribution of radiation therapy to a two cell type model. We do so by creating a mathematical model and a numerical optimization algorithm to find the distribution of dose which leads to optimal cell kill. We then create a data set of optimization solutions and use data analysis tools to learn the relationships between model parameters and the qualitative behaviour of optimization results. Analysis of the model and discussion of biological importance are provided throughout. We find that the key factor in predicting the behaviour of the optimal distribution of radiation is the ratio between the radiosensitivities of the present cell types. These results can provide guidance for treatment in cases where clinicians have knowledge of tumour heterogeneity and of the abundance of CSCs.

From: Using Math to Better Treat Cancer

University of Waterloo Media Relations (not otherwise attributed), 28 Nov. 2022, https://uwaterloo.ca/news/media/using-math-better-treat-cancer, accessed 29 Nov. 2022.

Researchers at the University of Waterloo have identified a new method for scheduling radiation therapy that could be as much as 22 percent more effective at killing cancer cells than current standard radiation treatment regimens.

While many mathematical studies have examined how to optimize the scheduling of radiation treatment for maximum effectiveness against cancer, most of these studies assume "intratumoral homogeneity" – that is, that all of the cancer cells are the same. In recent years, however, scientists have realized that tumours are made up of many different kinds of cells. Most importantly, they include cancer stem cells, which are more resistant to radiation than other kinds of cells.

"The problem with any calculation involving cancer is that it's super hard to get exact values because things vary from cancer type to cancer type, patient to patient, even within the tumour," said Cameron Meaney, a PhD candidate in Applied Mathematics at Waterloo and the lead researcher on the study.

This new algorithm can generalize the differing radiation resistances of stem cells and non-stem cells, allowing doctors to predict how a tumour will respond to treatment before gathering exact data on an individual's cancer.

The model has limitations, Meaney explained, as tumours contain far more than two kinds of cells. What it does, however, is provide clinical researchers with a better starting point for treatment research.

"The results of the algorithm are important because they shed light on the idea that heterogeneity in tumours matters for planning treatment," Meaney said.

The next step the researchers hope to see is an application of their algorithm to clinical studies: will their suggested therapy schedule outperform existing scheduling practices in a lab trial?

Universal Parity Quantum Computing

Michael Fellner, Anette Messinger, Kilian Ender, Wolfgang Lechner, *Phys. Rev. Lett.* 129, 180503, 27 Oct. 2022, https://journals.aps.org/prl/abstract/10.1103/PhysRevLett.129.180503, accessed 28 Nov. 2022.

Abstract

We propose a universal gate set for quantum computing with all-to-all connectivity and intrinsic robustness to bit-flip errors based on parity encoding. We show that logical controlled phase gate and R_z rotations can be implemented in parity encoding with single-qubit operations. Together with logical R_x rotations, implemented via nearest-neighbor controlled-NOT gates and an R_x rotation, these form a universal gate set. As the controlled phase gate requires only single-qubit rotations, the proposed scheme has advantages for several cornerstone quantum algorithms, e.g., the quantum Fourier transform. We present a method to switch between different encoding variants via partial on-the-fly encoding and decoding.

Applications of Universal Parity Quantum Computation

Michael Fellner, Anette Messinger, Kilian Ender, Wolfgang Lechner, *Phys. Rev. A* 106, 042442, 27 Oct. 2022, https://journals.aps.org/pra/abstract/10.1103/PhysRevA.106.042442, accessed 28 Nov. 2022.

Abstract

We demonstrate the applicability of a universal gate set in the parity encoding, which is a dual to the standard gate model, by exploring several quantum gate algorithms such as the quantum Fourier transform and quantum addition. Embedding these

algorithms in the parity encoding reduces the circuit depth compared to conventional gate-based implementations while keeping the multiqubit gate counts comparable. We further propose simple implementations of multiqubit gates in tailored encodings and an efficient strategy to prepare graph states.

From: New Form of Universal Quantum Computers

University of Innsbruck (unattributed), 28 Oct. 2022, https://www.uibk.ac.at/en/newsroom/2022/new-form-of-universal-quantum-computers/, accessed 28 Nov. 2022.

Computing power of quantum machines is currently still very low. Increasing it is still proving to be a major challenge. Physicists at the University of Innsbruck now present a new architecture for a universal quantum computer that overcomes such limitations and could be the basis of the next generation of quantum computers soon.

Quantum bits (qubits) in a quantum computer serve as a computing unit and memory at the same time. Because quantum information cannot be copied, it cannot be stored in a memory as in a classical computer. Due to this limitation, all qubits in a quantum computer must be able to interact with each other. This is currently still a major challenge for building powerful quantum computers. In 2015, theoretical physicist Wolfgang Lechner, together with Philipp Hauke and Peter Zoller, addressed this difficulty and proposed a new architecture for a quantum computer, now named LHZ architecture after the authors. "This architecture was originally designed for optimization problems," recalls Wolfgang Lechner of the Department of Theoretical Physics at the University of Innsbruck, Austria. "In the process, we reduced the architecture to a minimum in order to solve these optimization problems as efficiently as possible." The physical qubits in this architecture do not represent individual bits but encode the relative coordination between the bits. "This means that not all qubits have to interact with each other anymore," explains Wolfgang Lechner. With his team, he has now shown that this parity concept is also suitable for a universal quantum computer.

Parity computers can perform operations between two or more qubits on a single qubit. "Existing quantum computers already implement such operations very well on a small scale," Michael Fellner from Wolfgang Lechner's team explains. "However, as the number of qubits increases, it becomes more and more complex to implement these gate operations." In two publications in *Physical Review Letters and Physical Review A*, the Innsbruck scientists now show that parity computers can, for example, perform quantum Fourier transformations – a fundamental building block of many quantum algorithms – with significantly fewer computation steps and thus more quickly. "The high parallelism of our architecture means that, for example, the well-known Shor algorithm for factoring numbers can be executed very efficiently," Fellner explains.

The new concept also offers hardware-efficient error correction. Because quantum systems are very sensitive to disturbances, quantum computers must correct errors continuously. Significant resources must be devoted to protecting quantum information, which greatly increases the number of qubits required. "Our model operates with a two-stage error correction, one type of error (bit flip error or phase error) is prevented by the hardware used," say Anette Messinger and Kilian Ender, also members of the Innsbruck research team.

In Vivo Partial Reprogramming by Bacteria Promotes Adult Liver Organ Growth Without Fibrosis and Tumorigenesis

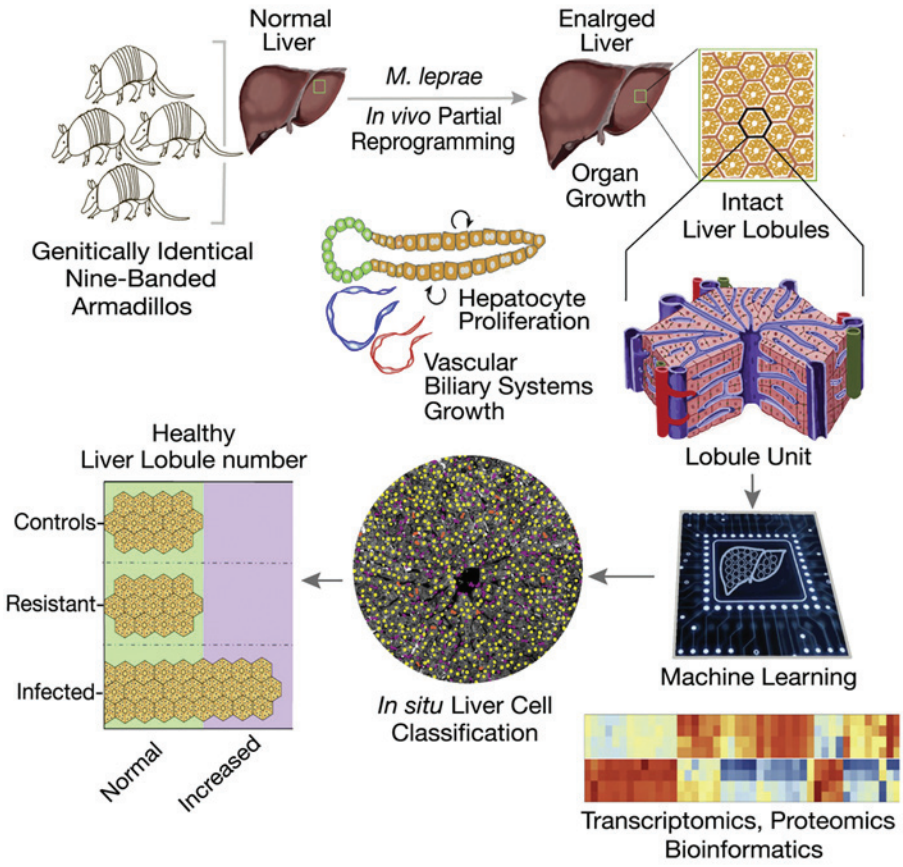
Samuel Hess, Timothy J. Kendall, Maria Pena, Linda Adams, Richard Truman, Anura Rambukkana, *Cell Reports Medicine* 3(11), 100820, 15 Nov. 2022, https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(22)00379-2?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2666379122003792%3Fshowall%3Dtrue, accessed 29 Nov. 2022.

Summary

Ideal therapies for regenerative medicine or healthy aging require healthy organ growth and rejuvenation, but no organ-level approach is currently available. Using *Mycobacterium leprae* (ML) with natural partial cellular reprogramming capacity and its animal host nine-banded armadillos, we present an evolutionarily refined model of adult liver growth and regeneration. In infected armadillos, ML reprogram the entire liver and significantly increase total liver/body weight ratio by increasing healthy liver lobules, including hepatocyte proliferation and proportionate expansion of vasculature, and biliary systems. ML-infected livers are microarchitecturally and functionally normal without damage, fibrosis, or tumorigenesis. Bacteria-induced reprogramming reactivates liver progenitor/developmental/fetal genes and upregulates growth-, metabolism-, and anti-aging-associated markers with minimal change in senescence and tumorigenic genes, suggesting bacterial hijacking of homeostatic, regeneration pathways to promote *de novo* organogenesis. This may facilitate the unraveling of endogenous pathways that effectively and safely re-engage liver organ growth, with broad therapeutic implications including organ regeneration and rejuvenation.

From: Ancient Disease has Potential to Regenerate Livers

University of Edinburgh Research (unattributed), 16 Nov. 2022, https://www.ed.ac.uk/research/latest-research-news/ancient-disease-has-potential-to-regenerate-livers, accessed 29 Nov. 2022 (lightly edited).



Scientists have discovered that parasites associated with leprosy can reprogram cells to increase the size of a liver in adult animals without causing damage, scarring or tumors. The findings suggest the possibility of adapting this natural process to renew ageing livers and increase healthspan – the length of time living disease-free – in humans. Experts say it could also help regrow damaged livers, thereby reducing the need for transplantation, which is currently the only curative option for people with end-stage scarred livers.

Previous studies promoted the regrowth of mouse livers by generating stem cells and progenitor cells – the step after a stem cell that can become any type of cell for a specific organ – via an invasive technique that often resulted in scarring and tumour growth. To overcome these harmful side-effects, Edinburgh researchers built on their previous discovery of the partial cellular reprogramming ability of the leprosy-causing bacteria, Mycobacterium leprae.

Working with the US Department of Health and Human Services in Baton Rouge, Louisiana, the team infected 57 armadillos – a natural host of leprosy bacteria – with the parasite and compared their livers with those of uninfected armadillos and those that were found to be resistant to infection. They found that the infected animals developed enlarged – yet healthy and unharmed – livers with the same vital components, such as blood vessels, bile ducts and functional units known as lobules, as the uninfected and resistant armadillos.

The team believe the bacteria "hijacked" the inherent regenerative ability of the liver to increase the organ's size and, therefore, to provide it with more cells within which to increase. They also discovered several indicators that the main kinds of liver cells – known as hepatocytes – had reached a "rejuvenated" state in the infected armadillos. Livers of the infected armadillos also contained gene expression patterns – the blueprint for building a cell – similar to those in younger animals and human fetal livers.

Genes related to metabolism, growth and cell proliferation were activated and those linked with aging were downregulated, or suppressed. Scientists think this is because the bacteria reprogramed the liver cells, returning them to the earlier stage of progenitor cells, which in turn became new hepatocytes and grew new liver tissues. The team are hopeful that the discovery has the potential to help develop interventions for aging and damaged livers in humans. Liver diseases currently result in two million deaths a year worldwide.

XNAzymes Targeting the SARS-CoV-2 Genome Inhibit Viral Infection

Pehuén Pereyra Gerber, Maria J. Donde, Nicholas J. Matheson, Alexander I. Taylor, *Nature Communications* 13, 6716, 16 Nov. 2022, https://www.nature.com/articles/s41467-022-34339-w, accessed 28 Nov. 2022.

Abstract

The unprecedented emergence and spread of SARS-CoV-2, the coronavirus responsible for the COVID-19 pandemic, underscores the need for diagnostic and therapeutic technologies that can be rapidly tailored to novel threats. Here, we show that site-specific RNA endonuclease XNAzymes – artificial catalysts composed of single-stranded synthetic xeno-nucleic acid oligonucleotides (in this case 2'-deoxy-2'-fluoro-β-D-arabino nucleic acid) – may be designed, synthesised and screened within days, enabling the discovery of a range of enzymes targeting SARS-CoV-2 ORF1ab, ORF7b, spike- and nucleocapsid-encoding RNA. Three of these are further engineered to self-assemble into a catalytic nanostructure with enhanced biostability. This XNA nanostructure is capable of

cleaving genomic SARS-CoV-2 RNA under physiological conditions, and when transfected into cells inhibits infection with authentic SARS-CoV-2 virus by RNA knockdown. These results demonstrate the potential of XNAzymes to provide a platform for the rapid generation of antiviral reagents.

From: 'Programmable Molecular Scissors' Could Help Fight COVID-19 Infection

University of Cambridge (unattributed), 16 Nov. 2022, https://www.cam.ac.uk/research/news/synthetic-biology-meets-medicine-programmable-molecular-scissors-could-help-fight-covid-19-infection#:~:text=Cambridge%20scientists%20have%20used%20synthetic,new%20generation%20of%20antiviral%20drugs, accessed 28 Nov. 2022.

Cambridge scientists have used synthetic biology to create artificial enzymes programmed to target the genetic code of SARS-CoV-2 and destroy the virus, an approach that could be used to develop a new generation of antiviral drugs.

Enzymes are naturally occurring biological catalysts, which enable the chemical transformations required for our bodies to function – from translating the genetic code into proteins, right through to digesting food. Although most enzymes are proteins, some of these crucial reactions are catalysed by RNA, a chemical cousin of DNA, which can fold into enzymes known as ribozymes. Some classes of ribozyme are able to target specific sequences in other RNA molecules and cut them precisely.

In 2014, Dr Alex Taylor and colleagues discovered that artificial genetic material known as XNA – in other words, synthetic chemical alternatives to RNA and DNA not found in nature – could be used to create the world's first fully-artificial enzymes, which Taylor named XNAzymes.

At the beginning, XNAzymes were inefficient, requiring unrealistic laboratory conditions to function. Earlier this year, however, his lab reported a new generation of XNAzymes, engineered to be much more stable and efficient under conditions inside cells. These artificial enzymes can cut long, complex RNA molecules and are so precise that if the target sequence differs by just a single nucleotide (the basic structural unit of RNA), they will recognise not to cut it. This means they can be programmed to attack mutated RNAs involved in cancer or other diseases, leaving normal RNA molecules well alone.

Now, in research published today in *Nature Communications*, Taylor and his team at the Cambridge Institute of Therapeutic Immunology & Infectious Disease (CITIID), University of Cambridge, report how they have used this technology to successfully 'kill' live SARS-CoV-2 virus.

Taylor, a Sir Henry Dale Fellow and Affiliated Researcher at St John's College, Cambridge, said: "Put simply, XNAzymes are molecular scissors which recognise a particular sequence in the RNA, then chop it up. As soon as scientists published the RNA sequence of SARS-CoV-2, we started scanning through looking for sequences for our XNAzymes to attack."

While these artificial enzymes can be programmed to recognise specific RNA sequences, the catalytic core of the XNAzyme – the machinery that operates the 'scissors' – does not change. This means that creating new XNAzymes can be done in far less time than it normally takes to develop antiviral drugs.

As Taylor explained: "It's like having a pair of scissors where the overall design remains the same, but you can change the blades or handles depending on the material you want to cut. The power of this approach is that, even working by myself in the lab at the start of the pandemic, I was able to generate and screen a handful of these XNAzymes in a matter of days."

The next step for Taylor and his team is to make XNAzymes that are even more specific and robust – "bulletproof," he says – allowing them to remain in the body for longer, and work as even more effective catalysts, in smaller doses. ■

A Roadmap to Revival

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

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

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

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

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

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

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

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

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

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

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

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

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

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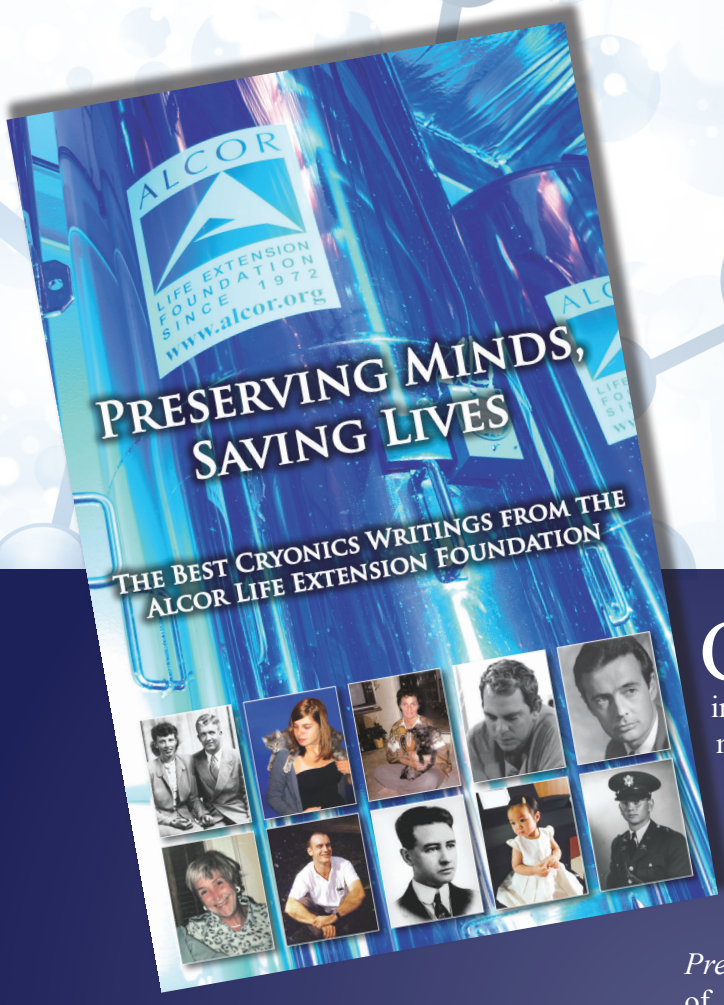

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– Max More, Ph.D.
Ambassador and President Emeritus of Alcor

Cryonics is an experimental medical procedure that uses ultra-low temperatures to put critically ill people into a state of metabolic arrest to give them access to medical advances of the future. Since its inception in the early 1960s, the practice of cryonics has moved from a theoretical concept to an evidence-based practice that uses emergency medical procedures and modern vitrification technologies to eliminate ice formation.

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

How do I find out more?

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

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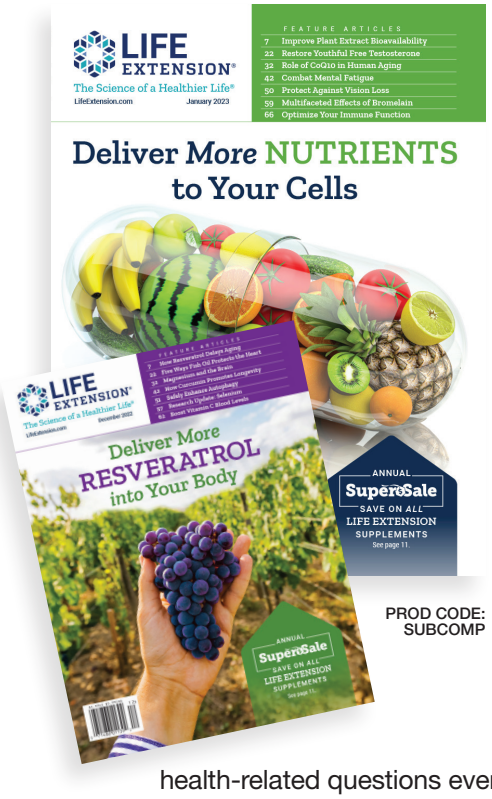

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