WINTER | 2024

InsideSalk

Connecting the dots

FROM THE IMMUNE SYSTEM TO THE BRAIN AND BACK

CONTENTS

ON THE COVER:

Crosstalk between the immune and nervous systems—and the role this intersection plays in health and disease—has long been understudied. Now, with support from the NOMIS Foundation, Salk Institute scientists are at the forefront of this emerging interdisciplinary field.

Dear Friends,

This issue marks the end of our "Year of Healthy Aging," but our commitment to this cause shows no signs of slowing down. Thanks to our generous supporters, Salk's Unlocking Healthy Aging Initiative will continue to champion research on this topic for years to come.

Our approach to healthy aging is rooted in collaboration and interdisciplinary thinking. We're excited to apply this same energy to the Salk Institute's new Neuroimmunology Initiative—a deep dive into the complex interplay between the immune and nervous systems. This underappreciated crosstalk plays a vital role in health and disease, and Salk scientists are at the forefront of this emerging field.

With initial funding from the NOMIS Foundation, the Neuroimmunology Initiative empowers our team to tackle critical scientific questions that could open entirely new avenues of research. Ultimately, this work may pave the way for innovative therapies for a range of disorders, including Alzheimer's disease, ALS, long COVID, and several forms of cancer.

I invite you to read on to meet Salk Fellow Talmo Pereira, whose AI-based motion-tracking technology is helping our scientists answer a surprising range of research questions. Also get to know Kay Watt, a program manager helping to mitigate climate change through our Harnessing Plants Initiative. Finally, learn how postdoctoral researcher Pau Esparza-Moltó's research on mitochondria ushers our healthy aging science into the new year.

Lastly, we pay our respects to Salk Professor Joanne Chory, pioneering plant biologist and founding director of our Harnessing Plants Initiative. She passed away last month and we miss her immensely, but her legacy will live on.

I hope you find this issue of *Inside Salk* magazine inspiring, and I wish you a wonderful holiday season and a healthy, happy 2025.

Thank you for being an essential part of our mission.

Warmest regards,

Gerald Joyce
Salk Institute President

"Our approach to healthy aging is rooted in collaboration and interdisciplinary thinking. We're excited to apply this same energy to the Salk Institute's new Neuroimmunology Initiative—a deep dive into the complex interplay between the immune and nervous systems."

Head to toe, lab to lab

In the human body, very little happens in isolation. Groups of immune cells team up to fight infections. Blood cells circulate them through the body, delivering fuel and oxygen to each organ along the way. Metabolic processes in the gut, liver, and kidneys go on to shape our blood pressure and heart health. The human body contains 11 different organ systems and hundreds of different cell types, but how they all interact and work together is what makes being, growing, and healing possible.

Salk scientists are also using teamwork to build something bigger than the sum of its parts. By blending disciplines and forging collaborations between labs, our scientists make more innovative, comprehensive, and impactful discoveries.

How can different cell types interact with each other? Could two seemingly separate bodily systems actually be intricately intertwined? By connecting these dots, we gain a more holistic understanding of ourselves.

Our researchers' recent studies reveal how our immune cells recruit their friends to help fight infections, how fat metabolism in the liver can affect our heart health, and how excessive exercise can have serious consequences across the entire body. The new frontiers of science lay at these exciting intersections between immunology, neuroscience, metabolism, and more—right where Salk scientists are hard at work.

CHOLESTEROL IS NOT THE ONLY LIPID INVOLVED IN TRANS FAT-DRIVEN CARDIOVASCULAR DISEASE

NATURE NEUROSCIENCE 11/2024

High cholesterol has long been the focus of many heart health campaigns due to its role in forming artery-clogging plaques that can lead to stroke, heart attack, or arterial disease. But new research from Professor Christian Metallo, postdoctoral researcher Jivani Gengatharan, and colleagues recently revealed that another class of lipids, called sphingolipids, can also contribute to arterial plaques and heart disease. When the team tracked the flow of dietary fats throughout the body, they found that trans fats were being metabolized into sphingolipids, and this drove the liver to secrete artery-clogging molecules into the bloodstream. The discovery that sphingolipids, and not just cholesterol, can directly contribute to atherosclerotic heart disease opens up a whole new set of molecules and pathways that could be targeted with new drugs to ward off cardiovascular disease, heart attack, and stroke.

"Eating trans fats is known to drive heart disease. We used this phenomenon to understand the biological mechanisms putting us at risk."

PROFESSOR CHRISTIAN METALLO

FUEL LEVEL LOW! ENERGY DEFICITS HARM ATHLETES' HEALTH, NEW RESEARCH TOOL REVEALS HOW

Depicted on a pot inspired by the ancient Greek origins of the Olympics, two torch-wielding athletes and their coinciding mouse models are shown with REDs (left) and without (right).

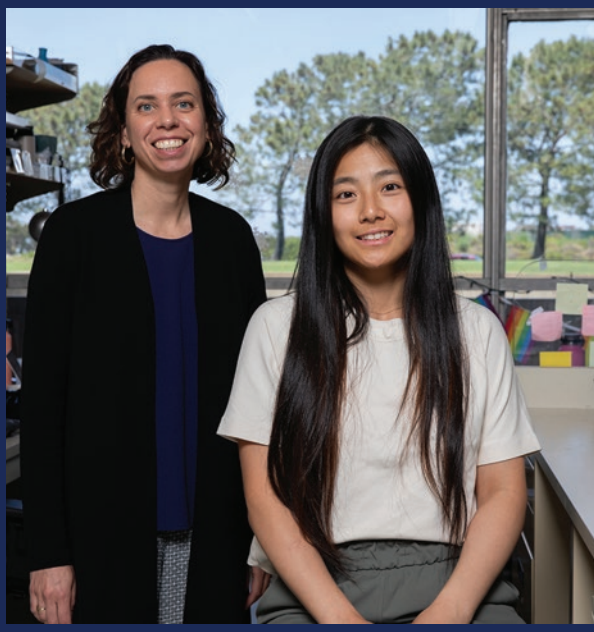
CELL METABOLISM 09/2024

In 2014, the International Olympic Committee named a syndrome affecting many of its athletes: relative energy deficiency in sport, or REDs. Athletes develop REDs when they consistently expend more energy through their physical activity than they take in through their diet. Over time, this prolonged energy deficit can lead to a wide range of symptoms, including hormonal and reproductive issues, insomnia and fatigue, bone weakness and injury, and a higher risk of anxiety and depression. It's now estimated that more than 40% of professional athletes have REDs, and the rate could be even higher in recreational athletes and exercisers. Despite its high prevalence, little is known about REDs on a cellular and molecular level—until Professor Satchidananda Panda, postdoctoral researcher Laura van Rosmalen, and colleagues created a landmark mouse model of REDs. By studying these mice, they discovered that REDs affects organ size and gene expression patterns across the entire body. What's more, the syndrome appears to impact male and female mice differently: In males, kidney health was most significantly impacted, while in females, reproductive health and muscle mass were most affected. This work is helping the researchers identify potential biomarkers to improve REDs diagnosis, and also reveals new molecular targets for future therapeutics to halt, reverse, or prevent the syndrome altogether.

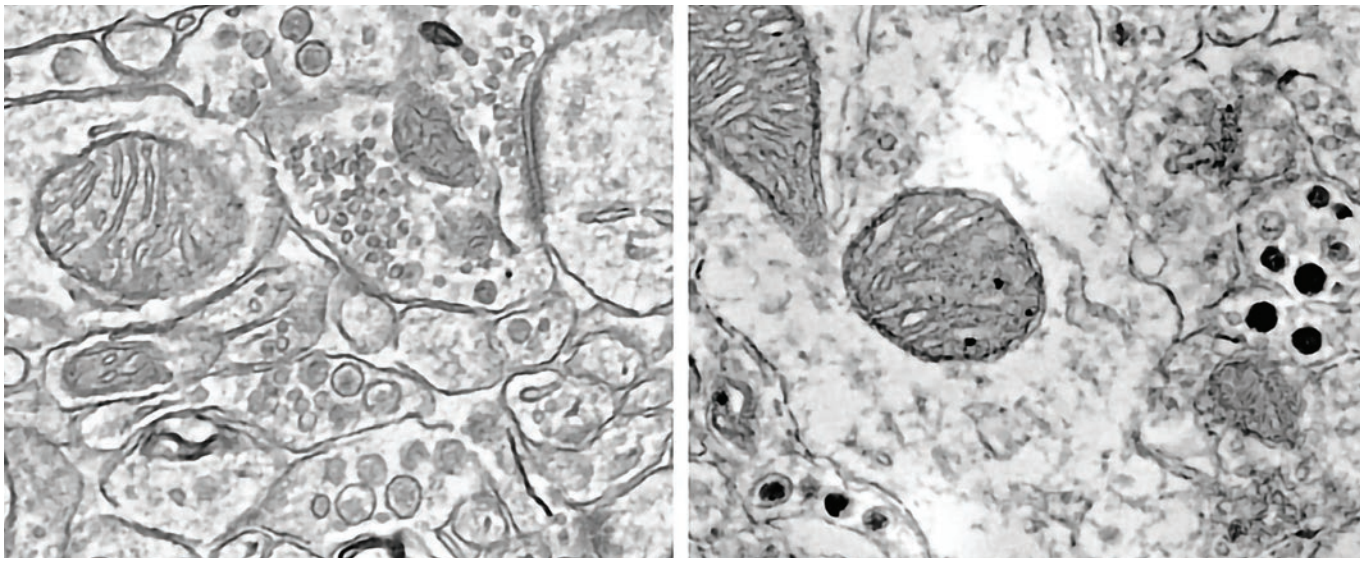
COOPERATIVE PROTEINS HELP THE IMMUNE SYSTEM IDENTIFY AND ATTACK INVADERS

IMMUNITY 06/2024

At the front line of the human immune response are cells called macrophages, which are responsible for identifying intruders and then directing how the entire immune system responds. Associate Professor Diana Hargreaves, postdoctoral researcher Jingwen Liao, and colleagues have now discovered a molecular mechanism that helps macrophages mount a coordinated response tailored to a specific immune challenge. Activating macrophages requires the work of three versions of a protein complex called SWI/SNF: cBAF, ncBAF, and PBAF. The researchers discovered that each variant plays a distinct role in initiating macrophages' responses to intruders and, consequently, how the immune system regulates inflammation. By delineating these SWI/SNF variants, the team has revealed new immune system mechanisms that could be targeted with therapeutics to regulate inflammation associated with conditions like sepsis, cytokine storm, COVID-19, and many more.



From left: Diana Hargreaves and Jingwen Liao.

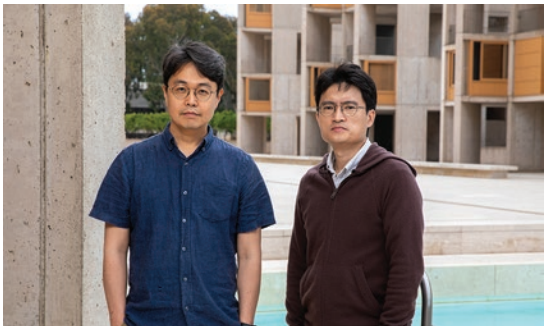


Two images of nerve endings in the amygdala, where fear signals are received and interpreted. On the left, smaller and larger circles depict two distinct types of vesicles inside the nerve endings. On the right, the lab's new sensor labels neuropeptides in black, which can be seen inside large dense core vesicles.

New tools reveal neuropeptides, not fast neurotransmitters, encode danger in the brain

CELL
07/2024

In the split second that you accidentally touch the hot handle of a cast iron skillet, pain and a sense of danger rush in. Sensory signals travel from the pain receptors in your finger, up through your spinal cord, and into your brainstem. Once there, a special group of neurons relays those pain signals to a higher brain area called the amygdala, where they trigger your emotional fear response and help you remember to avoid hot skillets in the future. Researchers assumed this process must be mediated by fast-acting neurotransmitters, but Salk scientists found that this was not the case. Associate Professor Sung Han, postdoctoral researcher Dong-Il Kim, and colleagues created two new tools to study larger, slower molecules called neuropeptides. These allowed the scientists to study their role in the danger circuit in live mice for the first time. Their findings revealed that neuropeptides, not fast neurotransmitters like glutamate, were the main messenger in this danger circuit—and more than one neuropeptide is involved. Their findings may explain why existing medications that target only one neuropeptide are often ineffective, and could inspire the development of new treatments for fear-related conditions like anxiety and post-traumatic stress disorder.



From left: Sung Han and Dong-Il Kim.

"We have created a novel way to trace neuropeptide travel and function in the brains of living animals. These tools will help further our understanding of the brain's neuropeptide circuits and enable neuroscientists to explore questions that were previously difficult to address."

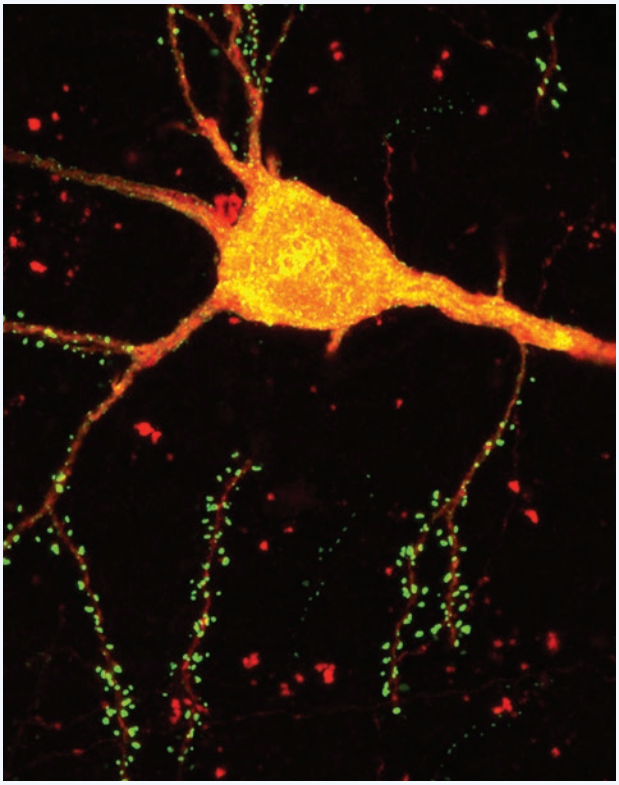
POSTDOCTORAL RESEARCHER DONG-IL KIM

NEUROSCIENCE

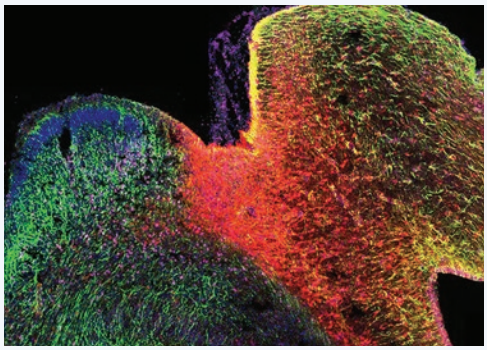
A new brain-mapping tool may be the "START" of next-generation therapeutics

NEURON 09/2024

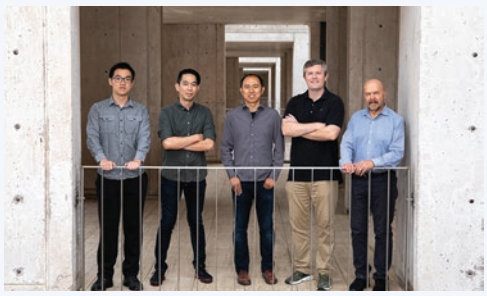
When repairing a car, it's important to understand its basic blueprint and how all the parts connect. Treating brain disorders is no different, except that scientists are still missing key details of the brain's wiring diagram. To address this, Salk Professor Edward Callaway, former graduate student Maribel Patiño, and colleagues developed a new brain-mapping technology called START. The cutting-edge tool allows neuroscientists to trace the connectivity between different types of brain cells with unprecedented resolution. Using this technique, the researchers became the first to resolve cortical connectivity at the resolution of transcriptomic cell types. The discoveries made with START will help researchers design new therapeutics that can target certain neurons and brain circuits with greater specificity. Such treatments could be more effective and produce fewer side effects than current pharmacological approaches.



A cortical neuron labeled with monosynaptic rabies virus (orange).



Fluorescent image of a developing human hippocampus.



From left: Jingtian Zhou, Dong-Sung Lee, Chongyuan Luo, Jesse Dixon, and Joseph Ecker.

Scientists create first map of DNA modification in the developing human brain

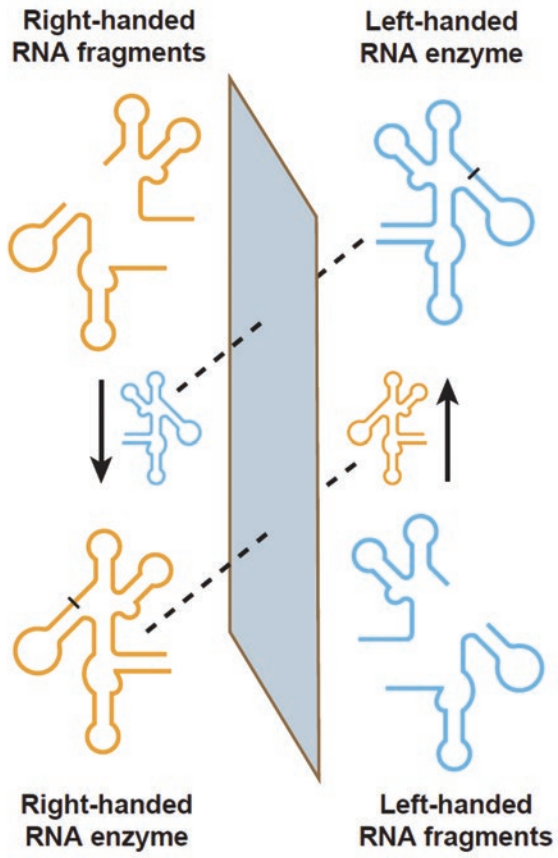
NATURE 10/2024

A new study has provided an unprecedented look at how gene regulation evolves during human brain development, showing how the 3D structure of chromatin—DNA and proteins—plays a critical role. This work offers new insights into how early brain development shapes lifelong mental health. The study was a collaboration between Professor Joseph Ecker's lab at Salk and colleagues at UC Los Angeles, UC San Francisco, UC San Diego, and Seoul National University. The team created the first map of DNA modification in the hippocampus and prefrontal cortex—two regions of the brain critical to learning, memory, and emotional regulation, and also frequently involved in disorders like autism and schizophrenia. The researchers hope the data resource, which they've made publicly available through an online platform, will be a valuable tool scientists can use to connect genetic variants associated with these conditions to the genes, cells, and developmental periods that are most sensitive to their effects.

Through the looking glass: A cross-chiral reaction challenges our definition of life

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 10/2024

Just like your left and right hand exist as mirror images of each other, many biological molecules have their own form of left- and right-handedness, called chirality. On Earth, all RNA exists in a right-handed chiral form. Even when scientists make synthetic left-handed versions, the two groups behave as if on opposite sides of a mirror, unable to interact with each other. But what if they could? What if a molecule could reach through the mirror and interact with the reflected world on the other side? What if this set off a chain reaction that got molecules on both sides working together in ways we've never seen before? Using sophisticated bioengineering techniques, Salk President and Professor Gerald Joyce, senior staff scientist David Horning, and colleagues engineered a chemical system in which left- and right-handed versions of an RNA enzyme could effectively "reach through the mirror" and replicate each other exponentially and indefinitely. This is the first evidence of a life-like chemical system that operates on both sides of the mirror of chirality, creating the opportunity to study an entirely new form of biochemical evolution. The achievement could also advance the development of cross-chiral therapeutics, diagnostics, and other biotechnologies.



Salk scientists engineered a right-handed RNA enzyme (bottom left) that can combine left-handed RNA fragments (bottom right) to create a mirror image of itself. The new left-handed RNA enzyme (top right) can then combine right-handed RNA fragments (top left) to produce more of the original right-handed enzyme, restarting the cycle of cross-chiral self-replication. Adapted from Cochrane et al., PNAS 2024.

From top left: Wesley Cochrane and Grant Bare.
From bottom left: David Horning and Gerald Joyce.

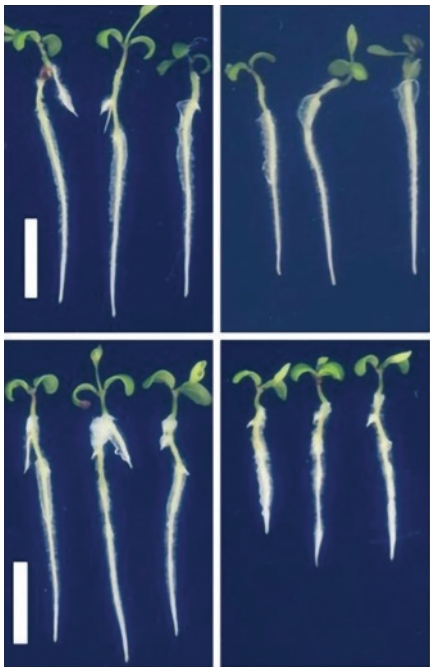
"We've come to expect that life on our planet and other planets will be single-handed, but our work suggests that doesn't have to be true for a bioengineer. We're essentially exploring the boundaries of what biology can be, and based on this study, it seems that our definition of life doesn't have to be as narrow in the lab as it is in nature."

SENIOR STAFF SCIENTIST DAVID HORNING

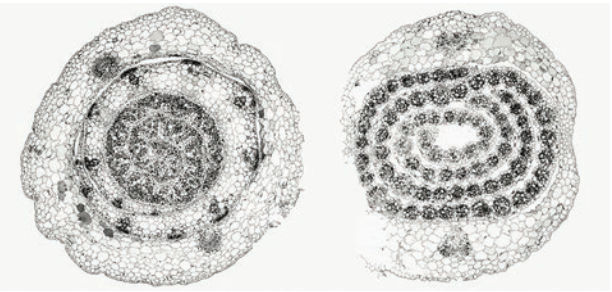
Study reveals key gene protecting plants from harmful metals in soil

NATURE COMMUNICATIONS 07/2024

The negative impact of human activity on Earth doesn't just affect our planet's atmosphere—it goes much deeper, into its soils. For instance, the excessive use of manure and sewage sludge can increase heavy metal concentrations in agricultural land where vital crops are grown. One of these heavy metals is zinc, a micronutrient necessary for plant and animal health. In excess, however, zinc can be extremely damaging to sensitive plant species. In a new study, Professor Wolfgang Busch, former graduate student Kaizhen Zhong, and colleagues identified a gene that helps plants manage excess zinc in the soil. The findings reveal that plants tolerate high levels of zinc by trapping it in their root cell walls, a process that is facilitated by a gene called trichome birefringence, or TBR. Scientists and farmers can now use this information to develop and grow crops that are more resilient to soil contamination. Enhancing plant resilience in this way is a major goal of Salk's Harnessing Plants Initiative.



Lotus japonicus sprouts containing the TBR gene for zinc tolerance (left) compared to sprouts with mutated TBR (right), in normal zinc levels (top) and high zinc levels (bottom).



Cross sections of rice (left) and sorghum (right) shoots show different cellular organization in C3 and C4 plants, respectively. The concentric circles are one of several features that make photosynthesis more efficient in C4 species.

"Answering this question is a huge step toward understanding how we can make the most robust and productive crops possible in the face of climate change and a growing global population."

PROFESSOR JOSEPH ECKER

Superior photosynthesis abilities of some plants could hold key to climate-resilient crops

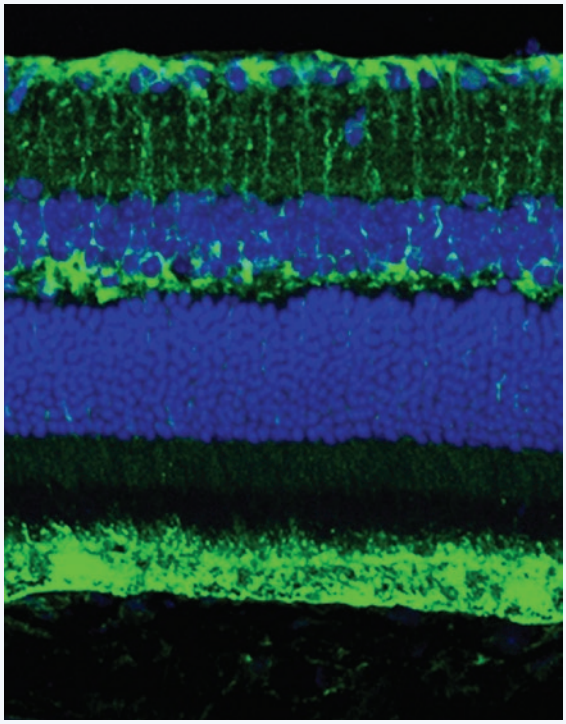
NATURE 11/2024

More than 3 billion years ago, on an Earth entirely covered with water, photosynthesis first evolved in little ancient bacteria. In the following many millions of years, those bacteria evolved into plants, optimizing themselves along the way for various environmental changes. This evolution was punctuated around 30 million years ago with the emergence of a newer, better way to photosynthesize. While plants like rice continued using an old form of photosynthesis known as C3, others like corn and sorghum developed a newer and more efficient version called C4. The difference? C4 photosynthesis is 50% more efficient. Because of this, C4 plants can thrive in hot, dry climates and are among the most productive crop species in the world. However, around 95% of plants still use C3 photosynthesis, a less efficient form that makes them more vulnerable to drought and heat. Now, Professor Joseph Ecker, postdoctoral researcher Joseph Swift, and and collaborators at the University of Cambridge have made a breakthrough in understanding the evolution of C4 photosynthesis. The researchers can now use these findings to drive C4 photosynthesis in important C3 crops like rice, wheat, and soybeans, making them more productive and resilient against our warming climate.

Exciting collaboration shows some age-related retinal disease is reversible

CELL METABOLISM 10/2024

Our bodies rely on little molecules called amino acids—aptly nicknamed the building blocks of life—that come together to form proteins and carry out bodily functions like digesting, growing, repairing, and so much more. Maintaining a constant supply of these important amino acids requires participation from the liver, kidneys, and circulatory system. But for people with an age-related retinal disease like macular telangiectasia, important amino acids like serine and glycine are depleted. New research from Professor Christian Metallo, visiting graduate student Esther Lim, Salk colleagues, and collaborators at Lowy Medical Research Institute and Scripps Research has revealed how a partial genetic deletion in an important metabolic enzyme (PHGDH) leads to lower levels of circulating serine, and how this contributes to dysfunction between the brain's visual and non-visual systems. Importantly, they show that dietary serine supplementation can reverse serine-associated retinopathy and peripheral neuropathies.



Mouse retina glial cells (top), a non-neuronal cell type abundant in the nervous system, and retinal pigment epithelium cells (bottom) stained to show the presence of PHGDH (green).

From left: Emily Manoogian and Satchidananda Panda

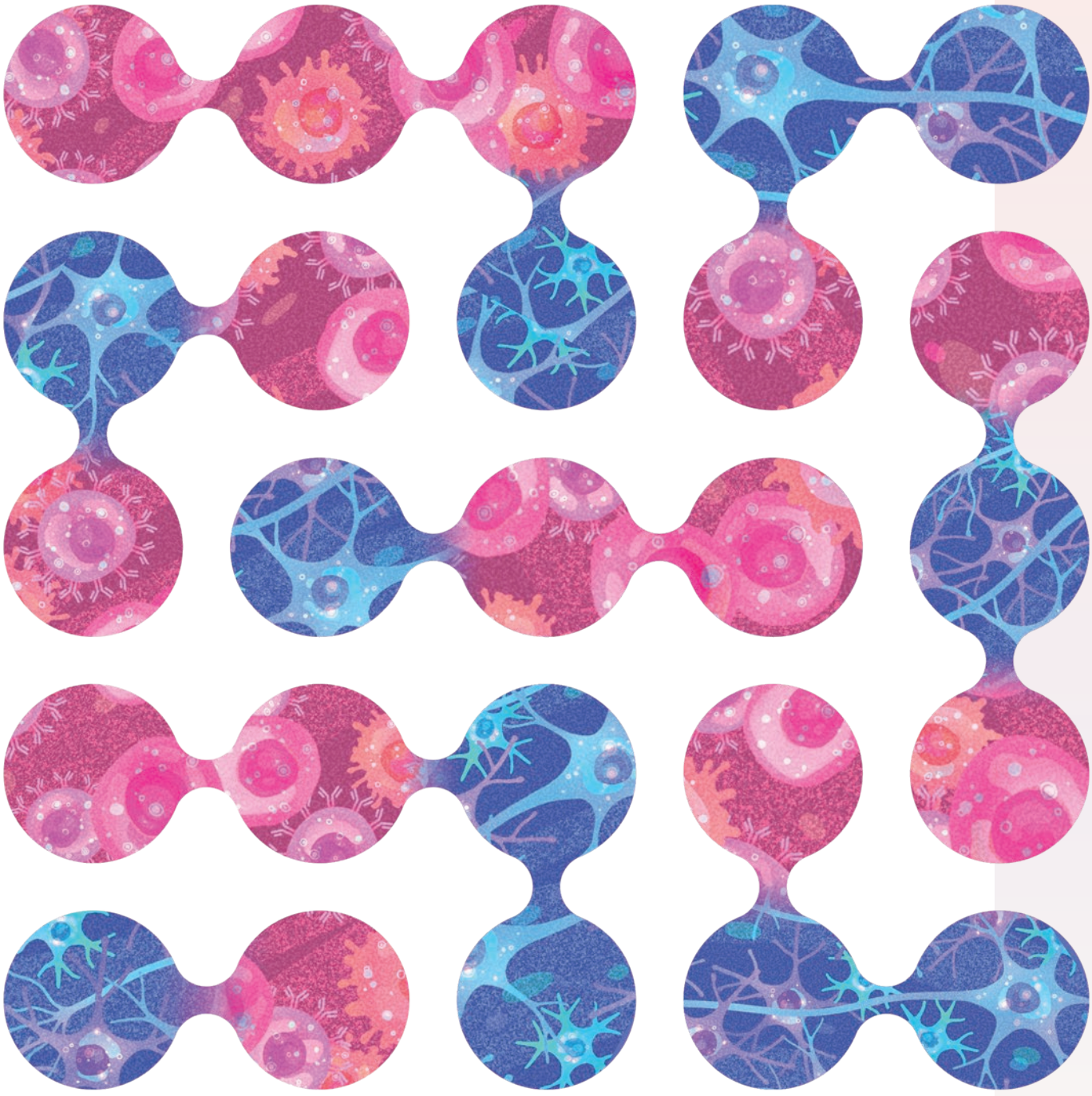
WATCH | https://youtu.be/1E-3bfABBGM

Scan here to watch Panda and clinical collaborator Pam Taub share more about the clinical trial.

One in three Americans has a dysfunctional metabolism, but intermittent fasting could help

ANNALS OF INTERNAL MEDICINE 10/2024

More than one-third of adults in the United States have metabolic syndrome, a cluster of conditions that significantly raise a person's risk of heart disease, stroke, and type 2 diabetes. These conditions include high blood pressure, elevated blood sugar, excess abdominal fat, and abnormal cholesterol levels. In a new clinical trial, Professor Satchidananda Panda, staff scientist Emily Manoogian, and colleagues at Salk and UC San Diego found that time-restricted eating—also known as intermittent fasting—could offer significant health benefits to adults with metabolic syndrome. Patients who ate within a consistent eight-to-ten-hour window each day for three months saw improvements in several markers of blood sugar regulation and metabolic function compared to those who received standard treatments. The researchers say that compared to other prescribed lifestyle changes, time-restricted eating could offer a more practical intervention accessible to a wider range of patients.



Connecting the dots

From the immune system to the brain and back

Colleagues used to call marketing specialist Cynthia Adinig "the human computer." She had a nearly photographic memory and was teaching her young son algebra and chess strategies. Then, in early 2020, she caught COVID-19. Initially, she had a mild case, but her symptoms lingered for weeks—and then began worsening. Adinig lost weight, developed new severe allergies, had unexplained episodes of paralysis, and became wheelchair-bound. At the same time, she felt her cognitive skills slipping away.

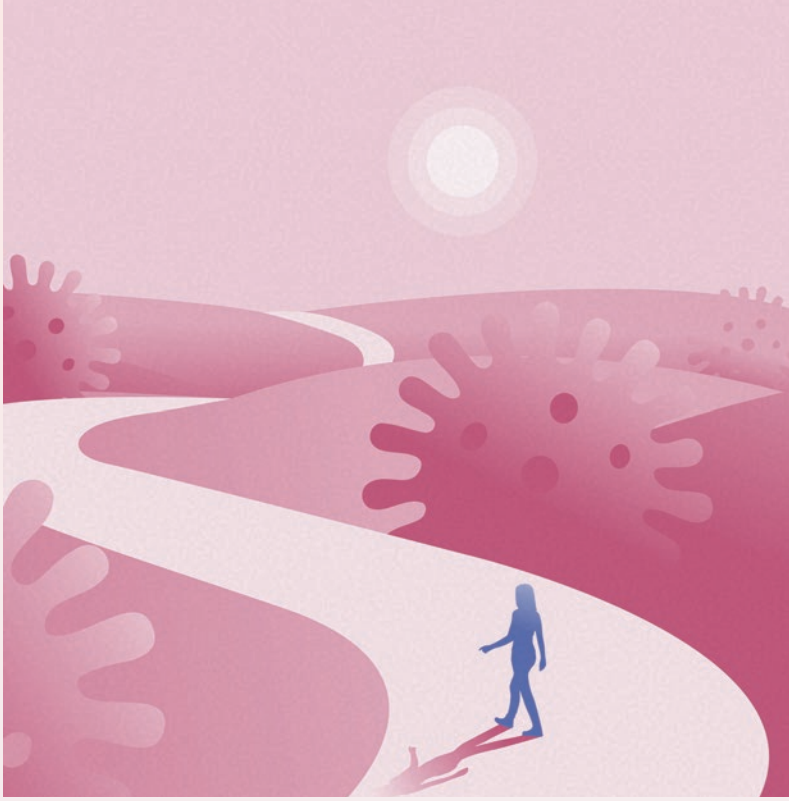
"I used to be the kind of person who memorized pi to the fiftieth decimal place and could recite lines from a television show I had watched one time," says Adinig. "Suddenly, I couldn't remember my own address or social security number. I needed help filling out forms because I so often struggled with understanding what was even being asked."

Four years later, Adinig has still not returned to a full-time job; she has been diagnosed with long COVID and works a few hours a week on long COVID advocacy and outreach efforts. She says she is using techniques like daily puzzles that she learned when her elderly grandmother was diagnosed with dementia to maintain her memory, but she still struggles with brain fog most days and must carefully plan and limit any mental and physical exertion to avoid severe fatigue.

"I've always been really on top of science and medicine and new technologies," says Adinig. "But until this happened to me, I had no idea that a virus could cause a chronic illness like this."

Adinig is not alone; an estimated 17 million adults have some form of long COVID, which encompasses a variety of symptoms that can last months or years after the initial infection. Clinicians still don't know who is most likely to develop lasting cognitive symptoms or why. These questions are part of a larger scientific mystery that is just beginning to be tackled: how do the immune system and the brain interact with each other?

"The scientific community is just starting to realize that there are a lot more connections between the nervous system and the immune system than we have ever appreciated," says Professor Susan Kaech, director of the NOMIS Center for Immunobiology and Microbial Pathogenesis and holder of the NOMIS Chair at Salk. "When our immune system responds to an infection, our brain and cognition are clearly impacted in ways that we don't fully understand."



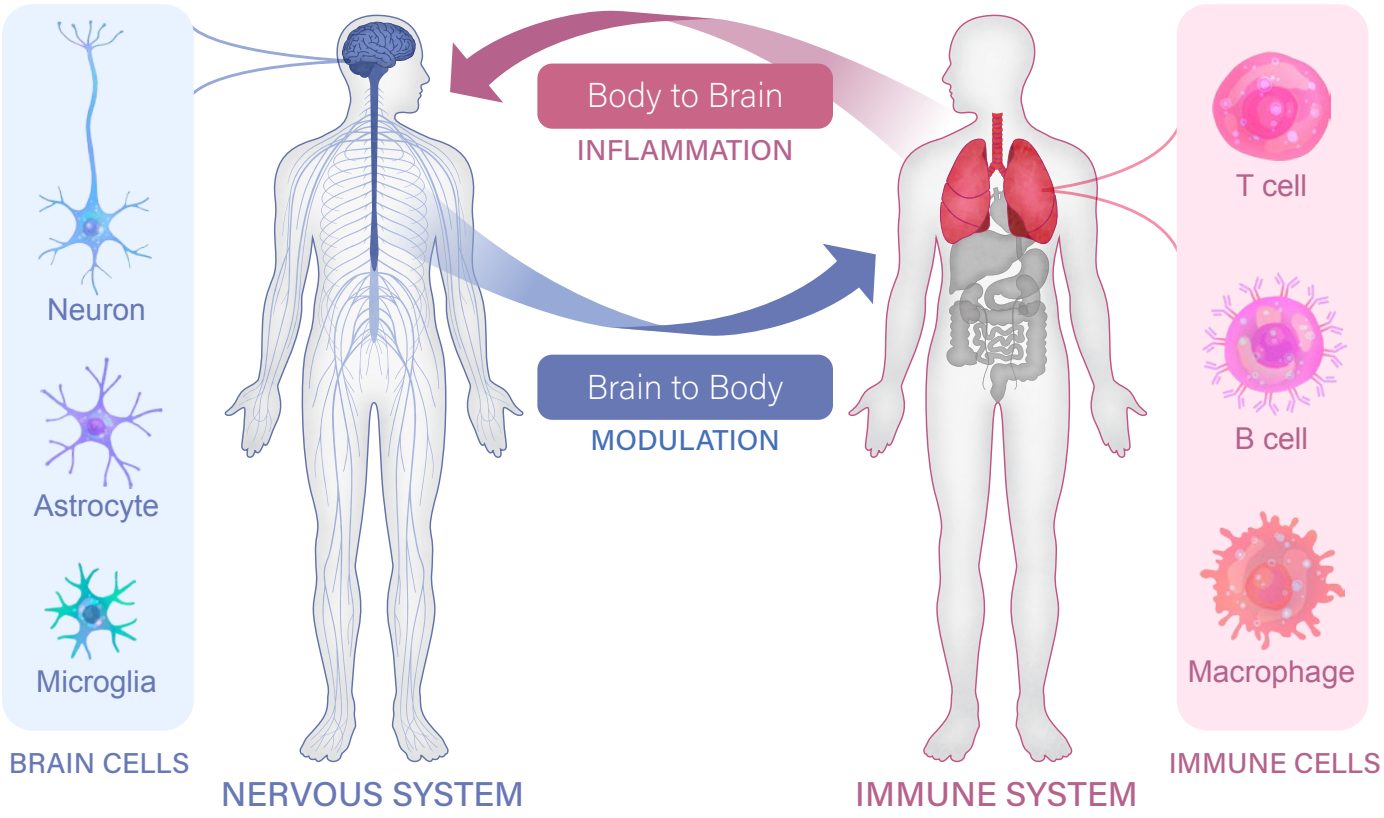
"Until this happened to me, I had no idea that a virus could cause a chronic illness like this."

CYNTHIA ADINIG, LONG COVID PATIENT

Armed with a new $20 million, five-year gift from the NOMIS Foundation, Kaech and her faculty colleague Associate Professor Nicola Allen are co-leading a new Neuroimmunology Initiative at Salk to focus on this topic. The Initiative will bring together Salk neuroscientists and immunologists, including Professor Axel Nimmerjahn and Associate Professor Diana Hargreaves, to connect the dots between the brain and the immune system.

This research will reveal fundamental insights into human biology that have been historically overlooked at traditional research institutions, where faculty from different disciplines rarely get the chance to interact. By choosing to support such collaborations, Salk is taking a front-row seat in shaping the future of this emerging field.

"Our initial goal is to understand the very basics of how our nervous system listens to our immune system, and vice versa, how our nervous system controls our immune system," Kaech explains. Their discoveries could guide our understanding and treatment of conditions as diverse as aging, Alzheimer's disease, Parkinson's disease, long COVID, cancer, and autoimmune disease.



Rethinking the blood-brain barrier

For most of the 20th century, scientists thought the brain and spinal cord were mostly cut off from the body's immune system, their essential functions protected by a nearly impenetrable wall called the blood-brain barrier. This mindset led to the view that the peripheral immune system likely played a very minimal role in the central nervous system.

"Today, that view is crumbling," says Nimmerjahn. "We realize there are all sorts of ways that these two systems can communicate, some of which don't even require immune cells to cross the blood-brain barrier."

It turns out that the blood-brain barrier acts more like a filter than a wall. Researchers have discovered that immune cells do, during many infections, interact directly with regions of the brain and spinal cord. But they have also realized that the immune system and brain can shape each other in more subtle or indirect ways. There is a constant two-way stream of communication between the two systems, facilitated by intermediary cells and a shared language of signaling molecules.

What do these newly appreciated connections mean for disease and aging? Their very existence could help explain, at a fundamental level, how it is possible for COVID-19 to cause brain fog, or for viral infections to contribute to multiple sclerosis—a link that was only discovered in recent years. They suggest that the immune system may play a role in Alzheimer's and Parkinson's diseases and that the brain could contribute to autoimmune diseases and chronic inflammation.

Mostly, the new understanding of the nervous system and the immune system as a tangled, interconnected web of cells and signaling molecules means that scientists need to study the systems together.

"In the past, it's been a very siloed approach," says Nimmerjahn. "Neuroscientists have studied cells and cell communication within the brain, but their work ends at the blood-brain barrier. Immunologists have studied what happens amongst immune cells, but again, their focus usually ends at the other side of the blood-brain barrier. We want to bridge that gap."

Brain changes

If you've ever felt tired, sluggish, forgetful, or unfocused while battling a case of influenza or a common cold, then you already know that a virus can impact your brain and cognition. The first goal of the new Neuroimmunology Initiative is to understand how an infection, or a cumulative history of viral and bacterial infections, can change your brain and spinal cord at a molecular or cellular level.

One reason to suspect that such changes exist is that during an infection, a few types of immune cells can, indeed, cross the blood-brain barrier. But even immune cells that don't make their way into the brain could have an impact. Scientists have recently discovered that immune cells circulating around the body can interact with nerve endings that extend from the spinal cord out into our organs and extremities. These immune cells can alter the electrical signals that these nerves carry back to the brain, likely sending the message, "We're fighting something out here," so that the brain can launch an appropriate response. This might include elevating the body's heart rate to increase the flow of blood and oxygen, or triggering fatigue to promote rest and recovery.

"If you have an ongoing infection in your lungs, there will be molecules produced by the immune system that circulate all through your body to coordinate the immune response," explains Kaech. "There's no question now that those molecules are going to be sensed by the nervous system."

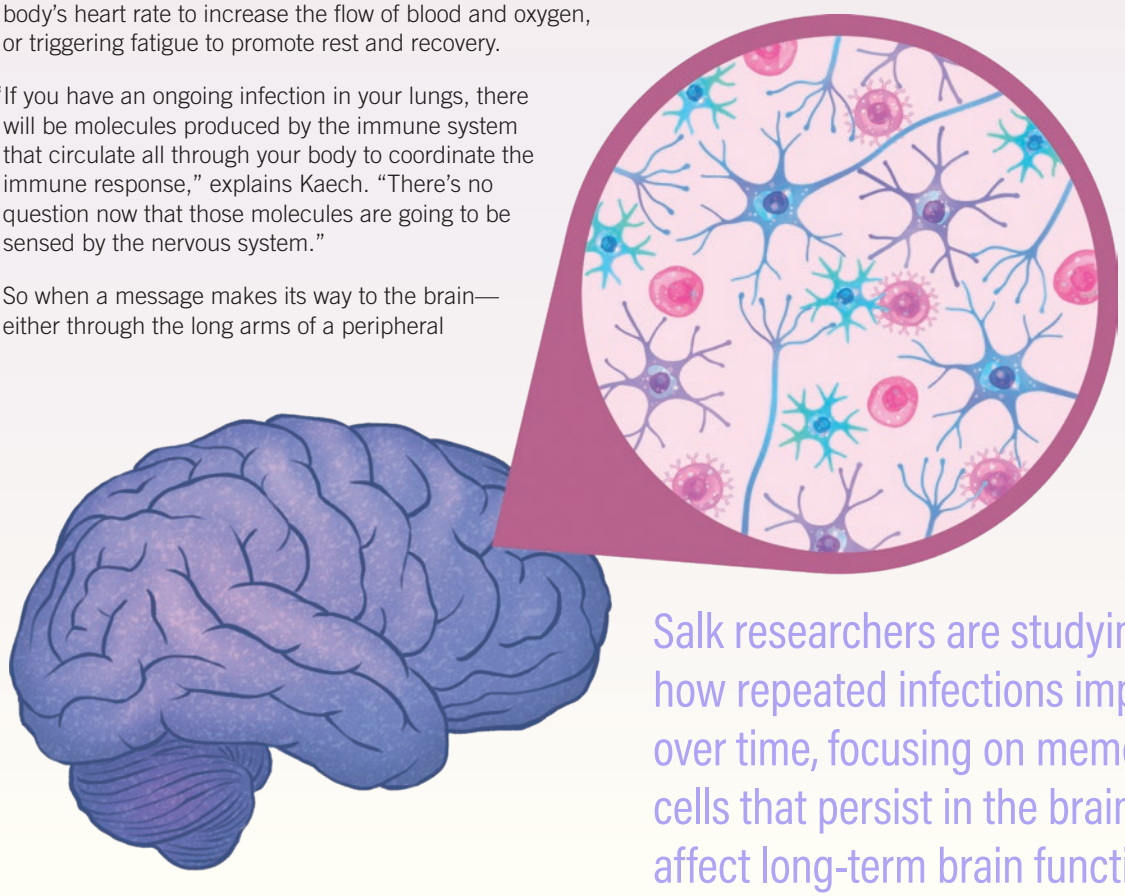
So when a message makes its way to the brain—either through the long arms of a peripheral neuron or by an immune cell crossing into the brain—what happens?

The Neuroimmunology Initiative team is creating a brain map that they've dubbed the "InflamMind" to capture how inflammation throughout the body affects the brain. Nimmerjahn, over the course of his career, has developed microscopy techniques to observe brain and spinal cord cells in living animals. He'll use those approaches to study how different types of brain cells change physically and functionally in response to viruses or bacteria.

Meanwhile, Hargreaves will use cutting-edge genomics technologies to follow how the cells change their gene activity. She wants to know which genes turn "on" or "off" in immune and brain cells during or after an infection.

"Looking at the gene expression of these cells can give us a clue about how they are responding to infection," says Hargreaves.

Scientists know that inflammation can remodel the physical structure of a cell's DNA so that certain genes become more accessible or less accessible. This affects which genes can be expressed and ultimately shapes the cell's health and behavior. Advanced tools at Salk let Hargreaves and her colleagues observe when a stretch of DNA has loosened to allow certain genes to be expressed, or identify which genes are actively being expressed at any given time. Analyzing the DNA's structure this way can suggest how sensitive neurons or immune cells in the brain might be and, therefore, how likely they are to launch an immune reaction.



Salk researchers are studying how repeated infections impact the brain over time, focusing on memory immune cells that persist in the brain and may affect long-term brain function.

Infection after infection

When Adinig was infected with SARS-CoV-2, the virus that caused her long COVID, it was not the first time she had ever gotten sick in her life. That pattern of repeated infection, while common in people, is rarely modeled in the lab. Salk researchers want to change that.

"Typically, in lab mice, we study the consequences of infection by infecting an animal with one pathogen for a few days, and we leave it at that," says Hargreaves. "But we, as humans, are exposed to a variety of pathogens throughout our lives, one after the other. What does that ultimately do?"

Studying the effects of a single pathogen is already costly work, so looking at several at the same time presents additional logistical and funding challenges. Such obstacles have precluded these kinds of experiments in the past, but with the NOMIS Foundation's support, Salk scientists are now accepting the challenge.

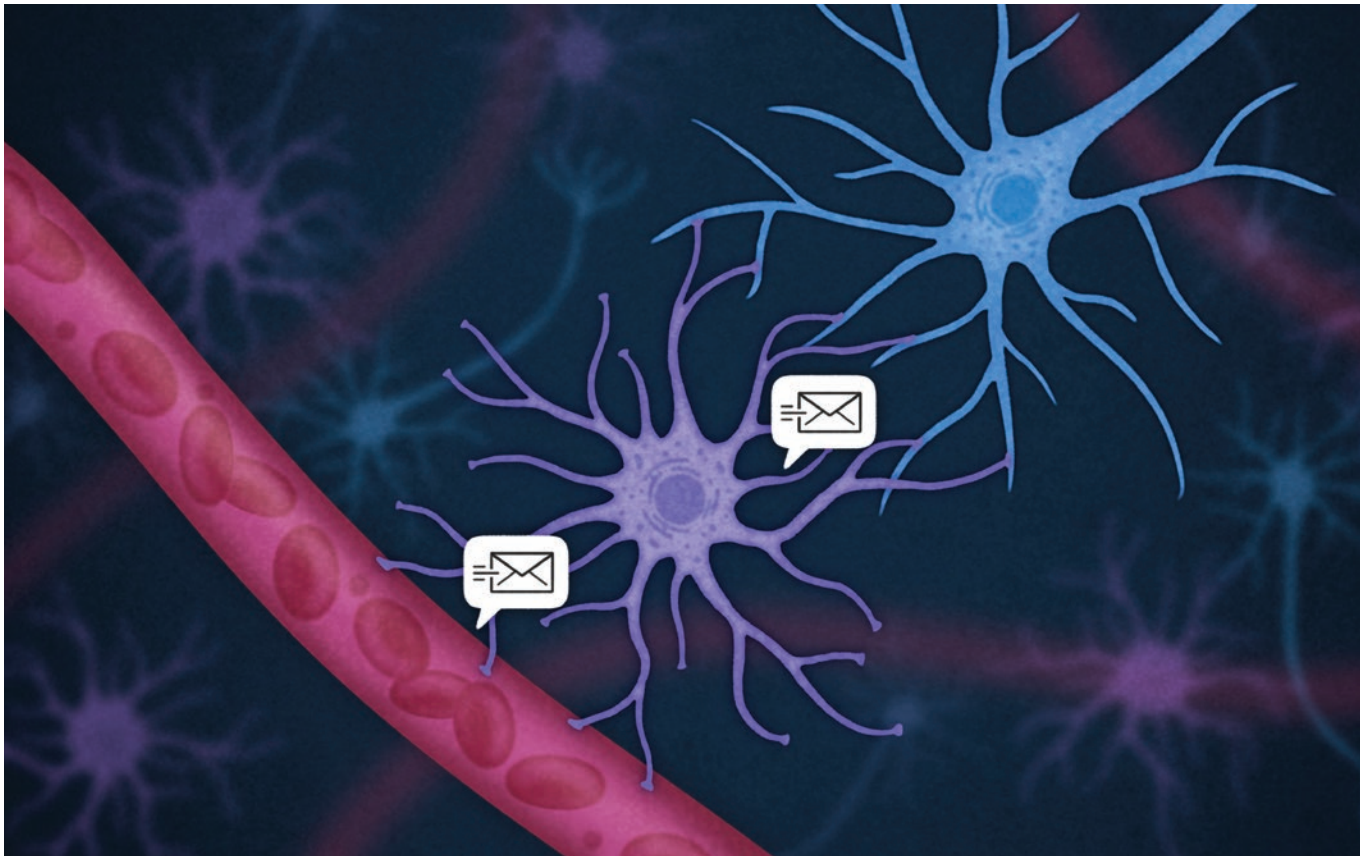
By producing more realistic models of pathogen exposure, the Neuroimmunology Initiative will finally be able to look at the cumulative consequences of repeat infections on the brain and spinal cord.

"How is the collective history of multiple infections over our lifetime impacting our central nervous system?" Kaech asks. "There has been nothing done in the past to explore this."

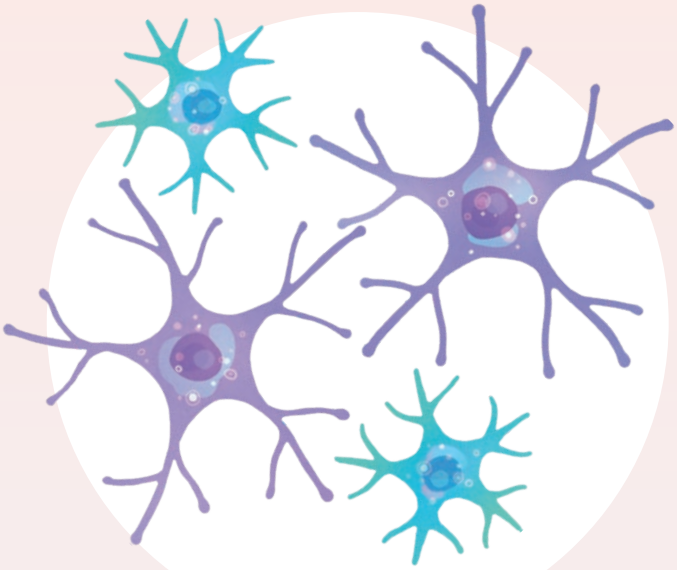
Kaech has long studied how the immune system develops long-term "memories" of the pathogens it encounters. She says that each time a mouse gets an infection, new immune cells enter the brain—a process her lab staff can observe under a microscope. Moreover, the immune cells persist in the brain even after the animal has recovered, ready to spot the pathogen should it ever be re-encountered.

"These cells are there to protect you if you get that infection again, but we don't know their long-term consequences," Kaech says.

Her lab is now working to better understand the activity of these memory immune cells and how they might affect brain function. The work requires time-consuming, expensive experiments that integrate classic immunology with detailed characterizations of animals' brain cells—the kinds of studies that are not possible without intentionally dedicated funding and support.



Immune cells (red) send molecular messages to astrocytes (purple), which can translate them to neurons (blue).



"When we're talking about communication between two systems, there need to be some cells that can speak both languages. Microglia and astrocytes are those cells in the brain."

PROFESSOR AXEL NIMMERJAHN

The brain cells to blame

Once Salk researchers identify the brain changes that follow an infection, their next task will be to figure out exactly how they come about. The brain and immune system likely communicate through cells that can transform the immune system's chemical signals into the nervous system's electrical messages, and vice versa. Today, scientists know about two types of cells within the brain that can fulfill these roles as translators: microglia and astrocytes.

"When we're talking about communication between two systems, there need to be some cells that can speak both languages," says Nimmerjahn. "Microglia and astrocytes are those cells in the brain."

Allen, the Initiative's co-director, is an expert on these non-neuronal brain cells. In 2018, her lab discovered that as animals age, their astrocytes change—genes that are turned "off" for most of an animal's life become reactivated over time. Many of those genes are related to astrocytes' ability to prune the connections between neurons—an important part of refining neural circuits during early brain development. Allen and her colleagues hypothesize that older astrocytes start to eliminate these connections at higher rates, potentially contributing to cognitive declines.

It is also known that aging is associated with higher levels of inflammation across the body. Because astrocytes also speak the language of immune cells, Allen now wonders whether their changes during aging are a response to these increased levels of inflammation.

"What my lab is following up on, as part of the new Initiative, is whether inflammation is contributing to these changes in older astrocytes," says Allen. "Are immune cells outside of the brain starting this cascade?"

If she can explain how age-related inflammation alters astrocytes, she may also be able to determine how astrocytes respond to other sources of inflammation, such as a viral infection or a chronic disease. This could inform how viruses like SARS-CoV-2 can trigger cognitive decline in some people or how neurodegenerative disorders could be impacted by immune changes. The key to understanding these diseases, Allen hypothesizes, is to study how astrocytes interact with immune cells and then alter the brain cells nearby.

"In some of these neurodegenerative disorders like Alzheimer's, we've been very focused on the neurons but have ignored the broader picture in terms of what other cells surround these brain cells and interact with them," Allen says.

Nimmerjahn is tackling the other brain immune cell of interest: microglia. Using his cutting-edge microscopy tools, he has already shown that microglia in the healthy brain are constantly changing shape, stretching their arms in all directions to patrol for threats. He has also examined the cells' role in diseases, including viral infections and Alzheimer's disease. Now, Nimmerjahn wants to know how these immune sentinels change with chronic inflammation, and how that could impact such diseases.

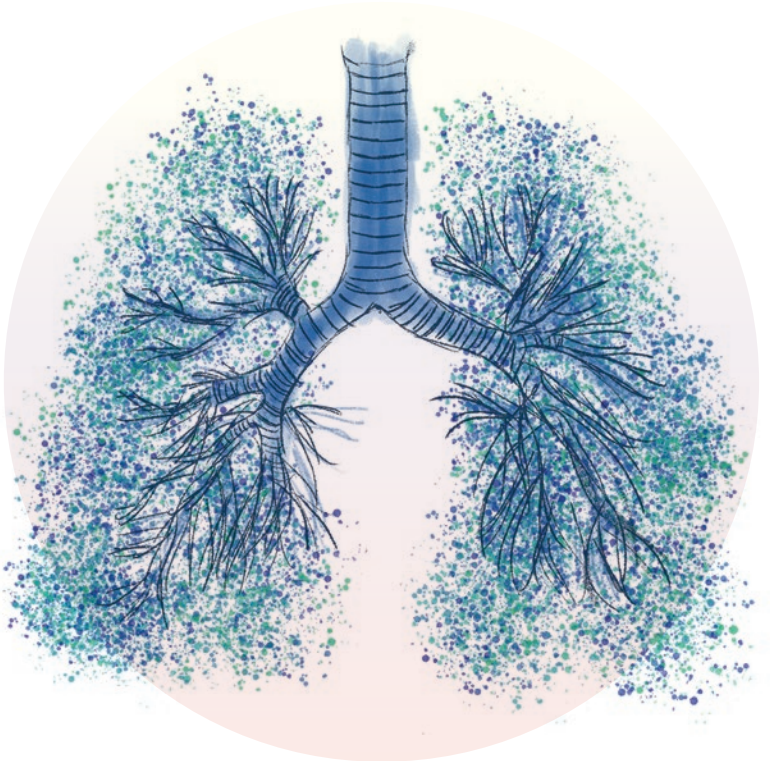
Nimmerjahn has also partnered with Salk Professor Rusty Gage, whose lab has pioneered methods for producing tiny clusters of cells that mimic the human brain so that it can be easily studied in the lab. Together, they recently showed that these "brain organoids" can be used to study not only neurons but also astrocytes and microglia. The researchers discovered that, in an organoid grown out of cells from a patient with autism, spectrum disorder microglia were larger and more reactive than usual—suggesting a possibility that the immune system and inflammation may play a role in autism. They plan to repeat similar experiments to study how microglia may function differently in other diseases or inflammatory conditions.

Listening to the brain

After probing how the immune system communicates to the nervous system and how cells in the brain respond, the final aim of Salk's Neuroimmunology Initiative is to better understand how the brain goes on to control immunity, closing the loop of neuroimmune interaction.

When Kaech opened her lab at Salk, she launched a project to better understand how nerves and immune cells, like T cells, talk to each other. T cells are a type of white blood cell that play a central role in fighting infection and disease. As Kaech tracked the behavior of T cells in various organs during chronic viral infection or cancer, she discovered something surprising: the T cells listened to neurotransmitters produced by nerves located within the organ tissue. Kaech went on to show that the T cells have receptors for these brain signals, letting them eavesdrop on the central nervous system.

"It was amazing to see that these immune cells actually have receptors for neurotransmitters that are produced by nerve cells," says Kaech. "Not only are the immune system and nervous system not separate, but they have this shared chemical language. It was a pretty big insight."



Kaech's group wondered how the T cells would behave if they didn't receive these messages from the nervous system. To test this, they blocked the cells' receptors using beta-blockers—a class of drugs commonly used to control blood pressure and heart rate. Surprisingly, the immune cells became better at destroying cancer cells when they no longer received the nerves' signals. The results were published in 2023 in *Nature*.

Interestingly, the molecule used as a messenger in this case was noradrenaline, a neurotransmitter typically associated with the body's "fight-or-flight" response. The research suggests that a person's stress levels could impact their immune response—something relatable to anyone who has become sicker than usual during exam week or another high-stress time.

Nimmerjahn has also helped scientists learn how our brains can contribute to asthma, a chronic inflammatory disease of the lungs. In this research, led by UC San Diego collaborator Professor Xin Sun, the team studied mice that had been exposed to dust mites, which can trigger asthma in humans. They discovered that when mice repeatedly breathe in these dust mites, immune cells activate nerve cells near the lungs, which then change the activity of neurons in the brain. In turn, those brain cells send signals back to the lungs to trigger inflammation. Over time, the animals' immune systems became even more sensitive and hyperreactive to the dust mites, eventually resulting in signs of chronic asthma. It was the first time asthma could be linked to a full circuit of communication from the immune system to the brain and back to the immune system in the lungs.

"Once you identify a circuit like that, you can start to think about treatments that potentially regulate it," says Nimmerjahn.

When the team blocked the communication between brain cells in this circuit, the mice no longer developed asthma in response to the dust mites. Treating asthma by targeting the brain rather than the immune system or lungs is exactly the kind of new idea that can come from studying these systems more holistically.

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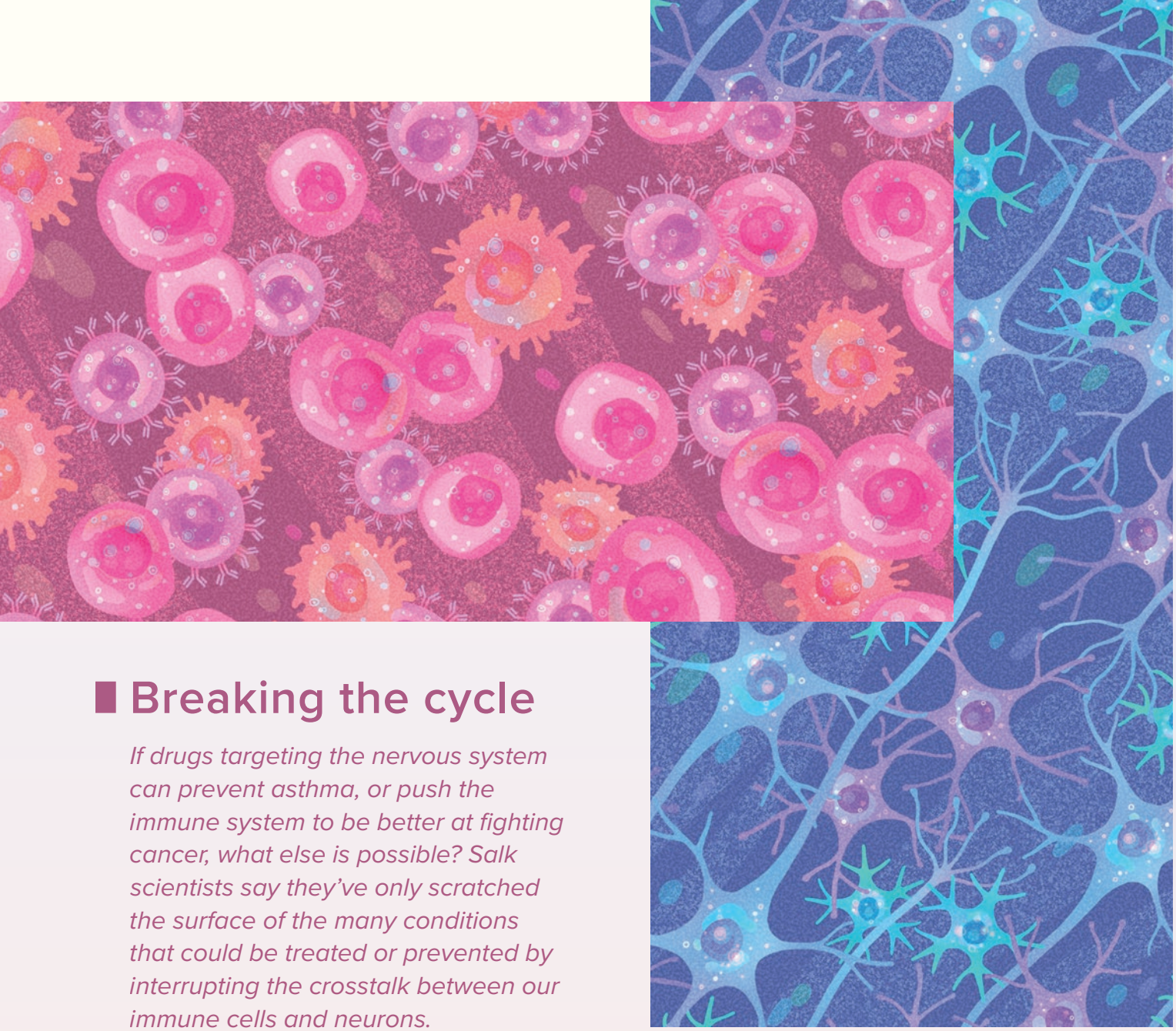


Breaking the cycle

If drugs targeting the nervous system can prevent asthma, or push the immune system to be better at fighting cancer, what else is possible? Salk scientists say they've only scratched the surface of the many conditions that could be treated or prevented by interrupting the crosstalk between our immune cells and neurons.

Recent studies are starting to suggest that people who have had certain viral and bacterial illnesses have higher rates of Alzheimer's and Parkinson's diseases later in their lives. Could immunotherapies one day treat or prevent these brain diseases? Could similar drugs stop the lasting brain fog and cognitive dysfunction of long COVID or chronic fatigue syndrome? Could our brains hold the key to treating allergies and autoimmune diseases?

By bringing neuroscientists and immunologists together, the Salk Neuroimmunology Initiative hopes to answer questions like these. Ideas that started as curious conversations in the hallways of Salk have now moved to regularly scheduled meetings, where scientists at the intersection of these disciplines can interact and collaborate. As they learn to speak each other's scientific languages, they'll come closer to deciphering the shared language of the brain and immune system.

"We've studied both these systems in isolation for a long time. But it's time to bring the fields together. It's a big shift in perspective, but that's often how the greatest innovations begin." (S)

ASSOCIATE NICOLA ALLEN

IN MEMORIAM

Salk mourns the loss of

Joanne Chory

1955-2024

Salk professor and pioneering plant biologist dies at age 69.

Chory at the Salk Institute in 1992.

Salk Professor Joanne Chory, one of the world's preeminent plant biologists who led the charge to mitigate climate change with plant-based solutions, died on November 12, 2024, at the age of 69 due to complications from Parkinson's disease. She was diagnosed with Parkinson's in 2004 and, despite the challenges, continued to lead her research team until the time of her death.

Chory, who was also a Howard Hughes Medical Institute investigator, spent more than 30 years studying how plants respond to their environments, and she made many important discoveries regarding how plants sense light and make growth hormones.

"Joanne was one of the most influential plant biologists of the modern era and a beloved member of the Salk community. Her leadership, compassion, and joy will be forever missed on our campus and beyond," says Salk President Gerald Joyce. "It has been a true privilege to know Joanne. Her brilliant work will live on, and just might save the world."

Chory joined the Salk Institute in 1988 as an assistant professor and one of the first plant biologists at the Institute. Most recently, she was a full professor, directed Salk's Plant Molecular and Cellular Biology Laboratory, and held the Howard H. and Maryam R. Newman Chair in Plant Biology.

"Joanne was a trailblazer in the field of plant genetics, and for more than 30 years, she made seminal discoveries about how plants interact with and adapt to the environment. In the past eight years, she used the fruits of these discoveries to reconceptualize the problem of global carbon and advance a solution which is affordable, scalable, and available in a reasonable timeframe," says Howard Newman, a long-time Salk Trustee. "She will thus leave commanding legacies in both pure and applied science."

Working with *Arabidopsis thaliana*, a small mustard plant and favorite laboratory model, Chory pioneered the application of molecular genetics to plant biology. She used emerging tools to reveal how plants alter their size, shape, and form to optimize growth and photosynthesis in various environments.

For example, shortly after arriving at Salk, Chory revealed that an Arabidopsis mutant called DET1 could grow in the dark. It turned out that the DET1 gene was responsible for how plants respond to light. She determined the gene's sequence and exact location in the genome. Further studies on another DET gene, DET2, ultimately unveiled the entire plant steroid hormone signaling system and the distinct roles of specific hormones.

Taking this work to one of the world's most pressing challenges, Chory was the founding director of Salk's Harnessing Plants Initiative, a bold effort to optimize crop and wetland plants to pull excess carbon dioxide out of the atmosphere to mitigate the effects of climate change. Under Chory's leadership, the Initiative received a $35 million award from the TED Audacious Project and $30 million from the Bezos Earth Fund. In 2022, the Initiative spun

out the company Cquesta Inc., co-founded by Chory, to scale up and commercialize carbon-sequestering plants. In 2023, Hess Corporation donated $50 million to support plant research at Salk. The Harnessing Plants Initiative is currently led by Executive Director Wolfgang Busch, Salk professor and holder of the Hess Chair in Plant Science.

"Joanne and I worked very closely together over the past several years," Busch says. "Her bright mind, her incredible passion, her energy, and her deep insights into science—and what science can be—were one of a kind. It had been such a privilege to work with her, to get to know her as a person, and to have her as a friend. The loss is immeasurable."

Chory was a member of several elite scientific academies, including the US National Academy of Sciences and the American Academy of Arts and Sciences. She was one of the most highly cited researchers in the world for her scientific publications, ranking in the top 1 percent. She was recognized with numerous awards, including the L'Oreal-UNESCO Women in Science Award, the Gruber Genetics Prize, the Breakthrough Prize in Life Sciences, the Princess of Asturias Award, the Pearl Meister Greengard Prize, the Wolf Prize in Agriculture, and the Benjamin Franklin Medal in Life Science.

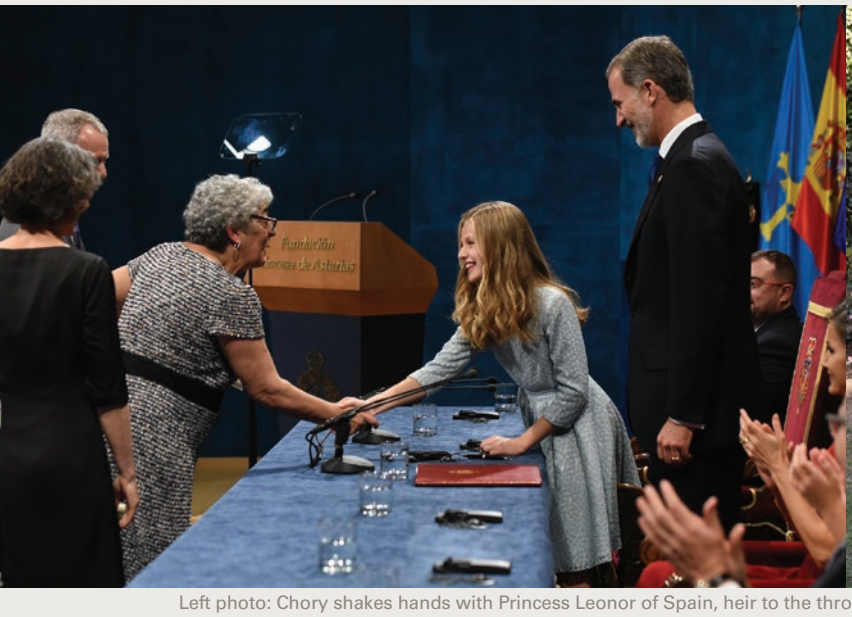
Born on March 19, 1955, in Boston, Massachusetts, Chory was raised with five siblings by Lebanese parents. She attended Oberlin College for her undergraduate degree in biology and completed her PhD in microbiology at the University of Illinois Urbana-Champaign in 1984. She was a postdoctoral fellow at Harvard Medical School under the mentorship of Frederick Ausubel.

Chory is survived by her husband, Stephen, her two children, Katie and Joe, and granddaughter, Sadie Jo.

Busch and Chory celebrate a donation from Hess Corporation in 2023.

"Her bright mind, her incredible passion, her energy, and her deep insights into science—and what science can be—were one of a kind. It had been such a privilege to work with her, to get to know her as a person, and to have her as a friend. The loss is immeasurable."

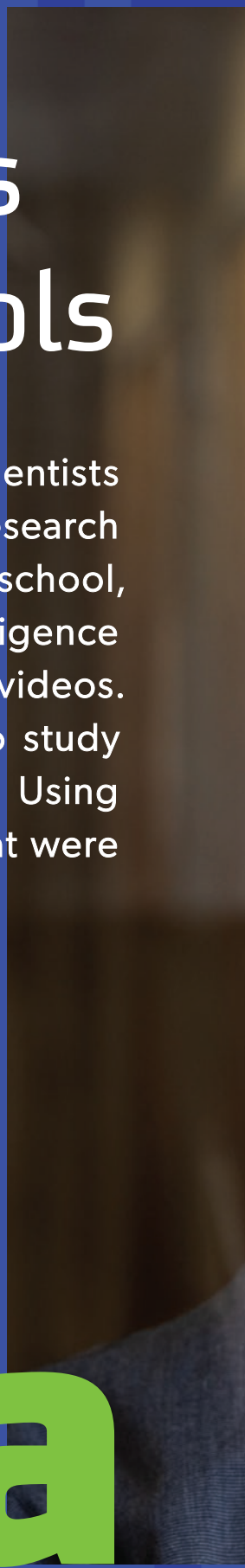
PROFESSOR WOLFGANG BUSCH



Left photo: Chory shakes hands with Princess Leonor of Spain, heir to the throne and for whom the Princess of Asturias award is named, while her father, King Felipe VI, looks on. Right photo: From left: Chory's husband (Stephen Worland), son (Joe), Chory, and daughter (Katie).

From video game bots to leading-edge AI tools

Talmo Pereira is a Salk Fellow, a unique role that empowers scientists to move straight from graduate school to leading their own research groups without postdoctoral training. While in graduate school, Pereira invented SLEAP—a tool that uses artificial intelligence and machine learning to track and quantify movement in videos. At Salk, he collaborates with many labs to apply SLEAP to study people, animals, and even plants in unprecedented ways. Using this technology, Salk researchers can now ask questions that were previously impossible to answer.



Talmo Pereira

Inside Salk sat down with Pereira to learn about his career journey.

What was your childhood like, and how did it influence your career path?

TP: When I was growing up in rural Brazil, my grandmother and uncle were constantly telling me to get off the computer.

I had built the computer myself, purchasing each part once I could afford it with my allowance. But money was tight in our family, so playing on the computer seemed like a waste of time.

When I was young, my mother left home and moved to the United States to find work. There, she delivered newspapers, cleaned houses, worked as a nanny, and sent as much money as she could back to us in Brazil. She wanted to build a better life for us, though it took longer than we had initially anticipated.

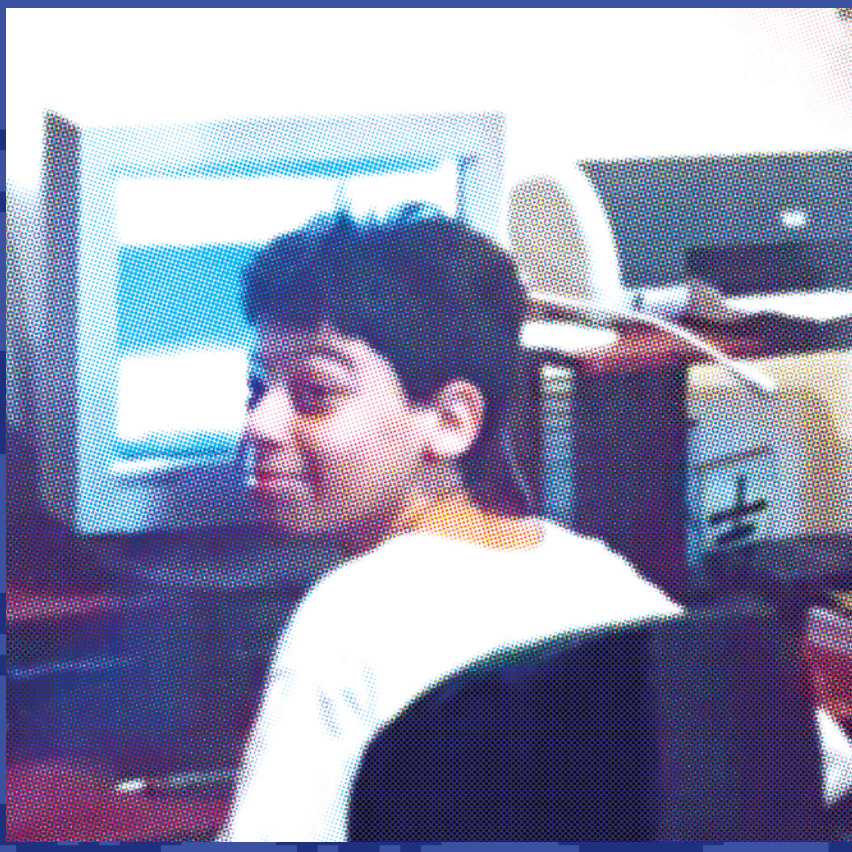
While she was away, my mom was constantly worried that she'd lose me to a street gang, which many of my peers were turning to for income and community. To ease her fears, I became very sheltered and nerdy. I didn't go out a lot, and we couldn't afford a lot.

In a way, computer games offered me an alternate life, one where I could live in a fantasyland and befriend other gamers from around the world. And the more time I spent at it, the more I saw ways to make the experience better. I learned to code so that I could automate the boring parts of online role-playing games by building avatars that could perceive the world and choose appropriate behaviors to achieve the objective—which, essentially, is what I still do today.

How is your work today related to your childhood experience with role-playing video games?

TP: My team and I created SLEAP, and we're frequently surprised by its far-ranging applications. To name just a couple, we are currently using our machine learning-based tool to diagnose Alzheimer's disease and ALS simply by analyzing body language. In a totally different project, we're tracking plant root growth to help develop crops that are more resilient to climate change.

Now we're reverse-engineering biological intelligence by mapping real-world movements onto digital avatars to simulate all sorts of scenarios—which, now that I think about it, is really just a super advanced version of my role-playing game characters back in Brazil.



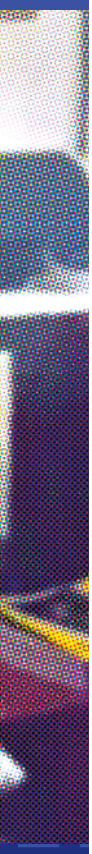
Talmo Pereira as a child in Brazil, playing games on the computer he built after buying the parts with his allowance.

What challenges did you face when you first moved to the United States?

TP: When I was 16, I was finally able to join my mom in Maryland after nearly 10 years of separation. I thought it would be my land of opportunity, but that wasn't my initial experience. The teachers in my high school didn't think I had a future in the sciences. I wasn't recommended for advanced classes or given the same opportunities as other kids.

I eventually got myself into a high school research program at the National Institutes of Health. That was my big break—a chance to prove myself. I spent the summer working in a neuroscience lab and continued during the school year, even though I had to take two buses and the subway to get there.

When it was time to apply to college, I hit another roadblock. I realized that there was this whole system I didn't know about, one that my peers had been preparing for since middle school. Nobody told me what I needed to do to get into a top-tier university.



How did you overcome those challenges?

TP: I was initially deeply disappointed by all the rejections. I ended up at the University of Maryland, Baltimore County, which offered fewer research opportunities than some other schools. But I was fortunate to be accepted to the Meyerhoff Scholars Program, an effort to increase diversity among future STEM leaders by supporting students who intend to pursue graduate or medical school.

My life would be totally different without that program. It starts with a highly disciplined boot camp, specifically formulated to bridge the gap in lack of institutional knowledge and give students like me the tools, opportunities, and confidence we need to get into and succeed in top graduate schools.

To supplement my education at UMBC, I also took advantage of summer research programs at the Broad Institute, MIT, and Caltech. I attended my first Society for Neuroscience meeting—a huge annual conference where I got so exhausted from trying to visit every poster that I had to find an empty room to take a nap. The meeting had a major impact on my career, as I woke up to find myself in a lecture by David J. Anderson, who I later interned with and who introduced me to the topics my lab still studies today.

Each of these experiences taught me a lot, but the most valuable part was finally feeling like I belonged. For the first time, I was being treated like an intellectual equal and a colleague. It was very different than my high school experience.

How did you come to invent SLEAP?

TP: By the time I was applying to graduate schools, I had a clear vision of what I wanted to accomplish: I wanted to find a way to look at natural, complex behavior and use computer vision and machine learning to extract and quantify patterns. I just needed a place that would let me do it.

This time, thanks in large part to the Meyerhoff Scholars Program, I had my pick of Ivy League schools. I ended up choosing Princeton University because I loved the vibe. I felt like I belonged, and my interests were being validated. I just wanted to do good science and dive deep into big questions.

Then I saw a documentary about the making of the animated movie *Shrek*, in which they used motion capture technology in the real world to generate detailed, 3D images. Around that same time, deep learning was coming around, as was markerless capture—the ability to capture movement with a camera without putting invasive tags on the subject.

I proposed this approach to my thesis advisors, but they didn't think it would be feasible. The problem was "Big Data." For markerless capture and deep learning to work as a research tool, we would be generating more data than we had the capacity to store, share, and use.

But I did it anyway, just in secret! Within a few months, we had a working product—the precursor to what is now SLEAP. After some initial challenges, it started to take off, and labs around the world have been using it ever since. When I attended my next Society for Neuroscience meeting, we had published SLEAP and it was a totally different experience—people stopped me on the streets to ask about it!

What brought you to the Salk Fellows program?

TP: Despite that success, I was uncertain about my future in academia. Typically, the next step would be to apply for a postdoctoral training position, working in another lab at another university. Then, hopefully, after an unknown number of years, I'd apply for faculty positions. The trouble with that path is you're living on a relatively low stipend for many years as a trainee and there's no guarantee that it'll pay off in the end with a stable, well-paying faculty position. My mother was also beginning to have health issues at that time and was

"I learned to code so that I could automate the boring parts of online role-playing games by building avatars that could perceive the world and choose appropriate behaviors to achieve the objective—which, essentially, is what I still do today."

TALMO PEREIRA

still working as a nanny. It was my turn to help support my family, and I wasn't convinced that academia was going to be the way to do it.

I had recently done an internship at Google AI, so I was planning to apply to similar industry jobs after I completed my PhD. Then Salk Professor Kay Tye gave a seminar at Princeton and mentioned that she was chairing the search for the next Salk Fellow. The program supported a small number of scientists to skip postdoctoral training and move directly into faculty-level roles. My advisor told her about me, and she encouraged me to apply. I'm thankful to both of them, as well as the postdocs in my lab, who helped me navigate the process of applying to a faculty-level job.

The Salk Fellows program is ideal for me because I get the best of both worlds—the academic freedom to follow my ideas as well as financial and career stability I need to support my family.

What's next?

TP: Historically, neuroscientists have studied the brain but largely ignored the rest of the body. Yet a large portion of the brain is dedicated to getting the body to move appropriately—toward food and away from danger, for example. To fully understand the brain, we must study it in the context of the whole body.

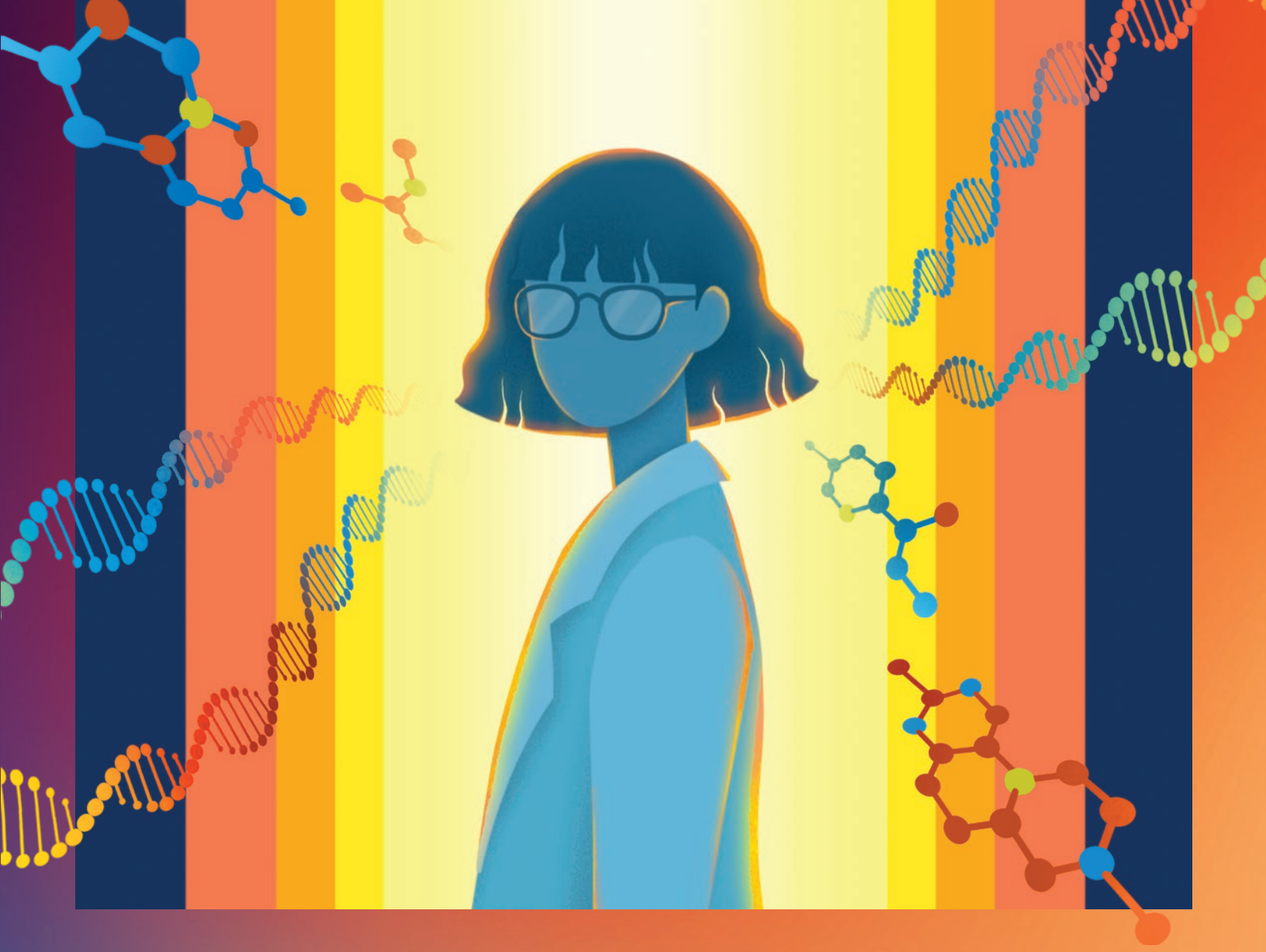
We're now doing that by using SLEAP's output to reverse-engineer the neural codes that produce those movements. In other words, what would have to be happening in the brain for that movement to occur? To do this, we're building AI-powered digital twins of real-life animals. These "avatars" are opening a whole new set of possible applications. With our digital twins, we can come up with hypotheses and perform virtual experiments. For example, what happens to behavior if we remove a part of the brain? My team just received our first big National Institutes of Health grant to pursue this, and we're excited to see where it will take us.

I'm also proud to serve as chair of Salk's Justice, Equity, Diversity, and Inclusion (J.E.D.I.) Council. We're a group of faculty members, graduate students, postdoctoral researchers, and staff members who support Salk's Office of Equity & Inclusion and advocate for these issues across the campus and beyond. As you might imagine, given my background, I feel very strongly that supporting J.E.D.I. efforts, including Salk's Summer Undergraduate Research Fellowship (SURF) program, is of paramount importance.

You never know where the next big idea will come from, and breakthrough science is often made possible by encouraging new voices and perspectives. S

Scan here to listen to Pereira's interview on Salk's podcast, "Beyond Lab Walls," at **salk.edu/podcast**.

Today, Pereira's Salk Institute team collaborates across disciplines to apply their AI-based technology in surprising ways.



Listen to all-new episodes of Salk's podcast "Beyond Lab Walls"

In our latest episode, Program Manager Kay Watt (featured on page 24) shares more of her inspiring story and explains how Salk's Harnessing Plants Initiative is using plants to fight climate change. Hear from more scientists like her as hosts Nicole Mlynaryk and Isabella Davis guide us through the latest discoveries in cancer, aging, climate science, and more. Here at Salk, we're unlocking the secrets of life itself and sharing them *beyond lab walls*.

BEYOND LAB WALLS

a Salk Institute podcast

Beyond Lab Walls is a production of the Salk Office of Communications and can be heard on **Apple** and **Google podcasts**, **Stitcher**, **Spotify**, or anywhere you listen to podcasts.

Scan the QR code to visit **www.salk.edu/podcast.**

INSIGHTS

From Peace Corps to plant science

Salk has long been known as the place where cures begin. But in recent years, it's also become a source of sustainable climate solutions. Through the Harnessing Plants Initiative, Salk scientists are optimizing crop and wetland plants to pull more carbon dioxide out of the atmosphere and better withstand the effects of climate change.

At the heart of the Harnessing Plants Initiative is Program Manager Kay Watt. She's a geneticist and plant biologist by training, but Watt isn't doing the experiments herself these days. Instead, she tackles all of the strategy, site operations, budgeting, reporting, communication, and outreach that keep the whole program on track.

Kay Watt

"We have incredible scientists on our team, but my job is to figure out how to get their great science out of the lab and into the world," Watt says.

This practical mindset comes from her years on the frontlines of food and agriculture, where she witnessed the real impact that heat, drought, and infectious disease can have on farms and farmers.

But long before she worked in the forests of Panama or the fields of California, Watt was getting her hands dirty in the garden at her family's Massachusetts home.

"As soon as I could walk, I was picking up a hoe or a rake and trying to help," she recalls. But as a child, Watt had yet to appreciate the relationship between gardening and science. Spending time in nature was just a part of her family's way of life.

"One thing that really stands out to me from my childhood is the beautiful red cardinals that we'd see in the wintertime," she says. "The sky would be cloudy, the trees would all be dormant, the ground would be blanketed with snow, and in all this monochrome, you'd see these beautiful bright flashes of color. They were one of my favorite animals to see when we'd go out for walks in the woods."

But it's not the beauty of this wintry scene that stands out to her now. It's what she didn't know at the time: cardinals are not native to New England. Only in the past few decades had the birds started coming up the coast and populating the warming North. This symbol of her idyllic 1980s upbringing was actually a sign that climate change was already well underway.

"It really struck me to learn that," Watt says. "Reflecting back and realizing that experience was due to climate change was very humbling."

After graduating college with a degree in philosophy and religious studies, Watt's desire to do good led her to join the Peace Corps. While on assignment in Panama, she was tasked with helping local coffee farmers learn new agricultural techniques for reducing the spread of crop-killing pathogens.

"Every plant counts when you're a farmer living season-to-season off of your harvest," she says, referring to the subsistence farmers who make up a quarter of the world's population. "Their entire livelihoods depend on agriculture, but the crop varieties they're growing aren't strong enough against disease and environmental stressors to sustain their food supply."

Watt wasn't just learning about food scarcity in a lecture hall—here, she was experiencing it firsthand. There were no cars or highways in the village she was living in, only horses and dirt roads. There was no constant stream of new goods coming into town, not a single delivery truck in sight. To eat, there was rice. To drink, there was rainwater. When night fell, kerosene lanterns were the only source of light.

"It made me very aware of how much I didn't know and hadn't experienced in my life," Watt says. She describes her return to the United States as "a massive culture shock."

"I would go to Whole Foods and spend several hours just looking at all the products because it was completely unimaginable to have that amount of variety available to you at all times."

It was then that she made two life-changing decisions: She was going to dedicate her career to improving global food security, and she would use plant and agricultural science to do it.

Within two years of intensive studying, Watt completed a second bachelor's degree in plant biology and was on her way to getting a PhD in genetics. While in graduate school, she used modern plant breeding techniques to develop new drought-resistant varieties of chickpeas.

"I thought California farmers would be especially excited to grow a heartier chickpea crop that didn't require as much water," she says. "But it turns out there wasn't much financial incentive for growers to use less water because of how the irrigation policies were set up."

After five years of painstaking work, her chickpea plant was deemed scientifically successful but commercially unviable.

"I realized then that a lot of smart people were concentrated on the science, but they weren't necessarily looking at all the other factors that can influence the application of that science in the real world," Watt says. "I decided I would focus on that moving forward."

Watt has been an integral part of Salk's Harnessing Plants Initiative since 2022. While its researchers continue optimizing the science of Salk Ideal Plants®, she skillfully oversees the strategy and logistics of getting them into public use.

"We're now at the exciting stage of advancing our first Salk Ideal crops into field trials," she says. "It's a major milestone for the program, so I'm optimistic that we'll soon see these plants moving beyond our greenhouses to support farms and farmers around the globe."

Hear more at www.salk.edu/podcast

NEXT GEN

> “Our hypothesis is that mitochondrial dysfunction or damage during aging promotes a type of inflammation that then drives the development of liver cancer.”
>
> **PAU ESPARZA-MOLTÓ**

PAU ESPARZA-MOLTÓ

The music of mitochondria

Pau Esparza-Moltó was born in a small town near Valencia along Spain's Mediterranean coast. Now a postdoctoral researcher in Professor Gerald Shadel's lab, he finds familiarity in his new home of San Diego. "The weather is actually quite similar," he says. "Very sunny, and when it rains, it pours."

Growing up in a rural town, Esparza-Moltó fondly recalls an active childhood spent mostly outside—hiking with his parents and brother, picking oranges and persimmons on his grandparents' land, and playing soccer with friends.

His mother was the first in his family to attend university, and she later became a professor of genetics. Esparza-Moltó shared his mother's scientific curiosity, but at the time, his attention was also drawn elsewhere—toward music.

In high school, Esparza-Moltó was torn between studying biology and playing the saxophone. "I was always interested in how things work and how things are made," he says, "especially in the biological sense—like how tiny molecular building blocks can make up entire living organisms."

Despite this dueling interest between genetics and jazz, Esparza-Moltó ultimately decided to study science in college. At the start of his undergraduate years in Valencia, he considered pursuing medical school but quickly realized anatomy wasn't for him. Then, he leaned into his lifelong curiosity for "building blocks" and pursued biochemistry and molecular biology to learn more about how genes self-regulate.

Esparza-Moltó did not entirely leave music behind, though. Instead, he used his continued training as a saxophonist to fuel his growth as a scientist.

"Music was how I learned discipline," says Esparza-Moltó. "Science is a lot of studying, practicing, and repeating experiments over and over. Then after all the discipline and practice, there's this bit of rest and reflection where you have a piece of music or a piece of data and think, how do I interpret this? What story is it trying to tell?"

Esparza-Moltó finished his bachelor's degree still gripped by questions about genetics and cellular regulation. His intrigue brought him to Madrid, where he earned a master's degree at the Universidad Autónoma de Madrid. But during his time there, Esparza-Moltó surprised himself by pivoting away from fundamental genetics.

"I decided to switch gears for my PhD after hearing some really interesting things about another lab at la Autónoma," recalls Esparza-Moltó. "They were working on mitochondria, studying the evolution of their function and communication."

Mitochondria are the small, bean-shaped organelles that generate energy to fuel our cells. Esparza-Moltó hopped on the mitochondria project, excited to dive deeper into the so-called "powerhouse of the cell." But what intrigued him about the lab's vision was looking beyond this clichéd identity. "Sure, that's their most known function," he says, "but could they also be used in another way?"

To investigate whether mitochondria serve a purpose beyond energy generation, Esparza-Moltó started exploring a protein called ATPase inhibitory factor 1. Instead of supporting mitochondria's role in energy production, this protein's activity seemed to be inhibiting it. If mitochondria weren't going to keep churning out

energy, perhaps this protein was helping them carry out another function instead? As he further characterized ATPase inhibitory factor 1, Esparza-Moltó began unveiling a bigger story about how mitochondria relay stress signals to the rest of the cell.

At Salk, Professor Gerald Shadel was reading into the very same story.

"In Spain, it's very common to go abroad for several months during your PhD to study in another lab," explains Esparza-Moltó. "After meeting Gerry at a conference in Italy in 2016 and realizing he was good friends with my previous advisor, I thought his lab would be a good fit."

Esparza-Moltó became a visiting PhD student in Shadel's lab at Salk, where they established a relationship that brought Esparza-Moltó back years later as a postdoctoral researcher. When he returned to San Diego, Esparza-Moltó eagerly continued his research on mitochondria, but now in a new context—aging.

"The risk of developing different neurological disorders gets higher with age," says Esparza-Moltó. "We really want to know what the mitochondria are doing in these pathological contexts, like how oxidative stress and inflammation may relate to Alzheimer's disease."

Oxidative stress is an imbalance of reactive oxygen molecules brought on by lifestyle and environmental exposures. Mitochondria are the main site of this dysfunction, and the main victims of its damaging effects. Shadel's lab has discovered important links between mitochondria, oxidative stress, and inflammation across the brain and body.

One way that Esparza-Moltó researches mitochondria is with sophisticated cultures of patient-derived skin cells, called fibroblasts. Salk scientists can turn these cells into what are called "induced neurons," allowing them to easily access and study human neurons in the lab. While developing and studying these cells with the help of Salk Professor Rusty Gage, Esparza-Moltó made an interesting discovery. He found a specific group of proteins were relocating to mitochondria when the cells were under stress. "We need to follow up on the relevance of these proteins and what they're doing there," adds Esparza-Moltó.

Esparza-Moltó is also collaborating with cancer biologists and immunologists at Salk to understand the role of mitochondria in other disease contexts.

"The incidence of cancer also increases as we age—especially so in the case of liver cancer," says Esparza-Moltó. "Our hypothesis is that mitochondrial dysfunction or damage during aging promotes a type of inflammation that drives the development of liver cancer."

The multitude of collaborations and engagements he's involved in—including Salk's American Heart Association-Allen Initiative in Brain Health and Cognitive Impairment—have kept Esparza-Moltó quite busy since settling in California, but he is beginning to explore new interests outside of science.

"I started surfing, but I don't think it's really my thing," laughs Esparza-Moltó. "But I did recently get a dog that I walk and explore the city with.. And there are so many opportunities to hike all around San Diego—I really like doing that."

Though he's a country's width and a cross-Atlantic flight away from Spain, family remains important to Esparza-Moltó, who makes time to travel back for visits at least once a year. He also keeps his artistic sensibilities alive through new creative hobbies, like cooking.

"I am always looking for the best technique or approach to get me to my goal, whether that's a new recipe, song, or research question," says Esparza-Moltó. "To this day, when innovating or changing directions, I definitely let my musical and creative principles guide me."

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BELONGING

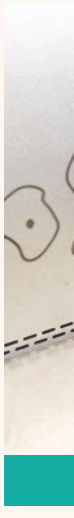
SALK SUMMER PROGRAMS

bring equity and opportunity to the STEM career pipeline

Each summer, the Salk Institute welcomes groups of high school and college students to campus, where they gain experience and insight into careers in the biomedical sciences. This year, we added a new program—Elevating Diversity in Graduate Education (EDGE)—to introduce top graduate students to the Institute and provide them with skills and experiences that will give them a competitive edge in applying for postdoctoral training opportunities.

These programs support current and future scientists from underrepresented populations at all stages of the research trajectory through hands-on research experiences, soft skills workshops, mentoring, networking, and more.

"These advocacy-centered efforts are a part of the Salk Institute's commitment to 'being good ancestors,'" says Jálin B. Johnson, head of Salk's Office of Equity & Inclusion. "As we do our part to carry on Dr. Salk's legacy, we are bringing together current and future innovators in science. This is done, in part, by championing diversity of thought, encouraging the amalgamation of scientific discipline and lived experiences, alongside curating supportive spaces for learning, research, training, and development. Each of these programs strives to create opportunities for members of the community to be a part of this legacy."



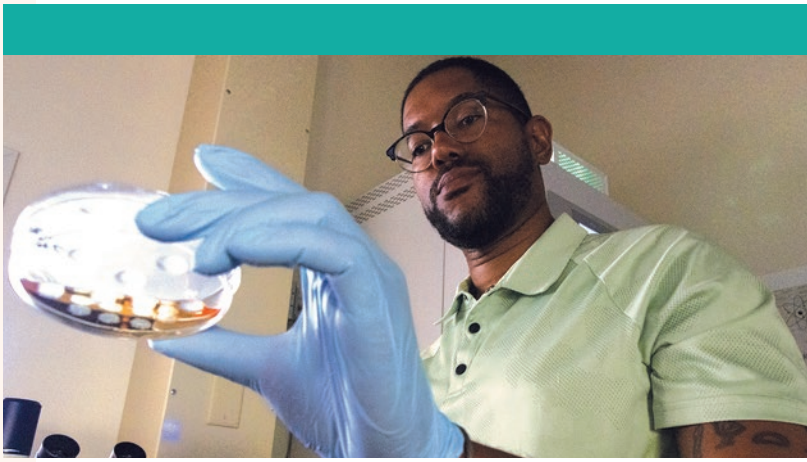
Heithoff-Brody High School Summer Scholars

Founded more than 30 years ago and led by Salk's Education Outreach team, the eight-week Heithoff-Brody High School Summer Scholars program provides paid opportunities for local high school students to explore how a scientific powerhouse like Salk is run. This year's cohort included 11 students who worked in various roles across the campus—from learning research techniques in the labs and core facilities to writing about scientific discoveries with the Institute's Communications team, or supporting their translation into commercial products with the Office of Technology Development (OTD).

"The Heithoff-Brody Summer Scholars program empowered me as a student, a leader, a rising professional, and an individual," says Danielle Dee, who interned with the OTD team. "Experiences such as company tours, career panels, presentation workshops, and professional branding seminars profoundly broadened my career perspectives and abilities, equipping me with essential skills such as organization, communication, time management, networking, and public speaking. The support of the Education Outreach team and my mentor, Ha Nguyen, gave me the skills and confidence to step out of my comfort zone. This experience has been a pivotal moment in my journey and ignited my ambition to pursue a career in technology transfer, where I can help bridge the gap between groundbreaking research and commercialization."

Elevating Diversity in Graduate Education (EDGE)

Spearheaded by Assistant Professor Christina Towers, Salk EDGE is a two-week summer program that equips graduate students from across the nation for competitive careers in academic science. Students are trained on cutting-edge techniques and provided with pilot grants to support the use of these new techniques in their



home labs. EDGE is a fully funded competitive program that helps prepare students for postdoctoral training positions in top-tier labs. This year's cohort included eight graduate students.

"When I first met Dr. Towers at a conference last year, I had no idea the Salk EDGE program would have such a profound impact on me as a scientist and professional."

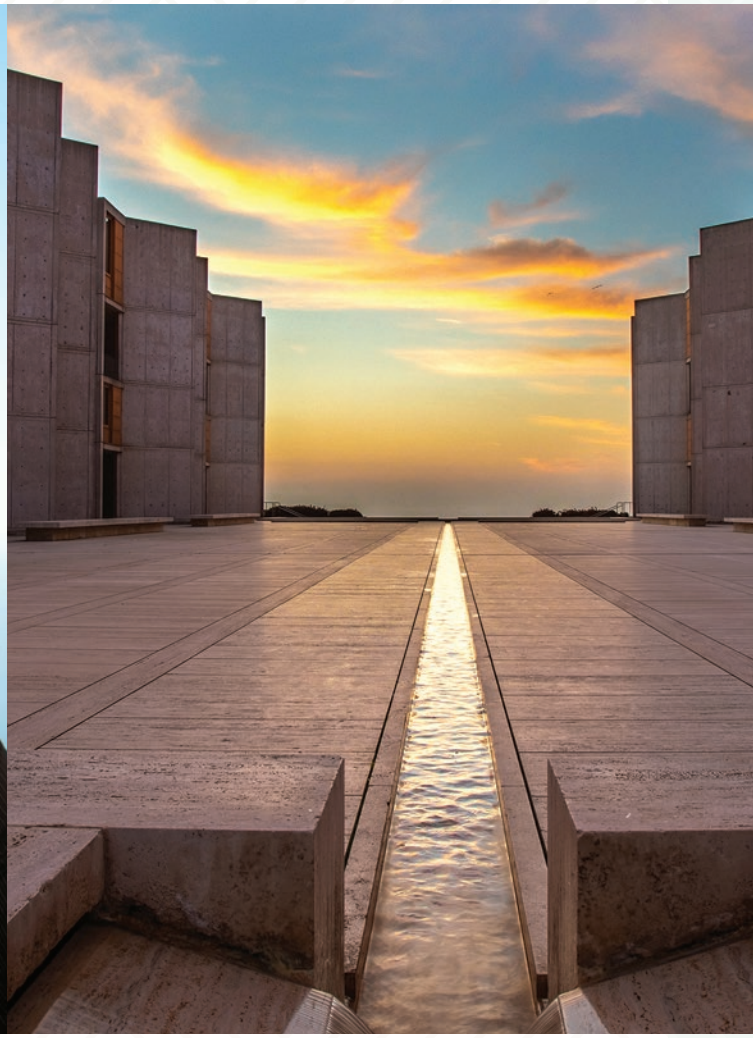
KOFI KHAMIT-KUSH (PICTURED ABOVE), SALK EDGE PARTICIPANT AND GRADUATE STUDENT AT CLARK ATLANTA UNIVERSITY

"During this program, I had the privilege of meeting esteemed Salk faculty and working alongside brilliant minds. This experience has deepened my understanding of cutting-edge biomedical research techniques and allowed me to present recent findings in my doctoral research to the Salk community. I am truly humbled and honored to be a part of the inaugural Salk EDGE cohort, which encompassed a broad range of expertise. Thank you to the Salk Institute for this incredible opportunity and for fostering an environment of innovation and collaboration."

Summer Undergraduate Research Fellowship (SURF)

Led by the Institute's Office of Equity & Inclusion, Salk SURF is a 10-week, paid, mentored research program that aims to broaden access to summer research experiences for undergraduate students who have little or no prior research experience. This year, Salk hosted 10 SURF students.

"My time here was rewarding," says Mhyraquel Quinto, a Nevada State University student who spent the summer in Salk Professor Joseph Ecker's lab. "This internship not only opened my eyes to pioneering methods and technology but has also taught me a lot about myself. To say the least, my journey in life and in science is as expansive as I want it to be. I just have to search for opportunities. I loved every second of learning the twists and turns of adaptable science."



REBECCA NEWMAN

Salk mourns the loss of Rebecca Newman

Rebecca Newman, who served as the Institute's Vice President of External Relations from 2008 to 2022, died last August.

For 14 years, Newman led Salk's fundraising efforts, including strategic planning and campaigns, donor relations, events, and communications. She successfully launched and exceeded the Institute's first major fundraising campaign to support scientific research, which secured more than $360 million in 2015. In addition, Newman oversaw 14 years of Symphony at Salk, the Institute's premier annual event, and created countless outreach programs, including the Salk Women & Science program, which she established in 2011 to raise the profile of women in science through fundraising and community engagement. Over her time at Salk, Newman increased private donations to Salk by an astounding 40 percent.

"Rebecca brought style and substance to her role as vice president. She was an icon in the local philanthropic community who did much to strengthen Salk's groundbreaking scientific research programs," says Salk President Gerald Joyce.

Suzanne Page appointed Chief Operating Officer

Page assumed the role of Vice President and Chief Operating Officer (COO) on October 14. She succeeds Kim Witmer, who retired after serving 39 years at the Institute.

Page served most recently as Vice President of Operations at Steadman Philippon Research Institute in Vail, Colorado, where she led operations and collaborated with researchers to lead laboratories for the research institute. She previously served as COO at Longeveron, Inc (NASDAQ: lgvn), a clinical-stage biotechnology company in Miami, Florida, that spun off from the University of Miami. As the company's first employee, Suzanne helped launch the start-up, built out manufacturing and R&D facilities, initiated clinical trials, and managed all business matters. Prior to that, she held the position of Executive Director of Research Administration and Revenue Cycle at the University of Miami, where she helped transform the university's research programs by creating a new department designed to accelerate research, increase revenue, and foster compliance.

As Salk's COO, Page will oversee operational functions, including facilities, security services, environmental health and safety, information technology, and campus events. As a key member of the Executive Leadership Team, she will work closely with Salk's President, Chief Science Officer, and other leaders to define and achieve the Institute's goals.

Page earned her Bachelor of Science in Finance and Juris Doctor at Indiana University. She holds state and federal bar memberships in California, Illinois, and Washington.

SUZANNE PAGE

"With a strong background in research, operations, and finance, Suzanne is poised to foster fresh ideas and innovation in a researcher-focused manner and will play a pivotal role in advancing Salk's mission. We look forward to benefitting from Suzanne's experiences as we work together to further enhance Salk's role as a global leader in foundational research."

SALK PRESIDENT GERALD JOYCE

JANELLE AYRES

Professor Janelle Ayres named Howard Hughes Medical Institute (HHMI) Investigator

The HHMI Investigator Program awards established scientists with approximately $11 million in funding over seven years to pursue boundary-breaking research in their field. This honor recognizes Ayres' influential work in immunology and microbiology and its applications to the global crisis of antibiotic resistance. She is among 26 other 2024 selectees, who will join more than 250 standing Investigators, including Salk Professors Joanne Chory (1997), Joseph Ecker (2011), and Kay Tye (2021).

Associate Professor Nicola Allen earns 2024 National Institutes of Health Director's Pioneer Award

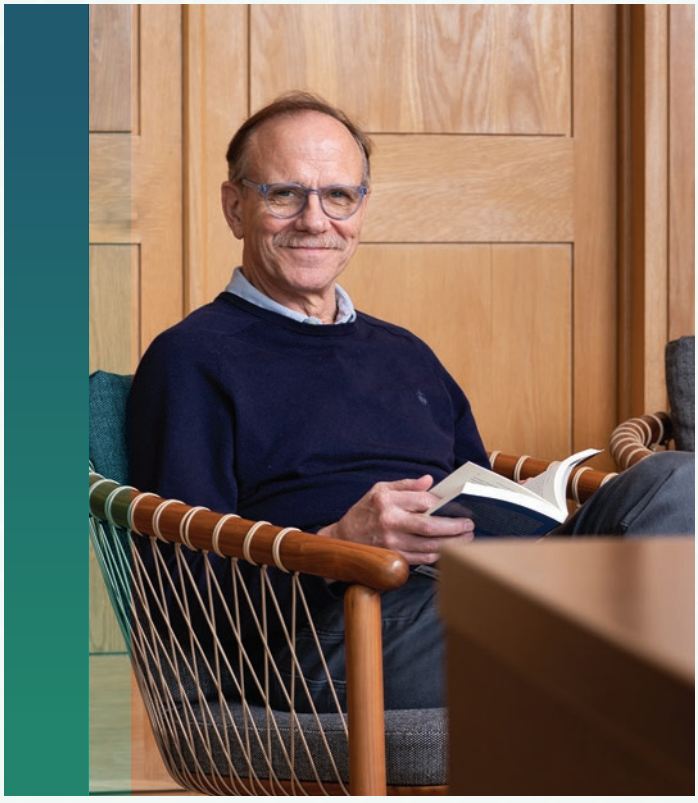
The award recognizes scientists with "outstanding records of creativity pursuing new research directions to develop pioneering approaches to major challenges in biomedical, social science, and behavioral research." Allen will receive $3.5 million over five years to support her research on the brain's ability to repair and rewire itself, also known as plasticity. Most research on the brain focuses on neurons, but Allen takes a unique approach by asking how non-neuronal cells help regulate brain function and plasticity. This work could inspire new therapeutics for boosting plasticity in disorders like Alzheimer's disease or after injury or stroke.

NICOLA ALLEN

Associate Professor Dmitry Lyumkis receives ACA 2025 Margaret C. Etter Early Career Award

This award, given by the American Crystallographic Association and named in honor of esteemed crystallographer Margaret C. Etter, recognizes Lyumkis' outstanding achievements and exceptional potential in crystallographic research. Lyumkis looks at the form and function of proteins to investigate how biological invaders interact with their hosts to establish and maintain infection.

DMITRY LYUMKIS



RUSTY GAGE

Salk Professor Rusty Gage awarded 2024 Taylor International Prize in Medicine

Given by the Schulich School of Medicine & Dentistry and the Robarts Research Institute at Western University, the prize is one of the most prestigious medical research awards in Canada. This year's prize specifically honors a research leader in aging-related medical science and research—a long-term focus of Gage and his lab. Gage received $50,000 and was celebrated at a Robarts Research Institute event in November.

JESSE DIXON

Assistant Professor Jesse Dixon named 2024 Pew Biomedical Scholar

This honor provides funding to 22 early-career investigators who demonstrate outstanding promise in science toward advancing human health. Dixon's recognition celebrates his recent work to help define the relationship between our genomes and cancer. His lab will receive $300,000 over four years to support their research.

Natanella Illouz-Eliaz wins 2024 Women's Postdoctoral Career Development Award in Science

A postdoctoral researcher in Salk Professor Joseph Ecker's lab, Illouz-Eliaz is this year's recipient of the Weizmann Institute of Science award. The program "supports Israeli women scientists during their postdoctoral training at leading institutions and laboratories abroad at a crucial stage in their career development." Illouz-Eliaz will receive career coaching and $70,000 over two years.

NATANELLA ILLOUZ-ELIAZ

Scan here or visit **www.salk.edu/podcast** to listen to podcast episodes featuring Dixon and Illouz-Eliaz as they share more about their career journeys and motivations.

New Salk Science Network (SciNET) enables research collaborations with swift data transfers

The Salk Institute has launched SciNET, a new state-of-the-art, high-speed network that enhances scientific data transfer between research collaborators. This offering is the latest advancement enabled by Salk's Biocomputation Initiative, which aims to provide the funding, technology, and expertise required for the increasingly data-intensive research in biological sciences, such as machine learning and artificial intelligence.

Salk awarded $3.6 million by the California Institute for Regenerative Medicine to advance research on brain aging

The state agency dedicated a total of $27 million to establish six new Shared Resources Laboratories designed to foster collaboration among California researchers. Salk Professor Rusty Gage will lead the new Shared Resources Laboratory at Salk, which will train other scientists to use his state-of-the-art stem cell-based models of aging and neurodegeneration. This initiative will help accelerate the discovery of new therapies, biomarkers, and drug candidates for age-related diseases like Alzheimer's and Parkinson's.

First row: Margarita Behrens, Sreekanth Chalasani, Dannielle Engle, Rusty Gage.
Second row: Aga Kendrick, Pallav Kosuri, Dmitry Lyumkis, Pamela Maher.
Third row: Graham McVicker, Christian Metallo, Joseph Noel, Satchidananda Panda.
Fourth row: Alan Saghatelian, Gerald Shadel, Christina Towers.

2024 Kavli Small Equipment Grant Program awards 15 scientists

The program supplies Salk Faculty and Research Professors working in neuroscience and related fields with funds to purchase or build small equipment necessary for their research. Three proposals were awarded: Pallav Kosuri, Dmitry Lyumkis, and Aga Kendrick's Atomic Force Microscope; Satchidananda Panda, Rusty Gage, Alan Saghatelian, Christian Metallo, Dannielle Engle, Christina Towers, Pamela Maher, Joseph Noel, and Gerald Shadel's Oroboros O2k Modular system for High-Resolution Respirometry; and Graham McVicker, Margarita Behrens, Sreekanth Chalasani, Christina Towers, and Aga Kendrick's qRT-PCR instrument.

EVENTS

Science and art converged at the 28th annual Symphony at Salk

The Salk Institute is grateful to the many generous sponsors who contributed to the spectacular night, and who continue to support life-changing research.

The 28th annual Symphony at Salk welcomed more than 400 attendees to the Salk Institute's iconic Courtyard on August 17. The concert under the stars showcased an outstanding performance by the San Diego Symphony Orchestra, conducted by Sean O'Loughlin and presented by Zenith-level sponsors Ann Tsukamoto-Weissman and Irv Weissman. The night also featured guest artists David Foster, sixteen-time Grammy Award®-winning musician, composer, and producer, and Katharine McPhee, acclaimed singer and television/Broadway star, with special guest Daniel Emmet, an outstanding, multi-lingual vocalist.

Many additional sponsors made the event possible, including Supernova-level sponsors BioMed Realty, Sarah and Jay Flatley, Joan and Irwin Jacobs, Rita and Brian Kaspar, and the Hutton-Zimmerman Family.

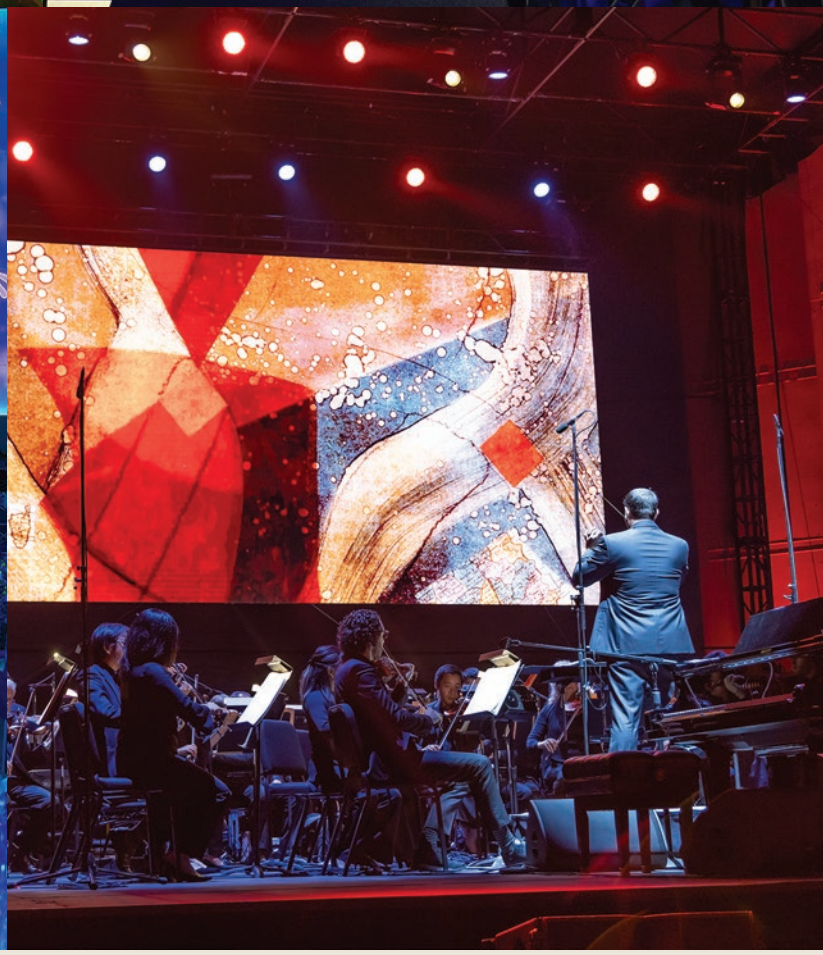
In addition to enjoying world-class musical entertainment, attendees were immersed in a multimedia experience that introduced Salk's Unlocking Healthy Aging Initiative. Historically, aging research has been approached with a kind of tunnel vision, with each scientific discipline focusing on individual aspects of age-related diseases. In contrast, the Salk Institute brings together multidisciplinary teams of experts to investigate the many underlying aspects of aging—including genome instability, mitochondrial dysfunction, and inflammation.

"Symphony at Salk is a unique event that brings together the two worlds of science and art, each enriching the other and helping us develop a deeper understanding of ourselves and our world," says Salk Institute President Gerald Joyce. "We are grateful to our many visionary sponsors who share Salk's appreciation for the arts and sciences, and who demonstrate their generous support for Salk with their precious time and philanthropic contributions. You are all true partners in helping us build a healthier world together."

Symphony at Salk helps drive the Institute's seven-year, $750 million Campaign for Discovery, which has now raised more than $455 million to support critical research.

Save the date for the 29th annual Symphony at Salk on August 16, 2025. Details will be available next year at **symphony.salk.edu**.


YAMAHA



Salk Institute appreciates pre- and postdoctoral researchers

During the week of September 16-20, Salk celebrated National Postdoc Appreciation Week by thanking both pre- and postdoctoral trainees, who collectively make up approximately one-third of the Institute.

To celebrate the week, Salk's Pre- & Postdoctoral Office, led by B. Bea Rajsombath, planned a variety of activities for Salk trainees, including an ice cream social, alumni panel, a night out at Petco Park for a Padres baseball game, networking opportunities, yoga, and more.

Rajsombath and her team support trainees throughout the year, serving as an invaluable resource that enhances the training experience at Salk.

"Graduate students and postdoctoral trainees are the backbone of Salk's research labs," says Salk Chief Science Officer Jan Karlseder. "These talented researchers design and conduct critical hands-on experiments, collect and analyze data, and drive new research directions. They co-author papers and grant applications and mentor other students and lab members. In short, their knowledge, ideas, and skills are essential for advancing science. Moreover, their fresh perspectives and enthusiasm often lead to innovative approaches and groundbreaking discoveries.

On behalf of Salk's leadership and faculty, we thank our grad students and postdocs—we appreciate your dedication, insights, and creativity."

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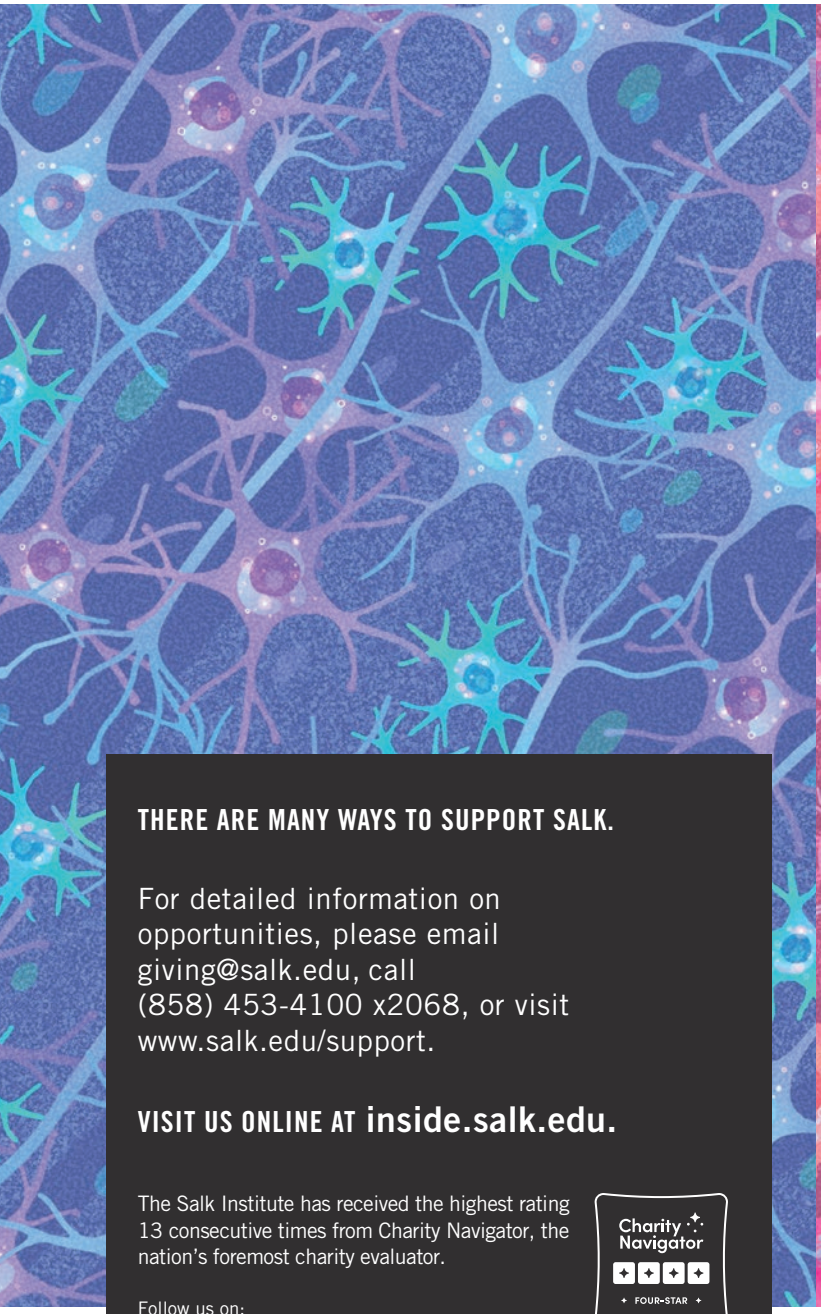

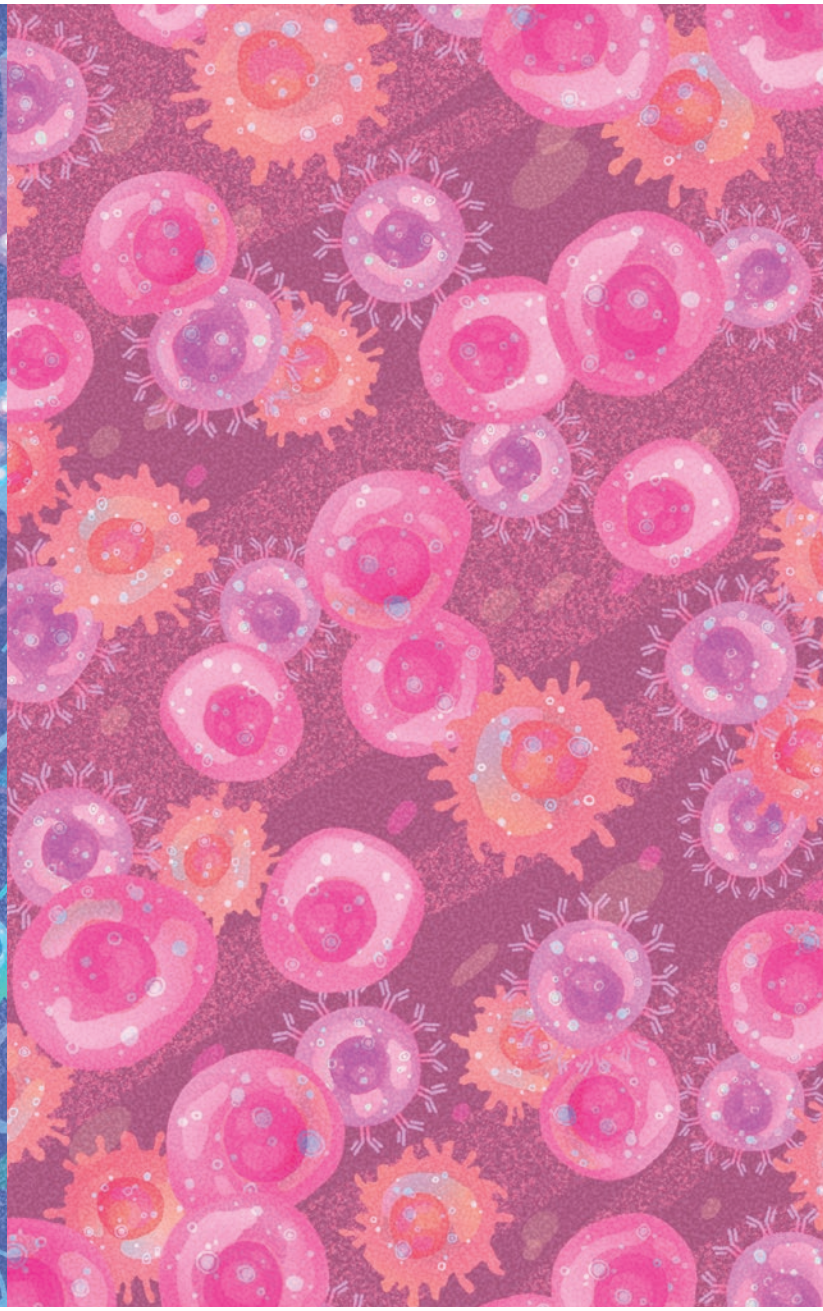

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