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Growing up

Scientists seeking to reverse or stall the effects of ageing are trying to make the leap from laboratory research to human trials.

BY NEIL SAVAGE

Anyone who's ever owned a pet dog knows that the relationship will end too soon. After 10 or 15 years, Fido's fur is grey, his hips are out of joint and he's unsteady on his feet. It's like watching a family member get old, but it happens much faster than with a spouse or parent. And therein might lie an opportunity for scientists seeking to delay ageing in humans.

"We all accept that dogs age about seven times faster than people do," says Matt Kaeberlein, a biologist who directs the Healthy Aging and Longevity Research Institute at the University of Washington, Seattle. "What's different about a dog and a person? It's just our DNA."

DNA studies have identified genes that affect ageing and longevity in a wide array of species, including humans. Over the past two decades, scientists have uncovered molecular mechanisms involved in ageing that should enable them to intervene in, slow or even reverse the process. Researchers have already shown that they can extend lifespans in yeast, roundworms and mice, so why not in dogs or people?

Human lifespan has increased markedly over the past century, in large part owing to improvements in nutrition and sanitation, and through the use of vaccines and antibiotics. In 1900, according to the World Health Organization, the global average life expectancy was just 31 years; even in the wealthiest countries it was under 50. By 2015, the average was 72, and it was as high as 84 in Japan.

Most anti-ageing researchers are not seeking immortality. They're hoping to extend the 'healthspan', the period in which people remain disease-free and vigorous, shortening old age and perhaps adding a decade or two to life. "The real question to me is not 'can we push the average lifespan up so it's closer to 100 instead of 70-something?' but rather 'can we have a healthier healthspan?'" says Elissa Epel, a psychiatrist who directs the Aging, Metabolism, and Emotions Lab at the University of California, San Francisco. "Who cares if you live to 100 if you are not able to do stuff?"

Kaeberlein is hoping to treat 500 dogs over a 5-year period with rapamycin, a drug that has been shown to lengthen life in mice by 30–40%. Because of the rate at which dogs age — their average lifespan is around 11 years — 5 years should be long enough to show whether rapamycin can extend the life of a middle-aged dog significantly, and to hint at whether the same might be possible for humans. The trial would be run in parallel with a larger longitudinal study looking at the genetic and environmental factors ▶

that are linked to longer life and better health in 10,000 dogs across the United States. Kaeberlein likens that study to the Baltimore Longitudinal Study of Aging, a project that has followed more than 3,000 human volunteers since 1958. "Except that in a dog, you can follow them from birth to death in a decade."

Kaeberlein sees his dog study as one of a series of steps that will ultimately lead towards translating laboratory findings into human medicine. On one level, his aim is conceptual. "A big challenge we have in this field is convincing non-scientists that ageing is just a biological process, and because it's a biological process it can be modified, genetically or pharmacologically," he says.

The study is also a way to test a potential anti-ageing drug in conditions that are similar to those of humans. Dogs live in our houses, breathe second-hand smoke, drink tap water and sometimes even sleep in our beds. "It's hard to imagine an animal that shares the human environment more than dogs," Kaeberlein says. "It's a huge step forward — closer to the human condition than laboratory studies."

PIECE BY PIECE

For researchers who want to investigate drugs that might slow ageing in humans, one approach is to test them not on ageing itself, but on conditions that become more common as people age — from arterial hardening, arthritis and heart disease to cancer, diabetes and Alzheimer's. "We're breaking ageing into pieces that we can tackle one piece at a time," says Joan Mannick, a clinician who serves as chief medical officer at resTORbio in Boston, Massachusetts, a spin-off of the Swiss pharmaceutical company Novartis. "We're tackling a common pathway that may be underlying multiple ageing-related conditions and looking at one condition at a time to see if we can have clinical benefit."

That approach is needed because the conventional view is that ageing is just to be expected, whereas an illness such as liver cancer is seen as something that went wrong. "The medical and scientific community have thought of ageing as something different from disease," says David Sinclair, a geneticist at Harvard Medical School in Boston and co-director of Harvard's Paul F. Glenn Center for the Biology of Aging.

Because ageing isn't viewed as an illness, Sinclair says, researchers are forced to find a specific disease to treat if they want funding to test a drug. Researchers hope that by tackling one age-related disease at a time while focusing on the underlying mechanisms, they can eventually build up the case that ageing itself is something that can — and should — be modified.

"If you started to get old at 60 or 70 and everyone around you lived to 200, your condition would be given a name and people would donate money to try and help your family," says Sinclair. "It's just how common it is that biases us to think that ageing is a natural — and therefore acceptable — way of life, just like cancer was 100 years ago."

Some people also question whether trying to treat ageing makes sense from a humanitarian standpoint. Brian Patrick Green, an ethicist at Santa Clara University in California, says that although there's nothing intrinsically wrong with extending human life, it does carry some risks. He worries, for instance, that people in rich countries will benefit while those in developing nations continue to die young. People living longer could also consume more resources, leading to social and environmental catastrophes, he says.

PROMISING PATHWAYS

In her former position as a researcher at Novartis, Mannick led a study that focused on immunosenescence, the decline of the immune system's function with age. The study showed that a rapamycin derivative, RAD001, helped to restore immune function in older people, such that their subsequent response to an influenza vaccine was more effective[1]. ResTORbio is now following that up with a small-scale study of whether the same drug can help older people to ward off lung infections. Mannick expects to get the results of that trial in the second half of next year.

AGEING IS JUST A BIOLOGICAL PROCESS.

Rapamycin is usually used to suppress the immune response, not to boost it — the drug is given to recipients of organ transplants to prevent rejection. It inhibits a protein known as mechanistic target of rapamycin (mTOR), which is part of a signalling pathway that affects ageing in organisms from yeast and fruit flies to mice. The protein senses environmental cues, such as whether a cell is getting sufficient nutrition. In good conditions, it signals cells to grow and reproduce; in times of stress, it shuts down reproduction and makes cells stress-resistant, which lets them live longer[2].

Although Kaeberlein hasn't yet received any funding for his dog study, he did run a trial funded by the US National Institutes of Health on 24 dogs. The work, published earlier this year[3], showed an improvement in the animals' cardiac function after just ten weeks of rapamycin treatment. Kaeberlein and his team had already seen the same effect in mice, demonstrating that it works in more than one species[4]. He says that Mannick's Novartis trial was the first to show that the results could be translated to humans using a measure affected by age — in this case, immune function.

One way that rapamycin might help to slow ageing is by tackling the problem of cellular senescence. Damaged cells can either undergo apoptosis, a form of cellular suicide, or they can become senescent, shutting down cellular division and sending out signals that lead to an immune response. That's beneficial for, say, dealing with a wound, but as people age, the mechanisms that clear away the senescent cells become less effective and the cells build up. That can lead to long-term inflammation of a variety of tissues, a risk factor in conditions such as heart disease. "Senescence is something that is good for the organism, but eventually it can become a problem," says Manuel Serrano, a cancer biologist at the Institute for Research in Biomedicine at the University of Barcelona, Spain.

Rapamycin can stimulate autophagy, the clearance mechanism for senescent cells. That could prove useful in diseases, such as Alzheimer's and Parkinson's, in which plaques build up in the brain. "All sorts of ageing-related neurodegenerative diseases might benefit from mTOR inhibition," Mannick says.

Rapamycin is not the only drug being explored to treat ageing. Another promising candidate is metformin, an oral medicine taken by people with diabetes. Metformin inhibits mTOR and has other effects related to cellular ageing: it improves autophagy and reduces tissue inflammation and DNA damage. Nir Barzilai, a geneticist who directs the Institute for Aging Research at Albert Einstein College of Medicine in New York City, has been trying to get funding for a metformin trial for ageing. His plan is to give the drug to people who already have one age-related disease — cancer, heart disease or Alzheimer's — and see whether the treatment reduces their likelihood of developing one of the others. Researchers have already found that people with diabetes taking metformin have lower rates of heart disease and cancer than a control group of people without diabetes; they also have less cognitive impairment and live longer overall[5]. "When you fix ageing on the cellular level, you fix a lot of other things," Barzilai says.

Both Barzilai and Sinclair are supported by the Glenn Foundation for Medical Research, which seeks to find ways to prolong healthy lifespan, and which funds ageing-research centres at 11 US universities. The US National Academy of Medicine is developing a Grand Challenge for Healthy Longevity, which will aim to encourage research by providing monetary prizes. Academics are not the only ones interested in this field of research. In 2013, Google founded Calico, a company it said would focus on health and wellness; the company put biologist Cynthia Kenyon, who discovered that a genetic mutation could double the lifespan of the roundworm *Caenorhabditis elegans*, in charge of ageing research.

In addition to Novartis, UK drug firm GlaxoSmithKline (GSK) has shown interest in ageing

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Red sea urchins have telomeres that do not shorten with age, so are of interest to researchers.

research. In 2008, it paid US$720 million for Sirtris Pharmaceuticals, a US company that Sinclair founded. Although the initial drug candidate, resveratrol, didn't work out and GSK absorbed Sirtris in 2013, the UK firm has continued to develop new molecules to activate a gene encoding the protein sirtuin, which has been shown to slow ageing in worms, fruit flies and yeast. James Ellis, who leads GSK's sirtuin research, says that the company is doing preclinical testing on these new molecules for a variety of inflammatory conditions. "Our compounds are being targeted to specific disease indications and not to ageing itself," Ellis says.

Drugs are not the only intervention that might slow or reverse ageing. "We know that exercise interventions can slow cellular ageing in many ways we can see," says Epel. Diet, exercise and social interaction can help people to live longer, healthier lives[6]. Epel aims to tie that to molecular measures of ageing, such as the length of telomeres. A telomere is an area at the end of a chromosome where DNA sequences repeat, protecting the chromosome from deterioration. The sequences get shorter with age as cells divide, and people with disorders that shorten their telomeres age faster. Some studies show that telomere shortening can be slowed, and that telomeres might even get longer under the right conditions[7].

Research is needed to see what, if any, effect exercise, diet and stress reduction have on the molecular mechanisms that underlie ageing, Epel says. "We know just observationally that longer telomeres predict less early disease and in some cases — not all — longer lifespan," she says. "But no one has ever shown that if you lengthen telomeres you then live with a longer healthspan. That is a gap."

A HUNDRED YEARS OR MORE?

So how much longer could people live if some of this research pays off? Some people talk about adding decades or centuries to life, perhaps by building new organs using stem cells and 3D printing, or by repairing cells using nanobots. British gerontologist Aubrey de Grey, for instance, thinks that humans could live for 1,000 years or more, and futurist Ray Kurzweil thinks that we will merge with machines in the next 30 years and become practically immortal.

Mannick thinks that longer health is the important focus. "I don't think about 'are we extending lifespan?' because we don't know if that is possible in humans, and many people don't want to live longer unless they remain healthy. I think an easier goal — and a very important goal — is to just keep elderly people free from the burden of disease," she says.

Sinclair is more optimistic. "Eventually, there's no biological reason why we couldn't live to 150," he says. "Many species on the planet do already. I think extending healthy lifespan by ten years is a goal that we will achieve in our lifetimes."

Just keeping people healthier for longer will be beneficial, says Kaeberlein, not only for the quality of life of individuals, but also for the economy, which will have to devote fewer resources to caring for ill people. "If we could keep people healthy an extra two decades, that would be more than has been accomplished in biomedicine over the past 50 years," Kaeberlein says. "We don't need to have people talking about immortality — and that's counterproductive in my mind — when the reality of what's possible and maybe not that far off is really exciting and really important." ■

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ANTI-AGING MEDICINE COMES OF AGE

Japanese medical doctors and researchers endeavour to promote people's healthy aging through ACTIVE INTERDISCIPLINARY RESEARCH and social outreach

In the era of longevity, anti-aging medicine is important not only for individuals but for society as a whole. Extending people's healthy lifespan and reducing medical expenses while maintaining the labour force is a top priority in countries such as Japan with a rapidly aging and shrinking population. Thanks to recent advances in the biological sciences, researchers are now able to intervene in aging processes at the molecular and cellular levels.

"It's time to use the scientific insights we have gained to directly enrich people's daily lives," says Shigeo Horie, president of the Japanese Society of Anti-Aging Medicine and professor and chairman of the Department of Urology at Juntendo University's Graduate School of Medicine.

INTERDISCIPLINARY RESEARCH

The society and its affiliated organization — the Japan Anti-Aging Foundation — have an unconventionally open modus operandi, which is characterized by a focus on interdisciplinary research and educating the general public about the latest medical breakthroughs.

"Medical research needs to move out of silos," says Horie. "Nowadays, much medical research has become excessively specialized. But anti-aging medicine is so complex it's important to exploit elements of many advanced research fields at the same time." The society consists of 9,000 practitioners and researchers with a variety of disciplinary backgrounds and provides opportunities for them to learn from each other. For example, researchers investigating a range of areas, such as longevity-linked sirtuin genes, bacterial flora in the intestine, and coenzymes involved in metabolism, gathered at the 2017 annual meeting to discuss the mechanisms of aging.

In 2015, the society launched an open access journal called *npj Aging and Mechanisms of Disease*, which covers all relevant disciplines of aging research. Two of the world's leading researchers in the field — David Sinclair from Harvard Medical School and James Kirkland from the Mayo Clinic,

Ryuichi Morishita, vice president of the Japan Anti-Aging Foundation (second from left), and Katsunobu Kato, minister for the MHLW (second from right), at the second Anti-Ageing Japan fair held in Tokyo in collaboration with Fuji Television.

The society's 18th annual meeting will be held in May 2018


Shigeo Horie, president of the Japanese Society of Anti-Aging Medicine

United States — have been invited to speak at the society's annual meeting next year, scheduled for 25–27 May 2018 in Osaka.

FOOD WITH FUNCTIONAL CLAIMS

Meanwhile, the Japan Anti-Aging Foundation is working hard to "improve people's health literacy, so they can take care of their health in a responsible way," says Ryuichi Morishita, vice president of the foundation and professor of the Department of Clinical Gene Therapy at Osaka University's Graduate School of Medicine.

The foundation played a role in developing Japan's new labelling system called 'Foods with Function Claims'. Two similar systems already exist in Japan, 'Foods for Specified Health Uses' (*tokuho* in Japanese) and 'Foods with Nutrient Function Claims', but companies need to spend tens of millions of yen for human clinical trials and wait 3 to 5 years to receive government approval. Moreover, due to strict regulations, the claims made on these labels do not typically provide detailed information — for example, a product might be labelled as "good for people who are concerned about bone health" rather than "helps prevent osteoporosis".

The new system allows companies to develop health products in a much shorter time at less cost. They can put their products on the market after submitting evidence of systematic literature reviews and simply reporting the results to the Consumer Affairs Agency. They can also label function claims more freely, and include a greater level of detail at their discretion — which makes it easier for consumers to understand the merit of health products.

MEDICAL RESEARCH NEEDS TO MOVE OUT OF SILOS

Since its introduction in 2015, more than 1,000 Foods with Function Claims have come to market, with products ranging from supplements and drinks to fresh foods such as mandarins, which a producer claims helps prevent osteoporosis.

In collaboration with the society, the foundation supports companies in accumulating reliable evidence on safety and functionality to help develop Foods with Function Claims. "Using drugs is one way to maintain health, but making healthy people healthier with foods is also important for the sustainable growth of society," says Morishita, who helped introduce the new system as a member of the government's Regulatory Reform Promotion Council.

SHARING KNOWLEDGE WITH THE COMMUNITY

Social outreach is another key mission for the foundation. In mid-September 2017, it hosted, in collaboration with Fuji Television, the second Anti-Ageing Japan fair in Tokyo. The event was supported by four ministries including the Ministry of Health, Labour and Welfare (MHLW) and the Japan Medical Association, and attracted more than 65,000 visitors in four days. In the opening speech, Katsunobu Kato, minister for the MHLW, discussed the government's policy on health care.

The foundation is also working with local governments to bring the 2025 World Expo to Osaka, Japan's second largest city. Under the theme of Designing Future Society for Our Lives, the Expo would present Japan's accumulated wisdom on how to lead a healthy life.

"People's health is closely linked with their social participation and relationship with other people," Horie explains. "Future anti-aging research should take this element more seriously, and that's why our efforts need to be so interdisciplinary and wide-ranging." ■

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