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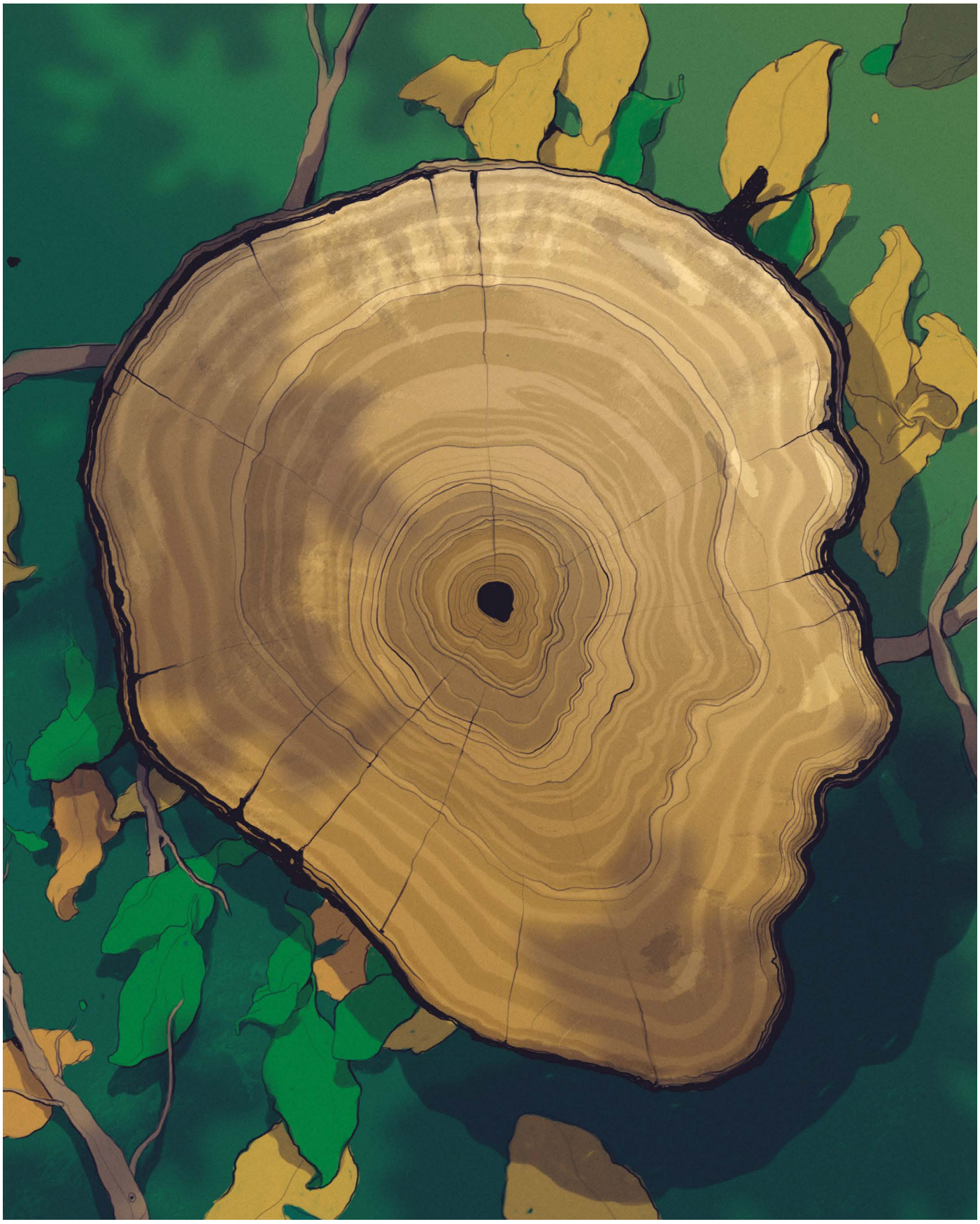


SIMON PRADES

Can geroscience slow the hands of time?

After rapid increases last century, life-expectancy gains have stalled. Scientists are now pursuing therapies targeting the ageing process that aim to make us feel younger for longer. **By James Mitchell Crow**

Will a human ever celebrate a 150th birthday? You bet, says Stephen Austad, a biology of ageing researcher at the University of Alabama at Birmingham. Austad is so sure that life expectancy is poised for another rapid rise, he put money down in 2000 that the first person to reach 150 was already alive.

It's a fantastical idea, counters Jay Olshansky, a longevity researcher at the University of Illinois Chicago, who took Austad's bet and foresees a payout for his descendants in 2150.

So far, the numbers seem to fall in Olshansky's favour. During the twentieth century, medical advances added 30 years to human life expectancy. Since then, the rise has slowed significantly – as Olshansky was sure it would.

"In 1990, colleagues and I forecast that the rise in life expectancy will slow, as more people live long enough to be exposed to the immutable force of ageing," Olshansky says[1]. When Olshansky revisited this analysis in 2024, he and his co-authors confirmed that life expectancy in the developed world was flatlining[2].

The human body has been pushed about as far as it can go by conventional medicine, Olshansky says. "As long as ageing remains unmodified, you can't push out the envelope of survival much beyond where we are today." The only path to further radical human lifespan extension, he concluded, is to slow the ageing process itself.

Austad agrees. "I think we're very close to being able to do it," he adds, noting numerous approaches that have shown promise in animals and, increasingly, in people.

Perhaps surprisingly, given their wager, Olshansky also sees great potential in this work. "I'm very optimistic that we will be able to slow down the biological process of ageing," he says. "I think it will happen in our lifetime." On how much this might impact lifespan, Olshansky and Austad differ, although both agree that such considerations are a distraction. Ultimately, the point is not how long we live, but how well we live.

Young of heart

Living longer is a secondary goal of geroscience, a fast-growing field focused on uncovering the biological changes that make our cells, tissues and organs more prone to conditions such as cancer, cardiovascular disease and neurodegenerative disorders as we age. Targeting individual diseases might extend lifespan, but it no longer guarantees a longer 'healthspan' – years lived fit and well, Austad says. For instance, age-adjusted deaths from heart disease have fallen by one-third since 2000, but people who don't die from it typically never fully recover, compromising their quality of life and burdening health-care systems.

"The fear is, if we continue with the disease model, we're going to live longer and longer in the 'red zone' – with frailty and disability," Olshansky says.

> **"Most people think about longevity arithmetically, but in biological time we operate on an exponential scale."**

Geroscience resets age-related disease management by targeting the biggest risk factor for their onset: ageing itself. One line of research has been to study centenarians who have remained naturally fit and healthy far beyond average life expectancy. "As a clinician, I was always intrigued by individuals who are very old and functioning very well" and finding out "what stimulates the longevity and healthspan in these individuals", says Andrea Maier, a healthy-ageing researcher at the National University of Singapore.

Other leads have come from the observation, first made in rodents a century ago, that animals fed a heavily calorie-restricted diet live longer. "In mice, it works, it slows down ageing," says Zahida Sultanova, a postdoc at the University of East Anglia, UK, who studies factors that affect ageing. Studying how cellular processes changed in these long-lived animals has delivered many insights into ageing.

Several processes identified in calorie-restricted animals have also shown up in healthy human centenarians. One such mechanism, identified by biology of ageing researcher, Leonard Guarente, and colleagues at the Massachusetts Institute of Technology in Cambridge, pointed to the importance of a set of genes and associated proteins called sirtuins[3]. Many organisms are now known to possess them. "If you make them more active, you extend the lifespan," Guarente says. Some centenarians also carry extra-active sirtuins. Sirtuins were found to play a role in DNA maintenance and repair, but they rely on a molecule called NAD^+, which naturally declines with age. In ageing mice, dietary supplements that increase cellular NAD^+ levels can boost sirtuin activity and extend healthspan and lifespan.

Guarente has spun off a company from his research to test this concept in people. "You can't realistically run a clinical trial to determine how long humans live, because you'd have to wait 50 years for the result. So, we look at surrogate markers of health," Guarente says. So far, in early-stage trials, boosting NAD^+ has safely lowered markers of inflammation thought to be at the core of conditions including non-alcoholic fatty liver syndrome[4] and chronic obstructive pulmonary disease[5].

Dousing inflammation

Chronic inflammation is so closely associated with ageing that it has been dubbed 'inflammageing'. This over-activation of the immune system involves a complex interplay of signalling molecules called cytokines, some promoting inflammation and some suppressing it.

Cytokine interleukin-11 (IL-11) was long thought to be anti-inflammatory until, in 2017, Stuart Cook from Duke-National University of Singapore Medical School and his colleagues showed the opposite was correct[6].

"We found that IL-11 was involved in multiple ageing processes," says Cook, a clinician scientist researching new biomedical targets for healthspan. Following a chance observation that IL-11 levels were increased in the organs of old rats, they investigated further. In a mouse study[7] published in 2024, the team showed that treating the animals with an antibody that binds IL-11 and blocks its effects extended lifespan by up to 25%. "The benefits of anti-IL-11 were apparent in every organ we looked at," says Cook, who suspects IL-11 is an

evolutionary appendage that once played a role in limb regeneration in ancient fish but has no beneficial function in humans.

Clinical trials of IL-11-inhibitors have already begun. In June 2025, Alphabet-owned Calico Life Sciences struck a licensing deal for one such IL-11 blocker, developed by Chinese biotech firm Mabwell, based in Shanghai. Some of the big companies collaborating with Calico — including US pharma company AbbVie — should enable large-scale clinical trials to test IL-11 inhibition in people, Cook says. "Then we will know once and for all if anti-IL-11 is an anti-ageing drug for humans."

Cleaner living

Of course, there's no guarantee that any potential anti-ageing medicine that generates results in mouse studies will succeed in human clinical trials. In the anti-ageing field, a group of drugs called senolytics have not, so far, fulfilled their preclinical promise.

Senolytics are designed to clean out dysfunctional 'senescent' cells, which accumulate in many tissues and cause inflammation, prompting the hypothesis that such cells could be a fundamental driver of ageing. Following animal studies looking at the potential healthspan and lifespan benefits of senolytics, multiple clinical trials have been launched in the past five years — but so far, have failed to show the anticipated benefits in people, Austad says. "Senolytics went from the laboratory to clinical trials extremely fast — we'll see if they fall out of favour just as fast," he says.

For Austad, one reason for the poor success rate in translating animal-study successes into human findings is the way animal studies are conducted. Lab animals are cosseted, kept continually warm, well-fed and protected from pathogens. "This artificial situation has completely misled us about how treatments are going to translate into the real world," says Austad, who is testing anti-ageing interventions in mice kept under a range of conditions to better approximate real life. "Treatments that work under all those conditions are the things that we should be most interested in," he says.

Reuse and recycle

Several anti-ageing approaches repurpose existing drugs, rather than looking for new ones. Two have been examined for their ability to mimic the metabolic effects of calorie restriction. One is the widely prescribed blood-glucose-lowering diabetes drug, metformin. Another is rapamycin, an immunosuppressant that inhibits a cellular nutrient sensor controlling cell growth and repair. Blocking this receptor can mimic caloric restriction by tricking the body into thinking food is scarce, Sultanova says. "You eat normally but hide it from yourself."

In 2024, Sultanova and her colleagues released a meta-analysis of 167 animal studies[8], looking at the lifespan impacts of rapamycin and metformin compared with actual caloric restriction. The analysis found that caloric restriction gave the largest and most consistent lifespan extension, closely followed by rapamycin. Metformin showed no clear benefit.

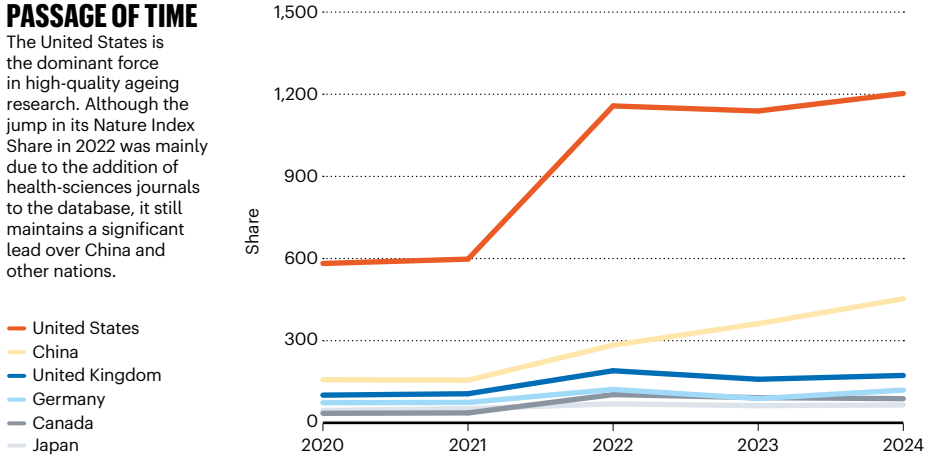
Early-stage human trials of rapamycin have been encouraging, Sultanova says. Last year, researchers reported the outcomes of intermittent, low-dose rapamycin in healthy adults[9]. "Even after just one year, they have some promising results and found minimal side effects," Sultanova says. Trials that test a wider range of rapamycin doses are now planned.

Six months ago, rapamycin was the intervention Austad was most excited about, he says. "It still looks extremely promising", but with the caveat that most of the data still come from animal studies, he says.

"Today, I'm most optimistic about GLP-1," says Austad, "because all the promising evidence comes from humans." Injectable mimics of the hormone GLP-1 such as Byetta and Ozempic, the first of which was approved in the United States in 2005, treat diabetes and obesity by stimulating insulin release and suppressing appetite. The drugs have now been taken by millions of people for several years — and researchers are discovering that they impact a host of age-related diseases, with few

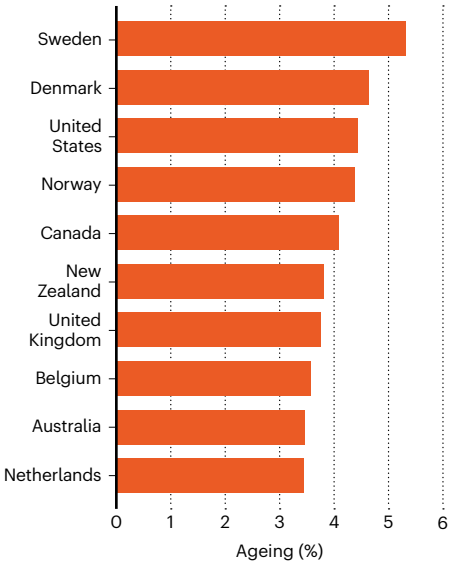
PASSAGE OF TIME

The United States is the dominant force in high-quality ageing research. Although the jump in its Nature Index Share in 2022 was mainly due to the addition of health-sciences journals to the database, it still maintains a significant lead over China and other nations.



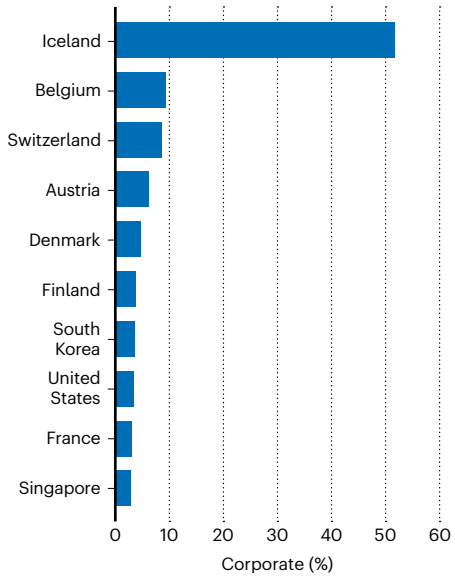
STRONG FOCUS

Of the leading 25 countries and territories for ageing research in the Nature Index from 2020 to 2024, these 10 had the highest proportion of Ageing Share relative to total Share (Ageing %). Sweden and Denmark stand out for having low Ageing Share but high Ageing %, whereas China has high output in ageing research but a low Ageing % (below 2%).



INDUSTRY RESEARCH

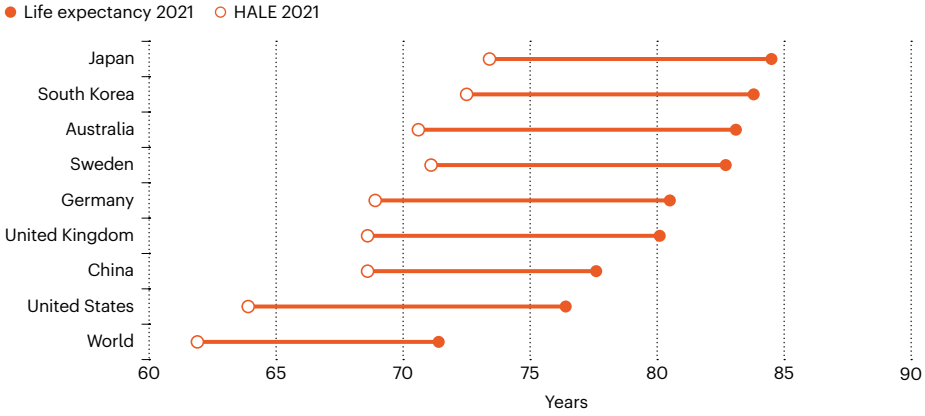
Of the leading 20 countries and territories by corporate Share in ageing research for the period 2020 to 2024, these 10 have the highest proportion of Corporate Share by overall Share in the topic (Corporate %). For example, more than 50% of Iceland's Ageing Share for the period came from its corporate institutions.



SOURCE: NATURE INDEX

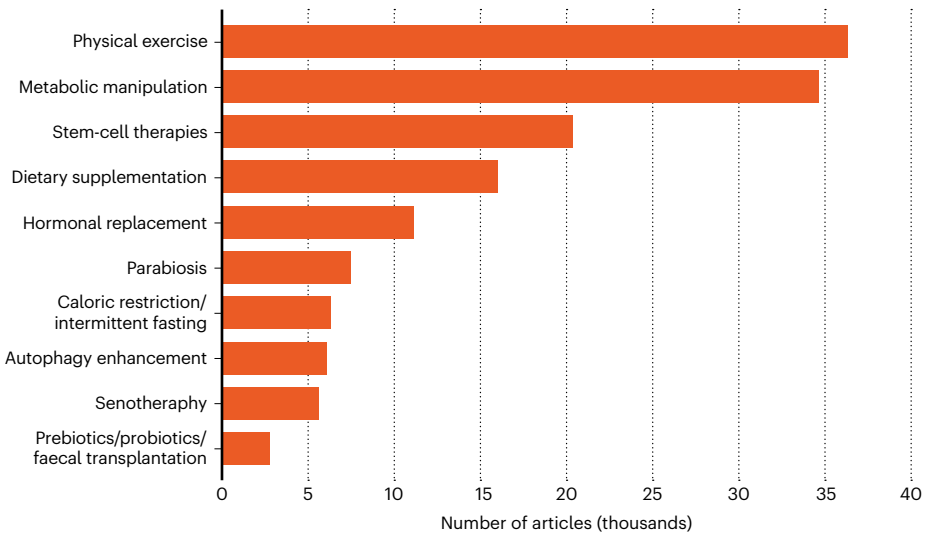
THE GOOD YEARS

The life expectancy and health-adjusted life expectancy (HALE) — the average number of years that a person can expect to live in full health — are shown for this selection of leading countries by Ageing Share in the Index from 2020 to 2024. The United States is the outlier, with both the lowest life expectancy and biggest gap between life expectancy and HALE among the group, despite being the largest producer of ageing research.



DIFFERENT ANGLES

This chart shows the most studied anti-ageing approaches in journal articles and patents published between 1 January 2018 and 30 September 2025, based on an analysis of the American Chemical Society's CAS Content Collection. They include techniques that might be less familiar to non-experts including senotherapy (targeting senescent cells to delay ageing) and autophagy enhancement (boosting cellular self-cleaning processes).



SOURCE: WORLD HEALTH ORGANIZATION; R. TENCHOV *ET AL. ACS CHEM. NEUROSCI.* **15**, 408–446 (2024).

to no side effects. "It seems like every week there's some new benefit reported," Austad says. Analyses of large GLP-1 patient cohorts have found that the drugs reduced the risk of age-related conditions as diverse as heart disease and Alzheimer's[10].

Guarente agrees that GLP-1 drugs are a current stand-out in the anti-ageing field. "GLP-1 drugs seem to have real health benefits, not least weight loss — but I think the effects are broader than that," he says. "Even the weight loss is probably not only due to appetite suppression." Drugmakers have launched numerous clinical trials to directly test GLP-1 drugs against age-related cardiovascular and neurodegenerative diseases, and are reporting successful trials of GLP-1 drugs in a daily pill form, which might enable a broader population rollout compared with the current weekly injections.

Precision anti-ageing

As a clinician working in healthy ageing, Maier says there is a clear need for more evidence-based anti-ageing therapies. The biggest benefits will come once we can identify the best anti-ageing treatment for each individual, she says. "From the different pace at which people go grey or lose muscle, we know that we all age differently." Geromedicine should be just as tailored to the individual as cancer therapy has become, says Maier. "We live in an era of precision medicine, so why would we not implement that into this new speciality?"

Maier is focused on identifying and validating biomarkers of ageing, both as surrogate endpoints for clinical trials and to guide precision clinical practice. She leads the HEAL project at Singapore's Alexandria Hospital, which is exploring whether data from a participant's genome, microbiome and smartwatch motion readings can be combined to identify their 'gero-phenotype' — a biological profile of ageing — and guide personalized anti-ageing treatments.

Even with strong, biomarker-based evidence about anti-ageing interventions in humans, broad public roll out for such precision treatments could take two or three decades, Austad cautions. "We have to be very certain that there are no long-term side effects, which is something biomarkers may not tell you," he says.

Geroscience's overall impact on human lifespan, however, remains anyone's bet. For Olshansky, the increase will be relatively modest. "Most people think about longevity arithmetically, but in biological time we operate on an exponential scale," he says. Each added year becomes harder than the last, because of all of the accumulated damage associated with the additional life lived. "So, 150 is so bizarrely out of reach, it's like leaving the natural universe in an airplane," Olshansky says.

But Austad sees the benefit of slower ageing not in tacking on years at the end of life, but slotting extra years into the middle. It's about making a person healthier at 50, and then equally healthier at 60 and 70 and 80, he says. "I think that fits much more with the data that we already have from animals."

For people already feeling the tick of their biological clock, one further insight from animal work is that intervention doesn't need to happen as early as we once thought, Austad adds. The first rapamycin study used mice that were the equivalent of 60 years old, he says, adding that if he'd been asked about the study design, "I would have said, 'Don't waste your time, start again with a young group'. Fortunately, they didn't ask me — because I was dead wrong on that."

James Mitchell Crow is a freelance writer based in Melbourne, Australia.

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