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Zombie cells central to the quest for active, vital old age

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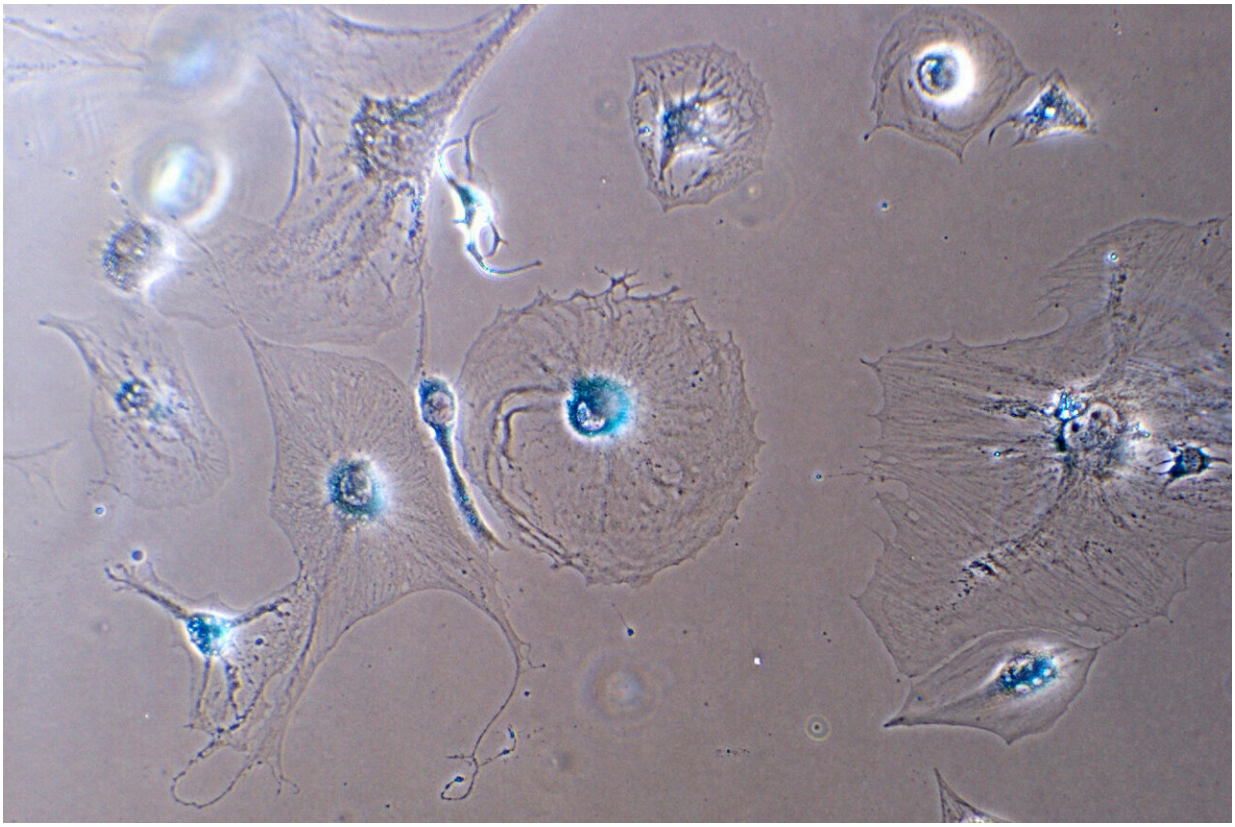


This microscope photo provided by the Mayo Clinic in August 2022 shows senescent myoblast cells. Senescent cells resist apoptosis, or programmed cell death, and characteristically get big and flat, with enlarged nuclei. They release a blend of molecules, some of which can trigger inflammation and harm other cells — and paradoxically also stimulate the growth of malignant cells and fuel cancer, says Mayo Clinic researcher Nathan LeBrasseur. Credit: Dr. Xu Zhang/Mayo Clinic via AP

In an unfinished part of his basement, 95-year-old Richard Soller zips around a makeshift track encircling boxes full of medals he's won for track and field and long-distance running.

Without a hint of breathlessness, he says: "I can put in miles down here."

Steps away is an expensive leather recliner he bought when he retired from Procter & Gamble with visions of relaxing into old age. He proudly proclaims he's never used it; he's been too busy training for competitions, such as the National Senior Games.

Soller, who lives near Cincinnati, has achieved an enviable goal chased by humans since ancient times: Staying healthy and active in late life. It's a goal that eludes so many that growing old is often associated with getting frail and sick. But scientists are trying to change that—and tackle one of humanity's biggest challenges—through a little known but flourishing field of aging research called cellular senescence.

It's built upon the idea that cells eventually stop dividing and enter a "senescent" state in response to various forms of damage. The body removes most of them. But others linger like zombies. They aren't dead. But as the Mayo Clinic's Nathan LeBrasseur puts it, they can harm nearby cells like moldy fruit corrupting a fruit bowl. They accumulate in older bodies, which mounting evidence links to an array of age-related conditions such as dementia, cardiovascular disease and osteoporosis.

But scientists wonder: Can the zombie cell buildup be stopped?

Richard Soller, 95, runs in the 200 meter race for men over 85 years old at the National Senior Games, Monday, May 16, 2022, in Miramar, Fla. After a torn hamstring stopped him from running track in high school, he fell into an unhealthy lifestyle in early adulthood, smoking two packs of cigarettes a day. But he and his wife Jean quit cold turkey when their daughter Mary came along. Credit: AP Photo/Marta Lavandier

"The ability to understand aging—and the potential to intervene in the fundamental biology of aging—is truly the greatest opportunity we have had, maybe in history, to transform human health," LeBrasseur says. Extending the span of healthy years impacts "quality of life, public health, socioeconomics, the whole shebang."

With the number of people 65 or older expected to double globally by

2050, cellular senescence is "a very hot topic," says Viviana Perez Montes of the National Institutes of Health. According to an Associated Press analysis of an NIH research database, there have been around 11,500 total projects involving cellular senescence since 1985, far more in recent years.

About 100 companies, plus academic teams, are exploring drugs to target senescent cells. And research offers tantalizing clues that people may be able to help tame senescence themselves using the strategy favored by Soller: exercise.

Although no one thinks senescence holds the key to super long life, Tufts University researcher Christopher Wiley hopes for a day when fewer people suffer fates like his late grandfather, who had Alzheimer's and stared back at him as if he were a stranger.

"I'm not looking for the fountain of youth," Wiley says. "I'm looking for the fountain of not being sick when I'm older."

MORTAL CELLS

An over 60 years and older group of women run a 200 meter race during the National Senior Games, Monday, May 16, 2022, in Miramar,Fla. Credit: AP Photo/Marta Lavandier

Leonard Hayflick, the scientist who discovered cellular senescence in 1960, is himself vital at 94. He's a professor of anatomy at the University of California, San Francisco, and continues to write, present and speak on the topic.

At his seaside home in Sonoma County, he leafs through a binder filled with his research, including two early papers that have been cited an astonishing number of times by other researchers. Before him on the living room table are numerous copies of his seminal book, "How and Why We Age," in various languages.

This scientific renown didn't come easily. He discovered cellular senescence by accident, cultivating human fetal cells for a project on cancer biology and noticing they stopped dividing after about 50 population doublings. This wasn't a big surprise; cell cultures often failed because of things like contamination. What was surprising was that others also stopped dividing at the same point. The phenomenon was later called "the Hayflick limit."

The finding, Hayflick says, challenged "60-year-old dogma" that normal human cells could replicate forever. A paper he authored with colleague Paul Moorhead was rejected by a prominent scientific journal, and Hayflick faced a decade of ridicule after it was published in Experimental Cell Research in 1961.

"It followed the usual pattern of major discoveries in science, where the discoverer is first ridiculed and then somebody says, 'Well, maybe it works' … then it becomes accepted to some extent, then becomes more widely accepted."

At this point, he says, "the field that I discovered has skyrocketed to an extent that's beyond my ability to keep up with it."

Phil Milliman of Washington State, competes in the pole vault during the National Senior Games, Monday, May 16, 2022, in Miramar, Fla. Credit: AP Photo/Marta Lavandier

ZOMBIE BUILDUP

Scientists are careful to note that cell senescence can be useful. It likely evolved at least in part to suppress the development of cancer by limiting the capacity of cells to keep dividing. It happens throughout our lives, triggered by things like DNA damage and the shortening of telomeres, structures that cap and protect the ends of chromosomes. Senescent cells play a role in wound healing, embryonic development and childbirth.

Problems can arise when they build up.

"When you're young, your immune system is able to recognize these senescent cells and eliminate them," says Perez, who studies cell biology and aging. "But when we start getting old … the activity of our immune system also gets diminished, so we're losing the capacity to eliminate them."

Senescent cells resist apoptosis, or programmed cell death, and characteristically get big and flat, with enlarged nuclei. They release a blend of molecules, some of which can trigger inflammation and harm other cells—and paradoxically can also stimulate the growth of malignant cells and fuel cancer, LeBrasseur says.

Scientists link some disorders to buildups of senescent cells in certain spots. For example, research suggests certain senescent cells that accumulate in lungs exposed to cigarette smoke may contribute substantially to airway inflammation in COPD.

Leonard Hayflick, the scientist who discovered cellular senescence in 1960, stands outside his home in The Sea Ranch, Calif., on May 23, 2022. At 94, he's a professor of anatomy at the University of California, San Francisco, and continues to write, present and speak on the topic. Credit: AP Photo/Laura Ungar

The idea that one process could be at the root of numerous diseases is powerful to many scientists.

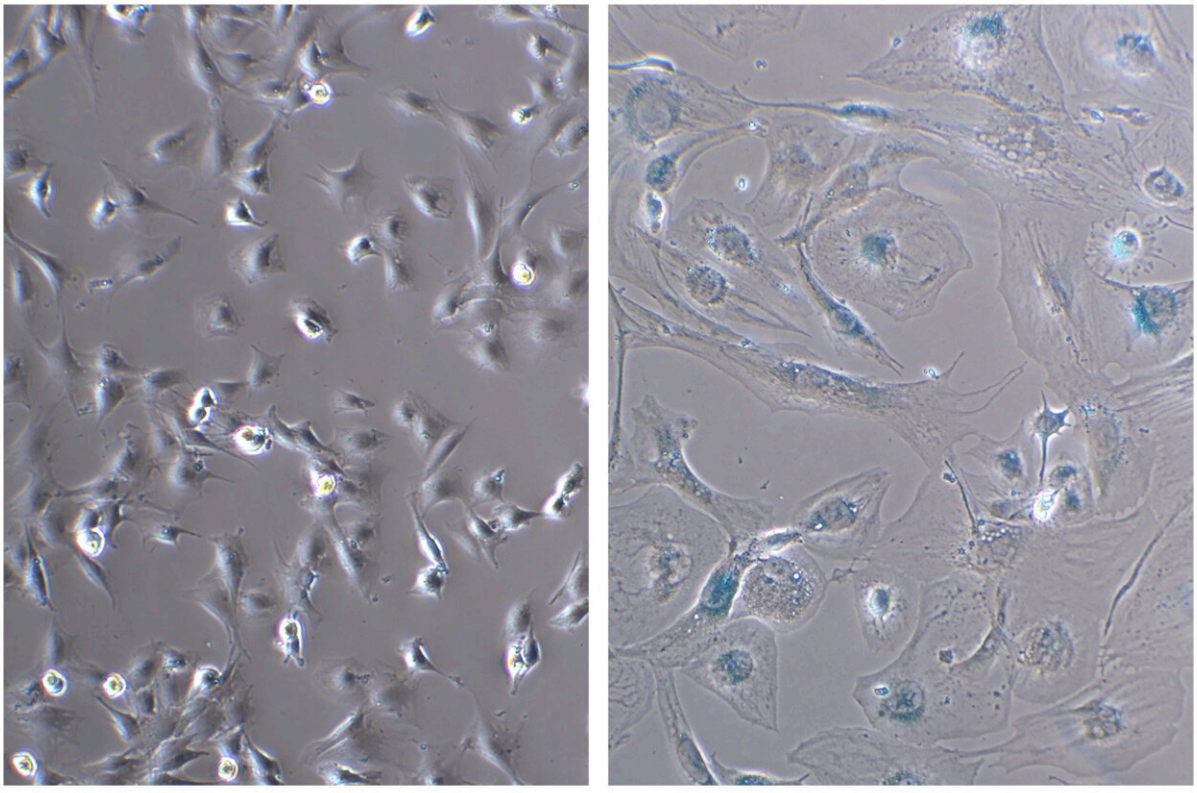
It inspired Dr. James Kirkland to move on from geriatric medicine. "I got tired of prescribing better wheelchairs and incontinence devices," says Kirkland, a professor of medicine at Mayo considered a pioneer of the senescence renaissance. "I wanted to do something more fundamental that could alleviate the suffering that I saw."

DRUG TARGETS

That quest leads him and others to develop medicines.

Experimental drugs designed to selectively clear senescent cells have been dubbed "senolytics," and Mayo holds patents on some. In mice, they've been shown to be effective at delaying, preventing or easing several age-related disorders.

Possible benefits for people are just emerging. Kirkland, LeBrasseur and colleagues did a pilot study providing initial evidence that patients with a serious lung disease might be helped by pairing a chemotherapy drug with a plant pigment. Another pilot study found the same combination reduced the burden of senescent cells in the fat tissue of people with diabetic kidney disease.



This combination of microscope photos provided by the Mayo Clinic in August 2022 shows healthy myoblast cells, left, and senescent ones. Senescent cells resist apoptosis, or programmed cell death, and characteristically get big and flat, with enlarged nuclei. They release a blend of molecules, some of which can trigger inflammation and harm other cells — and paradoxically also stimulate the growth of malignant cells and fuel cancer, says Mayo Clinic researcher Nathan LeBrasseur. Credit: Dr. Xu Zhang/Mayo Clinic via AP

At least a dozen clinical trials with senolytics are now testing things like whether they can help control Alzheimer's progression, improve joint health in osteoarthritis and improve skeletal health. Some teams are trying to develop "senomorphics" that can suppress detrimental effects of molecules emitted by senescent cells. And a Japanese team has tested a vaccine on mice specific to a protein found in senescent cells, allowing for their targeted elimination.

Scientists say serious work to improve human health could also bring fringe benefits—like reducing skin wrinkling.

"I tell my lab that if we find a drug that clears the bad senescent cells and not the good ones and we cure Parkinson's disease and Alzheimer's and osteoporosis and macular degeneration, it would be wonderful," says Judith Campisi, a biogerontology expert at the Buck Institute for Research on Aging. "But if we cure wrinkles, we'll be rich, and I'll never have to write another grant."

Amid the buzz, some companies market dietary supplements as senolytics. But researchers warn they haven't been shown to work or proven safe.

And there's still much to learn about clinical trial drugs.

"We know that senolytics work pretty well in mice," Wiley says. "We're still really figuring out the basics with people."

Leonard Hayflick, 94, the scientist who discovered cellular senescence in 1960, leafs through a binder containing his research at his home in The Sea Ranch, Calif., on May 23, 2022. He discovered cellular senescence by accident, cultivating human fetal cells for a project on cancer biology and noticing they stopped dividing after about 50 population doublings. This wasn't a big surprise; cell cultures often failed because of things like contamination. What was surprising was that others also stopped dividing at the same point. The phenomenon was later called "the Hayflick limit." Credit: AP Photo/Laura Ungar

'MOST PROMISING TOOL'

Today, LeBrasseur, who directs a center on aging at Mayo, says exercise is "the most promising tool that we have" for good functioning in late life, and its power extends to our cells.

Research suggests it counters the buildup of senescent ones, helping the immune system clear them and counteracting the molecular damage that can spark the senescence process.

A study LeBrasseur led last year provided the first evidence in humans that exercise can significantly reduce indicators, found in the bloodstream, of the burden of senescent cells in the body. After a 12-week aerobics, resistance and balance training program, researchers found that older adults had lowered indicators of senescence and better muscle strength, physical function and reported health. A recently-published research review collects even more evidence—in animals and humans—for exercise as a senescence-targeting therapy.

While such studies aren't well-known outside scientific circles, many older adults intuitively equate exercise with youthfulness.

Rancher Mike Gale, 81, installed a track and field throwing circle on his sprawling property in Petaluma, California, so he and some friends could practice throwing the discus and other equipment. Against a backdrop of rolling green hills, they twist, step, throw and retrieve over and over again.

Richard Soller holds the medal he won in the 200 meter final at the National Senior Games, Monday, May 16, 2022, in Miramar, Fla. Soller says exercise keeps him fit enough to handle what comes his way. "Do as much as you can," he says. "That should be the goal for anyone to stay healthy." Credit: AP Photo/Marta Lavandier

"I'd like to be competing in my 90s," Gale says. "Why not?"

Soller asked himself a similar question long ago.

After a torn hamstring stopped him from running track in high school, he fell into an unhealthy lifestyle in early adulthood, smoking two packs of cigarettes a day. But he and his wife Jean quit cold turkey when their daughter Mary came along.

He started running again just before turning 50, and since then has run in races across the U.S., including two marathons, and participated in decades of Senior Games competitions. In May, Soller joined 12,000 like-minded athletes in Florida for the latest national games in the Fort Lauderdale area—winning five medals to add to his collection of 1,500 prizes.

His daughter filmed his first-place finish in the 200-meter dash from the stands, cheering: "Go, Dad, go!"

Soller says exercise keeps him fit enough to handle what comes his way—including an Alzheimer's diagnosis for his wife of 62 years. They sometimes stroll neighborhood streets together, holding hands.

"Do as much as you can," he says. "That should be the goal for anyone to stay healthy."

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