yale medicine magazine

ISSUE
173

Aging: The science of longer and healthier lives

ALSO

SPECIAL REPORT

DEPA EN S

letters

Phenomenal job!

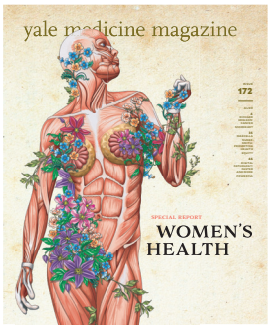
I'm reaching out to thank *Yale Medicine Magazine* for the beautiful article on heart disease in women that appeared in the spring issue. It has had a huge impact, and a number of people from around the country have reached out after seeing it. The article did a phenomenal job covering multiple complex topics, and provided real clarity to topics that are too frequently overlooked. One of our cardiology fellows was shocked to learn about the term "Syndrome X," which is a sign of positive change in the way that we talk about heart disease in women.

Samit Shah, MD, PhD
Assistant Professor of Medicine, Yale School of Medicine;
Director, VA Connecticut Cardiac Catheterization Laboratory

A true pioneer

I write to commend *Yale Medicine Magazine* on the fine article about Professor Rick Edelson ("Serendipity in Action," Spring 2024). When Dr. Edelson was developing the photopheresis treatment for cutaneous T-cell lymphoma (CTCL), the field of immunotherapy was in its infancy. Now, immunotherapy has become the standard of care in the case of many cancers. Dr. Edelson was truly a pioneer in this field. It can be somewhat lonely to be ahead of the curve, and it takes courage to buck the trends. The field has caught up to him, and now again he is pioneering in the Cancer Moonshot program with his new grant, "Curing the Uncurable via RNA-Encoded Immunogene Tuning." Congratulations to *Yale Medicine Magazine* for highlighting an individual who embodies the "triple threat" of an outstanding researcher, clinician, and educator.

Nancy H. Ruddle, PhD
Professor Emerita of Epidemiology, Yale School of Public Health and Yale School of Medicine



Artist Maira Kalman on aging and the human condition

Yale Medicine Magazine is delighted to feature the artwork of Maira Kalman to complement our special report on the science of aging.

Kalman is a celebrated painter, illustrator, and author whose work has been described as a "narrative journal" of the human condition. Her illustrations, which have appeared frequently in *The New Yorker* magazine and *The New York Times*, are known for their whimsical yet deeply evocative style.

Kalman's career began nearly 40 years ago with the publication of a children's picture book, *Stay Up Late*, which illustrates the lyrics to the like-named song popularized by David Byrne of the 1970s rock band Talking Heads. She has since published more than 30 books for both adults and children, while also working with embroidery, textile, and graphic design.

Kalman's artwork has been exhibited at the Metropolitan Museum of Art and other museums and galleries across the United States. Her latest book is *Women Holding Things*, and her forthcoming book is *Still Life With Remorse* (October 15).

"One of the delights of getting older is admiring my inconsistencies," she says. "What once was embarrassing is now an asset. To be smart or stupid. Lazy or energetic. Insecure or confident. All of it is interesting. All of the contradictions are part of the story."

Issue 173

Executive Editor
Rebecca Shannonhouse

Contributors
Isabella Backman
Robert Forman
David Freeman
Steve Hamm
Jill Max
Ashley P. Taylor
Rachel Tompa, PhD

Art Director
Jennifer Stockwell

Copy Editor
Rebecca Frey, PhD

Mailing List Inquiries
Davita Viale

Printing
The Lane Press

Correspondence
Editor, Yale Medicine Magazine
50 Division Street, 2 Science Park,
New Haven, CT 06511
Email: ymm@yale.edu

Yale Medicine Magazine is distributed to alumni, faculty, students, and friends of Yale School of Medicine.

Yale School of Medicine
Nancy J. Brown, MD
Jean and David W. Wallace Dean of Medicine and C.N.H. Long Professor of Internal Medicine

Zsuzsanna Somogyi
Acting Associate Vice President for Yale School of Medicine Development

Mary Hu
Associate Dean for Communications

Nicole Wise
Senior Director, Content Strategy & Development and Chief Communications Officer

Abbreviations used in Yale Medicine Magazine include HS to denote the final year of residency for house staff, FW for the final year of a fellowship, and YNHH for Yale New Haven Hospital.

Yale SCHOOL OF MEDICINE

x.com/YaleMed
facebook.com/YaleSchoolofMedicine
instagram.com/YaleSchoolofMed

KIMISA HA PHOTO

A CONVERSATION WITH DEAN NANCY J. BROWN

New frontiers in aging research

A FUNDAMENTAL UNDERSTANDING of the physiological changes that occur with age has always been essential to the practice of medicine. Now, advanced technologies combined with a greater emphasis on translational research are providing deeper and richer insights into the aging process.

At Yale School of Medicine, researchers are investigating everything from the molecular mechanisms of aging to novel therapeutics that may help forestall the damaging effects of age. To learn more about the strides being made and the newest areas of scientific inquiry, *Yale Medicine Magazine* spoke with Nancy J. Brown, MD, the Jean and David W. Wallace Dean of Yale School of Medicine and C.N.H. Long Professor of Internal Medicine.

What lessons can be learned from the ways in which aging has been studied in the past?
In the past, we associated aging with disease. Today, while we know that aging is one of the biggest risk factors for chronic diseases like Alzheimer's, cancer, and heart disease, we understand that disease is not necessarily a normal part of aging. So we are beginning to focus on healthy aging and how we can intervene in the aging processes to promote healthy aging.

How is research into the aging process now evolving? It's evolving in that we now differentiate what we refer to as chronological aging, or simply how many years somebody has lived, from biological aging, and the age-related function of a person's cells, tissues, and organs. That means we are working to identify the markers of aging in the cells and in the human body that can give us that information.

What is the most significant recent discovery related to the physiology of aging? Something that is not a single discovery but has evolved over time is the understanding of the relationship between obesity and calorie intake on energy metabolism, inflammation, and therefore biological aging.

What are the most promising areas of aging research being conducted at Yale School of Medicine?
There are many. In addition to the Claude D. Pepper Older Americans Independence Center, which we've had for many years, we now have the Yale Center for Research on Aging (Y-Age). We are creating longitudinal biorepositories of tissue so we can identify biomarkers associated with biological aging. There's research underway that focuses on rodents that live for a long time to understand what metabolites they have that are associated with slower biological aging. We have work ongoing related to energy expenditure in a cell and how that process can cause damage and promote aging—and, importantly, how we might intervene to slow that process. We also have work ongoing that slows organ damage when tissues are exposed to inflammation and changes in energy metabolism, as might occur when there's a lack of blood supply. We're now working to bring these activities together into a single research collaboration.

What is your hope for the aging research that is underway at Yale School of Medicine?
We have big hopes. We're working to bring together all of our researchers working on aging to make the whole bigger than the sum of the parts. We're in conversations with donors about that, and we're very excited about the vision.

Clemens Scherzer is the director of the Stephen & Denise Adams Center for Parkinson's Disease Research at Yale, the first such research center focused on precision medicine.

ANTHONY DECARLO PHOTO

Solving the mysteries of Parkinson's disease

Genomics and AI forge new paths

BY STEVE HAMM

WHEN CLEMENS SCHERZER, MD, WAS IN HIGH SCHOOL in the 1980s in South Tyrol, an idyllic mountain region of Italy bordering Austria, he decided to do something big and bold with his life. "The most exciting journeys of discovery are space exploration or a voyage into the unknown of the human brain. I chose the brain," says Scherzer, the Stephen and Denise Adams Professor of Neurology and director of the Stephen & Denise Adams Center for Parkinson's Disease Research at Yale.

Scherzer was a student at the Medical University of Vienna in the early 1990s when he had the epiphany that centered his work as a brain researcher on an enigmatic neurodegenerative disease: Parkinson's disease. He attended a lecture by the neurologist Thomas Brücke, MD, PhD, that featured a diagram of the circuit of the basal ganglia—a group of nuclei in the brain that are responsible for motor control. Brücke spotlighted the role that the basal ganglia play in Parkinson's disease. Scherzer was enthralled. "I wanted to understand and map the molecular circuits of brain cells and correct the glitches that cause diseases," he says.

After Scherzer earned his medical degree, he came to the United States to work with the creators of that diagram: Anne B. Young, MD, PhD, and the late John B. Penney, Jr., MD, researchers at Harvard Medical School; and with the late Mahlon DeLong, MD, former chair of neurology at Emory University and the pioneer of deep brain stimulation.

Now, as director of the first Parkinson's research center focused on precision medicine, Scherzer is making a much more expansive brain map of his own. The Adams Center, housed partially in temporary space, will occupy areas of three floors at 100 and 101 College Street, the built-for-purpose medical laboratory buildings that span the old Route 34 Connector in New Haven.

The center, which is expected to grow to about 70 scientists over the next few years, combines expertise in genomics and machine learning with a huge data trove. The goal is to map the RNA of brain cells—the genetic software that programs a cell—in Parkinson's patients and in people without the disease. At the core of the enterprise is the Parkinson's Cell Atlas, a database that Scherzer and his colleagues launched at Harvard to track the role of RNA in brain cells.

"We're going to use the revolutionary tools of genomics and AI to find the specific disease drivers in each patient, and to develop tailored medicines," says Scherzer. "We will then take those precision therapeutics all the way into proof-of-concept clinical trials."

Long-standing medical mystery

Parkinson's disease is named after James Parkinson, a 19th-century physician who called it "shaking palsy" in an essay published in 1817. Parkinson's is a long-term neurodegenerative disease that mainly strikes people after age 60. About 1 million people in the United States are living with Parkinson's disease, and an additional 90,000 new cases are diagnosed each year.

The earliest symptoms of Parkinson's include constipation, a loss of sense of smell, and sleep disorders, such as acting out dreams. When motor symptoms develop, they include tremor, stiffness, and slowed movements. Over time, people may experience mood swings, hallucinations, and dementia. Decades ago, researchers believed that Parkinson's was caused by exposure to pesticides and certain metals, but they now recognize that the disease is caused by multiple genetic risk factors in combination with these environmental influences.

There is no cure for Parkinson's, but a wide range of treatments, including dopamine-replacement medications such as L-Dopa (levodopa), deep brain stimulation, and focused ultrasound help control motor symptoms. These therapies don't address dementia and other disabling complications, however, and the disease will continue to progress.

Scherzer's goal is to help produce medications that prevent motor symptoms from developing and—for people who already have them—to stop the disease's progression. "We're focusing on disease-modifying medicines that actually slow or halt the disease progression," he says.

Inspired by his time at medical school in Vienna, where L-Dopa treatment was pioneered, Scherzer wanted to learn from the giants in the field. He applied for a research fellowship at Harvard and Massachusetts General Hospital, where Young was then chief of neurology. He remembers the day when the phone rang in his sparse room in Vienna, which had little more than a mattress, a desk, and an oil heater. It was Young, offering him a position. He was thrilled.

At Harvard, Scherzer gained experience as a laboratory researcher. He learned a method called RNA in situ hybridization, which allows researchers to explore gene expression in the human brain one gene at a time. It was, however, slow work.

After about two years at Harvard, Scherzer did his clinical residency at Emory. One of his mentors there was DeLong. Near the end of Scherzer's clinical training, he joined a lab exploring the use of microarrays, which are chips carrying printed microscopic spots of DNA designed specifically to analyze the expression of thousands of genes in parallel. In a breakthrough, the researchers discovered that the activity of a gene called SORL1 (LR11) is markedly reduced in Alzheimer's disease. Indeed, SORL1 (LR11) turned out to be one of the most important Alzheimer's genes.

Then it was back to Harvard, where Scherzer joined the faculty in 2001 as a clinical and research fellow in movement disorders. He established his own lab in 2003 with the goal of using the gene chips to analyze Parkinson's and Alzheimer's cells, spotting genes whose expression was too high or too low, which indicated potentially troublesome mutations.

"It's a different way of doing science," Scherzer says. "Traditional research is serial. It places a risky bet on one molecule at a time, often based on little more than a hunch with limited information. In our lab, we make discoveries based on massively parallel quantitative data. This provides a genome-wide view and allows nature to tell you what is truly important."

Around 2005, advances in high-throughput sequencing made it possible for researchers to sequence an individual's entire human genome (all genes) and transcriptome (all RNAs produced by the genome) quickly and cost-effectively. Genetic analysis could be done on an even more massive scale by using sequencing instead of microarrays. In the Scherzer lab, researchers extracted RNA from brain cell samples, created libraries, sequenced the libraries, and measured the expression of all active genes to spot potential trouble.

Only 1% of the human genome encodes proteins, meaning that everything we know about the brain comes from this very thin slice of information. When sequencing the RNA content of brain cells, however, Scherzer and his team made an astounding discovery: they found that a whopping 64% of the human genome is active in brain cells. "This is 'dark matter' RNA," Scherzer says.

The team began exploring the vast universe of both protein-coding RNAs (so-called messenger RNAs) and regulatory RNAs (so-called non-coding RNAs). Scherzer believes this network of RNA molecules encodes the genetic "software" of brain cells, providing vital information about human brain diseases, including Parkinson's. One of the lab's most important discoveries is that there are two types

Clemens Scherzer, MD //

> "With the exceptional ingenuity, brain power, and partners at Yale, I am confident we will make important advances toward this awesome mission."

of genes related to Parkinson's. Some are connected to susceptibility, others to progression. (A few do both.) This finding changed the way Scherzer thinks about drug development.

Traditionally, pharmaceutical companies designed drugs to target susceptibility genes. Scherzer's research, however, suggests that for patients who already have the disease, progression genes are the logical targets to prevent the disease from worsening.

These advances were made possible, in part, by the lab's vast biobank containing hundreds of thousands of human biosamples—including DNA, RNA, and plasma—collected over the past 15 years from more than 3,000 patients.

A new city and a new center

The Scherzer lab's 20-year run at Harvard came to an end earlier this year when Yale School of Medicine lured him away with a strong institutional commitment and support from Stephen and Denise Adams for an endowed, interdepartmental center. Stephen Adams, a businessman and private equity investor, suffered from Parkinson's and died in March at age 86. "Yale and Stephen and Denise Adams offered this once-in-a-lifetime opportunity to develop precision neurology for Parkinson's and other brain diseases," says Scherzer. "We are committed to making major headway toward solving these diseases."

The Adams Center is a large and complex project. It spans multiple domains of expertise—including genomics, high-powered computing, AI, big data analytics, clinical knowledge, and drug development.

The biobank samples are stored in New Haven in 12 laboratory freezers, kept at -80˚C, and in tanks chilled with liquid nitrogen. Additional samples will now be added from patients across New England—with a goal of including 10,000 patients. The center will also expand efforts to build a Parkinson's Discovery Engine that maps the entire biology of Parkinson's and to develop search algorithms to identify disease drivers and match them precisely to each patient. Scherzer calls this the "Google of Parkinson's disease."

Taking this project a step further, Scherzer envisions a Parkinson's clinic of the future in which a patient will give a few drops of blood for genome sequencing. Then, the data analytics engine behind the scenes will identify that patient's disease drivers and suggest precision medicines to correct those genetic defects.

A major element of the Adams Center is drug development. Scherzer and his colleagues are following two parallel tracks. One is using computers to screen massive health datasets to identify already-approved drugs that might be repurposed to combat Parkinson's. So far, they have identified asthma medicines that might be useful. The second track is new drug development: the researchers want to develop therapeutics that can directly recode the RNA defects. Scherzer expects to form drug-development partnerships with pharmaceutical companies and biotech startups—and even plans on setting up a startup incubator space at the center.

Scherzer believes that we are at a turning point in the effort to make precision medicine a reality. His lab at Harvard accomplished a great deal, including discovering susceptibility and progression genes, establishing the biobank, and launching the Parkinson's Cell Atlas. Now at Yale, he looks forward to bringing together clinical neurologists, scientists, and engineers from across the university's departments who share his passion for solving the riddle of Parkinson's.

"This is the right time to aim for a 'Mars landing' for Parkinson's: precision medicine that targets the genetic disease driver in the right patient at the right time and prevents disease from ever progressing," Scherzer says. "With the exceptional ingenuity, brain power, and partners at Yale, I am confident we will make important advances toward this awesome mission."

CAR–NK THERAPY FOR SOLID TUMORS

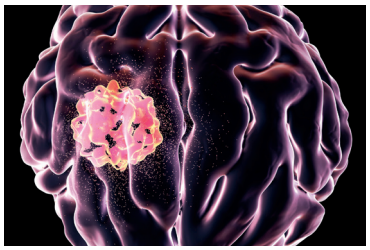
In chimeric antigen receptor (CAR)-T cell therapies, immune-boosting T cells are engineered to kill cancer cells. But because these therapies treat only certain types of cancer and may have severe side effects, researchers led by Sidi Chen, PhD, associate professor of genetics and of neurosurgery, investigated the CAR approach with another type of immune cell—natural killer (NK) cells. Although CAR-NK cell therapy is safer, NK cells have limited effectiveness in infiltrating solid tumors, so the team screened for genes that might overcome this shortcoming. According to the study reported in *Nature Biotechnology* (June 2024), NK cells were effective against colorectal tumors in mouse models when the *CALHM2* gene was deactivated. Chen said that the findings suggest that CAR-NK therapy may also work against other solid tumors.

from the journals

a collection of recent scientific findings

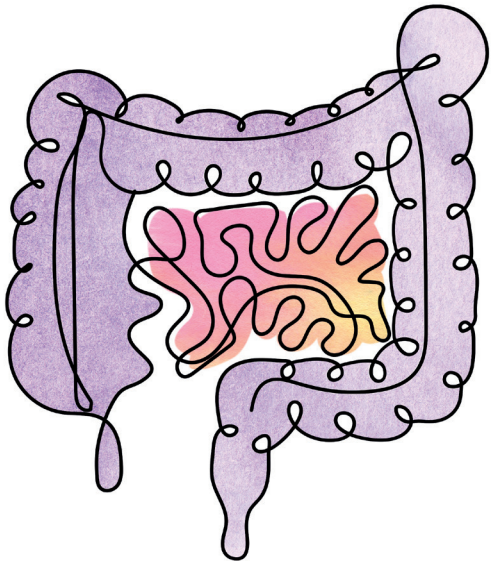
DIAGNOSING NEONATAL SEPSIS

Infants in a neonatal intensive care unit (NICU) are vulnerable to infection and sepsis. For late-onset neonatal sepsis, which begins three days after birth, it's well established that babies should be diagnosed by culturing blood samples drawn from two different sites. To diagnose early-onset sepsis, which occurs within 72 hours of birth, however, there's less evidence for taking two blood samples from babies who may have the condition. After analyzing data about neonatal early-onset sepsis, Noa Fleiss, MD, MPH, assistant professor of pediatrics, and colleagues reported in the *Journal of Perinatology* (February 2024) that performing two blood cultures rather than one can cause unnecessary pain for these infants and does not improve diagnostic accuracy. "It's not about how many blood cultures you take, but more about how you obtain the blood and the volume you obtain in a single culture," Fleiss said.



VASCULAR MIMICRY IN METASTATIC MELANOMA

Melanoma spreads to the brain more often than other solid tumors. According to research led by Lucia Jilaveanu, MD, PhD, associate professor of medicine (medical oncology), the reason may be related to the way in which brain metastases emerge. While cancers sometimes spread to distant organs and stimulate the body to produce more blood vessels (angiogenesis) to support their growth, malignancies may also metastasize by making their own blood vessels (vascular mimicry). In a study published in *Cellular and Molecular Life Sciences* (April 2024), Jilaveanu reported that melanoma brain metastases used vascular mimicry more often than melanoma metastases outside the brain. Jilaveanu hopes that this research demonstrates the potential therapeutic value of inhibiting both angiogenesis and vascular mimicry when treating melanoma.



INTERLEUKIN-10 AND IBD

Inflammatory bowel disease (IBD) is caused by the absence of the molecule interleukin-10 (IL-10), which prevents inflammation in the gut. A study published in *Nature* (February 2024) and led by Richard Flavell, PhD, Sterling Professor of Immunobiology, found that production of fatty acids called ceramides increases in mice without IL-10. When ceramide production was prevented, it alleviated IBD in these mice. Additionally, feeding the mice unsaturated fats, such as those found in olive oil, had the same positive effect. The researchers hypothesize that diets high in unsaturated fats could potentially help treat IBD in humans.

A NEWLY IDENTIFIED GENETIC SYNDROME

A new neurodevelopmental syndrome was recently defined after researchers had identified 18 patients with symptoms that included low muscle tone, seizures, and heart problems, among other challenges. In the absence of established genetic diagnoses with clinical testing for these patients, an international research team analyzed the patients' data alongside Yale's Saquib Lakhani, MD, clinical director of the Pediatric Genomics Discovery Program, and Lauren Jeffries, DO, associate research scientist in pediatrics. Using next-generation DNA sequencing, the scientists found that the patients shared rare changes in the *CRELD1* gene. The variants were confirmed at Yale to be pathogenic by using in vivo modeling in *Xenopus tropicalis*, the western clawed frog. In a paper published in *Genetics in Medicine* (February 2024), the researchers posit that certain variants in *CRELD1* cause what is now known as Jeffries-Lakhani neurodevelopmental syndrome (JELANS).

A NEW TARGET FOR PKD THERAPY?

The gene mutations that lead to polycystic kidney disease (PKD) have long been identified, but researchers don't know much about other genetic factors that affect the disease's severity. Stefan Somlo, MD, C.N.H. Long Professor of Medicine (Nephrology) and professor of genetics, and colleagues reported in *Nature Communications* (May 2024) that inactivating the transcription factor *Glis2* in the kidneys prevented cysts from developing in a mouse model of PKD. According to the study authors, the finding suggests that *Glis2* may be a potential therapeutic target.

OPPOSITE: LUISMMOLINA; THIS PAGE, CLOCKWISE FROM TOP LEFT: D3SIGN, KATERYNA KON/SCIENCE PHOTO LIBRARY, MAYA SZATAI

INTRODUCTION:
A SPECIAL REPORT ON THE SCIENCE OF AGING

Geroscience

A revolution to improve health span

BY STEVE HAMM
ILLUSTRATION BY MAIRA KALMAN

MEDICAL CARE FOR OLDER ADULTS didn't become a distinct practice until the dawn of the 20th century—a time, it is worth noting, when the average life expectancy in the United States was roughly 47 years. It emerged in part from the differing points of view of two medical pioneers: Élie Metchnikoff, a Russian microbiologist, and Ignatz Nascher, MD, who received his medical degree from New York University School of Medicine and later became New York City's chief physician.

Metchnikoff coined the term gerontology, the study of aging, in 1903, and later won the Nobel Prize in Physiology or Medicine. Focusing on immunology, he developed the theory that aging is caused in part by toxic bacteria in the gut, and he recommended daily consumption of yogurt to extend life.

Nascher had a different hypothesis. Based on his experiences with patients, some of whom lived in almshouses, he believed that natural death results from the decay of the body's organs and that the length of a person's life depends in large part on their "mode of living," including their diet. In 1909, Nascher set out to distinguish the medical treatment of older adults and coined the term geriatrics (from the Greek *geras*, meaning old age, and *iatrikos*, meaning physician).

Both terms stuck. Geriatrics has become a specialty for physicians, and gerontology has become a fast-evolving area of study for medical scientists and health professionals. These complementary domains—and the intersection of microbiology and medical practice—are now critically important because the world's population is rapidly aging. Over the last decade, more than 10,000 Americans have turned 65 each day—a trend that is projected to continue until 2030.

To address this wave of older adults, leaders in geriatrics and gerontology at Yale School of Medicine (YSM) say that nothing less than a revolution in medicine for older adults is underway. Advances in the understanding of the biological mechanisms, syndromes, and diseases of aging are enabling physicians to extend healthy lifespans, giving patients the power to choose their quality-of-life priorities, and perhaps even to slow the aging process.

"Formerly, the focus was on extending life," says Thomas M. Gill, MD, Humana Foundation Professor of Medicine (Geriatrics). "Now, we don't want people to just live longer; we want them to live longer and healthier. That's why we talk about 'health span' rather than 'lifespan.'"

The revolution in care for older adults came about in part because of discoveries that identified some of the fundamental mechanisms of aging at the cellular or organismal level. These mechanisms, including metabolic changes, inflammation, epigenetics (heritable traits that occur without changes to the DNA sequence), and protein regulation, are now known within the scientific community as "hallmarks of aging."

At Yale, one of the key research topics is geroscience, a field in which scientists explore the biological mechanisms of aging and use that knowledge to develop interventions that can delay the onset of age-related diseases. Last year, Yale launched a Translational Geroscience Initiative that funds cross-disciplinary research and brings visiting professors to campus. The recipient of the first research award was Daniel Jane-Wit, MD, PhD, associate professor of medicine (cardiology) and immunobiology. His project explores the molecular underpinning of the aging of blood vessels.

The first visiting professor was Luigi Ferrucci, MD, PhD, a geriatrician and epidemiologist who is the scientific director of the National Institute on Aging.

Ferrucci is best known for refocusing the landmark Baltimore Longitudinal Study of Aging to explore the geroscience hypothesis, which posits that it is possible to delay or prevent the onset of multiple age-related diseases and extend the healthy lifespan by targeting the biological mechanisms of aging. The hypothesis suggests that aging itself is the major risk factor for chronic conditions like heart disease, diabetes, and Alzheimer's, and that interventions slowing the aging process could have widespread health benefits.

In 1983, Yale recognized medical treatment for older adults as a distinct discipline by establishing geriatrics as a subsection within general medicine; it became a section within the Department of Internal Medicine in 1999 with Leo M. Cooney, Jr., MD, now Humana Foundation Professor Emeritus of Medicine (Geriatrics), as the first section chief. Since that beginning, Yale faculty members have stood at the forefront of many initiatives and discoveries in the field.

Mary Tinetti, MD, Gladys Phillips Crofoot Professor of Medicine (Geriatrics), who headed the geriatrics section for many years, is now leading a national effort called Patient Priorities Care, which seeks to transform the way geriatric medicine is practiced. Instead of physicians treating individual diseases of aging in isolation, Tinetti calls on physicians not only to treat patients' diseases holistically but also to discover the goals of each patient to personalize their care decisions. "It begins with a conversation with the patient," Tinetti says. "You start with the individual's goals, not by focusing on the disease or the organ."

Several Yale faculty members also have produced innovations addressing "syndromes of aging," such as falls, delirium, and functional decline, among others. Gill, Tinetti, and their colleagues observed that these syndromes have multiple risk factors and multiple consequences—many of which share the same causes and effects. Recognizing this pattern, the faculty members designed interventions aimed at forestalling the onset of such syndromes and helping people recover from them.

Similarly, it's well established that several major diseases are age related, including cardiovascular disease, cancer, arthritis, type 2 diabetes, hypertension, and Alzheimer's disease. Even though these diseases don't occur solely in older people, their incidence increases exponentially with age. In addition, some infectious diseases, among them COVID-19 and West Nile virus, take a greater toll on older adults.

To better understand the barrage of health risks facing older adults, much of the research at Yale seeks to identify the actual mechanisms of aging that contribute

Ruth Montgomery, PhD //

"If you can delay the process of aging, you can address the associated diseases, too."

Ruth Montgomery is researching the effects of aging on the immune system.

to age-related diseases. For example, Vishwa Deep Dixit, DVM, PhD, Waldemar Von Zedtwitz Professor of Pathology and professor of immunobiology, focuses on the role of inflammation in the diseases of aging. His lab helped establish that age-related inflammation can trigger chronic diseases; the team further demonstrated that reducing calorie intake can curb inflammation and potentially forestall the onset of disease.

Meanwhile, Ruth Montgomery, PhD, professor of medicine and professor of epidemiology (microbial diseases), researches the effects of aging on the immune system. She and her colleagues have studied the role of natural killer (NK) cells—the white blood cells we count on to fight off infections—in defeating West Nile virus. With close colleague Albert Shaw, MD, PhD, professor of medicine (infectious diseases), they also study how aging reduces the effectiveness of innate immune cell types and responses to vaccines. The end goal for much of this research is discovering methods for slowing the effects of aging on immune function. "If you can delay the process of aging, you can address the associated diseases, too," Montgomery explains.

Until very recently, scientists believed that nothing could be done medically to slow the body's tendency to decline with age. However, studies of the molecular mechanisms underlying aging indicate that by influencing those cellular processes, we may be able to slow the inherent physiological changes and live longer, healthier lives.

Researchers at Yale also are exploring the potential of senolytics, a new category of therapeutics designed to reduce aging's ill effects on cells. The idea is that if we can remove senescent cells from the body—the ones that have deteriorated—the remaining cells will be healthier and function better. To venture into this area of research, medical scientists are focusing initially on therapies that have already been approved by the U.S. Food and Drug Administration and repurposing them to address health in older individuals. An example is dasatinib (Sprycel), which is used to treat certain types of leukemia and is now used also as a senolytic. At the same time, investigators are doing early investigations that may produce novel senolytic therapies not yet approved for any medical use that may someday be available to patients.

The search for answers is all the more urgent, considering that there are only about 8,000 geriatricians in the United States today—not nearly enough to treat the more than 58 million Americans who are age 65 or older. That's why Yale School of Medicine, in addition to training geriatricians, embeds the principles of personalized holistic geriatric care into its medical school and residency programs.

As part of this training model, all Yale residents rotate through the Acute Care for the Elderly Unit in Yale New Haven Hospital. There, the attending physicians impress on residents the importance of listening to patients' stories and understanding their priorities. "Residents see the radical opposite of doing disease- or organ-based decision-making," says Terri Fried, MD, Humana Foundation Professor of Medicine (Geriatrics) and section chief for geriatric medicine. "This will have a profound effect on how they think about care for older patients throughout their careers."

To sum up the collective impact of Yale's intense focus on aging, Gill says, "We're all invested and committed to having Yale be a top institution for the entire continuum of aging research. And we're well on the way to making that happen." */yale medicine magazine*

RESEARCH

YSM investigates aging

Key initiatives that address questions on the aging process:

- The Yale Claude D. Pepper Older Americans Independence Center was established in 1991. Led by Gill, the center's researchers study multifactorial geriatric conditions and improve decision-making for patients with multiple long-term health conditions.
- The Yale Center for Research on Aging (Y-Age) focuses on studying the molecular mechanisms that control aging and on developing interventions that promote healthy aging. Led by Dixit, Y-Age was established in 2015.
- The Yale Alzheimer's Disease Research Center, established in 2015, concentrates on Alzheimer's and other related neurological diseases and conditions. The center is led by Stephen Strittmatter, MD, PhD, Vincent Coates Professor of Neurology; and Christopher van Dyck, MD, Elizabeth Mears and House Jameson Professor of Psychiatry and of Neurology and Neuroscience.

In addition, Yale faculty members are applying to the National Institute on Aging to establish a Nathan Shock Center of Excellence in the Basic Biology of Aging on the Yale campus. The center here would concentrate on research into the immunobiology of aging. Nathan Shock, PhD, was a long-time director of the Gerontology Research Center at the National Institutes of Health.

The biology of aging

Decoding the secrets of longer and healthier lives

BY ISABELLA BACKMAN
ILLUSTRATION BY MAIRA KALMAN

AS MORE PEOPLE LIVE LONGER, understanding the underlying processes of aging will be essential for meeting future medical needs.

By 2034, for the first time in U.S. history, people over the age of 65 will outnumber those under age 18, posing an unprecedented challenge to the American health care system. Understanding the role of aging in disease and infirmity is an urgent priority for mitigating the impact of this major demographic shift.

While growing older can benefit both individuals and society, aging itself is the biggest risk factor for nearly every chronic disease, including heart disease, cancer, Alzheimer's disease, and chronic kidney disease. All these conditions can significantly lower one's quality of life—but learning how to prevent each of them separately is like playing a frustrating game of whack-a-mole. "If you cured cancer tomorrow, the average life expectancy would probably go up only by a couple of years," says Albert Higgins-Chen, MD, PhD, assistant professor of psychiatry.

The gain in life expectancy is limited because even if clinicians successfully prevent cancer in a given individual, slow deterioration across organ systems will continue if left unaddressed, so that patient is likely to end up battling a different chronic disease. "If you're trying to put out an increasing number of forest fires one by one as they pop up, you're fighting a losing battle if you aren't addressing the climate change that's driving the increased fires," says Higgins-Chen.

Now, the burgeoning field of geroscience is exploring the processes underlying aging itself with the goal of simultaneously preventing many chronic diseases before their onset. New technologies enable scientists to better assess a person's risk of developing disease and identify appropriate interventions for future clinical trials. Researchers are learning more about how such devastating chronic diseases as cancer develop, as well as how natural physiological processes like pregnancy affect the way in which someone ages. The new field's ultimate goal is not only to help ensure that people live longer, but also to maintain their health and vitality in their final decades.

"If we maintain the same rate of age-specific disability that we have now, we will be facing a tsunami of health care needs that we will not be able to meet," says Luigi Ferrucci, MD, PhD, scientific director of the NIH's National Institute on Aging and Yale School of Medicine's first visiting director of geroscience. "[Studying aging] is not only important, but the only hope we have."

WHAT IS BIOLOGICAL AGE?

We're all familiar with the concept of chronological age—our age in years (and months) from the date of our birth. Biological age, on the other hand, refers to where our cells are in the aging process; in some individuals the pace can be faster or slower than chronological aging. Over time, our cells, tissues, and organs can accumulate molecular damage that may accelerate biological age relative to chronological age. In contrast, other people may experience lower levels of molecular damage compared to those of their peers, thus slowing biological aging. This distinction explains why there may be considerable variation in how "old" different men and women look across a group of 60-year-olds, for example.

We know that lifestyle choices affect biological aging. When a person smokes, they inhale carcinogens that directly damage lung cell DNA. Smoking also triggers immune system reactions that alter the composition of immune cells. Both of these processes drive up a person's biological age.

Some evidence suggests that exercise, on the other hand, might help slow down a person's biological aging processes. Research shows that individuals who engage in endurance training, for example, have a risk of dying that is three to five times lower than those of the same age who do not. Other research suggests that people who exercise regularly have epigenetic signatures associated with lower levels of biological aging; however, the epigenetic effects of exercise on aging are still poorly understood, and more

longitudinal studies—in which researchers follow subjects for a number of years—are needed.

BIOMARKERS OF BIOLOGICAL AGING

Researchers are investigating the drivers of biological age to uncover novel aging biomarkers, or biological signals of processes, in humans. This research involves utilizing blood samples from large cohorts, often numbering in the thousands, of patients spanning a range of ages. Then, a range of "omics"-based technologies enable the scientists to characterize and quantify the presence of various biological molecules. These fields of study include epigenomics, which measures such modifications of DNA as methylation—a chemical change in which structures called methyl groups attach to or detach from DNA and turn genes on or off. Other -omics include proteomics (the measurement of proteins expressed by an organism's genome) and transcriptomics (the study of the sum of an organism's RNA transcripts).

Researchers follow the health trajectories of their patients after the initial blood draw. Follow-up includes tracking which of the patients died, their cause of death, the diseases they developed, and any declines in physical or cognitive functioning. The researchers can then train artificial intelligence to build models based on different biomarkers that predict lifespan or risk of disease/decline in function. An epigenetic clock, for example, uses algorithms based on DNA methylation to measure an individual's biological age.

In Higgins-Chen's lab, his team is continuing the work initiated by his former mentor, Morgan Levine, PhD, assistant professor adjunct in pathology, to take it a step further by studying the biological aging process across multiple physiological systems. "Instead of trying to train a general predictor of all-cause mortality, we're trying to capture signals from, for example, cardiovascular aging, brain aging, or kidney aging, so we can develop a metric for each of those," he says. A model based on blood biomarkers, for example, could estimate the time it takes to develop leukemia, while separate models based on biomarkers from other physiological systems might predict time to heart disease or cognitive decline. "We're trying to develop a much richer tapestry of the biological aging process."

Furthermore, Higgins-Chen's team is studying how various interventions influence these biomarkers. In one ongoing study, the researchers are compiling a large number of DNA methylation datasets to see how various treatments like rapamycin (an immunosuppressive drug) or metformin (an antidiabetic medication), as well as such lifestyle factors as diet and exercise may mitigate the aging process. They are also studying how such factors as stress, chemotherapy, or radiation accelerate the aging process by comparing biomarkers before and after these events.

Intriguingly, the researchers have found that smoking cessation lowers heart and lung age; gastric bypass for weight loss lowers metabolic age; and metformin reduces inflammation as well as lowering metabolic and kidney age. But the team saw almost no effects in more general biomarkers that do not involve physiology, suggesting system-specific biomarkers of aging may be critical for detecting these effects.

These studies set the stage for future clinical trials on aging, in which researchers will compare the differences in the development of age-related conditions over a period of years among patients on a particular intervention and those given a placebo. Having measurable biomarkers that assess the rate of aging will be essential to understanding whether these interventions are effective. "A lot of prep work needs to be done to even identify what the most appropriate aging biomarkers are for different interventions before someone can actually go do the real test in humans," says Higgins-Chen.

Albert Higgins-Chen, MD, PhD //

"We're trying to develop a much richer tapestry of the biological aging process."

UNDERSTANDING CHRONIC DISEASE: BIOLOGICAL AGE AND CANCER

Researchers are also examining how biological aging contributes to the onset of such chronic diseases as cancer. In 2022, a team led by Jeffrey Townsend, PhD, Elihu Professor of Biostatistics and professor of ecology and evolutionary biology, published the first study to examine tumor genomes across a large cohort of patients to learn which mutational processes contributed directly to cancer development. His team studied the extent to which the cancer was driven by mutations associated with aging, compared to mutations related to exposure to carcinogens like tobacco or ultraviolet light.

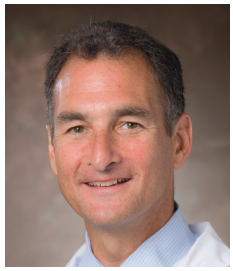
The study revealed that the role aging plays in cancer development compared to exposure to mutagens varies according to the type of cancer. Lung cancer, for example, was more likely to be caused by such exposures as smoking or viral infection. Glioblastoma, on the other hand, is driven almost entirely by mutations related to aging. "This wasn't surprising in a sense, because glioblastomas most of the time occur in people of advanced age, whereas lung cancer can occur at younger ages," says Townsend. "So it makes sense that it takes a certain amount of aging mutations to lead to cancers like glioblastoma."

Over the past several decades, the rates of early-onset cancers, in which the disease appears in people under the age of 50, have been on the rise worldwide. Younger adults are facing an increased risk of cancer, including breast, lung, prostate, endometrial, colorectal, and cervical cancers. Townsend hopes to apply the method he has developed to future studies—to examine early-onset tumors and better understand what types of mutations are driving this disturbing trend.

HOW PHYSIOLOGICAL PROCESSES DRIVE AGING

Drivers of biological age, including DNA methylation, can also be accelerated by psychosocial stressors. Could a natural physiological stressor like pregnancy also affect biological aging? researchers wondered.

A team led by Kieran O'Donnell, PhD, assistant professor in the Child Study Center and the Department of Obstetrics, Gynecology, and Reproductive Sciences at Yale School of Medicine, in collaboration with researchers



Gerald Shulman, MD, PhD //

"Insulin resistance is a major factor in the pathogenesis of type 2 diabetes, but [it] also ... drives heart disease, fatty liver disease, obesity-associated cancers, and even Alzheimer's disease."

at the University of California, Irvine, examined DNA methylation in blood samples collected from women during early, mid-, and late pregnancy, as well as at three months postpartum. "Going into the study, my hypothesis was that pregnancy would be associated with a sustained increase in biological aging," O'Donnell says.

To his surprise, this was not the case. The study, published in March in *Cell Metabolism*, found that pregnancy initially increased the biological age of women by about two years. But from late pregnancy to the postpartum period, biological age then markedly decreased by about two to six years, depending on which epigenetic modulations the scientists measured.

Changes in biological age were not uniform across the cohort, however—some women experienced more accelerated aging than others. Intrigued, the researchers next tried to determine the maternal characteristics associated with these patterns. They discovered that higher body mass index (BMI), for example, was linked to higher biological age estimates during the postpartum period. Breastfeeding, on the other hand, seemed to promote a reduction in biological age after birth.

The United States has "shockingly high" rates of maternal morbidity and mortality, says O'Donnell. Studying these variations in biological aging may help researchers understand which women are at greatest risk of adverse outcomes during and after pregnancy. "These measures of biological aging could be a suite of tools with relevance for predicting both short- and long-term maternal outcomes." Women who experience pregnancy-related complications, for instance, are at a higher risk of developing cardiovascular disease in later life. O'Donnell has recently received funding from the Burroughs Wellcome Fund to investigate biological aging in pregnant women and its long-term impact on maternal cardiovascular health.

DEVELOPING DRUGS FOR AGING

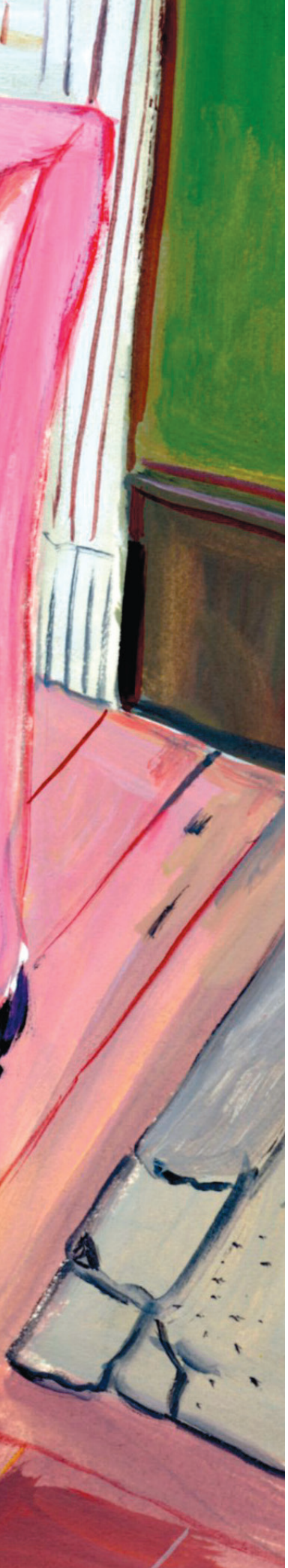
Right now, you can't visit your doctor's office and ask for a pill to treat aging. But new therapeutics may be on the horizon. Metformin, for example, is a drug that lowers glucose in people with type 2 diabetes. Emerging preliminary research suggests that the medication may also slow aging and extend lifespans. Ongoing clinical trials including the Albert Einstein College of Medicine-led MILES (Metformin in Longevity Study) and the American Federation for Aging Research's TAME (Targeting Aging with Metformin) are investigating its antiaging effects in humans.

In the laboratory of Gerald Shulman, MD, PhD, George R. Cowgill Professor of Medicine (Endocrinology) and professor of cellular and molecular physiology, his team is striving to understand the molecular basis of insulin resistance. This work may also have implications for improved treatment of many diseases associated with aging, Shulman says. As we age, we become more prone to developing insulin resistance. "Insulin resistance is a major factor in the pathogenesis of type 2 diabetes, but it's also a major factor in almost everything cardiometabolic," says Shulman. "It drives heart disease, fatty liver disease, obesity-associated cancers, and even Alzheimer's disease."

Shulman's team discovered in 2004 that insulin resistance associated with aging was linked to reduced mitochondrial activity. When our mitochondria slow down, lipids begin to accumulate in our muscle cells, which in turn triggers insulin resistance resulting in the development of type 2 diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD), and age-related cardiometabolic diseases. "So our lab is focused on ways of revving up the mitochondria to metabolize the intracellular fat," Shulman says.

To achieve this, the researchers are developing drugs that promote a process known as mitochondrial uncoupling—which make the mitochondria less efficient so that they have to metabolize more fat to generate the same amount of adenosine triphosphate (ATP), a nucleotide that carries and transfers chemical energy in cells. Mitochondrial uncoupling allows calories to flow out of a leaky mitochondrial membrane as heat rather than turn into ATP or be stored as fat, thus increasing the overall amount of calories burned. OrsoBio, a biotechnology company that Shulman helped co-found, has recently demonstrated the safety and efficacy of a novel liver-targeting mitochondrial uncoupling agent called TLC-6740 in Phase 1B clinical studies to safely promote whole-body energy expenditure in humans.

Many studies of therapeutics for aging are still in their early phases. Future aging research will focus on clinical trials in humans that test the efficacy of antiaging therapeutics—either repurposed drugs or novel compounds, says Higgins-Chen. While doctors may not be writing many antiaging prescriptions any time soon, the next decades will see the introduction of novel treatments that will help adults enjoy better health in their old age. "Progress is going to start off slowly, and then it's going to accelerate," he says. "We might not find very much in the next 10 years. But for the next 50 years, I have very, very high hopes." *yale medicine magazine*



Inside the labs

Elucidating crucial aspects of aging

BY ISABELLA BACKMAN
ILLUSTRATION BY MAIRA KALMAN

OF THE NEARLY 300 LABORATORIES investigating different aspects of basic science and translational and clinical research at Yale School of Medicine (YSM), dozens are dedicated to inquiries related to the aging process. For a sampling of the research that is underway, *Yale Medicine Magazine* spoke with laboratory leaders who study the effects of aging on the immune system, metabolism, the brain, and endocrine function.

ALBERT SHAW

One might not expect to find aging among the interests of an infectious disease specialist—but it is, in fact, the focus of research in the laboratory of Albert Shaw, MD, PhD, professor of medicine (infectious diseases) and a member of the Yale Center for Research on Aging (Y-Age).

Older adults are at increased risk of morbidity and mortality due to such infectious diseases as pneumonia or sepsis, and their immune systems mount a weaker response post-vaccination, which leaves them less protected than their younger counterparts. These disparities were highlighted by the COVID-19 pandemic. Research shows that in 2023, adults aged 65 and older accounted for up to 63% of COVID-related hospitalizations and 90% of deaths. "COVID-19 had a devastating impact on older adults, particularly those in long-term care facilities and nursing homes, and continues to do so even with the availability of excellent vaccines," Shaw says.

To better understand why older adults are more vulnerable to infectious diseases such as COVID-19, Shaw's lab is investigating how the function of various immune system cells changes with age. The researchers are particularly interested in uncovering mechanisms linked to increased levels of inflammation that occur in older adults. "We think this chronic inflammation is the source of some of the altered immune functioning with age," says Shaw.

Shaw's team uses a variety of techniques to analyze the immune response in older versus younger adults. Flow cytometry, for example, is a method that uses antibodies recognizing specific proteins within or on the surface of cells that are linked to fluorescent compounds; researchers employ instruments with multiple lasers to detect and quantitate such proteins. Mass cytometry is a newer technique in which antibodies are linked to heavy metal tags detectable through mass spectroscopy, allowing the simultaneous assessment of over 40 cell parameters. Shaw also uses such methods as RNA sequencing to analyze gene expression, proteomics for protein expression, metabolomics for elucidation of key metabolites, and spatial transcriptomics methods pioneered by YSM experts to analyze gene expression in sections of human tissue from older versus younger adults. The researchers' goal is to form a comprehensive picture of the mechanisms controlling the human immune response, as well as understanding how this response is affected by age.

Shaw's team is zeroing in on a few potential key factors affected by aging, including receptors of the innate immune system and recent work on human platelets. The innate immune system is the part of the immune system that controls the earliest responses to infectious agents or vaccines, and primes the activation of the more specific immune responses controlled by antibodies and T cells. Platelets are best known as the cells that mediate blood clotting, but emerging research is revealing their prominent role in regulating the immune response. "Even though they're very small cells, there are so many of them in the blood—millions in a teaspoon—that we think in aggregate they may

contribute to dysfunction in the immune system in older adults," Shaw says.

Their recent research—a collaboration with Steven Kleinstein, PhD, Anthony N. Brady Professor of Pathology; Ruth Montgomery, PhD, professor of medicine and professor of epidemiology (microbial diseases); Heather Allore, PhD, professor of medicine (geriatrics) and of biostatistics; and Thomas Gill, MD, Humana Foundation Professor of Medicine (Geriatrics)—shows that platelets have elevated levels of RNAs encoding genes critical for platelet signaling and activation in older compared to younger adults. Furthermore, the expression of these activation RNAs in platelets from older adults who met the criteria for frailty—a geriatric syndrome characterized by increased vulnerability to adverse health outcomes—was further increased compared to their expression in healthy older adults. The researchers believe that changes like these may play a role in driving age-associated chronic inflammation, as well as the higher rates of clotting-related diseases in older adults.

In addition, Shaw's team is studying immunological differences between younger and older adults who have received various vaccinations. In 2022, Shaw was among a group of Yale researchers who received a $12 million award from the NIH as part of the Human Immunology Project Consortium (HIPC) to investigate vaccine responses in vulnerable groups. His lab is comparing the immune reactions of older adults in long-term care facilities to those of healthy community-dwelling older individuals and younger adults following administration of two different influenza vaccines approved for adults aged 65 and older. Through identifying immunological, gene expression, and proteomic differences, the team hopes to gain insights into designing better vaccines and therapeutics to strengthen the immune response in older adults.

VISHWA DEEP DIXIT

Scientists have long believed that the immune system is important only for protecting us from disease. But over the past several decades, researchers have found that immune cells are present within and important to nearly every organ in the body. "In addition to pathogen defense, they play an important role in the normal functioning of those organs," says Vishwa Deep Dixit, DVM, PhD, Waldemar Von Zedtwitz Professor of Pathology and professor of immunobiology and of comparative medicine and the director Y-Age.

A vital function of immune cells includes regulating the metabolism of our organs. In Dixit's laboratory, his team is investigating the interactions between the metabolic and immune systems. "The interaction between these is absolutely critical for maintaining function and homeostasis," he says. The team's work provides important insights into why we age and clues for potential new therapies for enhancing health span.

As we grow older, fat cells start to accumulate within some organs. This fat accumulation triggers the activation of the immune cells residing in the tissues, which in turn can lead to increased levels of inflammation. "That is now recognized to be one of the major pillars of mechanisms of aging," says Dixit. "When the crosstalk between immune and metabolic systems goes awry, it leads to inflammation, immune and metabolic dysfunction, and the process of aging."

Dixit's team is using various transcriptomic technologies, including single-cell sequencing, RNA sequencing, proteomics, and metabolomics, to study the composition of fat tissues and identify potential targets that increase health span or delay the process of aging. The researchers' goal is to identify the underlying immunometabolic mechanisms that drive aging-induced disease risk so that specific interventions can be designed to improve the health of older adults.

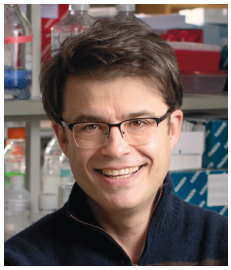
One finding is that a specific pathway that regulates inflammation, known as the NLRP3 inflammasome, is an important driver of the aging process. The Yale team's research has shown that blocking the activity of this immunological complex not only reduces inflammation but also extends the health span of animal models. Other groups have shown that lowering NLRP3 delays aging of certain organs and enhances lifespan. Now, multiple ongoing clinical trials are investigating how drugs that inhibit NLRP3 impact disease. "Time will tell whether these interventions will have beneficial effects in human aging, as they have in animal models," Dixit says.

Another avenue is caloric restriction, which may also offer insight into a mechanism to slow the aging process. In 2022, Dixit's team analyzed genetic data collected from fat tissue that was examined as part of a National Institute on Aging study called the Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy (CALERIE), in which participants reduced their calorie intake by 14% for two years. Caloric restriction extends the lifespan and reduces inflammation in animal models, but how this dietary intervention affects the related process

in human aging is not known. Dixit's new study offered evidence that mild reduction of calories significantly improves immune function and reduces inflammation and thymic aging in humans. However, long-term calorie restriction is difficult to maintain. "So we want to identify the drivers that mediate and mimic the effects of calorie restriction on health and lifespan," says Dixit.

This work has led to the identification of two molecules named PLA2G7 and SPARC, which are inhibited when people restrict their calorie intake. "These studies have identified that there are calorie restriction mimetics that can be harnessed," says Dixit. "And mechanisms such as these could be potential future drug targets that enhance health span and may even increase quality of lifespan."

NENAD SESTAN



Our brains are continuously changing throughout our lifetimes. A newborn's brain looks quite different from an adult's. And the brain of a healthy older person will differ from that of someone living with an age-related chronic disease.

Nenad Sestan, MD, PhD, Harvey and Kate Cushing Professor of Neuroscience and professor of comparative medicine, of genetics and of psychiatry, studies how the human brain develops over time. Over the years, his team has created a research biobank comprised of postmortem brain specimens donated for scientific study. The tissues collected from each donor contain billions of neural cells. Each cell is "a bag of RNA," says Sestan, produced when an enzyme transcribes a sequence of a gene's DNA. Cell types are differentiated by the RNA they contain. However, the RNA repertoire will change over time—even within the same cell.

Emerging technologies are now giving Sestan's team an unprecedented view inside these neural cells. Next-generation sequencing, for example, enables the team to study a large number of cells in parallel to see when and where genes are expressed in the brain tissue. These analyses are helping his laboratory to uncover biological differences between younger and older brains, which occur divergently in humans, nonhuman primates, mammals, and other species. "Instead of looking at only one molecule or one gene, as we did several years ago, we can profile every single gene, transcript, and protein to create a huge dataset," Sestan says. "Before, we could only see a few continents, but now we have a very detailed map where we can see countries, counties, towns, cities, and streets."

To make sense of these large datasets, and even to combine and integrate their features, Sestan's team uses bioinformatics and artificial intelligence. The results have applications for understanding how our most important organ ages. "Now, we can tell how one's brain cells change from age 3 to age 20, 40, 60, or even 90 and 100," Sestan says. In doing so, the researchers are studying how healthy individuals age compared to those who are affected by age-related neurological or psychiatric disorders.

Eventually, large datasets are curated and sculpted into "brain atlases," helping Sestan's lab understand the molecular and cellular signatures of brain aging and identify various biomarkers involved in healthy and unhealthy aging. This process, in turn, brings insight into potential targets that scientists can test in model systems to see whether they can slow or reverse certain negative effects of aging. Furthermore, understanding how cells change with age can help scientists build biological models for predicting someone's age based on signatures in the brain.

Sestan's research has shown that not all cell types age in the same way, and that some cell types are more vulnerable to the aging process than others. This finding may explain why some cognitive skills, such as spatial awareness and memory, decline with age, while others like verbal abilities may actually improve. "Now we're trying to understand why some cell types have different aging signatures than others," says Sestan.

Sestan hopes that studying human brain tissue will provide answers that will help people attain a higher quality of life in their old age. There is, however, much to learn from studying other species, as well. There are certain animals, and even mammals, that have impressive lifespans. The Greenland shark, for example, can live for 300 to 500 years, and bowhead whales can live for over 200 years.

By comparing the composition of cell types and their regulatory capabilities with age in these animal brains versus our own, Sestan hopes to better understand the evolutionary differences between them as well as to decode secrets to other species' remarkable longevity. "The notion that sharks have a complex brain and can live this long tells us that technically neurons can live 500 years," he says. "We would like [to] learn from other animals how to help humans live longer and have a healthy brain."

HATTIE CHUNG

In humans, the ovary is among the first organs to age—a transition marked by menopause. Scientists have traditionally believed that ovarian aging is simply the result of egg depletion. Hattie Chung, PhD, assistant professor of medicine, who joined Yale School of Medicine as a member of the Yale Cardiovascular Research Center this year, is studying how cells in the ovary interact with one another and how these interactions change with age. She is also a member of Y-Age and has secondary appointments in the Department of Molecular, Cellular, and Developmental Biology and the Department of Obstetrics, Gynecology, and Reproductive Sciences. Her lab's research is adding to the growing evidence that the ovaries play an important role beyond fertility—particularly in endocrine function—and that the ovarian aging process is much more intricate than previously thought.

All female organisms are born with a finite reserve of eggs, which are released monthly in humans through the menstrual cycle. "This is a very dramatic process that completely changes the [ovarian] tissue," Chung says. "And it's a very stressful process for the organ."

First, ovarian cells must incubate eggs in multicellular units called follicles that are spatially organized. These follicles mature with the egg inside until they are ready for ovulation. A number of different cellular interactions occur during this maturation process. But these interactions can go awry—in fact, only 1% of follicles reach the ovulation stage.

When the follicle does survive, the egg is released via ovulation—a process that requires it to physically rupture the surface of the ovary. "This is a very inflammatory process," says Chung. Ovulation occurs hundreds of times throughout a woman's lifetime, which over time leads to a buildup of cellular debris and chronic inflammation in the ovary.

After the egg is released, the remaining follicular cells that supported its growth take on a second life and become a transient structure called the corpus luteum. This is the structure that produces most of a woman's progesterone. "This change is also highly dynamic," says Chung, as a variety of cells together infiltrate the ovary. "All these coordinated changes are occurring in a tiny organ all at once."

At any given moment, the entire ovarian structure is undergoing change. Immune cells come and go to clear old structures. But like the rest of the body, the ovary is not a perfect machine. During each cycle, minor accidents occur that can contribute to inflammatory and fibrotic processes within the organ. "It's a miracle that our [ovarian] tissues are able to achieve hundreds of remodelings to begin with," says Chung. "Aging is highlighting all the ways that these processes can break."

As a systems and computational biologist, Chung believes that the numerous coordinated changes that occur repeatedly make the ovary a fascinating model system. Her new lab uses spatial transcriptomics and advanced computational methods to study ovarian tissue, and their early findings are already revealing new insights into the aging process.

For instance, through a collaboration with the Broad Institute of MIT and Harvard, where she trained as a postdoc, and the Buck Institute for Research on Aging in Novato, California, Chung and her team have learned that there are actually two types of corpora lutea—one that makes progesterone and another that breaks it down. "The ratio of these two types of corpora lutea, we suspect, is key to regulating how we might have spikes in progesterone levels versus a decay across a cycle," says Chung.

In older mice, the researchers found, the ratio of these two types of corpora lutea begins to change, which could hinder the regulation of progesterone production. Furthermore, as in other organ systems affected by aging, there is an extensive accumulation of immune cells in the aged ovary that have inflammatory functions. Understanding how and why immune cells linger in the ovary could uncover general principles of inflammaging (chronic, low-grade inflammation related to aging).

Ovaries are like the canary in the coal mine for general aging. Hormones have a protective effect on a woman's health. After menopause, women experience increased rates of cardiovascular disease, osteoporosis, and Alzheimer's disease. Researchers believe that the decline of the ovary's endocrine function triggers physiological changes in the body that accelerate the aging process. Among Chung's goals is to determine whether scientists can reverse or slow the loss of endocrine function in the ovary, which in turn could boost women's overall health. "We have big plans in the pipeline," she says. "We're taking it one small step at a time." */yale medicine magazine*

Living longer, living better

A roundtable conversation among experts on how we might reverse outdated beliefs about aging

BY JILL MAX
ILLUSTRATION BY MAIRA KALMAN

AFTER A DIP attributed to the COVID-19 pandemic, the average life expectancy in the United States has inched back up to 77.5 years. This is roughly three decades longer than the average lifespan at the beginning of the 20th century, before Americans benefited from a series of life-extending advances in medicine and public health.

Simply living longer, however, is not the ultimate goal for everyone—especially if it means enduring poor health, mobility issues, and other functional challenges. Fortunately, science offers new ways that may help people have a better chance than ever before to bypass such age-related impediments.

For insights on how society views older adults and ways to lead healthier, fuller lives as we age, *Yale Medicine Magazine* spoke with Thomas Gill, MD, Humana Foundation Professor of Medicine (Geriatrics) and professor of epidemiology (chronic diseases) and of investigative medicine, and director of the Yale Program on Aging; Becca Levy, PhD, professor of public health (social and behavioral sciences) and psychology; and Mary Tinetti, MD, Gladys Phillips Crofoot Professor of Medicine (Geriatrics).


Thomas Gill


Becca Levy


Mary Tinetti

Is disability inevitable as we age?

THOMAS GILL Older persons may develop significant functional limitations or disability at some point, usually in the setting of an illness or injury, but in most cases they'll recover. The likelihood of developing disability generally increases with age, and it's more common shortly prior to death. However, I wouldn't necessarily consider it an inevitable part of the aging process.

What are some strategies that can help prevent the onset and progression of disability and functional decline in older people?

TG There's compelling evidence for the value of physical activity. Several years ago, Yale was one of eight sites for the LIFE [Lifestyle Interventions and Independence for Elders] study, which was a multicenter clinical trial that evaluated whether a structured physical activity program could prevent the onset of major mobility disability, which is defined as the inability to walk a quarter mile. In a rigorously designed clinical trial, persons who were randomized to the structured physical activity program versus an educational intervention had substantially lower rates of major mobility disability. There are countless numbers of epidemiological studies demonstrating that older persons who are physically active experience benefits in cognition and physical function, reductions in hospitalizations, and a myriad of other positive outcomes.

MARY TINETTI This topic is closely related to early research that I was involved in when I was a fellow and new geriatric researcher in the 1980s. At that time, almost no work had been done on falls, because it was considered an inevitable part of aging. We started looking at whether we could predict who was likely to fall, and if we could identify the factors that put people at fall risk. We identified that every year about one out of three older adults fall, and about one out of 10 suffer a serious injury, such as a head injury or a hip fracture.

We found that the factors that put people at risk for falling include not only all the sensory changes that happen with age, but also conditions in the brain, the musculoskeletal system, and the cardiovascular system that increase with aging, and, very importantly, medications. Even more importantly, it's the chronic burden of medications that increases risk. And, finally, another factor is the activity that people are doing. Most of us will fall when we ski, many of us will fall when we walk on ice, but a much smaller percentage fall when they're doing their usual daily activities. We found that as you increase the number of risk factors, the likelihood of falling with usual activities will increase.

In our second set of studies, we found that if you intervene on as many of those factors as you can, through medication reduction, exercise, and making the environment safer, you could decrease the risk of falling. Then we went on to show that you could embed this understanding in the community so that fall prevention could be included in the care of older adults. We showed that you could decrease the likelihood of an older adult having to go to the emergency department or be admitted to the hospital because of a fall by about 10%. That doesn't sound like a lot, but in public health, 10% is an important change.

Another observation was that it's not just the physical effect of falls, it's the psychological effect. We identified how confident people felt in their ability to do their daily activities without a fall. The more confident they were, the less likely they were to fall during a usual daily activity. So when we talk about fall prevention, we also talk about decreasing the fear that occurs as a result of anxiety about falling.

The word "inevitable" is often used in discussions about aging, which speaks to our perception on aging and how we tend to pathologize it. What has your research shown about the ways that negative and positive age stereotypes affect the health of older people?

BECCA LEVY Our research has shown that when we take in negative age stereotypes that are generated by our culture—for example, from social media and advertisements—they can harm our cognitive, physical, and mental health in later life. We've also found that when we take in positive messages about aging, they can have a beneficial impact on those same health outcomes. Among the affected outcomes are cardiovascular incidents, Alzheimer's disease biomarkers, memory performance, stress levels, and longevity. These findings have been replicated by researchers in a number of different countries.

In your book *Breaking the Age Code*, you discuss the ramifications of ageism. How does ageism affect our society?

BL Ageism is one of the most pernicious, far-reaching, and accepted forms of discrimination that exists, and it can impact many different domains, such as education, the workforce, and health care. In the workplace, ageism can impact the hiring of older people and the opportunities for training they're given. Also, the firing of people often happens based on older age. There was a recent survey that found that 64% of older

Americans report experiencing ageism in the workplace, and among those, 90% report that it's common.

There's also a lot of evidence that ageism can operate in health care. A survey found that one out of five older people report experiencing ageism in health care interactions. We also know that there's a tendency for clinical trials to exclude people over a certain age, so it's difficult to know whether those treatments can improve the health of older people and how to best improve their health with those treatments.

Is ageism the reason behind the lack of diversity in clinical research?

TG I think there's strong evidence that older persons are underrepresented in clinical trials. Drugs are typically tested in middle-aged or young older persons, but then they're prescribed to persons who are much older, without strong evidence of benefit. It's a bit more challenging to enroll the older segment of the population in many clinical trials for a variety of reasons. They often have other chronic conditions, which may be exclusion criteria for trials. Those exclusion criteria may not be justified, but the pharmaceutical industry is typically trying to reduce the noise [factors that could skew the results] so they can isolate an effect of their agent of interest. That's a bit more challenging in older persons, but the flip side is that older persons often have the most to gain from the treatments that are available, because they have higher rates of developing the outcomes that these agents are designed to prevent or slow.

How can we dismantle ageism both as individuals and as a society?

BL Unfortunately, ageism operates in many sectors of our society, but we can dismantle it in each of these. I can give you examples for two domains: health care and the workplace. In health care, we could improve education so that all health care providers are trained in how to care for a diversity of older patients and are trained [in] how to avoid ageism in interactions. We could also think about places to intervene so health care providers could assess and screen for age beliefs and exposure to ageism, and then prescribe ways to overcome it when they interact with patients. In the workplace, one of the places that we could intervene on a structural level is diversity, equity, and inclusion programs. Most of them don't include overcoming ageism or age inclusivity as diversity goals. There was one survey showing that in 77 countries, only 8% of workplaces included age as a diversity inclusion category in these programs.

The ideal is to eliminate ageism so individuals do not encounter it, but until that happens it's important to strengthen our tools to resist it on an individual level, too. For the book, I developed a set of exercises based on my research that can help people of any age think about how to challenge ageism. It's called the ABC Method. The "A" is for increasing awareness of ageism, because we know that ageism often operates without our awareness. The "B" is for placing blame where blame is due by helping people recognize that ageism can be an upstream factor that impacts health rather than blaming age itself for a problem. The "C" is to challenge ageism on a structural and personal level; think about ways to flip it around, so some of those negative age beliefs become positive age beliefs.

Overcoming ageism is clearly important to providing better health care to older adults. What other steps can we take?

MT Older adults accumulate multiple chronic conditions, and their life circumstances change. Until now, health care has been predicated on managing individual diseases as silos. For some people, if you have one or two conditions and you don't have any functional limitations, that works quite well. The more functional impairments and chronic conditions you accumulate, the less evidence there is of the benefit of each individual intervention.

Older adults say that taking care of their multiple conditions is often more burdensome than the conditions themselves. And when you start accumulating all those conditions, what you want out of your health care varies. I might want to live for as long as possible even if I'm less functional; for somebody else, maybe function is most important. So it made sense to us that we should identify what people's priorities are in the face of all this uncertainty and complexity, and see if we can align care better with each individual's priorities in a way that's feasible in our fast-paced, ever-changing health care environment.

To address this issue, we spent about a year meeting with older adults, care partners, and health professionals of every type, and developed Patient Priorities Care to identify people's priorities using SMART (specific, measurable, actionable, realistic, and time-bound) goals to inform clinical decision-making. This takes decision-making from one disease at a time and raises it up to achieving each individual person's goal. Let's say the most important thing for me, given all my health conditions, is to be able to walk a mile a day so

that I can go to my favorite market. I know my heart disease and arthritis might be contributing to my ability to do it, but the fact that my neighborhood is unsafe also contributes. As a health professional, I'm going to consider how what I have to contribute is either going to help or not help achieve the goal, and every member of the health care team does that.

It sounds as if we need an age-friendly health care system.

MT Several years ago, I was part of a national effort to identify all the clinical models that had looked at the care of older adults to determine which seemed to have better functional outcomes, less unnecessary health care utilization, and improved quality of life. From this work, we developed this concept of the Four Ms. The first "M" is to ask about and act on what matters most to each individual. The second "M" is medications, because although older adults are underrepresented in the trials, they're overwhelmingly the major users of those medications. The third "M" is mobility, which is really a marker for function. For older adults, people of all ages, what matters most to them is their function. But we don't measure function. We have a $3 trillion health care system that doesn't ask what matters most to people in a systematic way. The fourth "M" is for mentation, which includes cognition and mood in all settings. There are now over 2,500 health care systems that are moving toward an age-friendly designation by the John A. Hartford Foundation and the Institute for Healthcare Improvement. Getting back to the ABCs [that Professor Levy mentioned], I think the age-friendly health system has at least done the "A" that involves increasing the awareness of what needs to be done.

There's been a lot of focus on the biology, including the genetics, of Alzheimer's disease and dementia. What has your research uncovered about the relationship between genetics and positive versus negative beliefs about aging?

BL In our research, we previously had shown that positive age beliefs can improve cognitive performance in older persons. I was interested in knowing whether we could extend this to people who have been born with the risky gene for dementia, APOE4. About a quarter of us are born with the APOE4 gene, but only about half of the people born with it develop dementia. We found that older persons who have the risky gene but who assimilated positive age beliefs from their culture were 49% less likely to develop dementia than those who had taken in negative age beliefs. In fact, their risk was as low as people who were not born with APOE4.

Geroscience, which examines the biology of aging and age-related disease, is a relatively new field. What have we learned so far?

TG Several years ago, a set of investigators led by the National Institute on Aging identified what they considered to be the hallmarks of aging, which include (among others) mitochondrial function, metabolism, inflammation—a lot of different factors that have been shown, particularly in animal models and increasingly in human studies, to accelerate the aging process. A fundamental tenet of geroscience is that we're not going to be able to improve health span, which means keeping people living healthier longer, unless we address the fundamental biological processes of aging. If you take a traditional disease-specific approach and you eliminate heart disease, for example, lifespan and health span will increase only modestly. The reason is that the person will die from another common condition, such as cancer. Even if you eliminate heart disease and cancer, you will have only an incremental improvement in both life expectancy and health span, because other chronic conditions will rise to the top.

There have been studies in model systems and animals showing that if you can delay or slow the biological aging process, which underlies many chronic conditions, you could have substantial improvements in health span. So a lot of work is underway to flesh out these hallmarks or mechanisms of aging with the goal of identifying specific targets for new pharmacologic interventions. The trials that have been completed or are underway in humans are early stage. Because bringing a new drug to market takes many years, there's a lot of interest in repurposing medications that are already approved for other conditions. Geroscience represents a paradigm shift from a disease-specific approach to a more biologically oriented approach to slow aging and ultimately increase health span. *Yale medicine magazine*

The aging brain

Progress in Alzheimer's disease and more advances on the horizon

BY RACHEL TOMPA, PHD
ILLUSTRATION BY MAIRA KALMAN

IT IS PERHAPS one of the greatest ironies of aging that once we reach the point in life when our memories tend to give us the most pleasure, our ability to preserve new ones can start to falter. All parts of our brains are subject to the ravages of time, but there are unique aspects of the regions responsible for memory and other higher-order cognitive functions that make them particularly vulnerable to aging.

Memory failures and difficulty with complicated brain processing tasks are common in older adults, even though many other brain functions typically remain intact well into our 80s and beyond. For example, we are more likely to forget where we put the car keys than to lose the ability to use our hands to pick up the keys.

The neurons and brain regions responsible for memory are typically the first to falter in people with Alzheimer's disease, a progressive neurodegenerative disease that is the most common form of dementia and the fifth-leading cause of death among those 65 and older in the United States. Although Alzheimer's disease is distinct from normal age-related memory loss, many of the same biological processes occur in both.

Researchers at Yale School of Medicine are deepening the understanding of the aging brain's biology, making headway into new therapies for Alzheimer's disease, and improving the efficacy of existing therapies. They're also learning more about ways to protect the blood vessels that supply the brain with precious oxygen and nutrients—vessels whose age-related damage can lead to strokes, brain hemorrhage, or even dementia itself.

A year ago, lecanemab (Leqembi®) became the first-ever disease-modifying treatment for Alzheimer's disease to receive full approval by the Food and Drug Administration (FDA). Following on the heels of many failed Alzheimer's drugs, the success of this monoclonal antibody may have been overlooked by many observers, but it represents a big step forward for the field and for patients, said Christopher van Dyck, MD, Elizabeth Mears and House Jameson Professor of Psychiatry and of Neurology and Neuroscience, and director of Yale's Alzheimer's Disease Research Unit and the Yale Alzheimer's Disease Research Center. "This comes on the end of decades of trying, so it is a huge moment in our field," van Dyck said. "It is also the beginning of a new era. We'll see still better drugs along the way."

THE FIRST SUCCESSFUL ANTI-AMYLOID THERAPY

Van Dyck led the publication of a large clinical trial showing that lecanemab slows cognitive decline in patients with symptoms of early Alzheimer's disease—the first such clinical success for any Alzheimer's drug. Other drugs previously approved for Alzheimer's can ameliorate cognitive symptoms to some extent but don't touch the disease's underlying neurodegenerative progression. The clinical trial of lecanemab ultimately led to the drug's approval. Although lecanemab's effect could be called modest—it slows cognitive decline by 27%—ongoing unpublished analyses of the original trial and its extension phase suggest that its effect is more pronounced for people with lower levels of brain pathology who take the drug at the earliest points in their disease. Researchers hope that addressing the disease as early as possible might slow its progression even more dramatically.

The hallmarks of Alzheimer's disease are the accumulation of what are known as amyloid plaques—sticky clumps of a protein called amyloid beta that form between neurons in the brain—and phosphorylated tau, a modified version of the tau protein that piles up in misfolded tangles inside the neurons. Lecanemab is an antibody that targets specific forms of amyloid, reducing their levels in the brain. A number of previous experimental therapeutics also targeted

amyloid but failed to alleviate patients' symptoms or slow the progression of the disease. Lecanemab's success appears to relate to the targeting of aggregated forms of amyloid. Many previous anti-amyloid therapies simply targeted monomers (single molecules) but not the more neurotoxic oligomers or "protofibrils."

"It was simply wonderful," van Dyck said when describing how it felt to see the approval of lecanemab after many decades working on Alzheimer's drug development. "When you think about what preceded this, we had some really dark decades with no tangible new developments." Further progress came on July 2, 2024, when the FDA also approved the amyloid-targeting drug donanemab (Kisunla®) for early Alzheimer's disease.

Van Dyck and his team are also engaged in another nationwide clinical trial, the AHEAD study, to test whether lecanemab may delay or prevent the onset of Alzheimer's disease in people who have yet to show symptoms. Alzheimer's is a disease of old age in part because it takes years, if not decades, for evidence of the accumulation of amyloid and other dysfunctional proteins in the brain to manifest outwardly. The AHEAD trial, which recently completed enrollment, uses blood tests and PET scans to look for the presence of amyloid in healthy older volunteers. Those who show elevated levels of amyloid are randomized to receive lecanemab or a placebo, and followed for four years to see whether their cognitive decline and amyloid accumulation in their brains are slowed.

If the AHEAD trial is successful, it could herald a new paradigm in Alzheimer's disease treatment, van Dyck said. Blood tests that indicate the presence of Alzheimer's-associated proteins have improved dramatically in recent years. One could imagine a point in the not-too-distant future when these blood tests are part of a routine physical once people reach a certain age. Lecanemab or other potentially preventive treatments could then be prescribed if those blood tests or brain imaging reveals early preclinical signs of Alzheimer's disease. The researchers hope that if the disease is caught early enough, anti-amyloid treatments or other therapies could slow decline to the point that patients could live most of their remaining years without experiencing debilitating cognitive symptoms.

THE SPECIAL ROLE OF CALCIUM

Accumulating amyloid plaques and tau tangles are key characteristics of Alzheimer's, but there are many other molecular and cellular changes that occur in the disease—some of which precede protein accumulation. Amy Arnsten, PhD, Albert E. Kent Professor of Neuroscience and professor of psychology, studies some of these changes to better understand why aging and Alzheimer's affect memory more than other brain functions.

Amy Arnsten, PhD //

"You need high levels of calcium for memory, but if it's not tightly regulated, levels can become too high and initiate toxic actions."

She's found that many age-related changes that happen in memory neurons are due to the dysregulation of calcium in the brain—a dysfunction that is even worse in Alzheimer's disease. Our neurons communicate by changing their internal calcium concentrations, but if these levels are out of balance, problems can arise. "You need high levels of calcium for memory, but if it's not tightly regulated, levels can become too high and initiate toxic actions," Arnsten said. "You can get abnormal mitochondria, which we need for energy. You lose connections between neurons, and you also see the beginnings of Alzheimer's-like pathology."

Although all neurons rely on calcium, an important dietary mineral, the neurons that represent our memories and perform higher cognitive functions are more vulnerable to calcium dysfunction. These neurons have an especially difficult task: they must keep firing even though they are not excited by stimulation from the outside world—meaning that they must maintain

a higher level of activity than other kinds of neurons. All that activity requires a lot of calcium, but if the calcium is not tightly controlled, things can go wrong. Aging, stress, traumatic brain injury, and inflammation can all erode the mechanisms that keep calcium under control in a healthy young brain.

Arnsten and her team have found that in older rhesus monkeys who, like humans, naturally develop cognitive deficits with age, calcium dysfunction spurs the accumulation of phosphorylated tau, another hallmark of Alzheimer's disease. The researchers showed that inhibiting inflammation with an experimental drug to restore calcium regulation improved the aged animals' cognitive functioning and can reduce the levels of phosphorylated tau, suggesting a strategy for early protection of the aging human brain.

PROTECTING NEURONS FROM AMYLOID

Despite lecanemab's success, researchers like van Dyck and Arnsten are hoping for more dramatic results from drugs that target other disease-related proteins.

Christopher Pittenger, MD, PhD //

"The impact of the world around us on our bodies and our brains isn't something that starts at age 65."

Ongoing studies are testing antibodies against tau, and it's possible that a combination therapy against both tau and amyloid could prove even more effective than targeting either alone, van Dyck said.

Stephen Strittmatter, MD, PhD, chair of neuroscience, Vincent Coates Professor of Neurology, professor of neuroscience, and a director of the Yale Alzheimer's Disease Research Center, is working on ways to directly protect neurons from Alzheimer's damages.

When amyloid plaques form between neurons, they trigger a cascade that ultimately leads to Alzheimer's broader effects. Immune reactions to the aberrant plaques prompt microglia, the brain's immune cells, to rush to the affected neurons. Microglia then remove damaged synapses, the specialized connections between neurons. But in Alzheimer's disease, their pruning is perhaps overzealous, leading to widespread synapse loss. In addition, amyloid plaques directly damage neurons, leading to even more lost synapses. It is the loss of these connections that manifests in Alzheimer's early clinical stages before the disease progresses to cause neuronal death.

Strittmatter and his team have discovered in mouse studies that two neuronal proteins, known as the prion protein and the mGluR5 receptor, are responsible for the loss of synapses associated with Alzheimer's disease. Blocking the activity of either of these proteins prevented Alzheimer's-like symptoms in mice engineered to mimic the human disease. In collaboration with Strittmatter, Adam Mecca, MD, PhD, associate professor of psychiatry and associate director of the Alzheimer's Disease Research Unit, is now leading a clinical trial to test an experimental drug that blocks the mGluR5 receptor's activity in healthy study volunteers and in those with Alzheimer's disease.

Though it is difficult, to the point of impracticality, to remove all the amyloid from the brain, said Strittmatter, "what really matters is protecting neurons from the amyloid plaques. If we can block these receptors at the synapse … you can have a brain with a lot of amyloid in it, but it doesn't have the synaptic derangements—and therefore symptoms are relieved, at least in animal models."

Strittmatter also co-leads the newly established Carol and Gene Ludwig Program for the Study of Neuroimmune Interactions in Dementia. Recognizing the importance of the immune system in healthy brain function and disease, this program focuses on bridging a gap between neuroscience and immunology research. The program's goal is to better understand how brain

cells and immune cells interact, and how those interactions go awry in Alzheimer's disease and other forms of dementia. Ultimately, researchers hope to identify new drug targets by studying these interactions.

BLOOD AND THE BRAIN

But it's not just brain cells that influence brain aging and disease. Our circulatory system also plays a vital role in keeping our brains healthy as we age. In fact, similar forms of the protein that triggers Alzheimer's disease—amyloid beta—can also build up inside blood vessels that supply the brain in older adults. Known as cerebral amyloid angiopathy, this phenomenon often accompanies Alzheimer's and leads to vessel damage that can, in turn, cause strokes or brain hemorrhage. Lifestyle and other risk factors, including smoking, high blood pressure, poor sleep or diet, and high cholesterol, can further contribute to blood vessel disease over time.

"Stroke is one consequence of having poor cerebrovascular health," said Kevin Sheth, MD, professor of neurology and neurosurgery, and a director of the Yale Center for Brain & Mind Health. "But when the vascular system goes awry, there are many other brain aging consequences." Those other consequences include such chronic disorders as cognitive decline, dementia, and depression. The good news is that, if caught early, vascular dysfunction can often be corrected with lifestyle modifications or medication.

Sheth led the development and deployment of a portable MRI machine that could be used to find signs of poor cerebrovascular health in hospital patients or even in individuals in community clinics before it has dire effects. The imaging method looks for reduced brain volume and a phenomenon known as white matter hyperintensities—brain matter lesions that often don't cause symptoms but signal a higher risk of Alzheimer's disease and stroke. Sheth and his colleagues found that in people with high blood pressure, more than 50% have white matter hyperintensities. Treating the underlying hypertension could go a long way toward improving brain health in this population, Sheth said.

The Yale scientists are hoping to use that technology in a not-yet-started trial to test lecanemab in patients with early stages of Alzheimer's who are also at high risk of vascular complications—a population that was excluded from the drug's initial trial. These patients can be difficult to treat, especially because one of the potential side effects of lecanemab is brain swelling and hemorrhage. But the researchers hope that the drug's benefits may outweigh the risk even in this more vulnerable group.

Sheth is also co-leading another trial of people with atrial fibrillation who've had a previous brain hemorrhage. Both of these conditions are more common in older adults, and atrial fibrillation is a risk factor for future strokes. Standard treatment for people with atrial fibrillation is to start an anticoagulant medication to prevent stroke, but it's not known whether these medications are safe for those with a history of hemorrhage. Through the ASPIRE trial, Yale researchers are asking whether the anticoagulant apixaban (Eliquis®) can prevent stroke in this population compared to daily low doses of aspirin.

BRAIN AGING IS LIFELONG

There are many other aspects of human lives that inform brain health in older age. Complicating matters, there have been few studies of how neurodiversity and psychiatric disorders affect age-related brain diseases. It is known that Down syndrome increases the risk of Alzheimer's disease, and that early-onset dementia is more common among adults with autism, but it's not clear what underlies these differences or how aging intersects with other forms of neurodiversity.

Insults to our brain and body during all stages of life can affect brain aging. Traumatic brain injuries, type 2 diabetes, chronic stress, and depression are all linked to Alzheimer's and other forms of dementia. Like Alzheimer's, depression and chronic stress cause loss of connections between neurons, said Christopher Pittenger, MD, PhD, Elizabeth Mears and House Jameson Professor of Psychiatry and a director of the Center for Brain & Mind Health. Antidepressants and exercise have been shown to enhance those connections—potentially explaining why exercise offers such potent protection against Alzheimer's disease.

Understanding how our entire lives impact the way we age is both daunting and empowering, Pittenger said. "The impact of the world around us on our bodies and our brains isn't something that starts at age 65," he said. "Cognitive decline may happen at the end of life, but it's the tail end of lifelong processes. That's depressing because we all want to preserve the fantasy of immortality for as long as we can. But it's encouraging because it means we can intervene in ways that can have profound benefits decades down the line." */yale medicine magazine*

Yale Ventures opens doors to entrepreneurship

BY DAVID FREEMAN

Pairing bench science with venture capital

WHEN YALE SCIENTISTS FOUND a monoclonal antibody that can temporarily disable the blood-brain barrier, they knew they were onto something big. A network of tightly packed cells in blood vessels and tissue, the barrier prevents toxins and pathogens from entering the brain—but also blocks the entry of therapeutic drugs. Anne Eichmann, PhD, Ensign Professor of Medicine (Cardiovascular Medicine) and professor of cellular and molecular physiology at Yale School of Medicine (YSM) and the leader of the team that made the discovery, saw the antibody as a potential drug delivery tool—one that might make the brain more accessible to drugs and thereby revolutionize the treatment of brain tumors and infections, Alzheimer's disease, depression, and other brain disorders.

Eichmann was eager to patent the antibody and develop its commercial potential. But as a basic scientist, she knew she needed help with the nuts and bolts of starting a company. She reached out to the robust technology transfer team that in 2022 became part of Yale Ventures, a newly launched initiative designed to provide faculty and student innovators with legal assistance, market research, financial analysis, and access to lab space—in addition to mentoring and cash awards. The new initiative can even help researchers connect with venture capitalists and assemble the teams needed to form successful startup companies.

"Yale Ventures makes the transition from bench science into entrepreneurial life really easy for all parties involved," said Eichmann, who was able to secure two patents and was awarded $400,000 in seed money to advance her enterprise. "They guide you through all these different steps and accompany you along the way … they're rendering a huge service to basically the world because scientists get their things out into the medical field and doctors get access to new medicine."

Eichmann now heads up the New Haven-based startup D2B3 (D squared representing "drug delivery," and B cubed representing the "blood brain barrier"), which is conducting animal experiments to gauge the safety and effectiveness of the antibody while seeking additional funding from venture capitalists. A clinical trial of the

antibody, which would be delivered intravenously, might begin within the next two years, she said.

Supercharging support for promising ventures

Yale has been patenting and licensing intellectual property developed at the university since 1980, when passage of the University and Small Business Patent Procedures Act (also known as the Bayh-Dole Act) allowed universities to claim ownership of inventions supported by federally funded research. But Yale Ventures, which consolidated the university's Office of Cooperative Research and other innovation and entrepreneurship programs at the university under a single umbrella, supercharged Yale's support of technology transfer.

"The university decided that it really wanted to increase its focus and support for Yale innovation and the people who are looking to translate our research discoveries and ideas into new ventures and into corporate partnerships to see those technologies developed into new products," said Josh Geballe, senior associate provost for entrepreneurship and innovation at Yale and the managing director of Yale Ventures.

Yale Ventures has "a number of programs that support faculty who are seeking to build a startup company to develop their research discoveries," Geballe said. "The one that is most central to serving faculty at the Yale School of Medicine is the Blavatnik Fund for Innovation at Yale," which provides awards of up to $300,000—and sometimes more—for promising ventures.

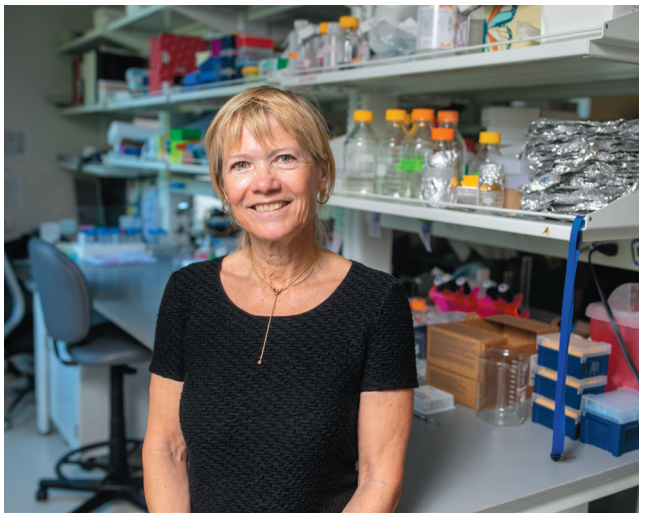
Geballe sees Yale Ventures not just as a mechanism for facilitating innovation and technology transfer, but also as a powerful tool for recruiting and retaining talented faculty members and students. "There are many students today who aspire to careers in entrepreneurship or in early-stage disruptive companies," he said. "And to be attractive to them, it's important that we have programs that they seek out as well."

Fueling New Haven's economy

Yale Ventures is also seen as a big win for the broader community.

"From an economic development perspective, these companies import hundreds of millions of dollars in investment capital," Geballe said of the dozens of businesses the initiative has fostered and which operate in and around New Haven. "That capital goes back into the economy. It creates jobs. It creates tax income for the state. It's good for our host city, and it fuels economic development around our campus."

It's also helpful if the startup companies can be close to their founding scientists at Yale, he said, so that principal investigators "can walk across the street on their lunch break and spend time with their startup company. It increases the chances that the company will be successful, particularly in those early years when they're still trying to advance the early science and get into the clinic." With a staff now totaling 60—up from 42 at the time of its launch—Yale Ventures operates out of multiple offices on campus. As of September, it will be headquartered at 101 College Street, a 10-story $300 million state-of-the-art life sciences building completed in late 2023.



Anne Eichmann worked with Yale Ventures after her research team discovered a monoclonal antibody with potential as a drug delivery tool.

Yale Ventures aids faculty and students across the university—including those in the School of Engineering and Applied Science, the School of the Environment, and the Faculty of Arts and Sciences. But most of its work involves members of the YSM community. "There's a lot of potential at Yale, especially in the life sciences," said Stephen Knight, MD, president and senior managing partner of F-Prime Capital, an investment firm with offices in Cambridge, Massachusetts, San Francisco, and London. "Yale has a great opportunity to both bring its wonderful discoveries faster to market, faster to patients ... and

ANTHONY DECARLO PHOTO

to do it within the New Haven ecosystem rather than exporting it to Boston or the San Francisco Bay area," both of which are centers of biotech entrepreneurship. A 1990 graduate of Yale School of Medicine and the Yale School of Management, Knight joined the Yale Ventures board of advisors in March 2024. F-Prime Capital has invested in several Yale startups, including RIGImmune, which aims to develop a new class of therapies for viral infections and cancer, and Rallybio, which is pursuing clinical trials of new treatments for rare diseases.

'Perfect bridge and incubator'

Other entrepreneurially minded Yale researchers who have received critical help from Yale Ventures and its predecessor initiatives include Sidi Chen, PhD, associate professor of genetics and of neurosurgery; and Rohan Khera, MD, assistant professor of medicine (cardiovascular medicine) and of biostatistics (health informatics). Khera is the director of the Cardiovascular Data Science Lab (CarDS) at YSM, which he says is one of the few programs in the country that is developing artificial intelligence for cardiovascular-specific applications.

With help from the university, Chen has launched several companies in recent years that are pursuing new treatments for cancer. Among them are EvolveImmune Therapeutics, launched in 2019 and based in Branford, Connecticut; and Cellinfinity Bio, launched in 2021, with operations in New Haven and San Francisco. He praised the Yale Ventures team for assisting with so many different aspects of the startup process, going far beyond protecting intellectual property and helping arrange licensing agreements.

"They won't start a company for you," Chen said. "You have to start it yourself. But they are well connected … they can help introduce you to investors and improve your pitches, which are used to raise funding. And they can help you find people who are the industry fit for starting companies, which is very different from doing research or clinical activities in the Yale School of Medicine."

Chen called Yale Ventures "the perfect bridge and incubator" for taking potential new therapies from the lab to the marketplace. He said he made new connections at the Yale Ventures Innovation Summit held at the university in late May. Now in its 10th year, the annual event brings together researchers, investors, and industry representatives—and this year attracted more than 2,200 attendees. Two hundred sixty researchers gave presentations at the event; 31 were awarded a total of $350,000 from the event's sponsors, which included the Blavatnik Fund.

Khera's startup, Ensight-AI, is developing AI software tools, including one that can perform advanced diagnostics of often-undetected heart problems. It does this by using machine learning to analyze photographs of electrocardiograms. Khera said the tool can detect the electrical "signatures" of cardiovascular anomalies that even experienced cardiologists have trouble spotting. These include cardiac amyloidosis, hypertrophic cardiomyopathy, and valvular disorders of the heart.

"It's augmenting human capacity in ways we didn't imagine before," he said of the tool, adding that he hopes it will enable cardiologists to diagnose problems earlier in the course of disease than is now possible—when treatment is likely to be more effective. "I think we'll get these tools to the FDA in the next six months to a year, and then they'll be used in practice," he added.

Working with Yale Ventures is a "very seamless" process, according to Khera, who was awarded $300,000. "They're ready to meet multiple times a week if you want them to," he said. "Different members of the community—they'll make time for us."

Of course, there's no guarantee that startup ventures will succeed or that their backers will make money. "The reality is that at this very early stage," Geballe said, "even the best investors in the world are wrong nine times out of 10." But that may not be much of a deterrent to researchers. "My dream is to make an impact with my research," Eichmann said. "I mean that's every scientist's dream. It's not about the money. It's about doing good."

Among her many accomplishments, Lisa Lattanza performed the first fully in-house 3D surgical procedure at Yale earlier this year.

ROBERT A. LISAK PHOTO

New dimensions of orthopædics

3D surgical planning and other innovations

BY JILL MAX

BEFORE ARRIVING at Yale School of Medicine (YSM), Lisa Lattanza, MD, chair and Ensign Professor of Orthopaedics & Rehabilitation, was already known internationally for performing the world's first elbow transplant in 2016. Earlier this year, she performed the first fully in-house 3D surgical procedure. With these achievements, she follows in the footsteps of, among others, YSM's Kristap Keggi, MD, who pioneered the anterior approach to total hip replacement, and YSM's Michael Baumgaertner, MD, whose identification of the optimal placement of screws for hip fracture repairs has become the international standard.

For more on the latest developments in her department and her vision for the future, *Yale Medicine Magazine* spoke with Lattanza about the convergence of personalized medicine, engineering, and 3D technology to resolve even the most complex cases.

You recently performed the first entirely in-house 3D surgical procedure. Can you explain what differentiates Yale's approach?

There are few academic centers across the country that have the capability of doing all the work in-house, meaning that you plan the operation virtually with an engineer. Then, based on that plan, bone models, guides, jigs [printed pieces that indicate where holes and cuts need to be made]—all the things that are needed in surgery to be able to execute that procedure exactly the way you planned it on the computer—are printed in-house.

Prior to this, we had been using an outside company to do the same types of cases. But the exciting thing about having it within the department is there's so much more we can do. For example, there was a case that David Frumberg, one of our pediatric orthopædists, wanted to do, but the commercial companies wouldn't do it because it required making a cut through the knee joint to correct the deformity. But because we were able to plan that, we could do the surgery.

We don't have as many restrictions on what we're able to do because we're the surgeons and we're the engineers, and we know what the technology can do—and that it's safe. It gives us more control, and it also helps with cost containment. It's much less expensive for us to do this [work] than to purchase these services from an outside vendor, which then makes it accessible to patients. It's an equalizer for access to this type of technology because many insurance companies won't pay for it due to the expense. Because we can do this in-house for about two-thirds of the cost, we can offer it to patients who wouldn't normally be able to access it.

Was developing a 3D surgery program one of your goals when you joined Yale in 2019?

I started doing 3D personalized surgery in 2012 at UCSF [UC San Francisco] and was an early adopter of this approach. I've done more than 500 cases using this technology—more than anyone in the United States and probably more than all but one other person worldwide. I know the power of what it can do. A lot of the cases we do now wouldn't have had a solution prior to the ability to do 3D planning. When I came to Yale, I wanted to make sure that I could continue to do these cases here because some centers don't allow it due to the expense.

But the other part was that I really wanted our department to be at the forefront of the use of 3D personalized surgery for complex deformity correction, congenital problems, post-traumatic problems, difficult arthroplasty cases, and tumor cases. I wanted to put Yale on the map for this. When I got here, I started a 3D task force with some like-minded colleagues in the department. When we got to the point where we had done all that we could do without an engineer on board, we recruited Alyssa Glennon, who was a lead engineer at Materialise, one of the biggest companies in this arena in the United States. She collaborated with us to establish our 3D Collaborative for Medical Innovation (3DC), where all of this happens within the department.

Obviously, this approach isn't applicable to every surgical procedure. How do you decide when to use it?

Many surgeries are very straightforward. But sometimes you have a complex deformity of a bone or joint, or a congenital malformation where the anatomy is difficult to understand in 2D on an X-ray, or even with a CT or an MRI scan. 3D technology comes into play when you think there's a way to correct this condition with an osteotomy [cutting of the bone].

There are other places, too. For example, we're developing a destination program for avascular necrosis [AVN] of the hip with Daniel Wiznia, one of our orthopædic surgeons, and we're printing guides so that he can go right to where the AVN is seen on a CT scan and core out just that area. In the past, we'd

look at the X-ray or the CT scan and hope to get in that same spot; now we can target it very precisely. As we learn what the technology can do, we'll continue to expand its uses.

Hopefully over time, someone with two years of experience will be able to do something just as well as someone with 10 years of experience, because they're using the same kinds of techniques and guides. It makes surgery shorter, decreases blood loss, and we can more accurately correct the deformity. All of these things have been shown with various types of research, [including] some that's happened here at Yale.

3D approaches are bringing personalized medicine to a new level. How is Yale leading efforts to train surgeons in this rapidly developing area?

We started the Master of Science in Personalized Medicine & Applied Engineering program in 2022 with Daniel Wiznia and Steven Tommasini, one of our research scientists. Having worked together since 2012, Alyssa Glennon and I noticed that neither surgeons nor engineers are trained how to do this. It's all learned on the fly. The bottleneck is getting engineers trained well enough that they can help plan a case with a surgeon. You also have to train surgeons to do it because you still have to understand the anatomy and what you're trying to correct. You need to know how it would've been done in the old way—if there was an old way.

In the master's program, we train engineers, computer scientists, medical students, physicians, and dentists, bringing together imaging, engineering, and anatomy. They graduate being able to not only understand how to do these cases, but also how to run the software that allows us to be able to plan and print what we need, in addition to many other skills. We're also changing things constantly to keep up with what we are doing with AR [augmented reality], VR [virtual reality], AI, and 3D printing of cellular components, bone, and cartilage. The program will grow as the technology grows, and it goes hand in hand with the 3DC, which creates 3D patient-specific models and tools. As far as we know, it is the only one of its kind in the world.

In what other areas has Yale expertise advanced the field of orthopædics?

We have a number of specialized programs that allow us to treat complex cases. The hip preservation program is a multidisciplinary program that uses hip arthroscopy, and if necessary, complex osteotomies around the hip—primarily for hip dysplasias, but also for hip problems from trauma. It's really about finding the right operation for the right patient, whether that be an arthroscopic approach or redirecting the hip, which might allow for better weight bearing on the native joint, all the way to joint replacement if none of the procedures short of hip arthroplasty will solve the problem.

Under the direction of David Frumberg, we have a limb-lengthening program, and he's also very adept with the use of techniques for bone transport [to fill bone defects]. For patients who have a bad defect in a long bone from trauma or infection, the techniques Dave [Frumberg] uses allow for healing of those bones in ways that we didn't previously have. The limb lengthening that he does is specialized treatment for children with congenital problems, as well as for adults who have a post-traumatic limb discrepancy.

We have a new foot and ankle surgeon, Arianna Gianakos, who specializes in minimally invasive approaches to ankle pathology. She's doing a type of in-office arthroscopy with nanotechnology that allows her to both diagnose and treat problems around the foot and ankle, sometimes right there in the office. We have a program for multi-ligament knee instability and knee dislocations. We are one of only a few sites in the country doing research in this area, and Michael Medvecky, a YSM orthopædic surgeon who specializes in athletic injuries, has written most of the sentinel articles on how to fix these knees to get the best result possible.

Orthopædic medicine has traditionally suffered from a lack of diversity. What are some

of the initiatives that you've undertaken to include women and other underrepresented groups in orthopædics?

I co-founded a nonprofit organization called the Perry Initiative in 2009 with Jenni Buckley, who's an engineer. It started off as a one-day program for female high school students, exposing them to the careers of orthopædic surgery and engineering [through a hands-on curriculum]. We now have about 17,000 young women who've been through this program. In 2012, we started a similar program for women in medical school. If you look at all medical students, 1% of women match into orthopædic surgery. If you look at the women who have gone through our program, 23% match into orthopædic surgery.

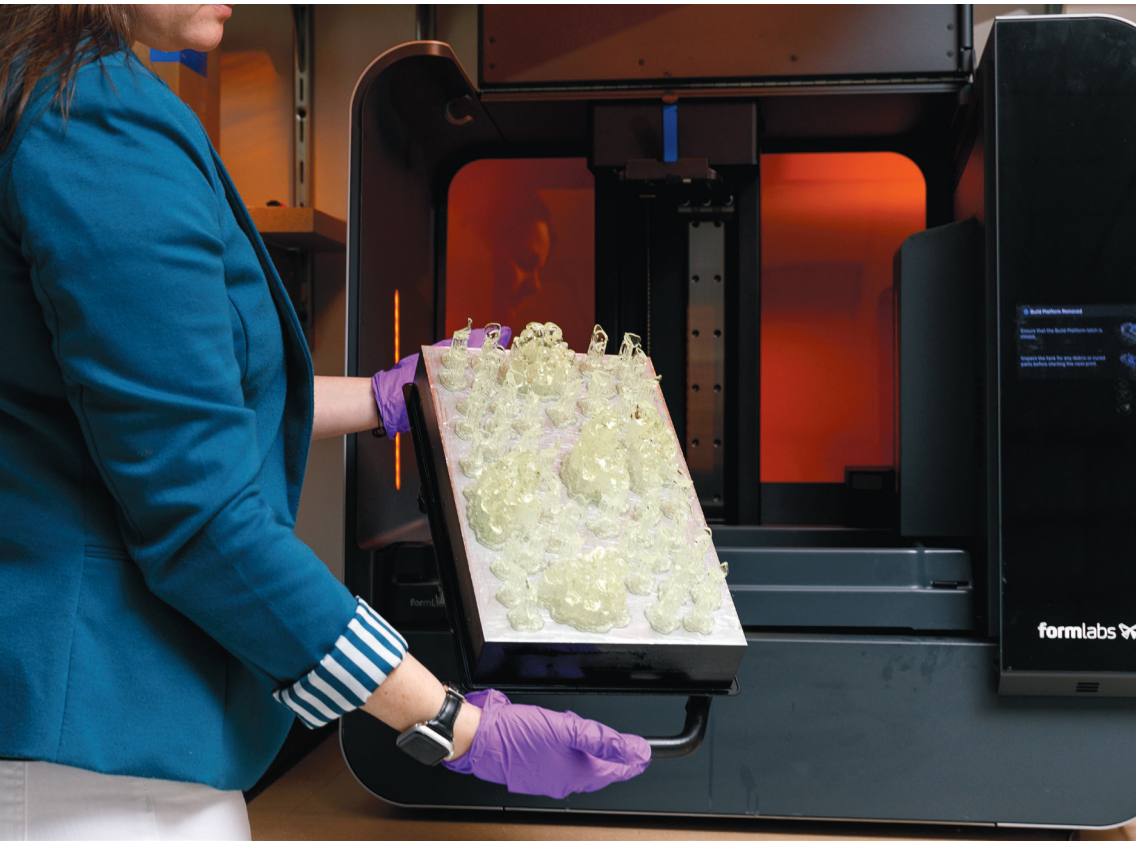
When I came to Yale, we also took a comprehensive look at how we select residents and decided to take a different tactic. We set out to make it a less biased process and use criteria that were part of our new culture and value set. We did away with board scores, and we don't look at school of origin as part of the criteria. Instead, we look at grit and resilience, leadership qualities, work ethic, and what we refer to as distance traveled—meaning ability to overcome obstacles in your life. We now have the most diverse class of residents in the history of Yale and one of the most diverse orthopædic residency cohorts anywhere in the country. We are at almost 40% women and those underrepresented in medicine. We've taken a similar approach to recruiting faculty. We have a diverse search committee that knows that inclusive excellence is part of our culture and values. We actively seek out diverse candidates for open positions.

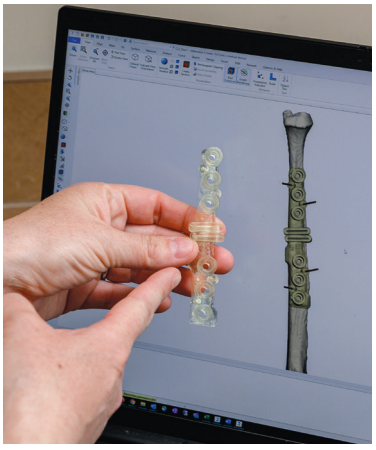
Other than 3D surgical procedures, what's next on the horizon for orthopædics?

We'd love to be able to grow bone and cartilage in the lab in 3D. Can you imagine if we didn't have to do joint replacements anymore because we could now grow cartilage? Eventually, printing in plastic will be a thing of the past because we'll be using augmented reality in the operating room to do the same thing.

BELOW, LEFT Alyssa Glennon, 3D Collaborative for Medical Innovation (3DC) program director and lead engineer, shows several surgical guides after resin drips off the anatomical models during the final stages of 3D printing.

BELOW, RIGHT, TOP AND BOTTOM Glennon shows the final 3D printed surgical guide next to the designed version, which was used intraoperatively by Lisa Lattanza to achieve the optimized virtual plan.





ANTHONY DECARLO PHOTOS

Akiko Iwasaki (left) and Harlan Krumholz are collaborating on a new way to make clinical trial participation more convenient.

ANTHONY DECARLO PHOTO

Decentralized trials bring research into people's homes

BY ISABELLA BACKMAN

APRIL 9, 2024, MARKED CINDY'S* FOURTH ANNIVERSARY of living with Long COVID. It started with severe fatigue that made her feel as if her limbs "weighed a million pounds," followed by shortness of breath and gastrointestinal issues after she became ill with COVID-19 in 2020. A single mom in Texas with a 6-year-old son, she says the disease forced her to get creative: She made up a game in which he rolled a ball around her while she lay still on their trampoline.

Over the years, Cindy's symptoms have ebbed and flowed. She suffered a sharp decline in January 2022—the height of the Omicron wave—when she was hit with her second acute bout of COVID-19. This episode signaled the start of a slow decline that eventually took a toll on her cognitive abilities, hindering her ability to perform her job as an aerospace engineer and eventually forcing her to take a leave of absence in the fall of 2023. At this point, she also began to experience another common Long COVID symptom known as post-exertional malaise (PEM), in which her symptoms significantly worsened after physical or mental activity—sometimes leaving her bedbound for days at a time.

"I was known for thinking outside of the box, being able to juggle things, look to the future, and solve problems. I knew how to put big, complicated puzzles together," Cindy says. "Suddenly, everything seemed so complicated. Living became so hard. I was just trying to survive day by day, if not hour by hour, managing all of my symptoms."

Desperate for answers, Cindy stayed on top of ongoing clinical trials. Last year, she applied for a stem cell therapy trial in Houston but was eliminated as a potential participant during the final screening. On the one hand, she was devastated. "I was absolutely convinced that the therapy was going to be the answer for me," she says. On the other hand, enrolling in the trial would have presented its own challenges. Cindy lives 45 minutes away from Houston and would have needed help getting rides to the city. And she wondered whether she had the capacity to participate in all that the trial required. "From an accessibility standpoint, most clinical trials require you to be there in person for exams, bloodwork, tests, or whatever else they need," she says. "That's just not feasible when you have a limiting condition."

*Not the patient's real name

Then Cindy came across the Yale Paxlovid for Long COVID (PAX LC) Trial, a Phase 2 investigational clinical trial that is exploring whether a 15-day course of Paxlovid (nirmatrelvir/ritonavir), an antiviral that now is prescribed for acute COVID, is beneficial in alleviating Long COVID symptoms. Participating in a clinical trial with a Connecticut-based university would ordinarily have been impossible for Cindy. But the Yale School of Medicine team was prepared to bring the study to patients no matter where they live in the United States.

Harlan Krumholz, MD, SM, Harold H. Hines, Jr. Professor of Medicine (Cardiology) and Professor in the Institute for Social and Policy Studies, is pioneering this new approach for making participation in clinical research as accessible as possible for those whose lives have been upended by the post-acute infection syndrome. Working closely with Akiko Iwasaki, PhD, Sterling Professor of Immunobiology, Krumholz is the principal investigator of the PAX LC Trial.

Removing common barriers

Health limitations, distance, work schedules, family obligations, and financial constraints are all barriers that prevent patients from participating in clinical trials. For those living with Long COVID, debilitating symptoms can make traveling to a study site impossible. To overcome this difficulty, the PAX LC Trial team brought the study to patients' homes throughout the contiguous United States. Participants received the drug or placebo in their mailboxes and filled out electronic diaries. They gave blood and saliva samples at home or at a nearby lab. Krumholz believes that his trial proves that future clinical research which allows patients to participate at their own convenience is not only possible but also more efficient and even more cost-effective than standard clinical trials.

"The PAX LC Trial is a historic contribution to the evolution of a new way of doing trials," says Krumholz. "I'm really proud of what we've been able to accomplish, and I'm hoping it will be a spark for the future."

Researchers currently have several hypotheses regarding the underlying causes of Long COVID, including lingering remnants of the SARS-CoV-2 virus, autoimmune dysfunction, reactivated latent viruses like the Epstein-Barr virus, and tissue damage. These hypotheses are not mutually exclusive, and it is possible that individuals with Long COVID may experience a combination of these mechanisms. Krumholz, Iwasaki, and their team designed the PAX LC Trial to test the persistent viral remnants hypothesis.

Cindy initiated the prescreening process by filling out a survey about any preexisting conditions and syncing her medical records to an app on her phone. Several months later, she received an email inviting her to move forward. The next steps in the prescreening involved a visit to her local medical laboratory to give blood samples, as well as adjusting some of her medications.

Once enrolled, Cindy received her course of either Paxlovid or a placebo by mail. Each night, she answered survey questions about her symptoms from her phone. She also gave blood and saliva samples five times. The PAX LC team sent a technician to her home on three of those occasions. "To be able to have somebody come to your house—that just made life so much easier," she says. For the other two sample collection dates, she went to a nearby laboratory.

Patients aren't the only ones who can benefit from decentralized trials, says Krumholz. For over a decade, he has been an advocate for reforming clinical research, arguing that its current structure stymies innovation. His colleagues in the laboratory are discovering potential avenues to treating diseases at a "dizzying pace," he says. But because standard clinical trials struggle to recruit and keep patients, the researchers have not been able to keep up with the pace of scientific discovery—a problem that prevents new drugs and medical devices from reaching the market. "We're in the midst of a life sciences revolution," says Krumholz. "The central chokepoint is evidence generation—cycle times are too slow, and trials are so expensive that our level of confidence has to be very high or no one will make the investment."

This obstacle exists because

the ability to participate in clinical trials and conform to the schedule they demand is a luxury for many people. Not only does this slow enrollment, but it also contributes to the stark lack of diversity in research. "The current way of doing things is often leaving us in a position where we are having to chase participants and cajole them to stay in the studies that were built for their benefit," says Krumholz. "Imagine how off-putting clinical trials must be when people who have the most to gain are left in the position where they don't want to continue."

The solution, Krumholz proposes, is to create clinical trials modeled on PAX LC that treat participants as partners and accommodate their constraints. PAX LC not only conformed to participants' schedules, but also worked to build a sense of community through running virtual town halls for people with Long COVID so that they could ask questions and stay updated on results as researchers got them. "People don't have any obligation to join trials, so we need to make it so they're something they want to join," he says.

An at-home clinical trial

Ezra*, a freelance cartoonist in Minnesota, began experiencing COVID-19 symptoms in September 2022 and never recovered. At the time, he suffered PEM so severe that exertion as small as microwaving lunch could put him in bed for days. He saw doctor after doctor at his nearby hospital, and when that failed, he decided to try traveling to the Mayo Clinic. "I feel very fortunate that I was able to get somewhere like Mayo a few times, but it is an hour and a half drive from Minneapolis," he says. "It cost my partner gas money and lost time at work."

In Ezra's search for answers, he learned of the PAX LC Trial and decided to enroll. "The effort to bring the trial into people's houses is valiant, especially for a population that is chronically ill," he says. "For disabled people to become a part of clinical trials already requires so much of us—even those of us who have support systems that are able to take care of us."

Other PAX LC Trial participants echo Ezra's sentiments. "Early on [in my illness], there was no way I could have traveled on my own [to a clinical trial]. It would have taken everything out of me," says Kyle*, a Vermont filmmaker who has been living with Long COVID since April 2022. While the launch of the ambitious clinical trial was not without its kinks—Kyle and others say they experienced scheduling delays, such as receiving the drug/placebo or payments late, that prolonged the process—he adds that the PAX LC Trial has opened a window for him that otherwise would have remained closed. "It was nice that the trial tried to make it work for people, understanding that part of our illness is incapacity."

The PAX LC Trial was largely made possible by the Yale Center for Clinical Investigation, with Yashira Henriquez, MSc, the New York-based clinical investigation project manager, playing a central role. Her daily activities included monitoring participants' surveys and checking in on anyone who had reported adverse events. "Since there are no study visits, we texted or called each other all the time," she says. The most common adverse event was dysgeusia, or a metallic taste in the mouth, which has also been a common complaint among patients with acute COVID who have received the drug. "In this type of trial where you never meet someone face-to-face, you need to show even more compassion to make them feel at ease," she explained.

Henriquez had previously worked on studies evaluating treatment for acute COVID-19 infections but wasn't as familiar with Long COVID. Her experience working for the PAX LC Trial has opened her eyes to the acute need for more research in treatments for the chronic condition.

Harlan Krumholz, MD //

> "Our trial is like Kitty Hawk [the 1903 Wright Flyer]; we just needed to show that it could fly."

"I've worked on clinical trials in numerous positions, but this is one where patients are in especially desperate need to find answers," she says. "It's hard to see people who were living a healthy life end up in a state where they're now debilitated and can't even get out of bed."

Most participants Henriquez worked with responded well to the design of the trial, she adds. Their cooperation allowed the study to run smoothly despite many of them being states away. "We didn't have to bother them to do the surveys to get their study visits done," Henriquez says, "because they all wanted to help."

The aid of new technologies

The "record rate" of enrollment speaks to the success of the PAX LC Trial's design. It can take years for clinical trials to finish the enrollment period, but PAX LC finished in under a year. Although PAX LC is a small trial of 100 participants, given its numerous restrictions around eligibility to participate and requirements for collecting blood and saliva specimens for Iwasaki's lab, enrollment would have taken significantly longer without its decentralized format, Krumholz says.

Previously, a trial like this one would not have been feasible. But now, the evolution of new technologies is making the possibility of decentralized trials more accessible than ever. For example, Krumholz recently cofounded Hugo Health, a platform that enables people to transfer their medical records more seamlessly, with their permission, to researchers. "Because of the 21st Century Cures Act [a 2016 law passed to advance medical product innovation], people can get access to their medical records and share them with trusted partners," he says. "Now we don't have to go through a Byzantine set of obstacles through a particular health system to access a patient's medical data—we just need to work in partnership with participants."

Traveling to each participant's home would seem to be a pricey endeavor. But given the greater efficiency of the the PAX LC Trial, Krumholz argues that its design has actually cut down on costs. If it had been run like a standard clinical trial, his team would have had to set up study sites across the country. The associated costs would have been extremely high; in addition, the complexities involved in obtaining the requisite approvals from a multitude of institutional review boards (IRBs) would have significantly slowed the study's progress.

"Despite the fact that our trial is sort of built as a concierge service for each individual patient, it was much less expensive than what we had been doing," Krumholz says. "What I hope will happen is that it will be a competitive disadvantage to not do decentralized trials."

Looking to the future

About a month into the PAX LC Trial, Ezra noticed that his symptoms had dramatically declined. He still doesn't know whether he had taken the drug or the placebo, but "the brain fog is gone, the memory issues are gone, the cognitive problems seem to have pretty much evaporated," he says. He can take a 45-minute walk again and was able to return to work. He is not cured, however. Ezra still has symptoms of postural orthostatic tachycardia syndrome (POTS), a disorder in which standing up triggers such symptoms as rapid heart rate, and he gets winded easily.

Unfortunately, for many people with Long COVID, there won't be a magic pill that restores them to normal. More clinical trials aimed at other possible underlying mechanisms of Long COVID, such as autoimmune dysfunction, will be needed. And these patients, many of whom are struggling to work and provide for their families, don't have years to wait. Decentralized trials could help bring much-needed answers to these individuals more quickly.

And this type of trial doesn't need to be confined to just Long COVID. "I'm confident that the way we set this up can work with almost any population," says Krumholz. He is optimistic that the PAX LC Trial will inspire other researchers to adopt a more participant-centric format for different kinds of research.

"Our trial is like Kitty Hawk [the 1903 Wright Flyer]; we just needed to show that it could fly," he says. "The hope is that soon there will be fleets of planes that adopt this approach."

ANTHONY DECARLO PHOTO

YALE SCHOOL OF MEDICINE AND YALE MEDICINE made their debut on Broadway this summer with a rotating electronic ad displayed on the Nasdaq building in the heart of Times Square.

The digital billboard recognized the medical school and its clinical service as "world leaders" in research and clinical care in neuroscience, cancer, cardiovascular health, inflammation science, metabolic health, genetics, women's health, orthopaedics, children's health, and biomedical engineering. The photos of four members of Yale's medical faculty were chosen to represent the tripartite mission of the Yale School of Medicine, a range of departments, and the school's diverse faculty.

The 15-second message, which rotated through the various specialties, appeared four times each hour, 20 hours per day from July 1 through July 8. An estimated 1.5 million New Yorkers and visitors to Times Square from throughout the world viewed the ad during one of the summer's peak weeks.

—Robert Forman