What it Takes to Reach...

The secrets to staying young may lie in the DNA of the oldest among us.

BY **LINDA MARSA**

"There are just two of us left now," Jemima Westcott says wistfully. Only she and her kid brother, a sprig at age 94, remain of a once-thriving family. Westcott's older sisters died at age 105 and 107, and she marked her own 105th birthday in January at a dinner party in her cozy condo in Brandon, Manitoba, surrounded by her children and grandchildren. Widowed for 50 years, she still lives alone, cooking and cleaning for herself — her only concession to old age is using a walker.

Westcott has lived through iconic events of the 20th century. She has vivid memories of the celebrations when soldiers returned home from World War I; of big picnics on her family's farm on the windswept prairies; of gas rationing during the second world war, when she was a young mother with five kids; and of traveling across Europe, North Africa and the U.S., and even diving in the Great Barrier Reef during a yearlong stint in Australia after she retired.

"I've had an adventurous life," says the former schoolteacher, an admitted night owl who stays up into the wee hours and likes to sleep in. Her secret to a long life? "Resilience."

Westcott may be on to something. She's a participant in the New England Centenarian Study, a long-term research project at the Boston Medical Center that studies why people like her enjoy such exceptional longevity. What they've found, thus far, is that healthy habits and positive attitudes will only get you so far: Centenarians are winners of the genetic lottery and, like Westcott, have a clustering of long-lived relatives. They are remarkably intact mentally, and up to 90 percent of them can function independently into their ninth decade. Surviving past age 100 means they've largely evaded the scourges that kill their peers before they reach their 90s (what's called compressed morbidity), or sidestepped the worst aspects of these life-threatening diseases — even if they strike sooner — because they have combinations of protective genes, what researchers call "greater functional reserves."

"Even though they have these illnesses, they handle them better than other people and

WILLIAM ZUBACK/DISCOVER; CANDLE ILLUSTRATION BY JAY SMITH

have better protective mechanisms," says Thomas Perls, a geriatrician at Boston University and director of the New England Centenarian Study. "In other words, the older you get, the healthier you have been."

Now scientists like Perls are sifting through millions of DNA markers to spot the constellation of longevity genes that's carried in every cell of these centenarians' bodies. Perls and his colleagues have uncovered 281 genetic markers that seem to perform a protective function, slowing aging and making this group less vulnerable to disease. Other researchers, in sequencing the genome of centenarians, have found they possess fewer of the genes that contribute to major diseases. "They live longer, in part, because they don't get sick," says Stuart Kim, one of the study co-authors and a geneticist at Stanford University.

How does this happen? Scientists suspect there may be some kind of intrinsic biological clock that runs slower in some people and quicker in


Jemima Westcott

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others, which would accelerate aging and wear down the body's protective processes. Those with faster clocks are then more vulnerable to the onset of fatal diseases and die sooner. Research into the genetics of long-livers, and into other biological systems that may influence aging, offers some tantalizing clues into the underlying mechanics of these clocks. Deciphering precisely how they work could enable us to tinker with these internal timepieces and genuinely slow down the aging process.

REAL AGE

Timing seems to be a key piece of the puzzle. Biological age doesn't always match what's on a person's birth certificate. After all, we're not surprised to see a 70-something debilitated by illness, or a 74-year-old who barnstorms around the country, running for president. Some people simply age faster than others, and scientists are beginning to understand why. New research using data from a landmark longitudinal study has been particularly eye opening. Known as the Dunedin study, it followed more than 1,000 people from their births in the early 1970s in the same hospital in southern New Zealand.

Most research looks at aging in older people, but the seeds of age-related diseases are planted decades earlier — that's why these researchers believe it's crucial to study aging in the young. They aim to shed light on why we become vulnerable to the assaults of time and the chronic diseases linked to aging, such as cancer, heart disease, diabetes, and loss of mental acuity. Scientists in the U.S., U.K., Israel and New Zealand looking at the Dunedin data used it to track 18 biological measures, including liver and kidney function, blood sugar and cholesterol levels, balance, cognitive ability, cardiovascular fitness and even gum recession in 954 study participants.

As expected, most people's biological age clustered around their early 40s, within a few years of their actual ages, according to results released last year. But there were wide variations: A handful were up to a decade younger, while many had a biological age in their 50s; one participant had a biological age of 61. Even before midlife, some participants were aging much faster. They were already having trouble with

TIM SMITH

climbing stairs and difficulties solving unfamiliar mental tasks, their balance was worse, their livers were starting to fail, and they were in poorer overall health.

"When we assembled all the data, we were quite struck about the coordinated changes we did see in all the systems of the body," says Daniel Belsky, the study's lead author and a gerontologist at Duke University's Center for Aging. "Clearly, there are basic molecular mechanisms of aging that cause the various diseases that disable and ultimately kill us."

THE CELLULAR COUNTER

More than 50 years ago, a researcher uncovered the first clues that an internal biological clock might regulate age — and that it's not just the daily assaults from the external wear and tear of life that cause us to wither and eventually die. That's when Leonard Hayflick discovered what would become known as the Hayflick limit. In the late 1950s, as a young microbiologist at the Wistar Institute in Philadelphia, Hayflick studied viruses that might cause cancer. While there, he worked with cell cultures derived from human fetal tissue. One day, the cell division in one of the flasks seemed to be slowing down, and after about the 40th doubling, the cells stopped reproducing.

At that time, scientists believed all cells were immortal — marinate them in the proper nutrients, and they would divide forever. Hayflick thought he had made a technical mistake or that the cells were contaminated. But then he observed the same halt in cell division in other cultures with different fetal tissues. He went back through his records, looking for clues to the anomaly, and discovered that of the many cultures he had made, it was always the oldest ones that had stopped replicating.

While cancer cells are immortal — their hallmark is wildly reproducing out of control — Hayflick discovered that normal cells have a limited life span. Even when cells are frozen for months, subsequent research demonstrated, when they thaw out, they pick up their cell division where they left off until they hit between 40 and 60 doublings.

"When I discovered that normal cells had a memory, I nearly fell of my chair. No one ever thought normal cells had a memory," Hayflick recalls. "There had to be some sort of intracellular counting mechanism or meter that tells the cells how many divisions it has gone through. But where?"

In 1975, Hayflick and graduate student Woodring Wright proved the counting device was in the cell nucleus, but they didn't have the technological tools to unlock the precise mechanism. Even though Hayflick's discoveries went against accepted scientific dogma — "I was the first one to show that aging had its origins inside the cell," he now says — they ultimately sparked an explosion in the study of aging. But another decade would pass before a candidate emerged for Hayflick's "replicometer."

DNA FRAGMENTS

Despite all the accolades heaped upon her for groundbreaking research, Elizabeth Blackburn retains the homespun warmth, sharp wit and plucky spirit of her native Australia. Early this year, the Nobel Prize-winning biochemist left her lab at the University of California, San Francisco, to head up the Salk Institute, the scientific incubator founded by polio vaccine pioneer Jonas Salk. The center is housed in a cluster of modern concrete and glass buildings perched on the coast in La Jolla, Calif. We sit at a conference table in her airy office, with floor-to-ceiling windows looking out on the Pacific.

Blackburn, who hails from Tasmania, an island off the coast of Australia, earned her doctorate degree in molecular biology from the University of Cambridge in England. In the 1970s she landed at Yale

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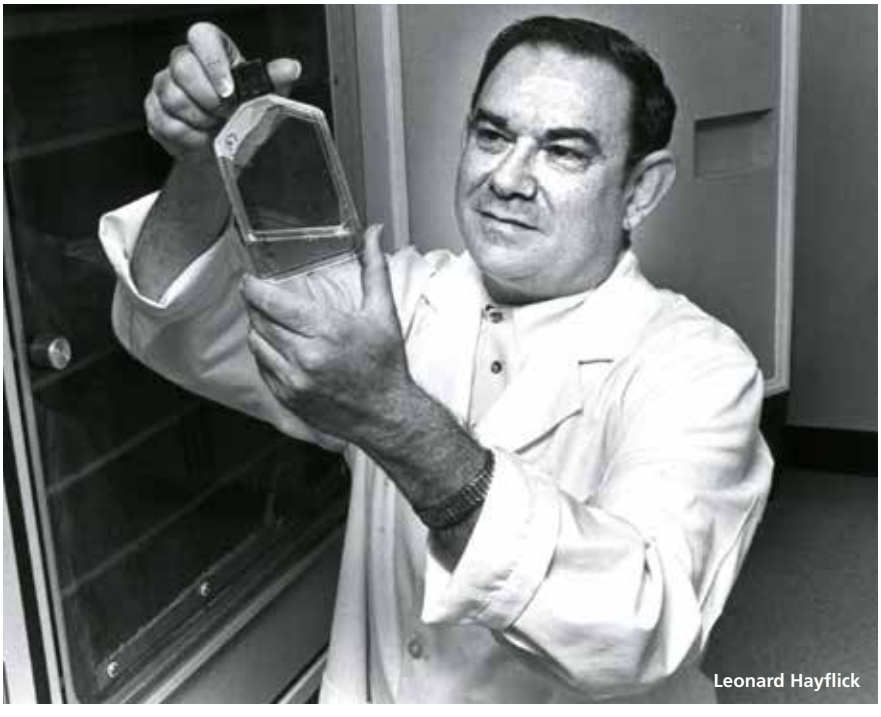

Leonard Hayflick

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University, where she sequenced the tips of chromosomes of a single-celled organism, *Tetrahymena* — "pond scum," she cheerfully offers. These tiny strips of DNA, called telomeres, cap the end of chromosomes. Scientists long suspected they stabilized the structure of the chromosome, preventing the tips from fraying, much like the plastic sheaths at the ends of shoelaces to prevent them from unraveling. But how?

Each time a cell divides, the telomere gets shorter, but its function had long been unclear. "We had the seeds of an idea [that] there could be a clocklike thing, because every time the DNA replicated, the end of the chromosome wasn't replicated," Blackburn recalls.

It wasn't until the late 1980s that a strong connection was made between telomeres and cellular aging, in a breakthrough that resulted from a bit of scientific serendipity. Blackburn's former graduate student, Carol Greider, was dating a biologist who shared lab space with Calvin Harley, a biochemist studying aging at McMaster University in Ontario. Casual conversations in the lab grew into a full-scale collaboration that melded Harley and Greider's areas of expertise — cell senescence and telomeres.

The result was two landmark papers published in 1990 and 1992 that made a convincing case that telomeres might be the cellular timing device behind the Hayflick limit. With each cell division, telomeres dwindle until they are just tiny nubs, which prompt cells to malfunction, stop replication and finally die off. This research provided "some good clues that we were going in the right direction," says Blackburn, "but it took years and years of observations by lots of scientists before the puzzle pieces were put together to form a real picture of what happens."

STUNTED TELOMERES

Telomere shortening is now considered a biomarker of cellular aging, and more evidence suggests that these tiny fragments of DNA may be one of the culprits behind age-related decline. Subsequent studies have shown that shortened telomeres are linked to many age-related diseases, including heart disease, diabetes, Alzheimer's, stroke and obstructive lung disease. "These are the major killers of the elderly," says Blackburn. "We're starting to go beyond just correlations and seeing a real element of causality here."

Even chronic stress can wear away our telomeres, according to research done in the early 2000s that looked at mothers caring for children with chronic diseases. Blackburn and UCSF psychologist Elissa Epel's work found that the most stressed-out women had shorter telomeres that translated into an extra decade or so of aging compared with their matched controls — showing that external stressors can throw a monkey wrench into the cell's molecular mechanics.

More recent research, presented at a scientific meeting in 2012, analyzed saliva samples from more than 100,000 people who belonged to Kaiser Permanente, an HMO in Northern California. The major take-home message: People with stunted telomeres die at younger ages. What was equally intriguing is that even though women outlive men, as young adults their telomeres are about the same length. While everyone's telomeres dwindle as they grow older, a big split occurs after age 50, when telomere shortening among men accelerates. The gender division continues to widen until about

TELOMERES AND AGING

Elizabeth Blackburn talks about the link.


Elizabeth Blackburn

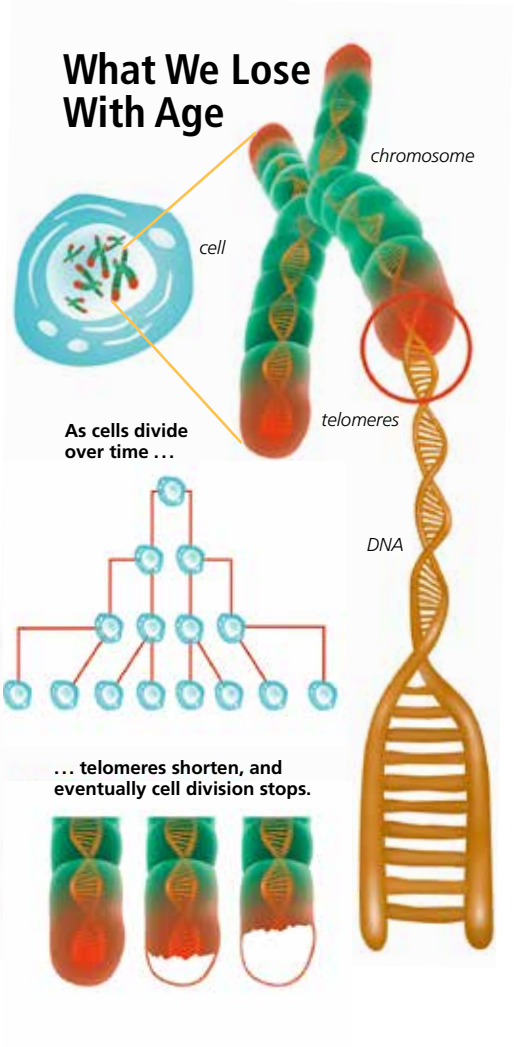
Telomeres are tiny fragments of DNA at the end of each chromosome. Nobel laureate Elizabeth Blackburn has spent her career studying their function. Here, she talks about the role they play in aging.

DISCOVER: Are telomeres the clock behind aging?

BLACKBURN: As a loose approximation, aging is clocklike because there's a progressiveness to it. But we've got to be smarter about what that word *aging* really means. Is human aging your risk of getting the *diseases* of aging? Well, in that case, centenarians never age. And yet, they clearly do age: They get wrinkled and frail and smaller — they're doing well but they're not young people. Aging has multiple aspects, and we tend to oversimplify it. A lot of different kinds of things come into play in different stages. If we avoid all the major diseases, there'll still be an aging process, which is not identical. Telomere shortening seems to underlie the risks for the diseases that kill you.

DISCOVER: In what way?

BLACKBURN: Every sign, including genetics, says there's some causality [between telomeres] and the nasty things that happen with aging, the really nasty diseases that kill us — heart disease, diabetes, cancer, even Alzheimer's. We know



age 75, when those with the blunted telomeres die from disease.

These results demonstrate at a molecular level what scientists tracking centenarians had observed: Longer-lived people have a biological advantage that enables them to escape or better withstand what Blackburn calls "the hail of bullets" that kill the majority of us. "Most mortality in the population happens around age 75, and anybody who lives longer has been somehow biologically selected," says Blackburn. "We know telomere shortening drives cells into senescence. So it is reasonable to say that this is driving pathologies in humans."

But telomeres aren't the whole story.

THE EPIGENETIC CLOCK

"There's a knot in here that's going to give you trouble," Jose Valencia warns me, speaking in Spanish through an interpreter while he massages the fleshy pad of skin between my left thumb and index finger, then flashes a mischievous, toothy grin, as if to tell me I'd better be careful. Barely 5 feet tall and clad in crisp khakis and a short-sleeve striped shirt, Valencia sits placidly on a bench in front of the cinderblock house he shares with his granddaughter, Keren Gonzales Valencia, in El Torito, Costa Rica, a tiny village honeycombed by dirt roads where the rainforest meets the beach.

It is a sultry November day with temperatures hovering in the low 90s. It's the end of the rainy season on the Nicoya Peninsula in the northwest corner of Costa Rica, and the jungle is lush from months of torrential downpours. A healer of local renown, Valencia taught himself anatomy by dissecting chickens — three of which lazily strut across the yard while we talk. He massages strained muscles and fixes dislocated joints when doctors are too busy, he says. Even the local expat surfers and retirees come see him when their backs hurt.

A farmer all his life, Valencia retired at age 80 when he was diagnosed with leukemia, but it barely slowed him down. He'll be celebrating his 97th birthday in a few days, he tells me, and shares bittersweet recollections of being a lovesick teenager eight decades earlier: There were no roads, and the only way he could visit his sweetheart in the next town was to walk along the beach. He attributes his long life

telomere shortening drives cells into senescence [aging]. If you look at people with wrinkled skin versus not wrinkled skin, the people with sagging, UV-damaged skin have shorter telomeres than people with smooth, unwrinkled skin. If you're in the bottom third of telomere length, your cardiovascular disease risk goes up 40 percent, which is not a trivial number. Pessimism correlates with shorter telomeres. So you can put all this together and say it's reasonable that some of this is really driving pathologies in humans.

DISCOVER: So the shorter the telomeres, the more likely it is you'll be stricken with diseases and that you'll age faster?

BLACKBURN: If you inherit very short telomeres, you get this terrible disease now being called the "telomere syndrome." It's extremely rare because these poor children don't survive into adulthood. But because there are billions of us on the planet, it's happened often enough that there are now hundreds of individuals and many afflicted families around the world. A child will come into the clinic with a skin disorder, but that's not the real problem: They have terrible gut disorders and their whole body is fraught with problems, and they have this whole spectrum of very nasty, very early onset diseases, which are the ones that often appear with age.

About 10 percent of them die of some rare cancer, and a lot of them die of infections, and their guts don't work properly and they're really sickly. But then you look at the parents and the grandparents because this gene has to come from somewhere. And you find the grandparent with the gene had pulmonary fibrosis. So the molecular cause is exactly the same base pair change in a telomerase gene. But it played out in the body differently. The grandparent's telomeres were shorter than their peers' and the parent's telomeres were even shorter, and the child's were really short.

So what if people inherited somewhat shorter telomeres and never completely recovered or do things that we know externally promote shortening of telomeres, like smoking or living in stressful situations? They might do just fine, but if there's something else going on combined with the shorter telomeres, that might be enough to kill them. Telomeres are not the end of the story, but they play a role.

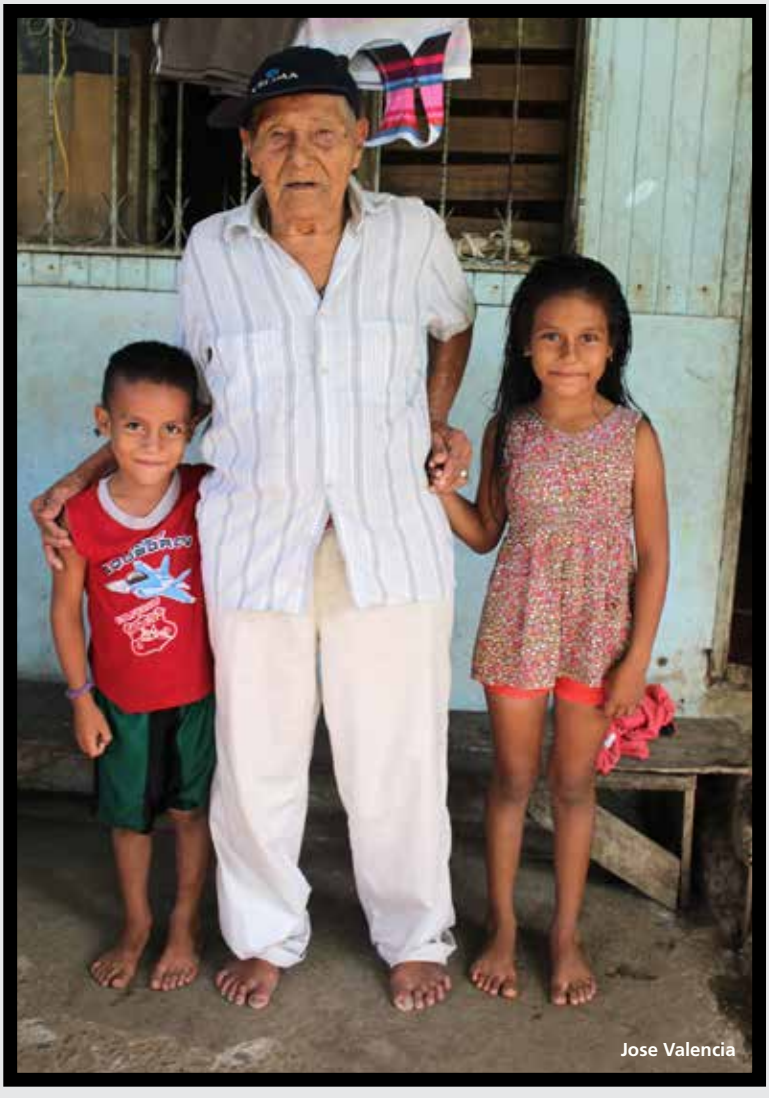
—L.M.

TOP: GWEN SHOCKEY/SCIENCE SOURCE. BOTTOM: JANERIK HENRIKSSON/AP/GETTY IMAGES

to hard work, good food and family — his wife died less than a year ago and his extended family of children, grandkids and great-grandkids all live nearby.

But his longevity is not unusual for the Nicoya Peninsula, an 85-mile sliver of pristine beaches, cow pastures, farms and wooded hills, where residents often reach ages of 90, 100 or even 110. Despite their poverty, locals live far longer than their wealthier counterparts elsewhere. The peninsula is one of the world's five Blue Zones, where more people live past 100 than in other parts of the world. The other four longevity hot spots are Okinawa, Japan; Loma Linda, Calif.; Sardinia, Italy; and Ikaria, Greece.

In 2005, Costa Rican demographer Luis Rosero-Bixby found that Costa Ricans who survive to age 60 end up having the longest life expectancy of anyone in the world. Subsequent research in 2012 found that older residents of Nicoya lived even longer, up to three years more than other Costa Ricans. In research published in 2013, Stanford University epidemiologist David Rehkopf and his colleagues wanted to find out why. They took DNA samples from Nicoya residents who were older than 60 to measure the length of their telomeres. They turned out to be longer than those of other Costa Ricans, with an average difference of about 81 base pairs, equivalent to the benefits of quitting smoking or getting regular physical activity.


Jose Valencia

Our life experiences exert a profound influence on how we age and can alter the ways genes function without changing the underlying DNA sequence; these genetic changes are called epigenetic traits.

Why do those on the Nicoya Peninsula live so long? The key seems to be in the nation's familiar catchphrase: pura vida, or "pure life." Costa Rica, a centuries-old democracy with universal health care, no standing army and the highest literacy rate in Central America, has been relatively insulated from the corruption, narco-terrorism and civil wars that have plagued neighbors like Panama, Nicaragua and Guatemala. Researchers believe Nicoyans' leisurely pace of life, plant-based diet, network of family and friends, regular exercise and purposeful lives seem to be their recipe for longevity.

While outside forces — stress, poverty, environmental toxins — can accelerate aging, the reverse seems to be true, too. Our life experiences exert a profound influence on how we age and can even alter the ways genes function without changing the underlying DNA sequence; these genetic changes are called epigenetic traits. A research team at UCLA led by biostatistician Steven Horvath has uncovered an epigenetic biological clock that may provide a key puzzle piece in deciphering how this happens — and help explain why Nicoyans live so long. "For those people who age more slowly, somehow their epigenetic clock ticks more slowly," Horvath says. "There's an intrinsic process that drives aging, and that may be what's captured by this epigenetic clock."

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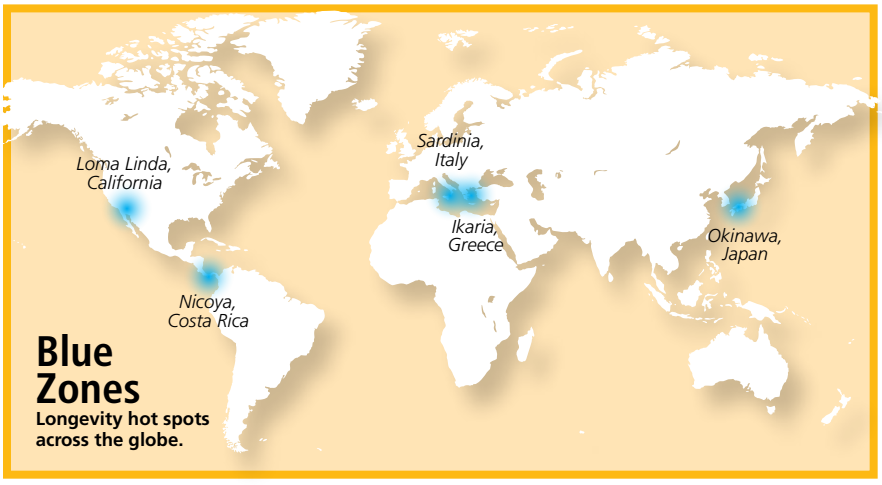

THE MECHANICS OF AGING

For the German-born Horvath, a boyish 48-year-old with broad features and a puckish sense of humor, the discovery is the fruition of a lifelong dream, dating back to high school, when he decided to devote his career to prolonging the human life span. But it wasn't until 2006 that the advent of big data allowed him to sift through millions of data points to ferret out biomarkers that correlated with age.

His team focused on a naturally occurring process that's part of the body's internal housekeeping system, called methylation, which makes chemical modifications to our genome that are strongly influenced by environmental factors. Horvath was able to obtain over 50 datasets — from researchers in Spain, Germany, Italy, the U.S., U.K. and Australia — that contained the genetic profiles of thousands of subjects in studies looking at methylations in healthy tissue.

Over the course of three years, Horvath and his team analyzed nearly 8,000 tissue samples from these datasets, which included blood, saliva and cells from organs like the brain and the colon. The UCLA team identified 353 DNA markers from 51 types of cells and tissues and examined how age affects their DNA methylation levels throughout a lifetime. They then used the data to devise an algorithm that can accurately determine the age of diverse organs, tissues and cell types.

When they compared a tissue's biological age and its chronological age, the clock proved to be remarkably accurate in predicting age. Stem cells plucked from embryos were deemed extremely young by the clock, while neural cells from centenarians were estimated to be about 100. And even cells that were young, such as white blood cells that may be just a few days or weeks old, still carried the distinct genetic imprint of their 50-year-old donor. "The 353 markers on the DNA provide a weighted average that gives you a very accurate measure of the age of the tissue," says Horvath.

Since then, he has used the epigenetic clock as a tool to begin to understand the mechanics of aging. Subsequent research on Italian centenarians revealed that the offspring of these centenarians were substantially younger, up to about five years, according to their epigenetic clocks, than the progeny of non-centenarians.


Steven Horvath

But perhaps Horvath's most significant finding had its genesis in 2013, when researchers from the Los Angeles Gerontology Research Group, which studies supercentenarians (those who live to 110 and older), supplied him with tissue samples from three centenarians and three supercentenarians, one of whom recently died at age 112. What Horvath uncovered was astonishing — and may eventually lead the way to extending our life.

The research team analyzed the epigenetic age of up to 30 anatomic sites from the 112-year-old woman. They discovered that the cerebellum is the youngest part of the body and didn't age nearly as fast as other areas. The neuron-packed brain region — it's tucked underneath the cerebral hemispheres and plays a role in motor control and cognitive functions, such as attention and language — seemed to stop aging at the 80-year benchmark, which meant it remained fully functional but somehow impervious to deterioration of time for decades.

Earlier this year, Horvath and his colleagues took a step toward answering this question. Their analysis uncovered small variations in two genes related to the accelerated aging of the cerebellum. What was especially "exciting" about this finding, he says, is that these variations were near a neural highway that previous studies have shown helps regulate life span in worms and flies, and that stopping chemical signals from this brain pathway extends the life span of mice. While this discovery is still not a "smoking gun," says Horvath, "if we can understand why the cerebellum ages more slowly, we can figure out how to slow down all the other parts and uncover interventions that might be able to reverse this process." D

Linda Marsa *is a* Discover *contributing editor and author of* Fevered: How a Hotter Planet Will Hurt Our Health and How We Can Save Ourselves.

FROM TOP: ILDOGESTO/SHUTTERSTOCK; UCLA