

Scientists' New Goal: Growing Old Without Disease

By Sumathi
Reddy



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Brian Harkin for The Wall Street Journal

March 16, 2015 5:43 p.m. ET

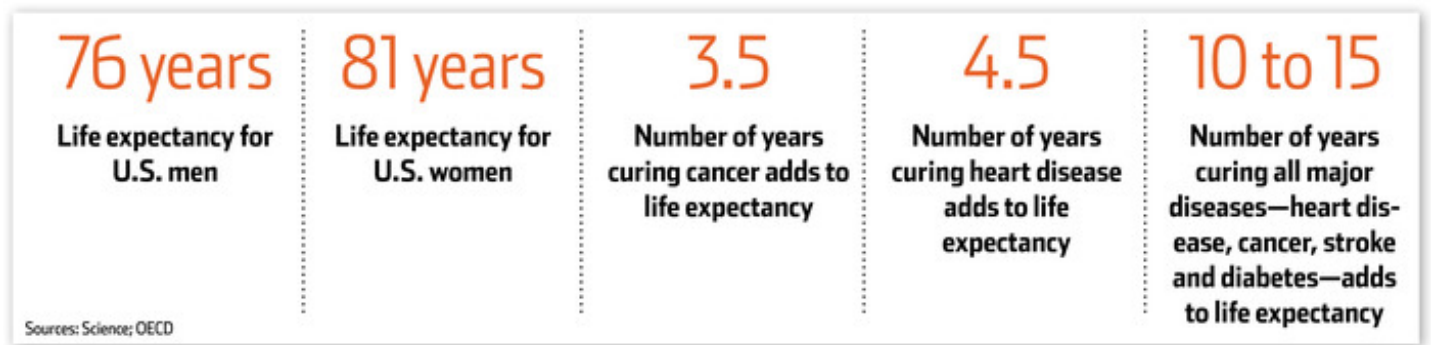
Some of the top researchers on aging in the country are trying to get an unusual clinical trial up and running.



They want to test a pill that could prevent or delay some of the most debilitating diseases of old age, including Alzheimer's and cardiovascular disease. The focus of the project isn't to prolong life, although that could occur, but to make the last years or decades of people's lives more fulfilling by postponing the onset of many chronic diseases until closer to death.

The project aims to tap into the growing body of research targeting aging, which has revealed a half dozen or more drugs that appear to delay the aging process in laboratory experiments on animals and observational studies of people. Some of the drugs also have been found to reduce the incidence of chronic diseases associated with old age.

“Aging is the major risk factor for all these diseases—heart disease, cancer, diabetes and Alzheimer’s,” said Nir Barzilai, director of the Institute for Aging Research at Albert Einstein College of Medicine in New York City who is leading the proposed study. “If you want to make a real impact you have to modulate the risk of aging and by that the risk for all those diseases of aging.”



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Dr. Barzilai expects to enroll more than 1,000 elderly participants in the randomized, controlled clinical trial to be conducted at multiple research centers and take five to seven years. The project is in the preliminary stages and permanent funding hasn't yet been secured. Funding for the planning phase is coming from the American Federation for Aging Research, a nonprofit organization of which Dr. Barzilai is deputy scientific director.

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The trial aims to test the drug metformin, a common medication often used to treat Type 2 diabetes, and see if it can delay or prevent other chronic diseases. (The project is being called Targeting/Taming Aging With Metformin, or TAME.) Metformin isn't necessarily more promising than other drugs that have shown signs of extending life and reducing age-related chronic diseases. But metformin has been widely and safely used for more than 60 years, has very few side effects and is inexpensive.

The scientists say that if TAME is a well-designed, large-scale study, the Food and Drug Administration might be persuaded to consider aging as an indication, or preventable condition, a move that could spur drug makers to target factors that contribute to aging.

A study that helped convince the gerontologists to pursue the TAME project was done in the U.K. and published last year in the journal *Diabetes, Obesity and Metabolism*. Researchers used data from a national registry of more than 180,000 people, comparing the treatment of metformin with that of sulfonylurea, another drug used for diabetes. They also created two control groups of nondiabetic people.

People who took metformin lived longer than those taking sulphonylurea, the study found. In addition, the people with diabetes who were 71-to-75-years-old at baseline and took metformin outlived their nondiabetic controls with a 15% greater survival rate.

“Observational studies like this are never definitive,” said Jill Crandall, director of the Diabetes Clinical Trials Unit at Albert Einstein College of Medicine and part of the TAME planning team. “But it is one of the observations that certainly supports our hypothesis—that certain pharmacological interventions, like metformin, may have broad effects in improving health and increasing health span.”

Dr. Crandall also participated in a federally funded study that found metformin and lifestyle changes were both effective in staving off diabetes in people at high risk for the disease for at least 10 years. Data from the study, which followed more than 3,000 adults for 15 years, are now being analyzed to see whether long-term use of metformin prevented the development of cardiovascular disease, cancer, cognitive decline and physical-function decline. The

results could help in the planning of the TAME study, she said.



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Dr. Barzilai, who is leading the effort to test if the drug metformin can delay or prevent chronic diseases, also focuses in his work on the genetics of centenarians. Photo: Brian Harkin for The Wall Street Journal

Research has found that metformin targets the chemicals produced by age-related senescent cells—normal cells that stop dividing and produce toxic substances damaging to the cells around them, said James Kirkland, director of the Robert and Arlene Kogod Center on Aging at the Mayo Clinic in Rochester, Minn., and part of the TAME planning team. Senescent cells usually develop as people age or at sites of age-related chronic diseases, such as the brain in Alzheimer's patients or around the plaques that lead to heart attacks and strokes, he said. It isn't proven if senescent cells actually cause the disease.

Metformin appears also to slow the development of age-related symptoms by increasing the enzyme AMP kinase, which normally declines with age, and decreasing the protein mTOR, which helps to regulate cell growth.

Several other drugs also have shown life-extension properties in mice and in laboratory work, Dr. Kirkland said. His research group last week published a study on mice in the journal *Aging Cell* which showed that a combination of two drugs—dasatinib, a cancer drug, and quercetin, a supplement that can be found in health food stores—were potentially effective.

"There's more and more evidence that by targeting aging itself we might be able to target these age-related chronic diseases that have been so intractable for us to try to come up with a cure for," Dr. Kirkland said.

Fighting each major disease of old age separately isn't winnable, said S. Jay Olshansky, another TAME project

planner and a professor at the school of public health at the University of Illinois at Chicago. “We lower the risk of heart disease, somebody lives long enough to get cancer. If we reduce the risk of cancer, somebody lives long enough to get Alzheimer’s disease.”

“We are suggesting that the time has arrived to attack them all by going after the biological process of aging,” Dr. Olshansky said.

Sandy Walsh, an FDA spokeswoman, said the agency’s perspective has long been that “aging” isn’t a disease. “We clearly have approved drugs that treat consequences of aging,” she said. Although the FDA currently is inclined to treat diseases prevalent in older people as separate medical conditions, “if someone in the drug-development industry found something that treated all of these, we might revisit our thinking.”

Other experts agree with the goal of delaying chronic disease for the elderly, but question whether medication is the best way to do that. “I can certainly see how medicine can play a role if it turns out this study shows some promising findings,” said Alicia Arbaje, a geriatrician and an assistant professor of medicine at Johns Hopkins School of Medicine. “But aging is very complex and it’s probably going to take a multifaceted approach to help people delay or ensure that they age in a healthy way,” said Dr. Arbaje, who isn’t affiliated with the TAME trial planning.

Effective interventions to delay aging already exist, Dr. Arbaje noted, such as exercise, nutrition, social engagement, stress reduction and getting adequate sleep. “These are reliable and effective ways to keep people healthy as they age,” she said. “The problem is they’re not as easy as taking a medication.”

Write to Sumathi Reddy at sumathi.reddy@wsj.com