LIVING LONGER | SCIENCE

AGE DISRUPTERS

A DRUG FROM DIRT AND SOME SIAMESE MICE HAVE RESEARCHERS INCHING TOWARD THE SEEMINGLY IMPOSSIBLE: A CURE FOR AGING

BY ALICE PARK

IF THERE WERE GUINNESS WORLD RECORDS DEDICATED to high-achieving rodents, Mouse UT2598 would deserve a mention. The average life span for a mouse is 2.3 years—so at age 3 and still going strong, Mouse UT2598 has a shot at beating the record for longest-lived, which stands at about 4. Translating that to a human life span, he’s hovering around the centennial mark, but on the outside, he looks no different from his much younger brethren. His fur is glossy black, he’s lean, and while he’s a bit on the small side, he’s scrappy and surprisingly active as he explores, sniffs and pokes around his cage at the University of Texas Health Science Center at San Antonio.

What gives Mouse UT2598 his edge is a compound called rapamycin, which seems to slow aging and the damage it can do, at least to certain cells. His liver and heart function as if they were far younger, and his tendons have more spring and flexibility than they should at his age. There’s also less evidence of tumors in his organs than is considered normal, so he could be spared the effects of cancer for quite a while longer. Place him alongside other mice his age, and the contrast is unmistakable.

The experiments involving Mouse UT2598 and rapamycin are just one example of the kind of research into aging that’s producing new findings—and raising new questions—every day. In labs around the world, researchers are testing all sorts of agents, some of which already exist as drugs to treat human conditions (rapamycin is given to transplant patients to prevent organ rejection.

Photograph by Evan Kafka for TIME
after surgery) and some of which are purely experimental. Scientists are also toying with ways to manipulate genes and pull out aging cells, all in a race to find a way to extend longevity to its outer limits.

These efforts mark a new push to examine the basic mechanisms of aging and find ways to counteract—or "cure"—them. And they are anything but fringe. Longevity research is being conducted by respected scientists with sound reasons for staking their careers on the hubristic notion that it's possible to slow down aging and maybe even reverse it.

“When I got into the field, the notion that you could actually do something about the aging process was viewed as a crackpot idea,” says Richard Miller, director of the Glenn Center for the Biology of Aging at the University of Michigan. “The argument that one can slow aging, and diseases of aging along with it, used to be fantasy, but now we see it like a scientific strategy.”

Nobody is talking about living forever. But as these experts see it, aging is the single most powerful factor in the diseases that are most likely to cut our lives short: cancer, heart problems, immune disorders and degenerative brain conditions like Alzheimer’s. “Everybody knows that the main risk factors for heart disease are high cholesterol, obesity and high blood pressure,” says Dr. Felipe Sierra, director of the division of aging biology at the National Institute on Aging (NIA). “But even stronger than those factors is just being 70 years old.”

And that’s why staving off aging—or at least slowing it—has become such a central focus of research. “We’re going at aging itself,” says David Sinclair, a geneticist at Harvard Medical School. “We might take someone who is showing signs of aging and be able to do something about it, to treat that as a disease. That’s something I didn’t expect to be seeing in my lifetime.”

A Modern Antiaging Elixir

MOUSE UT2598’S LONGEVITY DIET LACED WITH RAPAMYCIN traces its existence back to some dirt samples collected in 1964 on an expedition to Easter Island. Those soil samples became the basis for developing a new antibiotic, which was named rapamycin. Researchers noticed that mice that were given the drug tended to live longer—by about 20%, compared with those that weren’t taking it.

“Rapamycin is neat because it works in a wide variety of species, from yeast, worms and flies to mice,” says David Harrison, who is studying the compound at the Jackson Laboratory, where scientists mine the genome for solutions to human diseases. He and Miller, along with Randy Strong—in whose lab Mouse UT2598 resides—are also testing other agents in a program sponsored by the NIA. “Rapamycin is also neat because it works even when you start quite late in life.”

Because of a delay in formulating rapamycin so it remained stable in mouse chow, the first animals to try it were already getting gray—they were 20 months old, or the equivalent of 60 years in people—but they still showed slower aging once they took the compound. If the research eventually leads to a human treatment, that could bode well for older people; they could potentially enjoy the same benefits that this lucky mouse is experiencing, even if they start in their 60s or 70s.

It turns out that rapamycin interrupts the function of a gene called mTOR, found in both mouse and man, which acts as a traffic signal for directing how cells take in and use energy. If there’s plenty to eat, the

PUSHING THE LIMITS OF LONGEVITY

1925
Turn-of-the-century health regulations, requiring improvements such as clean water and better sewage disposal, curb outbreaks in the U.S. that are particularly deadly to children.

1955
Thanks to vaccines for smallpox, diphtheria, polio and other highly contagious—and often lethal—viruses, average life expectancy goes up.

1985
Public-health campaigns on heart health and the dangers of smoking reduce heart-disease deaths. Medical advances also help extend life.
gene is busy greenlighting cells to absorb nutrients and grow, grow, grow. When food gets scarce, the gene goes quiet, halting the cell-growing machinery until the next feeding time. While mTOR may explain, in part, the phenomenon of calorie restriction and its ability to prolong life—in the 1930s, studies in mice showed that cutting back on their daily diet could add nearly a year to their lives—there's also evidence that it taps into other energy-related pathways to longer life as well.

The more active state—the one in which cells are processing nutrients and growing—turns out to age cells considerably: as our cells are working hard to process our food, they also spew out toxic free radicals. The goal, then, is to keep mTOR as subdued as possible, preferably without requiring animals to starve themselves miserable. And that's what rapamycin appears to do.

So far it's the most promising compound under study, and Harrison and his colleagues are optimistic, though cautious, about its future. After all, resveratrol, a compound found in grapes and red wine, showed early promise in mice that gorged on high-fat diets, extending their lives, but it wasn't as impressive in helping animals on normal diets live longer. (Researchers aren't ready to give up on it yet, however, and it's still being studied at GlaxoSmithKline.)

While rapamycin dials up one antiaging circuit, it's clear that it is not yet a fountain of youth. "I'm 72, but I'm not popping rapamycin pills yet," says Harrison. Consider the downsides. In mice, it has resulted in a body size that is about 30% smaller than average, and mTOR-regulated mice were also more likely to develop cataracts and were more prone to diabetes. The males tend to experience gradual loss of testicular function—not exactly a selling point for a future longevity treatment.

Human patients who took the drug after kidney transplants to lower their chances of rejecting the organ, for instance, also had slightly higher chances of developing diabetes, and the risk of cataracts requires more study before a broad application of the drug would be possible. Still, given the fact that rapamycin is already approved and safely taken by patients, antiaging researchers are hopeful that they'll be able to arrive at the right doses to tip the balance in favor of longevity while minimizing potential risks.

Find the Switches to Flip

For other researchers, the key to longevity may be in our genes. Telomeres are the timekeepers of a cell's life; each time a cell divides, it copies its chromosomes' DNA, and like a knot tied at the end of a thread, telomeres signal the end of the copying process. With each cell division, these little squiggles, which are the final segments of DNA at the ends of chromosomes, shorten—eventually disappearing altogether. And because certain things like exposure to UV light can cause telomeres to shorten at different rates, they're a target of lots of new antiaging research too. (For more on how telomeres are being studied, see page 86.)

In healthy people there is a balancing dance between the shortening of telomeres and the work of an enzyme called telomerase, which lengthens them just a little bit, to restore some of the DNA that's lost. But that doesn't happen in people with telomere-syndrome conditions—which includes some bone problems, liver failure and immune-system disorders. It's what makes those terrible conditions research gold for antiaging scientists.
If they can figure out how to correct the misbehaving telomeres in those people, they may be able to correct them in normally—but inexorably—aging people too.

Twelve years ago, Dr. Mary Armanios met her first patient with such a condition while she was training with Carol Greider, a scientist who shared a Nobel Prize for the discovery of the enzyme telomerase. Through their lab at Johns Hopkins School of Medicine, Armanios met a college student with a blood disorder that required regular transfusions. He was in his 20s but had a shock of gray hair that had first appeared when he was 9. This alone was unusual, but his family history also intrigued her. Almost all his relatives on his father's side died young. His paternal grandmother, who had severe osteoporosis and bone disorders, died in her 60s. His father died at 59 while waiting for a liver transplant. His aunt and uncle died of pneumonia in their 60s. The young man, too, had been in and out of hospitals most of his childhood to treat infections. He eventually died, at age 31, of a staph infection.

"The cosmetic symptom was hair graying, but they all have a form of hair graying in other organs as well," says Armanios. It turned out that the family members all had dyskeratosis congenita, a rare condition with an extreme form of telomere dysfunction.

Armanios is confident she might learn something about how telomeres are supposed to work—and even how they might be manipulated and extended to halt aging-related problems, not just in those with dyskeratosis congenita but in healthy older populations as well.

One strategy may involve dosing cells with the right genetic ingredients to lengthen telomeres, as Helen Blau and her colleagues have done in petri dishes at Stanford University. "We turned back the clock on the cells by the equivalent of many years in human life," Blau says.

Even more encouraging, the cells didn't continue to divide indefinitely, which might raise concerns about uncontrolled growth, as occurs in cancer. "They start to [deteriorate] normally, and that bodes well for safety," she says. Eventually, Blau hopes the cells will be tested in the liver or lungs of patients with dyskeratosis congenita, where they can target the rapidly aging cells. If that is successful, the same techniques might turn back the clock on aging cells in the rest of us.

**So Simple and So Strange**

**BUT THERE MIGHT EVEN BE A QUICKER—IF ODDER—WAY**

to defy aging that literally exploits the power of young blood. Relying on an innovative technique in which young and old mice can be conjoined, Siamese twin-style, to share the same blood system while keeping everything else separate, Amy Wagers at the Harvard Stem Cell Institute found something in the blood of younger mice that seems to rejuvenate an aging animal. The older mice that were yoked to the younger ones showed more new nerve-cell growth in their brains, their muscles were stronger, and in one study, some of the enlarging of the heart that comes with aging was reversed. "Their tissues are functioning more like younger tissues," she says.

What appears to be one of the secret ingredients here is GD11, a protein that's abundant in young animals' blood but is scarcer in older ones. Wagers is conducting more studies in both animals and people to see if longer-lived people have higher levels of GD11 or whether people with low GD11 might be more vulnerable to age-related diseases such as heart problems, cognitive decline and muscle atrophy.

And GD11 isn't alone in showing such promise. At the University of California, San Francisco, neurobiologist Dena Dubal is investigating a hormone called klotho, named after the Greek fete responsible for spinning the thread of life for mortals. Increasing the klotho levels in mice helps animals live 30% longer, and in 5 people also carries a version of the klotho gene that boosts its amounts. On average, those individuals live an extra three to four years. It's not the hormone of immortality, but it's a start.

Manipulating klotho, GD11, telomeres or any of the longevity genes could involve some invasive and high-tech interventions, including gene therapy and even cell transplants. But what if all those efforts are overthinking the solution, and it's possible to put the brakes on aging by simply removing aging cells, like plucking out gray hairs? That's what Dr. Jan Van Deuren and his team are pursuing at the Mayo Clinic. By seeking and pulling out dying cells in the muscle, fat and eyes of mice, he's helping them live longer than control animals. "We're getting rid of a cell type you don't have when you're born, something that accumulates over time that may not really be needed for survival," he says.

He is the first to admit that there is still plenty about that strategy—as well as other promising aging interrupters—that scientists don't understand. For example, are rapamycin-fed mice living longer because their cells are actually functioning like younger ones or because they're simply delaying aging conditions like cancer and heart disease? Are the old mice infused with young blood truly younger again, or are their rejuvenated cells only temporarily acting more youthful? And while we know more every day about the roles telomeres play in the aging process, is the answer as simple as finding ways to safely lengthen them through drugs? They aren't easy questions to answer, but aging experts welcome them.

That's because what's happening in these labs is not just about extending a life indefinitely but rather extending a healthy life for a little bit longer. And researchers say they're truly optimistic that breakthroughs will come in their lifetime. After all, says Harrison, "It must not be all that complicated, or we wouldn't be having the success that we're having."