Associate Research Scientist Yun-Hee Youm looks over a slide of mouse thymus at Brady Memorial Laboratory in New Haven.
ARNOLD GOLD

AGING OUT

YALE RESEARCHERS STUDY LIFE-EXTENDING HORMONE

BY ERIK OFGANG

The mice at the Yale lab in New Haven were different.

Most mice start showing signs of aging by 2 years old. These mice didn't. Instead they entered what should have been their twilight years with vigor, approaching their third birthday free of the disease and the decreased mobility expected in animals their age.

In a laboratory setting, regular mice would have a life expectancy of around three years, but these mice lived much longer, almost four years.

Their secret was not a gluten-free diet, or lots of protein, but rather a hormone called fibroblast growth factor-21 (FGF21) that has an extraordinary effect on the immune system. While FGF21 may not be the fountain of youth that Ponce de León searched for in Florida, it could be the key to discovering a fountain of graceful aging.

Beginning in 2007, Vishwa Deep Dixit, professor of comparative medicine and immunobiology at Yale School of Medicine, and a team of researchers at his lab began studying the hormone and its effects on mice genetically engineered to produce more of it.

In 2012, scientists at the University of Texas Southwestern Medical Center published a study finding that the hormone increased the lifespan of mice by as much as 40 percent. Last January, Dixit's team published a study online in the *Proceedings of the National Academy of Sciences* demonstrating that in addition to extending the life expectancy of mice, FGF21 protects against the loss of immune function that comes with age. The study — whose lead author was Yale scientist Yun-Hee Youm, who works in Dixit's lab — produced findings that could have implications for improving immune function in the elderly, for obesity and for illnesses such as cancer and type-2 diabetes.

"If, *if* everything would work identically and as well as it works in mice, if someone had an average lifespan of 100 years you can expect that same individual to live to 140," Dixit says.

At press time, Dixit's lab was expecting a $12 million grant from the National Institute on Aging, one of the 27 branches of the National Institutes of Health. The grant will help fund the next stage of Dixit's research, which will examine mice given the hormone therapeutically instead of being genetically engineered to produce it.

The research into FGF21 builds on previous studies showing that severely restricting food intake can extend the lifespan of several different animals. Increasing levels of FGF21, which is secreted by the liver during fasting and helps the body adapt to starvation, seems to provide the benefits of dieting without limiting food intake.

FGF21 plays an important role in the thymus, a small organ located between the lungs that has an integral role in the immune system. When functioning properly, the thymus produces infection-fighting T cells, but as we age the thymus becomes fatty and stops producing T cells capable of fending off infection. As a result, the immune system is compromised, becoming more susceptible to both infection and certain forms of cancer. But increasing levels of FGF21 in the

thymus fends off the organ's age-induced decline, allowing it to continue to produce T cells to battle infection.

Dixit's research is at the forefront of an invigorated national effort to better understand aging that has also led to federal funding for dozens of additional projects in Connecticut, both at Yale and other universities.

Rebecca Fuldner, a health scientist administrator with the NIA who is overseeing the grant for Dixit's research team, says the aging field in general has picked up over the last five to 10 years. "There's more people proposing work related to aging and definitely more funding." But she adds there are challenges not found in more traditional research. "Normally you get a drug approved by the FDA to treat a disease. But this is different. You're not trying to slow the progression of disease. You're trying to slow the progression of aging, and aging is not a disease, so it's a different paradigm."

The focus on this new paradigm comes from a growing realization in the scientific community that as we age, we become more susceptible to such a wide variety of diseases that developing effective treatments for aging itself might be something of a cure-all.

Yale scientist Vishwa Deep Dixit
PHOTO BY ROBERT A. LISAK

"Aging is the biggest risk factor for chronic diseases. The association between aging and chronic disease is stronger than the association between smoking and lung cancer," Dixit says. "So, if you understand what is happening during aging, how it is happening and what are the mechanisms, cellular and molecular, then we may be able to delay the onset of diseases like Alzheimer's, arthritis, diabetes, certain cancers, kidney disease, macular degeneration, you name it. All these diseases are all linked to aging."

Dr. George A. Kuchel, director of the University of Connecticut Center on Aging, says much of the research conducted at his center, and in the field in general, is aimed at developing treatments designed not to slow the aging process, "but to slow the onset of the kind of chronic diseases that accompany the aging process."

This thinking is also central to Dixit's research. "I think the question we are more interested in is not just longevity, but actually the health and lifespan. So that extension of lifespan is associated

At 30 Years Old, UConn Center on Aging Still a Pioneer

The UConn Center on Aging is celebrating its 30th anniversary this year. The center's mission is "to improve the lives of older adults through research, education and clinical care," says its director, Dr. George A. Kuchel.

As part of this mission, it is dedicated to training and educating caregivers in geriatric medicine and to translating research from the lab bench to the bedside. Often the research conducted at the center (and in the aging field in general) falls within five categories: mobility and muscle/bone health, fending off infection, behavior and cognition, voiding and continence, and genomics. Here we look at some of the research being done at UConn in those areas.

MOBILITY AND MUSCLE/BONE HEALTH

As we age, our bones become weaker and more likely to break. Dr. Richard Fortinsky is involved in a study that looks at the effects of a broken hip on an older individual. "As many as a third of older adults who break a hip die within a year; another third fail to return to their previous level of function," Kuchel says. "This study looks at the ability of physical therapy in the community to improve function in older adults who have already broken a hip and have already been discharged from usual care."

Other studies at UConn are looking at the effect flu infection has on muscles. "We've recently published the first paper that shows infection in the lungs results in loss of muscle and this muscle breakdown is much greater with aging," Kuchel says.

FENDING OFF INFECTION

"Older adults are much more likely to develop infections or complications from an infection," Kuchel says. He adds, UConn scientist Laura Haynes' has research shows that older adults are "much more likely to develop infection after being exposed to the influenza virus." They are also more likely to require hospitalization and die after a flu infection, so this research highlights the need to protect the elderly from the flu.

BEHAVIOR AND COGNITION

Several studies are underway at UConn that examine the memory and cognition declines that occur with aging. One area of research being led by Dr. David Steffens looks at "how depression influences memory loss and vice versa," Kuchel says. "We know that older adults that become depressed are more likely to develop dementia and individuals that develop dementia are more likely to become depressed. He has done a lot of work defining the relationship between that."

Dr. Lisa Barry has received a federal grant to examine aging adults who are incarcerated. "She has done some very important work showing that prisoners age much faster than their counterparts who are the same chronological age," Kuchel says. "You see a lot of chronic disease and a lot of disability in terms of cognition and physical performance in prisoners in their 50s and 60s that you might see in people in the community in their 70s and 80s."

VOIDING AND CONTINENCE

Dr. Phillip Smith is one of the experts at UConn involved in this area of aging research. "He works on a bladder condition that is very common in the elderly, and is associated with difficulty voiding," Kuchel says. "He's one of the pioneers in this area. He has published many important papers. It's an area that we're very excited about."

GENOMICS

UConn researchers also frequently work with the Jackson Laboratory for Genomic Medicine in Farmington. "[They] are committed to studies using the powers of modern genomics to better understand human health and disease, and that interfaces perfectly with the mission of the Center on Aging. We have many, many collaborations with them." | ERIK OFGANG |

Postdoctoral Fellow Emily Goldberg prepares a slide of CD4 T cells for study at Brady Memorial Laboratory. ARNOLD GOLD

with reduction of morbidity, or a period of life where we are free of disability. That is the real goal. Nobody wants to live an additional 40 years in a bed."

Dixit's quest for this fountain of graceful aging began years ago and a continent away in Germany while he was studying for his Ph.D. While researching the organs of animals, he noticed that the thymus was always small in older animals. "I hypothesized, 'this is something we should study in more detail,'" he says.

He learned that in humans and all vertebrates, not only did the thymus grow smaller with age, it also converted into fat, which prevents it from producing new naïve T cells. There are two main types of T cells: naïve T cells that have not encountered pathogens before, and memory or antigen-experienced T cells that have seen and can recognize foreign invaders, such as bacteria or viruses, as well as some cancer cells. Naïve T cells can learn to respond to new pathogens the body has not encountered before. When the thymus stops producing new T cells, the immune system's ability to fend off new invaders is weakened and it falls victim to a host of diseases it would have been able to fight off in its younger days. "This loss of new T cells in the body is one cause of increased risk of infections and certain cancers in the elderly," Dixit says.

Dixit wanted to discover "why this organ no longer functions when we are just about 45 or 50 years old."

Today, Dixit believes a lack of FGF21 is a factor in the decline of the thymus. Dixit and his team later began studying the effect of the hormone on mice. While it is mostly positive, the FGF21 mice are smaller than their counterparts and the female mice were infertile. On the whole, however, FGF21 mice live longer, healthier lives.

When the next phase of research begins with NIA funding, Dixit and his team will study the benefits of therapeutic use of FGF21 in mice that have not been genetically engineered to produce more of it. If the next phase of studies shows similar benefits from therapeutic use of FGF21, Dixit hopes to one day "translate these findings to humans and see if there would be approaches to elevate these levels of hormone and potentially have it as a therapy in certain individuals." For instance, he says, "Elevating the levels of FGF21 in the elderly or in cancer patients who undergo bone marrow transplantation may be an additional strategy to increase T cell production, and thus bolster immune function."

But any human treatments would not be developed by Yale. "We are not a drug company; we are a research laboratory," Dixit says. "The hope of every scientist is that from this basic research work, the drug companies and other people will take that forward. This is a collective team effort and requires the whole scientific community."

Figuring out if a treatment increases lifespan is notoriously difficult. With conditions such as heart disease there are accepted biomarkers, indicators that can predict later development of a disease. But with aging there are no clear biomarkers. As a result, aging itself becomes a huge obstacle in the study of aging.

"There is no way to actually do human lifespan studies; you or I would have to live at least 300 years to do these studies," Dixit says. "So, obviously that cannot be accomplished during my lifespan, or your lifespan. Maybe in our kids' lifespan."

This is fine with Dixit, as the true goal of his research is healthy aging.

"We are interested in aging; we are not interested in lifespan extension. If that happens that's great, but that's not the only goal we have. Our main goal is to understand the process of aging and how to improve the quality of life."