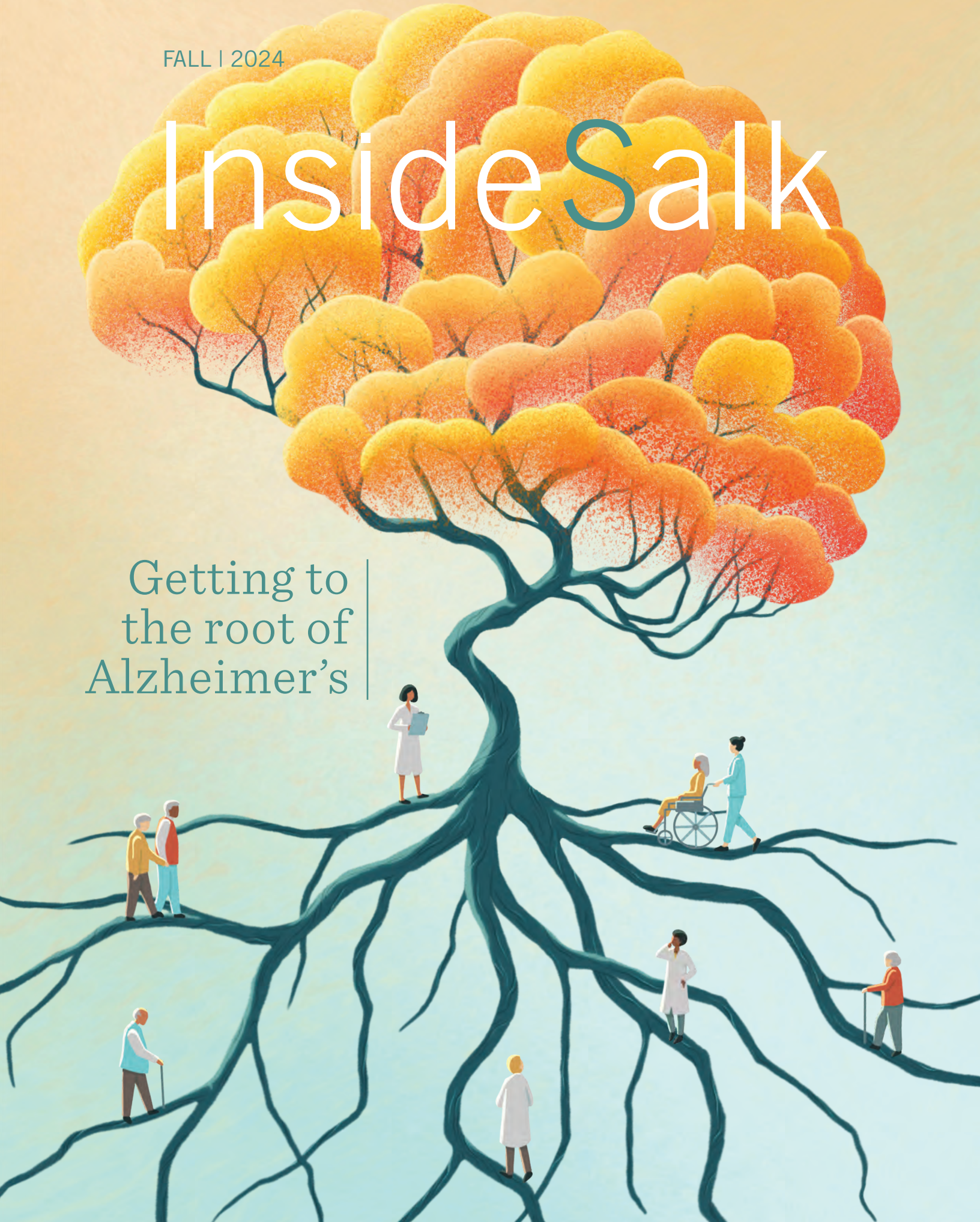
FALL | 2024

InsideSalk

Getting to the root of Alzheimer's



CONTENTS

ON THE COVER:

To get to the root of Alzheimer's, Salk scientists are looking at the disease from all angles and incorporating the latest insights from healthy aging science. Through the Unlocking Healthy Aging Initiative, the Institute is expanding efforts to understand aging on a more fundamental biological level.

Dear Friends,

As we continue the Salk Institute's "Year of Healthy Aging," this issue focuses on Alzheimer's disease, a devastating condition that directly affects nearly 7 million people in the United States. In addition, Alzheimer's indirectly affects 11 million people who provide unpaid care for loved ones with dementia—people like Annie Alessio, who you'll read about in the feature piece. Annie's mother, Carol, was diagnosed with Alzheimer's when Annie was in college. Fourteen years later, after trying every therapeutic approach, Annie lost her mother to the disease.

Alzheimer's disease is heartbreaking and frustrating for many families. What causes it? Why do some people experience dementia while others don't? Why do some respond better to certain treatments than others?

We need more answers. To address this, Salk's molecular biologists, neuroscientists, immunologists, and other experts are collaborating to investigate a range of factors—genetic, cellular, metabolic, and environmental—and to determine how these factors intersect and contribute to the onset and progression of Alzheimer's disease. Salk scientists are moving beyond the traditional viewpoints to develop a more comprehensive understanding of its underlying mechanisms and identify potential therapeutic targets.

This multidisciplinary approach wouldn't be possible without our many supporters. Your generosity empowers our researchers to pursue innovative avenues of inquiry, bringing us closer to a future in which Alzheimer's and other diseases can be mitigated or eradicated.

In addition to introducing you to many of the faculty members, trainees, and staff members who contribute to our high-impact science, this issue pays tribute to Joan Jacobs, one of the Salk Institute's greatest supporters and one of San Diego's most generous philanthropists. Joan's passing last May was a huge loss to our community, but her legacy will last for generations.

We appreciate your confidence in our mission, and we are grateful for your partnership. Please enjoy this issue of *Inside Salk* magazine.

Warmest regards,

Gerald Joyce
Salk Institute President

"Your generosity empowers our researchers to pursue innovative avenues of inquiry, bringing us closer to a future in which Alzheimer's and other diseases can be mitigated or eradicated."

DISCOVERIES

A WHOLE NEW world

Salk scientists don't just change what we know about the world around us—they change how we discover it. Whether they're developing brand-new methods and models or advancing existing techniques, our researchers create new, better ways to study science.

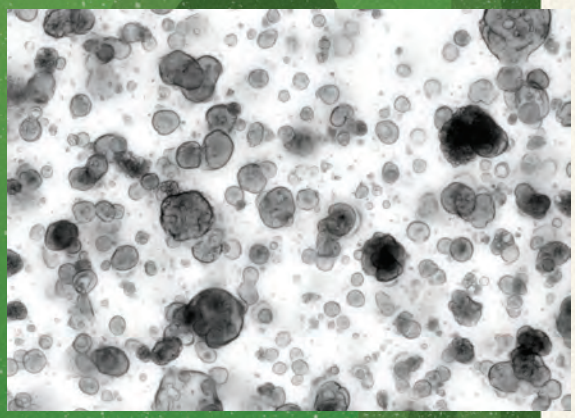
Here at Salk, innovation means asking questions so bold they require entirely new tools to answer. To get closer to a cure for pancreatic cancer, our scientists are developing and rigorously testing 3D miniature models of human pancreatic tumors. To engineer plants resilient against climate change, they teamed up across disciplines and combined plant science with artificial intelligence. To investigate telomere shortening in aging and disease, they designed a new tool to measure the length and sequence of telomeres on individual human chromosomes with unprecedented resolution.

As they change ***the very way we do science***, they make modern treatments and global solutions possible.

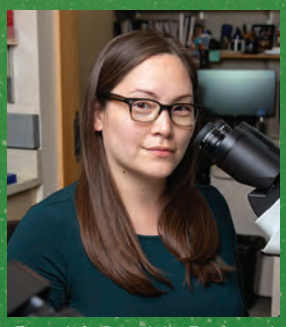
A STEP TOWARD CLINIC-READY PATIENT-DERIVED ORGANOIDS

JCI INSIGHT 01/2024

Pancreatic cancer has the highest mortality rate of all major cancers. It is especially difficult to treat because the tumors grow so quickly and are constantly evolving. But patient-derived organoids could change all that. In this emerging biotechnology, researchers obtain a small sample from a patient biopsy and use it to grow 3D tissues in the lab. These "organoids" act as miniature models of the patient's pancreatic tumor and can be used to quickly evaluate which cancer drugs might work best for them. A recent study by Assistant Professor Dannielle Engle, postdoctoral researcher Jan Lumibao, and colleagues provided critical insights into the robustness of patient-derived organoids as a clinical model of pancreatic cancer. They found the organoids' gene expression and drug responses were not affected by the brand of extracellular matrix used in the cell culture. Data like this increases confidence that clinical conclusions are reliable across different labs and batches of organoids. They also identified one matrix brand that sped up the growth of tumor organoids, making it particularly well-suited for the fast pace of pancreatic cancer treatment protocols.



A pancreatic cancer patient-derived organoid line developed at the Salk Institute.



From left: Dannielle Engle and Jan Lumibao.

From left: Talmo Pereira, Elizabeth Berrigan, and Wolfgang Busch.

ARTIFICIAL INTELLIGENCE HELPS SCIENTISTS ENGINEER PLANTS TO FIGHT CLIMATE CHANGE

PLANT PHENOMICS 04/2024

The Intergovernmental Panel on Climate Change declared that removing carbon from the atmosphere is now essential to fighting climate change and limiting global temperature rise. In support of these efforts, Salk scientists are harnessing plants' natural ability to draw carbon dioxide out of the air by optimizing their root systems to store more carbon for a longer period of time. To design these climate-saving plants, scientists in Salk's Harnessing Plants Initiative are using a sophisticated new research tool called SLEAP—an easy-to-use artificial intelligence (AI) software designed by Salk Fellow Talmo Pereira that tracks multiple features of root growth. Pereira, Professor Wolfgang Busch, bioinformatics analyst Elizabeth Berrigan, and colleagues have officially debuted a new protocol for using SLEAP to analyze plant root phenotypes—how deep and wide they grow, how massive their root systems become, and other physical qualities that, prior to SLEAP, were tedious to measure. Applying SLEAP to plants has already enabled the researchers to establish the most extensive catalog of plant root system phenotypes to date, giving Salk's Harnessing Plants Initiative a powerful boost.

UNVEILING TELO-SEQ: A BREAKTHROUGH IN TELOMERE RESEARCH ON AGING AND CANCER

NATURE COMMUNICATIONS 06/2024

Telomeres—the protective endcaps on our chromosomes—shorten as we age, eventually getting so whittled down that our DNA becomes exposed, and our cells die. However, the specifics of when and how this happens, and whether certain chromosomes are more affected than others, have been unclear—until now. Professor and CSO Jan Karlseder, postdoctoral researcher Tobias Schmidt, and colleagues teamed up with Oxford Nanopore Technologies to develop Telo-seq, a groundbreaking method for determining the precise length and entire sequence of telomeres on each individual human chromosome. They have already used the tool to discover features of telomere biology that were unobservable with previous methods. Telo-seq will facilitate a flurry of new insights into the molecular dynamics of cancer and aging, which will likely inspire future telomere-targeting therapeutics.

From left: Jeffrey Jones, Rusty Gage, Tobias Schmidt, and Jan Karlseder.

A neuron (left) sends a message to another neuron (right) through electrochemical signals, represented by flashes of yellow at the points where the two cells meet, called synapses.

Upgrading brain storage: Quantifying how much information our synapses can hold

NEURAL COMPUTATION 04/2024

Recalling each vocabulary word in a flashcard set faster with each flip through is evidence that our neural connections, called synapses, can grow stronger or weaker over time—a feature known as synaptic plasticity. Quantifying the dynamics of individual synapses can be a challenge for neuroscientists, but recent computational innovations from Professor Terrence Sejnowski, postdoctoral researcher Mohammad Samavat, and colleagues are changing that. To understand how the brain learns and retains information, scientists try to quantify how much stronger a synapse has gotten through learning, and how much stronger it *can* get. Synaptic strength can be measured by looking at the physical characteristics of synapses, but it is much more difficult to measure the precision of plasticity (whether synapses grow weaker or stronger by a consistent amount) and the amount of information a synapse can store. The new computational method can do all three, opening the door for new studies on human learning and memory and how those processes evolve or deteriorate with age or disease.

From left: Terrence Sejnowski, Mohammad Samavat, and Thomas Bartol.

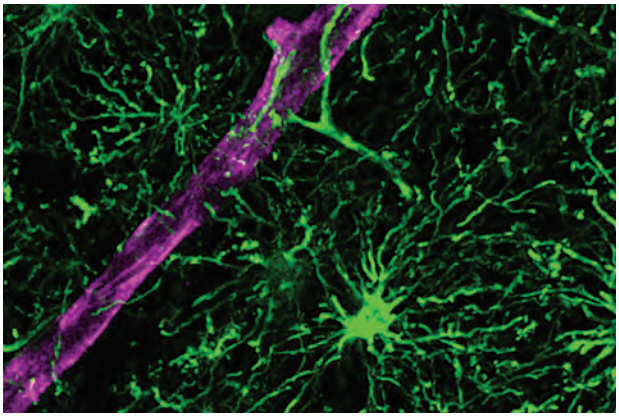
"We have now created a technique for studying the strength of synapses, the precision with which neurons modulate that strength, and the amount of information synapses are capable of storing—leading us to find that our brain can store 10 times more information than we previously thought."

PROFESSOR TERRENCE SEJNOWSKI

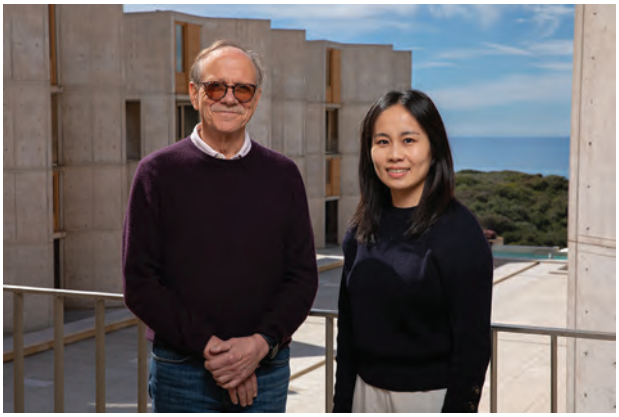
More than just neurons: A new model for studying human brain inflammation

NATURE BIOTECHNOLOGY 02/2024

Neurons only make up half of the human brain. The other half is composed of approximately 85 billion cells called glia. The most common type of glial cells are astrocytes, which are important for supporting neuronal health and activity. Despite the abundance of astrocytes in the brain, most existing laboratory models of the human brain fail to include astrocytes at sufficient levels or at all, which limits the models' utility for studying brain health and disease. Now, Professor Rusty Gage, postdoctoral researchers Lei Zhang and Meiyan Wang, and colleagues have created 3D organoids that mimic features of the human brain and contain mature, functional astrocytes. With this astrocyte-rich model, researchers will be able to study stress and inflammation in aging and Alzheimer's disease with greater depth and clarity than ever before. Already, the researchers have used the new organoids to reveal a relationship between astrocyte dysfunction and inflammation. This allowed them to identify a potentially druggable target for disrupting that relationship in the aging brain.

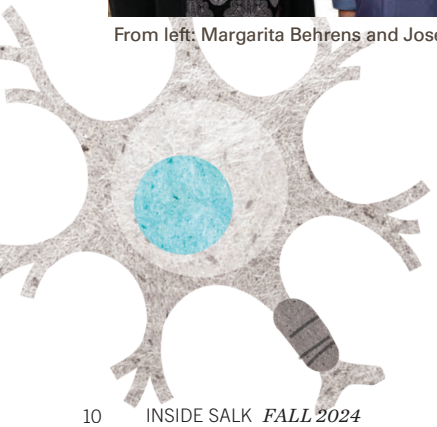


In Gage's latest brain organoids, astrocytes (green) are organized in more sophisticated arrangements that better mimic the human brain.



From left: Rusty Gage and Meiyan Wang.

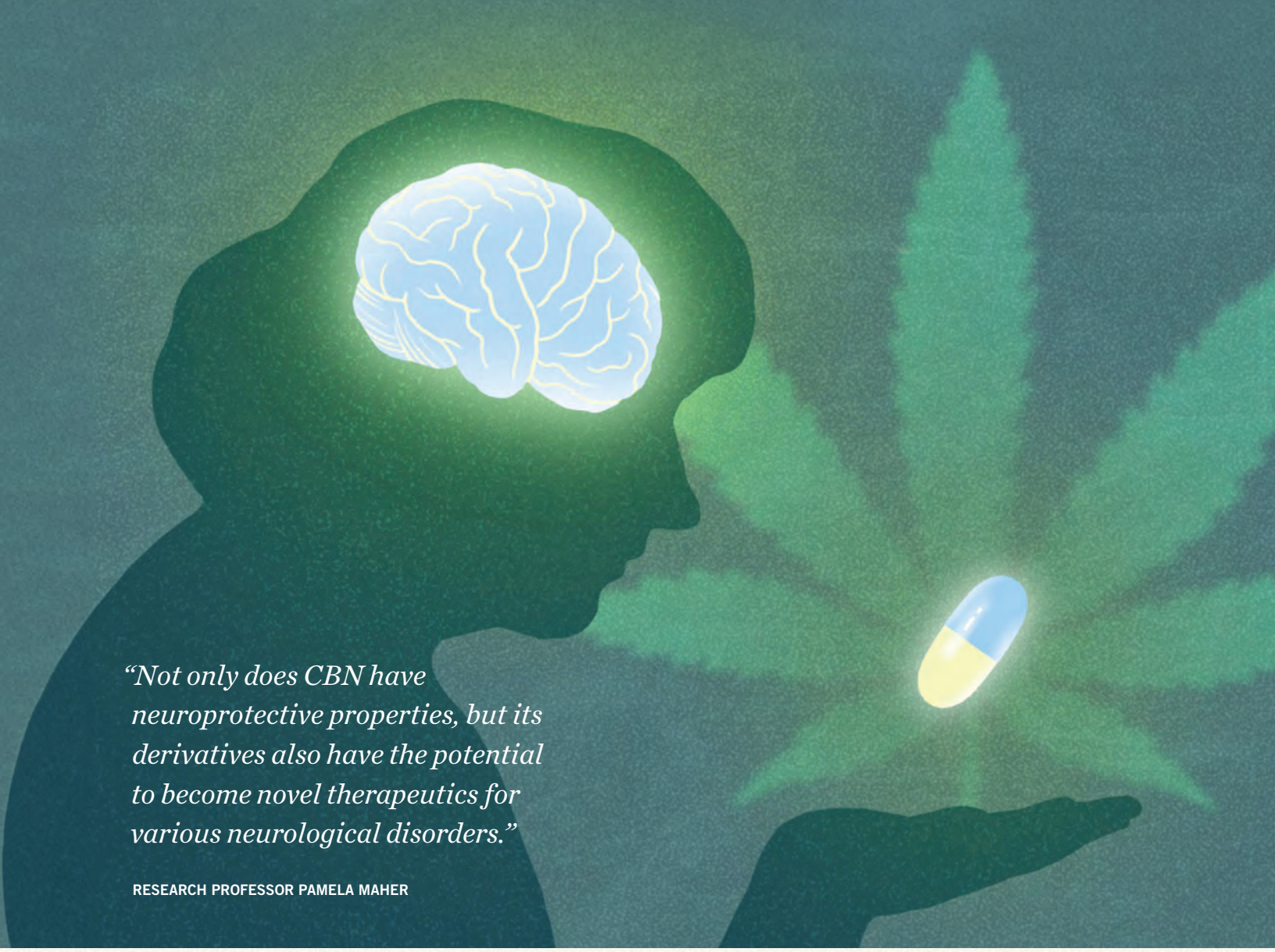
From left: Margarita Behrens and Joseph Ecker.



Neuron identities differ with age and sex

NEURON 06/2024

The human brain's message-sending neurons can behave differently with age. At the root of these changes are shifts in the regulation of neuronal genes—how and when these cellular instructions are read can change the identity of individual neurons. This in turn changes the ratio of different neuronal cell types in the brain. Research Professor Margarita Behrens, Professor Joseph Ecker, Salk colleagues, and collaborators at UC San Diego looked at human frontal cortexes from young adult and aged donors and found widespread age- and sex-related variation in neuronal cell types: both the amount and type of neuronal cells changed with age. Cells in older frontal cortexes expressed fewer genes involved in the active message-sending function of neurons but expressed more subtelomere genes, which help protect the ends of chromosomes from age-related damage. Their findings describe changes in gene regulation in the aging human brain with unprecedented detail. This will ultimately help researchers understand what happens to brain cells in both healthy aging and age-related diseases like Alzheimer's.



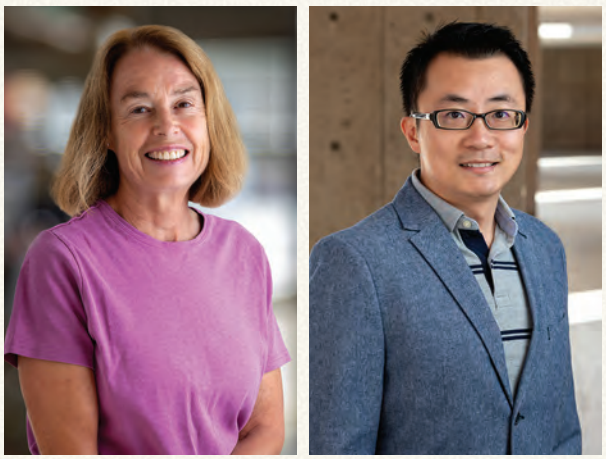
"Not only does CBN have neuroprotective properties, but its derivatives also have the potential to become novel therapeutics for various neurological disorders."

RESEARCH PROFESSOR PAMELA MAHER

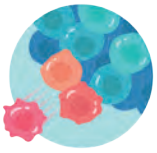
Protecting brain cells with cannabinol

REDOX BIOLOGY 03/2024

One in 10 individuals above the age of 65 develops an age-related neurological disorder like Alzheimer's or Parkinson's, yet treatment options for those patients remain sparse. Scientists have begun exploring whether cannabinoids—compounds derived from the cannabis plant, like well-known THC (tetrahydrocannabinol) and CBD (cannabidiol)—may offer a solution. A third, lesser-known cannabinoid called CBN (cannabinol) has recently piqued the interest of researchers, who have begun exploring the clinical potential of the milder, less psychoactive substance. In a recent study, Research Professor Pamela Maher, postdoctoral researcher Zhibin Liang, and colleagues explained how CBN protects the brain against aging and neurodegeneration, and used their findings to develop potential therapeutics.



From left: Pamela Maher and Zhibin Liang.

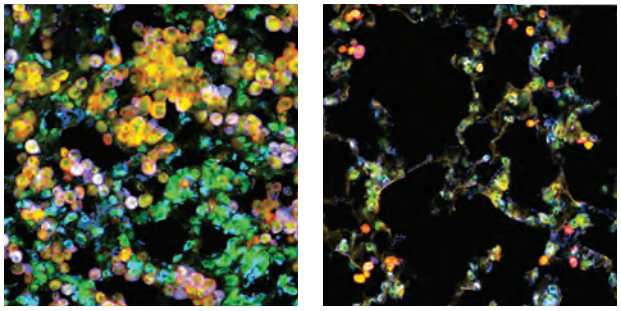


CANCER

Lung cancer hijacks immune cell metabolism to fuel its own growth

CANCER DISCOVERY 01/2024

Lung adenocarcinoma is the most common lung cancer and the cause of most cancer-related deaths in the United States. There are several ways lung adenocarcinoma can arise, one of which involves a mutation in a protein called EGFR (epidermal growth factor receptor). Modern immunotherapies don't work against EGFR-driven lung adenocarcinoma, and while other types of lung cancer drugs do exist, patients typically become resistant to them within a few years. Professors Susan Kaech and Christian Metallo, alongside Salk colleagues and collaborators at Yale University and UC Los Angeles, discovered that EGFR-driven lung adenocarcinoma hijacks immune cells called macrophages, pulling them into the tumor and turning them into cancer fuel suppliers. The findings could inspire new lung adenocarcinoma interventions that disrupt this tumor cell-macrophage relationship. They also suggest that treatments using EGFR inhibitors may be more successful when paired with statins, a class of drugs commonly used to lower cholesterol levels.



Lung adenocarcinoma tumor cells (green) and macrophages (red) accumulate in the lungs of control mice (left), but expansion of the tumor cells is hindered in macrophage PPARγ knockout mice (right), since the macrophages can't be metabolically co-opted by tumor cells. Cellular cholesterol is visualized in yellow.

From left: Susan Kaech, Alexandra Kuhlmann-Hogan, Katerina Politi, and Christian Metallo.

In this Rube Goldberg machine, scissors representing the ARID1A mutation set off a cascade of events in which loose DNA escapes the nucleus, sounding an alarm to trigger an immune response that can be co-opted to attack cancer cells.

This time, it's personal: Enhancing patient response to cancer immunotherapy

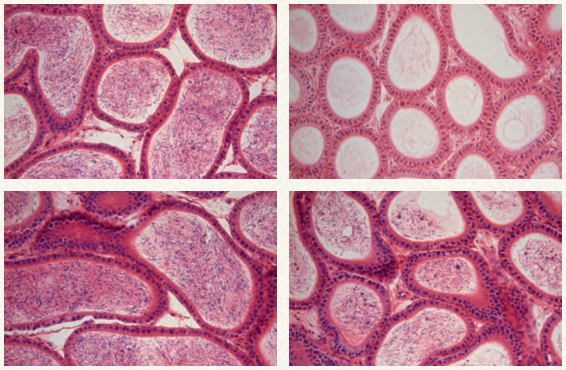
CELL 05/2024

Immunotherapy has revolutionized the way we treat cancer in recent years. Instead of targeting the tumor itself, immunotherapies work by directing patients' immune systems to attack their tumors more effectively. Still, fewer than half of all cancer patients respond to current immunotherapies, creating an urgent need to identify biomarkers that can predict which patients are most likely to benefit. Associate Professor Diana Hargreaves, postdoctoral researcher Matthew Maxwell, and colleagues have done just that, revealing that mutations in a gene called ARID1A make patients more likely to respond positively to immune checkpoint blockade—a type of immunotherapy that works by keeping cancer-fighting immune cells turned "on." The ARID1A mutation prompts an antiviral response that pulls more cancer-fighting immune cells into the tumor, and because the gene is present in many cancers—endometrial, ovarian, colon, gastric, liver, and pancreatic—the biomarker could have a huge impact on identifying patients for specific immunotherapies. The findings also encourage the development of drugs that target ARID1A and related proteins as a way of sensitizing other tumors to immunotherapy.

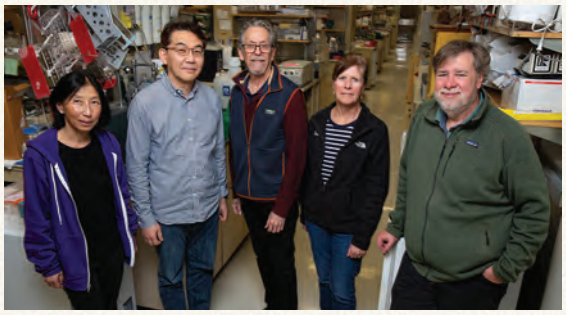
Salk scientists discover new target for reversible, non-hormonal male birth control

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 02/2024

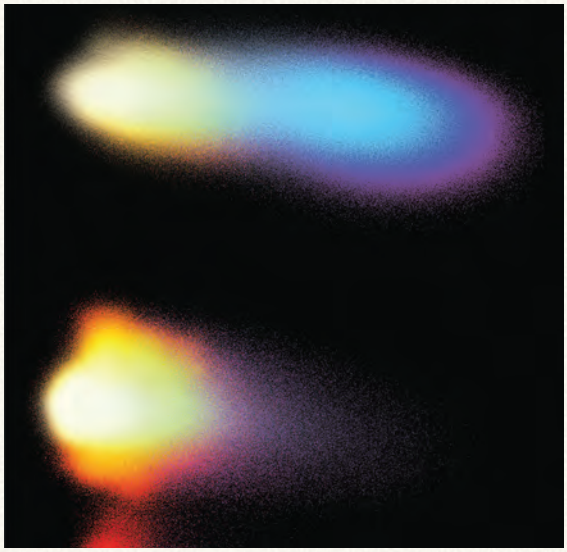
Surveys show most men in the United States are interested in using male contraceptives, yet their options remain limited to condoms or invasive vasectomies. Recent attempts to develop drugs that block sperm production, maturation, or fertilization have had limited success, providing incomplete protection or negative side effects. New approaches to male contraception are needed, but because sperm development is so complex, researchers have struggled to identify parts of the process that can be safely and effectively tinkered with. Now, Professor Ronald Evans, senior staff scientist Michael Downes, staff researcher Suk-Hyon Hong, and colleagues have found a new method of interrupting sperm production that is both non-hormonal and reversible. In a recent study, they demonstrated that treating male mice with an existing class of drugs, called HDAC (histone deacetylase) inhibitors, can interrupt the function of this protein complex and block fertility without affecting libido. The team hopes to see this therapeutic approach advanced to human clinical trials soon.



Sperm, pictured inside the cross-sectioned tube of the epididymis, were not generated while mice took the HDAC inhibitor drug (top right), but after 60 days off the drug, spermatogenesis was recovered (bottom right). The left column shows sperm at the same time points in a mouse that did not receive the drug.



From left: Ruth Yu, Suk-Hyun Hong, Ronald Evans, Annette Atkins, and Michael Downes.



Hammerhead sequences copied by the lower-fidelity polymerase drift away from their original RNA sequence (top) and lose their function over time. Hammerheads catalyzed by the higher-fidelity polymerase retain function and evolve fitter sequences (bottom).

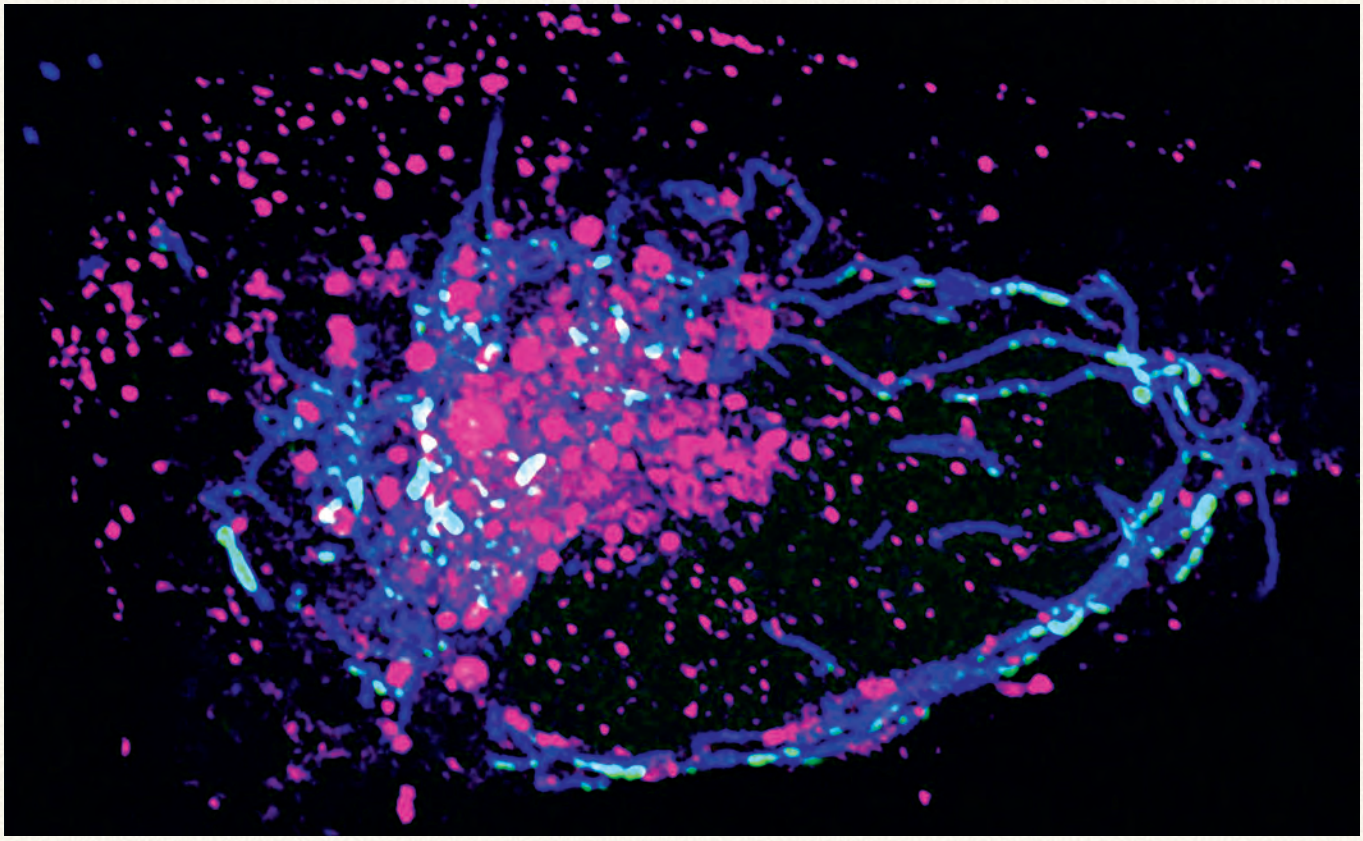
WATCH | www.salk.edu/joyce2024

Modeling the origins of life: New evidence for an "RNA World"

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 03/2024

Scientists in the 1960s, including Salk Fellow Leslie Orgel, proposed that life began with the "RNA World"—a hypothetical era in which small, stringy RNA molecules ruled the early Earth and established the dynamics of Darwinian evolution. New research by Professor and Salk President Gerald Joyce, research associate Nikolaos Papastavrou, staff scientist David Horning, and colleagues provides fresh insights on the origins of life, presenting compelling evidence supporting the RNA World hypothesis. The recent study unveiled an RNA enzyme that can make accurate copies of other functional RNA strands while allowing new variants of the molecule to emerge over time. These remarkable capabilities suggest the earliest forms of evolution may have occurred on a molecular scale in RNA.

IMMUNOBIOLOGY



Endosomes (magenta) collect around mitochondria (blue) after infection with virus HSV-1, which attacks mtDNA (green) and causes its release.

"We knew that mtDNA was escaping mitochondria, but how was still unclear. Using imaging and cell biology approaches, we're able to trace the steps of the pathway for moving mtDNA out of the mitochondria, which we can now try to target with therapeutic interventions to hopefully prevent the resulting inflammation."

PROFESSOR GERALD SHADEL

Faulty DNA disposal system causes inflammation

NATURE CELL BIOLOGY 02/2024

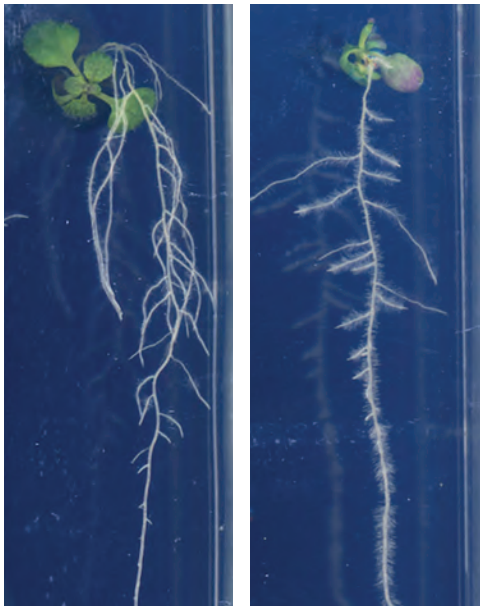
Cells in the human body contain power-generating mitochondria, each with their own mtDNA—a unique set of genetic instructions that mitochondria use to create life-giving energy. When mtDNA remains where it belongs (inside mitochondria), it sustains both mitochondrial and cellular health; when it goes where it doesn't belong, it can initiate an immune response that promotes inflammation. Now, Professor Gerald Shadel, Salk colleagues, and collaborators at UC San Diego and University of Virginia have discovered a mechanism that expels improperly functioning mtDNA from the mitochondria. When this happens, the mtDNA gets flagged as foreign DNA and activates an inflammatory pathway. This pathway is a promising target for new therapeutics that could disrupt or mitigate inflammation in aging or diseases like lupus or rheumatoid arthritis.

Controlling root growth direction could help save crops and mitigate climate change

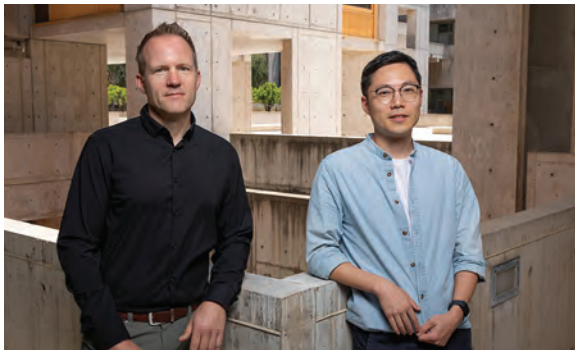
CELL REPORTS 02/2024

Roots are central to a plant's survival and productivity, determining the plant's access to nutrients and water and, therefore, its ability to tolerate nutrient depletion and extreme weather, like drought. Professor Wolfgang Busch, postdoctoral researcher Wenrong He, and colleagues recently determined how a well-known plant hormone controls the angle at which roots grow. The study is the first time the plant hormone, called ethylene, has been shown to be involved in regulating the lateral root angles that shape root systems—providing key insights for plant scientists looking to optimize root systems. Researchers in Salk's Harnessing Plants Initiative now plan to target the ethylene signaling pathway in their efforts to engineer plants and crops that can withstand the environmental stresses of climate change and drought.

WATCH | www.salk.edu/busch2024



Untreated (left) and mebendazole-treated (right) seedling of *Arabidopsis thaliana* growing on the surface of vertical agar plates. While the root branches of the untreated plant point downward, mebendazole leads to the branches pointing much more sideward, leading to a shallower root system.



From left: Wolfgang Busch and Sanghwa Lee.

"The fact that higher temperatures deplete these important nutrients in plants is a real concern for the future of human and animal diets and certainly something we want to account for as we work to design more resilient crops."

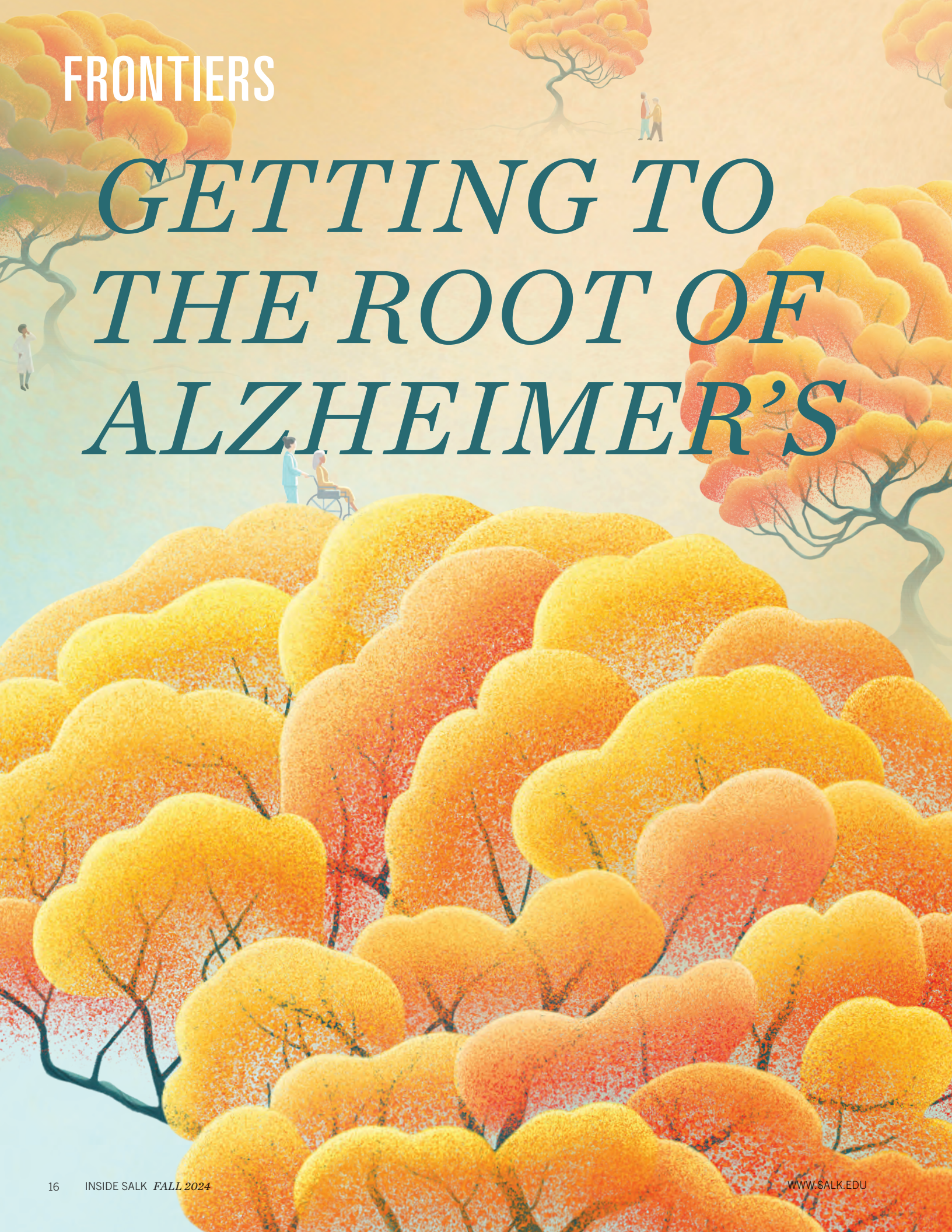
PROFESSOR WOLFGANG BUSCH

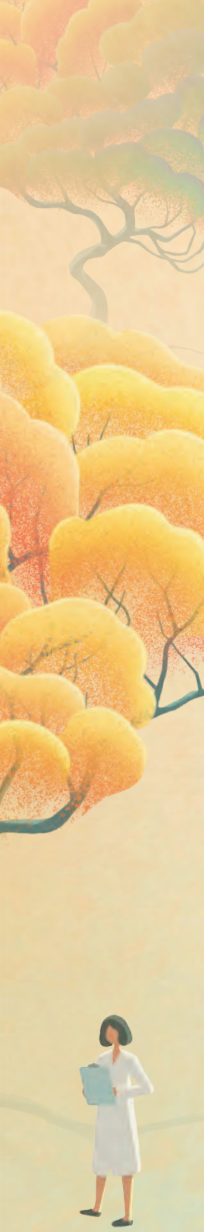
Key nutrients help plants beat the heat

NATURE COMMUNICATIONS 06/2024

Global temperatures are on the rise, with experts projecting an increase of 2.7°F by 2050. Plants are especially sensitive to these temperature changes. For example, in higher temperatures, plants instruct their root systems to grow faster, creating long roots that stretch through the soil to absorb more water and nutrients. While this response may help the plants in the short term, Professor Wolfgang Busch, postdoctoral researcher Sanghwa Lee, and colleagues have discovered that this ultimately reduces the plant's levels of two important nutrients—nitrogen and phosphorus—which makes them less nutritious when consumed. At the same time, if the soil contains low amounts of these nutrients, plants return to slower root growth and don't respond adequately to the higher temperatures. The new molecular details of this interaction between root growth and nutrient availability in the face of high temperatures will inform the engineering of Salk Ideal Plants®—a collection of carbon-capturing, climate change-resilient wheat, rice, corn, and other crops created by Salk's Harnessing Plants Initiative.

GETTING TO THE ROOT OF ALZHEIMER'S





SALK SCIENTISTS ARE TEAMING UP TO UNDERSTAND BRAIN AGING

Annie Alessio was about to start her junior year at the University of San Diego when her mother, Carol, was diagnosed with early-onset Alzheimer's disease.

"I remember it like it was yesterday—she walked through the door in her blue linen pantsuit, told me what happened, and said, 'I'm going to beat this,'" says Annie. "If there was someone at the time who could have beat it, she would have been the one."

Carol Alessio had always been an independent and strong-willed woman. In her youth, the spunky Midwestern girl often dreamed of a bigger and better life outside of her small town. At 18 years old, she bravely moved to Southern California, where she eventually met her husband, Mike, and immersed herself in San Diego's business and political scenes.

It was on a trip back home in the summer of 2000 that Carol was suddenly injured in a fall. In the aftermath of the accident, family members began to recall a few other peculiar incidents from recent years and ultimately encouraged her to undergo some tests. The doctors soon discovered abnormalities in her brain scans, and the diagnosis came shortly thereafter.

"Alzheimer's wasn't on the forefront of everyone's mind back then," says Annie. "We knew it had to do with memory loss, but we didn't know about the behavioral issues or the hallucinations. There weren't websites or pamphlets explaining these things to us, so we didn't know what to expect, and all of our lives just kind of stopped."

Annie moved back home to help take care of her mother in the years before she was transferred to a nearby care facility. For the next 14 years, the family tried every medication and rehabilitation strategy her doctors suggested, but Carol's mental and physical health continued to decline.

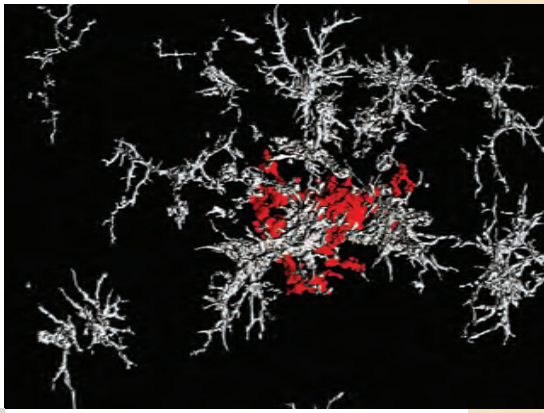
This perpetual struggle would be completely discouraging for most people, but Annie decided to channel her frustration into volunteer work. As a board member of the San Diego Alzheimer's Association, she met with local doctors, led multiple fundraisers, and helped raise awareness of the disease.

August 2024 marked the 10th anniversary of Carol's passing, and Annie hopes to honor her mother's legacy with continued advocacy.

"I want to fight even harder on her behalf," she says, "because I know that's what she would do."

Carol Alessio lived in San Diego with her husband, Mike, and their two children, Michael and Annie.

Nearly all clinical research on Alzheimer's has focused on amyloid plaques and tau tangles, but recent lab studies are pointing scientists in a new direction.



An amyloid plaque (red) surrounded by microglia (white) in the brain of a mouse with Alzheimer's disease.

BARKING UP THE WRONG TREE

Annie's enthusiasm comes at a good time, as the landscape of Alzheimer's research is currently experiencing a seismic shift. After decades of rather disappointing progress, scientists and clinicians are now reexamining the disease with new tools and a fresh perspective.

A main source of stagnation in Alzheimer's research has been the overemphasis on amyloid plaques and tau tangles. These abnormal clumps of proteins in the brain were first observed by Alois Alzheimer himself in 1906, and thus became the defining biomarkers of the disease. For decades, these proteins were the focus of nearly all Alzheimer's research, drug development, and clinical trials.

Many cases of the rare early-onset form of Alzheimer's, like Carol's, can be directly linked to gene mutations associated with amyloid and tau proteins. This was another early piece of evidence that got scientists and clinicians thinking these pathways must be the source of the pathology.

But over the years, it's become clear that only a small subset of Alzheimer's patients actually have these particular gene mutations and that not everyone who has these mutations goes on to develop the disease. So, there must be other factors at play.

"The field has really suffered from having this monolithic amyloid tau hypothesis. It had such a hold on the field that researchers had little opportunity to study other ideas. That is now changing dramatically."

PROFESSOR RUSTY GAGE

"The field has really suffered from having this monolithic amyloid tau hypothesis," says Salk Professor Rusty Gage, Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease. "It had such a hold on the field that researchers had little opportunity to study other ideas. That is now changing dramatically."

The current sense is that these plaques and tangles represent specific genetic subtypes of Alzheimer's or otherwise indicate a later stage of the disease that is likely much more difficult to treat. Scientists are now shifting their efforts to identify other sources of the disease—different genes, proteins, and pathways that, if treated early enough, could have much more success in improving patient outcomes.

HEALTHY AGING AND ALZHEIMER'S

To get to the root of Alzheimer's, Salk scientists are looking at the disease from all angles and incorporating the latest insights from healthy aging science. Through the Unlocking Healthy Aging Initiative, the Institute is expanding its efforts to understand aging on a more fundamental biological level. One major goal of these projects is to identify the cellular and molecular processes that contribute to aging in the brain.

Aging is the biggest risk factor for neurodegenerative disease, so much so that many assume one just inevitably comes with the other. And yet, everyone's aging experience is different, and not everyone develops Alzheimer's. So what makes the difference between mental fitness and frailty? What goes on in our brains as we age, and why does it sometimes lead to Alzheimer's?

"For many diseases, like cancer, the risk of developing the disease increases fairly steadily as we age, but there's a different trajectory for the risk of Alzheimer's, in that it's nearly flat for most of our lives and then it takes off around age 70," says Gerald Shadel, professor and Audrey Geisel Chair in Biomedical Science at Salk. "In my mind, that means there's a distinct set of aging-related phenomena that can happen around that point and trigger a quicker progression of Alzheimer's."

Shadel is the director of the San Diego Nathan Shock Center of Excellence in the Basic Biology of Aging, funded by the National Institute on Aging. The center was launched in 2020 to understand how intrinsic and environmental factors contribute to the heterogeneity of human aging. Its goal is to learn how these different factors affect each person's aging trajectory so that personalized interventions can be developed to extend their "health span," or the number of healthy years in their life.

"We all age, we all slow down and lose some abilities, and we all develop a higher risk of disease, but the issue is that for a long time, many people believed these things weren't malleable," says Shadel. "We're now learning that if you understand the genetic and biochemical pathways of aging, you can target them therapeutically and actually slow the aging process—not because we want to live forever but because we want to be healthy for as much of our lives as possible."

"For many diseases, like cancer, the risk of developing the disease increases fairly steadily as we age, but there's a different trajectory for the risk of Alzheimer's, in that it's nearly flat for most of our lives and then it takes off around age 70."

PROFESSOR GERALD SHADEL

When Salk scientists discuss their aging research, they often refer to the idea of an "aging dashboard." On each person's dashboard, they imagine various gauges reporting the health status of different cells, tissues, organs, and even specific molecular pathways in their body. For some people, aging might look like a steady decline across all gauges, while others might have one or two areas in which aging is taking a bigger toll.

In a future in which these sorts of measurements could be consistently collected, artificial intelligence could analyze each person's dashboard and predict their risk of developing an aging-related disease, such as Alzheimer's. The key is being able to not just treat the symptoms of the disease as they emerge but proactively target the biggest sources of aging in that person to delay or even prevent the onset of disease altogether.

In the case of Alzheimer's, scientists are finding that there are probably multiple potential starting points for the disease rather than one singular cause. This means the solution may come down to identifying which biological process (or processes) is being most affected by aging in each patient and targeting it as early as possible.

"If we could slow the major pathways contributing to someone's neurological aging," says Shadel, "even just delay them five or 10 years, that could make the difference between whether their final years are spent succumbing to Alzheimer's, or if they can have that time with their loved ones and eventually pass in a less devastating manner."

FINDING YOUR ROOTS

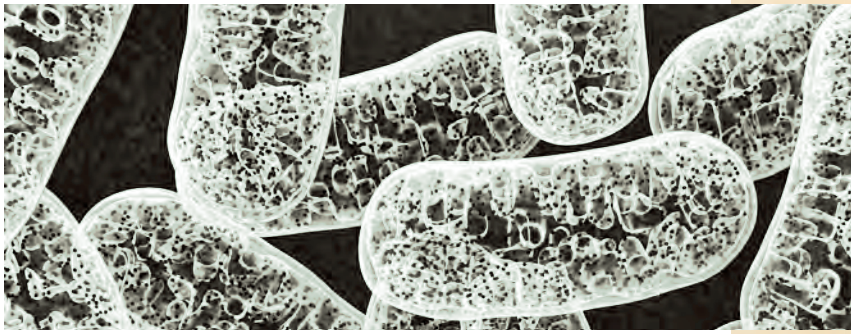
So what are these major brain aging pathways, and how can we slow them down to prevent disease? Gage, Shadel, and their Salk colleagues are hard at work figuring this out. In 2018, the team was awarded $19.2 million by the American Heart Association-Allen Initiative to launch a series of studies analyzing the interactions between proteins, genes, epigenetics, inflammation, and metabolism in Alzheimer's and the aging brain.

"This team is purposely composed of faculty from all different disciplines because we knew that tackling Alzheimer's and other forms of age-related cognitive decline would require us to think outside the box," says Gage, who leads the initiative. "It's an amazing group of people, and what's fun is that we really all learn from each other and make each other better scientists."

Gage and his team are pioneers of a modern research tool for modeling human brain aging in the lab. In this approach, the researchers collect skin samples from older adults, plate them on Petri dishes, and then use molecular tools to convert the skin cells directly into neurons. Recently, they advanced this technology to create 3D models called brain organoids, which include additional brain cell types like microglia and astrocytes to more accurately resemble human brain tissue. Their key breakthrough is finding a way to have these brain cells retain the molecular signatures of the patient's age, making them invaluable for studying age-related diseases.

Using these models, Gage's lab can compare the biology of brain cells from Alzheimer's patients and age-matched healthy adults. In 2022, they published a study showing that many neurons derived from Alzheimer's patients exhibit an age-related deterioration process called senescence. As these cells age, they become unable to produce enough energy to perform all their usual functions, eventually losing even the physical characteristics of neurons. In most cases, this much deterioration would cause cells to die, but senescent cells actually stay alive in this low-energy, zombie-like state and start to secrete inflammatory molecules. These leaky signals ultimately damage the surrounding tissue, exacerbating the problem and leading to cognitive decline.

To understand what triggers these cells to enter senescence, Gage has drawn on Shadel's expertise in mitochondrial biology. Colloquially referred to as the "powerhouse of the cell," mitochondria convert energy from the food we eat into chemical energy that our cells, tissues, and organs use to function. Human neurons require a lot of energy, so mitochondrial health is critical for normal brain function. However, aging can damage mitochondria in many ways, and, if left untreated, can lead to an energetic crisis, inflammation, and neurodegeneration.



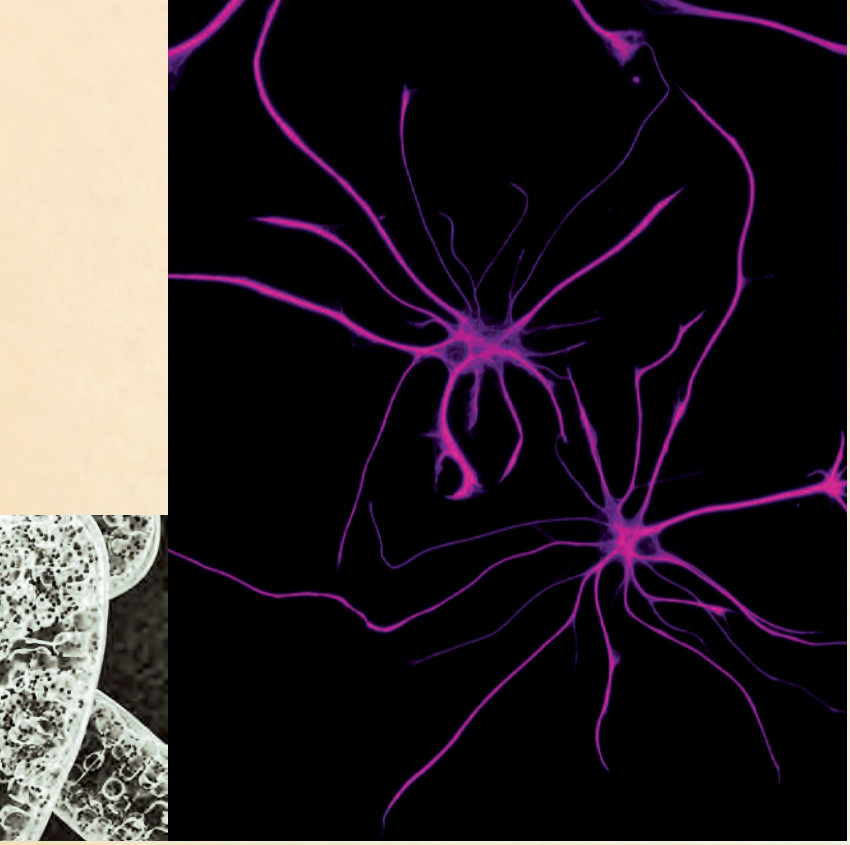
Mitochondria

Aging damages mitochondria in the brain, causing energetic crises, inflammation, and neurodegeneration. Salk scientists are repurposing existing drugs to target these pathways and seeing promising results.

Gage, Shadel, and other Salk scientists are now studying the various aging processes that weaken mitochondria in the brain. They are already seeing promising results from targeting these molecular pathways with existing drugs, offering hope for more effective treatments in the future.

In another line of research at Salk, scientists are looking at the ways that non-neuronal brain cells, called glia, can also contribute to Alzheimer's. Interestingly, when scientists compare the gene expression profiles of brain cells from Alzheimer's patients to those of healthy older adults, glial cells actually appear to be more affected by the disease than neurons.

Salk Associate Professor Nicola Allen is an expert on a subtype of glial cells called astrocytes, named for their star-like shape. Her lab is now uncovering the role that astrocytes play in Alzheimer's disease.



Astrocytes

Allen and her team have discovered that astrocytes are crucial for shaping communication across the brain. They mainly do this by guiding the formation and removal of synapses, where neurons meet and share electrochemical signals. Gene expression levels suggest that in Alzheimer's patients, astrocytes are less able to create or strengthen synapses, while their propensity to remove synapses increases. This results in a destabilized and overly pruned synaptic network that ultimately disrupts brain communication.

Allen is now characterizing a class of proteins that astrocytes use to encourage the formation of new synaptic connections. Current experiments are testing whether re-expressing these proteins in the Alzheimer's brain can restore synaptic function and delay disease progression.

Their initial results in mice are promising: Increasing the amount of these proteins in astrocytes restored the number of synapses in memory-related brain areas and improved animals' performance in memory and spatial cognition tasks.

Salk scientists are finding that boosting specific proteins in astrocytes can restore synaptic function and memory. New ideas like these offer hope for better treatments.

This study represents one of many cellular and molecular pathways that Allen's team is exploring for the treatment of Alzheimer's. Other lines of work in the lab are studying the relationship between astrocytes and neuroinflammation.

"Everyone's taking different approaches, which is really exciting," says Allen. "Some will work, and some won't, but we're going to learn a lot along the way."

Another Salk scientist studying inflammation is Professor Susan Kaech, director of the NOMIS Center for Immunobiology and Microbial Pathogenesis and NOMIS Chair. Kaech's research is centered on the immune system and cancer, but at Salk, she also lends her expertise to the study of aging and Alzheimer's.

"Almost all of what we know about aging in humans is from sampling blood," says Kaech, "and one of the biggest changes we see in our blood as we age is this large accumulation of memory T cells."

When the body experiences an infection, the immune system produces an army of cells to find and kill the pathogen. It also produces memory T cells, whose job is to remember the pathogen so that the immune system can recognize and attack it even faster next time. But memory T cells are designed to respond not only to that one specific pathogen but also to others that are similar to it. This broad response is a smart strategy for fighting infection earlier in our lives, but as we accumulate more memory T cells with every infection, the net result is a large population of overresponsive immune cells across the body. Immunologists think this could be contributing to the chronically higher levels of inflammation seen in older adults.

"There is probably a lot more immune involvement and possibly even autoimmunity in these neurodegenerative diseases than we've previously appreciated."

PROFESSOR SUSAN KAECH

"Long COVID showed people the lasting effects of that infection," says Kaech, "but a lot of infections have long-lasting effects, and we still don't know what they actually do to our tissues. There is probably a lot more immune involvement and possibly even autoimmunity in these neurodegenerative diseases than we've previously appreciated."

Kaech first got involved in Alzheimer's research at Salk to help study microglia, a type of immune cell found in the brain. But the more she spoke with her colleagues about their experiments, the more another question began to consume her.

"I was in these meetings, and I couldn't help but think, 'Man, all these people are studying the brain and behavior in animals that haven't encountered any pathogens,'" she says, referring to the sterile environment that laboratory mice are traditionally housed in. "None of their findings take into account the lifetime of infections that we experience in the real world and how that may also contribute to inflammation and deterioration in the aging brain."

Kaech is now pioneering a new experimental setup to introduce common infectious pathogens into the animals' living environment in order to study the effects of infection on aging and brain health. Researchers across the Institute are eager to learn from her findings, but amidst all the excitement, Kaech notes one of the reasons these kinds of experiments aren't done more often.

"Aging research is already expensive because the experiments take so long," she says, "but it's especially expensive and challenging to house mice in an environment that is considered biologically hazardous because of the presence of infectious pathogens."

It's obstacles like these that Salk's Unlocking Healthy Aging Initiative is looking to overcome, by generating funding support to make this critical and cutting-edge research possible. The Institute also provides a unique environment that brings immunologists like Kaech into the same rooms as neuroscientists like Allen and Gage, which inspires these ideas in the first place.

Kaech's work sets up a new paradigm for studying the biology of aging and Alzheimer's against the natural backdrop of infection—and she's not stopping there.

"Now that we're establishing these controlled ways to introduce environmental factors into our experiments, we can systematically build on that to add things like exercise or Western diets, incrementally creating conditions that more accurately model our real world," says Kaech. "Trying to study the effects of these environmental and lifestyle factors was previously considered too difficult or uncontrolled to be 'hard science,' but now we have the tools to do this in a systematic, scientific, and quantitative way."

A NEW SEASON OF ALZHEIMER'S SCIENCE

With all this scientific innovation emerging across the Institute, Salk researchers are feeling hopeful about the future of Alzheimer's treatments—but it may look a little different than we expected.

"Our studies are suggesting that there are different drivers of the disease in different people," says Salk Research Professor Pamela Maher. "This means there's probably not going to be one drug that can treat everyone. We're going to need different drugs for different people."

Maher was one of the first to take aging into account in Alzheimer's drug discovery. She was able to identify a class of compounds known as geroneuroprotectors that slowed brain aging in mice and protected their cognitive function. Maher's work has led to the development of several new drugs currently in clinical trials to treat Alzheimer's. Her sense is that Alzheimer's patients can likely be sorted into several groups based on biomarkers in their blood and that different classes of drugs could be prescribed based on which group one falls into.

Instead of treating the symptoms of Alzheimer's as they emerge, Salk scientists are developing drugs to proactively target the aging processes that may trigger the disease in the first place.

"Our studies are suggesting that there are different drivers of the disease in different people. This means there's probably not going to be one drug that can treat everyone. We're going to need different drugs for different people."

RESEARCH PROFESSOR PAMELA MAHER

"The good thing is, most of these aging pathways don't have to be completely corrected or restored to make a difference," says Gage.

When aging affects a specific molecular pathway in a person, he says, it's not that this pathway has dropped to zero percent functionality and has to be recovered back to 100 percent. It may be that by a certain age, that process is already hovering around 50 percent in most people, but if things go lower than, say, 30 percent, that's when Alzheimer's may start to kick in. This means that if a medication or lifestyle change could target that specific pathway in a person and get it back up and running around even 40 percent, that might be enough to prevent the onset of the disease.

"It's helpful that many of these fundamental aging pathways affect many aspects of our health at once," says Shadel, "so just by delaying aging, you'll likely delay many different things that could go wrong in the brain."

While there is much work left to be done, this new perspective on Alzheimer's research is finally paving the way to understanding its various root causes and how each can be best treated.

"I am confident that we will see disease-modifying medications for dementia in the near future," says Gage. "And they won't just decrease the rate of decline, which is what most current drugs aim to do—they will actually halt the disease progression, repair functional abilities, and improve patients' quality of life."

From left: Carol, Annie, Michael, and Mike Alessio.

IN THIS TOGETHER

In reflecting on her family's experience with Alzheimer's, Annie Alessio feels a certain kinship with its researchers.

"I don't know the scientists, and the scientists don't know me, but we need to fight for each other," she says.

"If things seem challenging, remember that what you're doing is for the benefit of families like mine. We're extremely grateful for what you do, and your efforts don't go unnoticed. I'm hopeful that in my lifetime, there will be someone that gets this diagnosis and comes through it on the other side."

OBSERVATIONS

Widening perspectives through plane windows and microscope lenses

Professor Axel Nimmerjahn grew up in a still-divided Germany; American soldiers were a familiar sight in his hometown in the southeastern region. The American cultural presence and leniency toward travel outside of Germany broadened Nimmerjahn's perspective on life, inspiring a curiosity and inventiveness that drew him to science and Salk.

Nimmerjahn studies the central nervous system with a focus on astrocytes—one of the most abundant cell types in the nervous system, responsible for regulating and protecting neurons—and microglia, the nervous system's resident immune cells. In addition to enriching our understanding of important nervous system cells, he also creates new tools to study them, including miniature microscopes and computational and genetic techniques.

His innovative and collaborative nature has landed him roles as the director of Salk's Waitt Advanced Biophotonics Center and the leader of a multimillion-dollar National Institutes of Health BRAIN (Brain Research Through Advancing Innovative Neurotechnologies®) Initiative Program. He has also been recognized with numerous awards over the years: a Whitehall Foundation Award, recognition as a Rita Allen Scholar, and National Institutes of Health honors and grants, such as a Director's New Innovator Award, Exceptional Unconventional Research Enabling Knowledge Acceleration (EUREKA) Award, and multiple BRAIN Initiative Awards.

Reflecting Nimmerjahn's many honors, he was promoted to full professor at Salk in April 2024—an exciting landmark in his ongoing scientific story.

Inside Salk *sat down with Nimmerjahn to hear about his journey to world-renowned researcher.*

AXEL NIMME

RJAHN

What was it like growing up in a divided country?

AN: I grew up seeing military personnel and hearing stories about people risking and losing their lives trying to cross the inner-German border, raveling from East Germany to West Germany. It felt normal. But now, in retrospect, I realize how strange these things were to witness growing up.

We were relatively lucky to live where we did, though. My parents grew up during World War II and had to flee from East Germany to West Germany, which landed us in the western part of Germany where there were no restrictions on travel to other countries. And my parents really wanted to travel with me and my older brother. Looking back, those trips were very important because they opened my mind to all different cultures and ways of life. Doing and seeing all these different things helps you understand that things can be done in a lot of different ways, and it made me really curious and explorative in all parts of my life. I realized there's no one way to do anything.

How did your interest in science develop?

AN: My parents are physical therapists. Since they grew up in postwar Germany, there wasn't an awful lot of opportunity to go to college or university, and they had lost everything they had. So they worked in a hospital, and that ended up influencing my trajectory. At the breakfast table, we'd discuss the things they were working on with their patients, which you'd think would prompt an interest in immunology or genetics, but instead I developed an early interest in physics. Yet when I got to the end of high school, I was still torn between studying medicine or physics.

In the end, I decided on physics, which, looking back now, was the best decision for me. It really helped me think deeply from the most basic principles, allowing me to tackle tough scientific problems for which there are no textbooks—problems for which you have to figure out how to even address the question.

And how did you get from studying physics to studying the central nervous system?

AN: Physics was great, but I always had this interest in medicine or neuroscience that stuck with me through university. At the end of my physics degree, I had the opportunity to do my master's and PhD at the Max Planck Institute for Medical Research, where I could combine both physics and neuroscience.

I joined the lab of someone who, like me, had a background in physics and then decided to move into another science. When I started my master's program, I worked on solving physics problems on light distortion in order to create miniaturized microscopes to study processes in the brain. We approached this problem of measuring the brain and other tissues through the lens of physics.

My PhD advisor had invented the very first miniaturized two-photon microscope during his postdoctoral research, and then I was his first graduate student. We worked together on the next generation of microscopes, and that was my entry point into neuroscience.

When did you begin to focus on glial cells?

AN: There weren't a lot of people studying glial cells where I was. If anything, they were interested in using them as something to compare neurons to. When you look at their electrical activity, they seem silent. When you measure their chemical activity, they show slow, varied changes. Glial cells were used as the "other" cell type to contrast neurons with. Discoveries were made about glial cells in this process, but it was in pursuit of new information about neurons.

While everyone was coming up with these new ways to measure and study neurons, we continued coming across glial cells. A lot of people I worked with were like, "Oh yeah, don't worry about those," to which I responded, "What?!" Thankfully my advisor was generous enough to let me explore glial cells—and the imaging tools we'd been creating to study neurons were already perfect for studying them. That's been the focus of my whole career since.

What made you decide to leave Germany?

AN: I had been reading about some researchers' work at Stanford University during my graduate studies, then was lucky enough to head to Stanford with those investigators as my new mentors. Being there allowed me to dig deeper into the biology of what I was studying while not losing touch with all the technical development—and what I did there became the basis for my lab at Salk. Earlier, I was looking mostly at the brain, but since coming to Salk, my lab and I expanded to the spinal cord, and we have continued to look at both of these nervous system regions since then.

You've created a microscope small enough to fit on the tip of a human finger. Is the plan to keep making smaller and smaller microscopes?

AN: So, it's a little more complicated—the microscopes I worked on as a graduate student were wearable two-photon microscopes (microscopes that capture images by exciting electrons using two massless particles of light called photons); the ones I worked on as a postdoc were wearable one-photon microscopes (microscopes that capture images by exciting electrons using one photon, which cannot image tissues as deeply as two-photon microscopes). We are continuing to develop wearable

> "We are continuing to develop wearable one-photon microscopes, which, like an iPhone, we can make more sophisticated with each generation."
>
> PROFESSOR AXEL NIMMERJAHN

one-photon microscopes, which, like an iPhone, we can make more sophisticated with each generation. We can create additional capabilities, such as offering more color channels, and upgrade features like light sensitivity and image resolution.

We're also hoping to establish a miniaturized three-photon microscope. One of the major challenges in the field is that light used for one- and two-photon imaging can only penetrate so far into a tissue. But there's a lot of interesting stuff happening at tissue depths we cannot reach, so three-photon microscopes will be a huge help.

What sorts of questions can you ask and answer with your sophisticated microscopes?

AN: Prior to our microscopes, you could only measure small tissue regions at a time. Now, we can image multiple brain or spinal cord regions at once without sacrificing resolution. This is crucial because we know that whenever our bodies experience a stimulus—like touching a hot stove—there aren't just a few neurons or a few cells stimulated by that. It's actually distributed over a large area of many cells. And in order to understand how that information is encoded, and how that process transforms in diseases, we need imaging techniques that can capture larger areas and measure multiple cell types at once to see how everything is connected.

In addition to microscopes, you've also been helping to develop organoids. How is that going?

AN: Collaboration is one of my favorite things. We've been working with Salk Professor Rusty Gage, who pioneered these organoids (3D lab-grown models of human tissues), to take a step closer to human biology with our microscopes. We want to get closer to human biology so we can treat diseases, which is a very long process that starts with models like organoids and moves into clinical trials before finally ending with a usable drug.

Rusty's lab has made a major step in creating human brain organoids that include both neurons and non-neuronal brain immune cells. Now we can see how neurons, immune cells, and pathogens or substances they produce interact. For example, if we catch a viral or bacterial infection, how do the immune cells in your brain react to that? Can we modulate that response? And what about genetic changes? We know that aging and Alzheimer's disease are linked to genetic mutations that affect immune cell function in the brain. Could we potentially modulate their function to protect neurons from dysfunction?

Organoids are a way to study these questions, and while it's not a perfect system, it's a good step toward one.

What future research questions excite you right now?

AN: Our microscopes have really opened up so many possibilities and revealed so much new information. Recently, we discovered that astrocytes are involved in pain signaling in mice. I'm really excited to figure out how exactly they contribute to pain signaling, and eventually extend our findings into human cells. Hopefully, this can inspire new treatments for chronic pain. I am also really excited about the upcoming Neuroimmunology Initiative at Salk, which the NOMIS Foundation is funding to support our investigation into the interface between the nervous and immune systems across a number of disease contexts.

Some of the greatest challenges of our time—treating chronic pain, Alzheimer's disease, and neuroimmune disorders like multiple sclerosis—require a team of investigators with expertise in all different areas. Going forward, when you look at papers in high-profile journals, you're going to start gradually seeing more authors, institutions, and complex problems. We need to work as a team—and I'm happy to participate in a leading or supporting role just the same.

INSIGHTS

Enhancing equity and inclusion at Salk and beyond

Over the course of nearly 30 years dedicated to advocacy work, Jálin B. Johnson has served those in need and has given a voice to the voiceless—a principle that has guided her throughout her career. This commitment continues to shape her work as she steps into the role of director of Salk's Office of Equity & Inclusion (OEI).

Jálin Johnson

ADVOCACY IN ACTION

Working with the state of California and the California State University system in the mid-1990s, Johnson aided the unhoused, members of the military community, first-generation and international college students, and parents and caregivers striving to return to school. These early experiences in education advocacy led her to work with special needs students in K-12 education. She simultaneously pursued her own academic advancement by earning a master's in business administration and a doctorate in education.

"The dual engagement in practice and academia enriched my perspective and expertise," Johnson recalls. "Working within the special needs education community, combined with advocacy experience in higher education, formed a solid foundation for my roles in academia."

Johnson later returned to higher education, advancing from assistant professor to full professor in business and organizational leadership, serving as a curriculum developer, doctoral mentor, dissertation chair, and member of an institutional review board. She also served in leadership as the vice chair of faculty personnel and, most recently, as the senior diversity officer and vice chancellor of Equity & Inclusion for the University of Massachusetts Global.

CREATING INCLUSIVE SPACES

Now at the Salk Institute, Johnson admires the community's diversity of backgrounds and scientific expertise.

Johnson is drawing on this dynamic to shape her role at Salk, aiming to uplift the community's values and ensure that the OEI team's work successfully enhances the cultural environment.

"At Salk, there is a collective desire to contribute, learn, and strengthen the community, with allies repeatedly asking how they can help. This engagement is not only refreshing but also provides an opportunity to understand what drives everyone."

JÁLIN JOHNSON

She is quick to emphasize that advocacy work doesn't live solely with her team—it is a collective community effort. She highlights the ongoing work of countless Salk colleagues, including the Office of People & Culture; the Development and Education Outreach teams; the Justice, Equity, Diversity, and Inclusion (JEDI) Council; and countless others who regularly collaborate to support the Salk community and our partners.

She recognizes the abundance of activities and programs the Institute has put in place to advance inclusion and community and is focused on creating an environment in which those who wish to be involved, and participate in JEDI-based efforts, may do so while maintaining a dedication to the science and innovation for which Salk is known. According to Johnson, achieving this level of enthusiasm and engagement will require consistent communication and time spent listening to and learning from knowledgeable peers.

Johnson is optimistic about these opportunities for connection and is looking forward to seeing them grow as she and her team work to enhance the Institute's inclusive culture.

DIVERSIFYING CAREER OPPORTUNITIES AT SALK AND BEYOND

Johnson celebrates the Institute's recent strides toward diversifying STEM careers, with particular praise for the collective efforts of faculty and the OEI team in developing several programs that provide opportunities in research, education, and networking for undergraduate students, graduate students, and postdoctoral trainees from underserved communities, giving them a competitive advantage when they pursue the next steps in their careers. These programs are known as Rising Stars, Symposium for a Diverse Inclusive Scientific Community Offering a Vision for an Ecosystem Reimagined (DISCOVER), Summer Undergraduate Research Fellowship (SURF), and Salk Elevating Diversity in Graduate Education (EDGE).

"It was a true team effort from our faculty, Office of People & Culture, JEDI Council, and affinity groups, who have all galvanized the Salk community to show up and make these initiatives happen," says Johnson.

"With this infusion of expertise, energy, and unwavering commitment, the future of our community and career opportunities at Salk looks promisingly diverse and inclusive."

LABARTA-BAJO

An immunologist's journey from Barcelona and ballet to the brain

Whether dancing in Spain or surfing in San Diego, Lara Labarta-Bajo has always celebrated the power of the human body. Now a postdoctoral researcher in Associate Professor Nicola Allen's lab at Salk, she studies how the immune system connects the body to the brain and how this relationship evolves as we age.

Labarta-Bajo grew up in Barcelona, a seaside city that doubles as a science education and industry hub.

"It's funny, people compare it to San Diego," says Labarta-Bajo, "and some will even refer to the region as 'little California.'"

Outside, she was swaddled by the sun and sea. At home, she was surrounded by numbers. Both her parents are engineers, and her brother a mathematician, "but I was more interested in the biology of our bodies."

Labarta-Bajo was an active child, always on the move. She spent most of her youth out in nature, playing sports, or dancing ballet.

"Ballet really wires your brain in a certain way," she says. "It makes you move in a very controlled manner, so you become aware of every muscle in your body."

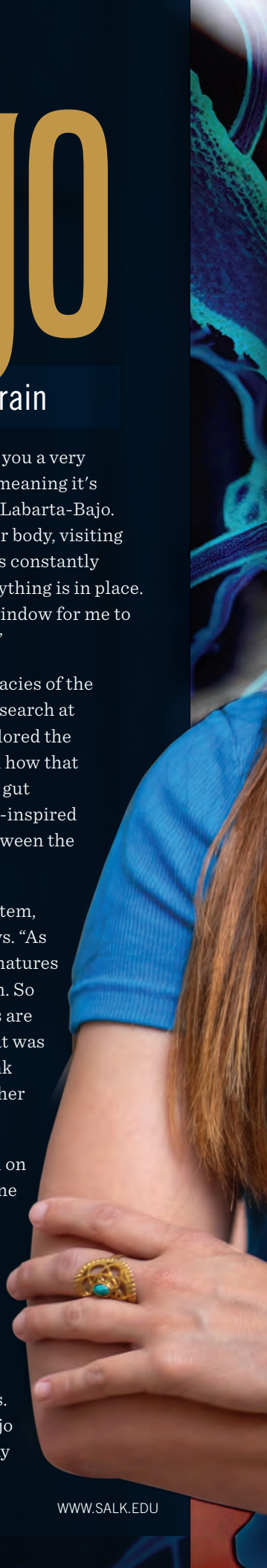
This deep awareness of her mind and body led Labarta-Bajo to pursue an undergraduate degree in biology. But while each class provided a peek into a different part of the body, she found herself most excited when studying its physiology as a whole. Then, during a summer internship in a lab at Virginia Tech, she found a way to satiate her wide-ranging interests.

"Immunology is a field that gives you a very systems-level view of your body, meaning it's not restricted to one location," says Labarta-Bajo. "Your immune system moves around your body, visiting your skin, your brain, your intestines. It's constantly circulating, surveying, making sure everything is in place. So I felt like the immune system was a window for me to better understand how our bodies work."

Labarta-Bajo went on to study the intricacies of the immune system through her graduate research at UC San Diego. During that time, she explored the body's response to chronic infection and how that constant immune activity can affect our gut health. She's since returned to her ballet-inspired interests by studying the connection between the brain and body here at Salk.

"When we're born, we have a nervous system, and we have an immune system," she says. "As we go through life, the immune system matures and ages, and so does the nervous system. So how is it possible that these two systems are present but don't talk to each other? That was an intriguing question to me. I don't think it's possible—I think they talk to each other often."

Her instincts appear to be correct, based on a growing body of research on the immune activity in and around the brain. Allen is a trailblazer in this field and an expert on a type of brain immune cell called astrocytes. These star-shaped cells were traditionally thought to simply feed and protect our neurons—the cells whose electrical signals are responsible for all our thoughts, feelings, and actions. But scientists like Allen and Labarta-Bajo are helping us realize that astrocytes may



have a much larger role in brain function than was previously appreciated.

The immune system's primary job is to find and destroy invading pathogens, but it also has to tell the rest of the body that this battle is happening. These messages come in the form of inflammatory signals, which serve as helpful warnings when sent in moderation but can become damaging in excess.

"Astrocytes are at the interface between your neurons and the rest of your body," says Labarta-Bajo. "They have this privileged position where they can read the memos that are getting sent through the blood in the form of inflammatory molecules. Your astrocytes are picking up the message, deciding how to interpret it, and conveying the message to the neurons. And that's what we're working on in the lab—how does this peripheral threat affect your brain?"

Labarta-Bajo and her colleagues are now identifying specific molecules that astrocytes use to read the incoming memos and trigger inflammatory responses in the brain. She's also especially interested in how this communication between the immune and nervous systems evolves throughout our lives.

Aging is associated with higher levels of inflammation across many organ systems, including the brain. But, interestingly, Allen's lab is finding that astrocytes become especially inflammatory in brain regions that control how we move.

"When we manipulate the activity of certain molecules in a mouse's astrocytes, we can see that has an effect on the way the mouse moves," says Labarta-Bajo. "So maybe we can manipulate these molecules during aging to delay the loss of motor abilities. That's the question now—how can we manipulate astrocytes to improve our brain function?"

Labarta-Bajo is hopeful this work will lead to future therapeutics for reducing brain inflammation and maintaining mobility in later life. In the meantime, she's looking forward to many more years of science and surfing ahead of her.

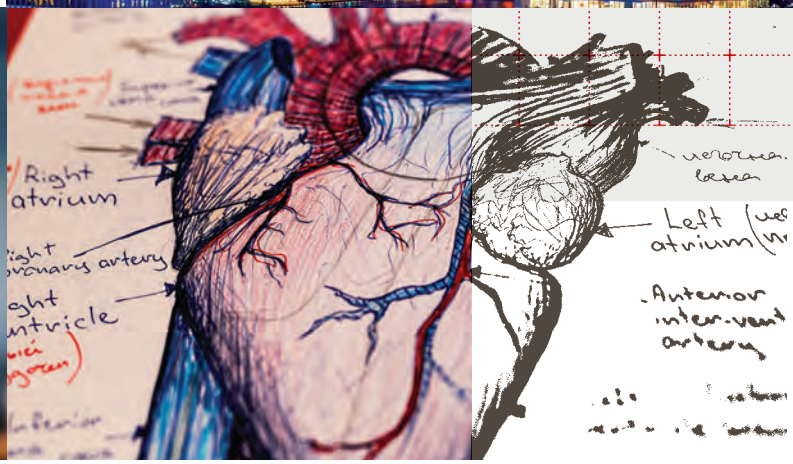
"It really gets me excited to see the new frontiers we can push," she says, "by having astrocytes and the immune system at the center of it all."

Hear more at www.salk.edu/podcast

GRATITUDE

Professor or partner?

Luc Jansen's switch from science to law



When Luc Jansen didn't get into medical school on the first try, he enrolled in a biology master's program. In the Netherlands, where Jansen grew up, only half of the applicants in the country could enroll in medical school each year based on a random lottery. He figured that, since biology and medicine had overlapping curricula, a year of biology wouldn't set him too far behind his peers if he transferred into medicine a year later.

But another year came and went, and Jansen was still studying biology. Unsure what career outcomes looked like with a biology degree, he took up a second academic track: law. For Jansen, simultaneously completing two master's degrees—one in biology and another in law—meant he would have to make a difficult career decision in the near future.

"I was actively deciding what career path to take when I came to Salk in 2003," recalls Jansen. "I wound up at the Institute through a series of connections—I knew a Dutch professor in New York City, who knew Jan Karlseder was at Salk doing his postdoctoral research, who suggested I join the lab of Andrew Dillin, an assistant professor at the time."

Jansen got the chance to work alongside Dillin for six months. One day, Jansen took a risk and asked Dillin to connect him with Salk's legal office to get their perspective on other career trajectories. While this could have been received as noncommittal or even rude, Dillin enthusiastically pushed Jansen to explore the option—a memory that has stuck with Jansen for 20 years as a reflection of the encouraging and collaborative nature of Salk scientists.

As his time at Salk came to an end, Jansen felt warmly about his experiences and the people he had met—but he still had another career track to try out, so he rotated in a law office next.

When he thought about a future in academia, Jansen contemplated funding insecurity and the potential need to relocate based on available academic opportunities. When he thought about a future in law, he saw stability and a more controllable trajectory. So he officially committed to law. "Though if someone had offered me a full professorship at Salk in that moment, I would have certainly taken that road instead," Jansen says with a laugh.

After finishing his biology and law degrees in the Netherlands, Jansen went to Columbia University to complete law school. He attempted to hold on to some of his scientific background by studying patent law, hopeful that he could work in biotechnology helping scientists license their discoveries. But he eventually switched to corporate law.

"I'm doing private equity fund formation now, which generally has nothing to do with science," says Jansen. "But thinking outside of the box, finding new ways to do things, collaborating with others—

Jansen's first Salk event in New York featured a presentation by Reuben Shaw.

"Thinking outside of the box, finding new ways to do things, collaborating with others—these are all scientific skills that are translatable to the legal field."

LUC JANSEN

these are all scientific skills that are translatable to the legal field. And now I have unique legal skills that can help me give back to Salk and support the incredibly impressive scientists and research happening there."

Two years ago, Jansen transferred to McDermott Will & Emery LLP as a partner in its corporate group. Despite the many twists and turns along his path to "Big Law," Jansen is happy with where he landed in the end. His office at One Vanderbilt is a landmark in New York City, which he is excited to share with Salk faculty after recently reconnecting with some familiar faces.

In April 2024, Jansen helped host what he hopes to be the first in a series of Salk events in New York. Surrounded by a view of the city's skyscrapers, Professor Reuben Shaw shared his science with an East Coast audience. Jansen's colleagues learned about genetics and cell metabolism and how studying these fundamental processes can help us one day treat or prevent diseases like cancer and diabetes.

Events like this help the Institute connect with leaders in different cities and industries and inform them about the importance of continued investment in basic research, which explores the fundamental principles of life. Jansen personally loves the challenge of communicating how exciting and life-changing basic biology research can be and hopes that this will translate into donations and collaborations with Salk in the future.

"I love Salk science because it's basic," says Jansen. "Basic science touches everything—if your findings are fundamental enough, everything connects. Everything has translational potential."

JOHN ADLER

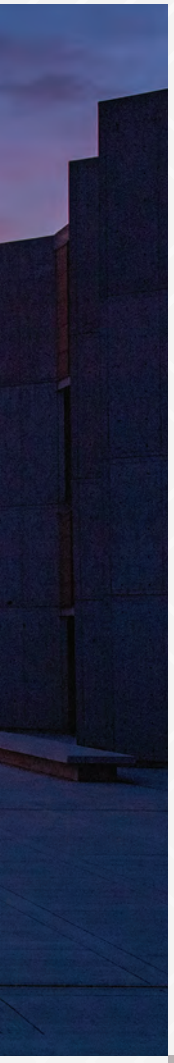
IN MEMORIAM

John Adler, friend and former trustee, dies at age 96

The Salk Institute mourns the loss of businessman and philanthropist John Adler, who served on the Institute's Board of Trustees from 1991 to 2004. He died June 11, 2024, in Greenwich, Connecticut, at the age of 96.

Adler generously supported the Salk Institute for decades, donating $6.7 million to launch the Adler Foundation Symposium on Alzheimer's Disease Endowment, establish the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease, and support many other research efforts. For more than 30 years, the annual Adler Symposium brought together scientists working on different aspects of Alzheimer's disease to share ideas and build new collaborations.

"John was an outstanding trustee for Salk for many years," says Professor Rusty Gage, former Salk president and current holder of the Vi and John Adler Chair. "His sage counsel and generosity of time and resources have benefited the Institute immensely. His legacy of the Adler Symposium, focusing on age-related neurodegenerative diseases, has brought international acclaim to the Salk Institute, forging strong bonds and research collaborations around the world. We are grateful that John was part of our community."



ELECTIONS

Professor Susan Kaech elected to US National Academy of Sciences

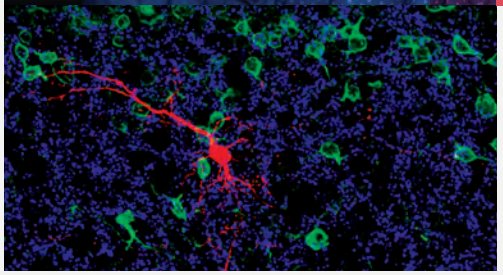
Kaech is a professor, director of the NOMIS Center for Immunobiology and Microbial Pathogenesis, and NOMIS Chair at Salk. Her work has helped transform the fields of immunology and cancer biology and inspired new approaches to cancer immunotherapy. She is one of 120 new members and 24 international members to be elected to the academy this year, in recognition of her distinguished and continuing achievements in original research. The election is considered one of the highest honors accorded to a scientist in the United States.

"Sue's work continues to shape the way we understand and treat viral infection, chronic disease, and cancer. We are inspired by her considerable influence on the field of immunobiology and thrilled to see her recognized by the prestigious National Academy of Sciences."

SALK PRESIDENT GERALD JOYCE

SUSAN KAECH

MARTYN GOULDING



Professor Martyn Goulding elected to American Academy of Arts & Sciences

Goulding is a professor and Frederick W. and Joanna J. Mitchell Chair at Salk. He is a neuroscientist who studies the sensory and motor circuits in the spinal cord that control a range of different behaviors, from simple reflexes like scratching to more complex actions like walking or catching a ball. The American Academy of Arts & Sciences honors excellence and convenes leaders from every field of human endeavor to examine new ideas, address issues of importance to the nation and the world, and work together "to cultivate every art and science which may tend to advance the interest, honor, dignity, and happiness of a free, independent, and virtuous people."

Professor Satchin Panda named Fellow of the American Association for the Advancement of Science

Panda is a professor and Rita and Richard Atkinson Chair at Salk. He explores the genes, molecules, and cells that keep the whole body on the same circadian clock, and how they are linked to health and disease. The American Association for the Advancement of Science (AAAS) is the world's largest general scientific society and publisher of the journal *Science*. This election recognizes Panda's contributions to the field of chronobiology, particularly as they relate to obesity and human health.

SATCHIN PANDA

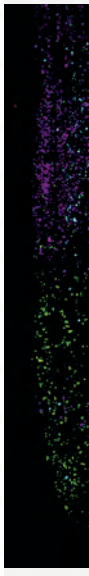
"His pioneering work in circadian biology has illuminated the intricacies of our body's internal clock and opened new avenues for understanding human health and preventing and managing chronic diseases. We are delighted to celebrate this prestigious recognition with him."

SALK PRESIDENT GERALD JOYCE

JANELLE AYRES

Professor Janelle Ayres elected to American Academy of Microbiology

Ayres is a professor, head of the Molecular and Systems Physiology Laboratory, and Salk Institute Legacy Chair. She uses evolutionary theory and microbes to understand how our physiological systems and brains interact with each other to promote optimal health. Fellows of the Academy, an honorific leadership group within the American Society for Microbiology, are elected annually through a highly selective, peer-reviewed process based on their records of scientific achievement and original contributions that have advanced microbiology.

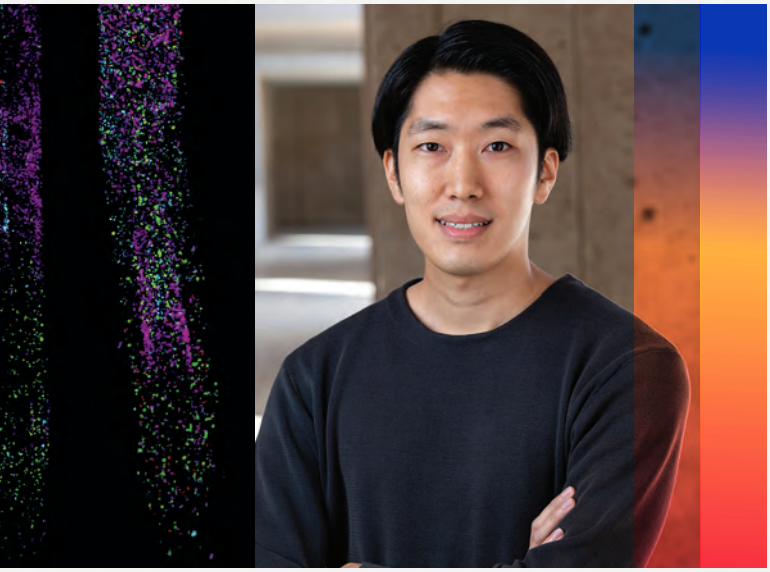


Professors Joanne Chory and Joseph Ecker win Arabidopsis Community Lifetime Achievement Awards

Chory, a professor, director of the Plant Molecular and Cellular Biology Laboratory, founding director of Salk's Harnessing Plants Initiative, Howard H. and Maryam R. Newman Chair in Plant Biology at Salk, and a Howard Hughes Medical Institute investigator, and Ecker, a professor, director of the Genomic Analysis Laboratory, Salk International Council Chair in Genetics, and Howard Hughes Medical Institute investigator, were chosen by the North American Arabidopsis Steering Committee as inaugural Arabidopsis Community Lifetime Achievement Award recipients, which honors the researchers for their distinguished research on the flowering weed *Arabidopsis thaliana*, the first plant to have its genome sequenced and an important research tool. They join three other outstanding awardees whose achievements in research, community service, mentoring, and innovative teaching have spanned decades and have positively impacted plant biology and society in numerous ways.

JOANNE CHORY

JOSEPH ECKER



TATSUYA NOBORI

Postdoctoral researcher Tatsuya Nobori wins Biochemical Society's Early Career Research Award

Nobori, a trainee in Professor Joseph Ecker's lab, was recognized for his studies of plant-microbe interactions, as well as for developing a new method called PHYTOMap, which allows the 3D analysis of gene expression in whole plant tissues. The award recognizes the "impact of research carried out in the molecular biosciences by early career scientists."

Professor Terrence Sejnowski wins 2024 Brain Prize and other honors

TERRENCE SEJNOWSKI

Sejnowski is a professor, head of the Computational Neurobiology Laboratory, and Francis Crick Chair at Salk. He received the 2024 Brain Prize—the world's largest neuroscience research prize—from the Lundbeck Foundation for "pioneering the field of computational and theoretical neuroscience, making seminal contributions to our understanding of the brain, and paving the way for the development of brain-inspired artificial intelligence." He shared the prize with Larry Abbott of Columbia University and Haim Sompolinsky of Harvard University. They received the award from His Royal Highness King Frederik of Denmark at an event in Copenhagen in May.

Sejnowski was also recently presented with the International Neural Network Society's Hermann von Helmholtz Award for his "paradigm-changing and long-lasting" contributions to the field of neural networks, and was awarded a Doctor of Science Honorary Degree from his alma mater, Princeton University, at its May 28 Commencement.

CHRISTINA TOWERS

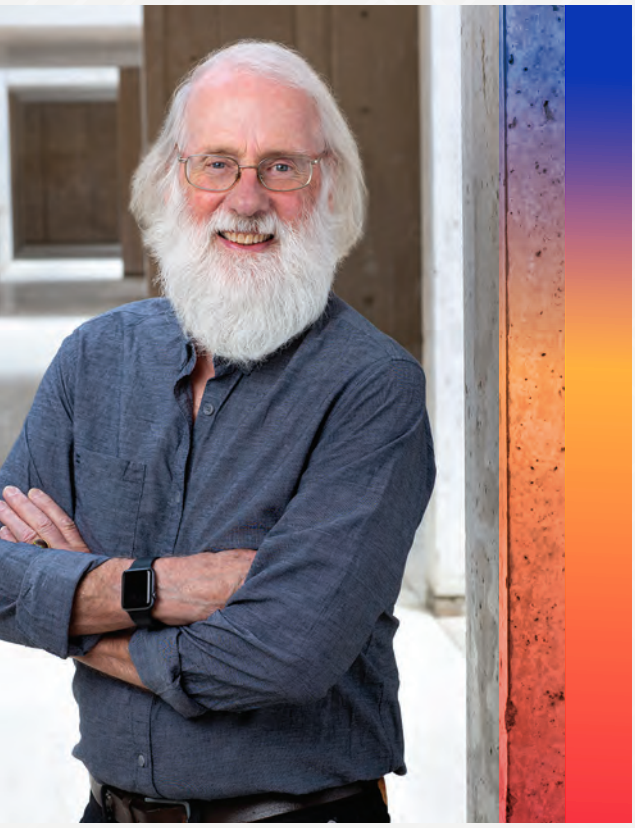
Assistant Professor Christina Towers earns Lustgarten Award

Towers is an assistant professor and Richard Heyman and Anne Daigle Endowed Developmental Chair at Salk. She uses a combination of techniques to uncover how cancer cells recycle both their own nutrients and the power-generating structures called mitochondria in order to survive. Her goal is to develop targeted cancer therapies that kill cancer cells by blocking cellular recycling pathways. Towers was recognized with a 2024 Lustgarten Foundation-AACR Career Development Award for Pancreatic Cancer Research, in Honor of John Robert Lewis, which aims to reduce the gap in funding for underrepresented minority scientists who conduct research that contributes to a better understanding and treatment of pancreatic cancer. Recipients are awarded a three-year, $300,000 grant for meritorious basic, translational, clinical, or population sciences research.

Professor Joanne Chory honored with Benjamin Franklin Medal in Life Science

Chory is a professor, director of the Plant Molecular and Cellular Biology Laboratory, founding director of Salk's Harnessing Plants Initiative, Howard H. and Maryam R. Newman Chair in Plant Biology at Salk, and a Howard Hughes Medical Institute Investigator. She was honored by the Franklin Institute in Philadelphia with the Benjamin Franklin Medal in Life Science for her achievements in plant science. She received a gold medal and a $10,000 honorarium at The Franklin Institute Awards Ceremony in April. Chory is now part of an esteemed group of exceptional scientists and engineers who have been recognized as Franklin laureates, including Nikola Tesla, Marie and Pierre Curie, Thomas Edison, Albert Einstein, and Jane Goodall.

JOANNE CHORY



TONY HUNTER

Professor Tony Hunter honored with American Association for Cancer Research Princess Takamatsu Memorial Lectureship Award

Hunter is an American Cancer Society professor and Renato Dulbecco Chair at Salk. He studies how cells regulate their growth and division and how mutations in genes that regulate cell growth lead to cancer. In 1979, his lab discovered that phosphate can be attached to the amino acid tyrosine in proteins—a finding that led to the development of the drug Gleevec, a targeted therapy for leukemia and other cancers. This early success has now led to the development of a new class of cancer drugs that target misbehaving tyrosine kinases. Currently, Hunter's group works to identify growth factors and cytokines produced in the pancreatic cancer microenvironment to promote tumor progression. The award recognizes an "individual scientist whose novel and significant work has had or may have a far-reaching impact on the detection, diagnosis, treatment, or prevention of cancer."

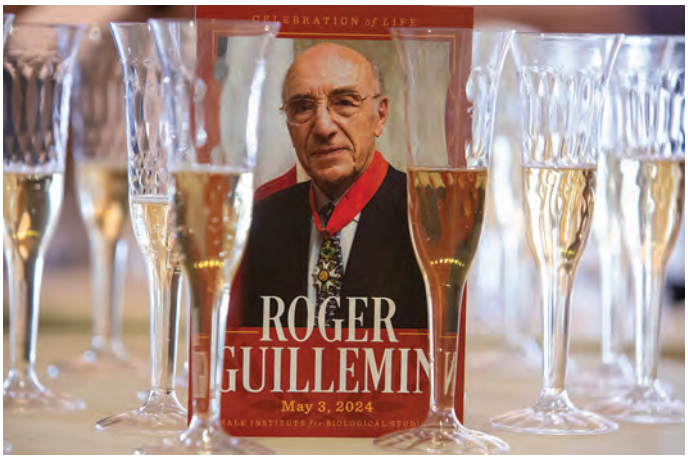
EVENTS

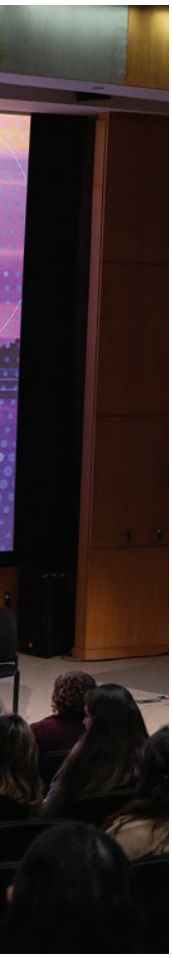
THE POWER OF PERSISTENCE—WOMEN TRANSFORMING CANCER RESEARCH AND CARE

In recognition of International Women's Day, Salk and the Lustgarten Foundation cohosted a symposium that aimed to foster collaboration, mentorship, and the exchange of ideas to support the continued advancement of cancer research and care. The program was chaired by Elizabeth Jaffee, professor at Johns Hopkins University, and featured scientists from around the country, including Salk Assistant Professor Dannielle Engle. Attendees took part in a speed mentoring session to help empower the next generation of scientists and drive the next wave of transformative breakthroughs in the fight against cancer.


Claire Guillemin

Jonathan Salk





From left: Julie Sutcliffe, Stephanie Dougan, and Dannielle Engle.

Diana Hargreaves

Christina Towers

SALK CELEBRATES THE LIFE OF DISTINGUISHED PROFESSOR EMERITUS ROGER GUILLEMIN

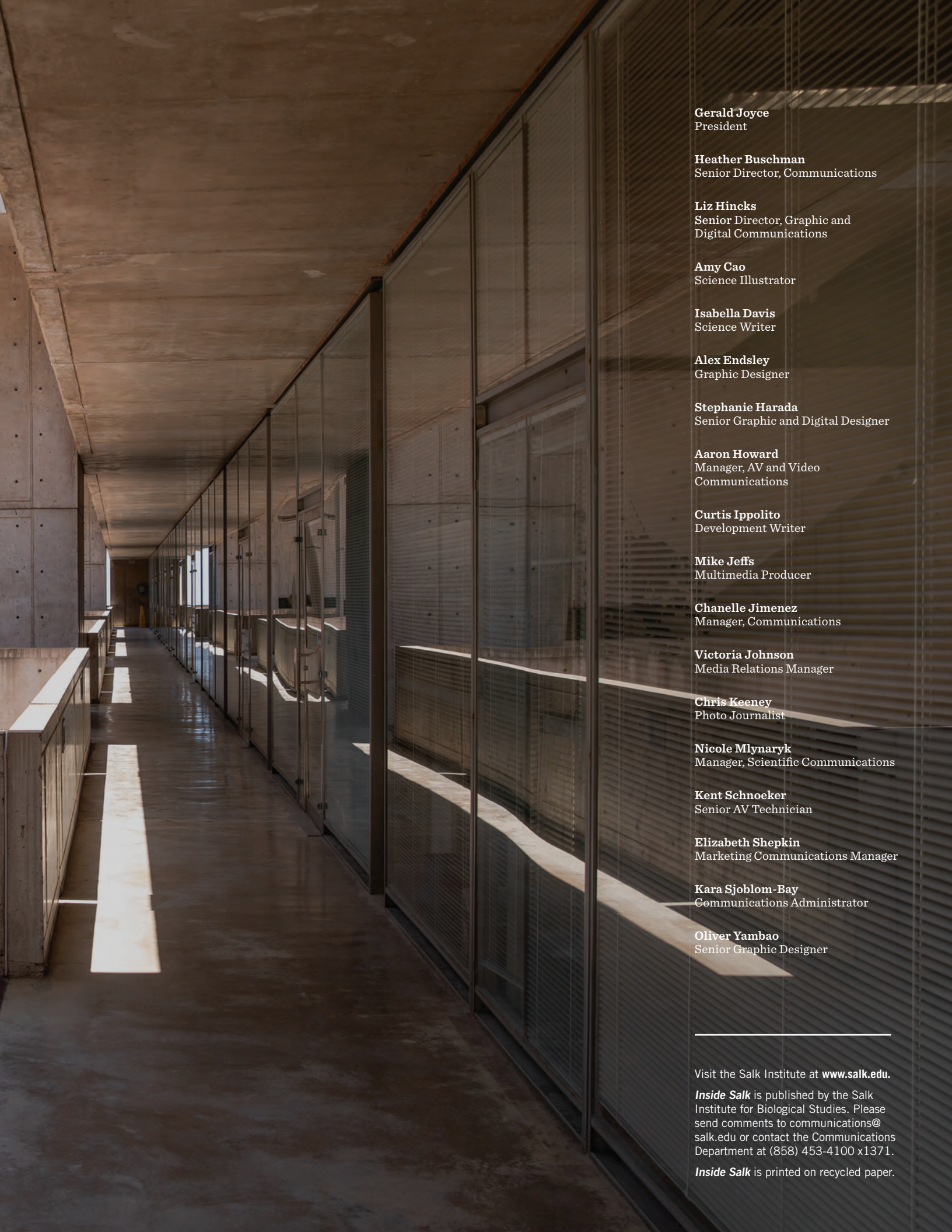
On May 3, the Salk Institute was honored to host a Celebration of Life for Nobel Laureate and Distinguished Professor Emeritus Roger Guillemin. The event featured a series of scientific lectures from fellow scientists and friends, as well as a remembrance, during which Guillemin's family and friends shared personal stories and photos, and concluded with a champagne toast.

Videos and photos of the scientific lectures and remembrance are available at:

www.salk.edu/guillemin-celebration

THE SCIENCE & (IN)JUSTICE OF HIV/AIDS

On June 11, Salk held the second annual Salk Science & Justice program: "The Science & (In)Justice of HIV/AIDS." The event featured San Diego Mayor Todd Gloria and Salk Associate Professor Dmitry Lyumkis, who discussed the intersection of research and social justice in relation to HIV and AIDS, held a Q&A with the audience, and held a closing with Jálin Johnson, director of Salk's Office of Equity & Inclusion.



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