The TAME (Targeting Aging with Metformin) Trial

OPPORTUNITY

The TAME (Targeting Aging with Metformin) Trial will establish a clinical trial to provide proof-of-concept that aging can be treated, just as we treat diseases.

Studies show that metformin—a safe, affordable drug approved for Diabetes—may influence metabolic and cellular processes that are associated with the development of age-related conditions.

Metformin and other drugs in development are expected to prevent the onset of these major diseases.

CHALLENGE

We hope the FDA will approve aging as an indication, to signify that aging can be “treated.” In medical terms, an “indication” for a drug refers to the use of that drug for treating a particular disease.

If aging is made an indication, the TAME Trial will mark a paradigm shift: from treating each age-related medical condition separately, to treating these conditions together, by targeting aging per se.

NEED

The estimated cost of the TAME Trial is $42 million, but targeting aging and age-related diseases through drug interventions holds the promise of extending years of health while saving trillions of dollars.

Goal: $42 M
Raised: $11 M from private donors

The TAME TEAM

EXECUTIVE MANAGER: Stephanie Lederman, American Federation for Aging Research

TAME Executive Committee

- Nir Barzilai, MD, PI
  Albert Einstein College of Medicine

- Steve Austad, PhD
  Nathan Shock Center of Excellence, University of Alabama Birmingham, AFAR Scientific Director

- James L. Kirkland, MD, PhD
  Director, Kogod Center on Aging, Mayo Clinic

- S. Jay Olshansky, PhD
  University of Illinois at Chicago

- David Sinclair, PhD
  Director, Glenn Center for the Biology of Aging, Harvard Medical School

TAME Trial Committee

- Nir Barzilai, MD, Co-PI

- Steve Kritchevsky, PhD, Wake Forest School of Medicine
  Co-PI: Clinical and Multi-Center studies

- Mark Espeland, PhD
  Wake-Forest School of Medicine, Co-PI: Study Design and Statistical

- George Kuchel, MD
  UConn Health
  Biomarker Development

- Vanita Aroda, MD
  Harvard Medical School
  Multi-Center Studies

- Jamie Justice, PhD
  Wake Forest School of Medicine
  Coordinator

TAME Trial Sites

- Johns Hopkins University
- University of Alabama
- Albert Einstein College of Medicine
- Northwestern University
- University of Connecticut
- University of Florida
- University of Tennessee
- University of Miami and Miami VA
- HealthPartners Institute
- Yale University
- University of Pittsburgh
- Brown University
- Brigham and Women’s Hospital
- Wake Forest School of Medicine

To support TAME and revolutionize aging, please contact Stephanie Lederman, at 212.703.9977 or stephanie@afar.org.
1. Establish proof of concept through metformin clinical trials

Metformin is an FDA-approved, first-line drug for the treatment of type-2 diabetes, used successfully for more than 60 years with an outstanding safety record. Studies have already shown that metformin can delay aging in animals. These findings point to the likelihood that metformin may influence fundamental aging factors that underlie multiple age-related conditions in humans.

Led by Nir Barzilai, MD, Deputy Scientific Director of AFAR, the TAME Trial is a series of nationwide, six-year clinical trials at 14 leading research institutions across the country that will engage over 3,000 individuals between the ages of 65-79. These trials will test whether those taking metformin experience delayed development or progression of age-related chronic diseases—such as heart disease, cancer, and dementia—compared with those who take a placebo.

The TAME Trial starts with metformin, but the impact doesn’t end with this drug.

WHY METFORMIN

Healthspan—our amount of time living independently and free of disability—can be extended. The key to living healthier longer is understanding the biology of how our bodies age.

During the last three decades, scientific research from around the world has demonstrated that the aging process itself is a catalyst for the most common, debilitating diseases, from cancer to diabetes to dementia and more—conditions that sap our health and well-being as we get older.

What if aging could be targeted so that diseases can be diminished and health can be extended?

Today, the scientific community has begun translating the basic science of aging into groundbreaking treatments that can extend our healthy years. One of the most promising efforts is a new study, the TAME (Targeting Aging with Metformin) Trial.

The TAME Trial is the first step in a four-step process that aims to:

1. Establish proof of concept through metformin clinical trials
2. Gain indication status for aging from the FDA
3. Slow down major diseases by targeting aging
4. Develop the next-generation of drugs that target aging
The TAME Trial seeks FDA approval to consider aging as an indication.

In medical terminology, an “indication” for a drug refers to the use of that drug for treating a particular disease. For example, diabetes is an indication for insulin.

Put another way, an indication is a valid reason to use a certain test, medication, procedure, or surgery.

The TAME Trial will offer the FDA the opportunity to review whether aging can be made an indication.

If aging is made an indication, we can dramatically speed the development of new treatments for a whole range of age-related diseases.

Science has helped us learn that the incidence of major diseases increases exponentially as we age. Research into the biology of aging, therefore, is a critical strategy towards helping us grow older, healthier.

Ultimately, drugs that target the basic biology of aging hold the promise of preventing a wide array of diseases.

If aging is made a medical indication and new drugs are developed, then age-related diseases can be treated more effectively and cost effectively.

Like metformin, several promising drugs show great potential and await trials. If successful, the TAME Trial would give the pharmaceutical industry impetus to advance these drugs and transform aging from a period of sickness to a time of extended vitality.

And the benefits of targeting aging extend well beyond us living healthier, longer.

A recent economic analysis showed that slowing or modifying age-related diseases by just 20 percent would save more than $7 trillion in health care spending in the United States alone over the next half-century.

The TAME Trial can extend healthy years and save health care costs by slowing the diseases of aging.

What’s Needed

The cost of the TAME Trial is an estimated $55 million, but targeting aging and age-related diseases holds out the promise of extending healthy life span while saving trillions of dollars.

As the leader in aging research for more than 35 years, AFAR is spearheading the effort to raise the money needed to fund the TAME Trial and help us all live healthier as we grow older.
The American Federation for Aging Research (AFAR) is a national non-profit organization whose mission is to support and advance healthy aging through biomedical research. Founded in 1981, AFAR has championed the cause and supported the funding of science in healthier aging and age-related medicine.

With this experience, AFAR will serve as manager of the TAME (Targeting Aging with Metformin) Trial, administering review processes, supporting fundraising, helping promote findings, and more.

**IDENTIFYING EXCELLENCE**

AFAR has been trusted by foundations, corporations, individuals, and government agencies to help shape their funding strategies and manage grant review processes in aging research, geriatric medicine, and age-related diseases such as Alzheimer’s disease. AFAR’s expert researchers and scientifically rigorous grant review processes are internationally respected. For 6 consecutive years, Charity Navigator has given AFAR a 4-star rating for fiscal management, accountability, and transparency—an honor that only 8% of non-profits are awarded.

**BUILDING THE RESEARCH PIPELINE**

AFAR offers a diverse grants portfolio providing funding for scientists and physicians at all stages of their careers, these include grants for medical students, postdoctoral fellows, junior faculty, and senior faculty. To date, AFAR has awarded over $181 million grants, ranging from $3,500 - $200,000, to nearly 4,200 talented scientists and trainees.

**FOCUSBING ON THE CAUSES, NOT THE SYMPTOMS**

The degenerative processes of aging underlie all the well-known diseases like cancer, stroke, and Alzheimer’s, as well as most causes of chronic pain and disability, such as falls and fractures, arthritis, vision, and hearing loss. As the connecting bridge between diseases and conditions that effect many of us in older age, aging research is the most cost-effective path to preventing, delaying, and curing many age-related diseases. What scientists learn today about the processes of aging may lead to better ways to live healthier, longer.


Pursuing the Dream of Healthy Aging

By Jane E. Brody

February 1, 2016

Jane Brody on health and aging.

Given their druthers, most people would opt for a long and healthy life. Few relish the idea of spending years, even decades, incapacitated by illness, dependent on caregivers and unable to enjoy the people, places and activities that make life worth living.

In 1980, Dr. James F. Fries, a Stanford University physician who studied chronic disease and aging, proposed that a "compression of morbidity" would enable most people to remain healthy until a certain age, perhaps 85, then die naturally or after only a brief illness.

Now, a prescient group of experts on aging envisions a route to realizing Dr. Fries's proposal: one or more drugs that can slow the rate of aging and the development of the costly, debilitating chronic ailments that typically accompany it. If successful, not only would their approach make healthy longevity a reality for many more people, but it could also save money. They say that even a 20 percent cut in how fast people age could save more than $7 trillion over the next half-century in the United States alone.

“Aging is by far the best predictor of whether people will develop a chronic disease like atherosclerotic heart disease, stroke, cancer, dementia or osteoarthritis,” Dr. James L. Kirkland, director of the Kogod Center on Aging at the Mayo Clinic, said in an interview. “Aging way outstrips all other risk factors.”

He and fellow researchers, who call themselves “geroscientists,” are hardly hucksters hawking magic elixirs to extend life. Rather, they are university scientists joined together by the American Federation for Aging Research to promote a new approach to healthier aging, which may — or may not — be accompanied by a longer life. They plan to test one or more substances that have already been studied in animals, and which show initial promise in people, in hopes of finding one that will keep more of us healthier longer.
As Dr. Kirkland wrote in a new book, “Aging: The Longevity Dividend”: “By targeting fundamental aging processes, it may be possible to delay, prevent, alleviate or treat the major age-related chronic disorders as a group instead of one at a time.”

His colleague S. Jay Olshansky, a gerontology specialist in the School of Public Health at the University of Illinois in Chicago, said it is often counterproductive to treat one disease at a time. Preventing cardiac death, for example, can leave a person vulnerable to cancer or dementia, he explained.

A better approach, Dr. Kirkland said, would be to target the processes fundamental to aging that underlie all age-related chronic diseases: chronic low-grade inflammation unrelated to infection; cellular degradation; damage to major molecules like DNA, proteins and sugars; and failure of stem cells and other progenitor cells to function properly.

The team, which includes Dr. Nir Barzilai, director of the Institute for Aging Research at Albert Einstein College of Medicine in The Bronx, and Steven N. Austad, who heads the biology department at the University of Alabama at Birmingham, plans to study one promising compound, a generic drug called metformin already widely used in people with Type 2 diabetes. They will test the drug in a placebo-controlled trial involving 3,000 elderly people to see if it will delay the development or progression of a variety of age-related ailments, including heart disease, cancer and dementia. Their job now is to raise the $50 million or so needed to conduct the study for the five years they expect it will take to determine whether the concept has merit.

The project represents a radical departure from ordinary drug studies that test treatments for single diseases. However, the group, spearheaded by Dr. Barzilai, said the Food and Drug Administration has endorsed their idea to test a single substance for effectiveness against a range of ailments.

“If metformin turns out not to work, there are several other substances in the pipeline that could be tried,” Dr. Barzilai said. “Under the auspices of the National Institute on Aging, three research centers have tested 16 substances in different animal models and got incredible results with four of them.”

Green tea, one of those tested, bestowed no health or life span benefits, despite its popularity. But the drug rapamycin, an immune modulator used following organ transplants, was most effective among those tested, Dr. Barzilai said.

The team is starting with metformin because it is a cheap oral drug — costing about two cents a pill — with six decades of safe use in people throughout the world. Among those with Type 2 diabetes who have taken it for years, there is evidence suggesting that, in addition to diabetes, it protects against cardiovascular disease, cancer and possibly cognitive impairment, Dr. Kirkland said, adding that “it targets the fundamental processes of aging, which tend to be linked.”

Dr. Barzilai said, “Our goal is to establish the principle of using a drug, or two in combination, to extend health span. The best we can expect from metformin is two or three additional years of healthy aging. But the next generation of drugs will be much more potent.”

Dr. Barzilai is already conducting a complementary study of centenarians, the results of which could identify more drugs to delay age-related diseases. He and colleagues are isolating genes that appear to keep these long-lived men and women healthy for 20 to 30 years longer than other people and shorten the length of illness at life’s end. Several studies have already found that individuals with exceptional longevity experience a compression of morbidity and spend a smaller percentage of their life being ill, Dr. Barzilai and his colleague Dr. Sofiya Milman wrote in the “Aging” book.

By analyzing the action of genes that extend health span, “it should be possible to devise drugs that mimic the genes’ effects,” he said. Two such gene-based drugs that show early promise against age-related diseases are already being tested. But until definitive studies are completed and substances are shown to be safe as well as effective in prolonging health, Dr. Olshansky cautioned against dosing oneself prematurely with widely touted substances like resveratrol, the antioxidant found in red grapes and wine, or growth hormone.

Consumers must exercise caution, he warned, because “there’s an entire industry out there trying to market the products we’re testing before they are adequately evaluated.”

He also emphasized that taking a drug found to ward off age-related ills is not a license to abandon a healthy lifestyle. Doing so “could completely negate the benefit of a compound that slows aging,” he said.
Aging as a Biological Target for Prevention and Therapy

Chronic health problems related to the unprecedented aging of the human population in the 21st century threaten to disrupt economies and degrade the quality of later life throughout the developed world. Fortunately, research has shown that fundamental aging processes can be targeted by nutritional, genetic, and pharmacologic interventions to enhance and extend both health and longevity in experimental animal models. These findings clearly demonstrate that the biological rate of aging can be slowed.

The geroscience hypothesis, for which there is abundant evidence in animal models, links these biological discoveries to human health by proposing that targeting biological aging processes will prevent, or at a minimum delay, the onset and progression of multiple chronic diseases and disabilities that are typically observed in older adults. For example, interventions that extend the life span of mice often also prevent or slow the progress of several types of cancer, reduce atherosclerotic lesions, improve heart function, alleviate normal age-related cognitive loss, and even improve vaccine response.

Aging Is the Major Common Risk Factor for Chronic Diseases and Disabling Conditions

The US government annually publishes the rate of death from individual diseases stratified by age. What is striking about these reports is that the rate of death increases logarithmically with advancing age for virtually all major causes of death, including heart disease, cancer, stroke, chronic obstructive pulmonary disease, chronic kidney diseases, type 2 diabetes, and Alzheimer disease. Furthermore, the incidence of multimorbidities, defined as 3 or more concurrent disease conditions from a list of 20 US Department of Health and Human Services–reported conditions, also increases exponentially with age. Thus, increasing numbers of individuals are being treated for at least 3 different diseases with at least 3 different treatments.

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Aging Processes Can Be Targeted

One of the main geroscience accomplishments is to highlight a small number of major “pillars,” interacting molecular and physiological processes that underlie the biology of aging, for instance, metabolism, proteostasis, macro-molecular damage, inflammation, adaptation to stress, epigenetics, and stem cells and their regeneration. The key feature of this conceptual framework is that these processes are understood to be tightly interrelated. These findings have emerged from the remarkable progress made in recent years in dissecting aging processes in model organisms.

The discovery of cellular and molecular pathways that modulate healthy aging in diverse species across great evolutionary distances offers an unprecedented opportunity for intervention. In animal models, both health and longevity have been extended by multiple genetic and dietary interventions. For example, knocking out the rps6kb1 gene extends the life and health of female mice, whereas overexpressing Sirt6 makes male mice live longer, and reducing caloric intake or methionine levels makes both mouse sexes live longer.

Health and longevity have also been extended by drugs. The National Institute on Aging–funded Interventions Testing Program (ITP) evaluates drugs to determine whether they prevent disease and extend life in genetically heterogeneous (outbred) mice. These studies are conducted independently at 3 centers to control for laboratory-specific environmental differences and to provide immediate experimental confirmation. The ITP has shown that of 26 candidate drugs evaluated to date, 6 (nordihydroguaiaretic acid, aspirin, acarbose, Protandim, rapamycin, and 17α-estradiol) extend life in at least 1 mouse sex. The largest overall longevity increase has been found using a combination of rapamycin and metformin, indicating that combination therapy may be applied for synergistic effects. A remarkable finding from these and other such studies suggests that interventions as late as the mouse-equivalent of older than 70 years of age could significantly extend life by more than 20 years and increase health span even more substantially.
The ITP studies also confirmed that simultaneous modulation of several of the pillars of aging is possible and that improvement of one of them often has a positive effect on the others. For example, restoring proteostasis, the cellular surveillance systems responsible for protein and organelle quality control, improves cellular metabolism, reduces macromolecular damage, and enhances the ability to adapt to stress. Most of the genetic and chemical interventions shown to extend life span exert an activating effect on autophagy, one of the key components of the proteostasis system that has also been shown to malfunction in many age-related diseases.

A connection with age-related disorders has also been established for cellular senescence, a program that many cells activate in response to damage and stress. During aging and in many pathologic processes (such as in idiopathic pulmonary fibrosis), senescent cells are not efficiently cleared by the immune system, and their persistent presence maintains a state of chronic inflammation that contributes to tissue dysfunction. Recent advances have resulted from the realization that many human pathologic conditions are associated with the presence of senescent cells. Interventions aimed at eliminating those senescent cells, commonly called senolytic, have also been shown to improve health and extend life in various mouse disease models.7

Targeting Human Aging

Maximal life expectancy for humans is theorized to be about 115 years. Since the average life expectancy in the United States is currently approximately 80 years old, 35 years have yet to be realized. Centenarians not only live longer than most individuals, they also have an extra 20 to 30 years of health as well as a shorter period of morbidity at the end of life. Some of the mechanisms underlying these extra health years have been discovered.8 Diet, exercise, and other lifestyle factors can certainly extend health, but to achieve the extraordinarily extended health of centenarians, drugs will likely be necessary. Some of the drugs mentioned above have shown interesting effects in humans. For example, acarbose not only prevents diabetes, it also prevents hypertension and cardiovascular events.9 Rapamycin use improves vaccine response in the elderly, demonstrating that this age-targeting drug may have a specific indication in immune deficiency of older persons. Metformin has shown particular promise in humans as well as in animal models, with published clinical trials and cohort studies reporting substantial reductions (up to 30%) in the risk of type 2 diabetes, cardiovascular disease, and cognitive decline.10 Similar reductions have been reported for cancer, dementia, and total mortality in observational studies. Metformin has shown an excellent safety profile across more than 60 years of use and is an inexpensive generic drug for treatment of type 2 diabetes.

Challenges in Targeting Aging

While geroscience has been exciting for the biological community and has resulted in important studies in experimental animal models, its significance has trickled down to the medical community at large. One major challenge for improving human health by treating aging processes is that from a regulatory perspective (e.g., the US Food and Drug Administration) there is no indication that is similar to targeting aging. Even if safe and effective drugs are available, health care payers will be reluctant to pay for such treatment without regulatory approval. Consequently, for now, drug companies are reluctant to invest in treatments targeting aging. Regulatory changes and further development of more drugs and drug combinations will be needed to start making major strides in improving human health. In the meantime, the so-called antiaging therapies are not regulated and may cause more harm than help because they are unsupervised and lack clinical data support. This is a challenge that geroscience has taken up in the hope of changing the aging process in the next decades.

ARTICLE INFORMATION
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REFERENCES
The assembled scientists and academics focused on one obstacle above all: the Food and Drug Administration. The agency does not recognize aging as a medical condition, meaning a drug cannot be approved to treat it. And even if the FDA were to acknowledge that aging is a condition worthy of targeting, there would still be the question of how to demonstrate that aging had, in fact, been slowed—a particularly difficult question considering that there are no universally agreed-on markers. What they needed, Barzilai and the others concluded, was a precedent-setting test case—a single study that would change the rules forever, not unlike how trial lawyers search for a perfect plaintiff when they’re going to the Supreme Court to set a new legal precedent.

If and when the FDA approves the first antiaging drug, Barzilai believes it will create a domino effect of health and economic benefits: Insurance companies will begin to cover antiaging drugs, and pharmaceutical companies, in turn, will begin investing more in antiaging research and produce new and better drugs that extend human health span.
FORGET THE BLOOD OF TEENS. THIS PILL PROMISES TO EXTEND LIFE FOR A NICKEL A POP.

NIR BARZILAI HAS a plan. It’s a really big plan that might one day change medicine and health care as we know it. Its promise: extending our years of healthy, disease-free living by decades.

And Barzilai knows about the science of aging. He is, after all, the director of the Institute for Aging Research at the Albert Einstein College of Medicine.
in the Bronx. And, as such, he usually talks about his plan with the caution of a seasoned researcher. Usually. Truth is, Barzilai is known among his colleagues for his excitability—one author says he could pass as the older brother of Austin Powers—and sometimes he can’t help himself. Like the time he referred to his plan—which, among other things, would demonstrate that human aging can be slowed with a cheap pill—as “history-making.” In 2015, he stood outside of the offices of the Food and Drug Administration, flanked by a number of distinguished researchers on aging, and likened the plan to a journey to “the promised land.”

Last spring, Barzilai traveled to the Vatican to discuss the plan at a conference on cellular therapies. It was the second time he’d been invited to the conference, which is a pretty big deal in the medical world. At the last one, in 2013, he appeared alongside a dwarf from Ecuador, a member of a community of dwarfs whose near immunity to diabetes and cancer has attracted the keen interest of researchers. The 2016 conference featured a number of the world’s top cancer scientists and included addresses from Pope Francis and Joe
That Barzilai was invited was a sign not only of his prominence in his field but also of how far aging research, once relegated to the periphery of mainstream science, has come in recent years.

That progress has been spurred by huge investments from Silicon Valley titans, including Google’s Sergey Brin and Larry Page, Amazon’s Jeff Bezos, PayPal cofounder Peter Thiel, and Oracle cofounder Larry Ellison. Armed with such riches, biotech researchers are now dreaming up a growing list of cribbed-from-science-fiction therapies to beat back death: growing new organs from your own DNA, infusing older bodies with blood and stem cells from young bodies, uploading brains to computers.

Almost nothing seems too far-fetched in the so-called life-extension community. And yet, while it’s certainly possible that this work will lead to a breakthrough that will benefit all of humanity, it’s hard to escape the sense that Silicon Valley’s newfound urge to postpone aging indefinitely is, first and foremost, an attempt by the super wealthy to extend their own lives. As one scientist recently put it to The New Yorker, the antiaging science being done at Google-backed Calico Labs is “as self-serving as the Medici building a Renaissance chapel in Italy, but with a little extra Silicon Valley narcissism thrown in.”

Barzilai’s big plan isn’t necessarily less quixotic than those being dreamed up at Silicon Valley biotechs. It’s just quixotic in a completely different way. Rather than trying to develop a wildly expensive, highly speculative therapy that will likely only benefit the billionaire-demigod set, Barzilai wants to convince the FDA to put its seal of approval on an antiaging drug for the rest of us: A cheap, generic, demonstrably safe pharmaceutical that has already shown, in a host of preliminary studies, that it may be able to help stave off many of the worst parts of growing old. Not only that, it would also shorten the duration of those awful parts. (“How To Die Young at a Very Old Age” was the title of his 2014 talk at TEDx Gramercy in New York City.)

The drug in question, metformin, costs about five cents a pill. It’s a slightly modified version of a compound that was discovered in a plant, Galega officinalis. The plant, also known as French lilac and goat’s rue, is hardly the stuff of cutting-edge science. Physicians have been prescribing it as an
herbal remedy for centuries. In 1640, the great English herbalist John Parkinson wrote about goat’s rue in his life’s work, *Theatrum Botanicum*, recommending it for “the bitings or stings of any venomous creature,” “the plague,” “measells,” “small pocks,” and “wormes in children,” among other conditions.

According to some sources, goat’s rue was also a centuries-old remedy for frequent urination, now known to be a telltale sign of diabetes. Today, metformin, which helps keep blood sugar levels in check without serious side effects, is typically the first-choice treatment for type 2 diabetics, and it’s sometimes prescribed for prediabetes as well. Together, the two conditions afflict half of American adults. In 2014 alone, Americans filled 76.9 million prescriptions for metformin, and some of those prescriptions went to Barzilai himself. (He’s been taking the drug since he was diagnosed with prediabetes around six years ago.)

A native Israeli, Barzilai speaks English with an accent, never letting grammatical slipups slow him down. He has short, boyish bangs and a slightly rounded face. His thick glasses and natural
exuberance give him the look of an actor typecast as an eccentric researcher. He traces his interest in aging to the Sabbath walks he took with his grandfather as a child. Barzilai could never quite reconcile the frailty of the old man with his grandfather’s stories of draining swamps in prestate Israel. “I was looking and saying, ‘This guy? This old guy could do that?’”

Barzilai first studied metformin in the late 1980s while doing a fellowship at Yale, never imagining the drug would later become his focus. When the FDA approved it as a diabetes treatment in 1994, there was little reason to think it would someday become one of the hottest topics in medicine. But in the following two decades, researchers started comparing the health of diabetics on metformin to those taking other diabetes drugs.

What they discovered was striking: The metformin-takers tended to be healthier in all sorts of ways. They lived longer and had fewer cardiovascular events, and in at least some studies they were less likely to suffer from dementia and Alzheimer’s. Most surprising of all, they seemed to get cancer far less frequently—as much as 25 to 40 percent less than diabetics taking two other popular medications. When they did get cancer, they tended to outlive diabetics with cancer who were taking other medications.

As Lewis Cantley, the director of the Cancer Center at Weill Cornell Medicine, once put it, “Metformin may have already saved more people from cancer deaths than any drug in history.” Nobel laureate James Watson (of DNA-structure fame), who takes metformin off-label for cancer prevention, once suggested that the drug appeared to be “our only real clue into the business” of fighting the disease.
The more researchers learn about metformin, the more it can seem like a medieval wonder drug poised for a 21st century resurgence. In addition to exploring its potential to help treat the most common afflictions of aging, researchers are now also investigating whether metformin might improve symptoms of autoimmune disorders, tuberculosis, and erectile dysfunction, among other conditions. And while much of this research is still in its early stages and may fizzle, metformin is already prescribed off-label to treat obesity, polycystic ovarian syndrome, infertility, nonalcoholic fatty liver disease, and acne—not bad for a plant that the USDA officially lists as a noxious weed.

Barzilai, like most in his field, was aware of the good news about metformin that had been trickling out year after year. But the true origins of his big plan have less to do with metformin itself than with a convergence of a number of different strands of aging research. The first breakthroughs came in
the ‘90s, when researchers demonstrated that a single mutation in a microscopic worm could double its lifespan. Among the takeaways: The aging process might not be as hopelessly complex as it had previously seemed. As this new understanding of aging was settling in, Barzilai was beginning a series of studies on people who live to unusually old ages—“superagers,” as Barzilai calls them.

In the course of that work, he began to notice a pattern that other researchers had also seen: The superagers died from the same diseases as everyone else, but they developed them years later and, critically, closer to the ends of their lives. In other words, if you could slow the aging process, you might do more than give someone a few more years. You could also be able to shrink the suffering and enormous expense that accompanies cancer, heart disease, dementia, and all the other plagues of growing old.

The true promise of antiaging drugs, Barzilai and his colleagues came to think, wasn’t immortality. The ideal drug might not even extend life for all that long. Instead, it would extend what Barzilai and his colleagues call our health span—the years of healthy, disease-free living before the diseases of aging set in. S. Jay Olshansky, a professor at the School of Public Health at the University of Illinois at Chicago, is advising a small team of researchers who are working with Barzilai on a new study of metformin’s antiaging properties. He believes that even a modest slowing of the aging process—and the subsequent extension of health span—would have a greater impact on health and quality of life than a cure for cancer. The upshot: a multitrillion-dollar economic benefit in the decades ahead.

In 2013, Barzilai and two other researchers received a small grant from the National Institute on Aging to explore how the field might move forward. That grant, in turn, led to a 2014 conference in the Spanish countryside, where several dozen researchers gathered in a medieval castle turned hotel to map out a path forward. The castle, surrounded by ancient stone walls and towers, was the sort of place where goat’s rue may have once been handed out by local herbalists. Barzilai describes it as a “Spanish prison.” But the isolation of the setting turned out to be a good thing. “We were stuck in this place with one another,” says Steven Austad, a researcher at the
University of Alabama. “It was really quite intense.”

The assembled scientists and academics focused on one obstacle above all: the Food and Drug Administration. The agency does not recognize aging as a medical condition, meaning a drug cannot be approved to treat it. And even if the FDA were to acknowledge that aging is a condition worthy of targeting, there would still be the question of how to demonstrate that aging had, in fact, been slowed—a particularly difficult question considering that there are no universally agreed-on markers. What they needed, Barzilai and the others concluded, was a precedent-setting test case—a single study that would change the rules forever, not unlike how trial lawyers search for a perfect plaintiff when they’re going to the Supreme Court to set a new legal precedent.

Which drug to use for this precedent-setting case was less obvious. Austad was among those who favored a drug called rapamycin, which has been shown to outperform metformin in studies of longevity in animals. But Barzilai was concerned about rapamycin’s powerful side effects. (An immunosuppressant, it raises the risk of opportunistic infections.) “One thing I don’t want to do is to kill anyone,” Barzilai tells me.
He was confident that metformin was good enough for the job. He has maintained this confidence ever since he read a 2014 study that reviewed the fate of 90,400 type 2 diabetics taking either metformin or another medication. The metformin patients in the study not only outlived the diabetics taking the other drug—a not especially surprising result if metformin is a superior treatment—but also outlived the nondiabetics studied as a comparison.

In the end, the scientists holed up in the Spanish prison settled on an unusual clinical trial designed to test whether metformin can, in addition to extending life, delay the onset of cancer, cardiovascular disease, and cognitive impairment. The FDA will not make its decision on whether metformin becomes the US’s first antiaging drug until the study, dubbed Targeting Aging with Metformin (TAME for short), is complete. That won’t happen for at least another five years. But, based on their June 2015 meeting with FDA officials, Barzilai and his colleagues are optimistic that the FDA is onboard. “Within five minutes, we were all in complete agreement that this is plausible” and “a good idea,” S. Jay Olshansky says.

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**Barzilai was not scheduled** to speak until the third and final day of the Vatican conference. So for the first two days he busied himself mingling with other conference attendees, often approaching them and lifting the IDs hanging from their necks up to his face so that he could make out their names. One night, he turned to an elderly woman in his hotel elevator and asked how old she was, something he often does out of professional interest. Regardless of what number these women offer up, Barzilai always tell them they are, in fact, biologically younger. When Barzilai and the woman got off on the same floor of the hotel, he took her hand and led her in a little dance. “My continuous mitzvah project is to dance with elderly women,” he tells me, using the Hebrew word for “good deed.”

When it was finally his turn to address the conference, Barzilai began by pointing out that the likelihood of being diagnosed with a deadly chronic
disease, such as cancer, heart disease, or Alzheimer’s, increases dramatically as we age. The current approach of treating each illness separately, he suggested, ultimately amounts to a fool’s errand. We survive cancer only to get heart disease a few years later, or vice versa. “Unless we target aging itself,” he announced, “all we can hope is that we switch one disease for another.”

If and when the FDA approves the first antiaging drug, Barzilai believes it will create a domino effect of health and economic benefits: Insurance companies will begin to cover antiaging drugs, and pharmaceutical companies, in turn, will begin investing more in antiaging research and produce new and better drugs that extend human health span. Whether all these benefits will come to pass is hard to know. Big Pharma’s hesitancy to dive into antiaging drugs may have as much to do with past failures as the FDA. In 2008, GlaxoSmithKline spent $720 million on a biotech company that many believed would develop antiaging drugs from resveratrol, a compound found in red-wine grapes. Five years later, after a series of failed trials, the company killed the initiative.

Thus far, getting the FDA excited about TAME has proven to be less challenging than convincing someone to pay for the study. Because metformin is a generic, there is no pot of gold waiting for investors at the end of the process. The TAME trial, which will enroll approximately 3,000 men and women between the ages of 65 and 79 at 14 centers across the country, is projected to cost $69 million. Barzilai is counting on the National Institutes of Health to cover a significant share of the cost, and he has been directly involved in lobbying the agency to back the study. (When he met with Mississippi senator Thad Cochran, he joked that Mississippians need a drug like metformin because they are victims of the state’s great food and can’t stop eating.)
The rest of the money will need to come from private donations. Barzilai recently told me that a billionaire, who insists on remaining anonymous, is considering matching the NIH funding. But, for now, Barzilai still has little to show in the way of locked-down TAME funding beyond the money that he, his wife, and his in-laws have given to the American Federation for Aging Research, the organization sponsoring the trial. “Rich people are interested in aging,” he says. “They call me to prescribe metformin, but they don’t understand that I’m doing something that’s more profound.”

But if the antiaging gurus aren’t ready to pour their millions into a metformin study just yet, that doesn’t mean they’re not interested in the drug. Another member of the aging panel at the Vatican, Robert Hariri, cofounder and president of genetic sequencing pioneer Craig Venter’s Human Longevity Cellular Therapeutics, noted during the discussion that he takes metformin (he claims that it has improved his eyesight), as do Ray Kurzweil, of Singularity fame, and Ned David, cofounder of Silicon Valley startup Unity Biotechnology, which is developing its own antiaging drugs.
In his recent book *Tools of Titans*, Silicon Valley self-help guru Tim Ferriss introduces readers to “billionaires, icons, and world-class performers” so that the rest of us might discover the secrets of their success. Ferriss estimates that a dozen of the people featured in the book take metformin. The problem is that “metformin is available” already, Barzilai told me. “The wealthy donors want to concentrate on the next one that will allow them to live forever.”

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**With so many potential uses**, it can be difficult to avoid the conclusion that metformin is too good to be true, and some of the hype may yet prove to be overblown. Many of the most exciting cancer findings linked to the drug, for instance, come from observational studies of diabetics. They show a correlation between metformin and lower cancer rates, but don’t prove that the compound is responsible for those outcomes or that they extend to nondiabetics. It’s possible that, rather than metformin lowering cancer risk, the other diabetes medications are increasing it.

It’s also possible that, as some metformin skeptics have argued, a lack of statistical rigor has exaggerated some of the most sensational cancer findings. And while evidence from observational studies of cancer patients has been supported by animal experiments as well as by human trials that measure markers of cancer, when it comes to the most important test of a cancer treatment—whether a drug actually extends life—metformin has thus far been a bust. In two controlled trials involving patients with advanced pancreatic cancer, a notoriously difficult cancer to treat, metformin failed to provide any benefit.

But while it’s possible that metformin won’t live up to the excitement it has generated, it’s also possible that the compound, or a very closely related one, may turn out to be even more promising than the current scientific literature suggests. Because it’s no longer under patent, metformin is widely studied, and yet, for the same reason, it doesn’t benefit from the rigorous (and expensive) multistage pharmaceutical drug development process that could determine the most effective dose for cancer or which patients are most likely to respond to treatment. “I don’t
think the trials have been done in a very rational way," says Navdeep S. Chandel, a metabolism researcher at Northwestern University who studies metformin. “The antidiabetic dose that you give to patients might not be enough metformin” for cancer.

If researchers don’t yet know the best way to treat cancer with metformin, they are making real progress on the long-standing question of how it works inside our cells. After a patient takes a metformin tablet, much of the drug ends up in the liver, where it disrupts the process by which cells break down and burn nutrients with oxygen for energy.

If metformin shut down the oxygen reactions completely, it would be deadly—that’s how cyanide works. But the drug merely interferes with one stage of the multistage process by which the energy from nutrients makes its way to oxygen. Michael Pollak, a cancer researcher at McGill University who has studied metformin, compares it to water that’s sprinkled on flames—the fire slows down but doesn’t get extinguished.

It’s possible that metformin treats cancer and other conditions directly by interfering with energy production and, in the process, reducing inflammation. But the cascade of metabolic changes that follow may be even more important. When liver cells are in a state of energy stress, they begin sending out less glucose. “If you’re running out of energy yourself, you don’t want to give it to the rest of your body,” Pollak says.
Lower glucose, in turn, means that the pancreas needs to send out less insulin, the hormone that tells cells to take up and store nutrients. And it’s this indirect influence on insulin that many researchers now point to as a possible explanation for many of metformin’s remarkable range of benefits. Too much insulin has been linked to almost every condition metformin appears to treat, including aging.

The biological logic of the link among glucose, insulin, and aging wasn’t hard for researchers to unravel. Insulin sends a message to our cells that nutrients are available, meaning it’s time to grow and proliferate. When the levels of the hormones drop, it’s a signal to cells that it’s time to enter a life-extending mode of conservation. Such a system makes evolutionary sense. It would have allowed an organism to survive periods of food scarcity with the hope of reproducing when better times arrived. It could also explain why very low-calorie diets can significantly extend life in animals. Metformin is often said to mimic the effects of a low-calorie diet—a pill that offers the benefits of eating less, without leaving you hungry.

Aging in humans is considerably more complicated than aging in microscopic worms and other model organisms, including fruit flies and mice. But evolution builds on what comes before, and the mechanisms have fundamental similarities across species. “Cancer in each individual is a different and specific disease. The genome of the cancer is different,” Barzilai says. “A lot of aging is the same in yeasts and in flies and in nematodes and in mice and in rats and in humans.” Barzilai’s English begins to falter under the weight of his enthusiasm. “We’re not going to prevent every disease in the world,” he says. But we can target “this risk factor of aging that is so important, and take it out of the table.”

When Barzilai’s Vatican panel ended, the conference paused for a scheduled break and the attendees surged forward to ask him about metformin. He told a man in an expensive-looking suit that if he didn’t want to pay $20 a month in the US, he could get metformin for $2 a month in Mexico. When another man asked Barzilai what dosage he should take, Barzilai turned to the woman by his side and asked her how much longer she wanted him to remain alive.

Barzilai seemed entirely in his element as he
whizzed around the room, shaking hands and cracking jokes. But when it was just the two of us, he looked momentarily deflated. I asked him what was wrong. He told me that the moderator had cut the session short before he’d had a chance to mention the most important thing about his plan to change health care with his groundbreaking metformin study: “I wanted to say what it costs, and ask if somebody here is ready to fund it.”

Sam Apple (@samuelapple) teaches science writing at the University of Pennsylvania. He is working on a book about cancer and nutrition.

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Artificial intelligence is now detecting cancer and robots are doing nursing tasks. But are there risks to handing over elements of our health to machines, no matter how sophisticated?
Metformin as a Tool to Target Aging

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Introduction

Over the past decades, remarkable progress has occurred in the science of aging in model organisms. Studies have demonstrated that genetic pathways modulate healthy lifespan in diverse species across great evolutionary distance and established that aging-related pathways constitute a target for intervention (Barzilai et al., 2012; Longo et al., 2015). Lifespan has been verifiably modulated by genetic, pharmacologic, and dietary interventions in multiple model systems.

With support from an R24 grant from the NIA (J. Kirkland, N.B., S. Austad), we gathered gerontologists with expertise in the biology of aging and in clinical geriatrics to discuss ways to target aging in humans. This effort resulted in the design of the study “Targeting Aging with Metformin” (TAME). This trial has been under reviews through several funding mechanisms and has received planning funding from the American Federation of Aging Research. An intended consequence of this effort is to create a paradigm for evaluation of pharmacologic approaches to delay aging. The randomized, controlled clinical trial we have proposed, if successful, could profoundly change the approach to aging and its diseases and affect healthcare delivery and costs. If TAME demonstrates that metformin modulates aging and its diseases, beyond an isolated impact on diabetes, it would pave the way for development of next-generation drugs that directly target the biology of aging. Here, we summarize the major reasons why metformin was chosen to initiate this research.

Targeting Health Span

Interventions that target aging pathways are capable of dramatically extending lifespan and, most importantly, health span, the period of life during which an individual is fully functional and free of chronic illness. There is overwhelming evidence that single gene mutations in nutrient-sensing pathways, such as insulin/insulin-like growth factor (IGF) signaling (Bartke et al., 2001) or the mechanistic target of rapamycin (mTOR) signaling pathways, extend lifespan and health span in invertebrates. More importantly, these pathways have been evaluated in mammalian models, in which health span and lifespan have been extended by genetic manipulation or drugs (Johnson et al., 2013). This raises hope for new interventions, including drugs that slow the aging process and slow the appearance of age-related disease by modulating conserved pathways of aging, as further discussed and developed in recent reviews (de Cabo et al., 2014; Fontana and Partridge, 2015; Fontana et al., 2010).

Interventions to Prolong Lifespan

Recognizing that aging can be targeted, the NIH developed the NIA Interventions Testing Program (ITP). The ITP tests diets, drugs, or other interventions to see if they prevent disease and extend lifespan in genetically heterogeneous (outbred) mice (http://www.nia.nih.gov/research/dab/interventions-testing-program-itp). This program is conducted at multiple centers in order to control for laboratory-specific environmental differences, and testing is done in both male and female animals (Miller et al., 2007; Nadon et al., 2008). Major findings of the ITP include that nordihydroguaiaretic acid and aspirin each increase lifespan of male mice (Strong et al., 2008) and acarbose and 17α-Estradiol extend mouse lifespan preferentially in males (Harrison et al., 2014). Studies of rapamycin (an mTOR inhibitor) have established the most compelling evidence for targeting aging. When rapamycin is administered late in life, it extends lifespan (Harrison et al., 2009; Miller et al., 2011), slows aging in a dose-dependent manner, shows differential effects by sex (Wilkinson et al., 2012), and is synergistic with metformin.

Metformin Modulates the Biology of Aging and Health Span in Model Organisms

Metformin is a drug approved to treat diabetes but appears to target a number of aging-related mechanisms. Some mechanisms are relevant to glucose metabolism, but with respect to aging these may not be the most important ones. Metformin’s multiple aging-relevant actions at the cellular and organismal levels are depicted in Figure 1. Specifically for aging, metformin leads to decreased insulin levels, decreased IGF-1 signaling (Liu et al., 2011), inhibition of mTOR (Kickstein et al., 2010; Nair et al., 2014; Pérez-Revelta et al., 2014), inhibition of mitochondrial complex 1 in the electron transport chain and reduction of endogenous production of reactive oxygen species (ROS) (Batandier et al., 2006; Bridges et al., 2014; Zheng et al., 2012), activation of AMP-activated kinase (AMPK) (Cho et al., 2015; Duca et al., 2015; Foretz et al., 2010; Lien et al., 2014; Lu et al., 2015; Zheng et al., 2012), and reduction in DNA damage (Aligre et al., 2012). Metformin favorably influences metabolic and cellular processes closely associated with the development of age-related conditions, such as inflammation (Saisho, 2015), autophagy (Song et al., 2015; Xie...
To date, there is no evidence for the mechanisms for metformin actions (De Haes et al., 2013). Investigators have suggested additional mechanisms for metformin actions (De Haes et al., 2013; Onken and Driscoll, 2010) supporting widely pleotropic effects. It is currently unclear whether metformin has multiple effects on multiple pathways or whether its observed effects reflect downstream consequences of a primary action on a single mechanism of aging. For example, an attractive explanation suggests (Foretz et al., 2014) that the primary action of metformin is to inhibit mitochondrial complex 1. This inhibition may have multiple downstream effects, but importantly, it would lead to a change in the AMP/ATP ratio, which then activates AMPK. This activation may be relevant to metformin’s known effects on hepatic glucose production (through decreased gluconeogenesis), but it also may suppress lipid synthesis and exert insulin-sensitizing effects, resulting in decreased plasma insulin levels and decreased mTOR activity. However, it is also possible that the singular effect of metformin has not yet been identified, and therefore metformin’s mechanisms of action are worth further investigation.

Beyond these cellular processes, there is a growing body of evidence that metformin can delay aging and increase healthy lifespan in vivo, specifically in nematodes and several rodent strains by adding metformin to the diet (Anisimov et al., 2011; De Haes et al., 2013; Cabreiro et al., 2013). It increases mean lifespan in female outbred mice by ~40% (Anisimov et al., 2008). When started early in life, mean lifespan was increased by 14%, but with initiation at older ages, this effect declined (Anisimov et al., 2011). Metformin delays the onset of carcinomas and extends lifespan by a mean of 8% in a breast cancer model (Anisimov et al., 2010), and extends lifespan by ~20% in a model of Huntington’s disease (Ma et al., 2007) only in males. A more recent study (Martin-Montalvo et al., 2013) demonstrated that metformin increased lifespan by 4%–6% in different mouse breeds. The effects on health span indices such as time on rotarod, distance on treadmill, open field tests, cata#ract index, oral glucose tolerance tests, insulin tolerance, and cognitive function (Allard et al., 2016) were improved by ~30%. As expected in these studies, metformin also increased AMPK activity and increased antioxidant protection, resulting in reductions in both chronic inflammation and accumulation of oxidative damage (Martin-Montalvo et al., 2013), all of which may contribute to health span and lifespan seen in animal models.

Not all studies have shown similar effects of metformin on life or health span. Feeding metformin to Drosophila resulted in a robust activation of AMPK and reduced lipid stores, but did not increase lifespan (Slack et al., 2012). One possibility is that the dose of metformin in this study was toxic. The dose of 1 mM is well above the comparable dose range in humans, and indeed doses higher than this increased mortality. This is also the case in mammals. When using a 10-fold increase in the dose that showed benefit in mice, mortality increased (Martin-Montalvo et al., 2013). Smith et al. (2010) did not demonstrate increased lifespan in metformin-treated rats, although the high dose used (~15 times the dose used in humans) may have been toxic. Additionally, the investigators used caloric restriction as a positive control and failed to observe the expected increased lifespan.

Human Studies of Metformin that Target Age-Related Diseases

If metformin can target and delay aging, its administration should be associated...
with fewer age-related diseases in general, rather than merely the decreased incidence of a single disease. Data from several randomized clinical trials and multiple observational studies provide evidence for such an effect, which would not be expected from glucose lowering alone.

**Clinical Trials**

*The Diabetes Prevention Program (DPP)*. The DPP was a randomized trial in U.S. adults at high risk for T2DM by virtue of obesity and impaired glucose tolerance (Knowler et al., 2002). Over 3,000 subjects were randomly assigned to placebo, metformin (850 mg twice daily), or a lifestyle-modification program. Metformin reduced the incidence of T2DM by 31% compared to placebo over a mean follow-up of ~3 years and was effective in all age categories in preventing diabetes, defined by HbA1c level, including the ~20% who were age 60 or older at baseline (Knowler et al., 2015). Further, metformin treatment was associated with improvement in cardiovascular disease (CVD) risk factors (Goldberg et al., 2013; Haffner et al., 2005) and subclinical atherosclerosis (coronary artery calcium) in male participants (Goldberg et al., 2015).

*The United Kingdom Prospective Diabetes Study*. Patients with T2DM allocated to metformin compared with conventional treatment had risk reduction of ~20% (p = 0.032) for CVD and 42% (p = 0.017) for diabetes-related death (UKPDS Group, 1998). This evidence from UKPDS provides rationale for metformin’s designation as first-line therapy for most patients with T2DM.

*Other Trials*. In the HOME trial of insulin-treated T2DM patients, addition of metformin resulted in 40% reduction (compared with placebo) in a CVD composite after 4 years of follow-up (Kooy et al., 2009). In non-diabetic subjects, the GIPS III study (Lexis et al., 2014) failed to demonstrate the benefit of short-term metformin treatment (4 months) on left ventricular ejection fraction, major adverse cardiovascular events, and mortality in post-myocardial infarction patients, and the CAMERA trial (Preiss et al., 2014) showed no effect of metformin (18 months) on carotid intimal medial thickness.

**Observational Studies**

The majority of observational data support metformin benefit in CVD, but residual bias and confounding cannot be ruled out (e.g., most studies have been conducted in patients with diabetes and include an active comparator, which could itself be cardio-toxic). Metformin’s potential CVD benefits—particularly in the area of primary prevention—remain an active area of research, including an ongoing randomized trial in the UK (The Glucose Lowering In Non-diabetic hyperglycaemia Trial, GLINT, http://www.isrctn.com/ISRCTN34875079; Anfossi et al., 2010; Whittington et al., 2013).

**Observational Studies Suggest Metformin Decreases Cancer Incidence**

Several epidemiologic studies have shown that metformin use is associated with reduced cancer incidence and mortality (Landman et al., 2010; Lee et al., 2011; Libby et al., 2009; Monami et al., 2011; Tseng, 2012). While one meta-analysis (Stevens et al., 2012) did not show that metformin prevents cancer, a more thorough analysis that included more data and accounted for heterogeneous comparators showed that overall cancer incidence was reduced by 31% and cancer mortality by 34% (Gandini et al., 2014). There is also evidence from studies performed both in vitro and in vivo of metformin’s role in attenuating tumorigenesis (Anisimov and Bartke, 2013; Kamevi et al., 2013; Liu et al., 2011; Quinn et al., 2013; Salani et al., 2012; Tosca et al., 2010). The mechanisms proposed relate to reduced insulin levels, improved insulin action, decreased IGF-1 signaling, and activation of AMPK. Numerous ongoing studies are testing the effect of metformin as adjuvant cancer therapy, with a recently published trial showing negative results in advanced pancreatic cancer (Kordes et al., 2015). Although no trials yet have reported effects of chronic treatment on cancer prevention, studies in early-stage cancer or pre-malignancy suggest this may be fruitful (DeCensi et al., 2015).

**Association of Metformin with Better Cognitive Function**

Emerging evidence suggests that metformin may preserve cognitive function. In the Singapore Longitudinal Aging Study, metformin use was associated with a 51% reduced risk of cognitive impairment (defined by modified Mini-Mental Status Exam score ≤ 23), which remained robust to adjustment for vascular and non-vascular risk factors. Further, the lowest risk was seen in those with longer-term (> 6 years) metformin use (Ng et al., 2014). A large observational study of metformin-treated T2DM patients reported lower rates of dementia than in those treated with other diabetes medications (Cheng et al., 2014). One study suggested that T2DM patients treated with metformin had increased risk for poor cognitive performance (Moore et al., 2013); however, it had a number of methodological flaws (Alagiarishnan et al., 2013) and has not been replicated. In one small clinical trial, T2DM patients with depression (n = 58) were treated with metformin or placebo for 24 weeks (Guo et al., 2014). The metformin group showed improved cognitive performance and reduced depressive symptoms, concurrent with improved glycemic control. In an unpublished trial, non-diabetic subjects (n = 80) with mild cognitive impairment showed significant improvements in some cognitive domains after 12 months of metformin treatment (Luchsinger et al., 2016). No definitive trials have been conducted.

**Association of Metformin with Decreased Mortality**

A recent study (Bannister et al., 2014) used retrospective observational data from the UK Clinical Practice Research Datalink. Patients with T2DM who were treated with metformin or sulphonylurea (SU) monotherapy were compared to separate age- and sex-matched control groups without diabetes. SU-treated patients had lower survival than both matched non-diabetic controls and metformin-treated diabetic patients. Surprisingly, metformin-treated diabetic patients had survival rates similar to (and, among those age > 70, even better than) their matched non-diabetic control group, despite the fact that the diabetic patients were more obese and had greater comorbidities at baseline. Mortality benefits have also been described in other observational studies and long-term follow-up of the UKPDS cohort, which showed 36% reduction in all-cause mortality in the metformin treatment group (p = 0.011) (UKPDS Group, 1998). Not all studies have been positive—for example, an analysis from the Medicare Current Beneficiary Survey showed only a non-statistically significant survival benefit for metformin-treated patients (Tinetti et al., 2015).
Considerations in Designing Human Metformin Trials

Dosing: While metformin can be prescribed at dosages of up to 2,250 mg/day, no further effects of decreasing glucose are noted after 1,600–1,700 mg/day. After a single oral dose, metformin is rapidly distributed to many tissues following partial absorption by the small intestine, but the luminal concentration in the gastrointestinal tract remains high. After a single 1.5 g dose, the peak plasma concentration of 18 mM occurs in 3 hr, with a mean plasma half-life of about 20 hr (Foretz et al., 2014). It is suggested, however, that an equivalent dose for mice would be up to 10-fold higher. Studies on biodistribution of metformin in mice showed accumulation mainly in the gastrointestinal tract, kidney, and liver.

Safety. Metformin has been used with an excellent safety record for over 60 years. Side effects are monitored closely within clinical trials, and the safety of metformin use in DPP/DPPOS was reported on in 2012, when over 18,000 patients-years of follow-up had accrued, and by which time ~20% of the cohort was age 70 or older (mean age ~64). There were no cases of lactic acidosis or significant hypoglycemia (Diabetes Prevention Program Research Group, 2012). Mild anemia occurred in ~12% of metformin-treated participants versus ~8% in the placebo group (p = 0.04). Vitamin B12 deficiency occurred in ~7% of metformin group versus 5% in placebo group after 13 years; risk of B12 deficiency increases with duration of use but was not greater in older compared with younger subjects in DPPOS (Lalau et al., 1990). Further, the risk of lactic acidosis appears to be related to renal function, not age per se, and is currently considered to be very low (Aroda et al., 2016).

In the TAME study, we plan to enroll 3,000 subjects, ages 65–79, in ~14 centers across the U.S. Rather than study the effects of metformin on each separate condition, we will measure time to a new medical condition to targeting aging per se. We expect this to facilitate the development of even better pharmacologic approaches that will ultimately reduce healthcare costs related to aging.

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A TRIAL FOR THE AGES

Nir Barzilai wants to launch the first rigorous test of a drug that could put the brakes on aging

By Stephen S. Hall

On a blazingly hot morning this past June, a half-dozen scientists convened in a hotel conference room in suburban Maryland for the dress rehearsal of what they saw as a landmark event in the history of aging research. In a few hours, the group would meet with officials at the U.S. Food and Drug Administration (FDA), a few kilometers away, to pitch an unprecedented clinical trial—nothing less than the first test of a drug to specifically target the process of human aging.

“We think this is a groundbreaking, perhaps paradigm-shifting trial,” said Steven Austad, chairman of biology at the University of Alabama, Birmingham, and scientific director of the American Federation for Aging Research (AFAR). After Austad’s brief introductory remarks, a scientist named Nir Barzilai tuned up his PowerPoint and launched into a practice run of the main presentation.

Barzilai is a former Israeli army medical officer and head of a well-known study of centenarians based at the Albert Einstein College of Medicine in the Bronx, New York. To anyone who has seen the ebullient scientist in his natural laboratory habitat, often in a short-sleeved shirt and always cracking jokes, he looked uncharacteristically kempt in a short-sleeved shirt and always cracking.

To anyone who has seen the ebullient scientist in his natural laboratory habitat, often in a short-sleeved shirt and always cracking jokes, he looked uncharacteristically kempt in a short-sleeved shirt and always cracking jokes. But his practice run kept hitting a historical speed bump. He had barely begun to explain the rationale for the trial when he mentioned, in passing, “lots of unproven, untested treatments under the category of anti-aging.” His colleagues pounced.

“Nir,” interrupted S. Jay Olshansky, a demographer of aging from the University of Illinois, Chicago. The phrase “anti-aging ... has an association that is negative.”

“I wouldn’t dignify them by calling them ‘treatments,’” added Michael Pollak, director of cancer prevention at McGill University in Montreal, Canada. “They’re products.”

Barzilai, a 59-year-old with a boyish mop of gray hair, wore a contrite grin. “We know incidence increases dramatically with age: cardiovascular disease, cancer, and cognitive decline, along with mortality. When it comes to these diseases, Barzilai is fond of saying, “aging is a bigger risk factor than all of the other factors combined.”

But the phrase “anti-aging” kept creeping into the rehearsal, and critics kept jumping in. “Okay,” Barzilai said with a laugh when it came up again. “Third time, the death penalty.”

The group’s paranoia about the term “anti-aging” captured both the audacity of the proposed trial and the cultural challenge of venturing into medical territory historically associated with charlatans and quacks. The metformin initiative, which Barzilai is generally credited with spearheading, is unusual by almost any standard of drug development. The people pushing for the trial are all academics, none from industry (although Barzilai is co-founder of a biotech company, CohBar Inc., that is working to develop drugs targeting age-related diseases). The trial would be sponsored by the nonprofit AFAR, not a pharmaceutical company. No one stood to make money if the drug worked, the scientists all claimed; indeed, metformin is not only generic, costing just a few cents a dose, but belongs to a class of drugs that has been part of the human apothecary for 500 years. Patient safety was unlikely to be an issue; millions of diabetics have taken metformin since the 1960s, and its generally mild side effects are well-known.

Finally, the metformin group insisted they didn’t need a cent of federal money to proceed (although they do intend to ask for...
Double dividends

Metformin acts on the mitochondria, the cellular power plants. The result is two sets of effects, one in the liver that explains the drug’s benefits in diabetes and the other, less well understood, that could slow aging.
nematodes. By manipulating individual genes and measuring effects on life span, researchers could test the role of specific molecular pathways in aging. In perhaps the most dramatic mammalian example, Andrzej Bartke, a biologist at the Southern Illinois University School of Medicine in Springfield, showed that mice with mutated growth pathways, which disabled both growth hormone and IGF-1, were much smaller—but lived much longer.

Within the last decade or so, researchers have settled upon what Felipe Sierra, director of the division of aging biology at the National Institute on Aging (NIA), calls “the major pillars of aging.” These pathways and mechanisms, roughly half a dozen in all, affect metabolism, growth, response to stress, stem cell vigor, inflammation, and proteostasis—the cell’s quality control system for proteins. And their identification has opened the door to a previously outlandish notion. It “allows us to think that, okay, if we understand how this happens, we can maybe manipulate it,” Sierra says.

MORE THAN A DECADE AGO, Barzilai and others began lobbying FDA to consider drugs that might do just that. But those discussions bogged down, he says, after the sides couldn’t agree on the kinds of biomarkers associated with aging that could be quantified and tracked during a clinical trial.

Barzilai now believes the answer is to design a drug trial that, rather than targeting aging per se, tries instead to delay the onset of “comorbidities”: the chronic diseases whose incidence rises sharply as people get older. “Basically, I think the FDA will be more willing to accept something called ‘comorbidities’ than it is to accept something called ‘aging,’” Barzilai says. “Even in our mind, in my mind, aging is not a disease,” he adds. “It’s, you know, humanity! You’re born, you die, you age in between … I’m kind of saying, ‘I don’t care what they want to call it, if I can delay it.’”

The comorbidity strategy is key to a concept known as the “longevity dividend,” first proposed by a group of public policy and health care experts in 2006. The idea is that slowing down the process of aging, even modestly, would have enormous benefits for quality of life and the economics of health care. “We’re not arguing—and we’ve never argued—that we’re trying to achieve life extension,” says Olshansky, who has pushed the concept while criticizing some of the more outlandish claims in the aging field, such as British gerontologist Aubrey de Grey’s prediction that human life spans of 1000 years are possible. “We’ll probably live a little longer if we succeed, but that’s not the goal,” Olshansky says. “The goal is the extension of the period of healthy life.”

Even a modest delay in aging could increase average life expectancy by 2.2 years, compress the period of morbidity at the end of life, and save perhaps $7.1 trillion in health care costs over a period of 50 years, Olshansky and colleagues estimated in a 2013 paper in the journal Health Affairs. To achieve those benefits, “we’ve got to act quickly,” he argues. “The numbers of people that are frail and disabled [are] rising fairly rapidly, and we’re seeing an increase in unhealthy life span.”

But the FDA drug approval process abides by the “one disease, one drug” model. Would the agency be open to a trial that had multiple illnesses as an endpoint? As an initial step, earlier this year Sierra organized seminars at FDA in which NIA researchers described recent findings in the biology of aging. In May, Robert Temple, deputy director of FDA’s Center for Drug Evaluation and Research, spoke at an NIA retreat.

Encouraged by the tenor of these discussions, Barzilai and a core group of collaborators—Einstein’s Jill Crandall; Austad; Olshansky; Stephen Kritchevsky at Wake Forest School of Medicine (where the multicenter trial would probably be based); and James Kirkland, a diabetes researcher at the Mayo Clinic, among others—pushed ahead with plans for the trial.

The next question was: What would be the best drug to test?

THERE WAS NO SHORTAGE of possibilities. Buoyed by the advances in basic research, NIA in 2003 inaugurated a program of animal experiments to test compounds that might alter or slow down the aging process. NIA-supported researchers have tested 16 compounds in mice. Five have shown a positive effect, Sierra says: aspirin, acarbose (a widely prescribed diabetes drug), 17-alpha-estradiol (the nonfeminizing form of estrogen), nordihydroguaiaretic acid (an herbal compound derived from the creosote plant), and the immunosuppressive drug rapamycin (used in organ transplant recipients). (Among the compounds that had no impact are fish oil, green tea extract, curcumin, and the much-ballyhooed red wine ingredient resveratrol.) Rapamycin was the most impressive. “It has advanced to the point in which we not only know it extends life span,” Sierra says, “but more importantly, it extends health span.”

Metformin, the drug the group ultimately decided to take to FDA, was not among the compounds that starred in the animal trials. But it has both a promising history and a long, reassuring track record.

“It all starts in the Middle Ages,” says McGill’s Pollak. “There were herbalists in Europe—and, independently, herbalists in China—who found plant extracts that were useful when people came in complaining of urinating too much.” The extracts derived from a perennial herb (Galega officinalis) known variously as goat’s rue, French lilac, Spanish sainfoin and false indigo. “It worked for some people,” Pollak says. “In retrospect, [we know] the people for whom it was working were diabetic.”

It wasn’t until the late 1800s that chemists isolated the active ingredient in French
Metformin has its roots in centuries-old herbal remedies including goat’s rue, which helped people with symptoms now recognized as diabetes.

Metformin—a compound known as guanidine. But guanidine itself proved too toxic to humans, so chemists began to synthesize less toxic analogs known as biguanides, including metformin. In the 1950s, a French physician and pharmacologist named Jean Sterne began to test biguanides in patients with type 2 diabetes at a hospital in Paris. “The best one in terms of efficacy was metformin,” Pollak says.

Sterne coined the name glucophage (“glucose eater”) when he published his results in 1957, the same year the drug was approved for use in France. Approved in the United Kingdom in 1958 and in Canada in 1972, metformin went on to become the biggest selling diabetes drug in the world. However, U.S. regulators didn’t approve it until 1994. (FDA requested additional studies, Barzilai dryly notes, “to see if metformin works in the same way as in the United Kingdom, because we are so different here.”)

By now, companies churn out an estimated 37,000 metric tons of the compound annually, most of it in India.

Hints that metformin might also prevent diseases associated with aging began to emerge over the past several decades. In a 1998 report by the United Kingdom Prospective Diabetes Study Group, metformin use not only reduced the risk of all diabetes-related complications (including death) by 32%, but also significantly lowered the risk of cardiovascular disease, including heart attack and stroke. A randomized, placebo-controlled trial called the Diabetes Prevention Program showed similar effects, cutting the onset of type 2 diabetes by 31% in a middle-aged population at high risk of developing the disease.

Epidemiological studies have also suggested that metformin reduces cancer risk and mortality and preserves cognitive function. And in a big-data study that, although observational, got the attention of many aging researchers, British researchers reported late last year that in a retrospective analysis of 78,000 adult type 2 diabetics in their 60s, those who took metformin on average lived longer than healthy age-matched controls.

None of these studies proves that metformin will delay the onset of age-associated diseases, and scientists haven’t identified an exact mechanism by which the drug might work. But it appears to act on some of the same molecular pathways identified by basic aging research. Besides its effects on blood glucose, metformin affects multiple pathways involved in growth, inflammation, and metabolism (see graphic, p. 1276).

Pollak has demonstrated what he and others see as the key effect, which may trigger the other benefits of the drug: It inhibits oxygen consumption in mitochondria, in effect turning down the cell’s metabolic thermostat. “When a furnace is burning,” he says, “it’s heating up and it’s cracking and it begins to degrade. When you keep your house at a lower temperature, your furnace is going to last longer.”

As it turns out, Barzilai is very familiar with metformin—not only as a doctor who has prescribed it and as a researcher who has studied it, but as a patient who has taken it for 5 years. (He says he is considered prediabetic.) He can testify to its safety and tell you exactly how to avoid its most common side effect, gastrointestinal upset. “There’s nothing we don’t know about metformin,” Barzilai says—especially its record for safety, which he calls “critical” to the proposed trial.

His colleagues agreed, sometimes reluctantly. “Rapamycin would have been my first choice, because the animal results have been so spectacular,” Aустad says. “But Nir said, ‘We can’t afford in this first trial to kill anybody.’ And I thought, ‘Strategically, he’s right.’”

Barzilai concedes that he and the AFAR-sponsored group are as interested in setting a precedent as in scoring an impressive initial success. Satisfying FDA concerns about a trial that breaks tradition and measures multiple disease endpoints in an aging population, they say, will open the door for pharma to enter the field.

“Metformin is for us a tool—a very exciting tool,” Barzilai said prior to the FDA meeting. “It’ll work, I think. But I don’t want to waste the hour talking about metformin. You know, we chose metformin in order not to talk about it anymore.”

When he and the rest of the AFAR delegation finally made it into FDA’s meeting room, Barzilai scanned the large contingent seated around the table. “Too many young people here!” he joked. “We should leave now!” But the turnout was encouraging—14 FDA staff members, including Temple and several division chiefs. The meeting ran nearly 30 minutes past the scheduled hour, and by the time Barzilai and the others emerged, they were surprised smiles. Aустад flashed two thumbs up. “I don’t think it could have gone much better,” he said.

Barzilai, whose enthusiasm occasionally exceeds his command of English, sent out an email the next day to everyone who had helped prepare for the FDA meeting, thanking them and describing the meeting as “hysterical.” Historical, Barzilai later explained, because “I think that in their heart, they buy it. Or many of them, or the important people, are buying what we are saying.” Olshansky left the meeting convinced that FDA had given a green light, contingent on several adjustments to the protocol, which the group is now making.

Other participants, like Sierra, struck a more cautious note. When asked whether FDA representatives expressed skepticism about the proposed trial, he said, “Conceptually? No. But in the details, yes.”

SANDY WALSH, an FDA spokeswoman, says the agency does not comment on drugs under development or under investigation. But in a followup communication to the AFAR group, Barzilai says, FDA indicated that although it is not yet convinced that the proposed trial design can establish that metformin has an anti-aging effect, the agency recognizes the potential value in a drug that could improve quality of life and survival—whether the indication sought is aging or multiple morbidities—and is not opposed to the idea of a trial.

Now, trial advocates need someone willing to foot the cost—“$50 million, plus or minus $20 million,” according to Barzilai—of tracking some 3000 people between the ages of 65 and 79 for a minimum of 5 years. Olshansky says the metformin group has already targeted “high net-worth individuals” to bankroll the trial. Federal funding would be welcome, Barzilai says, but private money would probably allow the trial to start sooner. “For me,” he says, “the best thing that can happen is that people are writing about it, the television will show it, somebody will call me one day and say: ‘You know, I’m rich like I don’t know what, and I don’t mind helping. Is $50 million enough?’ And then we’ll get going.”

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Substantial Health And Economic Returns From Delayed Aging May Warrant A New Focus For Medical Research

By Dana P. Goldman, David Cutler, John W. Rowe, Pierre-Carl Michaud, Jeffrey Sullivan, Desi Peneva, and S. Jay Olshansky

ABSTRACT Recent scientific advances suggest that slowing the aging process (senescence) is now a realistic goal. Yet most medical research remains focused on combating individual diseases. Using the Future Elderly Model—a microsimulation of the future health and spending of older Americans—we compared optimistic “disease specific” scenarios with a hypothetical “delayed aging” scenario in terms of the scenarios’ impact on longevity, disability, and major entitlement program costs. Delayed aging could increase life expectancy by an additional 2.2 years, most of which would be spent in good health. The economic value of delayed aging is estimated to be $7.1 trillion over fifty years. In contrast, addressing heart disease and cancer separately would yield diminishing improvements in health and longevity by 2060—mainly due to competing risks. Delayed aging would greatly increase entitlement outlays, especially for Social Security. However, these changes could be offset by increasing the Medicare eligibility age and the normal retirement age for Social Security. Overall, greater investment in research to delay aging appears to be a highly efficient way to forestall disease, extend healthy life, and improve public health.

US life expectancy has increased dramatically over the past fifty years, and there have been major improvements in the functional capacity of the elderly. These gains have been driven by advances in public health and nutrition. They have also been driven by physicians’ and scientists’ use of a highly focused “disease model” to improve the diagnosis and treatment of various major fatal conditions. The goal of the model is to reduce mortality rates by the earlier detection of these conditions and by the reduction of risk factors and the development of effective new treatments for them. But the longer lives that Americans now enjoy come with social and fiscal side effects. Today more people are qualifying for old-age entitlement programs, and they remain in these programs longer. Medicare spending alone is projected to almost double as a share of gross domestic product, from 3.7 percent in 2012 to 7.3 percent in 2050.1

Although attacking diseases has extended life for younger and middle-aged people, evidence suggests it may not extend healthy life once people reach older ages. Increased disability rates are now accompanying increases in life expectancy, leaving the length of a healthy life span unchanged2−4 or even shorter than in the past.5 The evidence is not completely one-sided, however: In one study of health status among successive birth cohorts in Denmark, researchers found that people born more recently experienced better health.6
In any case, as people age, they are now much less likely to fall victim to a single isolated disease than was previously the case. Instead, competing causes of death more directly associated with biological aging (for example, heart disease, cancer, stroke, and Alzheimer’s disease) cluster within individuals as they reach older ages. These conditions elevate mortality risk and create the frailty and disabilities that can accompany old age.

**Delayed Aging**

Fortunately, new research is emerging that has the potential to extend life while reducing the prevalence of comorbidities over the entire lifetime. Scientists have been asking whether we can decelerate the process by which the cluster of conditions described above arises, making people healthier at older ages and even lowering spending on health care. Simply put, can we age more slowly—thereby delaying the onset and progression of all fatal and disabling diseases simultaneously?

At the practical level, delayed aging means having the body and mind of someone who is years younger than the majority of today’s population at one’s chronological age and spending a larger proportion of one’s life in good health and free from frailty and disability. Experimental studies involving animal models have already succeeded in accomplishing this in the laboratory. In addition, there is evidence that centenarians (whose longevity is at least partially heritable) often have delayed onset of age-related diseases and disabilities, which suggests that they senesce (grow old biologically) more slowly than the rest of the population.

By manipulating genes, altering reproduction, reducing caloric intake, modulating the levels of hormones that affect growth and maturation, and altering insulin-signaling pathways, scientists have managed to extend the lifespan—and the healthy lifespan—of invertebrates and mammals. These specific manipulations are unlikely to be directly applicable in humans, but they may lead scientists in the right direction. In addition, some compounds, such as rapamycin (used to prevent organ rejection in transplant patients), may eventually be shown to extend healthy life, even when used in older individuals.

In addition, clinical interventions to delay aging have been proposed that involve interfering with chronic inflammation. In mice the selective removal of senescent cells has been documented to lead to significant improvements in health—an intervention that many researchers believe could be clinically effective in people. Some scientists contend that such interventions are sufficiently close to fruition that people alive today will benefit from them. Should we continue on this path of discovery?

In deciding whether and how much society should continue to invest in delayed aging, two specific questions arise. First, what are the social returns—in terms of health and spending—on continued investments in a “disease model” versus the returns on investments in delayed aging? Second, can society afford to invest in the accelerated development of interventions that extend healthy life, given fiscal uncertainties? In this article we compare the future health and economic benefits—as well as the costs—of continuing to place a priority on the “disease model” with the benefits and costs of placing a new emphasis on delayed aging.

**Study Data And Methods**

To estimate the potential benefits and costs, we used the Future Elderly Model (FEM), a microsimulation that tracks older cohorts of people and projects their health and economic outcomes. Prior work with the FEM has examined the impact of new medical technologies, changes in disability, improved prevention of diseases, and other health policy changes. We describe the model and methods briefly here; more detail is provided in the online Appendix.

The FEM models representative cohorts of people age fifty-one or fifty-two based on the Health and Retirement Survey, a biennial survey of Americans age fifty-one or older that began in 1992. For each individual, the FEM predicts medical spending, health conditions, functional status, and employment for the next two years, given initial demographic characteristics and health states. Medical spending is predicted using data from the Medical Expenditure Panel Survey for the non-Medicare population and from the Medicare Current Beneficiary Survey for Medicare beneficiaries, in each case adjusted to 2010 dollars using the medical Consumer Price Index.

Health states are derived from survey questions. Disability is measured by any limitations in activities of daily living or in instrumental activities of daily living, or by nursing home residency. Both functional status and the likelihood of developing a health condition depend on age, sex, education, race, ethnicity, body mass index, smoking status, and health at the time of entry into the study. All health conditions, functional states, and risk factors are modeled using first-order Markov processes that control for baseline unobserved factors, using health variables collected at baseline. These turn out to be effective
controls as revealed by goodness-of-fit tests.

**NEW COHORTS** Because of evidence of worsening health in younger cohorts, the FEM accounts for these trends for future populations. Specifically, the model includes trends in disability, obesity, smoking, and chronic disease among younger populations, based on projections from the National Health Interview Survey, the Current Population Survey, and other work of the Census Bureau. For instance, in the FEM, the prevalence of diabetes among people age fifty-one or fifty-two in 2030 is 27 percent higher than the prevalence for that age group in 2004.

**FISCAL OUTCOMES** We examined the costs of major entitlement programs—specifically, federal and state spending for Medicare and Medicaid, and federal income support through Old-Age, Survivors, and Disability Insurance and Supplemental Security Income. Economic outputs were aggregated into fiscally relevant variables using benefit rules for particular programs. Annual costs are given in constant 2010 dollars. All cumulative costs are discounted using a 3 percent annual discount rate.

**SCENARIOS** We developed four scenarios (one representing the status quo, or baseline) and compared the health and medical spending they would involve. For each scenario we conducted the simulation fifty times and averaged the outcomes.

We assumed that all changes were accomplished at no additional cost relative to baseline, to allow us to focus on population benefits. Each scenario assumed that changes in mortality and disease processes occurred in the period 2010–30. The scenarios also assumed that progress ceased after 2030 but that the effects of earlier changes continued to play out.

Two disease-specific scenarios were meant to represent optimistic developments in medical research, disease treatment, and improvements in behavioral risk factors. In other words, these scenarios assumed that if diseases were attacked individually through treatments or systemically through behavior modification, the incidence of disease and the impact of cases of disease would be reduced.

The fourth scenario (assuming delayed aging) is a hypothetical assessment of a successful effort to translate research on the biology of aging into therapeutic interventions that would reduce and compress both morbidity and mortality into a shorter period of time at the end of life. Unlike the delayed disease interventions in the two disease-specific scenarios—which face diminishing returns because of competing causes of sickness and death in aging populations—the delayed-aging scenario assumed that all fatal and disabling diseases were influenced simulta-
ology of aging, which suggests that the health benefits of delayed aging would begin at puberty—the time when mortality begins rising exponentially.31,32

Although this scenario altered the effects of getting disease, it was not the same as scenarios of disease prevention because it addressed the underlying biology of aging. The scenario reduced mortality and the probability of onset of both chronic conditions (heart disease, cancer, stroke or transient ischemic attack, diabetes, chronic bronchitis and emphysema, and hypertension) and disability by 1.25 percent for each year of life lived above age fifty (the period in life when most of these diseases emerge). This reduction was phased in over twenty years, starting with a 0 percent reduction in 2010 and increasing linearly until the full 1.25 percent reduction was achieved in 2030.

The impact of the changing rates of transition in disease and functional status can be seen in the change in average life-cycle characteristics. Life expectancy at age fifty-one in 2030 was 35.8 years in the status quo scenario, based on current Social Security Administration projections.28 It improved by about one year in both the delayed cancer (36.9 years) and delayed heart disease (36.6 years) scenarios. In the delayed aging scenario, however, it increased to 38.0 years—an improvement of 2.2 years (see Appendix Exhibit SI).24

As in the delayed cancer and delayed heart disease scenarios, in the delayed aging scenario we adjusted the prevalence of chronic conditions in the incoming cohorts.

**DELAYED AGING WITH AN ELIGIBILITY FIX:**

We modeled a variant of the delayed aging scenario that included an adjustment to the eligibility age for Medicare and the normal retirement age for Social Security. Social Security provides a strong precedent for such a policy fix: The normal retirement age was raised in 1983 from sixty-five to sixty-six, and the age will increase to sixty-seven for people born in 1960 and later. Our “eligibility fix” consisted of a gradual increase in the eligibility age for Medicare from sixty-five to sixty-eight, and for Social Security from sixty-seven to sixty-eight (extending the Social Security Amendments of 1983—which mandated gradual increases in the retirement age over a twenty-two-year period starting in 2000—for about ten years).

In this scenario people enrolled in Medicare Part A as soon as they were eligible to do so. Medicare Part B take-up was modeled as an age-independent probit, so the scenario assumed that take-up was at the same rate regardless of age and depended directly on health and functional status (see Appendix Table 22).24 Part D take-up was modeled in a similar way (see Appendix Table 24).24

Starting Social Security benefits was also modeled as a probit, but we used the normal retirement age (see Appendix Table 13).24 This yielded a conservative estimate of the eligibility change required to counterbalance the fiscal impact of extended life. The delayed aging scenario with the eligibility fix—because of the later official retirement age—would result in more taxes collected during working years than in the original delayed aging scenario without an eligibility change, and less money paid out as lifetime benefits because of the later start of retirement.

**LIMITATIONS** There are several limitations involved in this approach. First, this is a simulation of various scenarios of biomedical innovation. All of the usual caveats about simulations apply, including assumptions about no changes in the underlying parameters that model health-related behavior and economic outcomes.

Most important, the proposed eligibility fix was intended as a useful metric to see what changes would be necessary to fiscally accommodate delayed aging. Obviously, more study would be required before the implementation of any policy change—including an official scoring of such a change by the Congressional Budget Office, fuller consideration of distributional and health outcomes beyond the major entitlement programs, and consideration of the impact of any financing reforms such as those in the Affordable Care Act.

Finally, our model demonstrated the hypothetical benefits of scientific progress in various areas, but not the cost of that progress. People who decide what research to invest in need to consider the costs of the research and the likelihood of success. To identify medical breakthroughs, we have attempted to evaluate such issues in previous work, with reasonable success.25 However, a full accounting of the costs and probabilities involved is beyond the scope of this research.

**Study Results**

In the status quo scenario the number of elderly people—those age sixty-five or older—in the United States more than doubled, increasing from 43 million in 2010 to 106 million in 2060. The scenarios of delayed cancer and delayed heart disease diverged little from the first scenario, leading to only 0.8 percent and 2.0 percent more elderly people in 2060, respectively. In contrast, the delayed aging scenario added 6.9 percent more elderly people. These demographic gains would occur quickly, with 6.1 percent more elderly Americans than in the status...
scenario after only twenty years. When we conducted a sensitivity analysis after adjusting the scenarios to include relative changes in incidence over a wider range, the effects were similar (see Appendix Exhibit S7).24

Of course, it matters whether these survivors would be healthy or disabled. In the status quo scenario 31.0 million people age sixty-five or older were not disabled in 2010; the number was 75.5 million in 2060 (Exhibit 1).33,34 In the disease-specific scenarios there were very small increases in the number of nondisabled elderly people compared to the delayed aging scenario, in which there was a 15 percent increase from the status quo scenario.

These absolute numbers can also be translated into disability rates. Today the share of the elderly US population without disabilities is around 72 percent. In the status quo scenario this share increased to 78 percent in 2026 but then declined to 71 percent in 2060 (see Appendix Exhibit S2).24 This decline was due to the lower all-cause mortality rates projected for the future and the growing prevalence of health risks (such as obesity) among people entering the elderly group.

As Appendix Exhibit S2 shows,24 the disease-specific scenarios both had an effect nearly identical to the status quo scenario. In comparison, the delayed aging scenario yielded a larger share of nondisabled seniors in every year between 2010 and 2026, compared to the status quo scenario. Although the size of the difference declined from 2030 to 2060, during that thirty-year period an additional 5 percent of elderly people were nondisabled in the delayed aging scenario. Per capita Medicare spending was also lower in the delayed aging scenario than in the status quo scenario.

At the population level, the aggregate costs demonstrate the fiscal strain imposed by delayed aging (Exhibit 2). In that scenario more elderly people were alive. Consequently, more people qualified for entitlement programs, and costs were higher. In 2060, spending in the delayed aging scenario was $295 billion more than in the status quo scenario. In contrast, the delayed cancer scenario led to only a modest increase, and the delayed heart disease scenario brought spending below the level in the status quo scenario.

The gap in income support was also considerable. Spending beyond that in the status quo scenario was relatively low in the disease-specific scenarios (Exhibit 3). In comparison, it climbed to around $125 billion in the delayed aging scenario by 2055. Delayed aging would add nearly $420 billion to the entitlement deficit in the status quo scenario in 2060, 70 percent of which...
would come from increased outlays for Medicare and Medicaid.

Exhibit 4 shows the fiscal effects of the four main scenarios as well as the effect of delayed aging with the eligibility fix to Medicare and Social Security described above. The eligibility fix would more than offset the additional costs of delayed aging relative to the status quo.

Discussion

Our results demonstrate that shifting the focus of medical investment to delayed aging would lead to a set of desirable, but economically challenging, circumstances. The potential gains are significant. Although the disease model has reduced mortality from lethal conditions dramatically in the past century, its influence is now waning because of competing risks. As people live longer, they are more likely to fall victim to multiple diseases. Our simulations of reduced incidence of heart disease and cancer suggested incrementally smaller gains in longevity going forward. The medical costs of treating these diseases independently would rise but, for example, would produce only a 3.2-year increase in life expectancy for sixty-five-year-olds from 2010 to 2060.28

Recent research has shown that the decades-long improvement in the functional status of older Americans halted in 2002.2,3 This suggests that many of the historical drivers of better health in the elderly may no longer work. Declining disability buttresses the case for research on slowing aging by compressing morbidity and extending healthy life, which would provide an adequate workforce for producing the goods and services that the future aging society would use and would yield direct benefits to those older people who remain socially engaged.

Still, the fact remains that longer lives would mean greater fiscal burdens for Social Security and other income support programs and increased Medicare and Medicaid expenditures, even as per capita medical costs declined. An unequivocal answer to the question of whether the current focus of medical research and investment should be shifted from the disease model to delayed aging depends on whether the potential gains could be realized and the adverse consequences allayed.

One way to think about the future gains is to look at the present discounted value of all the additional quality-adjusted life-years that would arise from delayed aging relative to the status quo. These life-years can then be valued using a conservative metric, such as $100,000 per life-year. Doing so yields a social benefit of approximately $7.1 trillion—without even considering
the cognitive benefits to individuals that could arise from these interventions.\textsuperscript{6}

Given the large social return, the question then becomes how we could accommodate these changes fiscally. Several policy measures might arise from these interventions.\textsuperscript{6} The major challenges of delayed aging appear to be of a fiscal nature, but they are manageable. The benefits to society of delayed aging would accrue rapidly and would extend to all future generations. Investing in research to delay aging should become a priority.\textsuperscript{9}

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NOTES


5 Hulsegg G, Picavet HS, Blokstra A, Nooijens AC, Spijkerman AM, van der Schouw YT, et al. The major challenges of delayed aging appear simultaneously. Not surprisingly, we see extremely large population health benefits in our delayed aging scenario.

The benefits to society of delayed aging appear to be of a fiscal nature, but they are manageable. The benefits to society of delayed aging would accrue rapidly and would extend to all future generations. Investing in research to delay aging should become a priority.

Conclusion

It is clear that competing health risks limit the impact of major clinical breakthroughs for specific diseases—in other words, making progress against one disease means that another one will eventually emerge in its place. However, evidence suggests that when aging is delayed, all fatal and disabling disease risks are lowered simultaneously. Not surprisingly, we see extremely large population health benefits in our delayed aging scenario.

The major challenges of delayed aging appear to be of a fiscal nature, but they are manageable. The benefits to society of delayed aging would accrue rapidly and would extend to all future generations. Investing in research to delay aging should become a priority.


24. To access the Appendix, click on the Appendix link in the box to the right of the article online.


Taming the Diseases of Aging

In pursuit of a global wisdom dividend

By Ivan Amato

from The Moonshot Catalog,
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in collaboration with the American Association for the Advancement of Science (AAAS).

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The Moonshot Catalog is an on-line home for an engaging and uplifting series of articles about ambitious but doable science- and technology-anchored challenges whose realization would do a lot of good for a lot of people.

The Moonshot Catalog is a communications project funded by the philanthropic organization Schmidt Futures in collaboration with the American Association for the Advancement of Science (AAAS).
A HEALTHSPAN MOONSHOT

Delaying the onset of cancer, cardiovascular disease, dementia, frailty, and other diseases and conditions of aging extends the healthspan — the period of life during which people are disease-free, pain-free, and independent. The young field of geroscience, which focuses on the biology of aging, appears to be on the cusp of uncovering interventions that can extend the population’s average healthspan. This could lead to economic benefits estimated to be as much as $7 trillion-dollars over the course of 50 years, as well as more seniors living longer lives for the most part without suffering from diseases of aging.

THE PHILANTHROPY OPPORTUNITY

As a new field, geroscience is in need of funding for students and young researchers aiming to join its ranks. In addition, translating scientific discoveries in labs into FDA-approved, healthspan-promoting medicines entails clinical trials that can cost tens of millions of dollars with no guarantee of success. As the portfolio of potential geromedicine agents worthy of clinical trials grows, it will take more resources to make those trials happen.

Earlier this year, Nir Barzilai, head of the Institute for Aging Research at the Albert Einstein College of Medicine in the Bronx, New York, was preparing for an invited trip to Singapore to advise the government about trends in aging and health. He asked the country’s prime minister, Lee Hsien Loong, to send any questions that were of interest to him. One of these stood out. Barzilai says Loong asked if spiking his country’s water supply with metformin, a common diabetes drug with an anecdotal reputation for staving off diseases of aging, was worth considering. “The answer was no,” Barzilai was quick to say. But he also tells The Moonshot Catalog that the question was not entirely crazy. Rather, Barzilai explains, “think how forward looking the government is to ask such a question.”

Often wearing his enthusiasm in plain sight, 63-year-old Nir Barzilai is a prime mover in an accelerating biomedical research and development campaign to extend the healthy years of billions of people and to keep many of them alive and healthy well beyond their hundredth birthday. Imagine a planet within the next few decades rife with many more healthy, independent, and active centenarians who are disease-free, pain-free, and physically and mentally active. Barzilai, who runs his institute’s 40 aging-research laboratories, routinely catches glimpses of this future in the human centenarians and senior rodents that star in his own investigations.

Realizing this vision of a general population that lives healthy longer has become the mission of Barzilai and colleagues in the emerging field of geroscience, a term coined about a dozen years ago by geneticist Gordon Lithgow of the Buck Institute, which is a research center in Novato, California, devoted to the science of aging. “It will be a catastrophe if we do not succeed,” says S. Jay Olshansky, a social scientist and epidemiologist at the University of Illinois at Chicago, who a decade ago coined the term “longevity dividend” to refer to the health and economic benefits of delaying the aging process.
Water sanitation, vaccines, antibiotics, ever-better medical practice, and other public-health advances over the past century have reduced infant and childhood mortality and prolonged the lives of sick and injured adults who otherwise would have died. This accounts for why people today, in developed countries at least, are living 30 years longer on average than their progenitors who were born and living a century ago. But today’s longer-living men and women are also suffering longer with cardiovascular disease, cancer, dementia, frailty, and other diseases and conditions associated with aging. “The time has come for us to take control of our own biology,” Olshansky says. “Instead of dealing with the consequences of aging, let’s modify aging itself. Let’s try to slow the process of aging because to do so would have a cascading effect on every fatal and disabling disease that appears in old age today.”

This is not just another expedition in search of the mythical fountain of youth driven by wishful thinking. This time, the geroscience community contends, the science is in. Researchers over the past few decades have uncovered molecular and cellular bases of the aging process, many of which apply across the animal kingdom, from worms and flies to mice and people. By using drugs to intervene in these fundamental aging processes — among them protein biochemistry gone awry and the accumulations of senescent cells that have stopped dividing but remain alive in tissues where they can act like disease-causing bad apples — it may be possible to stave off the onset of many of the diseases of aging.

HERE’S TO YOUR HEALTH

“We are not talking about having 500-year-old people, but we are talking about people who stay healthy another decade or two relative to what we do now,” explains biologist Steven Austad of the University of Alabama at Birmingham, who also serves as scientific director of the American Federation for Aging Research (AFAR), a grant-giving and advocacy organization in New York City. Rather than pursuing a goal of extending how long people live, Austad stresses, the goal of geroscience is to apply the growing insight into the biology of aging into interventions and practices that extend people’s healthspan. Fellow geroscientist and gerontology physician James Kirkland of the Mayo Clinic in Rochester, Minnesota, defines healthspan as “the period of a life when individuals are able to live independently, free of disease, free of pain, and basically can do what they want to do.”

Extending healthspan so that it coincides as long as possible with overall life span, says Austad, “is one of the signature problems of the 21st century.” People will be living longer, he says, but the driving question is whether “we are going to be living longer in a healthy fashion or are we just going to extend our period of debility?” Every additional year of senior life without one or more of the diseases of aging is a year with less physical, emotional, psychological, medical, and economic costs. Anyone who has taken care of aging and infirmed loved ones has a first-person understanding of this reality.
One of the most-cited analyses of the health and economic returns to society that delayed aging would bring, published in 2013 in Health Affairs, estimated the economic value derived from longer health on a population scale in the United States would amount to $7.1 trillion over the half-century spanning from 2010 to 2060. That’s more than $140 billion per year. Although taxpayer costs for Social Security and other entitlements for a healthier, longer-living senior population would also grow, the analysis indicates these could be more than offset by other factors. For one, the effect of compressing the diseases of aging into a shorter stretch of time before death would dramatically reduce medical expenses on a national scale. Beyond health-cost savings in dollars, delayed aging would yield unquantifiable gains in categories like quality of life, the joys of living, and prolonged access to the wisdom that comes with age.

The Health Affairs analysis also states that, “with people staying healthy until a much later age, it might be more feasible to justify raising the eligibility age for public programs for seniors.” That too would reduce the public costs of a generally increased healthspan. “It would allow people to remain in the workplace longer, if they want to,” explains Olshansky, one of the authors of the analysis. “It would allow them to avoid high health costs during their last decade of life. The economic benefits are huge, even for a minor slowdown in aging.”

HEALTHSPAN MANIFESTO

There are two foundational concepts underlying the healthspan movement and the geroscience that accompanies it. One is that chronological age, the number of years a person has lived, is the single most influential risk factor when it comes to contracting any of the diseases of aging. “About 80% of risk of getting Alzheimer’s disease is chronological age,” Kirkland says. A family history of high blood pressure, high blood sugar, and high cholesterol boosts your risk of having a heart attack by factor of two to four, he says, “but if you are 85 instead of 30, your risk is increased 1000-fold.” What’s more, he adds, “if you get one of these age-related disorders, your time to get the next one is shorter, and then shorter for the next one after that. So older individuals become completely dependent, or you find people with multiple conditions on 10 or 20 drugs.”

Felipe Sierra, director of the Division of Aging Biology at the National Institute of Aging, headquartered in Baltimore, Maryland, argues that only by way of a radical new framework, such as geroscience, will society be able to “avert the incoming health and economic disaster represented by the silver tsunami of population aging.”

A midterm goal for the next few years, he says, is to develop a platform of basic biology, drug development, and clinical studies “to delay the onset of a panel of major diseases as well as conditions [that], while not lethal, rob us of our quality of life.” Among these conditions are urinary incontinence, fatigue, and frailty. “A longer-term goal is to achieve a 5-year delay in the onset of most chronic diseases,” Sierra says.
Geroscientists often talk in terms of “pillars of aging,” each of which represents a fundamental aging process that has become more or less accessible to biomedical interventions that can slow them down, stop them, and sometimes even reverse them. Most of the evidence for these slowdown effects derives from molecular biology and animal studies. However, it’s the accumulating epidemiological and drug-trial data that has geroscientists shifting into a drug-development phase. With fervor, they have entered the pharmaceutical startup game, forming venture capital and development firms such as the multi-company hub Life Biosciences (Barzilai is the chief medical advisor) and Unity Biotechnology, which has raised hundreds of millions of dollars and is conducting human clinical trials for an arthritis drug. Other geroscientists have pivoted into opening up nonprofit and advocacy organizations such as AFAR and the new Academy for Health and Lifespan Research. And still others are working to design potentially transformational drug trials, which they hope will convince the U.S. Food and Drug Administration (FDA) to designate aging itself as a medical indicator just as high blood sugar is a druggable indicator for diabetes and declining bone density is a druggable indicator for osteoporosis.

“A long-term goal is to achieve a 5-year delay in the onset of most chronic diseases.”
— Felipe Sierra, National Institute of Aging

Kirkland organizes his own geroscience thinking around four pillars of aging. One is low-grade inflammation, which in elderly people can smolder in many tissue types and locations associated with chronic diseases. Inflammation in blood vessels associates with atherosclerosis, for example; in the brain, it appears to be linked to Alzheimer’s disease. A second pillar of aging for Kirkland amounts to things going awry inside cells. Misfolded proteins, DNA and chromosomal flaws, and mitochondrial and metabolic problems reside in this pillar of aging. Kirkland’s third pillar encompasses stem and progenitor cells going awry by, for example, failing to replicate or differentiate into specific cell and tissue types. Senescent cells and the tissue damage they can wreak demarcate a fourth pillar of aging for Kirkland, who observes also that the pillars of aging are interlinked. Targeting one pillar genetically or with drugs tends to affect the rest, he says. “It is beginning to look like there are a number of interventions that can delay, prevent, or alleviate multiple age-related diseases and conditions as a group, as opposed to picking them off one at a time,” Kirkland explains.

That view accounts for the name of the healthspan-driven company Unity Biotechnology. It “comes from the idea that [cellular] senescence is perhaps an underlying theme across multiple diseases of aging,” explains Keith Leonard, CEO of the 8-year-old firm based in Brisbane, California. Its osteoarthritis drug candidate, UBX0101, has shown initial promise in a Phase I trial to test its safety. And now Unity is queuing up a second compound, designated UBX1967, for clinical trials against a bevy of eye conditions, including age-related macular degeneration. In earlier phases of development are drug candidates for lung, liver, kidney, and brain-related conditions of aging. “We are a moonshot company in that we are charting a future where one by one these accepted aspects of aging are defeated and we just won’t have to deal with them anymore,” Leonard says.
GEROSCIENCE COMES OF AGE

Austad identifies two facts of life as persuasive signs that an era of increased healthspan is in the offing. First, he says, “we already have a subgroup of people who [naturally] stay healthy to the age of 100 and all we are trying to do is expand that group of people by using some kinds of intervention.” Secondly, he says, almost everyone in his field feels that increasing the healthspan is plausible because of what they have collectively shown is possible in lab animals, especially mice. “We now have dozens and dozens of ways to keep laboratory animals healthy longer,” Austad points out.

Results in animal studies over the last decade with rapamycin (a well-known soil-bacterium-derived drug for preventing rejection of transplanted organs in recipients and for coating stents to keep cells from clogging them up) has had a rallying effect on the geroscience community. Among its benefits are keeping senescent cells in check and helping to recycle molecular debris from cellular activity. It’s at the heart of the University of Washington-based Dog Aging Project to study and promote longer healthspans in dogs. Adding to the excitement about rapamycin for the healthspan movement, Austad says, is that rapamycin treatment also preserves cognitive function and immune function and lowers cancer rates in test animals. This is just the sort of multi-condition effect that is consistent with the geroscience hypothesis that positive interventions in one or more of the pillars of aging can prevent — or at least delay — the onset of multiple diseases of aging.

Metformin is another poster-child compound for the geroscience club, as well as for the Prime Minister of Singapore and for those Barzilai describes as an “underground” of healthspan-minded people who are not waiting for FDA-approval or doctors’ advice. Metformin is the most commonly prescribed drug in the world for treating type 2 diabetes (the kind that usually starts later in life and often can be managed by diet and exercise). It has a solid safety record dating back more than 60 years. “From an observational epidemiology point of view, it looks like metformin is protective against a whole range of things, including cancer, dementia, and cardiovascular disease,” Austad says. “If untreated, diabetes looks a lot like accelerated aging, so it makes sense that something effective for treating diabetes will slow down a lot of aging processes.”

Metformin (left) and rapamycin are celebrities among the enlarging roster of candidate drugs for extending the healthspan. (Left image from Wikipedia under Creative Commons status; right image courtesy of the American Chemical Society)
“It has been shown that metformin delays the onset of many diseases of aging,” notes Stephanie Lederman, executive director of AFAR, which was founded in 1981, around the same time that the National Institute of Aging was established as one of the National Institutes of Health (NIH). The most head-turning study revealed that diabetes patients taking metformin come down with “less cancer, less heart disease, and less Alzheimer’s than the general population that has not taken metformin,” Lederman says. It’s complicated, of course. One recent study with a small group of people in their 60s hinted that a metformin regimen also could confer some negatives, including reducing the aging-battling benefits of aerobic exercise. What has been lacking is a rigorous, large-scale, gold-standard clinical trial (double blind, placebo-controlled) to test if a regimen of metformin given to a diverse group of non-diabetic individuals will delay the onset of major age-related diseases.

This is where the Targeting Aging with Metformin (TAME) trial comes in. Beginning this year, TAME researchers at 14 medical centers will begin recruiting 3500 men and woman, ages 65 to 80 years, who have just begun to show age-related diseases and/or deficits, among them slow gait, cardiovascular disease, cancer, and mild cognitive impairment. The primary question of the 6-year trial is this: Does the incidence rate of new age-related chronic diseases in the metformin-receiving test group differ from the incidence rate of these diseases in the placebo-receiving control group? The TAME researchers, which includes Barzilai and Olshansky among others, will also be looking for differences in the incidence of age-related declines in physical and cognitive abilities between the metformin and control groups. A third aim is to test whether measured improvements in health parameters are mirrored in cellular and molecular biomarkers that previous research in cells and animals has associated with slowing aging. “The research protocol we came up with for the TAME trial was designed to find an answer quickly, because we were not interested in waiting 20 years for an answer,” Olshansky says.

Lederman says AFAR has raised some $20 million, mainly from philanthropists, in support of the TAME trial, though that is only about half the amount originally envisioned for a broader agenda of tests and measurements.

A lot is riding on the TAME trial. A prospectus of the trial, which Barzilai, a principal investigator, says was developed in consultation with Robert Temple in 2015 when the latter was the deputy director of FDA, states that the greatest possible payoff of the trial is “a proof-of-concept that by targeting aging itself, healthy lifespan can be increased, paving the way for a new indication for drugs to prevent age-related diseases.” In a pivotal meeting of the TAME planning team and Temple that filmmaker Ron Howard captured in “The Age of Aging” episode of his documentary series, Breakthrough, Temple projected that “it would be revolutionary if they could pull it off.”
“The main issue in regard to treating aging as an indication is when such a broad, and so far unprecedented, claim would be considered supported,” explained FDA press officer Amanda Turney in an email exchange in March. “We would consider whether an overall anti-aging claim was supported based on the scientific evidence presented to us,” Turney wrote. “We are aware of interest in studying aging and the FDA is looking forward to seeing this area of science evolve.”

An FDA acknowledgement of this new application for drugs could greatly boost an already building R&D momentum among startups and large pharmaceutical companies to develop novel and more effective compounds to extend the healthspan. The potential market for such drugs could be huge. An NIH-funded Census Bureau report in 2015 assessed the above-65-year-old global population at 617 million. But a healthspan drug regimen designed to preempt the onset of diseases of aging would likely begin earlier in life, thereby upping the potential market into billions of people.

**LET THE HUMAN TRIALS BEGIN**

Even as recruiting for the TAME trial begins, Kirkland is among a cadre of scientists and entrepreneurs homing in on senescent cells and a class of candidate drugs called senolytics. These agents can kill senescent cells, which are also referred to as “zombie” cells. Many factors can drive cells into senescence, among them high levels of glucose in the blood and signals from pathogens. Senescent cells can accumulate in many tissues where they emit inflammatory, protein-destroying, stem-cell-poisoning, and other disease-promoting factors, including ones that induce other cells into senescence.

By asking how senescent cells manage to survive even as they are causing the destruction of cells around them, Kirkland and colleagues discovered that the zombie cells manage to shut off a variety of pathways associated with the normal, health-promoting, cell-death process known as apoptosis. He and colleagues searched for agents that would turn the apoptosis process back on in senescent cells without harming normal cells. The researchers found at least eight. “They work by transiently disabling these pro-survival pathways in senescent cells that normal cells don’t need to survive,” Kirkland says. In an interview with The Moonshot Catalog in March, he noted that the count of senolytic agents reported in the scientific literature then stood at 16 or 17. “There are many more that people have in their laboratories and in companies,” he said.

So far, the strongest data indicating that senolytics work as envisioned derive from mouse studies. “We found with collaborators here at Mayo that we could alleviate age-related osteoporosis and partially reverse it. We found reduced cirrhosis in mouse models of that condition. Others found that in mouse models of Alzheimer’s these drugs would partially reverse brain atrophy and improve neurogenesis and nerve-cell thickness.” The list goes on. “We found that all age-related diseases were delayed as a group in mice,” Kirkland said.

The accumulating data that senolytics can target fundamental evolutionarily-conserved processes of aging has inspired researchers, entrepreneurs, and financial backers to take the leap into human clinical trials. Kirkland, for one, is involved with various collaborators on six human clinical trials with two different senolytic compounds. One is quercetin, a plant pigment found in fruits and vegetables and foods made of them, among them apples, onions, red wine, and green tea. The other is dasatinib, an FDA-approved drug for treating certain leukemia conditions. “We are planning another six trials at Mayo very shortly,” he said.

“We found that all age-related diseases were delayed as a group in mice.”
— James Kirkland, Mayo Clinic
Always vigilant for signs of serious side effects and other potential showstoppers in clinical trials, Kirkland says development of senolytic medicines should progress cautiously, building from small-scale safety trials like one that he and colleagues reported in January 2019 and ultimately building toward trials that represent the general population. That first tiny trial using a “dasatinib plus quercetin” (DQ) regimen enrolled 14 patients with idiopathic pulmonary fibrosis, a fatal lung disease in which senescent cells accumulate in the lungs and cause inflammation and fibrosis. Five days after the patients received their last DQ dose, the researchers documented what Kirkland described as “clinically meaningful improvements” in a battery of physical performance tests including gait speed, walking distance, and the ability to get out of a chair. “This told us we should move to bigger studies” with senolytics, he says. What he has in mind now is a “slow march” from 1) trials with patients who are seriously ill with senescent-cell-caused conditions, to 2) trials with senescent-cell-bearing patients who are not as sick, to 3) trials with still-well patients whose tissue-loads of senescent cells suggest they are likely to get sick, and finally to 4) trials that represent the general public.

A MARKET GROWS IN HEALTHSPAN-LAND

Quickening the march toward what could become a new era of healthspan medicine are the proliferating startup companies that are determined to bring new healthspan-extending medicines to what potentially can be one of the largest markets possible.

An early and visible commercial venture into this new era of healthspan medicine is Unity Biotechnology, a Bay Area firm established in 2011 that subsequently amassed $385 million in funding. Among its contributors are billionaires Jeff Bezos and Peter Thiel. Drug trials for the company’s candidate osteoporosis drug candidate, UBX0101, began in June 2018. Among other medical targets for its senolytic candidates are kidney disease, glaucoma, idiopathic pulmonary fibrosis, and chronic obstructive pulmonary disease (COPD). Another early-in powerhouse is Calico Life Sciences, which was founded with Google money in 2013 and is now involved in multiple collaborations. Its goal, as stated on its web site, is “to devise interventions that enable people to lead longer and healthier lives.”

The list of healthspan startups is extensive and growing. Life Biosciences, a Boston-based geromedicine incubator, by itself accounts for six entrants, each one pursuing therapeutic platforms based on different pillars of aging. “Life Bioscience is a family of companies that uses shared resources and knowledge,” co-founder David Sinclair told Peter Attia on the latter’s long-form podcast, The Drive, which focuses on “the applied science of longevity, the extension of human life and well-being.” Sinclair is a celebrity among geroscience researchers and entrepreneurs, and his book, Lifespan: The Revolutionary Science of Why We Age — and Why We Don’t Have To, is slated for release in September. Like many in the healthspan R&D trenches, he personally is not waiting for all of the science to come in before trying his own regimen of healthspan interventions. His personal untested cocktail of agents includes daily doses of metformin, the focus of the TAME trial, and resveratrol, the red-grape compound long touted for its alleged heart-protective and longevity-promoting powers.

Among the roster of companies with their technical and commercial sights on senotherapeutics (drugs that target senescent cells) and other healthspan blockbusters include the Oisin Biotechnologies, Juvenescence, Grail, Apollo Ventures, Antoxerene, and Cellularity. The list is growing. “There is lots of room for lots of winners,” says Unity Biotechnology’s Leonard.
As the community of healthspan researchers and entrepreneurs grows and companies move candidate drugs toward and into human clinical trials, pressure to raise the money it will take to get the drugs to the clinical finish line will intensity. Small phase I clinical studies designed primarily to test the safety of new candidate drugs can cost between $250,000 and $1 million, according to Kirkland. Phase II trials involving 150 to 200 subjects in tests of efficacy and side-effects can cost between $1 million and $4 million. In the senolytics category alone, there are around 40 conditions for which drug candidates have shown preclinical benefits, Kirkland says. The larger phase III studies, which involve many more subjects to help gather far more data on efficacy and adverse effects, can be hugely expensive. Small companies on the innovation front typically can only undertake these in partnership with big pharma players and with large-scale venture capital or philanthropic support.

“This is all scalable. The more funding we have coming in, the faster we can move. And especially with the clinical trials.” — James Kirkland, Mayo Clinic

“This is all scalable,” Kirkland says. “The more funding we have coming in, the faster we can move. And especially with the clinical trials.” When it comes to the challenge of keeping the new field growing, geroscience pioneer Felipe Sierra says he would like to see a return of the sort of philanthropic presence that Oracle billionaire Larry Ellison brought to aging research during the first decade of the century, in his case to fund basic and applied academic research in geroscience. When the flow of those funds — some $430 million from the Larry Ellison Foundation since its founding in 1997 — ended a few years ago, Sierra says, that left “a gaping hole in the research pipeline that affects primarily early- and mid-career researchers. Renewal of such an effort would provide much needed support for early innovators entering the field.”

“We are all sick of prescribing better wheel chairs and walkers and incontinence devices,” says Kirkland, speaking for himself and other geriatricians. “We want to have something that targets fundamental aging processes.” What these doctors want is what everybody wants — for all of us to be disease-free, pain-free, and capable of doing what we want to do until the day we die.

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The American Federation for Aging Research (AFAR) is a national non-profit organization that supports and advances pioneering biomedical research that is revolutionizing how we live healthier and longer.

For nearly four decades, AFAR has served as the field’s talent incubator, providing more than $178 million to more than 4,100 investigators at premier research institutions nationwide. A trusted leader and strategist, AFAR also works with public and private funders to steer high quality grant programs and interdisciplinary research networks.

AFAR-funded researchers are finding that modifying basic cellular processes can delay—or even prevent—many chronic diseases, often at the same time. They are discovering that it is never too late—or too early—to improve health. This groundbreaking science is paving the way for innovative new therapies that promise to improve and extend our quality of life—at any age.