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Can a 'Magic' Protein Slow the Aging Process?

By EILENE ZIMMERMAN

Several years ago, scientists studying aging at the Harvard Stem Cell Institute used a somewhat Frankensteinian technique known as parabiosis — surgically joining a young mouse and an old mouse so that they share blood — to see what would happen to the heart and skeletal muscle tissue. They knew from previous research that putting young blood in old mice caused them to grow biologically younger, and that young mice exposed to old blood aged faster.

The Harvard researchers, Amy Wagers and Dr. Richard Lee, found that the old mouse's heart tissue had been repaired and rejuvenated, becoming young again. In fact, the size of the old mouse's heart had reduced to that of a young heart.

"We all wondered, what's the magic stuff in the blood?" said Lee Rubin, a professor of stem cell and regenerative medicine at Harvard and the co-director of the neuroscience program at the Stem Cell Institute. The "magic" they identified was a protein, GDF11, one of tens of thousands produced in the human body. Dr. Rubin's lab also found that GDF11 in mice stimulated the growth of new blood vessels in the brain and neurons in the hippocampus, a part of the brain associated with learning and memory. Dr. Wagers's lab found that GDF11 rejuvenated skeletal muscle tissue, too. The scientists' discoveries were published in the journals *Cell* and *Science* in 2013 and 2014.

The obvious next question: Could GDF11 be harnessed to promote regeneration and repair in humans? In 2017, Drs. Rubin, Wagers and Lee, along with five others, founded the pharmaceutical start-up Elevation with the aim of commercializing GDF11-based therapies to stop, slow or reverse diseases associated with aging. It's a big step from mice to humans, but one that could have profound consequences.

"We're interested in proteins like GDF11 that are excreted into the bloodstream because those can cause changes throughout the body," said Dr. Mark Allen, the chief executive of Elevation. "And those are the kind of changes we want."

Dr. Allen started his first health care



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Top, the GDF11 protein in a lab at Elevation's headquarters in Newton, Mass. Lee Rubin, above, a Harvard professor who co-founded Elevation, discovered that GDF11 in mice stimulated the growth of new blood vessels in the brain. It may be a powerful tool in fighting age-related conditions, such as strokes.

company while in medical school at the University of California, Los Angeles, and he left his residency position in 2000 to start a second. In early 2017, he and his in-

vestment partner, Sebastian Giwa, an economist, were looking to start a new one that would develop therapies targeting the degenerative processes involved in aging. They looked at two dozen potential research projects before deciding on GDF11.

"I had this idea that aging itself could be a target for therapeutic intervention," Dr. Allen said, "because if we target one aspect of the aging process, then we have the potential to treat many different diseases."

The initial research into the rejuvenating properties of GDF11 has gotten some pushback from the scientific community. In 2015, after Dr. Wagers and Dr. Lee had published their results, a group of researchers led by David Glass, the executive director of the Novartis Institutes for Biomedical Research in Cambridge, Mass., at the time, challenged the accuracy of their findings in an article in the journal *Cell Metabolism*. The Harvard researchers subsequently countered the Novartis team's findings in another paper published later that year in the journal *Circulation Research*, in which the Harvard researchers cited a problem with the Novartis team's findings.

Dr. Glass, who is now at the bio-technology company Regeneron, said in a recent email that he stands by his original work, which showed that GDF11 inhibits, rather than helps, muscle regeneration. But, he added, "our work still leaves open the possibility that there could be positive effects of GDF11 in particular settings."

Dr. Allen said that since the original controversy, Elevation's research team

has reproduced and extended its original findings in multiple studies, but none have yet been published in peer-reviewed journals. However, institutions unrelated to Elevation have conducted and published many preclinical studies demonstrating the therapeutic efficacy of rGDF11 (the form of GDF11 developed in a lab) in treating age-related diseases.

The company is on track to begin human clinical trials in the first quarter of 2023 and has raised \$58 million in two rounds of funding, with another round set for mid-2023.

Elevation is one of many companies racing to find ways to increase the human life span by increasing “health span,” the period of life when a person is in generally good health. This emerging sector of the pharmaceutical industry is often referred to as “longevity therapeutics” and includes companies like Altos Labs, which started in January with \$3 billion in funding; Calico Life Sciences at Google; Unity Biotechnology; Alkahest; and Juvenescence. About \$2 billion in venture capital was invested in pharmaceutical companies focused on anti-aging in 2021, according to Longevity Technology, a market research company and investment platform focused on the longevity sector.

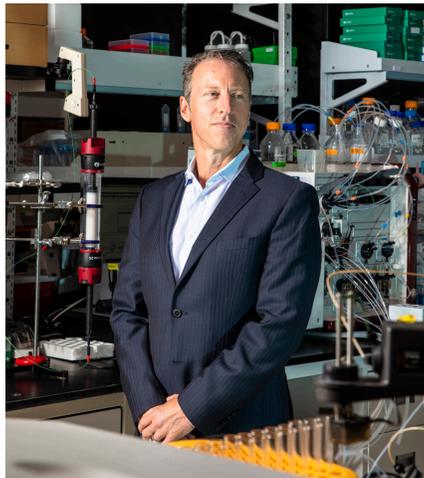
For years, researchers have been looking for drugs that can extend life span and health span. The Interventions Testing Program at the National Institutes of Health began testing drugs — some approved by the Food and Drug Administration, some not — in mice 17 years ago to see if these interventions would extend their lives. Dr. Richard A. Miller, a professor of pathology at the University of Michigan and the director of the Paul F. Glenn Center for Biology of Aging Research, said anti-aging therapies are often tested on mice because aging in mice is very similar to aging in humans. “Mice and people share organs, cell biology and most varieties of neurons and neurotransmitters, and they often respond to drugs in similar ways,” he said.

A significant challenge lies ahead for all of these companies: Commercializing a drug for aging is nearly impossible because the F.D.A. doesn’t recognize aging as a disease to be treated. And even if it were considered a disease, the clinical



PHOTOGRAPHS BY CODY O’LOUGHLIN FOR THE NEW YORK TIMES

Scientists at Elevation’s headquarters looking at markers of new neuron formation in rats treated with GDF11.



Dr. Mark Allen, the chief executive of Elevation, at the company’s headquarters.

studies required to prove that a treatment for it worked would take many years.

“It is likely that clinical studies to see if some drug slows aging — and thereby delays the many consequences of aging — would take a long time,” Dr. Miller said.

So Elevation’s founders determined that the fastest way to market for GDF11 was to target a specific medical condition.

“We thought, what’s the worst disease that has no good treatment and that we could treat for the shortest possible duration and show clinical effects?” Dr. Al-

len said. “We decided that stroke was the right one to target, because it’s the No. 1 cause of long-term disability with very limited treatment options.”

Dr. Elisabeth Breese Marsh, the medical director of the comprehensive stroke program at Johns Hopkins Bayview Medical Center in Baltimore, said the best treatments for strokes caused by clots (about 87 percent of them) is a type of medication known as tissue plasminogen activators, or tPA, which must be given within 4.5 hours of the stroke, and the surgical removal of large clots.

But according to experts, only about 20 percent of stroke victims receive tPA, either because the stroke is not recognized soon enough or because the patient doesn’t qualify because of pre-existing conditions. Elevation’s researchers said their preclinical (and as yet unpublished) studies have shown that just a few days of treatment with GDF11 can improve recovery after stroke. They have found that GDF11 reduces inflammation, improves metabolism and stimulates the brain to regenerate blood vessels and neurons.

The next big hurdle for Elevation is scaling its manufacturing, which requires specialized equipment and conditions. So much research is being conducted in biotech that contract manufacturers are “full up,” Dr. Allen said. “They are busy with Covid-related work, and there has been a lot of funding in biotech generally,” he added. “So it’s a challenge finding the space that meets our specifications.”

And, like almost all other sectors of the economy, biotech research is facing supply chain issues, which make it harder for Elevation to get some of the basic materials it needs to conduct research. But the company is moving forward as fast as it can, and Dr. Allen said he believed the results of its work would have a profound impact on the way we age and how long we live.

“By targeting fundamental mechanisms of aging, we have the opportunity to treat or prevent multiple aging-related diseases and extend the health span,” he said. “We want to make 100 the new 50.”

This article is part of Upstart, a series about companies harnessing new science and technology to solve challenges in their industries.