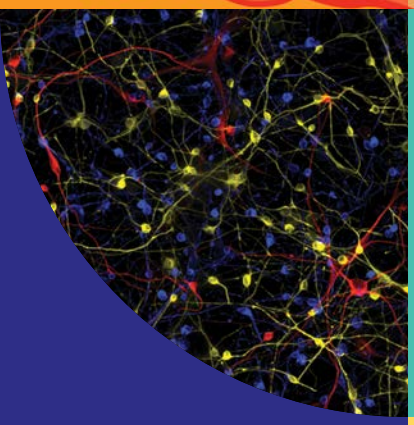
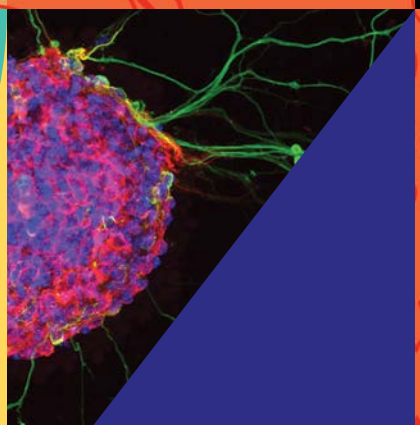
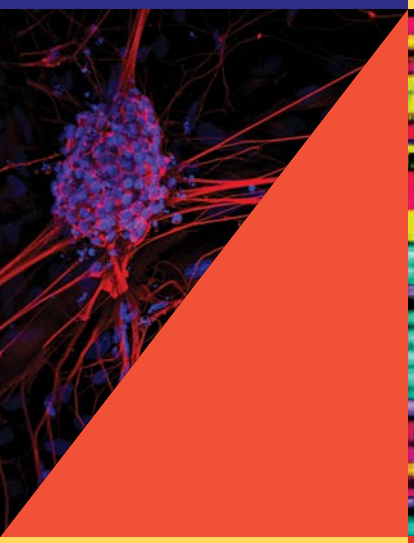
SPRING | 2021

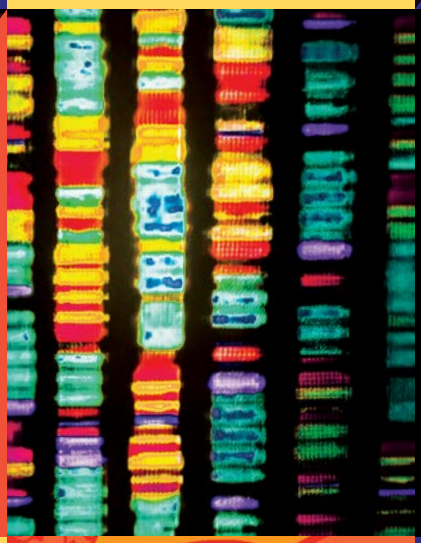
WHERE CURES BEGIN.

InsideSalk



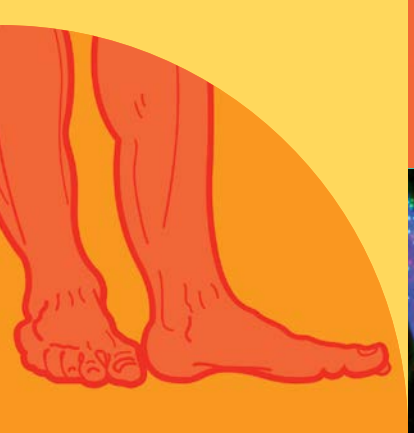


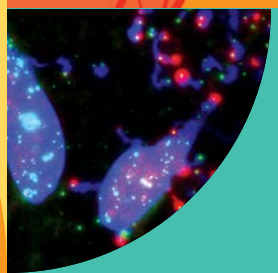


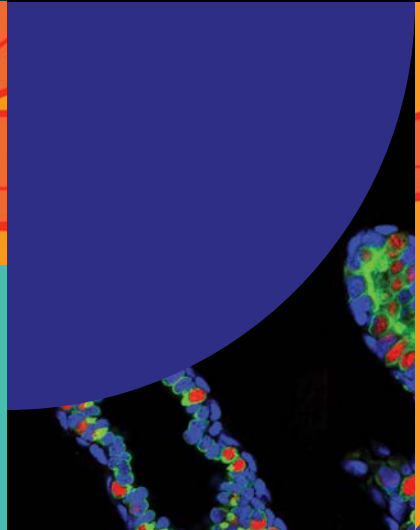


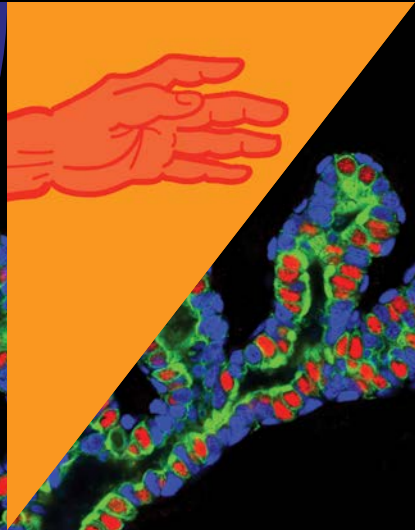
THE AGING PUZZLE COMES TOGETHER

Salk Science Through a New Lens









CONTENTS

ON THE COVER:

The Salk Institute's unique and collaborative approach to science is paving the way to new insights into the challenging problems of our lifetime. This issue's feature focuses on the enigma of aging.

PRESIDENT'S LETTER

Dear Friends,

When historians tell the many stories of the COVID-19 pandemic, one of the main narratives will follow the story of how scientists from across the globe came together in an urgent effort to develop effective vaccines against COVID-19. The actions would lead to not one but several successful vaccines in less than a year and others in development. It is an astonishing scientific achievement unparalleled in history, especially when considering the average time it takes to develop a new vaccine had typically been more than 15 years.

Six months into the COVID-19 vaccination effort, we are beginning to see the impact. As I write this, more than one-third of all Americans are fully vaccinated, and new cases have dropped to levels not seen in over a year. There is a growing optimism that we are turning a corner on the darkest days of the COVID-19 pandemic in the U.S. It is the beginning of the journey that is taking us from shelter-in-place to more normal activities. But it is early, and only the beginning, and what is unfolding in the U.S. has yet to reach a global scale. Most of the world's population does not have access to vaccines, and the threat of infection and death remains tragically high in countries such as India. As supply increases and distribution expands, a path forward is emerging to control this devastating pandemic.

As this magazine goes to print, planning is underway to welcome back to Salk offices our staff members who have been required to shelter and work from home for the past year. Friends and supporters will be welcomed back to Salk on August 21, for the 25th anniversary of Symphony at Salk. With guest performances by GRAMMY Award-nominated singer, songwriter and actor Josh Groban and the San Diego Symphony, the event will celebrate Salk science and a return to public events. It will also be the first time for many of us to share company in more than a year while we enjoy a gourmet dinner and spectacular evening of entertainment. It will also mark the official re-opening of the Salk campus to the general public.

We are shifting our perspective and adjusting our approach as we pursue answers to many of the biggest questions facing us. At a fundamental level, the goal is to strengthen the natural resilience in our bodies (and our planet) to prevent illness and extend our healthy life span to be free of age-related disease. It is a shift from a focus on the causes of disease to a holistic view on health and understanding of the interdependence of our systems, organs, and cells in shaping our life span. It is pursuing bold Salk science through a different lens. You will hear more about this shift in the months ahead, but our feature story on aging introduces you to our approach.

In the pages of this issue, we also introduce four new members to Salk's esteemed faculty and interview Assistant Professor Dmitry Lyumkis, who opens up about his scientific influences. We profile Senior Staff Scientist Pamela Maher about her search for novel Alzheimer's treatments, a mission she shared with her late husband and Salk Professor David Schubert. And we also introduce you to Postdoctoral Fellow Rajasree Kalagiri, who shares her journey from a small town in southern India to the campus of Salk. Today, she works alongside some of her scientific heroes to help unravel the mysteries of cancer.

I am excited about what is ahead for Salk and the bold, audacious science we are exploring. Salk researchers are expanding scientific boundaries while seeking answers to some of our most challenging problems, from climate change to Alzheimer's. And with your continued support and partnership, we will pursue the future with passion and resolve that builds on our 60 years of success.

Rusty

Fred H. Gage
President

"Most of the world's population does not have access to vaccines, and the threat of infection and death remains tragically high in countries such as India. As supply increases and distribution expands, a path forward is emerging to control this devastating pandemic."

The Institute has welcomed four new faculty since last winter. Professor Christian Metallo and Assistant Professor Christina Towers were recruited from outside Salk, while Assistant Professor

FOUR INNOVATIVE RESEARCHERS APPOINTED AS SALK FACULTY

Jesse Dixon and Assistant Research Professor Uri Manor were appointed to new positions from within the Institute. These exceptional researchers are poised to make big discoveries in metabolism, cancer, computational biology, imaging and more, and are a testament to the importance of bringing the best and brightest minds to Salk to continue the Institute's legacy of cutting-edge research for the benefit of humanity.

New Faculty

Professor Christian Metallo tracks metabolic pathways that lead to diseases like cancer, obesity, neuropathy and eye diseases, using tracer molecules and advanced mass spectroscopy techniques. Taking this approach, his lab has made key discoveries about the metabolic processes that drive tumor growth and macular telangiectasia type 2 (MacTel), an eye disease that causes vision loss. At Salk, his research will focus on elucidating how metabolism contributes to both health and disease. Prior to joining Salk, Metallo was an associate professor of bioengineering at UC San Diego. He received his MS and PhD degrees from the University of Wisconsin-Madison, and conducted his postdoctoral studies at the Massachusetts Institute of Technology. He is the recipient of an NSF CAREER Award; an American Cancer Society Fellowship; and a Searle Scholar Award, among other honors.

New Faculty

Assistant Professor Christina Towers uses a combination of DNA-editing techniques, light-based genetic manipulation (optogenetics), three-dimensional miniature organs ("organoids"), and detailed imaging to uncover how cancer cells recycle both their own nutrients and the power-generating structures called mitochondria in order to survive. Her goal is to work with local clinicians to develop new targeted cancer therapies that can block the cancer cell recycling pathways that allow these cells to survive. Her research could lead to decreased cancer recurrence and improved cancer patient outcomes. Towers obtained her PhD from the University of Colorado, where she also conducted her postdoctoral fellowship. Her many honors include an Outstanding Dissertation Award from the University of Colorado, an NIH Pathway to Independence Award and an American Cancer Society Postdoctoral Fellowship.

Faculty Appointment

Assistant Professor Jesse Dixon uses molecular and computational biology to explore how abnormal genome folding leads to errors in critical stretches of noncoding DNA that cause many diseases, such as cancer. His team is also developing new methods to study gene organization and gene function in single cells, to gain extremely detailed ("high-resolution") information about the different genes in each cellular system as well as insights into the molecular mutations that lead to disease. Dixon obtained his MD and PhD degrees from UC San Diego and was a Helmsley-Salk Fellow. Among his many honors are an NIH Early Independence Award, the UC San Diego Chancellor's Dissertation Medal for Biological Studies and the California Institute for Regenerative Medicine Pre-Doctoral Fellowship.

Faculty Appointment

Assistant Research Professor Uri Manor applies artificial intelligence-based computational approaches (deep learning) that integrate data from optical and electron microscopy techniques increasing image resolution, sensitivity, and collection speed beyond what's possible with any individual method. He investigates a number of biological targets involved in processes that, if disrupted, can lead to disorders including Charcot-Marie-Tooth disease, hearing loss, and age-related neurodegenerative diseases such as Alzheimer's. Manor obtained his PhD from Johns Hopkins University and was a postdoctoral fellow at the National Institutes of Health. The recipient of a Chan Zuckerberg Initiative (CZI) Imaging Scientist award, he is also director of the Waitt Advanced Biophotonics Core Facility at Salk.

THE POWER OF MODELS

Life is stunningly complex. To unravel its mysteries, scientists wield a powerful yet fundamental tool in research: the model.

Models mimic and simplify complicated systems and allow researchers to ask scientific questions that may otherwise be difficult or impossible to answer. For example, a simple plant can serve as a model for revealing fundamental principles of plant biology as well as animal cells, while brain-based computer models, like artificial intelligence, can show how deficits arise in disease or help machines mimic human intelligence.

Now, scientists at Salk have harnessed and developed model systems that could reveal novel insights about how plants grow, how the brain stores short-term memories and more.

NATURE METHODS
03/2021

New method could democratize deep learning-enhanced microscopy

Deep learning is a potential tool for scientists to glean more detail from low-resolution images in microscopy, but it's often difficult to gather enough initial data to train computers in the process. A new method developed by Salk Assistant Research Professor Uri Manor, director of Salk's Waitt Advance Biophotonics Core Facility, and first author Linjing Fang, Salk image analysis specialist, could make the technology more accessible by taking high-resolution images and artificially degrading them. The method could make it significantly easier for scientists to get detailed images of cells that have previously been difficult to observe, as well as allow scientists to capture high-resolution images even if they don't have access to powerful microscopes.

WATCH | www.salk.edu/manor202105

Computational model reveals how the brain manages short-term memories

NATURE NEUROSCIENCE
12/2020

If you've ever forgotten something mere seconds after it was at the forefront of your mind, then you know how important working memory is. Although it's critical in our day-to-day lives, exactly how the brain manages working memory has been a mystery. Now, Professor Terrence Sejnowski and Salk and UC San Diego MD/PhD student Robert Kim have developed a new computational model showing how the brain maintains information short-term using specific types of neurons. Their findings could help show why working memory is impaired in a broad range of neuropsychiatric disorders, including schizophrenia, as well as in normal aging.

The Power of Models continued...

Teaching artificial intelligence to adapt

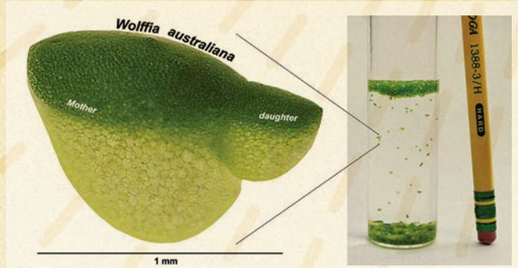
From left: Terrence Sejnowski, Kay Tye and Ben Tsuda.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 11/2020

Getting computers to "think" like humans is the holy grail of artificial intelligence, but human brains turn out to be tough acts to follow. Now, Professors Terrence Sejnowski and Kay Tye, along with first author Ben Tsuda and colleagues, have used a computational model of brain activity to simulate "adaptability" more accurately than ever before. The new model mimics how the brain's prefrontal cortex uses a phenomenon known as "gating" to control the flow of information between different areas of neurons. The findings could inform the design of new artificial intelligence programs.

"I think one of the most exciting parts of this is that, using this sort of modeling framework, we're getting a better idea of how the brain is organized. That has implications for both machine learning and gaining a better understanding of some of these diseases that affect the prefrontal cortex"

BEN TSUDA



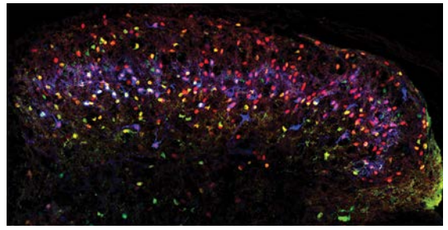
The tiny aquatic plant *Wolffia,* also known as duckweed, is the fastest-growing plant known. Credit: Sowjanya Sree/Philomena Chu.

Research catches up to world's fastest-growing plant

GENOME RESEARCH 02/2021

Wolffia, also known as duckweed, is the fastest-growing plant known, but the genetics underlying this strange little plant's success have long been unknown to scientists. Now, a multi-investigator effort led by Todd Michael, research professor and first author of the paper, along with coauthor and Professor Joseph Ecker, reports new findings about the plant's genome that explain how it is able to grow so fast. The research will help scientists to understand how plants put down roots and defend themselves from pests, with implications for developing plants that are optimized to increase carbon storage to help address climate change.

From left: Todd Michael and Joseph Ecker.



The researchers studied the organization of interneurons in the spinal cord, like those shown here.

From left: Martyn Goulding and Graziana Gatto.

WHEN IT COMES TO FEELING PAIN, TOUCH OR AN ITCH, LOCATION MATTERS

NEURON 11/2020

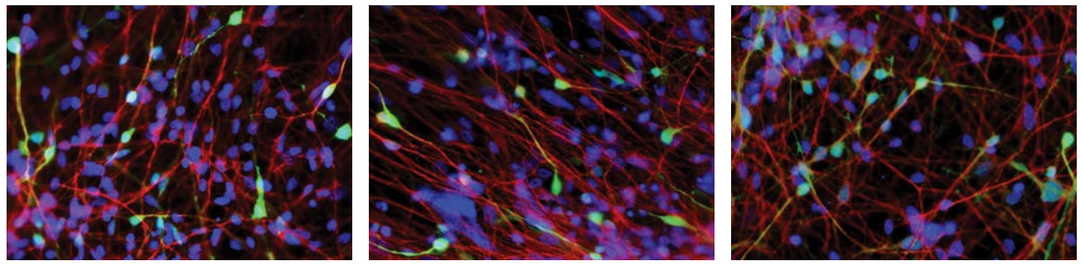
When you touch a hot stove, your hand reflexively pulls away; if you miss a rung on a ladder, you instinctively catch yourself. Both motions take a fraction of a second and require no forethought. Professor Martyn Goulding, first author Graziana Gatto and colleagues have mapped the physical organization of cells in the spinal cord that help mediate these and similar critical "sensorimotor reflexes." The new blueprint of this aspect of the sensorimotor system could lead to a better understanding of how it develops and can go awry in conditions such as chronic itch or pain.

NEW CLUES WHY GOLD STANDARD TREATMENT FOR BIPOLAR DISORDER DOESN'T WORK FOR MAJORITY OF PATIENTS

From left: iPSC-derived dentate gyrus (DG)-like neurons (green) from control subject; bipolar lithium responder; and bipolar lithium nonresponder. While the percentage of DG-like neurons is the same for control and bipolar, the gene activation profiles are different and the nonresponder has low levels of Lef1.

MOLECULAR PSYCHIATRY 01/2021

Lithium is considered the gold standard for treating bipolar disorder (BD), but nearly 70 percent of people with BD don't respond to it. Now, Salk Professor and President Rusty Gage, co-first authors Renata Santos and Shani Stern, co-corresponding author Carol Marchetto, and colleagues have found that decreased activation of a gene called LEF1 disrupts ordinary neuronal function and promotes hyperexcitability in brain cells—a hallmark of BD. The work could result in a new drug target for BD as well as a biomarker for lithium nonresponsiveness.



MICROBIOME

SCIENCE ADVANCES
01/2021

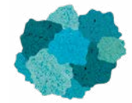
SPECIFIC BACTERIA IN THE GUT PROMPT MOTHER MICE TO NEGLECT THEIR PUPS

The microbiota are the microorganisms that colonize the body, but scientists are unsure about how they affect the brain. Professor Janelle Ayres, first author and former graduate student Yujung Michelle Lee and colleagues have identified a strain of *E. coli* bacteria that, when living in the guts of female mice, causes them to neglect their offspring. The findings show a direct link between a particular microbe and maternal behavior, demonstrating that microbes in the gut are important for brain health and can affect development and behavior.

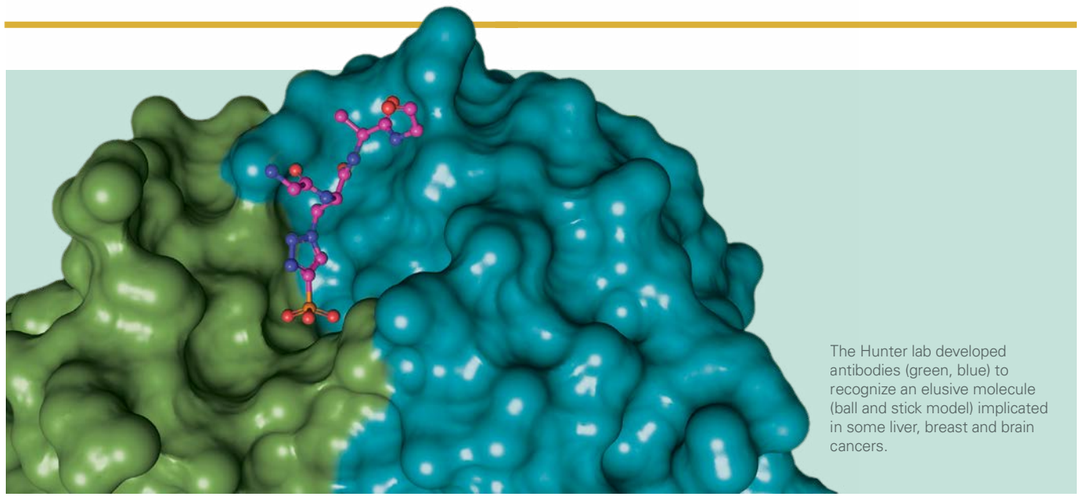
"It is very interesting to me that establishment of a healthy mother-infant relationship is driven by factors beyond hormones, and that the microorganisms residing in our bodies play a significant role in it."

YUJUNG MICHELLE LEE

Escherichia coli (E. coli) bacteria, pictured here, is a common gut bacteria in both humans and animals. There are many different strains, some of which cause disease.



CANCER



The Hunter lab developed antibodies (green, blue) to recognize an elusive molecule (ball and stick model) implicated in some liver, breast and brain cancers.

SALK TEAM REVEALS NEVER-BEFORE-SEEN ANTIBODY BINDING, INFORMING BOTH LIVER CANCER AND ANTIBODY DESIGN

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES
02/2021

Some molecules are so elusive that scientists require a unique set of tools to capture their structure. That's precisely how a multi-institutional research team led by Salk scientist Tony Hunter and Salk postdoctoral fellow Rajasree Kalagiri, featured in this issue's "Next Gen," defined how antibodies recognize a compound called phosphohistidine—an unstable molecule that's implicated in certain cancers, such as liver and breast cancer and neuroblastoma. These insights could help researchers understand the molecule's role in cancer pathways and also enable the design of more efficient antibodies in the future.

"We are excited that these new antibody structures reveal novel principles of antigen binding. Now we can redesign these antibodies and engineer their properties to make them more efficient."

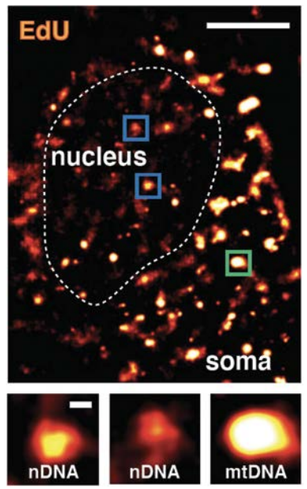
TONY HUNTER

AGING

HOW BRAIN CELLS REPAIR THEIR DNA REVEALS "HOT SPOTS" OF AGING AND DISEASE

SCIENCE
04/2021

Neurons lack the ability to replicate their DNA, so they're constantly working to replicate damage to their genome. A new study by Salk Professor and President Rusty Gage and colleagues reports that these repairs are not random, but instead focus on protecting certain genetic "hot spots" that appear to play a critical role in neural identity and function. The findings give novel insights into the genetic structures involved in aging and neurodegeneration, and could point to the development of potential new therapies for diseases such as Alzheimer's, Parkinson's and other age-related dementia disorders.



In this image of a neuron nucleus, bright spots show areas of focused genetic repair.

INFECTIOUS DISEASE

From left: Juan Carlos Izpisua Belmonte and Mo Li.

FAST, PORTABLE TEST CAN DIAGNOSE COVID-19 AND TRACK VARIANTS

MED
03/2021

Salk Professor Juan Carlos Izpisua Belmonte and collaborators have developed a new viral screening test that can not only diagnose COVID-19 in a matter of minutes with a portable, pocket-sized machine, but can also simultaneously test for other viruses—like influenza—that might be mistaken for the coronavirus. Called NIRVANA, this test can sequence the virus, providing valuable information on the spread of COVID-19 mutations and variants.

PLANT BIOLOGY

eLIFE
03/2021

"The Venus flytrap, which has a very fast response to touch, provides an opportunity to study a sensory modality that historically has been poorly understood."

JOANNE CHORY

NEW PROTEIN HELPS CARNIVOROUS PLANTS SENSE AND TRAP THEIR PREY

The brush of an insect's wing is enough to trigger a Venus flytrap to snap shut, but the biology of how these plants sense and respond to touch is still poorly understood, especially at the molecular level. A new study led by Salk Professor Joanne Chory and co-first author and Staff Scientist Carl Procko identifies what appears to be a key protein involved in touch sensitivity for flytraps and other carnivorous plants. The findings could help scientists better understand how plants of all kinds sense and respond to mechanical stimulation, and could also have a potential application in medical therapies that mechanically stimulate human cells such as neurons.

WATCH | www.salk.edu/chory202105

THE AGING PUZZLE COMES TOGETHER

WHAT IS AGING?

That question is more complex than it may appear. On an intuitive level, it's our bodies becoming less resilient. Strenuous exercise, minor muscle strains, late nights out with friends—we just can't bounce back like we used to.

Aging has even greater ramifications for disease. The risk of developing cancers, neurodegenerative conditions, heart disease and diabetes all increase as we get older. One current example is COVID-19, which tends to generate only mild symptoms in young people, while many over 65 are hospitalized.

We recognize, from personal experience, what aging does to our bodies; we just don't fully understand why. Something is happening at the molecular, cellular, tissue and organ levels to make our bodies less resilient and more prone to disease.

"We lack the mechanistic scientific understanding of what health really means at different stages of life," says Martin Hetzer, vice president/chief science officer and professor. "Health at age 20 means something different from when we are 40, 60 or 80. But what does that look like biologically? How do these systems change over time?"

If aging is the critical switch that sets the stage for multiple conditions, scientists want to understand what happens if we adjust that switch to increase *health span*—the number of years we are free from age-related decline and disease. By restoring some of the body's youthful resilience, we could revolutionize public health, the way scientists did with vaccines and antibiotics.

"Aging is the biggest risk factor for most diseases, but our health care system tends to manage these one at a time," says Gerald Shadel, professor and holder of the Audrey Geisel Chair in Biomedical Science. "We go to the cardiologist if we have a heart problem, a rheumatologist if we have arthritis. But, if we could manage aging itself, push these age-related conditions down the road, we could dramatically reduce the overall burden of disease on society and increase individual health span."

UNDERSTANDING AGING'S MANY PIECES

Aging is multifaceted, making it the perfect puzzle for Salk researchers to piece together. The Institute is approaching aging from multiple, converging angles: genomics, epigenetics, neurology, immunology, cell biology, data science and more. Understanding how these mechanisms interact may reveal how human biology changes with age and how that makes our bodies more vulnerable to disease.

INFLAMMATION'S CENTRAL ROLE

"Inflammation is a hallmark of aging," says Susan Kaech, professor and director of the NOMIS Center for Immunobiology and Microbial Pathogenesis. "But when we say inflammation, what molecules are we talking about and what are they doing? Defining the elements of inflammation most associated with age-related pathologies is a cornerstone of aging research right now."

Chronic inflammation, which often happens when the immune system goes on permanent alert, can generate body aches, fatigue, insomnia and other issues, and is often linked to biological stresses, such as repeated infections. Consider our emotional response to a near-miss on the freeway: stress floods our bodies. Cells have their own stress responses, and they may leave a mark.

"Maybe you had a pulmonary infection, like COVID-19, which caused inflammation in your lungs," says Kaech.

"Maybe you had a pulmonary infection, like COVID, which caused inflammation in your lungs. Those cells have acquired a history of seeing inflammation; they are basically imprinted by that inflammatory exposure. Now, take that over the course of a lifetime, with multiple infections. We want to understand the long-term impact that could have on health."

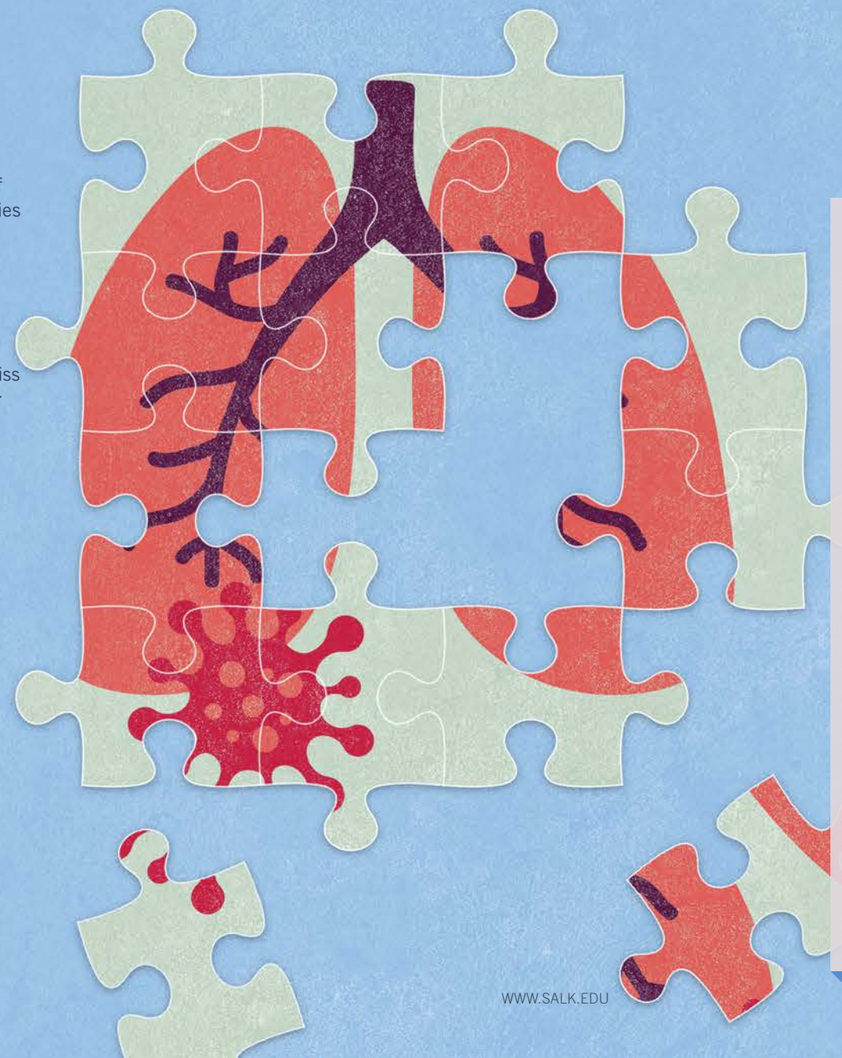
SUSAN KAECH

"Those cells have acquired a history of seeing inflammation; they are basically imprinted by that inflammatory exposure. Now, take that over the course of a lifetime, with multiple infections. Cells may remember that history, making them hyper-prepared for the next infection. We want to understand the long-term impact that could have on tissue health."

This is part of a larger effort to determine how cells and tissues get remodeled with age. In another immune-related example, T cells infiltrate the brain, though nobody is quite sure what they do there.

"T cells can live in the brain long-term after an infection," says Kaech. "We believe this is an evolutionary process to seed the body with long-lived memory cells that could respond to a second infection and protect us."

Kaech and colleagues wonder if these and other infection-related changes can have long-term consequences, contributing to cellular changes that make the body less resilient against Alzheimer's disease and other conditions.

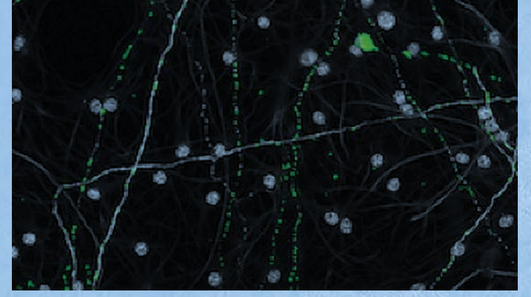


ENERGY CONSUMPTION

Neurons consume a great deal of energy—using ten times more cellular energy packets, adenosine triphosphate (ATP), than other cells, on average. Most of this energy is consumed at the synapse, the critical part of the neuron that enables new memories to form. Understanding this energy economy is vital to dissect neuronal aging and perhaps the memory loss associated with Alzheimer's.

The problem starts with mitochondria, the cellular factories that manufacture ATP. As we age, mitochondria become less efficient and generate less energy. To make matters worse, aging mitochondria give off reactive oxygen species, which can damage the neuron and its DNA. Repairing this damage is, in itself, an energy-consuming process, which sets up a vicious cycle: aging mitochondria damage DNA; DNA repair mechanisms require more energy to fix the damage; stressed mitochondria fail to meet those energy needs.

"We're very excited to be able to begin to understand the connection between mitochondrial aging and age-related cognitive decline," says John Reynolds, professor in the Systems Neurobiology Laboratory and Fiona and Sanjay Jha Chair in Neuroscience. "Now, we can visualize the mitochondria in neurons in a dish and see how they change with age. We're finding that animals showing age-related cognitive decline have mitochondrial aging signatures not present in healthy animals. With this approach, we're beginning to get a handle on how this system may be driving vulnerability to Alzheimer's disease."



Aged mitochondria (green) in old neurons (gray) appear mostly as small punctate dots rather than a large interconnected network.

Once again, the story circles back to inflammation. Mitochondria are relics from a symbiotic union between bacteria and other single-celled organisms around 1.4 billion years ago. They make multicellular life possible but, because they're biological hitchhikers, mitochondria have their own DNA (mtDNA). The relationship works great, mostly, but sometimes mitochondria break down and release mtDNA into the cellular environment. This "foreign" DNA is treated like an invader—a bacterium or virus. Inflammation ensues.

"We've connected mitochondria and mtDNA to the inflammation axis and are trying to drill down on the relevance of this to aging," says Shadel. "If we can prevent that release of inflammatory molecules from mitochondria, we predict it could have a health span-promoting effect."

The Rewards of Circadian Optimization

The body is often likened to a machine, but that comparison is not entirely accurate. For example, whether you start a car at 8 a.m. or 8 p.m., its performance will hardly vary. But our bodies are governed by a 24-hour clock. How we perform varies significantly with the timing.

Circadian rhythms influence every tissue in our bodies and have a profound impact on metabolism, sleep, digestive function, mental acuity and much more.

"During the daytime, circadian rhythms delineate the timing of peak performance in various organs," says Satchin Panda, professor in the Regulatory Biology Laboratory. "But they also govern repair and reset at night. Only when we have this performance and repair, on a daily basis, can we sustain better health."

It's easy to feel we can ignore these cycles—after all, we have artificial light and lots of great coffee—but the body needs to rejuvenate at night, whether we like it or not. Without this opportunity to refresh, the liver accumulates fat, which can lead to insulin resistance, diabetes and fatty liver disease. Denying kidney and heart cells their repair cycles can lead to high blood pressure.

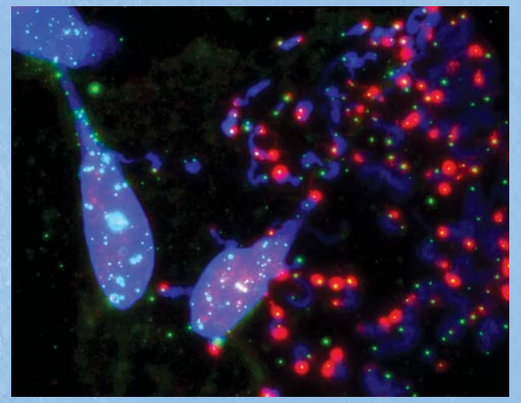
"Every organ has its own clock, which means every organ needs to 'sleep,'" says Panda. "But it's not sleep they need so much as time without food. You cannot repair a highway while traffic is flowing, and you cannot repair your gut lining if you just ate."

Panda's research evokes a concept called circadian optimization. The entire genome is programmed to go through these up and down cycles at different times of the day in different cells. By acknowledging circadian rhythms, and adjusting our lifestyles to collaborate with them, we can empower this repair cycle at night and amplify biological performance by day.

"We suggest that people not eat immediately after they wake up, for one to two hours," says Panda, "when the hormonal balance is flipping from nighttime repair to daytime functionality. Then eat during a 10 hour window, maximum 12 hours."

Panda believes circadian rhythms could be harnessed as a therapeutic strategy. He points to emerging research, from his lab and others, that suggests drugs targeting our body clocks could help treat certain cancers, neurodegenerative conditions and other diseases.

"We think the circadian rhythm theory of health will have a tremendous public health impact," says Panda. "By changing a few simple habits, we could reduce the risk of diabetes, cardiovascular disease, colon cancer and chronic inflammation and even accelerate healing."



Salk researchers show how the disabled protection of ends of chromosomes (blue) called telomeres (green) during cell division (mitosis) prompts cell death.

TELOMERES AND AGING

Telomeres are small DNA stretches at the end of each chromosome that play an oversized role in determining whether cells can divide indefinitely or not. In most human cells, telomeres are whittled away after each cell division. Early in life, this shortening process has little impact on human health, but once telomeres are too short, cells stop dividing and enter a state of irreversible arrest, which can be highly inflammatory.

Jan Karlseder, professor in the Molecular and Cell Biology Laboratory, has spent years investigating how these truncated telomeres send a DNA damage signal that prevents cancer cells from becoming immortal, as well as keeping their genome stable.

"Until recently, I had not considered that shortened telomeres send signals far beyond the ends of chromosomes," says Karlseder, "but my lab recently discovered that this process activates inflammation pathways via the mitochondria, which surprised all of us."

Karlseder's group is now working with Gerald Shadel's lab to decipher this cross talk between telomeres and mitochondria, as part of Salk's focus on understanding the synergy between different cellular systems during the aging process.

But not all human cells undergo telomere shortening at the same rate. In adult stem cells, a telomere-dedicated machine called telomerase intervenes to slow down the shortening process. Vicki Lundblad, also a professor in the Molecular and Cell Biology Laboratory, studies how telomerase functions inside cells, which has led to an unexpected discovery.

"It had been widely assumed that telomerase acts only after chromosomes have been fully replicated, just prior to cell division," says Lundblad. "Much to our surprise, we discovered that telomerase instead prefers to act at sites of chromosome replication failures."

This unexpected result has revealed a new network of genes that control telomerase access to these sites—providing potential targets for further aging research.

CELLULAR GARBAGE DISPOSALS

Like Karlseder, Reuben Shaw has long studied mechanisms associated with cancer. He directs Salk's NCI-designated Cancer Center and has spent years investigating a protein pathway called AMPK, which helps govern how cells respond to scarce nutrition—a major issue for tumors. These studies helped him unwind how metabolism can be weaponized against cancer, but they also led in an unforeseen direction—neurodegenerative disease.

The key has been understanding what AMPK, and associated proteins, do outside of disease: their day jobs. The Shaw lab found AMPK was talking to another protein called ULK1, which regulates a cellular recycling system called autophagy. It turns out ULK1 modulates an autophagy gene called Parkin, which is closely linked to early onset Parkinson's disease, as well as recycling mitochondria.

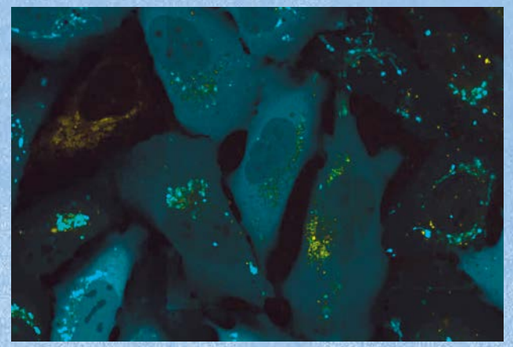
"In three biochemical moves we went from a cancer suppressing enzyme, called LKB1, which is mutated in around 20 percent of lung cancers, to AMPK to ULK1 to Parkin, which is directing the cell's recycling center and playing a role in preventing neurodegenerative disease," says Shaw.

Normally, this pathway gets turned on when cellular machinery goes awry to get it back on track. This protective effect could also be harnessed to control age-related diseases.

"The AMPK pathway has potent anti-cancer properties," says Shaw, "as well as anti-diabetes properties and, at least in the case of Parkinson's, anti-neurodegenerative disease properties."

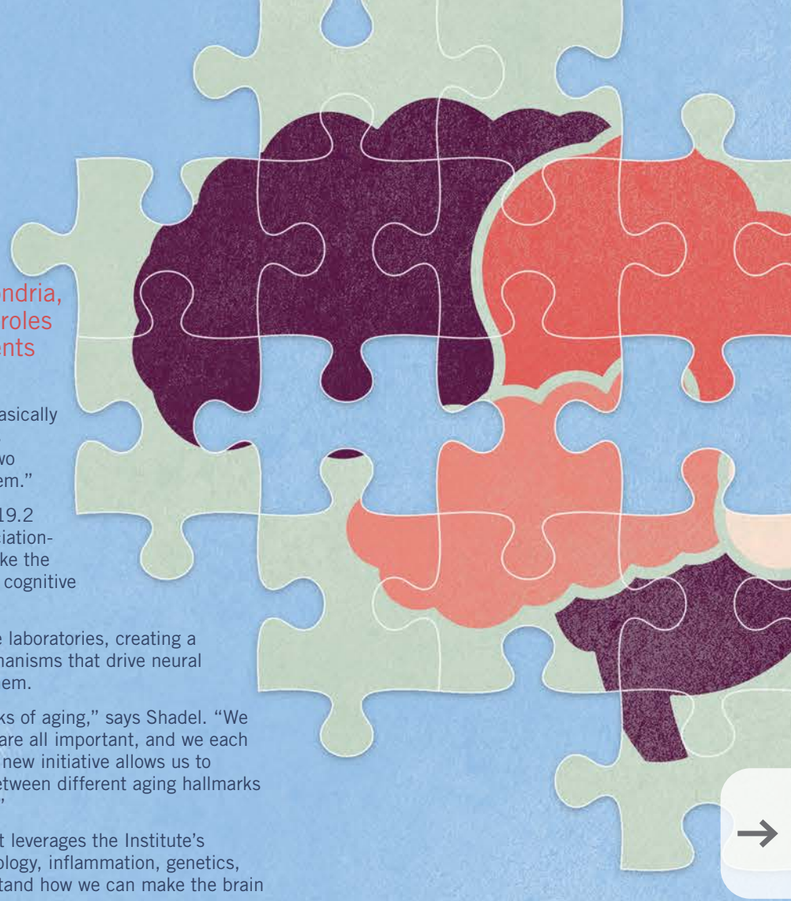
"This AMPK pathway has incredible anti-cancer properties, anti-diabetes properties and, at least in the case of Parkinson's, anti-neurodegenerative disease properties."

REUBEN SHAW



Parkin (above) is an autophagy gene that helps regulate the cellular recycling system. Parkin is also linked to early onset Parkinson's disease.

PUTTING THE PIECES TOGETHER



Inflammation, telomeres, mitochondria, and autophagy all play individual roles in aging. But how do these elements work in unison?

"We have the parts list," says Hetzer. "We basically know how a cell works. Now, we can put this together and look at more than just one or two components—we can look at the entire system."

In late 2018, the Salk Institute received a $19.2 million grant from the American Heart Association-Allen Initiative to study mechanisms that make the brain susceptible to Alzheimer's disease and cognitive decline and develop new therapies.

The grant is directly funding research in nine laboratories, creating a collaborative consortium to identify the mechanisms that drive neural aging and find creative ways to counteract them.

"We all study cellular and molecular hallmarks of aging," says Shadel. "We know that mitochondria, inflammation, etc., are all important, and we each study these things in our own ways. But this new initiative allows us to collaboratively investigate the interactions between different aging hallmarks and get the big picture of aging in the brain."

Led by Salk President Rusty Gage, this effort leverages the Institute's intellectual firepower in metabolism, immunology, inflammation, genetics, epigenetics and other areas to better understand how we can make the brain more resilient as it ages.

"It's not just finding a cause or cure for Alzheimer's disease," says Gage, "it's fortifying a healthy brain to make us less susceptible to disease."

But before this large research collaboration could fully investigate the aging brain, and align their studies, they needed a robust model to test their ideas.

HOW TO STUDY THE BRAIN

Scientists are always looking for better ways to model biology. By changing an input, such as shutting down a gene, they can see how the model responds.

But studying aging in the brain is tricky. Researchers need models that are age-equivalent to the patients they are modeling, as well as replicating the neural environment at different ages. Fortunately, the Gage lab has developed two key tools—age-equivalent neurons and 3D brain organoids—that help solve both problems.

The technique starts with skin cells reverted into induced pluripotent stem cells (iPSCs), which can then be differentiated into virtually any cell type. However, when cells revert to iPSCs, their age resets to zero. Gage discovered a way to maintain the cell's original age, so the neurons being studied reflect the age of the donor.

By maintaining this cellular time stamp, researchers throughout the AHA-Allen collaboration can do in-depth studies to better understand how various cellular characteristics change with age.

This model is a big deal, elevating research throughout the Institute. Whether scientists are studying immune cells, inflammatory pathways,

"We all study hallmarks of aging. We know that mitochondria, inflammation, etc., are all important, and we study these things in our own ways. But this allows us to step back and investigate the interactions between different mechanisms and get the big picture of aging in the brain."

GERALD SHADEL

telomeres, mitochondria, or other components, the Gage lab's brain organoids give them tremendous opportunities to assess the aging brain. Equally important, the model gives collaborators common ground to investigate how these different functions play off each other.

"Understanding aging is more complicated than saying there's a decrease in mitochondrial function or a shortening of telomeres or increased inflammation," says Gage. "It is the interaction between all of them, creating a brain environment that is conducive to disease."

GENOMIC ON/OFF SWITCHES

Many of the mechanisms described throughout this article are influenced by the epigenome, the molecules that control which genes get turned on and off. Epigenetic markers often change based on environmental inputs over time, making them critical to understanding aging.

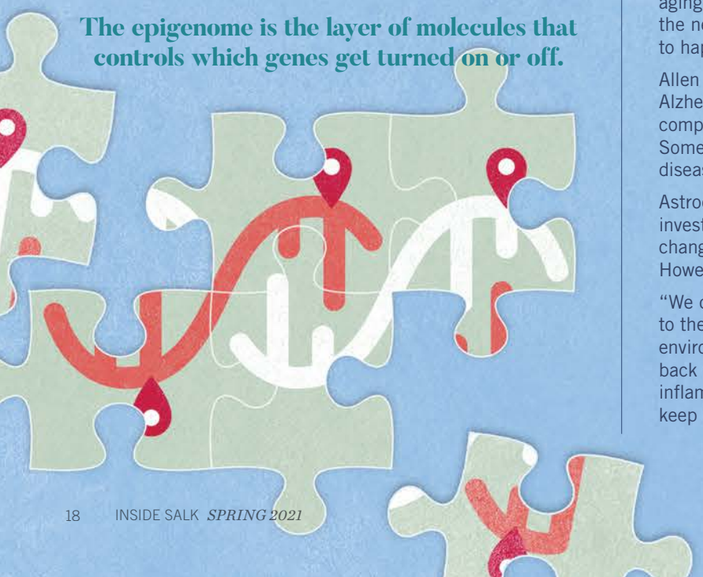
Joseph Ecker is a professor in the Plant Molecular and Cellular Biology Laboratory and an expert on the epigenome. Epigenetic markers are ubiquitous and so is Ecker, collaborating with multiple labs in the AHA-Allen project, as well as the Cancer Center and the Harnessing Plants Initiative.

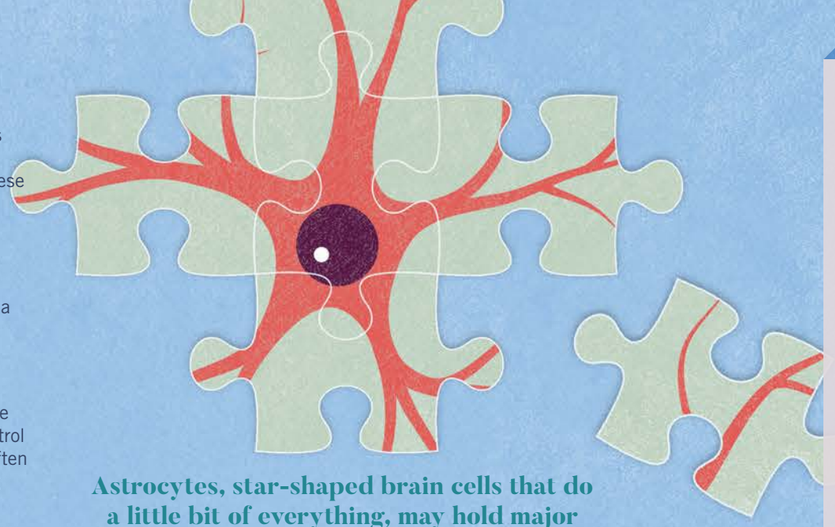
Ecker is working closely with Gage and others to understand the epigenetic profiles in aging brains. Like inflammation, mitochondrial dysfunction, immune cell migration and other mechanisms, epigenetic changes could be making older brains more susceptible to disease.

"We have a nice collaboration with Rusty's lab to go deep into single-cell profiles and ask how much of the aging signature is epigenetic," says Ecker. "Can we see differences between aging in Alzheimer's versus in individuals without Alzheimer's? The results are already looking pretty interesting."

Ecker, a Howard Hughes Medical Institute investigator, believes they are getting closer to understanding how epigenetics, and thus gene expression, change in the brain over time, insights that could eventually power new interventions.

The epigenome is the layer of molecules that controls which genes get turned on or off.





Astrocytes, star-shaped brain cells that do a little bit of everything, may hold major clues to making the brain environment more resilient against disease.

HOW THE BRAIN REMODELS WITH AGE

Neurons are the popular kids in the brain, getting the most attention from researchers. But they don't act alone.

"If we want to come up with new therapies for developmental disorders, neurodegenerative diseases and aging, we need to think about the many other types of cells in the brain, not just neurons," says Nicola Allen, associate professor in the Molecular Neurobiology Laboratory.

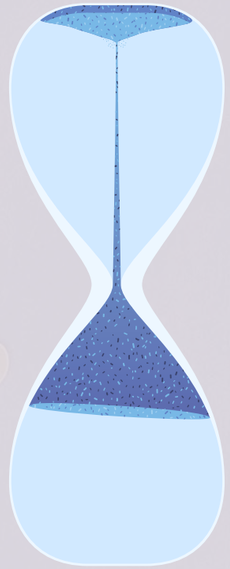
Allen is particularly focused on astrocytes, star-shaped brain cells that do a little bit of everything: maintaining neurons, regulating blood flow, providing neurons with energy sources. Astrocytes are brain generalists.

The Allen lab was studying astrocytes in development when an interesting question crept into their discussions. "We know astrocytes are incredibly important during development," says Allen, "but what about the rest of life? Do the molecular properties of these cells change with age and, if so, what do those changes mean? We're not thinking aging astrocytes trigger Alzheimer's so much as they change the neural environment, allowing neurodegenerative disease to happen."

Allen wants to know what aging has to do with disease. Alzheimer's, ALS and Parkinson's all have genetic components, but they generally appear later in life. Something is changing in the brain that allows these diseases to gain traction.

Astrocytes may hold major clues. The Allen lab is investigating whether they can reverse some of these changes and make the brain environment more resilient. However, the intervention must be just right.

"We don't want to send these cells all the way back to the development stage; that's a very different brain environment," says Allen. "But perhaps we can send them back from aging to an adult status. We could get rid of the inflammatory pathways actively damaging neurons, but still keep everything stable."



The Opposite of Aging

Induced pluripotent stem cells (iPSCs) were a brilliant breakthrough by Japanese scientist Shinya Yamanaka , for which he won the Nobel Prize in 2012. By exposing adult skin cells to four types of proteins, called transcription factors, he reprogrammed them epigenetically, nudging them into an immature state, similar to embryonic stem cells. From there, he could differentiate the iPSCs into virtually any cell type, while keeping the genome from the original cell.

This process intrigued Juan Carlos Izpisua Belmonte, professor in the Gene Expression Laboratory. His lab showed that during the reprogramming process, cells lose the molecular characteristics of aging that normally accumulate over time. He wondered if this technique could be used to rejuvenate cells to make them healthier, rather than reprogramming them all the way back to a pluripotent state.

"If we put these four factors in a live organ, for example a heart, we no longer have beating heart cells or cardiomyocytes," says Izpisua Belmonte. "You convert heart cells into embryonic stem cells and the heart will stop beating, which is not what we want."

To solve the problem, Izpisua Belmonte and colleagues brought time into the equation. Rather than bathing the cells in the four factors for a long time, they pulsed them for short periods. This made the cells de-differentiate, like Yamanaka's. They just didn't go all the way back to the starting line.

To test the beneficial effects of this process, Izpisua Belmonte used Yamanaka factors therapeutically in a mouse model of progeria, a rare disease that ages children prematurely. The mice would normally have lived around four months; however, this treatment extended their lives significantly.

Izpisua Belmonte is quick to point out that there are differences between premature and normal aging. This rejuvenation approach has now been tested in physiologically aging mice. His group has recently shown that it can also increase the capacity of some tissues, such as muscle, to regenerate and become functional again.

"We now have the ability to rejuvenate an organism in the lab," says Izpisua Belmonte. "We need to better understand how this process happens so that the knowledge could be used in clinical settings in the future.

THE POWER OF COLLABORATION

Since the AHA-Allen grant, Salk has become a nexus for aging research, particularly neurological aging. In 2019, Ecker and three other researchers received a $12.9 million grant from the NIH BRAIN Initiative to illuminate how the brain works and what can go wrong to cause disease.

More recently, in late 2020, Shadel helped create a scientific consortium between Salk, UC San Diego and Sanford Burnham Prebys Medical Discovery Institute to establish the San Diego Nathan Shock Center (SD-NSC) of Excellence in the Basic Biology of Aging.

"The SD-NSC is this incredible collaboration we just started that is studying the basic biology of aging and promoting aging research," says Shadel. "Specifically, we are focusing on how and why different cells and tissues age at different rates and how this variability contributes to how individuals age and become susceptible to certain diseases."

In 2021, John Reynolds and colleagues received a $1.2 million grant from the Larry L. Hillblom Foundation to examine aging and disease. "This grant came out of collaborative efforts made possible by the American Heart Association and the Allen Institute support," says Reynolds. "This has really opened up the opportunity for me as a cognitive neuroscientist to work with some fantastic cell biologists and others who have been studying aging in different ways. It brings the science together."

FROM RESEARCH TO POTENTIAL THERAPIES

The AHA-Allen grant, and other support, is producing insights into how the body ages that could lead to new therapeutic approaches to mitigate it. For example, Senior Staff Scientist Pamela Maher (see "Insights," page 24) and colleagues have shown two potential drugs slow aging in a mouse model of Alzheimer's disease.

Martin Hetzer was one of the first to show that different tissues naturally age at different rates, a process called age mosaicism. And new machine-learning techniques may help predict how quickly an individual's cells could age, which might encourage lifestyle changes to potentially mitigate some of these effects. The Hetzer lab has identified molecular targets that could slow blood vessel aging. This is particularly important for neurological diseases, as hard, leaky vessels may play a significant role.

AHA-Allen and other funding has supercharged Salk's natural collaborative approach. While different scientists bring their own knowledge to the table, there is tremendous cross talk between disciplines. This convergence of expertise is providing new insights that could illuminate the aging process and boost resilience against multiple diseases.

"We all study different things, but our work comes together with aging," says Shaw. "It's like that proverb of the blind men and the elephant. One investigates the trunk, another the tail, another the legs—so their descriptions are all different. But what if these men could suddenly see? Imagine their amazement at discovering they had been talking about the same thing all along."

DMITRY LYUMKIS

When asked to name a scientist he admires, Assistant Professor Dmitry Lyumkis struggles to choose just one; he admires so many for different reasons. Eventually he goes with Charles Darwin, citing his "meticulous attention to detail, his ability to simplify and interconnect complex data, of course, his pioneering work, and his love for the natural world." After an interview with Lyumkis, who answered questions roadside during a break from his bike ride home along San Diego's Mission Bay, it's clear why Darwin stood out.

Inside Salk ***chatted with Lyumkis about his science and his own methodical approach to the process.***

WWW.SALK.EDU

Can you talk about why you became a scientist?

DL: I've known that I wanted to be in research for a long time because I just enjoy being in the lab. I enjoy the process of discovery, which is kind of a tedious process really, because the discovery aspect happens so rarely. But when it does happen, it's really neat. I've considered many other paths, but none of them really stuck.

As a chemistry undergraduate at UC San Diego, I worked with a graduate student on the total synthesis of a natural product called Bielschowskysin. This is a very complex molecule that has shown antimalarial and anticancer activity, and to this day chemists have not been able to make this molecule in the lab. This project got me interested in chemistry, chemical reactions and experimental research. Eventually, I began taking biochemistry courses and learning about larger molecules like proteins and protein assemblies. I did my PhD work at the Scripps Research Institute and afterwards came to Salk as a fellow and then as an assistant professor.

I see it as a very logical transition from chemistry, going from small molecules to larger macromolecules, to macromolecular assemblies, and putting them all together to try to understand how they work inside a cell.

Speaking of other paths, in a TEDx talk a few years ago, you mentioned a brief stint studying philosophy in college. Did that experience inform how you approach science?

DL: I think in both fields you have to be curious and open-minded. You always have to question what you're studying and question the data. Don't get too stuck on an idea. The idea could be wrong, and if you test the idea—essentially your hypothesis—you might find something quite unexpected.

What's your favorite part of the scientific process?

DL: I love looking at new data; everyone does, especially if that data is telling you something interesting. I must admit I do very much like the troubleshooting aspect, basically working through a problem and trying to find the right approach. I think if you don't, then science is a very tough career trajectory.

Let's talk about the work you're doing now. What does your lab study?

DL: My lab is a structural biology lab. That means that we determine the atomic structures of proteins and protein assemblies that are responsible for a variety of molecular processes, and we use the structural insights, together with biochemical experiments, to understand how they function. The majority of the work in the lab focuses on protein assemblies that functionally interact with chromatin, which is the material inside a cell that packages your DNA.

For example, one of the processes that we're interested in is called retroviral integration. It's the process by which retroviruses, like HIV, gain access to the genome of a host cell—which is packaged into chromatin—and insert their own viral DNA into the host DNA to establish a permanent infection in that target cell. What we try to do is isolate, purify, and determine the structures of the proteins involved in this process, and how exactly they engage the chromatin assemblies. Then we can create 3D models of those molecular processes to understand the biology. For example in this particular case, we want to understand how viral DNA is integrated into the genome and why certain regions are selected. These models often also act as blueprints for designing small molecules that can potentially be developed into therapeutics. We have an ongoing project in the lab to understand how small molecules bind to and inhibit the integration process, and also the mechanisms by which the virus evolves resistance against therapeutic treatment strategies.

The other projects in the lab have a similar theme but are focused more on other cellular events surrounding chromatin, with implications in cancer and other diseases.

Your lab uses cryo-electron microscopy (cryo-EM), an imaging technique that won the 2017 Nobel Prize in Chemistry. What makes this method so powerful?

DL: There are a few things: First, this approach doesn't require as much biological sample as you would need for other, more traditional structural biology approaches, like X-ray crystallography. Second, the sample does not have to take the form of a crystal, which right away dramatically expands the types of questions that you can ask and the types of proteins or protein assemblies that you can study.

The third, and I'd say most exciting feature, is that it allows you to understand complex protein assemblies. Because cryo-EM lets you interpret many different states of protein assemblies, it gives you a much more dynamic representation of how they move, and by extension, how they function. You simply cannot study those types of assemblies using crystallographic methods.

Is there a specific discovery or moment in lab that you're particularly proud of?

DL: A few years ago, we developed a new method for collecting cryo-EM data that turned out to be important and gave rise to a lot of new ideas. It was really fulfilling because we had a simple idea at the spur of the moment, and it turned out to be very useful.

We were trying to collect cryo-EM data, but we couldn't collect good data, due to the way in which the specimen

was oriented on our support grids. So we had the very simple idea to basically tilt the stage inside the microscope.

People have thought about doing this before, but it never worked because there were a lot of practical problems. In many ways, ours was an engineering effort. We were able to solve prior issues, and the tilting worked, which gave us much better data. We ended up building upon the idea slowly but methodically, and now a large portion of the field is using our tools. What was really interesting from a scientific perspective, was that the approach also generated a number of new directions in my own lab, which I think are equally, if not more important, and address fundamental theoretical concerns in the cryo-EM field. For example, working with tilted data made us look deeper into the question of how do cryo-EM images lead to a good 3D reconstruction of the imaged protein specimen. We found that the way in which we evaluate our reconstructed cryo-EM maps was inadequate, and we need to take into account an additional factor to properly describe the object. This has direct implications for how we evaluate resolution in cryo-EM. It can all be explained mathematically and appears to line up with experiments. That was a real discovery, and it continues to generate new ideas. So that's neat. Such moments don't happen very often, but I like when they do.

What do you find unique about conducting research at Salk?

DL: Being at Salk gives you a wide appreciation of the types of questions that people are interested in and the scientific challenges outside of your immediate field. And occasionally, that leads to productive and fruitful collaborations that you might not have found anywhere else. My lab has a couple of those kinds of collaborations. We worked with Patrick Hsu, and we determined atomic

"You always have to question what you're studying and question the data. Don't get too stuck on an idea. The idea could be wrong, and if you test the idea—essentially your hypothesis—you might find something quite unexpected."

DMITRY LYUMKIS

structures of the novel CRISPR/Cas13d enzymes that he discovered while he was a fellow at Salk. The structures, together with biochemical data, gave us a good understanding of what the enzymes were doing and provided insights into how they could be modified and used for ongoing genetic engineering efforts in Patrick's lab. We are now starting an exciting project with Joe Noel, where we are trying to isolate the chromatin assemblies that my own lab has been studying for multiple years. In my lab, we're studying the mammalian forms of these protein assemblies, but with Joe, we are now trying to isolate them from plant cells!

Do you have a favorite spot on Salk's campus?

DL: The coffee cart. I like coffee and I enjoy having scientific conversations there.

What do you like to do for fun?

DL: I enjoy many outdoor activities. My wife and I really like to hike and camp. Occasionally, we will go mountain biking together or with friends. But, more regularly, I cycle to and from work at least several days a week. This is very refreshing for me mentally and often allows me to think through some problems and ideas. I'm actually awaiting the arrival of my electric bike, which will nicely complement my road bike, and between the two, hopefully will allow me to completely ditch my car and cycle to and from work on a daily basis.

What are you most looking forward to, post-pandemic?

DL: I very much liked the ability to discuss ideas with the people in the lab in person. I'm looking forward to getting a little bit more momentum and getting back into lab.

LISTEN | www.salk.edu/podcast/dmitry-lyumkis

INSIGHTS

Pamela Maher

Seeking treatments for Alzheimer's disease

Pamela Maher has always enjoyed working at the bench. Decades into a scientific career that has spanned two countries and five institutions, she makes sure to find time to run her own experiments amid the many demands of running a research lab.

Maher leads the Cellular Neurobiology Laboratory, taking charge of the group after her late husband, longtime Salk Professor David Schubert, passed away last summer. Schubert arrived at Salk in 1965 as a graduate student and five years later established the Institute's first neurobiology lab. In 2004, Maher joined Schubert's lab as a senior staff scientist after professorships at nearby institutions. Since then, Maher has made important contributions towards understanding and finding a treatment for Alzheimer's disease—a long-standing goal that continues to motivate her. "Being able to treat or at least delay the onset of Alzheimer's could have a huge impact on people's lives—not only for the lives of patients but also their families," she says.

DAY-TO-DAY

When Maher isn't at her bench, she's making sure the lab runs smoothly. She spends much of her time helping members of the lab over weekly group meetings and one-on-one talks via videoconference on Zoom in addition to managing grants, publications and administrative duties.

PATH TO SALK

Maher grew up in Connecticut and was drawn further north to study biochemistry at McGill University in Montreal as an undergraduate. She stayed in Canada for her PhD, also in biochemistry, at the University of British Columbia, where she studied the molecules that regulate the cellular membrane. This interest in cell membranes brought her to UC San Diego, to work as a postdoctoral researcher with cell biologist Jon Singer, extending the lab's groundbreaking work on the regulation of cell membrane structure and function.

During her time at UC San Diego, she grew to love the area and decided to look for research opportunities in San Diego. She found an opportunity as an assistant professor at the Whittier Institute for Diabetes and Endocrinology in La Jolla, where she worked for five years until the institute closed. She then moved to the Scripps Research Institute as an associate professor. Then, in 2004, when the department was changing directions, her husband, Dave, suggested, "Why don't you come to Salk and work with me?"

Maher accepted his offer, citing the appeal of being able to spend more time at the bench and the fact that her research topics and Schubert's had begun to converge.

RESEARCH AT SALK

Since joining Salk, Maher's major focus has been on Alzheimer's disease. Together with Schubert, Maher has worked on identifying pathways involved in the loss of nerve cells and finding compounds that can target those pathways. More recently, Maher has also studied how these pathways affect aging. "Since aging is a major risk factor in Alzheimer's disease, if you can slow down processes that are involved in aging, you should be able to slow down or stop the development of Alzheimer's," she says.

One compound based on the natural product curcumin that was discovered in the lab and the focus of much of Schubert's recent work is now in phase 1 clinical trials for the treatment of Alzheimer's. Maher helped develop another compound based on a natural product found in strawberries that just received investigational new drug approval from the FDA, which means the researchers are allowed to start clinical trials on the compound.

Yet, identifying a compound that becomes an actual drug is still a challenge. Maher says despite the field's many "shots on goal," so to speak, no new drugs have been approved to treat Alzheimer's since 2003. So, although the compounds the lab has developed so far are promising, Maher says she'll continue to search for additional compounds with therapeutic value.

LEISURE TIME

Maher has a large garden in her backyard, which includes a variety of plants including cycads, succulents, palm trees and orchids. She enjoys not only the garden's spectacular views but also the satisfaction of knowing that it's the result of the time that she and Schubert spent creating it and that she continues to devote to it.

INSPIRATION

Plants are also a great source of inspiration for Maher because of their potential to possess compounds that could treat diseases. She points out that plants have been used in medicine for thousands of years and offer a bountiful starting point for scientists. "I think there's a lot of possibilities still out there that haven't been explored," she says.

FUN FACT

Maher and Schubert got to know each another in the mid-1980s while training for triathlons. Neither were very good swimmers and they ended up taking the same swim class at UCSD. "We met in the slow lane," Maher says with a laugh. They married in 1988.

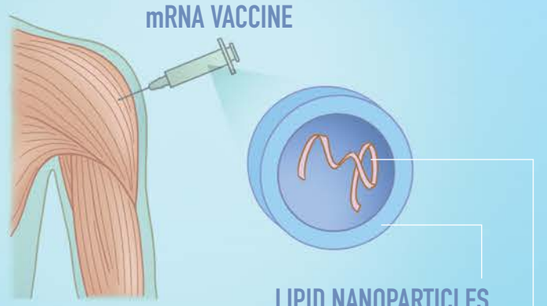
LONG VIEW

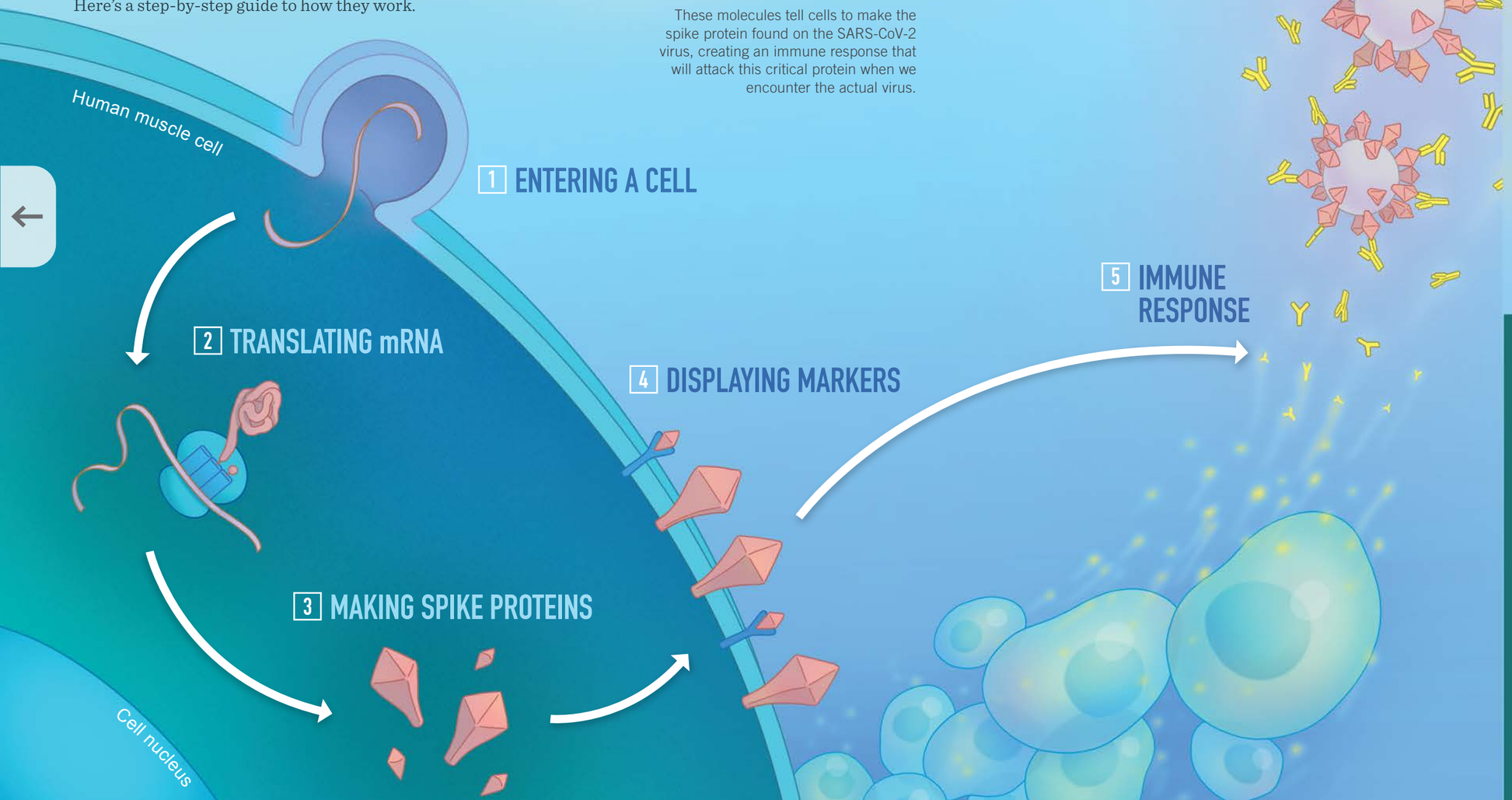
People don't realize the extent to which Alzheimer's disease is heterogenous, Maher says. She likens it to the early days of cancer research, when scientists believed there might be a "magic bullet" to treat all cancers. Many patients with Alzheimer's have different pathologies in their brain, which suggests that a single drug may not be able to treat all patients. She says that this heterogeneity is yet another motivator to discover as many compounds as possible with the potential to treat Alzheimer's disease. Ⓢ

ANALYSIS

HOW THE mRNA VACCINES WORK TO FIGHT COVID-19

Multiple vaccines are now available to help curb the threat of COVID-19, caused by the SARS-CoV-2 virus. Two of the earliest vaccines approved in the US were delivered by Moderna and Pfizer-BioNTech. Neither vaccine contains any real virus. Instead, each carries molecular instructions, called messenger RNA (mRNA), that tell our bodies how to fight off the virus. Here's a step-by-step guide to how they work.





1 Entering a Cell

The oily nanoparticles merge with the oily surface of our cells, then mRNA slips inside.

2 Translating mRNA

The cell's genetic machinery reads the mRNA's instructions, and any leftover mRNA is ultimately destroyed by the cell.

3 Making Spike Proteins

Those instructions tell the cell to make spike proteins. These proteins combine to form the telltale spikes on the SARS-CoV-2 virus.

4 Displaying Markers

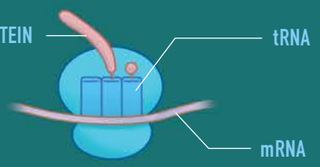
Spikes and spike protein fragments move to the outside of the cell and protrude from the surface where they will be recognized by the immune system.

5 Immune Response

Some immune cells latch onto the spikes and produce antibodies—Y-shaped molecules that will recognize spike proteins and block them from getting inside other cells. Other immune cells will be activated that can seek out and destroy future coronavirus-infected cells displaying the spike.

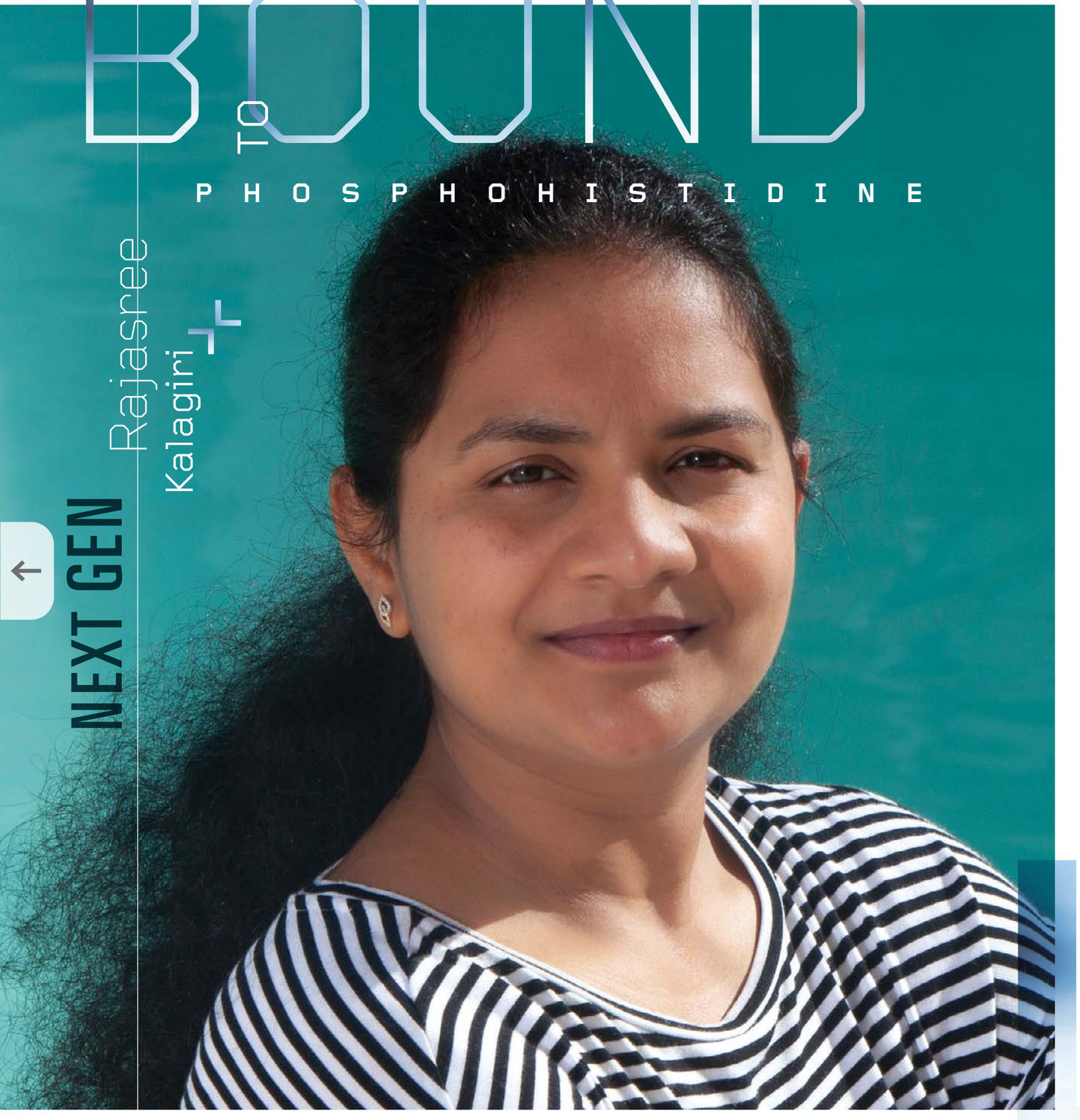
WHY BASIC RESEARCH MATTERS:

In 1964, American biochemist Robert Holley became the first person to isolate transfer RNA (tRNA)—molecules that help mRNA build proteins—and map its structure. Four years later, while a professor at the Salk Institute, Holley shared the Nobel Prize for his work on how these genetic molecules control protein synthesis. The development of the COVID-19 mRNA vaccines was possible, in part, because of the groundwork Holley's foundational science provided.



BOUND TO PHOSPHOHISTIDINE

NEXT GEN Rajasree Kalagiri



Growing up in the small town of Karimnagar in southern India,

Rajasree Kalagiri attended a school funded by the Indian government to uplift talented students from rural communities. "I wanted to give back to the society," she says.

But toward the end of high school, a biology teacher's detailed answers to her many questions during class stoked Kalagiri's interest in science. She went to Vivekananda Degree College, where she studied chemistry and microbiology. Her college couldn't afford textbooks, so lessons were taught from Xeroxed handouts assembled from various sources. Kalagiri says it wasn't until her master's education at Osmania University that she got her first real textbook, Lehninger's *Principles of Biochemistry*, which completed her understanding of many concepts. "That really opened me up to the scientific world," she says.

After her master's degree, Kalagiri assumed she would look for a job in industry. "In my small town, we didn't have much information about how science is done in the laboratory or how to pursue science as a career," she says. "Even during my master's, I never thought that I could be a scientist or that I could get into a PhD program."

Luckily, Kalagiri's mentors convinced her to apply, and she received offers from five different PhD programs, ultimately picking the prestigious Indian Institute of Science for its molecular biophysics division. There, she joined an X-ray crystallography lab headed by Professor Balasubramanian Gopal—a decision she says was inspired by English chemist Rosalind Franklin, who in the early 1950s was one of the first scientists to use X-ray crystallography to determine the structure of DNA.

In X-ray crystallography, scientists shoot a beam of X-rays at a crystalline sample and analyze how the X-rays are spread to reconstruct the sample's atomic structure. Over the past several decades, researchers have made great advances in image reconstruction and have revealed the structure of important biological molecules such as insulin and antibiotic compounds using this approach.

As a graduate student, Kalagiri used the technique to study how the common yet deadly bacteria *Staphylococcus aureus* communicates. Specifically, she focused on a molecule known as phosphohistidine that serves as a switch in signaling pathways in bacteria. The molecule is also present in humans, and although its role is largely unknown, its dysregulation has been connected to a number of diseases such as liver and breast cancer and neuroblastoma.

Phosphohistidine is an incredibly sensitive molecule present in proteins, which makes it great for rapid signaling in cells but very difficult for scientists to study. She would sometimes travel to a collaborator's lab and set up a full day of phosphohistidine experiments, only to watch them fail when the molecule fell apart. Though this molecule was frustrating to study, she persisted and completed her project successfully.

After her PhD, she joined her husband, Praveen, in San Diego and took a break from research to have her first child, Prahersh. Her second son, Dhruvin, was born this past summer.

Soon after arriving in Southern California, Kalagiri heard that a nearby lab, run by Professor Tony Hunter at the Salk Institute, had developed antibodies that bind to phosphohistidine. At the time, only a few labs around the world had been able to do so successfully. These antibodies could be used to study phosphohistidine in great detail, providing insights into the molecule that Kalagiri wishes she would have had during graduate school.

In 2016, Kalagiri reached out to Hunter about becoming a postdoctoral researcher in the lab. She was unsure if she'd be good candidate, as she didn't have experience in the lab's focus area, cancer biology, but she couldn't resist asking anyway. Her request paid off: Hunter invited Kalagiri to give a talk on her research to the group, and afterwards offered her a position.

> ***Kalagiri paved a path to Salk through her perseverance in pursuing an incredibly challenging protein modification.***

Using her X-ray crystallography expertise, Kalagiri examined the antibodies' structures to figure out what made them so good at binding to phosphohistidine. She recently published her findings jointly with collaborators in a *PNAS* paper that revealed never-before-seen details about the antibodies' binding sites (see this issue's "Discoveries"). These insights could help scientists understand phosphohistidines' potential role in certain forms of cancer and also design better antibodies.

It's been a thrill to do research at the same institute as many of her scientific heroes, Kalagiri says. When she first arrived, she recalled having attended a talk years earlier at her university by past Salk President Elizabeth Blackburn, after Blackburn won the Nobel Prize in Physiology. "I saw her, and thought, 'Is this real? Am I going to work in the same place as her?'"

Although she finds it surprising, Kalagiri paved a path to Salk through her scientific excellence and perseverance in pursuing an incredibly challenging protein modification. "During my PhD, I sometimes despised working with this elusive molecule. I would think, 'Maybe I should move away from phosphohistidine,' but somehow I was obsessed with it," she says with a laugh. Like the lab's antibodies, Kalagiri is firmly bound to phosphohistidine for the foreseeable future.

25TH ANNUAL

SYMPHONY at SALK

a concert under the stars

AUGUST 21, 2021

The Salk Institute celebrates 25 years of the iconic Symphony at Salk on ***Saturday, August 21, 2021***. This annual, outdoor concert under the stars is returning for a thrilling night of music with a private performance by the legendary ***Josh Groban*** and the talented ***San Diego Symphony***.

SPONSORSHIPS
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(858) 597-0657

This exclusive concert supports Salk Institute's world-renowned research.

Due to the pandemic, we are required to reduce attendance of this year's Symphony at Salk in order to maintain attendee safety. Individual tickets will not be distributed or sold. Other changes will also be implemented to ensure guest and staff safety.

salk®
Where cures begin.

DONOR SPOTLIGHT
TIM SCHOEN

Tim Schoen is the CEO of BioMed Realty, a San Diego-based leading provider of real estate solutions for life science and technology industries, and a generous Salk Institute supporter. He's also a Salk Trustee and chairman of Salk's Conquering Cancer Initiative Advisory Committee. We wanted to learn more about his journey from businessman to avid supporter of scientific research, and what he enjoys doing in his spare time.

Q: What was it about Salk that encouraged you to become a supporter of scientific research?

A: Being in the biotech industry, I recognized the value of basic science research and Salk is at the top of the mountain regarding fundamental research. BioMed Realty has supported Salk since its inception, so we wanted to continue our commitment with both our time and treasury. Another reason for our support was Salk's Conquering Cancer Initiative. It really attracted me personally. My mother passed away from glioblastoma, and the Conquering Cancer Initiative was established, in part, to provide support and fund research to combat this very deadly cancer. While I'm not the only one to lose a loved one to cancer—cancer has touched many of our lives—it definitely motivated me to support CCI.

Q: What is the strategy of the Conquering Cancer Initiative and how is Salk's approach different?

A: Salk is going after six deadly cancers: colon, pancreatic, ovarian, lung, glioblastoma and triple-negative breast. I really think there's something exciting about taking on difficult challenges. And it's not just about finding cures, but also looking at improving early detection to provide better outcomes for patients. Right now, you have many people who don't have much hope when they receive a cancer diagnosis and I believe Salk's approach has the potential to change that trajectory.

Q: The BioMed Realty Management Team recently gave a $1M matching gift to Salk to fund the Institute's groundbreaking cancer efforts as well as recruit award-winning cancer researcher Christina Towers. Can you tell us why the management team is excited to support her?

A: I credit Salk's leadership. Rusty and Reuben Shaw (director of the Salk Cancer Center) called me one day and said they wanted to recruit Dr. Christina Towers because her work dovetailed perfectly with Salk's cancer research, but they lacked the funds. For the BioMed management team it wasn't even a question. We immediately decided this is a mission worth supporting financially, and wanted to demonstrate to Dr. Towers our confidence in her work aimed at improving treatment options for cancer patients. We also made the gift a matching pledge to expand the base of supporters for the Salk, and to encourage the community to come together in support of her and the Institute.

Q: What is your hope for cancer research for the future?

A: Our most precious asset is time, so I hope we can one day soon find effective treatments for people to live longer and also help improve their quality of life after diagnosis.

Q: What do you enjoy doing when you're not working or donating your time to Salk?

A: Before the pandemic, I enjoyed playing basketball. I'm looking forward to getting the vaccine in part so I can get back on the basketball court. I also enjoy mountain biking and hiking—I recently went on a 26-mile hiking trip in Sedona.

Q: Speaking of the pandemic, what have you done to take care of yourself during this time?

A: I took up walking five miles a day—I think I've walked every street in Rancho Bernardo at this point. I have also gotten to know my neighbors better since I am home more often.

Q: Is there anything else you'd like to share with readers about Salk or your experiences?

A: I think it's incumbent on all of us to get the community more involved with supporting Salk. It's a gem in the biomedical research arena; a world-renowned institution boasting some of the very best researchers in their given fields. I'm excited to play a small role in helping the Salk expand its already impressive influence.

BIOMED REALTY EXECUTIVE TEAM

From top left: Jonathan Bergschneider, Bill Kane, Karen Sztraicher, John Lu, Kevin Simonsen and Denis Sullivan.

To learn more about the matching fund, visit: http://www.salk.edu/conqueringcancer

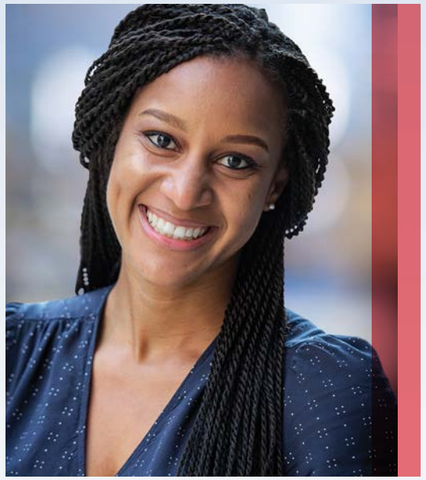
SALK RECEIVES $1 MILLION FROM BIOMED REALTY TO SUPPORT INNOVATIVE CANCER RESEARCH AND FACULTY

The Salk Institute received a matching $1 million gift from the BioMed Realty Management Team, which was used to fund the recruitment of award-winning cancer researcher Christina Towers and to support her research and that of the Salk Cancer Center. The challenge match—where BioMed Realty matches dollar for dollar, up to $1 million—will also support Salk's bold Conquering Cancer Initiative, which is harnessing cutting-edge approaches to fight some of the deadliest cancers, including: pancreatic, ovarian, lung, colon, brain (glioblastoma) and triple-negative breast cancer.

Spearheading the gift was BioMed Realty's CEO, Tim Schoen, who is a Salk Trustee and chairman of the Institute's Conquering Cancer Initiative Advisory Committee.

"The BioMed Management team is excited to support a world-class researcher such as Dr. Towers as she joins the leading scientists at Salk to tackle cancer. Now, more than ever, investments in innovative science are needed to help win the war against deadly diseases."

TIM SCHOEN



Christina Towers

Towers, who joined Salk's renowned NCI-designated Cancer Center as an assistant professor in December, examines how cancer cells recycle both their own nutrients and the power-generating structures called mitochondria in order to survive. By using a combination of gene-editing techniques, light-based genetic manipulation (optogenetics), three-dimensional miniature organs ("organoids") and detailed imaging, she aims to identify the best ways to target the recycling pathways that tumors use to survive. Her research aims to lead to new targeted cancer therapies that can improve patient outcomes and survival.

THREE PROFESSORS HONORED WITH ENDOWED CHAIRS

Wolfgang Busch

Satchin Panda

Tatyana Sharpee

Professors Wolfgang Busch, Satchin Panda and Tatyana Sharpee were recently recognized for their contributions and dedication to advancing science through research by being named to endowed chairs at the Salk Institute.

Busch, inaugural holder of the Hess Chair in Plant Science, studies plants' roots, which are not only critical for obtaining water and nutrients from the soil but also for storing potentially billions of tons of carbon per year from the atmosphere, thereby constituting a powerful tool for mitigating climate change.

Panda, holder of the Rita and Richard Atkinson Chair, studies the body's circadian timekeeping system to better understand a wide range of health issues, including digestion, cancer, cognitive functions and more.

Sharpee, holder of the Edwin K. Hunter Chair, uses advanced methods from information theory, mathematics and physics to chart the principles by which the brain manages energy and information, with implications for understanding psychiatric and neurodegenerative conditions as well as aging.

NEUROSCIENTISTS RECEIVE $4.4 MILLION FROM NIH BRAIN INITIATIVE

Edward Callaway

Sreekanth Chalasani

Nancy Padilla Coreano

Salk Institute neuroscientists Edward Callaway, Sreekanth Chalasani and Nancy Padilla Coreano were named recipients in the 2020 round of grants from the National Institutes of Health (NIH) to gain new insights into brain function.

The grants, totaling $4.4 million, are awarded through the BRAIN Initiative, as part of a large effort to use knowledge about how the brain works to develop more effective therapies for neurological disorders. Additionally, the BRAIN awards support scientific teams in order to advance neurotechnologies and provide a deeper understanding of the link between brain function and behavior.

SALK SCIENTISTS RECEIVE $1.5 MILLION FROM THE CONRAD PREBYS FOUNDATION'S INAUGURAL GRANT CYCLE

In March, Salk Professor Thomas Albright was awarded $1 million and Assistant Professor Edward Stites awarded $500,000 by The Conrad Prebys Foundation as part of its inaugural round of grants. The funding will support Albright's project looking at how our visual sense changes as we age or gain experience at new visual tasks, and Stites' project investigating how specific FDA-approved drugs function against three types of melanoma mutations, which drive approximately 80 percent of melanomas.

In total, The Conrad Prebys Foundation allocated $78 million in grants to fund 121 projects. Salk joins a long list of recipients, which included other prominent San Diego institutions such as Rady Children's Hospital, Sharp HealthCare, KPBS, Scripps Research, Museum of Contemporary Art San Diego and Mingei International Museum, among others. A complete list of awardees can be found at www.ConradPrebysFoundation.org.

Thomas Albright

Edward Stites

Professor Thomas Albright, director of Salk's Vision Center Laboratory and Conrad T. Prebys Chair in Vision Research, will use novel approaches to understand how experience and age affect the brain's abilities—in visual sensation, perception and decision-making—to adapt. His team will investigate how the visual system functions to improve performance on demanding visual tasks and decisions as well as how to reverse or mitigate impairments of visual function that are associated with aging.

Assistant Professor Edward Stites, who is a physician-scientist and the Hearst Foundation Developmental Chair, combines mathematical and computational approaches with experimental cancer biology to unravel the relationships between cancer-causing mutations and the response to treatment. Despite personalized cancer medication being within reach, physicians and scientists still aren't able to use specific genomic data to predict which cancer drugs will provide the biggest benefit for an individual patient. In 2019, the Stites lab discovered the mechanism of why some patients with a certain gene mutation benefit from a chemotherapy drug called cetuximab. Now his lab is applying their computational and experimental approach to three common forms of melanoma, each of which is caused by a different mutation within the biological system that causes cancer growth.

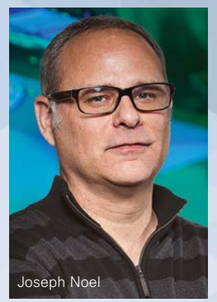
Helen McRae

TANG INSTITUTE AT ANDOVER

SALK AWARDS THE 2021 TANG FELLOWSHIP

Helen McRae, a postdoctoral fellow in the lab of Professor Diana Hargreaves, was selected as the 2021 Salk Institute Tang Prize Foundation Fellow to support her work of identifying novel ways to convert tumor-promoting macrophages into tumor-fighting macrophages. The one-year Tang Prize Foundation Fellowship, created by Tony Hunter, is awarded through an internal competition to a postdoctoral fellow in their first or second year who is conducting a research project investigating the molecular basis of cancer.

$200,000 GIFTED TO SALK'S COASTAL PLANT RESTORATION PROGRAM TO FIGHT CLIMATE CHANGE



Joseph Noel

salk® HARNESSING PLANTS INITIATIVE

Recently, donors completed a matching challenge, gifting $200,000 to Salk's Coastal Plant Restoration (CPR) program to address increasingly urgent needs to preserve some of the world's largest carbon reservoirs and restore global wetland ecosystems. This approach, led by Salk Professor Joseph Noel, holds great promise for safeguarding these tremendous carbon sinks while stabilizing and, in many cases, rebuilding land lost to erosion and unprecedented sea level rise.

Salk's Harnessing Plants Initiative is a scalable, simple and bold approach to drawing down excess carbon dioxide (CO_2) from the atmosphere by developing coastal and crop plants that are efficient at capturing and storing carbon deep in the ground for long periods.

Kristy Kitzmiller, a founding member of the HPI Advisory Committee, and her husband, Brandon Moran, committed $100,000 to CPR in June of 2019, in the form of a matching challenge. The list of generous donors completing the challenge included Greg and Rebecca Arnold, Thomas and Tomomi Duterme, David and Cheryl Lawrence, Goldman Sachs Gives – Tom Morrow and Audry Ai, Eric Ross and Nicole MacNeel, and Neal and Margaret Schmale.

This support will enable Salk scientists to, for the first time in history, sequence the genomes of many of the critical plants that comprise wetland ecosystems. The resulting insights will allow the team to assemble a roadmap for the successful preservation and restoration of these global ecosystems with native plant varieties that can withstand current and future climate conditions.

COLLABORATIVE TEAM AWARDED $1.2 MILLION BY LARRY L. HILLBLOM FOUNDATION TO STUDY BRAIN AGING AND DEMENTIA

John Reynolds

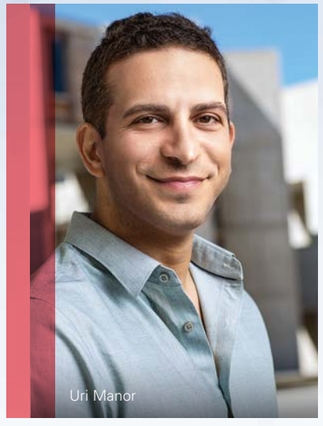
LARRY L. HILLBLOM FOUNDATION
Advancing Medical Knowledge

A collaborative team of Salk scientists led by Professor John Reynolds will receive $1.2 million over four years as part of a Network Grant from the Larry L. Hillblom Foundation to examine aging across the life span, including age-related neurodegenerative diseases such as Alzheimer's disease. The research will advance our understanding of aging mechanisms at the cognitive, genomic and cellular levels with potentially direct translatability to humans. Other members of the team include Salk President and Professor Rusty Gage, Staff Assistant Research Professor Uri Manor, Senior Staff Researcher Courtney Glavis-Bloom and Carol Marchetto, an assistant professor at UC San Diego.


Dmitry Lyumkis

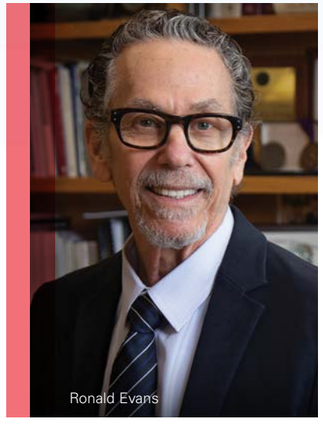
DMITRY LYUMKIS RECEIVES CAREER AWARD FROM NSF

Assistant Professor Dmitry Lyumkis has received a Faculty Early Career Development Program (CAREER) award from the National Science Foundation. The CAREER award supports early career scientists who serve as academic role models and lead scientific advances in their organization. Lyumkis will receive almost $1.8 million over four years to examine how some viruses such as HIV hijack and interact with host protein machinery to permanently alter the host genome to sustain infection.


Uri Manor

URI MANOR TO RECEIVE MORE THAN $690,000 FROM CHAN ZUCKERBERG INITIATIVE TO ADVANCE BIOLOGICAL IMAGING

Assistant Research Professor Uri Manor, director of the Waitt Advanced Biophotonics Core Facility, will receive $690,116 over three years from the Chan Zuckerberg Initiative (CZI) as one of 22 CZI Imaging Scientists. With the funding, Manor will create imaging tools such as probes and image-processing as well as analysis software for biologists, including software that relies on AI technology, to make previously invisible cellular dynamics visible.


Ronald Evans

RONALD EVANS RECEIVES 2021 ASAN AWARD IN BASIC MEDICINE

Salk Professor Ronald Evans was awarded the 2021 Asan Award in Basic Medicine by the Asan Foundation. This Korean foundation supports critical medical research as well as social and medical welfare programs. The award, which totaled $250,000, recognizes "medical scientists who have achieved remarkable accomplishments in the fields of basic and clinical medicine to promote human health," according to the Asan Foundation. Evans, who is the director of Salk's Gene Expression Laboratory and March of Dimes Chair in Molecular and Developmental Biology, is the first international recipient of this prestigious award.

LIKE FATHER, LIKE SON

Salk Professor Tony Hunter on collaborating with son Sean Hunter to find new ways to tackle pancreatic cancer


From left: Sean Hunter and Tony Hunter.

The unexpected collaboration started with a phone call.

A few years ago, Salk American Cancer Society Professor Tony Hunter was catching up with his older son, Sean, who at the time was a new graduate student in the cancer biology program at Stanford University. Sean had recently joined a lab led by bioengineering Professor Jennifer Cochran and wanted his dad's opinion about a research project he might pursue.

In 2015, Sean had attended a talk by cancer researcher Frank McCormick about his work on a protein made and exported by pancreatic cancer cells called leukemia inhibitory factor (LIF). LIF is a powerful cytokine (a type of protein) that signals cells to adopt a primitive, less differentiated state and could be a promising target for treating cancer. For his project, Sean told his father, he was proposing to engineer proteins to inhibit LIF function.

"And I nearly fell off my chair when he said that, because, unbeknownst to Sean, my lab had been working on this same protein in pancreatic cancer for several years," Hunter says. "And I said 'yes, of course I think it would be a great project for you because we think it's a great project too!'" A few years later, in 2019, Hunter's lab at Salk reported the results of their work showing how LIF is involved in pathways that drive pancreatic cancer progression and could be blocked by an antagonist antibody to slow pancreatic cancer progression in a mouse model—a discovery that points to LIF as a potentially useful therapeutic target as well as a biomarker to help diagnose the disease more efficiently.

Hunter and his son decided to team up for the next step in their next investigation: Using protein engineering, Sean designed a therapeutic protein that could bind tightly to LIF and sequester it. Then, using a mouse model of pancreatic cancer developed in Hunter's lab, the researchers tested the new therapy and found that it indeed blocked LIF signals involved in pancreatic cancer. They published their work in the journal *Communications Biology* on April 12, 2021. The publication marks the Hunters' first formal research collaboration.

"It obviously is very exciting to be able to publish a paper with Sean," Hunter says. "He's turned out to be an excellent scientist and he knows what he's doing ... It's been great working with him."

Before this collaboration, Sean got his introduction to running experiments in his dad's Salk lab, volunteering there for three summers during high school before building on his scientific education as an undergraduate and in graduate school. Sean's path to science was inspired by his parents, both of whom are biologists.

While the son has moved toward translational research and the father remains focused on basic science, both are continuing to pursue new avenues to treat cancer.

WATCH | www.salk.edu/hunter202105

POSTDOCTORAL FELLOWS WIN DISTINGUISHED AWARDS FOR CANCER, NEUROSCIENCE AND MORE

Tom Franken, a senior postdoctoral fellow in the lab of John Reynolds, was awarded an NIH Pathway to Independence grant to fund a 5-year project to study how the brain distinguishes objects from background. A deeper understanding of this process is important to develop better diagnostic tools and treatments for central visual processing disorders.

Heather McGee, a radiation oncologist and a senior postdoctoral fellow in the lab of Susan Kaech, was awarded over $1 million by NIH with a Pathway to Independence grant from the National Cancer Institute. This 5-year project will enable McGee to study how radiation activates cancer-fighting immune cells in different tumor micro-environments. McGee will conduct the research jointly at Salk and UC San Diego.

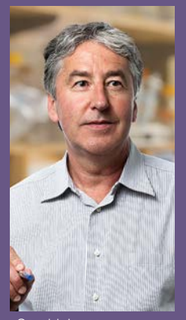
Nuttida Rungratsameetaweemana, a postdoctoral fellow in the lab of Terrence Sejnowski, garnered the prestigious Cell Press Anuradha Rao Memorial Award. Rungratsameetaweemana uses computational methods to investigate various dynamics of different types of epileptic seizures, with the goal of identifying unique signatures that could be used to guide personalized patient- and type-specific seizure treatment.

EVENTS

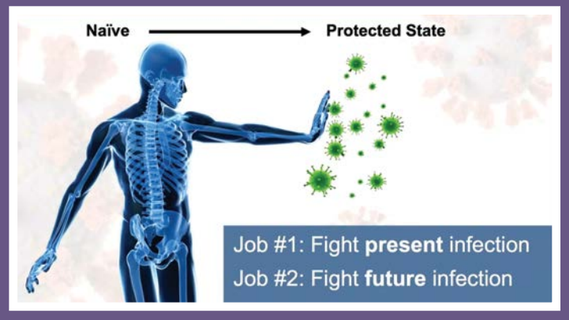
SALKEXCELLERATORS GET EXPERT VIEW ON COVID-19 VACCINATIONS

On January 27, in a virtual discussion with Salkexcellerators, Professor and Director Susan Kaech and Professor Gerald Joyce gave their expert view on the underlying science of the vaccines being deployed in the fight against COVID-19 and how the immune system responds to the vaccine to protect against infection. Salkexcellerators are an extraordinary group of community members, entrepreneurs, and business professionals who share a passion for supporting and learning about Salk's recent discoveries.

Susan Kaech

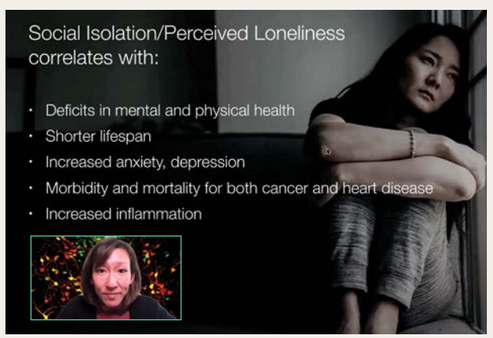


Gerald Joyce



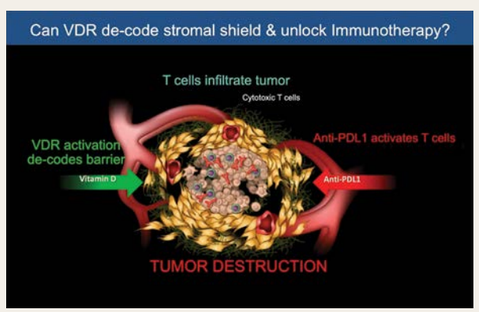
POWER OF SCIENCE: NEUROADAPTATIONS OF SOCIAL ISOLATION

On February 3, Professor Kay Tye shared how her lab is employing cutting-edge neuroscience approaches to understanding the mechanisms of how our brains respond to social isolation.



POWER OF SCIENCE: CONQUERING PANCREATIC CANCER

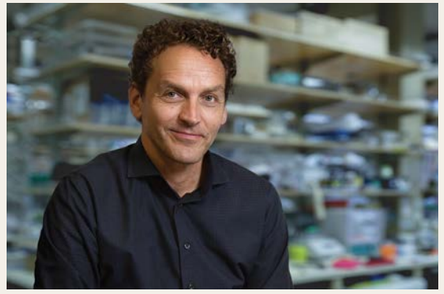
On November 16, Professor and Director Ronald Evans shared clinical trial updates on pancreatic cancer, a devastating disease with only 8 percent of patients surviving more than five years. Evans shared research breakthroughs, including immunotherapy and a vitamin D derivative.



The virtual Power of Science lectures are engaging talks that share cutting-edge research directly from the labs to the public. Learn more: **www.salk.edu/powerofscience**

POWER OF SCIENCE: UNDERSTANDING AGING IN HUMANS

On November 9, Professor and CSO/VP Martin Hetzer discussed aging and how it is the most significant risk factor for human disease. Human cells and tissues age at different rates depending on their intrinsic properties, where they are in the body and environmental exposures. The Hetzer lab aims to understand this variability ("heterogeneity") and how it contributes to overall human aging, risk for disease or therapeutic responses.



Martin Hetzer

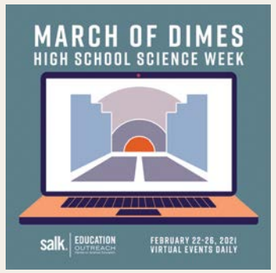
Joanne Chory

WOMEN & SCIENCE TACKLE CLIMATE CHANGE

Salk's Women & Science program collaborated with the Del Mar Garden Club on its annual community outreach program to offer an exciting and informative virtual event focused on how plants can help tackle climate change. Professor and Director Joanne Chory spoke about climate change and the effect plants have on it.

THOUSANDS OF STUDENTS GATHER VIRTUALLY FOR MARCH OF DIMES HIGH SCHOOL SCIENCE WEEK

In February, Salk's annual March of Dimes High School Science Day took place virtually, and was extended from one day to an entire week. The annual outreach event was designed to encourage high school students to consider an exciting career in science and research. In this virtual event, students from around the country had the opportunity to remotely visit with Salk scientists, hear about their work, take lab tours and participate in current experiments.



"Our greatest responsibility is to be good ancestors."

JONAS SALK

Discover your legacy at the Salk Institute

Jonas Salk changed the world. You, too, can have a transformative impact on the future of humanity.

Leaving a gift to the Salk Institute in your will or by beneficiary designation will support foundational research that could help manage cancer, fight climate change, treat Alzheimer's and more.

Making a lasting impact through a planned gift can be simple. Gifts of any size can help accelerate innovation, support the next generation of scientists and enable life-changing discoveries.

Whether you would like to put your donation to work today or benefit us after your lifetime, you can find a charitable plan that lets you provide for your family and support the Salk Institute.

Plan your future. We can help you get started.

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Where cures begin.

Contact Cheryl H. Dean, Esq., at cdean@salk.edu or **858.500.4884** for help finding the right gift plan.

WHERE CURES BEGIN
SALK INSTITUTE PODCAST

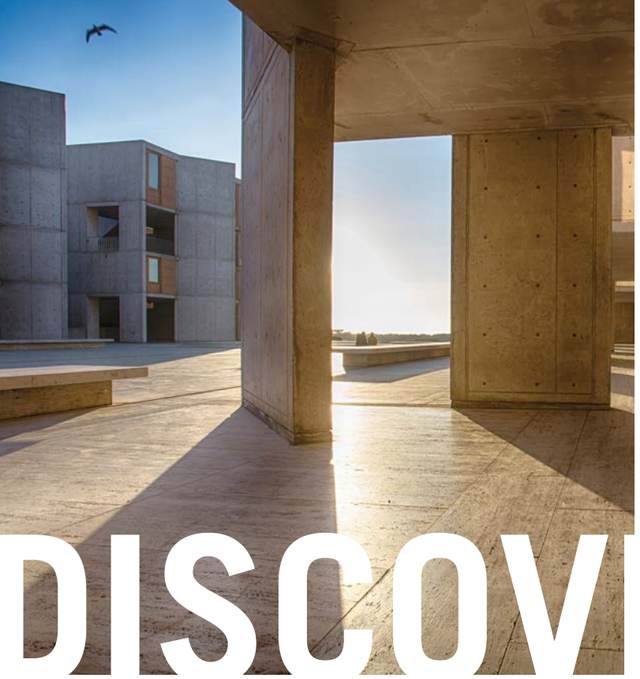
Groundbreaking Salk discoveries *on the go!*

Salk's award-winning podcast *Where Cures Begin* has completed its third season! In season 3, go behind the scenes at the Salk Institute and learn about cutting-edge research and recent science discoveries. Hosts Allie Akmal and Brittany Fair interview Salk's internationally renowned scientists about biological clocks, the neuroscience of vision, the coronavirus and more. Highlights include Ron Evans talking about how heart surgery changed his attitude about playing the guitar; Tom Albright explaining why he's not a fan of sweet potatoes; and Nikki Lytle relating why she said she'd never work on cancer (but does now).

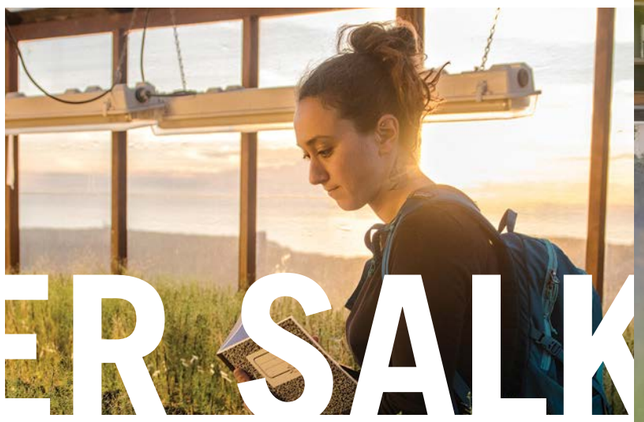
The podcast's first two seasons are also available. Tune in to season 1 to hear about Professor Tony Hunter's 50 years as a scientist (most of them at Salk); postdoctoral researcher Emily Manoogian's tips on what times are best to eat and work out; and how Professor Joanne Chory thinks plants can help mitigate against climate change.

Season 2 highlights include learning how childhood hearing loss affected the life of Staff Assistant Research Professor Uri Manor; what growing up in a family of coal miners taught Professor Joseph Noel; and what insights into human behavior postdoctoral researcher Molly Matty has gleaned from her work with microscopic worms.

To listen to episodes of *Where Cures Begin*, search in your favorite podcast app or go to **www.salk.edu/podcasts**.



Salk programs offer a range of ways to get involved. Learn about Salk science and support vital research.



DISCOVER SALK

EDUCATION OUTREACH
Salk offers a wide variety of programs to inspire—and launch—the next generation of scientists. The Education Outreach program includes a Mobile Science Lab, Heithoff-Brody Scholars curriculum and teacher training.

SALK SCIENCE & MUSIC SERIES
Sunday afternoons bring together virtuosos from the worlds of science and music.

PARTNERS IN RESEARCH
Partners in Research invest in the future of cancer, aging, Alzheimer's disease and diabetes research by incorporating their philanthropic support for Salk in their estate plans.

SALKEXCELLERATORS
Designed for young business professionals and community members committed to supporting Salk scientific discovery, Salkexcellerators offers a unique opportunity to support cutting-edge research while connecting with like-minded people.

PRESIDENT'S CLUB
The President's Club helps recruit top-tier scientists, acquire cutting-edge technology and embark on innovative research initiatives.

ARCHITECTURE TOURS
The Salk Institute has been described as one of the most significant architectural sites in the United States and has garnered accolades for its design and preservation.

SALK WOMEN & SCIENCE
Showcasing the achievements of Salk's women of science, this program welcomes community and business leaders interested in inspiring women to embrace scientific research personally and philanthropically.

CHAIRMAN'S CIRCLE
Visionary donors in the Chairman's Circle provide the vital resources Salk researchers need to pursue breakthrough science.

EXPLORE SALK
The Institute's free open house allows the community to see Salk science up close through fascinating talks, interactive booths, a self-guided tour and a kids' discovery zone.

SYMPHONY AT SALK
This annual concert under the stars features the incredible San Diego Symphony and a guest artist while supporting the Institute's world-renowned research and award-winning education outreach programs.

INSTITUTE COUNCIL
This group of highly engaged individuals focuses on advancing Salk's scientific initiatives and supporting groundbreaking discoveries.

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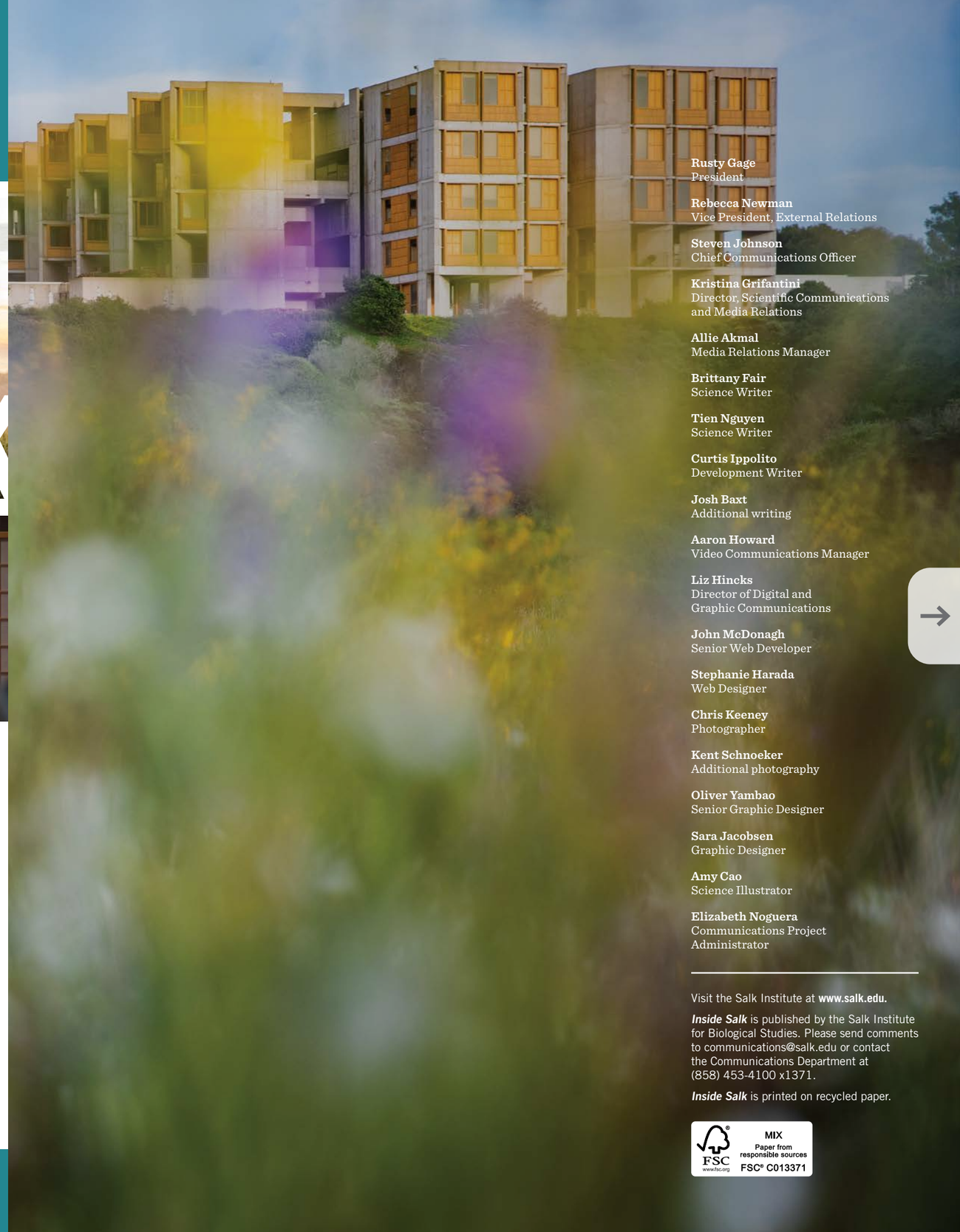
VISIT US ONLINE AT SALK.EDU/ENGAGE



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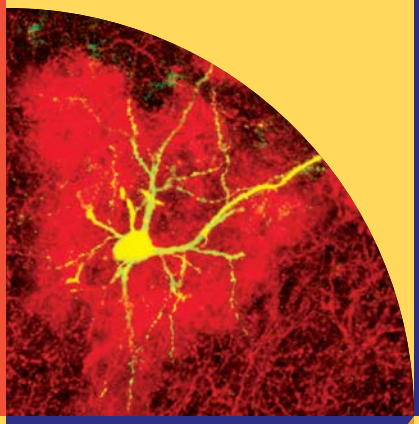

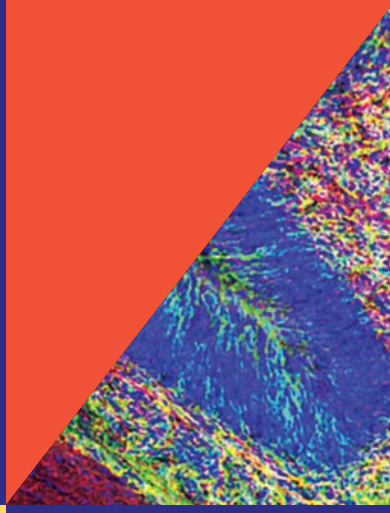

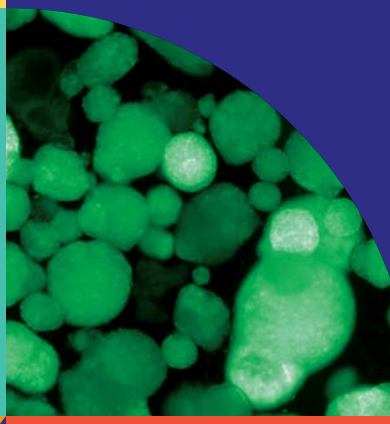

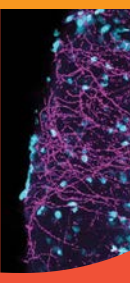

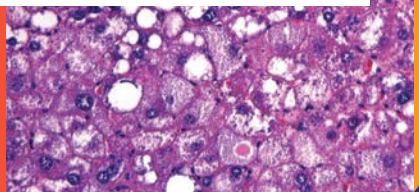

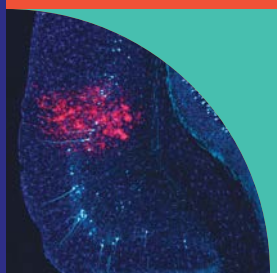

THERE ARE MANY WAYS TO SUPPORT SALK.

For detailed information on opportunities, please email giving@salk.edu or call (858) 453-4100 x1201 or visit www.salk.edu/support

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Salk Institute has received the highest rating 9 consecutive times from Charity Navigator, the nation's foremost charity evaluator.

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★★★★
Four Star Charity

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