

The start-ups seeking a cure for old age

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When Nir Barzilai specialised in anti-ageing science 30 years ago, it was an act of hope. Now, the Israeli-American scientist believes the world is on the cusp of turning hope into reality, finding transformational drugs that prevent the effects of ageing that used to be viewed as inevitable.

“We are done with hope and promise. We are at the point between having promise and realising it”, says the director of the Institute for Aging Research at New York’s Albert Einstein College of Medicine.

He plans to run a huge flagship trial to test whether a cheap generic diabetes drug — metformin — can extend lifespan by years, after a promising UK study of real world patients.

If regulators approve metformin to target ageing, he believes large pharmaceutical companies and biotechs would jump into the “longevity” field. “Once we prove it, I think it will be an earth-shattering moment for everyone”, he says.

The fantasy of living forever has endured for centuries, from finding renewal in a fountain of youth to gaining immortality from a philosopher’s stone.

Although we are still unable to elude death, we have learnt to forestall it: science has improved life expectancy significantly, initially with more mundane measures such as sewers and vaccines, and then with new drugs to tackle chronic conditions such as heart disease. In the UK, life expectancy at birth almost doubled between 1841 and 2011.

But as many people now spend their last decades in poor health, scientists like Barzilai are on a quest to further increase not just lifespan but also healthspan: the number of healthy years we live.

Longevity researchers reject the hype that they are “curing death” but their vision still has the potential to ease some of the biggest problems of our time: soaring healthcare costs for a population whose health is creaking as it ages, and lacklustre productivity as people become too sick to work.



Israeli entrepreneur Yuri Milner, from left, Amazon founder Jeff Bezos and Google co-founder Larry Page © Rory Griffiths/FT/AP

And yet Barzilai is still searching for money to fund the trial, which could take four or six years and cost \$50mn to \$75mn. So far, he has \$22mn, including \$9mn from the US National Institutes of Health. “It is terribly upsetting but we are now on the hunt for the rest of the money”, he says.

Finding the key to prolonging life would benefit us all, but money to fund the search is hard to come by. Healthcare investors typically want to see short-term returns — unlikely, in metformin’s case, since its patent has long expired. Governments, meanwhile, prioritise research into diseases.

Into this gap have stepped tech billionaires including Amazon founder Jeff Bezos, Israeli entrepreneur Yuri Milner, and through Alphabet, Google co-founders Larry Page and Sergey Brin, who are funding new models that aim to combine the best of business and academia without the pressure for short-term returns. Barzilai hopes to pitch to some of this class of investors at an upcoming longevity conference.

The billions being made available to longevity researchers could be a gift to a humanity too distracted by today’s problems to fund a long-term revolution in healthcare. Their interest could be a “win-win”: billionaires tempted by the idea of living ever longer fund a longevity field that would not thrive without them.

But critics worry that if wealthy individuals dominate, future advances could create an elite not of designer babies but of designer elderly. Christopher Wareham, a bioethicist at Utrecht University who studies the ethics of ageing, says advances in longevity science risk widening the gaps between the rich and poor in health, wealth and power, including concerns that dictators could extend their lives.

“Suppose, for example, we had a kind of vaccine for the pandemic of age”, he hypothesised. “This is going to potentially exacerbate all the kinds of existing inequalities that we have . . . The longer you’re around, the more your wealth compounds, and the wealthier you are, the more political influence you have”.

Turning back the biological clock

As the field of longevity research began to expand, scientists convened to ask the most fundamental question: what is ageing? In 2013 an influential group laid out the “nine hallmarks of ageing”, genetic and biochemical processes that lead to impaired function and vulnerability to death.

Eric Verdin, chief executive of the Buck Institute for Research and Aging in California, says scientists have completely changed how they think about ageing, from presuming it was a passive process — if you wait long enough, things fall apart — to learning how to modify it.

Eventually, a breakthrough could simply prevent us reacting to the chronic illnesses that kill. “The biggest risk factor of all diseases is ageing: It is not cholesterol or smoking, it is your age”, he says.

In the UK, life expectancy at birth almost doubled between 1841 and 2011

James Peyer, chief executive of Cambrian Biopharma, which incubates and invests in longevity companies, says the “north star” for the field is creating a new generation of preventive drugs, which he believes will have as much impact on human health as vaccines and antibiotics.

Before developing drugs, scientists have to investigate what is happening on a cellular level. One important discovery was that the biological clock on cells can be turned back, using “rejuvenation factors” that create the potential to reverse disease.

Another was that senescent cells build up in older people — ageing, not dividing, but refusing to die — causing health problems. Scientists at the US Mayo Clinic discovered that if you engineer mice so the senescent cells die off, they became healthier and live 20 to 30 per cent longer.

But so far, the majority of these discoveries have been in animals, not humans. “It’s a great time to be a rich mouse. And you could live for a long time as a rich mouse, but I think we want to have human beings that live healthier”, jokes Vijay Pande, general partner at venture capital firm Andreessen Horowitz, which invests in longevity start-up BioAge.

Testing these hypotheses in humans presents huge challenges. It would take too long to wait to see whether humans on a drug live longer. So scientists must find “biomarkers”: signals that track the ageing process to see if it slows.

Researchers also have to contort their trials into the existing regulatory framework, which does not define ageing as a disease. They must target specific diseases, even though some hope the drugs will have broader applications.

While Barzilai thinks metformin has the potential to extend life, his trial will aim to show that the drug delays a basket of diseases, including stroke, heart failure, cancer and dementia, as well as death.

But by far the biggest hurdle is getting enough money to fund large trials, to accelerate this exploration, and find other factors that influence ageing.

Funding ‘engines of discovery’

When Rick Klausner began to raise money for Altos Labs, he created a deck for investors like no other. Instead of coming to potential shareholders with a list of projects and a timetable of milestones, the former director of the US National Cancer Institute hoped they

would invest in what he called an “engine of discovery”.

His pitch was that Altos would hire the best minds in the business — including the former GSK chief scientific officer Hal Barron as chief executive — and set them free. Working in a way he hopes will be more collaborative than academia, they will tackle the big problems around rejuvenating cells with the ambition of reversing diseases.

The approach paid off: the company raised \$3bn, a life sciences industry record, in a round led by Arch Venture Partners, and reportedly including funds from Bezos and Milner, the cofounder of Mail.Ru and founder of tech investment firm DST Global.

Barron says the money will allow them to fail multiple times in pursuit of their goal: an “incredibly novel way of thinking” about reversing disease. Pursuing such a “complicated, disruptive idea” needs \$3bn, he adds.

“If you had a typical \$60mn or \$100mn investment, it wouldn’t really be thoughtful to try to tackle this problem”, he explains.

Billions of dollars has been raised thus far in this pursuit of science

Altos, which launched at the start of 2022, is now the best known of the well-funded experiments trying to turbocharge anti-ageing science. The first was Calico Life Sciences, an Alphabet company, founded in 2013, where Barron used to lead research.

Klausner and Barron criticise the academic funding model for creating an environment that doesn’t encourage tackling the biggest questions. Instead of putting pressure on their researchers to publish in the best journals, or placing a premium on being the first author on a paper, they will be judged on whether they are working on the hardest problems.

“It’s an experiment, but I think it is an experiment that’s worth all of us committing the rest of our careers to”, Klausner concluded.

Robert Nelsen, co-founder at Arch Venture Partners, says the company only wanted very long-term investors. His group can hold shares in Altos for 10 to 15 years if necessary, though he believes other investors will see the value long before it lands on a “Holy Grail”.

“If this works, it doesn’t matter if we’ve waited. If you cure disease in my business, you are going to make money”, he says.

Jonathan Lewis, chief business officer at Calico, says a “chunk of funding” from Alphabet, then known as Google, allowed the company to focus on early biology when it launched in 2013.

But since then, it has attracted funding from the pharmaceutical company AbbVie. The partnership has been renewed twice, and Alphabet and AbbVie have now both committed to investing \$3.5bn.

The money is significant for the 275-person organisation, but small fry for Alphabet, with its \$1.2tn market capitalisation, and AbbVie, at \$292bn. Now, Calico has three potential drugs in early clinical trials.

More conventional venture capitalists are entering the field, but they focus on companies that are testing broader principles of anti-ageing science in specific trials that could produce drugs more quickly. However, the step-by-step approach could be slower, and if the first trial fails, a company may suffer, potentially undermining its larger vision.

The ethics of private research

The well-funded new kids on the block have ignited debates about whether governments have their scientific priorities right, and the consequences of shifting more early stage science into private institutions.

Government funding is growing but is still nowhere near matching the investment raised by organisations like Altos. The US National Institutes of Health has an ageing division, but a rise in its budget in the past decade was mainly devoted to Alzheimer's. The UK has begun to take notice, but the money is spread thinly: the government's national research funding body, UK Research and Innovation, spent £2mn setting up 11 networks.

James Wilsdon, director of the Research on Research Institute at the University of Sheffield, says public funds need to be directed where they can deliver benefits more immediately.

"The need is great enough as it is, without then taking on much longer term, more speculative questions", he says.

He added that there is a suspicion that those who stress the need for "long-termism" are actually dressing up their "individual, narcissistic, selfish desires to find ways of extending their own life as long as possible". "You can paint as much lipstick on a pig as you want, but it is still a pig of an argument for allocating health funding", he says.

Wareham, the bioethicist, says we need to get away from the "disturbing image of these kinds of vampire-like billionaires, concocting extension potions and experimenting on themselves", and realise that even if they are self-interested, they can "afford to make a lot of mistakes", which governments cannot.

Governments are also contributing in less obvious ways. Lewis describes the UK as "prescient" for setting up the UK Biobank, a genetic and health information database of half a million participants. This proved so useful that Calico is helping fund more scans to improve

its understanding of how disease progresses in older adults.

Within the field, some envy peers who no longer have to fill out endless funding applications. Lynne Cox, an associate professor at the University of Oxford who specialises in ageing science, spends most of her time “scrambling around for little pots of money”. Even basic resources like pipettes can be in short supply.

She contrasts this with a colleague who recently joined Altos. “He has the freedom to do science the way science should be done”, she says.

Cox has taken funds from Jim Mellon, a British former fund manager who also co-founded Juvenescence, a biotech devoted to longevity, who she describes as a “one of those ideal donors” who does not micromanage.

Others worry that the private companies engaging in early research could restrict access to innovations. While Altos researchers will be free to publish their findings, and Calico declares itself “pro-publishing”, some suspect they are less free than in academia.

The pharmaceutical industry has often been accused of setting drug prices too high

The pharmaceutical industry already guards its intellectual property closely, and has been accused of setting drug prices too high. As anti-ageing science gets closer to market, there will be big ethical questions about how fairly treatments are distributed.

Mehmood Khan, chief executive of Hevolution Foundation, a non-profit devoted to longevity research backed by the Saudi royal family that has pledged \$1bn a year in investment, says its vision is to “extend healthy lifespan for the benefit of all humanity”, to ensure it doesn’t exacerbate the gap in life expectancy between the rich and poor. He says Hevolution is only funding work that could be “democratised”.

“If this is going to be a gazillion-dollars’ worth of treatment for a handful of people, it is of no interest”, he says.

Altos says it wants to help as many patients with serious medical needs as possible, and is committed to working with the healthcare ecosystem on access and equity.

To speed innovation and encourage wider access, governments have usually been the main contributors to fundamental science, answering essential questions, which do not lead directly to products.

Ronald Kohanski, director of the division of ageing biology at the US National Institute on Aging, says that while in the Renaissance scientists relied on wealthy people’s pockets, in modern times western governments have supported open science.

“Not everybody who was offered the large salaries by Altos went. Some prefer to stay in academia”, he says.

He adds that people with private funding are not subject to the same “compulsion” as those with government money: to ensure their findings are accessible, and that any positive consequences are available to everyone.

“If you’re doing something to make money, you’re going to optimise your profit. That’s capitalism in a nutshell”, he says.

By **Hannah Kuchler**.