AGING AS A MODIFIABLE RISK FACTOR

BY JENNY BLAIR

FOREVER YOUNGISH

Johanna Quaas is a gymnast. In recent videos, she does somersaults, headstands, and lithe leaps and turns. With arms bearing her entire weight on the parallel bars, she holds her body horizontally or upside-down, pausing for long, graceful moments before lowering herself again. It's more than impressive—it's astounding. Quaas was born in 1925.

Though she's in her 90s, Quaas would put most young people to shame with her athleticism. Biological pathways we're just beginning to understand give some people extraordinary resilience to aging, while leading others to become worn down in their 50s. Researchers at the University of Pittsburgh Aging Institute are working to unlock the genetic and metabolic secrets inside people like Quaas—and duplicate them with practical therapies.

This summer, the Institute welcomes new director Toren Finkel, who will lead a basic and translational research effort on aging that is unprecedented at Pitt.

Pitt researchers want to slow the rate at which we age.

ILLUSTRATION | JULIETTE BORDA

"Aging is the biggest risk factor for every [chronic] disease that we have to deal with, but it's always been dismissed as nonmodifiable," says Finkel, who comes to Pitt from the National Heart, Lung, and Blood Institute.

"It's becoming possible to think about intervening in the rate of aging, pharmacologically. You could really slow the rate that you age, and thereby, slow the rate that you develop all of these diseases. That's incredibly exciting."

As we age, a lot of things tend to go wrong in our bodies. Our cells' housekeepers fail to show up. Our energy sensors sense wrong. Our nondividing cells sit there and cause trouble. The telomeres—caps on the ends of DNA—wear down. Genes get switched on and off at the wrong times. The bacterial population in the body can veer away from a healthy mix.

What scientists are beginning to realize is that these processes are often connected, that they can show up as many different diseases that have a lot in common, and that certain points along these pathways offer promising drug targets. In other words, the common chronic diseases of aging—including neurodegeneration, cancer, and heart disease—are linked.

Pitt and UPMC officials believe a holistic research effort that unites researchers from a variety of fields under a leader who's willing to totally rethink aging could yield enormous benefits.

"Toren Finkel is a fantastic researcher and wonderful human being who's going to fit into our culture extremely well," says Steven Shapiro, the executive vice president and chief medical and scientific officer of UPMC. "He has not only a great understanding of basic science, but an urgency to translate this into clinical programs and help patients. He spent the first half of his career defining these pathways. Now he wants to do something to help people."

With the renowned Charles Reynolds, UPMC Endowed Professor of Geriatric Psychiatry, at the helm for many years, the Institute already offers top-notch clinical care for Western Pennsylvania elders and caregivers. It educates professionals and laypeople in geriatrics. And it has conducted important clinical research while building its basic science portfolio.

Finkel will expand the Institute's investigations in geroscience, the study of the relationship between aging and disease. That's not to be confused with gerontology, the study of aging, or with geriatrics, the branch of medicine dealing with treating disease in elders.

Geroscience aims to discover, test, and develop drugs and lifestyle changes that could lengthen not only life span, but also health span—the period of life during which a person remains free from serious illness.

An interesting thing about people who survive nearly a century or longer is that they tend to remain in good health for most of their lives. Life span and health span are, somehow, tightly linked.

Finding drugs that alter aging pathways enough to lengthen health span could fundamentally alter the practice of Western medicine, which now emphasizes the diagnosis and treatment of disease.

"Your DNA is repaired. Your mitochondria are strong. You avoid developing that cancer in the first place, you avoid developing that lung fibrosis, you avoid developing that coronary disease," says Mark Gladwin, who holds the Jack D. Myers Chair of Medicine and helped recruit Finkel to Pitt.

"We're not trying to make people live beyond 120," he adds. "But wouldn't it be great if you could live a strong, healthy life until you're 95 to 120 and die peacefully in your sleep? Wouldn't that be the dream we'd all have?" No one dies purely of "old age," but a sudden deadly stroke or fall might be an enviable exit.

In the United States today, there are 46 million people age 65 or older, a number expected to double to 98 million by 2060—nearly a quarter of the country's population. By 2030, about 2.3 million older U.S. residents will require skilled nursing care, a 75 percent increase from 2010. This isn't just happening in this country. Sometime before 2020, the number of people on the planet age 65 and older will surpass the number of children under age 5, a first in human history.

Caring for these folks can be difficult. More than 90 percent of elderly people today have at least one chronic health problem, and three-quarters have at least two. Such diseases consume three-quarters of U.S. health care dollars. A 2013 study published in *Health Affairs* concluded that delaying aging's complications by just 2.2 years would lead to a savings of $7.1 trillion throughout 50 years.

Industry has caught on to the promise of anti-aging drugs. A small study by the drug company Novartis made headlines in late 2014 when it found that giving a drug called rapamycin to elderly people boosted their response to the flu vaccine. (We'll come back to rapamycin in a bit.) Google's life-sciences company Calico partnered in 2014 with pharma giant AbbVie to run clinical trials on anti-aging compounds.

"[Geroscience] really started to gain traction in the last five years. There's a lot of interest in trying to look at common themes across the system so that we can be able to treat aging more systemically and less from a disease-specific approach," says Fabrisia Ambrosio, an associate professor of physical medicine and rehabilitation who has helped nurture basic aging research at the Aging Institute for the past several years. "Why is it that over time our cells seem to default toward this more dysfunctional nature? And what can we do to counteract it?"

Finkel and his colleagues are determined to find out. The chief strategy: to identify and test small molecules in house, then pass them along to the Institute's translational and clinical scientists for human trials and eventual commercialization.

The son of a NASA physicist, Finkel majored in physics. But thanks to an inspiring professor, the biology bug bit him. As an MD/PhD, Finkel tried his hand at molecular biology bench research, mentored by physicist-turned-biologist Wally Gilbert, shortly before Gilbert jointly won the 1980 Nobel Prize in Chemistry. After completing his training as a cardiologist, Finkel joined the National Institutes of Health, where he remained for 24 years until his jump to Pitt this year.

Finkel first made his name in 1995 with a paper in *Science* describing his lab's discovery that reactive oxygen species (ROS)

within the cell, specifically hydrogen peroxide, are actually important in cell communications. This was a surprise. For decades, these molecules were thought to be purely destructive, to be gotten rid of, pronto, with antioxidant foods and pills. Yet clinical studies found that antioxidant foods and pills didn't bring the hoped-for benefits.

"Our work provided an explanation for why it may not be so good for you to just completely scavenge off oxidants," Finkel says. The paper has been cited more than 2,000 times. It touched off a new field called redox signaling.

At that time, Finkel didn't consider himself an aging expert. Then *Nature* asked him to write a review of aging research to appear in 2003. The editors knew he was an outsider. Finkel believes that by selecting him, they were tacitly acknowledging cracks in the foundation of the oxidation-causes-aging theory (cracks that Finkel's own work had helped put there).

As Finkel prepared to write the review by reading scientific literature on aging, he recalls, he was "blown away" by some of the discoveries in the field.

"This central question was so fundamentally important, and so poorly understood, that I was hooked on the topic," he says.

Finkel soon steered his lab toward questions of aging in mammals. Through time, he has helped to illuminate some pathways down which aging proceeds, and some promising ways to intervene.

In any complex system, be it a spaceship or a cell, maintenance is a must. Cells constantly recycle broken parts and repair damaged DNA to stay fully functional.

One crucial kind of cellular housekeeping is called autophagy—literally, self-eating. It's a process in which cells break down and reuse their own damaged or aged components in response to stress. Autophagy recovers energy and resources while clearing away useless organelles, membranes, and protein. As autophagy slows with age, though, debris can accumulate, and evidence suggests that cancer, impaired immunity, and neurodegenerative disease can result. Aging Institute researchers would like to find a drug to rev up widespread autophagy or mitophagy.

Finkel is studying the latter, a type of autophagy in which mitochondria are the objects recycled. The descendants of ancient symbiotic bacteria, these cylindrical organelles are the cell's power plants, and they're also important in cell signaling, metabolism, and trafficking. Mitophagy helps cells regulate energy production and protects cells from defective mitochondria, which can more or less poison their surroundings.

The Finkel lab has demonstrated that, in the area of a mouse's brain that encodes learning and memory, mitophagy slows dramatically with age.

"We think that may be important for why memory and learning decline as we age—you're not able to turn over [and] get rid of the damaged mitochondria," Finkel says.

There is an unpleasant but effective way to activate autophagy: a near-starvation diet. Cells normally scavenge their own damaged components for energy; if they sense starvation, they go on a scavenging frenzy. Calorie-restricted diets are known to dramatically increase life span in yeast, fruit flies, nematodes, and mice.

Beibei Bill Chen, an assistant professor of medicine and a drug discovery expert, has met humans who are privately experimenting with this approach.

"I went to a lot of meetings recently, and all the big shot scientists—everybody I know—is on this calorie-restriction diet," he says. (Finkel is not one of them—"I love eating too much," he says.)

"Of course we all want to live a happy life," Chen says. "You tell me I cannot eat cheeseburgers, I can only eat one meal a day—that's kind of hard. That's why we're trying to see whether we can come up with a therapy approach, maybe a pill or small compound inhibitors … that can still achieve the same goal here. That's the ultimate dream—to find a way to activate autophagy without doing the calorie-restriction diet."

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Chen, who is also director of the Small Molecule Therapeutics Center, is well equipped to help with the search. The center includes libraries of molecules that can be tested by the thousands—first virtually, via supercomputer, then with real-life assays—for various functions, like stimulating autophagy. He has already found one compound that boosts mitochondrial function and another that induces autophagy, and he's working to commercialize them.

Another aspect of cellular housekeeping is DNA repair. This, too, is a constant necessity. DNA is always under assault from one thing or another, be it oxidative stress, replication errors, botched corrections, tobacco and alcohol, air pollution, or infections. Mutated DNA can lead to cancer or simply malfunctioning cells. Fortunately, we have enzymes that read and repair our DNA. Stronger DNA repair systems could mean better resistance to age-related complications in general, so they're something we'd like to learn to shore up as well. (As long as they don't promote

cancer—cancer cells themselves are famously good at DNA repair.)

Pitt has one of the strongest groups in the world dedicated to understanding DNA repair and genome stability. This summer, Aditi Gurkar from the Scripps Research Institute in Florida will join Pitt as an assistant professor of medicine. She studies how DNA damage leads to aging.

"Until now, we have not found anything that can keep our DNA completely safe. That's almost impossible—in fact, it's not good for us," Gurkar says, pointing out that DNA mutation allows for adaptation and evolution. "What is then important is: how do we react to the damage that is already there?"

Gurkar's research focuses on the fact that repairing DNA damage costs the cell a lot of energy, which is supplied by mitochondria. Under normal circumstances, mitochondria are recycled as needed (mitophagy!), with a process that keeps destructive ROS at a safely low level. But when DNA requires constant repairs, there is an ongoing demand for the intracellular energy-transfer molecule ATP, and the cell halts its ordinary recycling of mitochondria to save energy. In the process, more ROS are created, an increase that can lead to age-related disease.

It is perhaps not surprising that the many processes that control the creation, folding, and destruction of proteins (an aspect of cellular housekeeping known as proteostasis) can go wrong. Protein folding alone is an immensely complex process that challenges the powers of supercomputers to model. Proteins tend to misfold more with age, and age-related diseases like Alzheimer's and Parkinson's involve the buildup of clumps of nonfunctional proteins. It's the job of autophagy to recycle those botched proteins, perhaps 800 other proteins, and it's a star player in the world of aging.

In yeast, worms, flies, and mice, what inhibits mTOR lengthens life. Inhibiting mTOR blocks cellular proliferation (which effectively also blocks cancer growth), activates cell-cycle arrest, improves the growth of new mitochondria, and improves insulin sensitivity. Giving a genetically normal mouse the drug rapamycin inhibits mTOR and boosts the animal's life span by 10 percent.

Perhaps it's not surprising that rapamycin, originally used as an antifungal, is also an immunosuppressant and a cancer suppressor. Drugs like it are studied and used for a wide variety of indications—its derivative sirolimus, for example, is used in drug-eluting coronary stents, as well as to prevent rejection of transplanted kidneys. (Note how distinctions blur, at this level of cellular function, among heart disease, cancer, and an overactive immune system.)

So stimulating that might help. But there are other molecules involved in detecting and preventing misfolding that we might be able to work with, too.

"Improving the body's repair processes, either at the nucleus with DNA or [outside the nucleus], are really hot areas in aging biology," Finkel says. He'll be recruiting some proteostasis experts to fill out the Aging Institute's perspective.

In 2013, Finkel's lab knocked a mouse gene down to a quarter of its normal activity. The result: mice that lived 20 percent longer. That's the equivalent of a 75-year-old life span stretching to 90 years. The gene encodes a protein called mTOR, part of a complex called mTORC1, for "mechanistic target of rapamycin." The protein is a kinase that controls the activity of

The mTOR protein is part of a piece of cellular machinery called the AMPK pathway, whose job is to sense low energy levels in the cell. The pathway appears to protect cells from aging, perhaps because mTOR inhibition is one of its effects. Fasting activates this pathway, as does exercise, which evidence suggests keeps us young. Another group of molecules involved in energy sensing and life span are the sirtuins, which help the cell figure out how many mitochondria it needs.

There's a familiar drug that acts on AMPK: metformin, an old standby for treating type 2 diabetes. Researchers have noticed that people who take metformin have lower rates of cancer and longer life spans—results that can't be accounted for by metformin's effect on blood sugar. It turns out the drug gears down mTOR via an upstream effect on AMPK. Pitt leaders are planning an internally funded human trial of metformin in post-op and critical care patients. They're also working out a way to surveil other familiar drugs, in case more of them have anti-aging properties scientists have overlooked.

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Senescent cells are those that have stopped replicating. As with damaged mitochondria, as they accumulate, they become a toxic, inflammatory nuisance to their neighbors. The immune system takes them out, but assisting with that process by preventing senescence or selectively destroying senescent cells with so-called senolytic drugs could help slow down aging.

Gurkar has worked on this problem, too. In 2015, she was part of a group that

Led by Toren Finkel, Pitt's Aging Institute will focus on geroscience, which points a finger at aging itself as the cause of many chronic diseases.

demonstrated health span got longer in mice after treatment with senolytics. One drug they tried was quercetin, a plant pigment found in olive oil and blackberries and suspected of having a number of healthful effects in humans, including lowering blood pressure and potentially reducing cancer risk. (Olive oil could be one reason the Greek island of Ikaria is home to so many nonagenarians. It's been nicknamed "the island where people forget to die.")

So, with all these pathways, with all their linkages to one another, to cancer, to inflammation, to other chronic diseases, how close are we to untangling aging and slowing it down with a couple of pills?

"It's a thing that all of us have and will get—aging. It's probably the most fundamental thing," says Finkel. But it's poorly understood in terms of: What are the unifying drivers of aging, the basic molecular mechanisms that everybody can agree on?"

There's no unifying theory of aging yet—just a set of tantalizing associations.

"There is an association of free radical damage," Finkel says, "but it's not clear that that's causative. There is this idea of sterile inflammation [i.e., inflammation without bacteria, as happens in gout or atherosclerosis] that occurs in elderly people; but again it's not clear if that's cause or consequences. Is there DNA damage as we age? Yes. Is it driving aging, or is it accompanying aging? If you block DNA damage, would you block aging? Or would you just block one aspect of aging? People really don't know. There [are] a lot of candidates, but there's no clear winner at this point," he says.

"They certainly have all been linked to aging. They're certainly all in play. Certainly you can get something that looks like aging by perturbing all of those things," Finkel says. "But the question is, *What really is the most important? And what really drives the others?*"

Finkel wouldn't be here if he weren't optimistic.

"Twenty-five years ago, nothing was really known about the basic mechanisms. Now, quite a bit is known. There are still a lot of gaps, but I think there are rational targets out there that make sense. Pitt [is] very good at clinical translation, and I think that is where the field is moving," he adds. "It's going to be a great place to figure out, *Can we really slow the rate of human aging?* It's a great unknown, but a great target to go after."

It's a heck of a challenge.

"Oh, yeah," Finkel, age 59, replies. "I'm young."