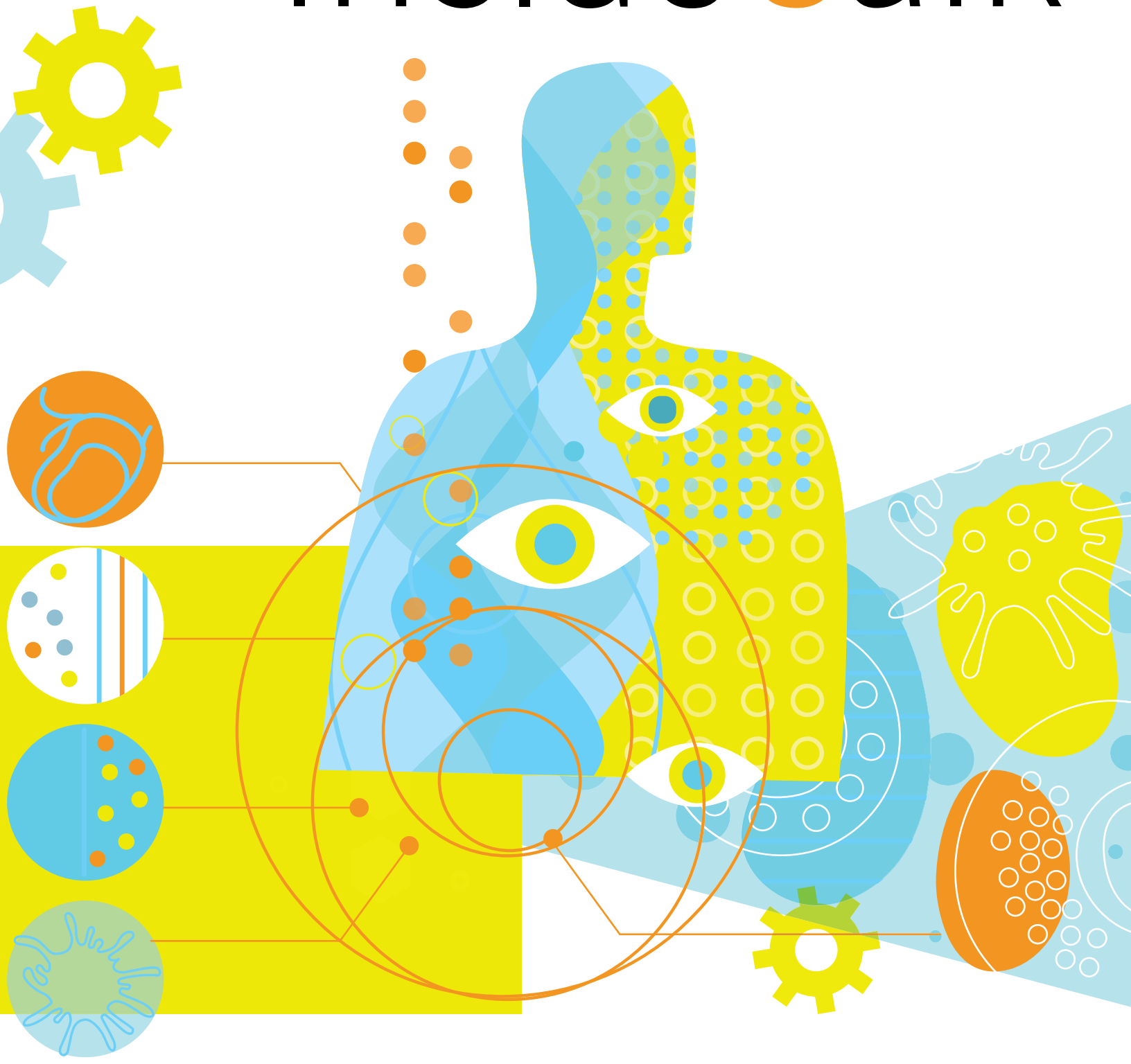
FALL | 2018

WHERE CURES BEGIN.

insideSalk



CONTENTS

ON THE COVER:

The immune system is a powerful biological force, made up of diverse cells that keep us safe in a hostile world. Scientists in Salk's NOMIS Center for Immunobiology and Microbial Pathogenesis are exploring how these mechanisms work—and ways to harness them to better stave off disease.

PRESIDENT'S LETTER

Dear Friends,

A few members of our staff recently began a project to preserve and archive original 16mm film that was taken during the Institute's earliest days more than half a century ago. Subject notes that are written on tape on the old film canisters—Jonas Salk's vaccine reports from the mid-1950s, interviews with the late Nobel Laureate and Salk Professor Renato Dulbecco, reels of the original meetings of Salk Fellows in La Jolla—remind us how the Salk Institute is deeply steeped in a history of discovery.

With our history as a guide and the goal of revealing answers to some of science's most challenging questions as our focus, the adventure of discovery continues every day at the Institute. At Salk, we explore the very foundations of life for the benefit of all. From our many labs to our landmark courtyard, conversations and collaborations help shape new and innovative approaches to the big questions we are working to answer. The Harnessing Plants and Conquering Cancer Initiatives are two of the most recent examples that have resulted from this effort.

We are so very thankful for the passionate community of individuals and organizations dedicated to Salk, helping to guide the Institute and empower our researchers to transform the future of humanity as Jonas Salk did. This support is the cornerstone on which our future will be built. Because of this commitment, the Institute is able to remain dedicated to asking big questions and tackling challenging ideas in biology, as you'll see in this edition of *Inside Salk*.

What is past is indeed prologue at Salk; it has set the stage for an incredible amount of progress. Our feature in this edition focuses on the 10th anniversary of the creation of the NOMIS Center for Immunobiology and Microbial Pathogenesis, made possible by the longtime support of the NOMIS Foundation. Our pioneering work in immunology harkens back to the global implications of Jonas Salk's discovery of the polio vaccine.

NOMIS Center members strive for similar breakthroughs, seeking to unleash the power of the immune system against cancer and other illnesses. Led by Professor Susan Kaech, the NOMIS Center is uncovering processes by which the body responds to injury and infection, as well as mechanisms related to the microbiome and inflammation, to develop entirely new lines of treatments for myriad diseases.

Additionally, this edition of *Inside Salk* highlights the numerous accolades received by and discoveries coming from our remarkable researchers, as well as exciting updates about the Institute. Yet everything within these pages can be traced back to the community of individuals and organizations that stand with Salk. Every Salk advocate is on this journey with us; collectively they are part of the storied legacy of discovery that the Salk Institute embodies, and they play a central role in securing its future.

Sincerely,

Rusty

Fred H. Gage
President

DISCOVERIES

In the last few months, Salk scientists have had groundbreaking work published in top journals and covered in notable media outlets. Read on to learn more.

READ

View the full news reports and more discoveries online at **www.salk.edu**

RESEARCH
AT SALK

NEUROSCIENCE

We are entering a new era in neuroscience where our knowledge is beginning to meet the urgent need to prevent and treat diseases of the brain.

PLANT BIOLOGY

To support human population growth, world agricultural production must double over the next quarter century. We study plants so that humans will have the food, clothing, energy and medicines they need now and in the future.

GENETICS

In many ways, we *are* our genes. At Salk, we explain the role of genes in everything from how tumors form to why certain people are at higher risk for neurological disorders.

CANCER

We are rapidly demystifying cancers and leading the search for the next generation of targeted cancer therapies. We see a future where transformational treatments destroy tumors before they develop drug resistance.

COMPUTATIONAL BIOLOGY

Modern scientific research has yielded massive amounts of data—but few good ways to understand the information. We are developing mathematical and analytical frameworks to uncover new connections in biological systems.

REGENERATIVE MEDICINE

Many disorders and life-threatening diseases could be cured by replacing or fixing dysfunctional cells. We aim to uncover novel ways to transplant new cells, tissues and even organs while minimizing their rejection.

AGING

Getting older doesn't have to mean getting sicker. We are committed to discovering the fundamental causes of aging and finding new ways to prevent and treat age-related diseases.

IMMUNE SYSTEM BIOLOGY

In a world full of dangers, from bacterial infections to cancer, our immune system is our fortress. We study the immune system to boost our ability to fight off numerous diseases.

METABOLISM

At Salk, we seek to understand human metabolism and what happens when this biological system breaks down. The problem is important as diabetes becomes more prevalent and more of a burden on an already-taxed healthcare system.

PROTEIN INTERACTIONS

Proteins—large, complex molecules—catalyze virtually all of the chemical reactions that take place in the body. We study their interactions to discover how they heal or how they harm.

MAKING CONNECTIONS

Salk scientists explore the mysteries of the brain

NEURON
02/2018

How the brain tells our limbs apart

Neural regulation by the regions of the spinal cord that connect to the arms and those that connect to the legs are not well understood. A study in mice by Professor Samuel Pfaff, first author Marito Hayashi, bioinformatics specialist Shawn Driscoll and others revealed contrasts in the neurons that underlie these various types of motor control. The results could one day lead to tailored, stem-cell-based treatments for repairing spinal cord injuries.

eLIFE
05/2018

Where brain cells get their information may determine their roles in diseases

In the striatum, a brain region associated with action control and learning, 95 percent of neurons communicate with outside regions while 5 percent communicate only within the region. Associate Professor Xin Jin, first author Jason Klug and colleagues mapped where information to the 5 percent is coming from and, in the process, clarified the relationship of two types of neurons to psychiatric and sensory/movement disorders, respectively. The communication pathways represented by these two neuron types may offer new drug targets for disorders as diverse as Parkinson's, OCD, depression and autism.

PNAS
02/2018

Making new memories is a balancing act

Professor and co-corresponding author Terrence Sejnowski, along with collaborators at the University of Texas at Austin and the University of Otago, in New Zealand, found that connections in the brain not only expand as needed in response to learning or experiencing new things, but that others shrink as a result. The work could shed light on conditions in which memory formation is impaired, such as depression or Alzheimer's disease.

WATCH | www.salk.edu/sejnowski201808

SCIENCE
03/2018

Early life experiences influence DNA in the adult brain

Research led by Salk Professor Rusty Gage showed that the type of mothering a female mouse provides her offspring actually changes their DNA. The work lends support to studies about how childhood environments affect brain development in humans and could provide insights into neuropsychiatric disorders, such as depression and schizophrenia.

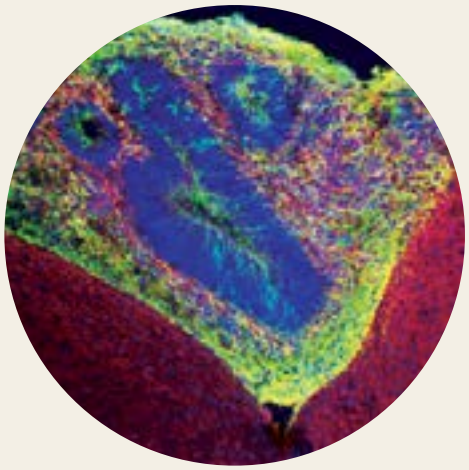
WATCH | www.salk.edu/gage201808

NEUROSCIENCE

SALK SCIENTISTS GAIN INSIGHT INTO NEUROLOGICAL DISORDERS

Researchers in the lab of Rusty Gage use myriad strategies to study the cellular underpinnings of neurological disease, from the interactions of a single layer of cells in a dish to those in a 3D brain-like "organoid." In work published in *Cell Stem Cell* in May 2018, Gage, first author Anindita Sarkar and colleagues created multiple types of neurons from stem cells to study the connections between brain cells, showing how communication between neurons is altered in people with schizophrenia.

In a paper in *Nature Biotechnology* in April 2018, Gage, first author Abed Mansour and colleagues reported a new approach to develop more sophisticated organoid models by ensuring they receive sufficient oxygen and other nutrients via transplantation into rodents. The work could yield insights into the development of cures for brain disorders; speed up the testing of drugs; and even pave the way for someday transplanting healthy populations of human cells into people's brains to replace damaged or dysfunctional tissue. S



Human organoid tissue (green) grafted into mouse tissue. Neurons are labeled with red.

WATCH | www.salk.edu/gage201803

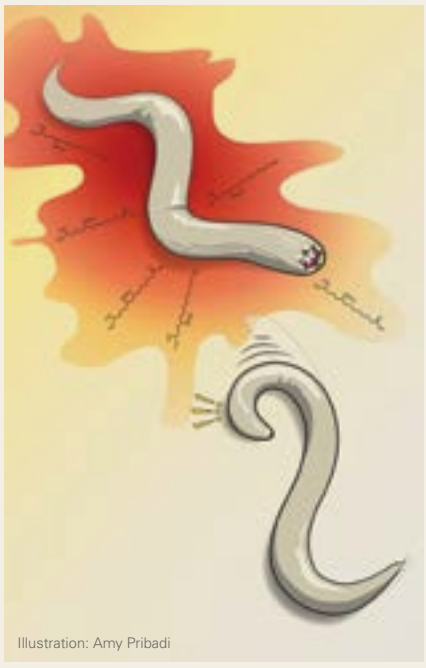


Illustration: Amy Pribadi

DECODING THE CHEMISTRY OF FEAR

The complexity of the human brain makes fear—and its close cousin, anxiety—difficult to study. Associate Professor Sreekanth Chalasani, UC San Diego graduate student and first author Amy Pribadi and colleagues discovered new clues about the mechanisms of fear and anxiety through an unlikely creature: the tiny nematode worm. By analyzing the responses of worms exposed to chemicals secreted by its natural predator and studying the underlying molecular pathways, the team uncovered a rudimentary fear-like response that has parallels to human anxiety. The work was published in March 2018 in *Nature Communications*. Such insights may eventually help refine prescriptions for current anti-anxiety drugs and enable the development of new drugs to treat, for example, PTSD and panic disorder. S

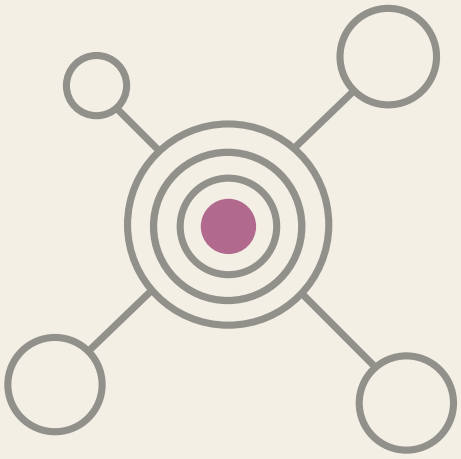
In this illustration, a *C. elegans* worm (lower right) exposed to sulfolipid chemicals from one of its natural predators, a worm called *P. pacificus*, quickly reverses direction in a response analogous to human fear.

WATCH | www.salk.edu/chalasani201808

IMMUNE SYSTEM BIOLOGY

DISCOVERY REVEALS HOW CELLS TRY TO CONTROL LEVELS OF KEY HIV PROTEIN

Salk Professor Katherine Jones, first author Muyu Xu and colleagues discovered a small molecule called JIB-04 that destroys the HIV protein called Tat, responsible for revving up the virus. The molecule, while itself too toxic to serve as a therapy for HIV, reveals enzymes in host cells that can potentially target Tat and halt this runaway replication process. The work was published in *PLOS Pathogens* on May 23, 2018.



PLANT BIOLOGY

UNDERSTANDING HOW DNA IS SELECTIVELY TAGGED WITH "DO NOT USE" MARKS

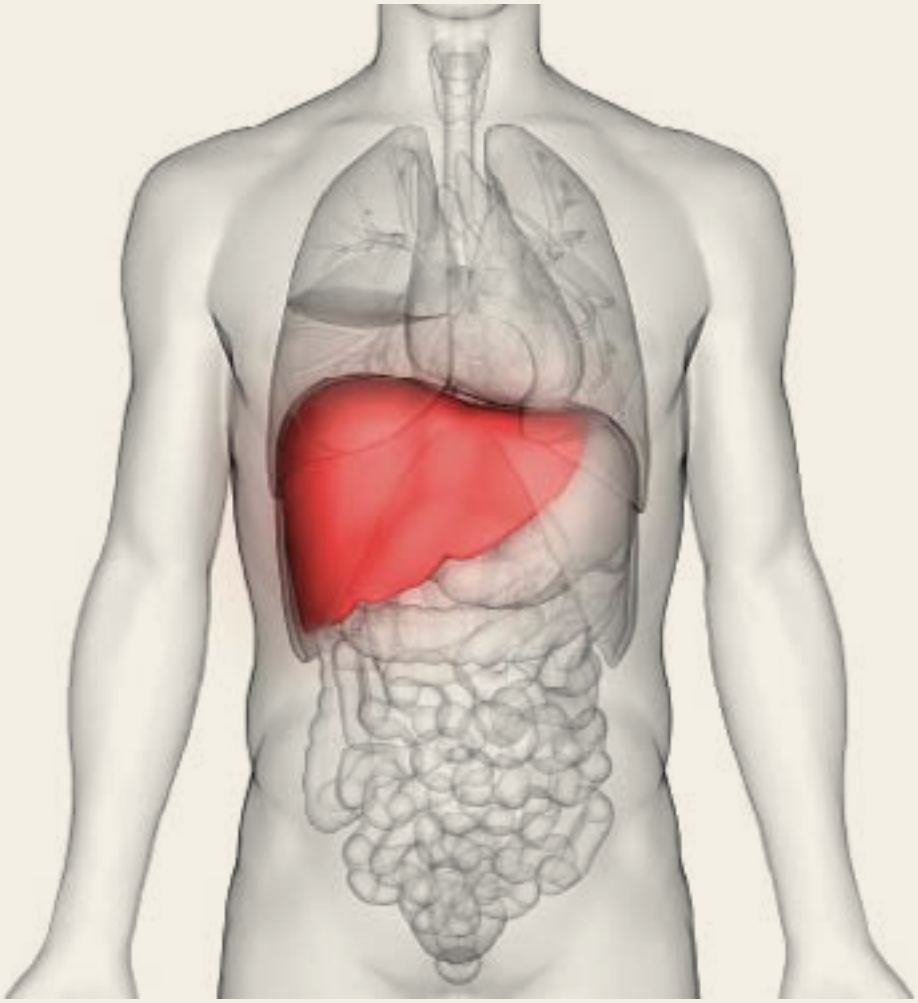
Assistant Professor Julie Law and first author Ming Zhou discovered a small family of proteins that control where in the genome DNA methylation marks (chemical "do not use" signs) are added. Their work on this aspect of genetic regulation is highly relevant for processes that range from normal development to cellular defects and diseases, which can arise due to erroneous DNA methylation patterns in plants and/or humans. Their paper appeared in *Nature Genetics* on May 7, 2018.

WATCH | www.salk.edu/law201808

METABOLISM

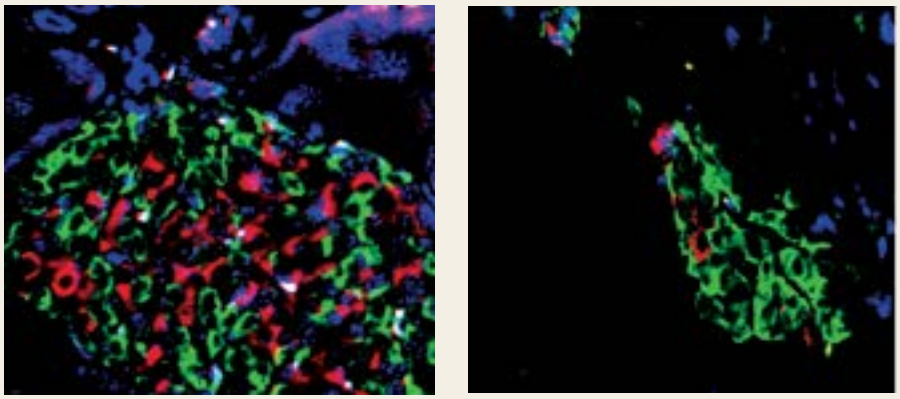
TIMING IS EVERYTHING, TO OUR GENES

A pair of studies from the lab of Professor Satchidananda Panda sheds light on the importance of timing to our health. One, led by Panda, co-senior author and visiting scientist Howard Cooper, and staff scientist Ludovic Mure, and published in *Science* on February 8, 2018, found that the activity of nearly 80 percent of genes follows a day/night rhythm in many tissue types and brain regions. The other, which appeared in *Cell Metabolism* on February 6, 2018, uncovered how the liver can have such a speedy response to food, making massive shifts in how it breaks down and stores fats and sugars within minutes of a meal. Both discoveries could inform new therapies for obesity and diabetes.



BOOSTING THE EFFECTS OF VITAMIN D TO TACKLE DIABETES

Salk researchers reported a potential new approach for treating diabetes by protecting beta cells—the cells in the pancreas that produce, store and release insulin. Co-senior authors Ronald Evans and Michael Downes, first author Zong Wei, and colleagues showed that using vitamin D in cells and mouse models proved beneficial in treating damaged beta cells. It also provided new insights about gene regulation that could be applied to developing treatments for other diseases, including cancer. Their paper was published May 10, 2018, in *Cell*.

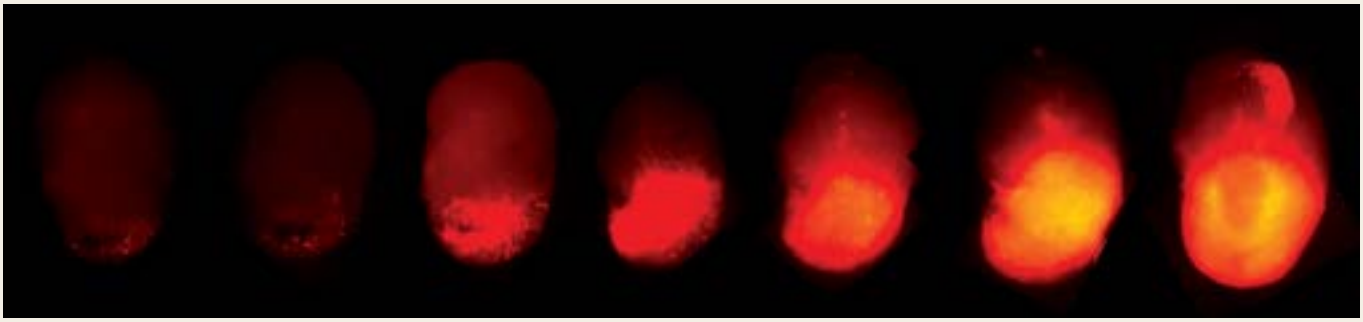


Enhanced activation of vitamin D curbs type 2 diabetes progression in animal models. Left: damaged insulin-positive B cells (red) in a diabetic mouse pancreas. Right: B cells (red) were protected in a diabetic mouse pancreas treated with a combination of a vitamin D activator and BRD9 inhibitor.

SALK SCIENTISTS ELUCIDATE MYRIAD FUNCTIONS OF THE PROTEIN ERRγ

Researchers in the lab of Professor Ronald Evans published two papers clarifying the functions of the molecule ERRγ (ERR gamma) on energy production and expenditure. First, in *Cell Reports* on March 6, 2018, Evans, co-senior author Michael Downes, first author Weiwei Fan and colleagues showed that ERRγ helps deliver many of the benefits associated with endurance exercise by activating genes that create more mitochondria (the power houses of cells). This makes ERRγ a potential therapeutic target for conditions with weakened muscles. In *Cell Reports* on March 13, 2018, co-senior authors Evans and Downes, together with first author Maryam Ahmadian and others, discovered how ERRγ gives "healthier" brown fat its energy-expending identity, potentially offering a new therapeutic target for diseases related to obesity.

CANCER



ORGANOIDS REVEAL HOW A DEADLY BRAIN CANCER GROWS

From left to right, tumor cells labeled with red fluorescent marker tdTomato spread in a cerebral organoid over a time period of 2, 3, 4, 6, 8, 10 and 13 weeks after the delivery of a gene editing virus.

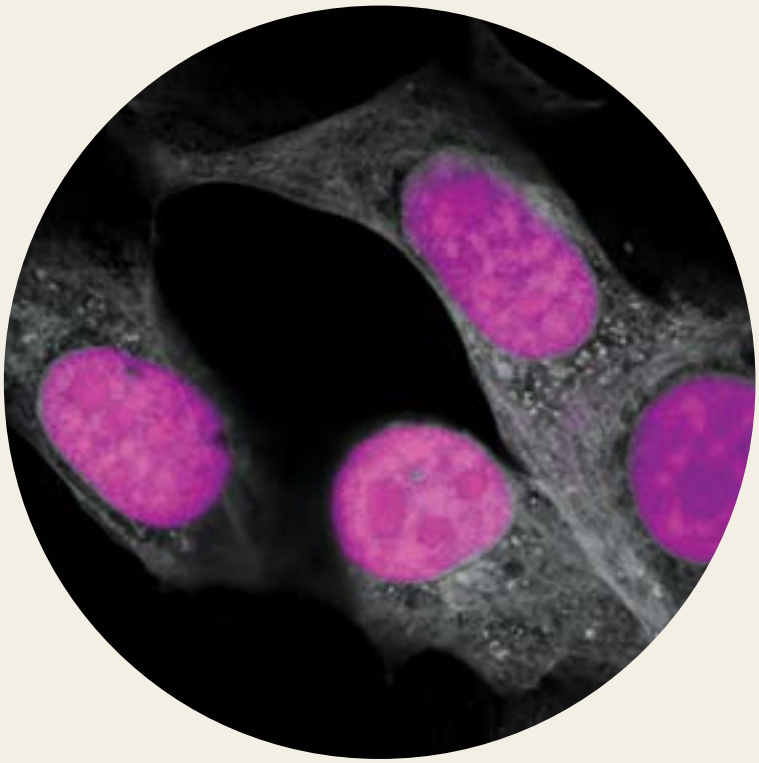
Glioblastoma multiforme (GBM) is an incredibly deadly brain cancer and presents a serious black box challenge. By editing two genes in just a few cells in human cerebral organoids, first author and Senior Research Associate Junko Ogawa and colleagues generated aggressive GBM tumors. This new model could be used to study tumor progression, investigate new drugs or even personalize treatments for patients. The study was published in the journal *Cell Reports* on April 24, 2018.

TUMOR SUPPRESSOR PROTEIN TARGETS LIVER CANCER

Salk Professor Tony Hunter and colleagues, together with researchers from Switzerland's University of Basel and University Hospital Basel, discovered a protein called LHPP that acts as a molecular switch to turn off the uncontrolled growth of cells in liver cancer. The tumor suppressor, which could be useful as a biomarker to help diagnose and monitor treatment for liver cancer, could also be relevant for other cancer types. The work appeared in the journal *Nature* on March 29, 2018.

CRISPR GENETIC EDITING TAKES ANOTHER BIG STEP FORWARD, TARGETING RNA

Helmsley-Salk Fellow and senior author Patrick Hsu, first author Silvana Konermann, and colleagues have created a new genetic-editing tool that targets not DNA, but RNA, and uses it to correct a protein imbalance in cells from a person with dementia. The new Salk tool, called CasRx, opens up the vast potential of RNA and proteins to genetic editing, giving researchers a powerful way to develop new gene therapies as well as investigate fundamental biological functions. They described CasRx in *Cell* on March 15, 2018.



CasRx (magenta) targeting RNA (pink) in the nucleus of human cells (gray).

WATCH	www.salk.edu/hsu201808

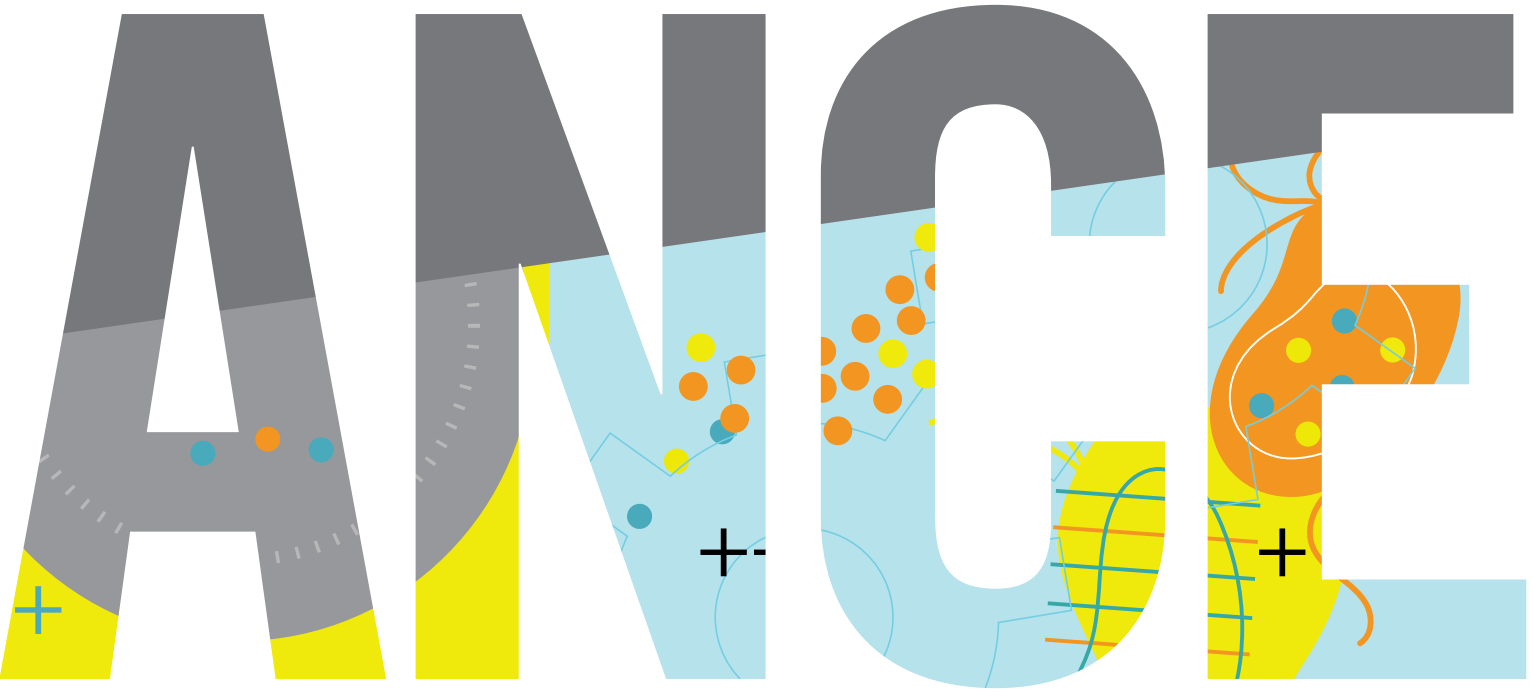
THE IMMUNE SYSTEM: A QUESTION OF

THE SALK INSTITUTE is the house that immunology built. Jonas Salk's groundbreaking work on the first polio vaccine propelled him to national attention and helped create a world-class research institute in Southern California. Even as the Institute has branched out into cancer, neurology and other fields, we still remember our roots.

And those roots run deep. The immune system is a powerful biological force—a liquid organ that permeates our bodies. Diverse immune cells are constantly on patrol, hunting for miscreants to roust: bacteria, viruses, tumors, cellular trash. The immune system keeps us safe in a hostile world.

"The immune system plays a profound role in maintaining human health," says Martin Hetzer, a professor in the Molecular and Cell Biology Laboratory and Salk's chief science officer. "Most of the time, it works so effectively, we don't even realize how much we rely on it. But if we look at pandemics or rare immune conditions, like severe combined immunodeficiency ('Bubble Boy' syndrome), we realize how vulnerable we can be when our immune system is overwhelmed."

THE IMMUNE SYSTEM IS A POWERFUL BIOLOGICAL FORCE—A LIQUID ORGAN THAT PERMEATES OUR BODIES. DIVERSE IMMUNE CELLS ARE CONSTANTLY ON PATROL, HUNTING FOR MISCREANTS TO ROUST: BACTERIA, VIRUSES, TUMORS, CELLULAR TRASH. THE IMMUNE SYSTEM KEEPS US SAFE IN A HOSTILE WORLD.



But not every immune component is poised to attack. Some cells control the response, keeping it from running amok and attacking our own systems. These checks and balances are critical to healthy immunity. If the response is too weak, a pathogen or cancer can take hold. If it's too strong, autoimmune conditions such as lupus, rheumatoid arthritis or multiple sclerosis can cause havoc.

Scientists call this careful balancing act between biological counterforces homeostasis, and researchers at the Salk Institute's NOMIS Center for Immunobiology and Microbial Pathogenesis are working to delineate the mechanisms that make it possible. As the NOMIS Center celebrates its 10th anniversary this year (see sidebar "NOMIS Center: past, present and future"), its researchers are answering many questions to illuminate immune function. How do different types of T cells respond to their environment, form memory and regulate immunity? Which mechanisms go awry in autoimmune diseases? Can we control infectious diseases without killing microbes?

Multidisciplinary researchers Susan Kaech, Björn Lillemeier, Ye Zheng, Janelle Ayres, Greg Lemke and others are investigating new ways to prime the immune system to attack disease or bring overactive cells under control. The goal? Restore balance.

SUSAN KAECH

UNDERSTANDING THE PLAYERS

Immune cells are segregated into two major types: innate and adaptive (See sidebar "immune cells"). Innate cells are the first responders. They recognize a threat, mount an attack and call for help. Soon, the adaptive response kicks in. These cells are custom-designed to meet specific threats. Even better, the adaptive response remembers pathogens from years before, the mechanism that powers vaccines.

While accurate, that description vastly oversimplifies immunity. Scientists are still delineating the many signals that kick the immune system into high gear or keep it from overreacting. Even the number and types of immune cells are being questioned. For example, T cells are among adaptive immunity's most prominent weapons, but it's only recently that researchers have learned how varied they can be.

"Now we know there are subsets within subsets within subsets of T cells," says Susan Kaech, professor and director of the NOMIS Center and holder of the NOMIS Foundation Chair. "The T cell population, as a whole, is being shaped by the inflammation that's in the environment. That can dictate the types that form."

Understanding this diversity is crucial on many levels. The immune response often weakens with age. Does this reflect fewer immune cells, a loss of diversity or other factors? Similar questions come up with cancer.

"We are investigating what central types of T cells, or functional traits they express, are critical to the anti-tumor immune response," says Kaech. "We already know of some, but we want to figure out how we can orient therapies to produce and enhance that type of T cell to better enable the immune system to fight cancer."

On a broader scale, Kaech and colleagues are exploring how different immune and non-immune cells communicate. This constant "cross-talk" is similar to pilots and air traffic controllers in busy air space. Immune cells alert other immune cells to potential danger. Normal tissue tells

the immune system it is not dangerous. Tumors and pathogens try to fool immune cells into not responding at all.

Understanding these various inputs could offer new tools to control immunity. For example, like people, immune cells may not function optimally when they are hungry. Kaech is investigating how diseases, like cancer, could be "starving" T cells to limit their responses.

"Another level of cross-talk could be how the environment alters the availability of different metabolites and nutrients," says Kaech. "How does this regulate immune cell function in cancer or infection? How might the metabolic state of particular non-immune cell types affect nutrient availability for the immune cells, and how does that in turn affect their metabolic state and functionality?"

This could be especially important in tumor microenvironments, which can be nutritional deserts. Kaech wants to understand, and ultimately control, these mechanisms to boost the immune response against cancer.

immune cells

THE IMMUNE SYSTEM HAS TWO MAJOR ARMS: INNATE AND ADAPTIVE. THE INNATE SYSTEM, WHICH INCLUDES MACROPHAGES, DENDRITIC CELLS, NATURAL KILLER CELLS AND OTHERS, IS THE FIRST LINE OF DEFENSE AGAINST ATTACK. IT TAKES ON INVADERS AND ALERTS THE ADAPTIVE ARM. THE ADAPTIVE RESPONSE MOUNTS A MORE SOPHISTICATED ATTACK, CUSTOM-DESIGNING SMART WEAPONS FOR EACH UNIQUE PATHOGEN. HERE ARE SEVERAL IMPORTANT IMMUNE CELL TYPES:

B cells/B lymphocytes latch onto bacteria, viruses, and other invaders and produce antibodies–proteins that thwart pathogens and mark them for destruction. They also identify molecular markers, called antigens, and present them to T cells, programming them to attack cells that carry those antigens.

Cytotoxic (Killer) T cells/T lymphocytes are custom-designed to attack infected or malignant cells. Each T cell is programmed to identify a specific cell surface antigen. When it finds that antigen, it attaches to the diseased cell and destroys it.

Many **Helper T cells** secrete molecules that alert and activate other immune cells, helping orchestrate the overall response.

Regulatory T cells (Tregs) are helper T cells that monitor and inhibit cytotoxic T cells, preventing an overactive immune response.

Memory T cells can be either killers or helpers. Each one remembers a specific antigen it encountered in the past, giving the body a leg up if that antigen (and the pathogen it's attached to) reappears. Immune memory is the mechanism that makes vaccines possible.

Innate-like lymphocytes are similar to T cells but lack the receptor that makes T cells so specific. Part of the innate immune response, these cells were only discovered a few years ago, illustrating how much we need to learn about immunity, and may act as an intermediary between the innate and adaptive responses.

Microglia are macrophages in the brain and spinal cord, engulfing cellular garbage and other threats. They are the main immune component in the central nervous system.

BJÖRN LILLEMEIER

DECODING INTERNAL CHIT CHAT

Immune research has been focused on external factors—the pathogens and molecular signals that kick the immune response into high gear. But what about internal signaling? What's happening inside immune cells that spurs them into action?

There are two ways to investigate this. The classic approach studies which proteins talk to each other, a game of telephone that often extends to a cell's DNA. But there's also the spatial/temporal approach. How are these molecules in the right place at the right time to even have these conversations? Associate Professor Björn Lillemeier studies both.

"We are interested in how T cell receptors, which can sense a single molecule, are actually activating the entire T cell and inducing functional programs that are different between various T cell types," says Lillemeier.

The system isn't random—there's no way T cells could respond fast enough. So how do key signaling proteins know where to be and when? These are difficult questions to answer because the scales are so small. The molecules the lab is tracking are around 2 nanometers and roam an area between 50 and 200 nanometers—a space 500 times smaller than the width of a human hair.

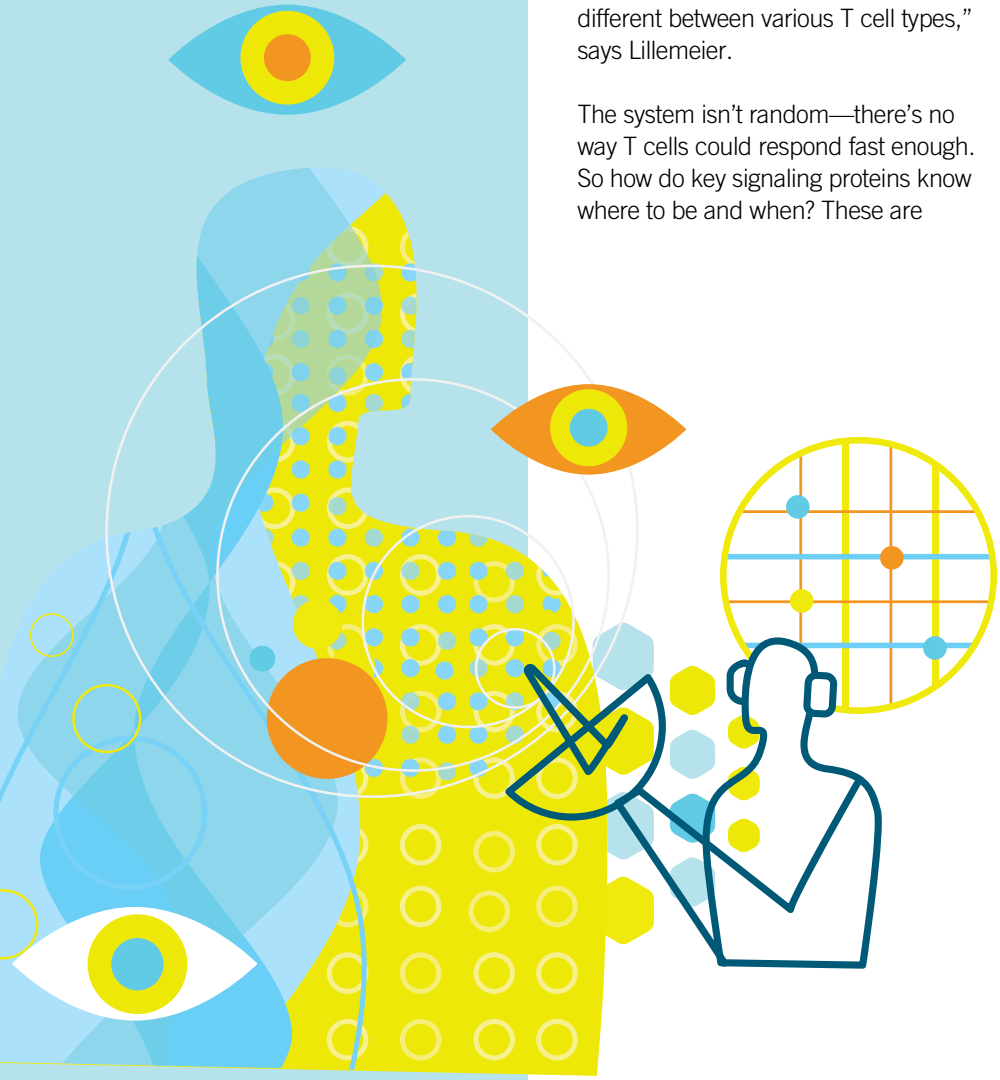
Traditional light microscopy can visualize objects as small as 250 to 300 nanometers, hardly suitable for such high-resolution studies.

If researchers try to image a 300-nanometer area, light sources that come too close together (in this case proteins) blur into indistinguishable blobs, like seeing a large city from space at night. The lab solved this problem by imaging individual proteins. The lab has embraced leading-edge super-resolution microscopy, which allows them to image areas as small as 25 nanometers. They take thousands of images to painstakingly piece together the larger picture. Lillemeier combines this approach with traditional biochemistry and cell biology, mutating proteins to see how the changes alter T cell function.

These efforts could have a major impact. Normal tissue turns on a T cell protein called PD-1 to counterbalance the activation of T cells. Tumors use the same trick to avoid immune attack. Cancer immunotherapies called checkpoint inhibitors turn off the enzyme to take the brakes off T cells and coax them to attack tumors. But this is a binary approach and only works for around 20 percent of patients with specific cancers, such as lung and melanoma.

Lillemeier's lab has begun studying PD-1 to better understand how the proteins in this circuit move and interact. Eventually, he wants to provide more nuanced strategies to influence T cells. Being able to exert such precise control could open more patients to immunotherapies and mitigate side effects.

"These mechanisms involving PD-1 can be potential drug targets," says Lillemeier. "Instead of targeting the activity of an enzyme, we can target where it is or how likely it is to be in a particular place."



GREG LEMKE

TAKING OUT THE TRASH TO DETER INFLAMMATION

Greg Lemke, a professor in the Molecular Neurobiology Laboratory, studies TAM receptors (Tyro3, Axl, and Mer), which are found on macrophages and other cells and shut down an immune response after it has completed its work. But, as Lemke and others have shown over the years, that's just the beginning of their responsibilities.

TAM receptors are also in charge of detecting dead cells. Millions of cells die each second—more than a hundred billion a day. It's a normal process, but macrophages have to clean up the mess. With reduced TAM signaling, they stop engulfing dead cells, kind of like a garbage strike, causing a cascade of problems. It starts with chronic inflammation. Then, because the immune system stays ramped up, the body can slip into an autoimmune response.

"That's bad because these dead cells will present antigens to the immune system, and the system will start making antibodies, and many of these antibodies are autoreactive—they attack the body's own organs," says Lemke. "Diminished TAM signaling leads to autoimmune disease."

The Lemke lab has shown that TAM signaling is a lot more important than previously thought. Just as tumors can turn off T cells, influenza, West Nile and other viruses can activate TAM receptors to evade immune surveillance. The lab also found that losing the Mer receptor in retinal cells can lead to blindness.

Dysfunctional TAM signaling also generates adverse consequences for microglia, the macrophages in the central nervous system. Without TAM-directed signals, microglia also stop disposing of dead cells, which contributes to, and exacerbates, neurodegenerative disease.

"Many of the genetic variables that increase the risk of developing Alzheimer's disease turn out to be in and around genes that are only expressed in microglia," says Lemke. "It's clear that the regulatory functions of microglia—including controlling inflammation and engulfment—are important in Alzheimer's."

YE ZHENG

THE CURSE OF AUTOIMMUNITY

TAM receptors are one of many mechanisms designed to modulate the immune system. Tregs, which keep T cells from overreacting, are another way to dial down the immune response. In some ways, they are a firewall against autoimmune disease.

"Tregs are quite unique," says Associate Professor Ye Zheng. "Most of the immune cells we know are designed to attack, to kill bacteria or viruses or whatever. Tregs suppress other immune cells from attacking."

Tregs make up around 10 percent of all T cells and could hold the key to immune system homeostasis. Making them more suppressive could help researchers address autoimmune conditions. Making them less suppressive could promote the immune response against cancer.

For Zheng, the quest to better understand them begins with a protein called Foxp3, which is essential for Treg development.

"Some people have a mutation in Foxp3 and experience a massive autoimmune response called IPEX syndrome," says Zheng. "Without the Tregs to suppress other immune cells, the body's system becomes totally imbalanced and starts attacking everything."

The Zheng lab has been focused on understanding the role Foxp3 plays in Treg development. That means identifying hundreds of interrelated genes—the ones that control Foxp3 and the ones that it controls. Through this detailed process, the lab has identified anomalies that can transform Tregs into cytotoxic T cells, generating autoimmunity in animal models. Zheng believes these and other findings could help lead to Treg-based therapies.

"If we can modulate Tregs, we could potentially take more precise control over the immune response," says Zheng. "We could increase it to mitigate an autoimmune condition or decrease it to fight cancer. It could be a very powerful tool."

JANELLE AYRES

WHAT BACTERIA CAN TEACH US

Learning how various immune cells respond to pathogens—both individually and collaboratively—could give us better tools to manage infections. But the body has other mechanisms to deal with hostile microbes and the damage they cause. Associate Professor Janelle Ayres has a unique way to learn about these systems—by querying the pathogens themselves.

"The body has defense mechanisms that mitigate the damage associated with an infection," says Ayres. "We focus on how microbes have evolved ways to induce these mechanisms themselves. We're finding that microbial recognition by our immune system, to a large degree, drives these responses."

Ayres is looking for alternatives to vaccines and antibiotics. It's not that she's against them, she just recognizes their limitations. Vaccines are not available for all viruses, and bacteria are developing resistance to our most powerful therapies. While many people believe the solution is new antibiotics, evolution is an unstoppable force. Sooner or later, microbes will develop resistance to the latest penicillin reboot.

On the other hand, what if evolution could be our friend? Around ten years ago, Ayres discovered the cooperative defense system, a collection of mechanisms that prevent physiological damage during

infection. The system promotes health without killing the microbe and, in fact, is often initiated by microbes themselves.

A good example is sickness-associated anorexia (SAA), during which patients don't feel the need to eat. The lack of nutrients can make infections like *Salmonella* more virulent, but that's not a great outcome for bacteria. They need to keep their host healthy enough to keep hosting. But *Salmonella* has its ways. By blocking inflammation in the intestines, *Salmonella* prevents SAA and keeps its host alive.

"*Salmonella* has found a way to block this response from happening," says Ayres. "It stays in the intestine, causes less virulent disease and lives to transfer to a new host. We can use microbes to teach us how to promote health because they've already figured it out."

Rather than killing the pathogens, Ayres believes we can exploit cooperative defense mechanisms to protect people from collateral damage from *Salmonella*, sepsis and other conditions. Limiting the damage could give patients' immune systems the opportunity to take care of the pathogen without pushing microbes to evolve.

"We predict our approach will not drive drug resistance because we are targeting the physiology, rather than killing the pathogen," says Ayres. "They have no reason to evolve around it."

"Our immune system has the potential to interact with every cell type in our body and intersects with virtually every biological process."

– Susan Kaech, professor and director of the NOMIS Center

ALL ENCOMPASSING

Because the immune system is everywhere in our bodies, NOMIS Center scientists collaborate on efforts throughout Salk's many research areas: cancer, neurobiology, gene expression, cell biology, aging, metabolism.

Successful cancer immunotherapies are lighting the way for researchers to really deconstruct immunity. This work will eventually lead to new treatments for cancer, infectious diseases and autoimmune conditions, but it also illustrates how biology functions on the deepest levels.

"The immune system is a liquid tissue," says Kaech. "It's one of the few systems in our bodies where the cells go out and infiltrate all the other tissues. Thus, our immune system has the potential to interact with every cell type in our body and intersects with virtually every biological process. That makes it an important crossroad in science and an incredible opportunity for collaboration."

NOMIS

CENTER: past, present and future

Ten years ago, Salk launched the NOMIS Center for Immunobiology and Microbial Pathogenesis. The center was initially funded by an $11.5 million grant from the Zurich-based NOMIS Foundation, which supports groundbreaking research around the world. It was the first gift the foundation ever made. In 2010, NOMIS donated an additional $6.5 million to establish an endowed chair and support continuing research. Overall, the NOMIS foundation has provided more than $30 million to support Salk and the NOMIS Center, making it one of the Institute's most generous supporters.

"The NOMIS Center at Salk is a great reference for how basic research should be conducted," says Markus Reinhard, managing director at the NOMIS Foundation. "Its focus on the researcher—whose outstanding collaborative and innovative approaches, and dedication to understanding the immune system—make it a truly unique place."

Over the past decade, Salk's NOMIS Center researchers have made great strides toward understanding the immune system's various components and the complex signaling mechanisms that turn them on or off. These findings are part of a global effort to combat autoimmune conditions, infectious diseases and cancer.

More recently, as immunotherapies have become an important part of the anti-cancer armamentarium, NOMIS Center scientists have refocused their efforts to delineate these pathways and improve treatments. In addition, the center has become an important resource for investigators at Salk and other institutes in San Diego and around the world.

The next ten years look equally bright. In 2017, acclaimed immunobiologist Susan Kaech joined Salk to direct the center and orchestrate plans to hire new faculty and postdoctoral fellows; advance immunometabolism, neuroimmunology and other initiatives; and expand the center's visibility throughout the immunology community.

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Where cures begin.

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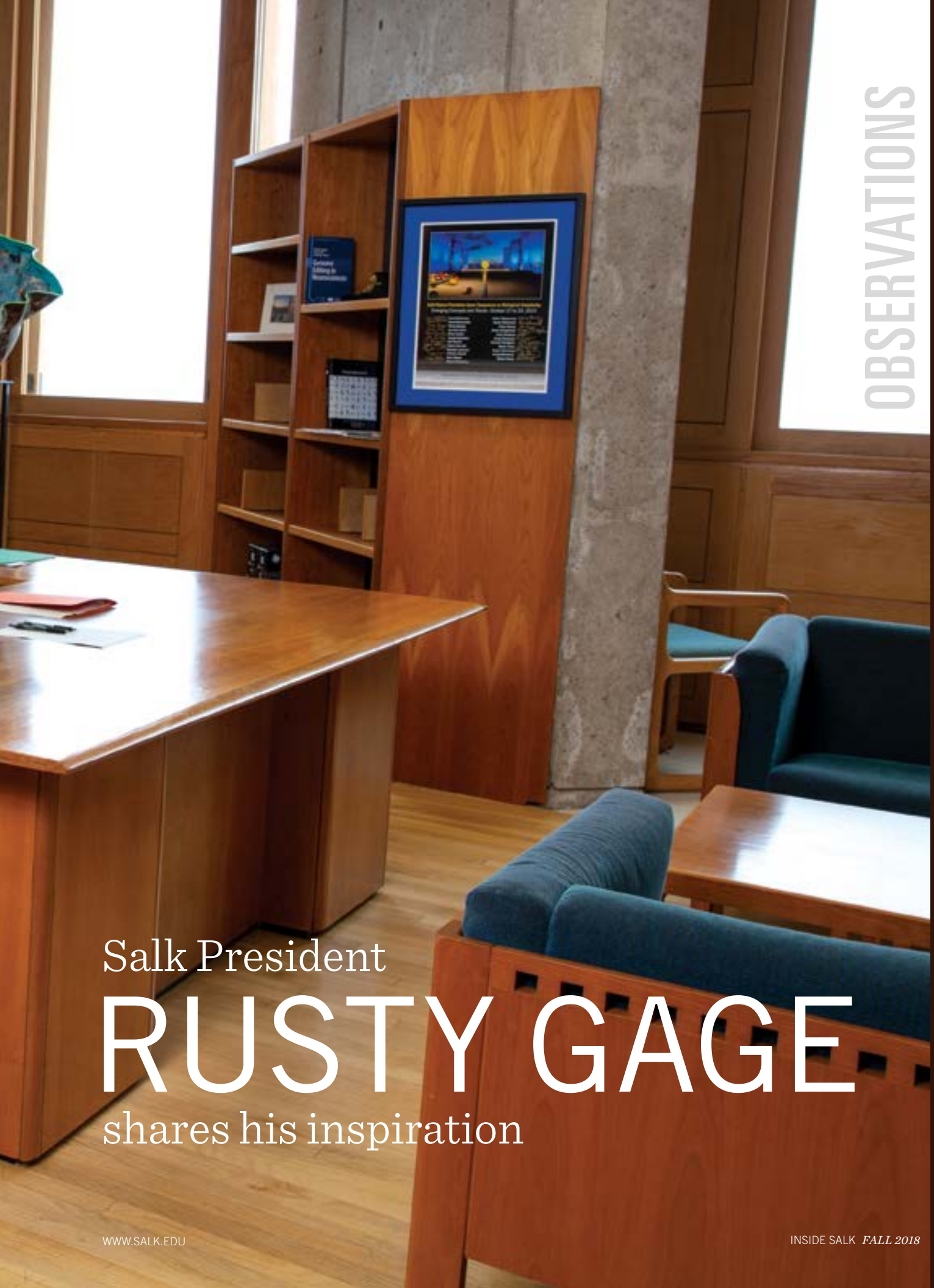
Complacency has never been part of Fred (Rusty) Gage's genetic make-up, neither as he has ascended to the ranks of the world's most renowned neuroscientists nor as he's taken the helm as President of the Salk Institute.

With a quiet intensity and knack for explaining even the most complex biological principles in simple terms, Gage often speaks in analogies akin to scientific processes. Having called the Salk home for nearly 25 years, he has made critical discoveries in what has been considered one of the "last frontiers" of biology: the human brain. Among his most seminal breakthroughs, Gage found that neurogenesis occurs in adults—that humans are capable of growing new neurons throughout their lifespan—launching entirely new fields of research.

Maintaining a large and robust lab today, Gage continues to make discoveries around how the brain can change over time, an area called neuroplasticity. His lab explores myriad topics in neuroscience, developing cutting-edge tools and methods to reveal what happens to brain cells as we age or suffer from diseases such as Alzheimer's and schizophrenia. He also explores how mobile genetic units dubbed jumping genes generate individual diversity between neurons, and how those activities contribute to making us who we are.

After receiving his BS from the University of Florida and PhD from Johns Hopkins University, Gage—who speaks Italian, German and Swedish—did research at Lund University in Sweden and at the University of California San Diego before arriving at the Salk Institute. During his scientific explorations, he has garnered numerous accolades and broad recognition, including from the National Academy of Sciences, National Academy of Medicine, American Academy of Arts & Sciences, and American Philosophical Society, as well as having served as president of the International Society for Stem Cell Research and the Society for Neuroscience. In addition to being a member of more than a dozen prestigious scientific organizations, he holds the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease at the Institute.

Inside Salk sat down with Gage to discuss what he is most excited about in the realm of scientific discovery and what he looks forward to at Salk.



Salk President RUSTY GAGE shares his inspiration

Tell us about your path to Salk.

In 1995, I was a professor in the Department of Neuroscience at UC San Diego, and I was considering a new position heading a new center. The Salk Institute offered me a position in a new laboratory of genetics, so with little hesitation, I left UC San Diego, where I had been for the previous 10 years. My years there were a great experience, but at the time I felt that I was at a place in my own research that I wanted to go in new directions. I needed to be in a new environment and found it appealing that there were no "walls" at Salk: you are free to pursue your research however you see fit. That's a rare environment.

From the moment I got here, I knew I had made the right decision. Francis Crick, who was President of Salk at the time, in negotiating with me about the position, said something to the effect of, "we're not hiring you for what you're doing, we're hiring you for what you are—just continue doing great and creative work!" That's what happens at Salk. Fields of research can change over time, but having an ethos of exploration, of going where the science may lead you, even if it's unexpected, that's the important thing.

From Crick and others at Salk, I learned to think of science in a broad perspective and ask: "Is this really the most important question?" Another thing Crick advised was to consider how you are going to prove your theory wrong. Think about the critical experiment that can destroy your hypothesis and use that to make your science stronger. We have a tendency to hang onto our own hypotheses much longer than we should, which can prevent us from looking at the larger picture and asking what are the big ideas we should be investigating.

As the Institute's President, what is your vision for Salk?

At Salk, we have a history of focusing on innovative ideas and we continue that legacy today as we embark on several major pushes to tackle the biggest issues facing our time. I am looking ahead to identify what we should do next. Of all the questions that intrigue me, that's the most exciting: what is the next game-changing idea?

Together with Salk's supportive board and leadership team, we're aiming to build upon the dedication and commitment to science of my predecessors to address the next set of "big ideas" in biology. In particular, I am expanding upon the groundwork that Nobel laureate and former Salk President Elizabeth Blackburn laid out for what we're calling "Salk Next 50," in which we're looking at where we want to be in 50 years in terms of science and as an Institute. Part of this entails evaluating ways to continue to enhance the Salk experience and ways in which we can continue to support our faculty and recruit new talent to the Institute.

What are some of the big ideas happening at Salk right now?

We are already pursuing several ambitious projects: tackling five of the world's deadliest cancers; optimizing plants in order to mitigate the effects of climate change; and developing strategies to make big strides in neuroscience, healthy aging and metabolism. Some of these efforts are what we call "high-risk, high-reward" projects—the ideas may not be conventional enough for traditional types of funding and support and the payoff may not be immediate, but we believe they have potential. These thoughtful forays into new areas of research are what make the Institute fertile grounds for truly groundbreaking and interdisciplinary ideas.

In regards to my area of neuroscience, I am excited about some of our upcoming efforts to investigate the most intractable neurological mysteries and diseases of the brain. Specifically, we are setting our sights on Alzheimer's disease.

Can you tell us more about the challenges of understanding Alzheimer's?

Alzheimer's is an aging-related neurodegenerative disorder that results in severe memory loss and cognitive decline; nearly 50 million people worldwide currently suffer from this disease and related dementias. The human and global costs of this devastating disease are immense, yet numerous clinical trials targeting Alzheimer's have failed to stem this public health crisis. It is imperative to explore alternative mechanistic drivers for Alzheimer's and to understand the disease within the broader context of aging.

The biggest risk factor of Alzheimer's is age. More than 90 percent of Alzheimer's cases are sporadic, meaning the presence of the disease is rarely linked to genetics. There is no single mutation driving it. Rather, it appears that age is setting you up for some other event that triggers the disease. And, as people worldwide live longer, the need to find novel treatments and therapies for diseases of aging becomes more urgent.

So we need to understand how to slow down aging and, even more fundamentally, define what aging *is* from various perspectives in the cell: mitochondria, proteins, nuclear pores, and energy production to name a few. All of these are seemingly separate areas of study, but they are all linked together; if we perturb one area in the cell, the other areas are impacted. We need to explore and understand this network and connection.

Do you think new treatments for Alzheimer's are within reach?

There are so many exciting developments in neuroscience that it really feels like a golden age for the field. I'm optimistic that we will make significant progress in our lifetimes.

For example, with a recent gift from South Korea's NANOS company to establish an Alzheimer's bank of human cells, we will gain an invaluable experimental resource for both researchers at Salk and the Alzheimer's disease research community at large. The funds will establish a dedicated laboratory space called the NANOS Alzheimer's Disease Stem Cell Suite, which will serve as a cell bank focused on Alzheimer's. This cell bank will house both stem cells and somatic [body] cells from human donors, which are critical for analysis and testing of therapeutic drugs.

With the body of knowledge we have accumulated at Salk and the committed support from companies such as NANOS, we believe novel therapies for Alzheimer's may be feasible.

In addition to your own research, you've had a profound influence on a number of scientists who have come through your lab over the years and with whom you regularly reunite at your alumni events. What is your mentoring approach?

When I first started mentoring, some of the trainees were not much younger than I was. I was learning how to mentor while mentoring. It felt a bit like building an airplane while it's in flight. In general, I like people to figure out what they really enjoy doing within science. But it can be especially helpful to ask students, "What's fun for you? What do you enjoy doing?" It's not just about the conceptual stuff, but technical interests too. What you understand matters, but what you're good at and what you like matter, too. For postdocs, I try to help them build a line of discovery, not just a single set of experiments; once you've solved a problem, how will you build on it?

Once I think I have a clear view of a where a student or trainee wants to go, I ask them: "Do I have this right?" Mentoring is an intuitive process where you check in periodically to see that trainees are moving along the trajectory they want to be on.

You cannot minimize the responsibility that a mentor has when taking somebody on as a trainee. Over time, I've learned to be more proactive in reflecting to my trainees how they appear to me. Honest discussions with trainees are difficult for mentors but they are incredibly important. Some way through my career I realized that if you just let people go along a direction that you believe to be incorrect, without intervening, you're not being an effective mentor.

You still enjoy working in the lab when time allows—what brings you back to the bench?

I think it's incredibly important for laboratory heads to stay connected to the research and keep up to date on techniques. Being at the bench, even once in a while, reignites a passion for experimentation, which is what drew many of us to science to begin with. Maintaining involvement with the generation of the lab's data helps keep me connected to the fundamental science. Plus, it's fun.

Given the enormous demands of running both an institute and a laboratory, from where do you draw inspiration? What keeps you motivated, excited, inspired?

Aside from exercise and a moderated diet, over the last few months I've gotten into the habit of writing down inspirational quotes from historic figures—world leaders, philosophers, poets—people who, in the turn of a phrase, have gifted us with words that afford us perspective, lift us up or motivate us into action. Inspirational thinking emerges from functional crises.

What I've been reminded of, however, is that I don't need to look far at all for inspiration; it's right here, every time I set foot on our campus. It's here because, at this Institute, we literally and figuratively set our sights on the horizon. At Salk, we are bold enough to say we are fearless in the face of any challenge and are not afraid to look at who we are as an Institute—and who we are as an institutional family. Jonas Salk had a notion that there are people who are evolvers, and there are people who are maintainers of the status quo. He wanted this Institute to be populated with evolvers who consistently ask the big, hard questions.

I find that everyone at Salk—from administrators to laboratory heads and staff to our donors—want to be part of a place founded by a big thinker so that more big thinking can be done to improve the lives of people around us, and around the world. Our charge is to be truly fearless in the face of any challenge and to look beyond ourselves and continually seek to enrich the lives of others, for those at Salk now and the generations who will follow us in coming here to set their own sights on the horizon.

All of us, at Salk and beyond, are united through a mission to better humanity. We embrace that mission on a scientific level every day. The best version of humanity demands that we, as humans, are the best versions of ourselves. To me, nothing is more inspiring than that.

IT'S ABOUT TIME

SALK'S EMILY MANOOGIAN ON CIRCADIAN RHYTHMS AND LIFE

When Emily Manoogian was growing up, "scientist" wasn't even on her list of potential careers. First Manoogian wanted to be a Broadway tap dancer; then a gymnast; later, a lawyer; and finally, towards the end of high school, a veterinarian.

She started at UC Berkeley on a pre-vet track but, two years in, realized it wasn't the right choice. There was so much rote memorization, and Manoogian prefers theories and concepts. She felt lost.

Then she took a class called "Hormones and Behavior" and felt found. "The running joke was that my roommate could take the tests, because I talked about the class so much," she recalls, laughing. "I loved it."

Manoogian was determined to get into her professor's lab as an undergraduate research assistant—and she did, wearing down his repeated assertions that the lab didn't have any openings with sheer enthusiasm. She was fascinated by all the interrelated processes of the endocrine system, the collection of glands that produce hormones to regulate growth, metabolism, sleep and pretty much every other physiological function in the body. When she took another of the professor's courses, called "Biological Clocks," her interest in the connection of circadian (daily) rhythms to the endocrine system was born. For her doctorate, Manoogian studied the master clock in the brain, which synchronizes all the individual clocks in the body.

Each of our cells has a circadian clock in it, telling the cell when to be active and when to rest. Increasingly, scientists are learning the myriad negative health consequences of not living in sync with our circadian clocks, which operate on a 24-hour cycle.

"The circadian system is this core pillar of how our body works that affects everything," says Manoogian emphatically. "You are mentally and physically a different person at different times of day."

After graduate school, Manoogian came across an opening in the lab of Satchidananda Panda, a professor in Salk's Regulatory Biology Laboratory. For Manoogian, who was tiring of conducting basic biological research with rodents, the transition to researching circadian rhythms in humans came at the perfect time.

"The fact that the lab was studying humans from a basic science point of view was really exciting," she says. Now, after two years in the lab, Manoogian is doing a stimulating combination of bench work and project management of the lab's circadian health app, which collects data on the diet, exercise and sleep habits of thousands of participants around the world who are attempting to live in better sync with their biological clocks. She is also working with local firefighters to determine whether restricting dietary intake to a 10-hour window of time can help combat the negative health consequences of shift work.

Manoogian is nothing if not an evangelist for circadian science. Recently she spoke about the field and her own research at a sold-out TEDx event held at Salk in July. "No one knows about it! It's not taught in medical school," she says, eyes widening. "How can you be a doctor and not know what circadian rhythms are? They're determining everything!"

Eventually, Manoogian plans to explore how people take in cues like light and food and use them to train their circadian clocks. "I want to understand how these cues vary for people, and use that information to help people live their best life."

"The circadian system is this core pillar of how our body works that affects everything. You are mentally and physically a different person at different times of day."

—Emily Manoogian

LENDING A **ROBOTIC** HAND

Without plants, life as we know it wouldn't exist. But how plants process environmental information and which molecular mechanisms help them adjust to change are still open questions. A better understanding of plants could help scientists grow more resilient crops in the face of the planet's shifting climate and increasingly extreme environments.

In order to hasten such discoveries, plant scientists at Salk recently acquired a custom seed-planting robot thanks to a crowdfunding campaign and longtime Salk supporters Larry and Carol Greenfield, one of whom lent the robot his name. "Larry the Robot" carries out high-throughput planting of thousands of seeds in environmental variations faster than a human.

"Not only is the robot much faster than humans in preparing the experiments but it has a much lower error rate and allows for more sophisticated experimental designs. This enables us to seek answers to questions in plant biology that we couldn't ask before," says Salk Associate Professor Wolfgang Busch.

1 EFFICIENCY

When it comes to repetitious and precise tasks, there is no match for Larry the Robot, who can complete more experiments in a single day than a human researcher can complete in five weeks. By tirelessly performing the same motion millions of times, the robot is allowing scientists to ask new kinds of questions, particularly around plant root function.

2 SPEED

The robot distributes approximately 1,000 seeds per hour, placing them about 8 millimeters apart. Each tiny seed of the model plant *Arabidopsis thaliana* has only a thickness of a fifth of a millimeter (about the size of a period), requiring high accuracy for picking up and placing each one. The robot is able to place seeds as precisely as .01 millimeters apart.

3 PRECISION

Almost like a high-tech vacuum cleaner, the robot pulls up seeds and measures very subtle changes in air pressure at its tip to tell when a seed has been taken up. It then delivers the seed with submillimeter precision to an agar plate and can detect whether the seed was correctly placed or not.

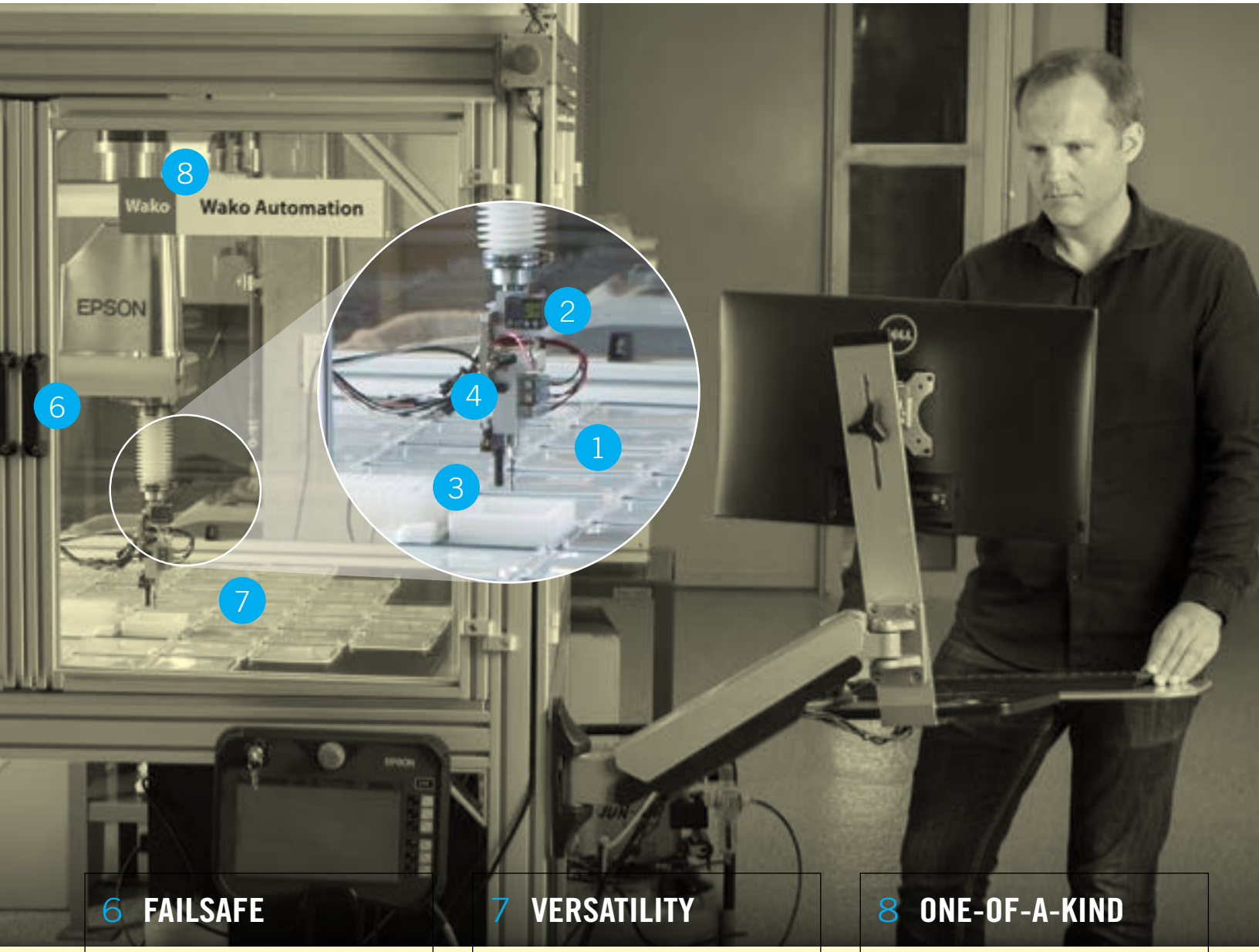
4 VISION

The robot "sees" via an ultrasound system, which lets it determine the surface height of the agar plates on which the seeds are placed. This allows it to account for variation in the agar plates on which the plants will be grown.

5 STERILIZATION

The robot lives in a temperature-controlled room and, within that, a contained box through which air is filtered to ensure no germs enter the system. Before each run, ultraviolet lights glow to kill off any outside intruders. This internal sterilization system makes experiments as consistent as possible to yield the highest quality data.

ANALYSIS



6 FAILSAFE

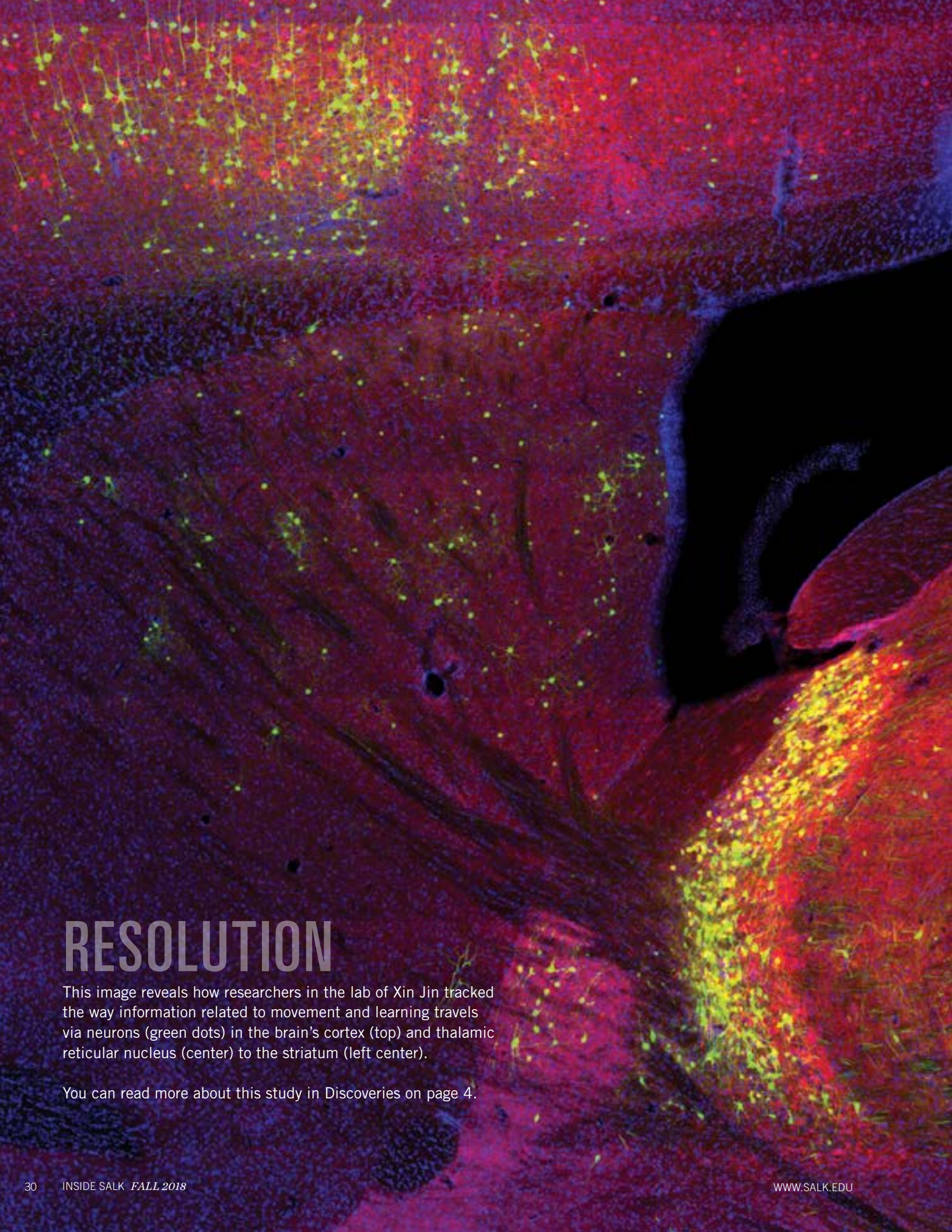
Because the robot arm is moving very fast, the system is equipped with a fail-safe shut-off mechanism that stops the robot when someone opens the door to the enclosure.

7 VERSATILITY

With different seed-handling tips, the robot could be used to conduct similar experiments for different plant species or other types of experiments in the future.

8 ONE-OF-A-KIND

The robot is the only one of its kind in the world regarding its ability to precisely place seeds. Custom designed by Salk scientists and constructed by WAKO Automation, Larry the Robot is a game changer in plant science experimentation.



RESOLUTION

This image reveals how researchers in the lab of Xin Jin tracked the way information related to movement and learning travels via neurons (green dots) in the brain's cortex (top) and thalamic reticular nucleus (center) to the striatum (left center).

You can read more about this study in Discoveries on page 4.

The power of charitable gift annuities

Did you know a gift to the Salk Institute of $20,000 or more can provide fixed payments for you and your loved ones? Charitable gift annuities provide tax savings and an income for you, while benefitting research and discovery at the Salk Institute. By creating a charitable gift annuity, you can be confident that you've made a smart decision about your financial and philanthropic priorities.

Sample Rates

YOUR AGE (S)	RATE
70	5.6%
80	7.3%
90	9.5%

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SPOTLIGHT

salk® | WOMEN & SCIENCE

Inaugural Trailblazer Awardee Catherine Rivier

Professor Emerita Catherine Rivier was honored with the inaugural Trailblazer Award from Salk Women & Science. The Trailblazer Award recognizes outstanding achievements made by women in a STEAM (Science, Technology, Engineering, Art or Mathematics) field. Recipients have pioneered changes within the STEAM fields as innovators, groundbreakers, collaborators and mentors. They have dedicated their lives to making significant advances in both their professional and personal realms. Trailblazers forge their own paths to achieve their vision.

Professor Rivier originally joined the Salk Institute in 1970, alongside Baylor University colleagues Roger Guillemin (who was her mentor and would go on to win the 1977 Nobel Prize in Physiology or Medicine) and Wylie Vale (a former Salk Institute professor and world-renowned expert on brain hormones who passed away in 2012), as well as her husband, Jean, who is an equally esteemed researcher and someone whom she credits in her success. During her tenure at Salk, Rivier studied the mechanisms through which the brain is alerted to stressors, such as psychological threats, infections or drugs, as well as the hormones used by the brain to respond to these challenges. She identified a large number of hormonal functions and new endocrine pathways throughout the body; among researchers in the field, her work is considered exceptional. Published in hundreds of papers, she earned numerous consecutive "Highly Cited Researcher" awards, her articles paving the way for many future discoveries.

Mentorship was a particularly important theme for Rivier throughout her career. "I think mentorship is important for everyone," says Rivier, "but it's particularly critical for women because we face many gender-specific problems. For example, younger women often asked me how I managed to bring to this world and raise two children while pursuing my career, and how I balanced work with family life and responsibilities. I always considered sharing my experience in dealing with these issues to be an important and enjoyable part of my job." According to Betty Vale, "Catherine is an original Salk trailblazer for her contributions as a visionary scientist, early role model and mentor, and partner in founding Symphony at Salk."

"Catherine is an original Salk trailblazer for her contributions as a visionary scientist, early role model and mentor, and partner in founding Symphony at Salk."

– Betty Vale

Catherine Rivier, PhD, GG
Professor Emerita, Salk Institute
Clayton Foundation Laboratories
for Peptide Biology

Salk faculty receive promotions

IN RECOGNITION OF THEIR CONTINUED EXCELLENCE IN RESEARCH AND INNOVATION, TWO SALK FACULTY RECEIVED PROMOTIONS WITHIN THE INSTITUTE.

Xin Jin

Xin Jin was promoted to associate professor. Jin, an innovative neuroscientist providing significant insights into neurological and psychiatric diseases, such as Parkinson's and Huntington's, joined Salk in 2012. He uses a variety of tools to uncover the underlying neural circuits and molecular mechanisms of how actions are learned and selected. Part of Salk's Molecular Neurobiology Laboratory, his team recently discovered that the concentration of a brain chemical called dopamine governs decisions about actions so precisely that measuring the level in mice right before a decision allows the researchers to accurately predict the outcome. In addition, his lab has used cutting-edge molecular tools to dissect how the different cell types in the downstream brain regions work together with dopamine for control of actions. The work could open new avenues for treating disorders both in cases where people cannot properly initiate an action, such as Parkinson's, and in ones where they cannot stop performing certain actions, as in obsessive-compulsive disorder or drug addiction.

Dmitry Lyumkis

Dmitry Lyumkis was promoted to assistant professor. Lyumkis is well known for his significant, early contributions to the up-and-coming field of single-particle cryo-electron microscopy, a cutting-edge technology that enables the visualization of large proteins and protein complexes under near-native conditions. He uses this technology to build three-dimensional models of the imaged objects that reveal never-before-seen aspects of protein function to show, for example, the core components behind how HIV and other retroviruses insert viral DNA into the host genome and replicate. Lyumkis came to the Institute in 2014 as the inaugural Salk Fellow, part of a program designed to bring scientists from broad disciplines to the Institute to trigger innovation and perpetuate the collaborative spirit of Salk. A 2015 recipient of the prestigious National Institutes of Health Director's Early Independence Award, Lyumkis has consistently pursued innovative approaches to major contemporary challenges in biomedical research.

THREE SALK SCIENTISTS NAMED TO ENDOWED CHAIRS

Katherine Jones

Susan Kaech

Gerald Shadel

Salk scientists Katherine Jones, Susan Kaech and Gerald Shadel have been recognized for their contributions and dedication to advancing science through research by being named to endowed chairs at the Institute.

Jones, named to the Edwin K. Hunter Chair, serves in Salk's Regulatory Biology Laboratory. Her work focuses on the genetic processes involved in the expression of HIV and cancer genes, as well as on other disease research. The Edwin K. Hunter Chair was established in 2013 thanks to a generous philanthropic collaboration between the Olive Tupper Foundation, the Chambers Medical Foundation, the Jenkins Family Charitable Institute, and the Joe W. and Dorothy Dorsett Brown Foundation. It is named for Edwin K. Hunter, attorney and member of the Salk Institute Board of Trustees.

Kaech has been named to the NOMIS Foundation Chair and leads the NOMIS Center for Immunobiology and Microbial Pathogenesis (NCIMP). Kaech is internationally recognized for her efforts to understand how memory T cells are produced during infection and vaccination, how they function and why they can fail to induce long-term immunity during immunization. The NOMIS Foundation Chair was established in 2010 thanks to a $6.5 million gift from the Switzerland-based organization.

Shadel, who joined Salk in early 2018 and has been appointed to the Audrey Geisel Chair in Biomedical Science, is one of the newest leaders within Salk's Molecular and Cell Biology Lab. His work focuses on mitochondria, known as the powerhouses of the cell, and their role in aging, cancer, and metabolic and degenerative diseases. The Audrey Geisel Chair in Biomedical Science was established in 2012 thanks to a generous gift from San Diego philanthropist Audrey Geisel. It is one of several chairs made possible by the Joan Klein Jacobs and Irwin Mark Jacobs Senior Scientist Endowed Chair Challenge.

SPOTLIGHT

Ronald Evans

RONALD EVANS AWARDED PRESTIGIOUS HONORS

Salk Professor Ronald Evans has received two prizes, each providing $10,000 to advance the research of his lab. The first, the Bert and Natalie Vallee Award in Biomedical Science, was established by the Vallee Foundation to recognize international achievements in the sciences essential to medicine. The second, the Louisa Gross Horwitz Prize, was initiated through a bequest to Columbia University and honors scientists who have made outstanding contributions to basic research in the fields of biology and biochemistry.

As professor and director of the Gene Expression Laboratory, a Howard Hughes Medical Institute investigator, and the March of Dimes Chair in Molecular and Developmental Biology, Evans has been instrumental in reshaping medical research. Recent discoveries that have taken shape in his lab include finding the gene responsible for enabling endurance exercise and muscle repair, as well as identifying a modified form of vitamin D that may offer new treatments for diabetes and cancer.

JANELLE AYRES WINS BLAVATNIK NATIONAL AWARD FOR YOUNG SCIENTISTS

Salk Associate Professor Janelle Ayres has been named one of three winners of the Blavatnik National Awards for Young Scientists, one of the world's largest unrestricted prizes for early career scientists. Ayres, the laureate in the life sciences category, will receive $250,000 for her pioneering research in physiology and the study of how bacteria interact with humans.

Ayres' work resides at the leading edge of understanding infections and treatments. Rather than seeking out new antibiotics to treat the rising rates of drug-resistant illnesses, Ayres seeks to create drugs that allow individuals to survive and tolerate disease—i.e., minimize the amount of damage infection inflicts—while it runs its course. She has received many awards for her work, including a DARPA Young Faculty Award, a Searle Scholars award and a Ray Thomas Edward Foundation Award.

Janelle Ayres

Saket Navlakha

SALK ASSISTANT PROFESSOR SAKET NAVLAKHA NAMED PEW SCHOLAR

The Pew Charitable Trusts announced that Saket Navlakha of Salk's Integrative Biology Laboratory is one of 22 researchers named a 2018 Pew Scholar in the Biomedical Sciences. Additionally, Navlakha is one of five Pew Scholars also supported by the Kathryn W. Davis Peace by Pieces Fund to investigate health challenges in the brain as it ages.

Navlakha, who holds the Pioneer Fund Developmental Chair at Salk, develops new algorithms to understand the interactions and dynamics of complex biological networks by bridging theoretical computer science and systems biology. By mining massive amounts of data in new ways, he aims to reveal the evolution and organization of molecular and cellular networks. Navlakha also studies "algorithms in nature"—for example, how groups of distributed molecules and cells communicate and process information to collectively solve computational problems. Discovering such shared principles can lead to the design of improved computing algorithms and can provide a way to understand, quantify and predict the behavior of large, distributed biological systems.

SALK PROFESSOR TONY HUNTER RECEIVES PEZCOLLER FOUNDATION-AACR AWARD, TANG PRIZE

Tony Hunter, who holds an American Cancer Society Professorship at the Salk Institute, was awarded the 2018 Pezcoller Foundation-AACR International Award for Extraordinary Achievement in Cancer Research, one of the most prestigious honors in the field. According to the American Association for Cancer Research (AACR) and the Pezcoller Foundation, the prize "recognizes a scientist of international renown who has made a major scientific discovery in basic or translational cancer research." The Pezcoller-AACR award includes €75,000 (approx. $87,000) and was awarded at a ceremony held at the Teatro Sociale in Trento, Italy, in late May. Hunter also gave a special lecture at the AACR Annual Meeting in Chicago in April.

In addition, Hunter was also recently named one of four recipients of the 2018 Tang Prize. The award recognizes and encourages "original research and major contributions in biopharmaceutical science." The other three Tang Prizes are given for sustainable development, sinology and law. Held in Taipei, the Tang Prize ceremony included a lecture from Hunter as part of a weeklong event and NT$50,000,000 (around $1.5 million) for his research, split evenly with two other researchers. The Pezcoller Foundation-AACR Award and Tang Prize are the latest of many notable awards for Hunter, including the Sjöberg Prize for Cancer Research, the Royal Medal in Biological Sciences, the Clifford Prize for Cancer Research and the Wolf Prize in Medicine.

Tony Hunter

Nicola Allen

NICOLA ALLEN AWARDED GRANT FROM COINS FOR ALZHEIMER'S RESEARCH TRUST

Salk Assistant Professor Nicola Allen has received a grant for $112,500 from the Coins for Alzheimer's Research Trust. The award, supported by the Rotary Clubs of North America, will enable a two-year study to identify how support cells called astrocytes regulate the brain when healthy; to understand how astrocytes go wrong in Alzheimer's disease; and to test whether astrocytes can be used as a therapy to repair damaged neurons.

Allen, who holds the Hearst Foundation Development Chair in the Molecular Neurobiology Laboratory, is internationally recognized for the caliber of her research. Allen's other accolades include being named a 2015 Pew Scholar, a Human Frontier Science Program Long Term Fellow and an EMBO Long Term Fellow. Allen's previous findings include the discovery of a class of proteins secreted by astrocytes that help neurons form synapses, the critical spaces between neurons that allow individual cells to communicate with one another and send signals to the rest of the body.

Margarita Behrens

NEUROSCIENTIST MARGARITA BEHRENS NAMED FIRST RESEARCH PROFESSOR AT SALK

Margarita Behrens recently was promoted to research professor, the first appointment of its kind at Salk. Her promotion recognizes her enormous contributions to neuroscience with non-tenure faculty status. Behrens, a Salk staff scientist in the Computational Neurobiology Laboratory since 2009, received her master's degree in biochemistry from the Universidad de Chile, in Santiago, and her doctorate in biochemistry and molecular biology from the Universidad Autónoma, in Madrid. She conducted postdoctoral research in the neurology department of Washington University School of Medicine, in St Louis, before arriving at Salk where she has made tremendous contributions to understanding brain circuitry implicated in a range of mental disorders, including schizophrenia and autism. Her work was critical to Salk's receipt of a $25 million grant from the BRAIN Initiative, a five-year project designed to revolutionize humanity's understanding of the brain by systematically identifying and cataloging its many cell types.

Recognizing that scientific progress has become increasingly dependent on new technologies, Salk has set out to support scientists such as Behrens who have technology-based capabilities that can support research programs across the Institute. The Institute's senior faculty and administration established a formal research professor track to expand career advancement opportunities to staff scientists who maintain individual labs and are engaged in research that is highly collaborative with existing programs.

EIMAN AZIM SELECTED FOR MCKNIGHT SCHOLAR AWARD

Eiman Azim earned a prestigious McKnight Scholar Award for his work in neuroscience. The McKnight Foundation gives out no more than six of these awards each year to encourage "neuroscientists at early stages of their careers to focus on disorders of learning and memory." As part of the award, Azim will receive $225,000 over three years in support of his research.

Azim currently serves as an assistant professor in the Molecular Neurobiology Laboratory. His research uses a multidisciplinary approach to identify how neural circuits solve the challenges of motor control. He leverages genetic and viral tools, anatomical analysis, electrophysiological recording, imaging and detailed motor behavioral tests to advance his studies. Held in high regard for his efforts, he has also received an NIH Director's New Innovator Award, Kathryn W. Davis Aging Brain Scholar award, and is both a Pew and Searle Scholar.

Eiman Azim

Joanne Chory

JOANNE CHORY WINS GRUBER GENETICS PRIZE

Salk Professor Joanne Chory recently was named a recipient of the Gruber Foundation's 2018 Gruber Genetics Prize in recognition of her "groundbreaking work in identifying the basic regulatory and biochemical mechanisms underlying the development of plants." The award includes $500,000 for continued research, which Chory will share with Elliot Meyerowitz of Caltech in Pasadena.

Chory's efforts leading Salk's Plant Molecular and Cellular Biology Laboratory, in addition to her roles as professor, a Howard Hughes Medical Institute investigator, and the Howard H. and Maryam R. Newman Chair in Plant Biology, have been widely acclaimed. She recently was awarded the 2018 Breakthrough Prize in Life Sciences and was made a Fellow of the National Academy of Inventors. Her work focuses on creating Salk Ideal Plants, genetically modified plants that store more carbon in their root networks to help mitigate the effects of climate change, which form a key piece of Salk's Harnessing Plants Initiative.

Front row (from left): Leslie Williams, Jason Seo, Seon-Gil Yang, Rusty Gage, Ki Tae Kim, Jin Ho Han, Rebecca Newman and Richard Jiang.
Back row (from left): Chul Jun Park, Alex Myung, Justin Kim and Martin Hetzer.

SALK INSTITUTE RECEIVES $1.5 MILLION FOR ALZHEIMER'S RESEARCH FROM NANOS CO., LTD.

Korean company funds laboratory devoted to stem cell–based aging research

On May 18, the Salk Institute announced a $1.5 million gift from NANOS Co., Ltd., of the Republic of Korea to establish the NANOS Alzheimer's Disease Stem Cell Suite, which will serve as a cell bank focused on Alzheimer's. The new suite will allow Salk scientists to collect samples and data from a large number of individuals to more accurately pinpoint processes, like DNA repair, that go awry in Alzheimer's and to identify novels avenues for intervention. By collecting skin samples from hundreds of individuals and transforming these cells into neurons in the NANOS Alzheimer's Disease Stem Cell Suite, Salk scientists will be able to analyze these brain cells and test novel therapeutic compounds.

SALK RECEIVES "FOUR STARS" FROM CHARITY NAVIGATOR FOR SEVENTH CONSECUTIVE TIME

The Salk Institute's strong financial health and continued commitment to accountability and transparency have earned it its seventh consecutive four-star (out of four) rating from Charity Navigator, America's largest independent charity and nonprofit evaluator. Receiving the highest ranking puts Salk in a distinguished class of nonprofits—only 4 percent of nonprofits evaluated achieve that status seven times in a row. In a time when traditional sources of research funding are becoming more scarce and donors are increasingly attuned to how the organizations they support leverage philanthropic gifts, Salk remains committed to being a place donors can support with confidence.

nature INDEX

SALK INSTITUTE RANKED AMONG TOP 5 NONPROFITS IN THE WORLD FOR HIGH-QUALITY RESEARCH IN LIFE SCIENCES

The Salk Institute has been ranked one of the top 5 nonprofit institutions in the world focused on the life sciences and one of the top 10 nonprofits generally, according to a report, known as the Nature Index, released by Springer Nature on June 7. The rankings are based on Nature Index data from 1 January 2017 to 31 December 2017.

The Nature Index tracks by country and institution the research published in 82 high-quality science journals each year, counting both the total number of papers and the share of authorship of each paper.

The Nature Index is compiled by Nature Research and is among their wider efforts to provide the research community with relevant information about the state of global science and publishing trends. The Nature Index database was launched in November 2014 and provides a close-to-real-time proxy for high-quality research output at the institutional, regional and national levels.

salk. CONQUERING CANCER INITIATIVE

Clockwise from top: Former Vice President Joe Biden provides the keynote at the launch of Salk's Conquering Cancer Initiative; Director of Salk Cancer Center Reuben Shaw addresses the audience; Salk Board Vice Chair Marna Whittingham (left) moderates a panel of Salk Faculty members Geoffrey Wahl, Susan Kaech, Diana Hargreaves, Ronald Evans and Tony Hunter.

"Cancer research comes with its own complex mazes to navigate. That's what [Salk] has been so successful at for decades—at taking on the big challenges and delivering new breakthroughs."

— Former Vice President Joe Biden

Salk takes aim at five of the deadliest cancers

Conquering Cancer Initiative launched at special event with former Vice President Joe Biden providing keynote address

Jonas Salk used basic science to rid the world of polio and alter the course of the 20th century in a bold endeavor that changed the lives of untold millions. Now, the Salk Institute has launched a similarly bold approach to take aim at five deadly cancers: triple-negative breast, pancreatic, ovarian, lung and glioblastoma. The Conquering Cancer Initiative is a roadmap to the future of cancer care and will empower our world-renowned research team to transform cancer therapy.

The initiative was formally launched April 20 at a special event with former Vice President Joe Biden providing a keynote address to the more than 300 people in attendance.

"Cancer research comes with its own complex mazes to navigate," said Biden in his speech. "That's what [Salk] has been so successful at for decades—at taking on the big challenges and delivering new breakthroughs."

Indeed, the Institute has a long history of focusing the best minds on the most difficult problems. Ever since Jonas Salk's discovery of the first safe, effective polio vaccine, he and the Institute that bears his name have made taking on the biggest challenges a hallmark of their efforts.

Yet cancer holds a unique place in Salk's work. Since establishing the Salk Cancer Center in 1970, the Institute has had a history of cancer breakthroughs. Nobel Prize winners, such as Robert Holley (1972) and Renato Dulbecco (1975), have played key roles in Salk's efforts, as have other luminaries, such as Leslie Orgel, Walter Eckhart and Tony Hunter. The fruits of their efforts have been manifest in new treatments for leukemia and other cancers, as well as entirely new classes of drugs, such as tyrosine kinase inhibitors, which turned death sentence diagnoses into manageable chronic conditions.

More recently, new breakthroughs have paved the way for Salk researchers to take on some of the most difficult to treat cancers. Ronald Evans discovered receptors that are now targets in treatments for breast cancer, prostate cancer, pancreatic cancer and leukemia. Diana Hargreaves investigates common genetic mutations found in many solid tumor cancers to find new drug targets. Susan Kaech discovered that stimulating the CD40 receptor on immune T cells can suppress tumor growth. Geoffrey Wahl seeks to identify new therapeutic targets for drugs that can be tailored to individual cancer genomes.

The Initiative is led by Salk Cancer Center Director Reuben Shaw, himself a pioneer in exploring the links between metabolism and cancer that saw the testing of Metformin, a type 2 diabetes drug, in clinical trials for various cancers.

"The Salk Cancer Center will pursue scientific discoveries that fundamentally change the understanding, diagnosis and treatment of cancer," says Shaw.

Cancer research is at an inflection point requiring determination and collaboration among researchers and scientists to speed up progress, expedite personalized medicine and discover new treatments faster. By focusing on some of the hardest cancers to treat, Salk scientists aim to unlock foundational knowledge and develop powerful tools to help treat all cancers.

Jonas Salk said upon the founding of the Institute, "we cannot be certain what will happen here, but we can be certain it will contribute to the welfare and understanding of man." Conquering Cancer's objective remains the same.

To learn how you can join in Conquering Cancer, please visit www.salk.edu/conqueringcancer.

EVENTS

salk INSTITUTE COUNCIL

THE SALK INSTITUTE COUNCIL GATHERS TO EXPLORE NEXT-GENERATION SCIENCE

The Salk Institute Council held its annual gathering on Salk's campus. Salk ambassadors and philanthropic leaders received the latest research updates on our scientific initiatives. Attendees had an opportunity to participate in exciting discussions surrounding these presentations in addition to dinner with faculty and leadership.

LYUMKIS GOES BACK TO BASICS

Recently promoted Assistant Professor Dmitry Lyumkis presented at the most recent Salk Back to Basics event, discussing the use of cryo-electron microscopy to understand the atomic structures of viral machinery used by HIV and other illnesses to infect the body.

salk EXCELLERATORS

SALKEXCELLERATORS CONTINUE TRANSFORMING SCIENCE

Salkexcellerators are a dynamic group of influencers, based in San Diego and New York City, who share a commitment to supporting scientific discovery at Salk. As part of the program, they are invited to come to Salk and participate in lab tours and meet-and-greets with faculty who benefit from their generous support.

Salkexcellerators learn more about the science they make possible.

SALK HOSTS *URANIUM + PEACHES*

The Salk Institute was home to the premiere performance of the one-act play *Uranium + Peaches*. The event, devoted to exploring science and its social consequences, was generously underwritten by Joan and Irwin Jacobs and included a panel discussion after the play.

Dmitry Lyumkis discusses advancements in transmission electron microscopy techniques.

BEHIND THE SCIENCE HIGHLIGHTS EXCITING BREAKTHROUGHS

Several Salk faculty provided an insider's look at the May Salk Behind the Science gathering. Eiman Azim, Wolfgang Busch, Sung Han, Gerald Joyce, Susan Kaech, Gerald Shadel, and Edward Stites all presented, in addition to Salk Vice President and Chief Science Officer Martin Hetzer.

Salk President Rusty Gage presents at the Salk Behind the Science event.

EVENTS

Panelists discuss new advancements in plant biology at the Women & Science event.

SALK WOMEN & SCIENCE HONORS AWARDEES, REVEALS NEW INSIGHTS INTO CLIMATE RESEARCH

A Salk Women & Science event took place on March 21, giving attendees a chance to hear from the women who are helping usher in the next generation of breakthroughs. Additionally, 20 Salk scientists—including Professor Emerita Catherine Rivier —were awarded professional development grants. Three students, one each from middle school, junior high and high school, also were recognized.

Salk Women & Science Special Award Recipients (above, left to right): Kathleen DelGiorno, Cuiqing Zhong, Neeraja Vegesna, Shani Stern, Kathleen Quach, Rusty Gage (President), Lydia Daboussi, Emily Manoogian and Isabella Farhy-Tselnicker. Not pictured: Shefali Krishna.

THE HEITHOFF-BRODY SUMMER SCHOLARS PROGRAM

The Heithoff-Brody High School Summer Scholars program represents a lasting expression of Jonas Salk's desire to provide young learners with a foundation on which they can become scientific leaders. Participants are able to work in the labs, and they receive a stipend for their work, as well as hands-on experience. This year, 12 students participated in the program. Some of the research areas they were able to explore included stem cells, plant biology and molecular neurobiology.

Heithoff-Brody Scholars learn how to use some of the sophisticated equipment available in the Salk labs.

Salk Education Outreach

Tomorrow's breakthroughs depend on today's students and teachers

teach

the community about scientific literacy

inspire

enthusiasm and interest in science

promote

public awareness about research at Salk

Jonas Salk firmly believed that the Salk Institute had a duty to mentor the next generation of scientists. Salk's Education Outreach Department fulfills that vision and aims to meet two critical challenges: improve science literacy and stimulate students' interest in STEM careers.

Salk Education Outreach serves the entire San Diego County through its core hands-on programs. While its programs serve San Diego school children of all ages, the majority of students are from economically disadvantaged communities and are underrepresented in the STEM education and career pipeline. Over the past 40 years, the Salk Institute has worked with thousands of students, sparking their interest in science and inspiring them to pursue careers in the field.

For more information or to donate, please contact:

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EDUCATION
OUTREACH
Hands-on Science Education

Every cure begins with you.

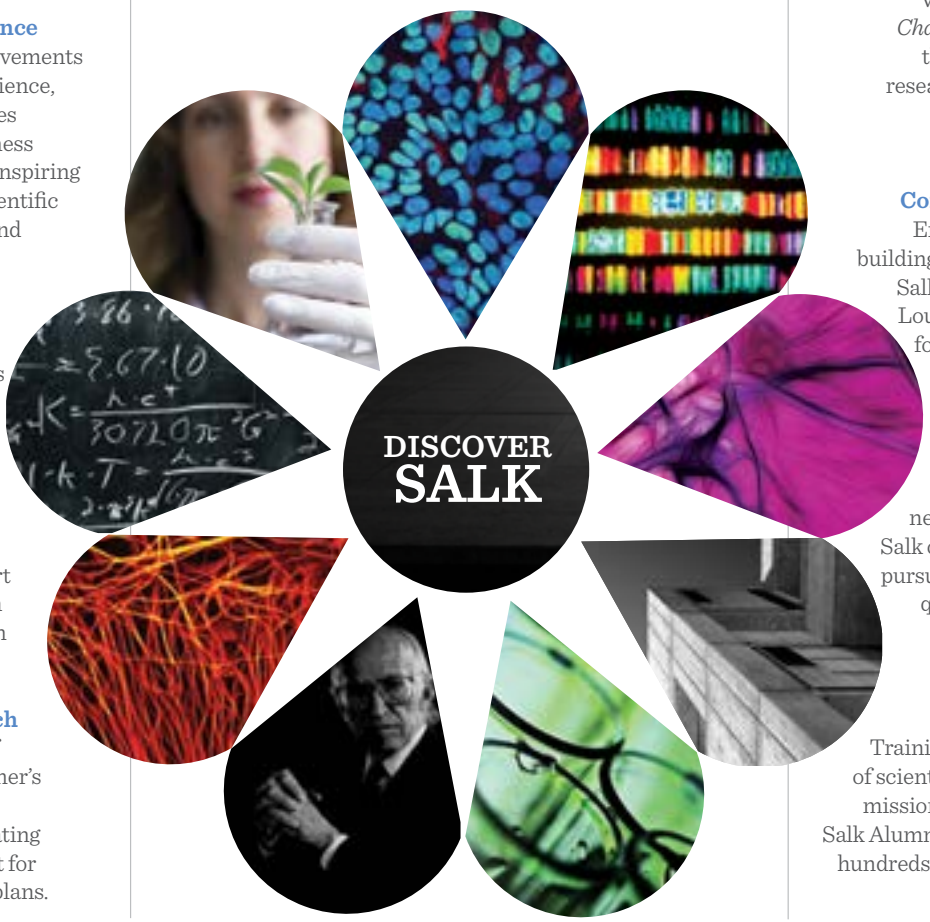
Salk giving programs offer a range of ways to get involved. Learn about Salk science and support vital research.

Education Outreach
Offering nearly half a century of programs to inspire—and launch—the next generation of scientists, Salk's Education Outreach program includes a Mobile Science Lab, High School Scholars curriculum and SciChats@Salk.

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

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.

Partners in Research
Invest in the future of cancer, aging, Alzheimer's disease and diabetes research by incorporating philanthropic support for Salk into your estate plans.



President's Club
Fuel Salk's ability to recruit top-tier scientists, acquire cutting-edge technology and embark on innovative research initiatives by joining the *President's Club.*

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

Architecture Conservation Program
Ensuring the Modernist buildings envisioned by Jonas Salk and brought to life by Louis Kahn are preserved for generations to come.

Cancer Center Director's Fund
Dedicated to spear-heading the ambitious new research directions Salk cancer researchers are pursuing in their continued quest for novel avenues into cancer therapies.

Alumni/Faculty Fellowship Fund
Training the next generation of scientists is central to Salk's mission. Contributions to the Salk Alumni program support the hundreds of research associates at the Institute.

Get involved.

Learn more about the many options for joining the Salk community by visiting **www.salk.edu/support** or calling **(858) 453-4100 x1201.**

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CALENDAR

SEPTEMBER

12 Back to Basics lecture series

OCTOBER

03 Salkexcellerators

10 Women & Science Design and Discovery

21 Salk Science & Music Series
featuring Wei Luo

27 Explore Salk: Free community open house

Salk Institute has received the highest rating 7 consecutive times from Charity Navigator, the nation's foremost charity evaluator.

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