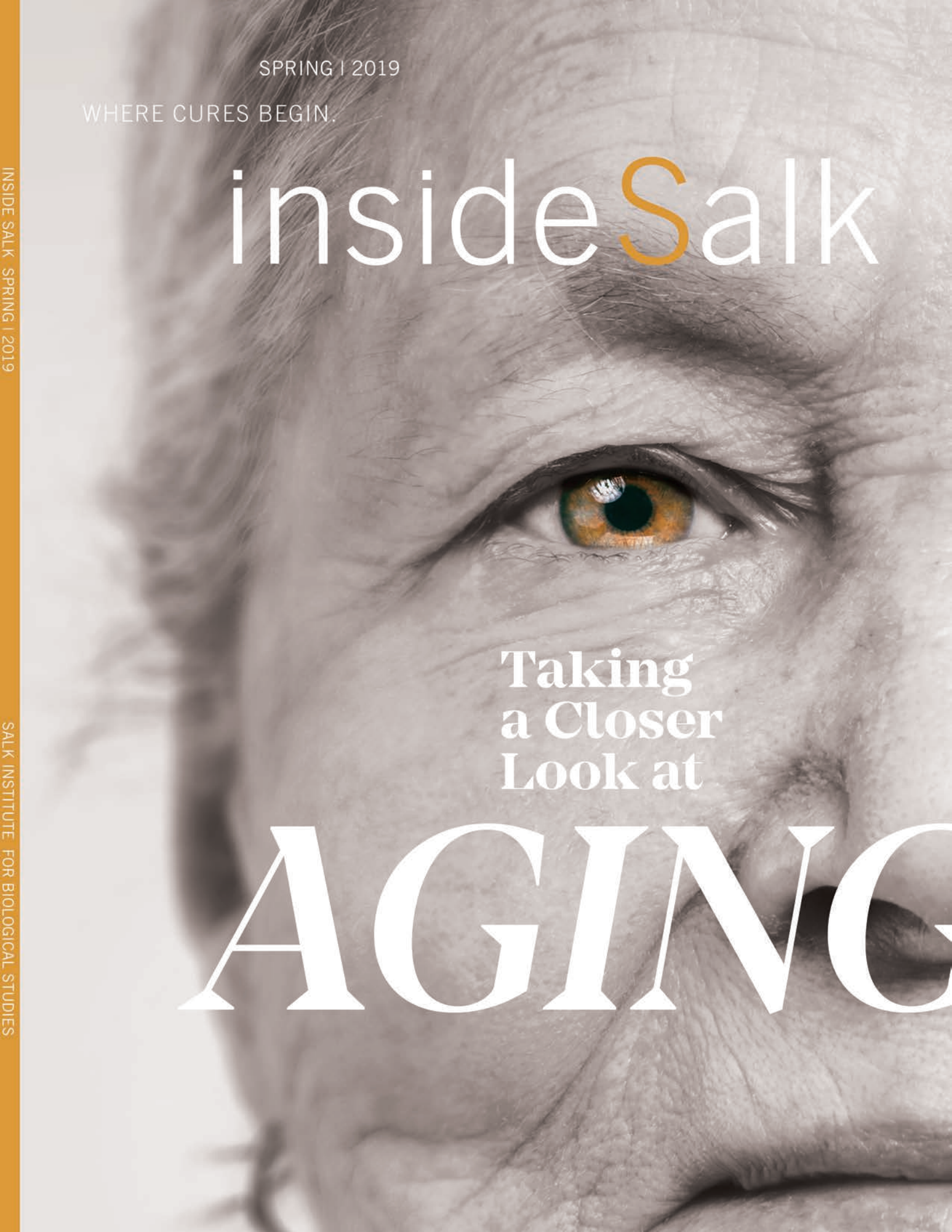
SPRING | 2019

WHERE CURES BEGIN.

insideSalk



Taking a Closer Look at AGING

INSIDE SALK SPRING | 2019

SALK INSTITUTE FOR BIOLOGICAL STUDIES

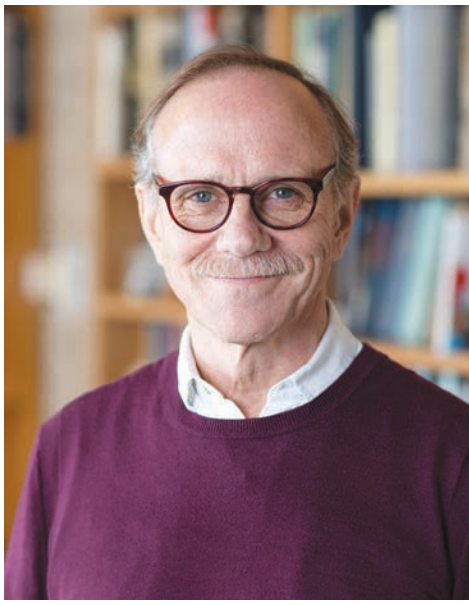

UNDERSTANDING
THE SCIENCE
BEHIND LIFE'S
GREATEST MYSTERY

CONTENTS

ON THE COVER:

Aging—loosely defined as a systems-wide deterioration of our genetic material, cells and organs that results in disease or damage—is a collective and complex process in the body. Salk scientists are paving the way to a new understanding of age-related diseases and therapies.

PRESIDENT'S LETTER



Dear Friends,

On Wednesday, March 20, as the setting sun lined up with the River of Life, spring took hold. The renowned courtyard water feature, designed to represent the constant stream of scientific discoveries spilling out from the labs into the greater body of knowledge, aligned perfectly as the setting sun sank into the horizon. If only for a brief moment, those attending witnessed a special Salk experience and participated in a symbolic transition from one season to the next. It is, and will always be, a powerful reminder of the beauty of this architectural masterwork that serves as the scientific starting point for our researchers to transform our world for the better—just as Jonas Salk encouraged us to do.

Today our efforts are focused on deploying plants to tackle climate change, identifying strategies to conquer cancer, and working to uncover the mysteries of Alzheimer's for effective interventions, just to name a few. These endeavors are the product of dedicated and passionate people pursuing scientific research in the glass, metal and concrete "cathedral to science" that we call home, regardless of the season.

For more than a year now I have had the privilege and honor to serve as president of the Institute. And while Salk has been my scientific home for more than 23 years, the view from the president's office has given me a deeper, more profound appreciation for the people, events and discoveries that comprise the larger Salk community. This experience, the selfless support of our faculty and administration, our committed and passionate community of supporters, and the confidence in me expressed by the Board of Trustees all helped shape my decision to continue in this role. Being part of Salk's past, present and future is what motivates me. It is this community of people who share a passion for asking big questions and pursuing bold ideas—a core philosophy of Salk—that inspires me. I am excited that together we will build on Jonas' desire to "dare to make dreams into reality."

"Being part of the Salk past, present and future is what motivates me. It is this community of people who share a passion for asking big questions and pursuing bold ideas—a core philosophy of Salk—that inspires me."

Within the pages of this edition of *Inside Salk* you will discover how Salk scientists are pursuing bold research on aging, pay a visit to Professor Gerald Shadel and learn more about our efforts to promote environmental sustainability at the Institute. You'll also meet some of the individuals that make this place so special and get caught up on the exciting activities from around Salk.

The future is bright for Salk because of our loyal and passionate community of supporters: people like you who care so deeply about science and how it can be used to better the world we live in. Thank you for your support of Salk and for being part of our mission. Our goal remains to leave our world better than we found it.

Sincerely,

Fred H. Gage
President

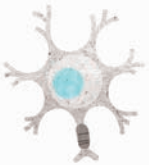
DISCOVERIES

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/news**

RESEARCH
AT SALK



NEUROSCIENCE

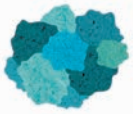
We are entering a new era in neuroscience, where our knowledge is beginning to meet the urgent need to prevent and treat diseases of the brain.

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

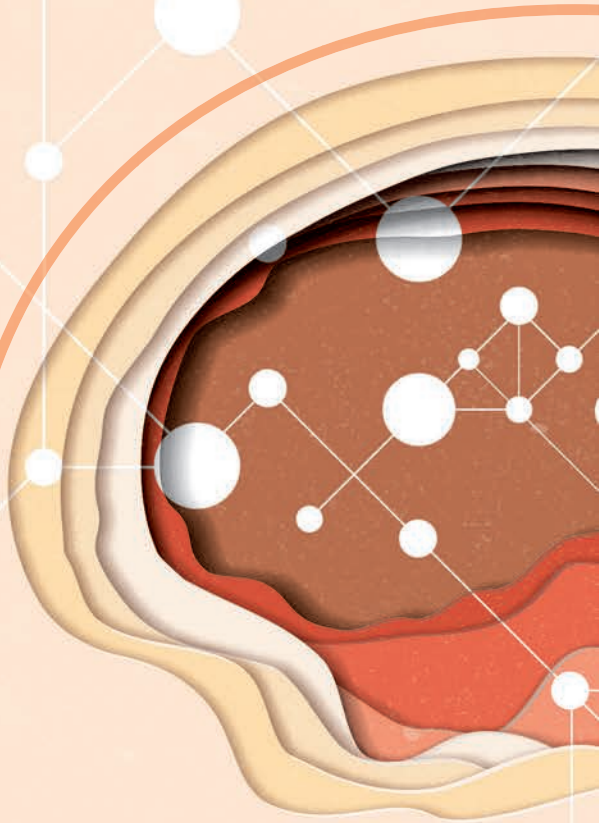
At Salk, we seek to understand human metabolism and what happens when this biological system breaks down. The problem is important as diabetes becomes more prevalent and more of a burden on an already-taxed healthcare system.

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.

NEUROSCIENCE

Busy Brain



CELL
06/2018

How the office org chart in your brain helps to organize your actions

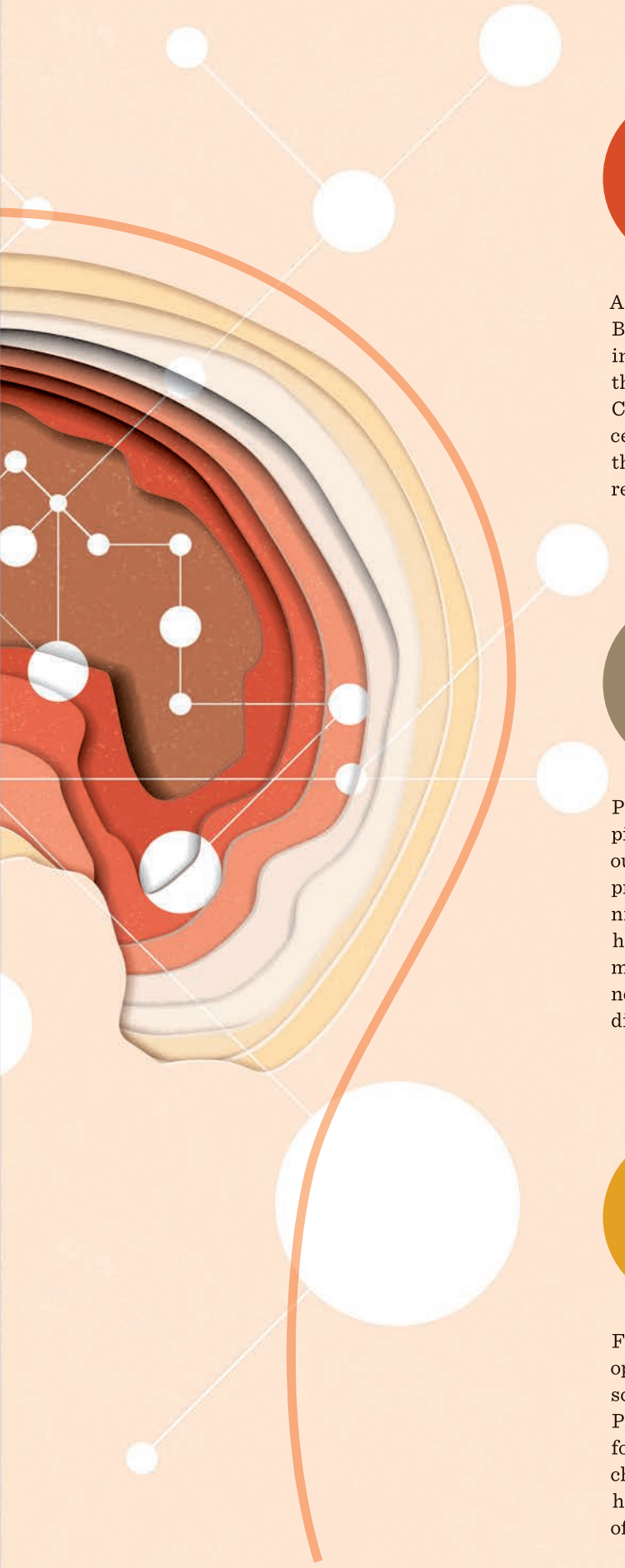
Salk researchers have resolved a long-standing scientific debate about how behavior is organized in the brain. Associate Professor Xin Jin and first author Claire Geddes, a UC San Diego graduate student, discovered that learned behavior is organized in a hierarchy with multiple levels of control, offering possible new therapeutic targets for disorders that involve an inability to control one's actions. The study used mice trained to carry out a series of lever presses in a specific order, left-left-right-right, to make the discovery.

WATCH | www.salk.edu/jin201904

NATURE NEUROSCIENCE
01/2019

Scientists reveal clues into early development of autism spectrum disorder

Autism spectrum disorder (ASD) affects roughly 1 in 59 children in the United States. Salk President and Professor Rusty Gage, first author Simon Schafer, and colleagues compared stem cells created from the skin cells of individuals with ASD against stem cells created from individuals without ASD to uncover, for the first time, measurable differences in the patterns and speed of development in the ASD-derived cells. The findings could lead to diagnostic methods to detect the disorder at an early stage.



NEURON
10/2018

Brain cells called astrocytes have unexpected role in brain "plasticity"

A Salk team led by Associate Professor Nicola Allen and first author Elena Blanco-Suarez showed that astrocytes—long-overlooked supportive cells in the brain—enable the brain's plasticity, a previously unknown role for these cells. The team found that a protein secreted by astrocytes called Chrdl1 increases the number and maturity of connections between nerve cells, enabling the stabilization of neural connections and circuits once the connections finish developing. The findings could point to ways to restore connections lost due to aging or trauma.

CELL REPORTS
11/2018

Why screen time can disrupt sleep

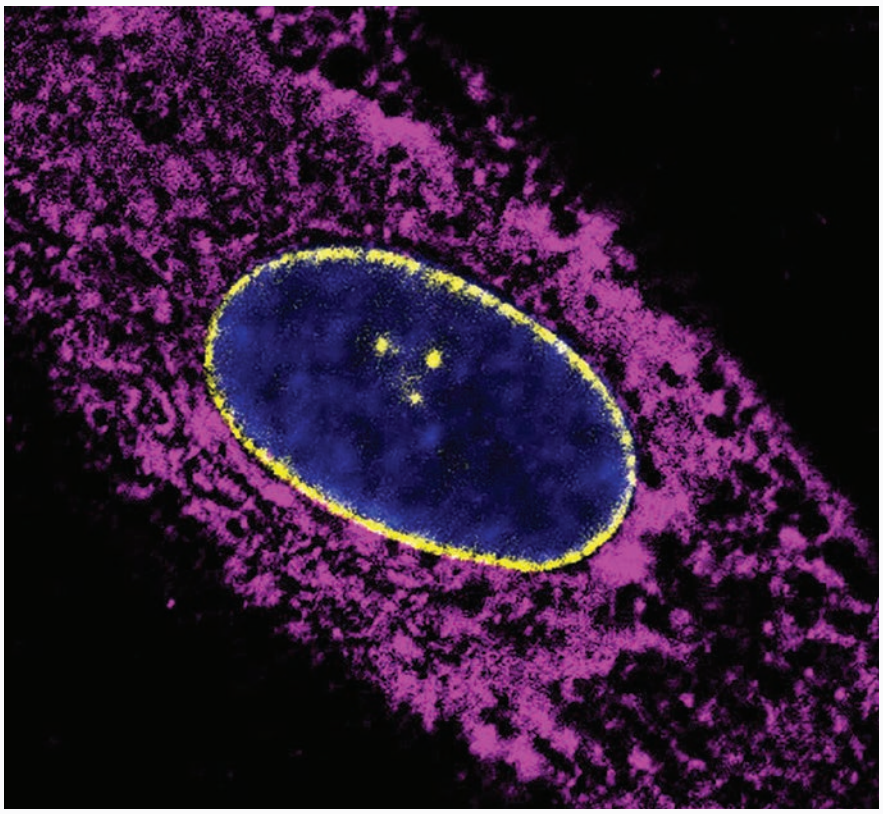
Professor Satchin Panda, first author Ludovic Mure and colleagues pinpointed how certain cells in our eyes process ambient light and reset our internal clocks, or circadian rhythms—the daily cycles of physiological processes. When these cells are exposed to artificial light late into the night, our internal clocks can become disoriented, resulting in a host of health issues. By detailing the interactions of the light-sensitive protein melanopsin and how the eyes react to light, the research may lead to new treatments for migraines, insomnia, jet lag and circadian-rhythm disorders.

NEURON
12/2018

Thriving on teamwork: new research shows how brain cells filter information in groups

For decades, scientists studying the visual system thought that neurons operated as filters. Some neurons preferred coarse details of the visual scene and ignored fine details, while other neurons did the opposite. Professor Thomas Albright, first author Ambarish Pawar and coauthors found that the same neurons that preferred coarse details were able to change to prefer finer details under different conditions. The work could help to better understand neural mechanisms that shape our perceptions of the world.

AGING



A human fibroblast cell,
derived from a skin biopsy.

AGE IS MORE THAN JUST A NUMBER: MACHINE LEARNING MAY BE ABLE TO PREDICT IF YOU'RE IN FOR A HEALTHY OLD AGE

GENOME BIOLOGY 12/2018

Assistant Professor Saket Navlakha and Vice President, Chief Science Officer and Professor Martin Hetzer, along with first author Jason Fleischer and colleagues, analyzed skin cells ranging from the very young to the very old and found molecular signatures that can be predictive of age. By better understanding the biological processes of aging, this work could help to address health conditions that are more common in advanced age, such as heart disease and dementia.

From left:
Dave Schubert
and Pam Maher

TRENDS IN PHARMACOLOGICAL SCIENCES 11/2018

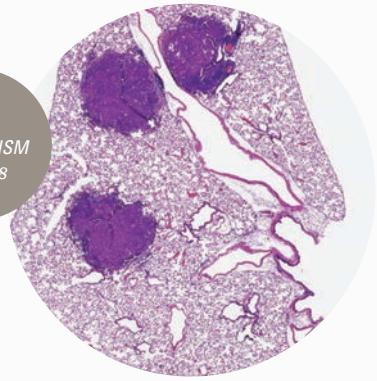
RESEARCHERS REPORT NEW METHODS TO IDENTIFY ALZHEIMER'S DRUG CANDIDATES THAT HAVE ANTI-AGING PROPERTIES

Old age is the greatest risk factor for many diseases, including Alzheimer's disease (AD) and cancer. First author and Professor David Schubert, senior author Pamela Maher and colleagues identified a unique subclass of anti-aging compounds, dubbed geroneuroprotectors. These potential AD-drug candidates slow the aging process in mice.

GENETIC "WHODUNIT" FOR CANCER GENE SOLVED

CELL METABOLISM 11/2018

Long thought to suppress cancer by slowing cellular metabolism, the protein complex AMPK also seems to help tumors grow in some cases, confounding researchers. The lab of Professor Reuben Shaw, including first author Lillian Eichner, showed that advanced cancers can trigger AMPK's cellular recycling signal to cannibalize pieces of the cell, supplying large lung tumors with the nutrients they need to grow, despite being far from blood vessels. Blocking AMPK in some conditions could stop the growth of advanced tumors in the most common type of lung cancer.



Salk research yields insight into the metabolism of lung tumors (solid purple).

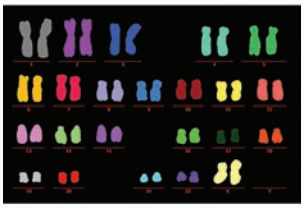
WATCH | www.salk.edu/shaw201904

IN SURPRISING REVERSAL, SCIENTISTS FIND A CELLULAR PROCESS THAT STOPS CANCER BEFORE IT STARTS

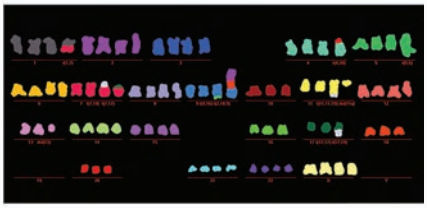
NATURE 01/2019

From left: Adriana Correia, Joe Nassour, Jan Karlseder, Robert Radford, Reuben Shaw and Javier Miralles Fusté

Cells regularly break down and recycle their components in a process called autophagy. Professor Jan Karlseder, first author Joe Nassour and colleagues made a surprising discovery: autophagy—generally thought of as a survival mechanism for both cancerous and normal cells—can actually promote the death of cells, thereby preventing cancer initiation. The work reveals autophagy to be a novel tumor-suppressing pathway and suggests that treatments to block the process in an effort to curb cancer may unintentionally promote it very early on.



The 23 pairs of chromosomes of cells in which autophagy is functioning look normal and healthy with no structural or numerical aberrations (each color represents a unique chromosome pair).

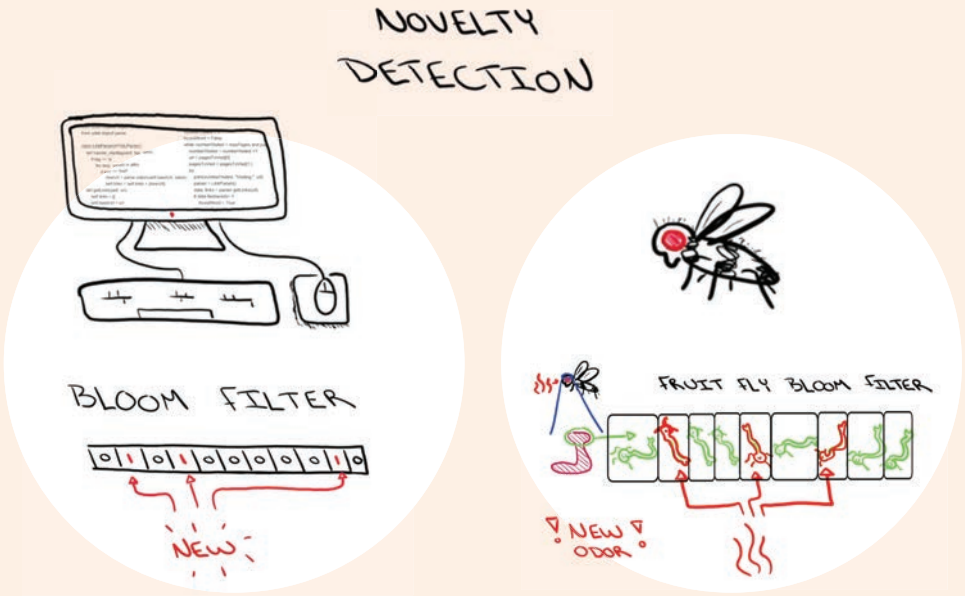


The chromosomes of cells in which autophagy is not functioning reveal both structural and numerical aberrations, with segments added to, deleted from, and/or swapped between chromosomes—a hallmark of cancer.

COMPUTATIONAL BIOLOGY

"What makes this work especially exciting to us is that it represents one of the first data structures discovered in the brain, along with a simple algorithm for how the brain may actually perform novelty detection."

SAKET NAVLAKHA



This image illustrates how flies detect novel odors using a tactic similar to that of a computer using a computational tool called a Bloom filter.

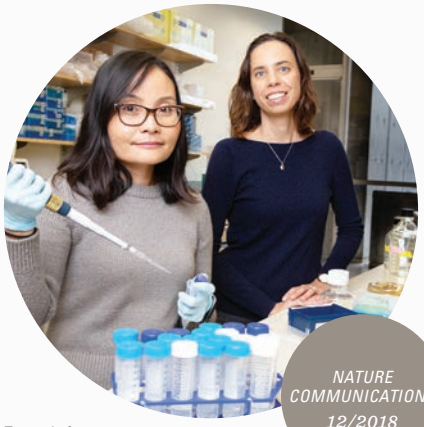
TO DETECT NEW ODORS, FRUIT FLY BRAINS IMPROVE ON A WELL-KNOWN COMPUTER ALGORITHM

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 12/2018

It might seem like fruit flies would have nothing in common with computers, but Assistant Professor Saket Navlakha and collaborators from Salk and UC San Diego found that fruit flies and computers identify novel information in similar ways.

The work not only sheds light on an important neurobiological problem—how organisms detect new odors—but also could improve algorithms for novelty detection in computer science.

WATCH | www.salk.edu/navlakha201904



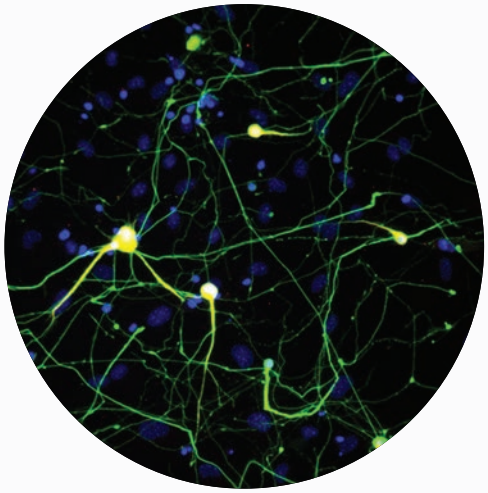
From left:
Jovylyn Gatchalian and
Diana Hargreaves

NATURE COMMUNICATIONS 12/2018

MAINTAINING THE UNLIMITED POTENTIAL OF STEM CELLS

Embryonic stem cells (ESCs) are the very definition of being full of potential, given that they can become any type of cell in the body. But once they start down the process of turning into a particular type of tissue, they lose their unlimited potential. Assistant Professor Diana Hargreaves, first author Jovylyn Gatchalian and colleagues discovered a new protein complex that keeps the brakes on stem cells, allowing them to maintain their indefinite potential to become any cell type. The new complex, called GBAF, could provide a future target for regenerative medicine.

WATCH | www.salk.edu/hargreaves201904



Induced neuronal cells

RESEARCH CONFIRMS NERVE CELLS MADE FROM SKIN CELLS ARE A VALID LAB MODEL FOR STUDYING DISEASE

LIFE 01/2019

Professor Joseph Ecker, co-first author Chongyuan Luo and collaborators at Stanford University and Baylor College of Medicine showed that cells induced to grow into nerve cells have molecular signatures matching neurons in the brain.

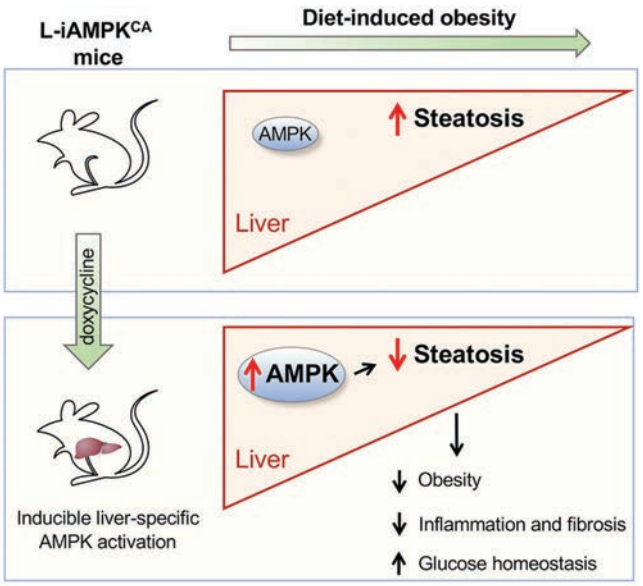
The study opens the door for better ways to model an individual patient's disease and could help advance research into gene therapies that are derived from a patient's own cells.

"This research is charting the path for the most optimal way of creating neurons in the lab."

JOSEPH ECKER

From left: Joseph Ecker and
Chongyuan Luo

METABOLISM



When Salk scientists used the antibiotic doxycycline to activate AMPK in the livers of obese mice, steatosis–the accumulation of fat in the liver–declined. Mice also had lower levels of obesity and inflammation, and healthier blood sugar levels.

SALK SCIENTISTS UNCOVER THE HEALTH EFFECTS OF METABOLIC "MAGIC BULLET" PROTEIN

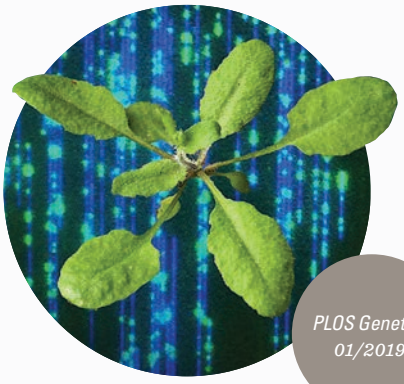
Cell Reports 01/2019

The metabolic protein AMPK has been described as a kind of magic bullet for well-being because it can improve cardiovascular health, treat mitochondrial disease and even extend life span.

Now, Professor Reuben Shaw, first author Daniel Garcia and collaborators have developed a new system that lets them study in detail exactly how, where and when AMPK carries out its molecular and therapeutic functions.

"This model will allow us to answer questions that scientists could not answer before. It really gives us a new way to define the health benefits of this specific enzyme in a wide variety of diseases."

REUBEN SHAW



PLOS Genetics
01/2019

An *Arabidopsis* plant overlaying DNA molecules of the T-DNA-transformed *Arabidopsis* genome.

NEW TECHNOLOGIES ENABLE BETTER-THAN-EVER DETAILS ON GENETICALLY MODIFIED PLANTS

Professor Joseph Ecker, along with co-first authors Florian Jupe, Angeline Rivkin, Mark Zander and Todd Michael (of the J. Craig Venter Institute) and colleagues mapped the genomes and epigenomes of genetically modified plant lines with high resolution to show what happens at a molecular level when a piece of foreign DNA is inserted. Their findings not only elucidate the routine methods used to modify plants but also offer new ways to minimize potential off-target effects.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES
12/2018

"Just as a building with structural damage can be unsafe, cells with DNA damage that goes unnoticed or unrepaired can be dangerous."

JULIE LAW

TO REPAIR DNA DAMAGE, PLANTS NEED GOOD CONTRACTORS

Associate Professor Julie Law and first author Clara Bourbousse showed which genes are turned on or off, and in which order, to protect and repair the genome in response to DNA damage.

The research reveals the genetic framework controlling a complex biological process that has broad implications for understanding how plants in particular, and organisms in general, cope with DNA damage to ensure long-term health and fitness.

The science of aging

Salk scientists are solving the mysteries of optimal aging for the body and mind

Jeanne Calment, a Frenchwoman born in 1875, stayed physically active and mentally alert until passing away at almost 123 years of age. She outlived her daughter and her grandson and has been recognized as the longest-living human. She cycled regularly until she sustained a leg fracture at age 100; smoked a daily cigarette until 117; and enjoyed "considerable" quantities of chocolate until her death.

Aside from Calment, a handful of people worldwide lived well into their 110s. Researchers have scrutinized the habits of these supercentenarians, but such long-lived humans have surprisingly little in common, aside from the observation that women tend to live longer than men.

So what is their secret?

What we know about longevity so far: Minimizing smoking, obesity and overeating while maximizing exercise and social interactions seem to correspond to longer and healthier lives, but not always. While many factors have been touted as panaceas for extending life—everything from adhering to a Mediterranean diet to regularly imbibing red wine—a "fountain of youth" has remained stubbornly elusive.

"Aging is such a profound part of not only the human experience but all life on Earth," says Salk Vice President/Chief Science Officer Martin Hetzer. "It's one of the big, untapped opportunities in biomedical research, particularly around questions on what role exercise, nutrition and cognitive stimulation play in staying healthy throughout life. It is important not to forget that getting older also comes with benefits; we want to take a holistic view of human health at all ages and understand it from all angles."

Scientists want to answer intriguing questions: Why are some people able to "age well," trekking up mountain ranges or rafting through white water in their nineties, while others live just as long, disease-free, but grow inexplicably frail decades sooner? Worse yet, why does advanced age sometimes diminish cognitive ability or even lead to dementia?

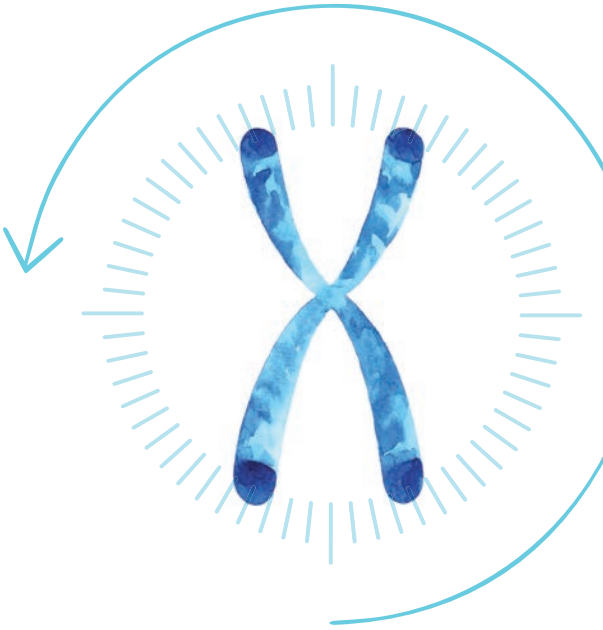
"It appears that many factors talk to each other and influence the whole system of the body in relation to aging. Here at Salk we are well positioned to get to the bottom of this 'crosstalk' of aging because labs in different specialties are working closely together."

JAN KARLSEDER

In numerous diseases, age itself is the major risk factor. Cancer, Alzheimer's, heart disease and many other afflictions become profoundly more likely the older we get. Aside from extending our life spans, scientists want to know how we can also extend our health during advanced age. What is emerging from research is that aging—loosely defined as a systems-wide deterioration of our cells, organs and genetic material that results in disease or damage—is a collective and complex process in the body.

"While we know that exercise and dietary restriction generally increase the lifespan of an organism, the molecular mechanisms are still unknown," says Professor Jan Karlseder, director of the Paul F. Glenn Center for Biology of Aging Research at Salk. "It appears that many factors talk to each other and influence the whole system of the body in relation to aging. Here at Salk, we are well positioned to get to the bottom of this 'crosstalk' of aging because labs in different specialties are working closely together."

Salk Institute researchers are forging new partnerships across fields—computer science, genetics, epigenetics, neuroscience, immunology and other areas of molecular biology—in order to spearhead ambitious studies to reveal how we can live longer and healthier. These scientists are diving into molecular, genetic, cellular and systems-wide processes in the body; peering into the fundamental workings of cells; and developing cutting-edge techniques to replace and repair failing organs and tissues. Together, Salk scientists are paving the way for a new view of age-related diseases and pointing to therapies to extend our healthy lifespan.



CELLS

Telomeres—a ticking clock in cellular aging

Telomeres, the protective tips at the ends of chromosomes, are a focal point in the field of aging. The length of telomeres, which consist of repetitive pieces of DNA encased in proteins, is tied to a cell's—and an organism's—well-being.

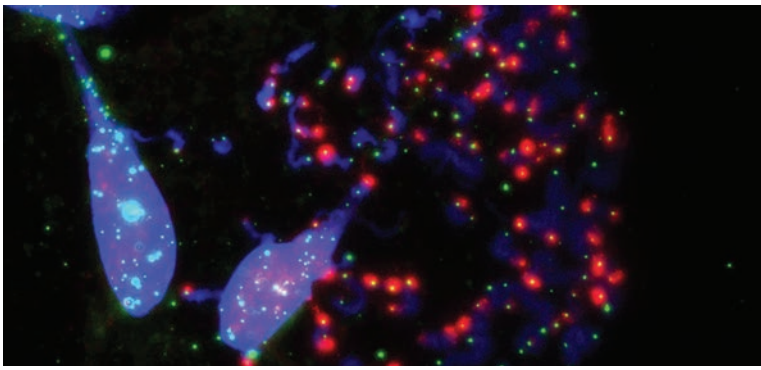
When cells replicate their DNA and divide, a small portion of each telomere is whittled away. This shortening acts as a ticking clock for cells, prompting cells to stop dividing as a way to prevent duplicating damaged DNA. That is bad news when it comes to maintaining our lungs, skin, liver and several other organs, which need to be continually replenished by stem cells throughout our life. Fortunately, stem cells produce an enzyme called telomerase, which can partially counteract this telomere erosion. But even stem cells cannot completely escape this cell-division clock, so they eventually succumb to the consequences of telomere loss.

If we can stop telomere erosion, scientists reason, maybe we can add time to the ticking clock affecting the health of our cells.

"All of us have heard stories about a relative or neighbor who had a nightly shot of bourbon and a cigar into their nineties and were just fine," says Salk Professor Vicki Lundblad, holder of the

"Our research suggests that a delicate balance between activities that elongate telomeres—such as telomerase—and the newly discovered erosion genes we have uncovered might dictate whether we can all live into our nineties, even with the nightly shot of bourbon."

VICKI LUNDBLAD



Salk researchers show how the disabled protection of ends of chromosomes (blue) called telomeres (green) during cell division prompts cell death. This happens when the telomere-protecting protein, TRF2, is inhibited.

Becky and Ralph S. O'Connor Chair. "Those aren't tall tales; some humans break all the so-called rules and live a healthy and long life. We want to know if telomeres shorten more slowly in these people, enabling them to live decades longer than someone else with the same lifestyle."

Lundblad, who serves as associate director of Salk's Glenn Center, has recently developed a new methodology to observe at a very high resolution how telomeres change in length. Using this technique, her group has uncovered a wide category of genes, not previously implicated in telomere biology, that alter the rate at which telomeres shorten. In addition, Lundblad has gained insights into mechanisms that contribute to the erosion of telomeres.

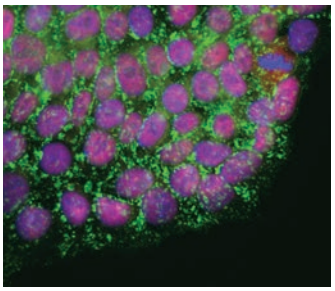
"Our research suggests that a delicate balance between activities that elongate telomeres—such as telomerase—and the newly discovered erosion genes we have uncovered might dictate whether we can all live into our nineties, even with the nightly shot of bourbon," Lundblad says.

Other research at Salk has shown that long telomeres aren't necessarily always a good thing.

"In recent work we found that forcing cells to generate overly long telomeres can lead to stress and likely the initiation of cancer, indicating the need for a better understanding of the complexity of telomeres," says Karlseder, who holds the Donald and Darlene Shiley Chair. If a telomere doesn't have the right protein composition regardless of length, the cell suffers, indicating that lengthening telomeres to reverse signs of aging is not as simple as it might seem.

In addition to exploring how telomere function and other DNA repair activities change with age, Karlseder is collaborating with Salk Professor Gerald Shadel, an expert in mitochondria, the energy factories of the cell (See this issue's "Observations" article to learn more about Shadel's research). The duo wants to explore the potential crosstalk between cellular processes related to damage of a cell's DNA and its mitochondria.

"Somehow signals from the nucleus, which recognizes that it's aging through telomere shortening, get to the mitochondria to change the energy metabolism seen in aging cells," says Karlseder. He is also exploring telomere activity in brain cells. "This is a completely unexplored area, a better understanding of which could inform treatments for a range of age-associated diseases, including dementia," he says.



Salk scientists discover details into the optimal telomere length of human induced pluripotent stem cells (shown), a finding that could help advance stem cell-based therapies related to aging.

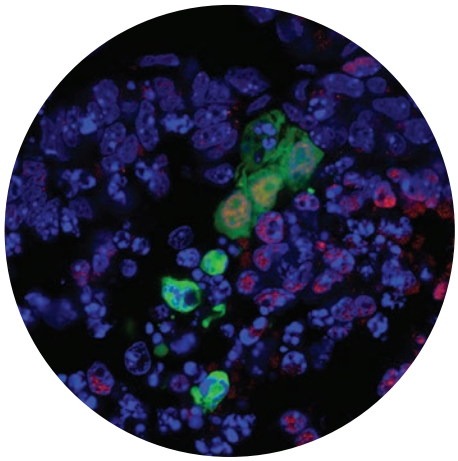
"In recent work we found that forcing cells to generate overly long telomeres can lead to stress and likely the initiation of cancer, indicating the need for a better understanding of the complexity of telomeres."

JAN KARLSEDER

ORGANS

Deciphering—and reversing—signs of aging in organs

A human stem cell is shown in green integrating and developing into the surrounding cells of a mouse embryo. The new type of stem cell holds promise for one day growing replacement tissues.



While one critical area of study in the field of aging involves studying telomeres in dividing cells, the body is full of cells that seldom replicate, such as those in the brain, heart, bones and pancreas. These long-lived cells have different pathways of aging, and must protect their DNA from damage and threats.

"It turns out that organs age at different rates, in part because they have unique strategies to maintain their integrity over time," says Hetzer, who holds the Jesse and Caryl Philips Foundation Chair.

Hetzer studies changes in these cells—specifically their nuclei and mitochondria—as they age. He looks at the security membrane around the nucleus and why it malfunctions and mistakenly lets in dangerous molecules as the cell ages, as well as how components called long-lived proteins contribute to a cell's health and degeneration over time.

Recently, Hetzer partnered with computer scientist and Salk Assistant Professor Saket Navlakha to determine people's age based on biomarkers in their cells. Published in *Genome Biology* in December 2018, the study sampled a type of long-lived skin cell from over 100 people ages 1 to 94. By blending the expertise of molecular biology; machine-learning algorithms; and a technology called RNA-Seq, the team was able to identify the age of a person based on changes in expression across the cells' genomes.

Next, the researchers plan to look for biomarkers in other cell types and see whether this analysis could be used to predict age-related

"As we continue to develop stem-cell models of human aging and aging-associated diseases and discover new drivers of aging, we are very optimistic for our work's potential to extend lifespan and promote healthy aging."

JUAN CARLOS IZPISUA BELMONTE

health conditions, determine aging changes during times of stress, and even develop targeted interventions.

In another approach to combating organ and tissue aging, Salk Professor Juan Carlos Izpisua Belmonte is developing stem-cell-based techniques to create therapies that can halt and, in some cases, even reverse signs of aging.

Stem cells have the ability to become virtually any cell in the body. After development, we retain limited reserves of specialized stem cells throughout adulthood to help replenish our tissues and organs, but scientists believe that harnessing the power of stem cells could lead to ways to repair or replace aging organs.

Izpisua Belmonte's team starts with induced pluripotent stem cells—cells taken from an organ (skin, typically) and coaxed to revert back to a stem-cell-like state using a mixture of signaling proteins called Yamanaka factors. Since the discovery of Yamanaka factors, labs throughout the world have used induced pluripotent stem cells for research because, like embryonic stem cells, they are capable of dividing indefinitely and becoming almost any cell type.

But, as with telomerase, too much of a supposedly good thing can be bad. Attempts to introduce Yamanaka factors into cells inside the body to encourage them to take on stem-cell-like properties and regenerate tissue have failed—until recently.

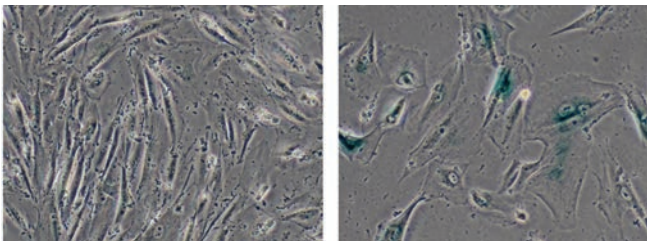
In December 2016, the Izpisua Belmonte lab published a landmark study in *Cell*, showing for the first time that by exposing cells to Yamanaka factors for short periods of time, the researchers were able to keep cells stable while reversing age-associated hallmarks. In mice with Hutchinson-Gilford progeria syndrome (a genetic disorder also found in humans that causes accelerated aging), the results were striking: Compared with untreated mice, the reprogrammed mice looked younger; their cardiovascular function and the function of other organs improved; and, most surprisingly, the mice lived 30 percent longer yet did not develop cancer. Additionally, when this cyclic introduction of the Yamanaka factors was applied to normally aged mice, the team saw improved regenerative capacity of the pancreas and muscles.

"Our work showed that aging is a very dynamic and plastic process and therefore will be more amenable to therapeutic interventions than we previously thought," Izpisua Belmonte says.

The lab is pursuing another solution for organ failure associated with aging and disease: Izpisua Belmonte's 2017 *Cell* paper, which made international headlines, provided the first proof-of-concept study for how functional organs from one species can be grown in another—an early step in addressing the critical shortage of human donor organs available for transplant. His lab was successful in both growing rat organs in a developing mouse and in integrating human cells and tissues in early-stage pig and cattle embryos, marking the first step toward the generation of transplantable human organs using large animals whose organ size, physiology and anatomy are similar to humans'.

"As we continue to develop stem-cell models of human aging and aging-associated diseases and discover new drivers of aging, we are very optimistic for our work's potential to extend lifespan and promote healthy aging," Izpisua Belmonte says.

In addition to these stem-cell approaches, the lab is developing technologies related to genome and epigenome editing that allow for the activation of genes without creating breaks in DNA. In a study published in December 2017 in *Cell*, Izpisua Belmonte's lab reported on a new technology that can be used to treat age-associated diseases that are caused by abnormal gene expression. And in a 2019 *Nature Medicine* paper, the lab used the CRISPR/Cas9 technology to prevent the accumulation of progerin, a toxic form of the lamin A protein, in mice with progeria.



Salk scientists compare normal cells (left) to cells associated with a genetic disorder that leads to premature aging (right). The deterioration of bundles of DNA is seen in the prematurely aging cells, giving new clues to age-related disease.

BRAIN

Saving the brain from cognitive decline and Alzheimer's

Generating new pancreatic tissue is one thing, but how does one repair an aging or damaged brain?

Alzheimer's disease, for example, represents a global health crisis with tens of millions of people afflicted, and the number of cases expected to grow. Aside from the disease being a public health burden worldwide, the erosion of one's mind is terrifying and isolating for those afflicted and is devastating for families. Cognitive decline is one of the top fears of people over 50, according to a recent survey by AARP.

Currently, there is no cure for Alzheimer's and other age-related dementias, but Salk scientists are working to change that.

Professor David Schubert, together with Senior Staff Scientist Pamela Maher, Staff Scientist Antonio Currais and colleagues, created a way to screen compounds from plants for their ability to protect and help recover damaged brain cells. With this technique, the lab can sift through thousands of molecules and pick out compounds for drugs to target neurodegenerative disease. The team can then home in on these molecules and, in some cases, make them more therapeutic by tweaking their chemical properties through medicinal chemistry.

"Age-related disease, particularly neurodegeneration, is one of the most pressing issues facing modern society ... I believe we will start to see effective treatments emerge."

RUSTY GAGE

Using this method, the Salk team has uncovered a handful of compounds that show promise for improving neural health and protecting against dementia, including fisetin, found in fruits and vegetables; curcumin from turmeric; and, most recently, a chemical called sterubin from a California plant called Yerba santa. These explorations are paying off: a curcumin derivative the team developed, called J147, is now in clinical trials for Alzheimer's. J147 and the other drug candidates appear to reduce many of the toxicities that occur with aging and engage the same molecular pathways as several other anti-aging approaches (such as calorie restriction), according to Schubert.

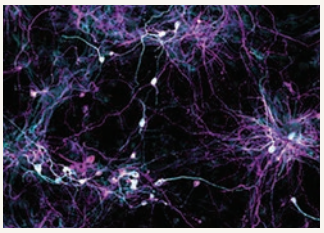
130M*

people will be living with dementia by 2050

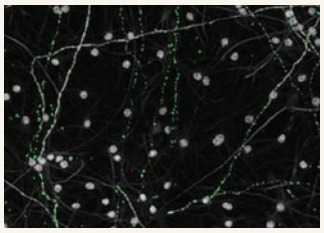
*Source: Alzheimer's Disease International

$19.2M

awarded to 10 Salk labs to research age-related cognitive decline



Salk scientists developed a technique to grow aged brain cells from patients' skin (shown) while retaining cellular signatures of aging. The new technique will enable better studies of age-related disease.



Salk researchers discovered that neurons (gray) from older individuals had impaired mitochondria (green) and reduced energy production, a finding that could reveal more about the link between mitochondrial dysfunction and age-related brain diseases.

"We have found a number of plant-derived molecules offer a range of protective properties, with many resulting in improved cognition in animal models of Alzheimer's," Schubert says. "These have the potential to be affordable and effective treatments for the disease, and, perhaps most importantly, they extend lifespan in model organisms and may delay or prevent the diseases of aging in humans."

Salk research on Alzheimer's continues to gain steam. In May 2018, the Institute received $1.5 million from the Korea-based company NANOS to establish the NANOS Alzheimer's Disease Stem Cell Suite. This dedicated laboratory space enables Salk scientists to collect and store samples and data from a large number of individuals to more accurately pinpoint processes, like DNA repair, that go awry in Alzheimer's disease.

Additionally, in November 2018, the American Heart Association-Allen Initiative in Brain Health and Cognitive Impairment awarded a team of 10 Salk labs $19.2 million over eight years to investigate mechanisms underlying age-related cognitive decline.

This unprecedented, interdisciplinary effort, led by President Rusty Gage, approaches age-related cognitive decline as a failure of complex, interdependent biological networks in our bodies that break down over time. These systems include metabolism, immunology and inflammation, genetics and epigenetics and protein interactions. By understanding why a breakdown in one of these systems causes a domino-like crash resulting in devastating dementia, the team aims to reveal new targets for therapeutic research and biomarkers of early-stage cognitive decline.

The Salk research teams are forging new tools and techniques to explore these interconnected networks and this cellular crosstalk. Novel cell cultures and brain organoids, a new primate model of cognitive aging, and state-of-the-art machine-learning algorithms will allow scientists to better understand how the brain ages.

"We are hopeful that, by looking into the role of inflammation and other cellular processes in Alzheimer's, we can find breakthroughs humanity so desperately needs," says Professor Susan Kaech, director of Salk's NOMIS Center for Immunobiology and Microbial Pathogenesis, holder of the NOMIS Chair, and a member of this project's leadership team.

In addition to Gage, Hetzer, Kaech, Karlseder, Navlakha and Shadel, other Salk investigators on the grant include Nicola Allen, an expert in supportive brain cells called astrocytes, Joseph Ecker, who has made groundbreaking discoveries in epigenetics, John Reynolds, who uses new models to chart the brain, and Reuben Shaw, who directs Salk's Cancer Center and is an expert in cellular metabolism.

"Age-related disease, particularly neurodegeneration, is one of the most pressing issues facing modern society," says Gage, who holds the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease. "By exploring the effect of these biological systems on one another, as well as incorporating a strong computational piece to analyze all of the new data, I believe we will start to see effective treatments emerge."

With the advent of new technologies, bold efforts and innovative collaborations, Salk scientists are optimistic that these—and many other—endeavors will lead to longer, healthier lives.

ANALYSIS

Sustainability *SALK STYLE*

Since its inception in 1960 by the developer of the first effective polio vaccine, Jonas Salk, and world-renowned architect Louis Kahn, the Salk Institute has been a monument to science and innovation for the ages.

ENERGY

More than 2,300 photovoltaic panels cover 100 percent of available roof space on the Institute's main buildings, providing almost half a megawatt of power on the sunniest days—the energy equivalent of powering nearly 400 homes.

The Institute's four electric-vehicle charging stations are kept busy by the several dozen electric cars owned by Salk faculty and staff.

WATER

A mix of California native plants and other drought-tolerant vegetation reduces the amount of water needed for landscaping. Additionally, tree trimmings are recycled and used as chippings and compost around the grounds to help retain precious moisture in the soil.

A 250-thousand gallon underground cistern collects rainwater to replenish the "River of Life" and the fountain at its west end.

Inside the buildings, water-conserving faucets are standard.

SUSTAINABLE RESTORATION

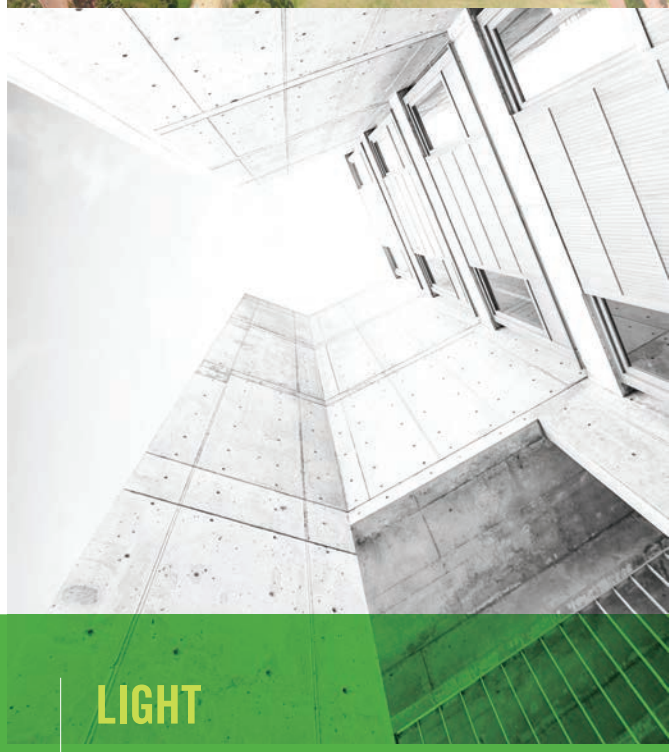
Since 2003, the Institute has incorporated sustainable design strategies for renovation and construction projects. The Institute's iconic teak window-walls, which needed attention after 50 years of exposure to the elements, were painstakingly restored in 2017 in collaboration with the Getty Conservation Institute, preserving 75 percent of the original hard-to-source wood.

Below: Electric cars parked at the Institute's charging stations. Right: A bird's eye view of the Institute's rooftop solar panels.

Salk and Kahn's collaborative genius resulted in a building that isn't just an architectural masterpiece drawing admirers from across the globe, but it is also the very embodiment of sustainable principles. Environmentally the Institute was, and continues to be, ahead of its time by using sustainable practices that cut its carbon footprint.

Kahn chose materials for the Institute that he thought would endure—concrete, steel and teak. But equally important to the Institute's durability is what Salk called "an investment in flexibility." This flexibility has enabled the Institute to adapt to the ever-changing needs of science and technology, while conserving natural resources.

WATCH	www.salk.edu/buildings-of-wonder



GREEN ROOFS

What looks like lawns on the north and south sides of the Institute are actually green roofs over Salk's central plant and other underground facilities. Green roofs offer many environmental benefits, including preserving roof materials from life-shortening exposure to sunlight, reducing rainwater runoff (which can pollute waterways and burden sewers) and improving air quality by trapping dust and other airborne particles. They also provide spaces for picnics, volleyball, soccer and other activities.

GREEN PRODUCTS AND PARTNERS

The Institute looks at purchasing "green" products as a first choice. For example, the Facilities Department selects hand soap and cleaning products that are certified green, biodegradable and nonpolluting, so that they can go into the waste stream without causing environmental damage.

Salk's landscaping contractor, Heaviland Landscape Management, uses quiet, non-polluting, electric mowers and blowers to keep the Institute's surroundings immaculate.

Paper, plastic and battery recycling is practiced Institute-wide.

LIGHT

Kahn's ingenious design included large windows and "light wells" to take advantage of natural daylight and reduce the need for artificial illumination. Today, the labs are additionally fitted with efficient, motion-sensing LED lighting, so that electricity is not wasted illuminating empty spaces whether day or night.

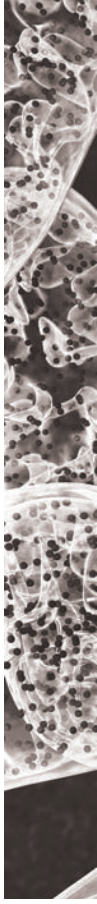
OBSERVATIONS

Gerald Shadel explores stressed-out mitochondria

When Gerald Shadel gives public talks, he likes to begin by posing a question to the audience. *"Who remembers what mitochondria are?"* he prompts. *"The powerhouse of the cell!"* people tend to respond in enthusiastic unison.

Mitochondria have that memorable moniker for their role in converting carbohydrates and fats in our food into a high-energy chemical called ATP, which fuels all the activities in our cells.

Because of that fundamental metabolic role, mitochondrial dysfunction is associated with many common diseases, including cancer, heart disease, diabetes, autoimmunity and neurodegeneration (also known as dementia). And underpinning them all is aging, whose pathologies—such as hearing loss or muscle wasting—closely overlap with those of mitochondrial diseases. By studying mitochondrial function in both disease and health, Shadel seeks to gain insights into both aging and longevity.



Inside Salk sat down with Shadel to find out how he became interested in mitochondria, what he is driven by scientifically and what he has learned about aging along the way.

How did you begin studying mitochondria?

GS For my PhD, I studied a form of communication in bacteria called quorum sensing, which is regulated by a unique gene-expression circuit. For my postdoctoral studies, I wanted to move into more complex organisms. I guess I sort of stopped halfway and decided to study mitochondria in yeast and human cells. Mitochondria are basically bacteria within our cells, being derived from an ancient bacterium billions of years ago, with their own DNA called mtDNA. I continue to study how the genes in this mtDNA are expressed, but the majority of my lab is now working on how stressed-out mitochondria are involved in diseases, aging and the immune system in mammals.

In early 2018, you were recruited to Salk from Yale University via the Rockstar Fund. What drew you to the Institute?

GS One of my long-standing interests is in the molecular mechanisms of aging. Yale is a great place, and I was the director of the Center for Research on Aging there. But when I was deciding whether to come to Salk, I asked myself, "What is it I would do at Salk that's new?" I knew about the Institute's strength in neurobiology, and mitochondria are clearly involved in age-related neurodegeneration, so I saw it as an opportunity to get into that research space. The Salk community has really embraced me. It's clear they want me to forge into new areas, and I already feel like an integral part of what's going on here. I am especially excited to be involved, along with nine other Salk investigators, in the $19.2 million American Heart Association-Allen Initiative grant on aging and Alzheimer's disease.

That sounds pretty ambitious. Will you have time for other projects?

GS It is ambitious, but it is a collaborative effort between many labs. Simultaneously, I will pursue multiple other research fronts. In my lab, I have an awesome group of dedicated people who are all smart, work hard and work well together. We have a new way of thinking about the role of mitochondria in aging and disease that has to do with molecules known as reactive oxygen species, which are toxic by-products of the process by which mitochondria make ATP. These molecules are normally thought of as being damaging to cells, but my lab is finding they actually have a second function, which is to act as signaling molecules that can lead to beneficial adaptive responses.

So a normally toxic by-product of the cell can be beneficial? How does that work?

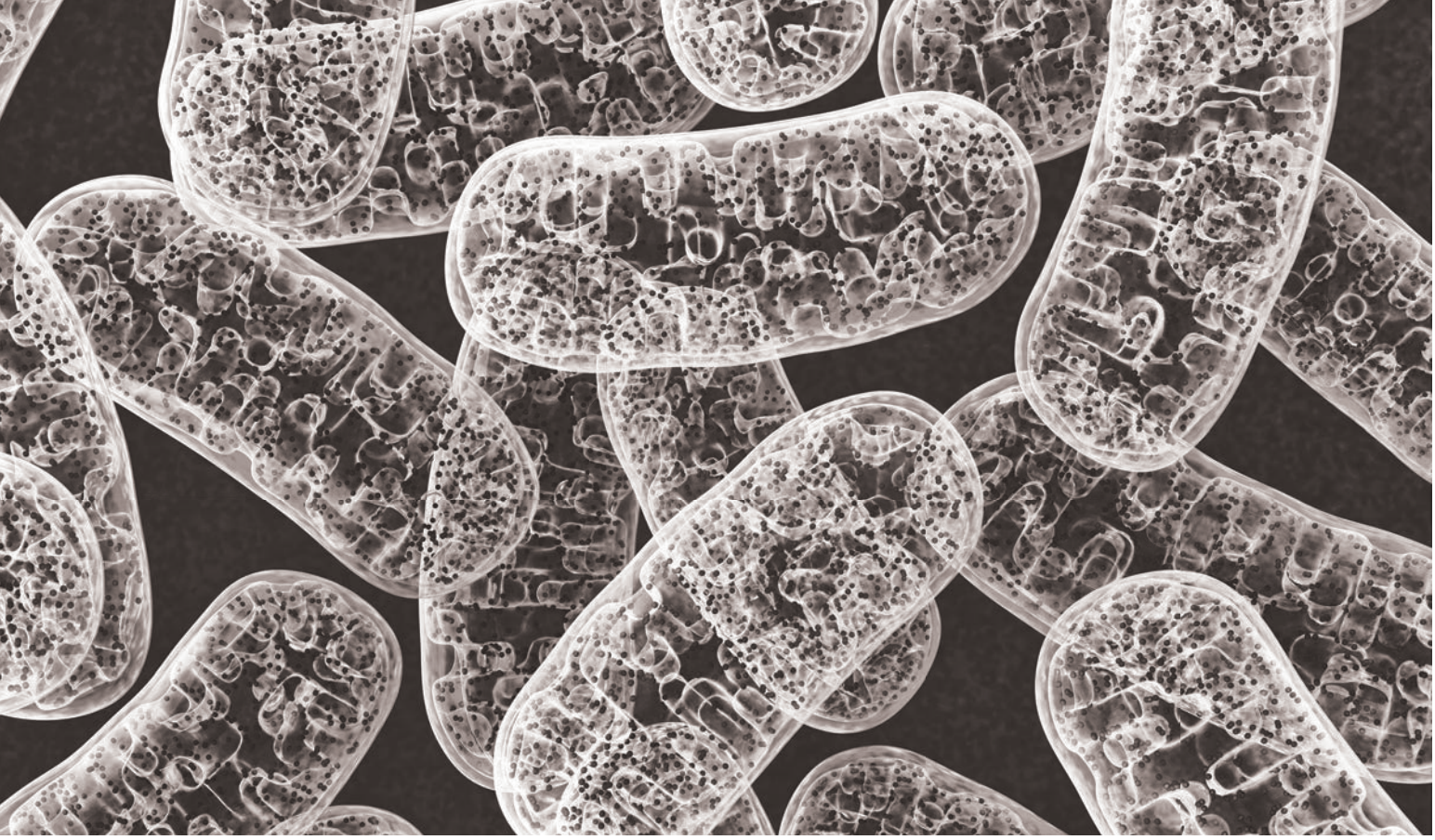
GS Reactive oxygen species are "oxidants." You've probably heard of antioxidants; these are enzymes or compounds that counter the effects of oxidants. Aside from getting antioxidants from food (such as fruit) or supplements, our bodies also make them. My lab actually developed a model in which we can turn off antioxidant production in mitochondria in a reversible way. This allows us to induce mitochondrial oxidant stress for a controlled time window and ask what adaptive changes occur.

Compared to cells that saw no stress, those that experienced a little mitochondrial stress responded by remodeling mitochondria to produce fewer reactive oxygen species and were resistant to a second oxidant challenge. In other words, the cellular version of "What doesn't kill you makes you stronger."

What else are you working on?

GS I have an exciting new project with my wife, Susan Kaech [Kaech is the director of Salk's NOMIS Center for Immunobiology and Microbial Pathogenesis]. We just received a grant to look at the role of mitochondria in melanoma. Sue studies cancer immune responses and immunotherapy, and we want to manipulate mitochondrial function in both tumors and immune T cells and see how this affects tumor immune responses.

My lab also has ongoing investigations into how mitochondrial DNA promotes inflammation and contributes to aging and diseases. These studies are based on a 2015 paper we published, showing that when the mitochondrial DNA you inherit from your mother gets released from mitochondria into the rest of the cell,



Shadel studies the function of the cellular powerhouses called mitochondria in both health and disease.

it triggers an inflammatory, antiviral, innate immune response. There is now an explosion of activity in this area, whereby mitochondrial DNA and other constituents from mitochondria trigger inflammation and associated diseases.

With this many projects, do you get to enjoy any time outside the lab?

GS I have three daughters. Two still live at home (fifth and sixth grade), and when Sue and I aren't working, we spend the rest of our free time together as a family. Part of our negotiation with the girls to move to San Diego was to get a dog, so we have a new German Shepherd we like to take hiking or to one of San Diego's many dog beaches.

Do you ever bring your daughters to Salk?

GS Before we brought them to visit the Institute for the first time, we told them about the great architecture. Once they saw it, they said, "Looks like cement with holes in it. When are they going to finish it?"

They've been to a few events like the Salk Science & Music concerts, and they like to come and draw on the whiteboards in my study and office. Then they came to the ceremony when Sue and I received our endowed chairs, and after all the pomp and circumstance was over they said, "All this was for a chair? It's an actual chair?"

Any last thoughts?

GS At Salk, the faculty get a lot of airplay, and thus I think we often do not give enough credit to the students, postdocs and staff that are the real driving force of the science. I get a lot of gratification out of seeing them succeed and move on to have careers and trainees of their own. It's a very satisfying feeling.

LILLIAN

"The ability to test hypotheses in living systems points to a clear route for eventual translation into the clinic to help patients."

NEXT GEN

Reading the clues to fight lung cancer

EICHNER

Lillian Eichner grew up in Seattle, engrossed in mystery novels—books starring Nancy Drew and, of course, tales by Agatha Christie. Eichner's innate inquisitiveness drew her to the stories' unanswered questions and led her to piece together clues to reveal the perpetrator or solve the crime.

Although Eichner isn't a private investigator, she is on the path to becoming the other type of PI—a principal investigator. She pieces together molecular and genetic clues to reveal how cancer commits its crime. In the research laboratory, she looks for evidence, pursues leads and exhausts dead ends in an attempt to solve "whodunit."

"Cancer is one of biology's biggest mysteries; it is still so undefined, and the clues are not all known," Eichner says. "In a mystery novel, if you can't see the crime scene, and you don't know what the weapon was, how can you possibly ask the right questions to find the culprit? The intriguing part about studying lung cancer is following the questions and clues."

Eichner began studying cancer while pursuing her PhD at McGill University in Montreal. She was drawn to the Salk Institute for her postdoctoral studies because Reuben Shaw, director of the Salk Cancer Center and a professor in Salk's Molecular and Cell Biology Laboratory, has taken a new approach to cancer by studying the metabolic pathways of deadly tumors. Eichner's work at Salk focuses on an antitumor protein called LKB1, which is missing in 25 to 30 percent of patients who have lung cancer.

"If we understood the mechanisms of how LKB1 functions, we could find new targets for therapies," Eichner says. "Unlike many scientific inquiries, this question is a discrete, defined puzzle that we can genetically address. The ability to test hypotheses in living systems points to a clear route for eventual translation into the clinic to help patients."

Eichner was the first author of a paper in *Cell Metabolism*, published online this past November, that described the role of another important enzyme involved in lung cancer: AMPK. The Shaw lab has shown that this elusive protein supports tumor growth. In lung cancers, AMPK can supply tumors with the nutrients needed to grow; by blocking AMPK, researchers may be able to stop the growth of advanced tumors.

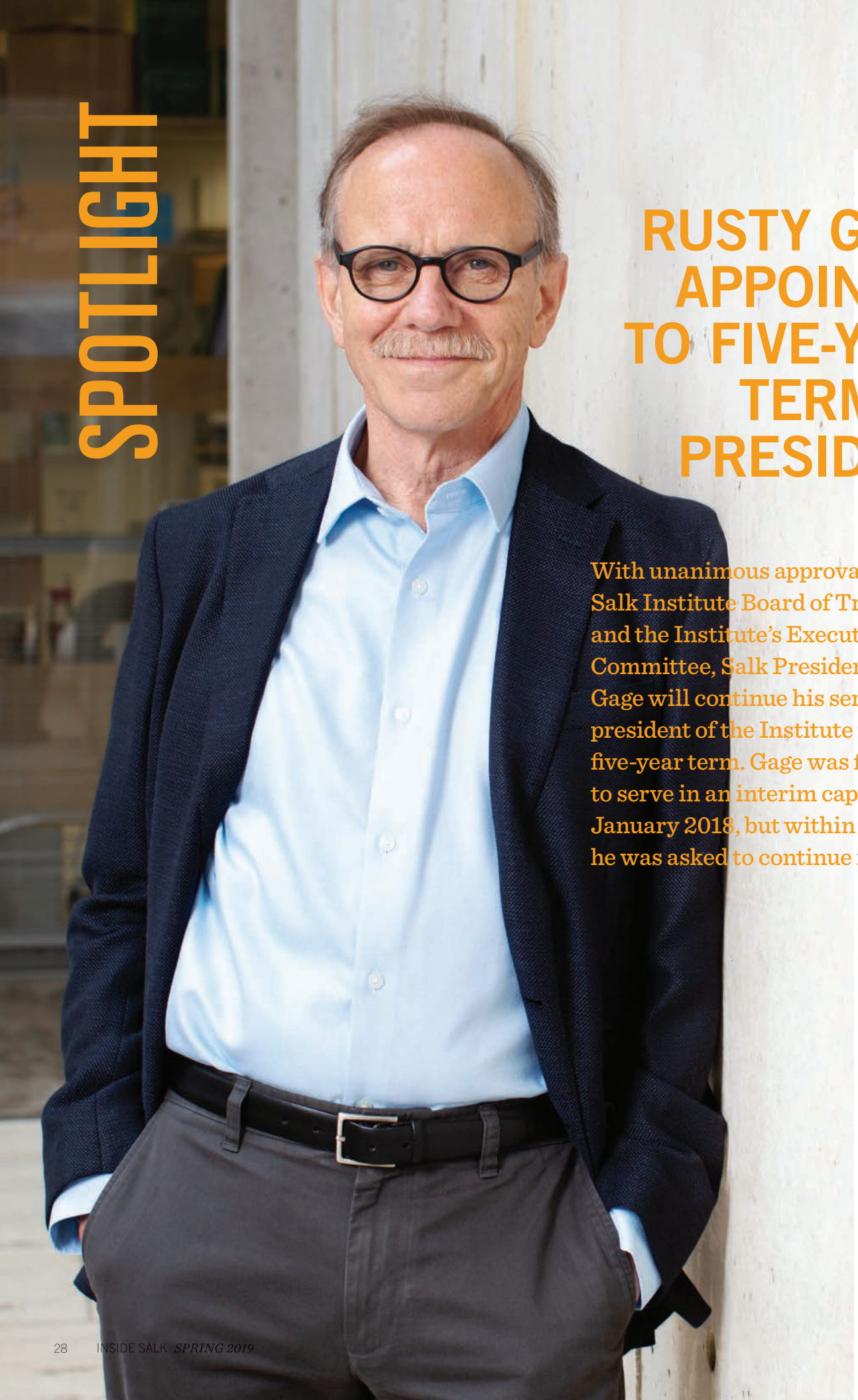
After completing her postdoctoral studies at Salk, Eichner plans to start her own lab.

"My dream is to inform targeted therapies for cancer," Eichner says. "If we can understand exactly what goes wrong to cause tumor growth in a lung, then we can design effective therapeutic strategies targeting the molecular pathways that we identify."

Outside of the lab, Eichner focuses on being a role model for her two daughters, a six-year-old and a ten-month-old. She's even brought her older daughter to the Shaw lab to gaze through a microscope at lung-tumor cells.

"I hope my daughters grow up to do something they love. Science is not an easy career, but I want them to see that as a woman in science, you can not only be successful but also pursue what you love," Eichner says. "I want science to be a choice they feel they can confidently consider."

In the meantime, Eichner continues to piece together clues at her bench in the Shaw lab.



RUSTY GAGE APPOINTED TO FIVE-YEAR TERM AS PRESIDENT

With unanimous approval by the Salk Institute Board of Trustees and the Institute's Executive Search Committee, Salk President Rusty Gage will continue his service as president of the Institute for a full five-year term. Gage was first asked to serve in an interim capacity in January 2018, but within months, he was asked to continue in the role.

"Aside from being a globally renowned scientist, Rusty is an inspiring leader whose energy, steadfastness and thoughtfulness have been invaluable in helping to guide the Institute. He has accomplished a great deal over the past year," says Board of Trustees Chair Dan Lewis. "The Board is delighted that he will lead Salk forward into our next chapter as we continue to tackle the most pressing questions in science and to work for the betterment of humanity. Together, working with the Salk faculty, we will set a vision for how scientific research will evolve going forward."

Having twice served as interim president, Gage will now serve a full term. An internationally recognized leader in neuroscience, he will also continue in his scientific roles as a professor in the Laboratory of Genetics and as the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease.

"Rusty is an extraordinary individual, and I am very excited to see how the Institute continues to evolve under his leadership," says former Salk Board Chair and philanthropist Irwin Jacobs, cofounder of Qualcomm.

During his nearly quarter century at Salk, Gage has acquired a wealth of experience in scientific research, bolstered by an intimate knowledge of the Institute's history and culture. Under his leadership, the Institute has recruited dynamic new faculty and launched major research efforts: the Harnessing Plants and the Conquering Cancer initiatives. He was also instrumental in establishing Salk's Office of Equity and Inclusion.

In December 2018, Gage and a team of nine other scientists at the Institute were awarded $19.2 million from the American Heart Association-Allen Initiative in Brain Health and Cognitive Impairment. The award will fund a comprehensive eight-year investigation of the mechanisms underlying Alzheimer's disease and aging-related cognitive decline in an effort to uncover new therapies.

"Rusty exemplifies the synthesis of qualities that all top-notch research institutions want in a president—great individual science, a great nose for science in other people, and the honesty and humility to personally connect with people," says Joanne Chory, professor and director of the Plant Molecular and Cellular Biology Laboratory. "He is a consensus builder who will lead by example—treating others with respect and helping them to reach their goals. I look forward to working with him to craft and implement a vision for Salk for the rest of this century."

Professor Jan Karlseder, the incoming chair of the Salk Institute Academic Council, also lauds the decision. "The faculty looks forward to Rusty's leadership. It's rooted in his long history with the Institute and, as a long-standing faculty member, he is intimately familiar with the challenges faced by scientists," he says.

In addition to these recent achievements, Gage's work has been recognized with numerous awards. He also belongs to several prestigious societies, including the American Academy of Arts and Sciences, the National Academy of Medicine, the National Academy of Sciences and the American Philosophical Society. He previously served as the president of the Society for Neuroscience and the International Society for Stem Cell Research.

"Rusty is an extraordinary individual, and I am very excited to see how the Institute continues to evolve under his leadership."

IRWIN JACOBS

Former Salk Board Chair and philanthropist
Cofounder of Qualcomm

"Rusty exemplifies the synthesis of qualities that all top-notch research institutions want in a president—great individual science, a great nose for science in other people, and the honesty and humility to personally connect with people."

JOANNE CHORY

Professor and director of the Plant Molecular and Cellular Biology Laboratory

Salk promotes Nicola Allen and Julie Law to associate professor

The Institute has promoted Nicola Allen and Julie Law to associate professor, in recognition of their notable contributions to neurobiology and plant biology, respectively.

NICOLA ALLEN

Molecular Neurobiology Laboratory

Nicola Allen is studying how astrocytes control the formation and function of neuronal connections called synapses. She is applying these findings to develop ways to repair damaged synaptic connections in disease to improve cognition and memory. She is part of a newly launched, multidisciplinary $19.2 million effort from the American Heart Association-Allen Initiative supporting 10 Salk labs in the investigation of the mechanisms underlying Alzheimer's disease and aging-related cognitive decline.

JULIE LAW

Plant Molecular and Cellular Biology Laboratory

Julie Law is investigating how epigenetic modifications facilitate gene regulation and promote genome stability to enable normal growth and development. By employing genetic, genomic and biochemical approaches, Law is linking the recognition of epigenetic modifications to specific protein complexes and uncovering their roles in gene regulation in plant cells. Law is one of five Salk plant biologists driving an ambitious effort to tackle climate change via the Harnessing Plants Initiative, which aims to make plants much more efficient at storing carbon.

TRIO OF SALK SCIENTISTS NAMED AMONG MOST HIGHLY CITED RESEARCHERS IN THE WORLD

Clarivate Analytics

Professors Joanne Chory, Joseph Ecker and Rusty Gage have once again been named to the Highly Cited Researchers list by Clarivate Analytics. The list selects researchers for "exceptional research performance" demonstrated by the production of multiple highly cited papers that rank in the top 1 percent by citations for field and year. Additionally, among the 4,058 researchers named as Highly Cited, Ecker is one of 194 appearing in two separate categories: Plant and Animal Science in addition to Molecular Biology and Genetics. The Salk trio has been named to this list every year since 2014—when the regular annual rankings began—for their contributions to plant biology, genetics and neuroscience.

Rusty Gage

Joanne Chory

Joseph Ecker

CRICK-JACOBS CENTER CELEBRATES 15 YEARS OF SALK INNOVATION

2019 marks the 15th anniversary of the establishment of the Crick-Jacobs Center for Theoretical and Computational Biology at the Salk Institute. This interdisciplinary research unit integrates experimental and theoretical approaches to better understand the brain, from a molecular to a whole-system perspective. The center also investigates how behaviors arise from the interactions between the brain's many components.

The Crick-Jacobs Center is named in honor of Francis Crick, Nobel laureate and Salk founding nonresident fellow, and Joan and Irwin Jacobs (former Salk board chair) whose philanthropic gift made the center possible.

"The Crick-Jacobs Center is unique because it combines so many different fields of scientific inquiry into a streamlined, cutting-edge research unit," says the center's leader and holder of the Francis Crick Chair, Salk Professor Terrence Sejnowski. "The center is also a testament to Irwin Jacobs' vision and philanthropy. Fifteen years ago not many people foresaw the coming influx of big data and subsequent challenge to fuse that with scientific inquiry. Irwin did and he made it a point to invest in that work at Salk. He's empowered us to be at the forefront of this exciting field and the dividends continue to be highly significant to many areas of research."

The scientists who work at the Crick-Jacobs Center combine approaches from biology, physics, chemistry, mathematics, computer science and engineering to understand the complexity of the brain. By using techniques that include computer simulations, imaging, viral vectors and molecular genetics they have uncovered insights into everything from how the brain encodes sensory signals to new ways to track brain activity. These researchers are joined by collaborators at UC San Diego, Princeton, the California Institute of Technology (Caltech), and the Massachusetts Institute of Technology (MIT).

Xin Jin

XIN JIN RECEIVES MCKNIGHT MEMORY & COGNITIVE DISORDERS AWARD

Xin Jin, an associate professor in Salk's Molecular Neurobiology Laboratory, has been selected as one of four scientists to receive the McKnight Memory & Cognitive Disorders award from the McKnight Endowment Fund for Neuroscience to study how the brain learns, remembers and executes actions. The competitive award, which includes $300,000 over three years and participation in the annual McKnight Conference on Neuroscience, supports "investigators whose research shows promise in bringing society closer to preventing, treating, and curing many devastating diseases," including Alzheimer's and Parkinson's diseases.

SALK BOARD WELCOMES TECHNOLOGY, BUSINESS GIANTS DAVID DOLBY AND MARK KNICKREHM

The Salk Institute Board of Trustees is pleased to announce its two newest members, David Dolby and Mark Knickrehm, both innovative leaders in business and technology.

"I am thrilled to have David and Mark coming on board as part of our team at Salk," says Board Chair Dan Lewis. "They both bring an incredible amount of knowledge and experience to the Board. I know they will be integral in identifying the best paths forward to support research and innovation here at the Institute."

The Salk Institute Board of Trustees comprises proven leaders from global business and nonprofit sectors in order to leverage their expertise and perspective as the Institute continues its important work. These individuals are committed to science, innovation, high-quality research and supporting the Institute's mission.

David Dolby

David Dolby, an investor and philanthropist based in San Francisco, is focused on science, technology and media. Specifically, he is the managing director of Dolby Family Ventures, where he specializes in accelerating the path to a cure for Alzheimer's disease. This is in addition to roles as director of Dolby Laboratories, director of Cogstate Limited, and CFO of the Ray and Dagmar Dolby Family Fund. He also directly manages a portfolio of more than 40 venture investments ranging across Internet technology, medical diagnostics, consumer products, and much more. Dolby is a graduate of Duke University where he earned a bachelor of science in engineering (civil engineering). He earned his MBA from Stanford University. Dolby represents the family on a number of philanthropic and business initiatives that honor the legacy of his late father, Ray Dolby.

Mark Knickrehm

Mark Knickrehm is currently the group chief executive at Accenture Strategy and serves on the Global Management Committee at Accenture, one of Fortune's "World's Most Admired Companies." He is widely known as a thought leader on how emerging trends and technologies will impact industry and business models. Prior to his current role, Knickrehm was the director of Accenture's Global Health Industry Group and led the growth of their Health & Public Service Operating Group. Before joining Accenture in 2005, he spent more than a decade at McKinsey & Company where, as a partner, he guided strategy, operations and organization. Knickrehm earned his bachelor's degree in economics from Northwestern University and an MBA from the University of Chicago. His writing on artificial intelligence and traditional employment was published in the *Harvard Business Review.* and is frequently invited to speak at business conferences on the future of employment and the workplace.

SALK INSTITUTE EARNS CHARITY NAVIGATOR'S HIGHEST RATING FOR EIGHTH CONSECUTIVE TIME

For the eighth consecutive time, the Salk Institute's strong financial health and continuing commitment to accountability and transparency have earned it a coveted four-star rating (out of four stars) from Charity Navigator, America's largest independent charity and nonprofit evaluator. Receiving the highest ranking for eight consecutive review periods puts Salk in a distinguished class of nonprofits—only 3 percent of nonprofits evaluated achieve that status, "indicating that the Salk Institute outperforms most other charities in America," according to a letter from Michael Thatcher, president and CEO of Charity Navigator.

Innovation thrives at Salk

Salk's Innovation Grants program launched in 2006 from the forward-thinking minds of then-Board Chair Irwin Jacobs and his wife, Joan. This program fuels out-of-the-box ideas that hold significant promise but do not yet have the track record of success that traditional funding sources require. More than a decade later, the program continues to thrive. Salk is proud to recognize recipients of last year's competition.

Salk Innovation Grant Recipients

SPRING / SUMMER AWARDEES

THOMAS ALBRIGHT AND SERGEI GEPSHTEIN:
Sensory neuroscience for better eyewitness identification

WOLFGANG BUSCH, SAKET NAVLAKHA AND URI MANOR:
Root nutrient seeking algorithms

JESSE DIXON:
Single cell structural variant profiling in cancer genomes

XIN JIN:
Bridging functionality with connectivity: striatal single-cell in vivo patch recording and rabies tracing during action sequence

SUSAN KAECH AND RONALD EVANS:
Targeting cholesterol metabolism to refuel T cell responses in pancreatic cancer

FALL / WINTER AWARDEES

EDWARD CALLAWAY:
Identifying cortical inhibitory neuron-specific enhancers via epigenetic profiling and high-throughput in vivo screening

SREEKANTH CHALASANI, CHEN-MIN YEH AND GERALD PAO:
Using activity recorded from a living zebrafish brain to control a robot

JOSEPH ECKER:
Recording the transcriptional history of cells

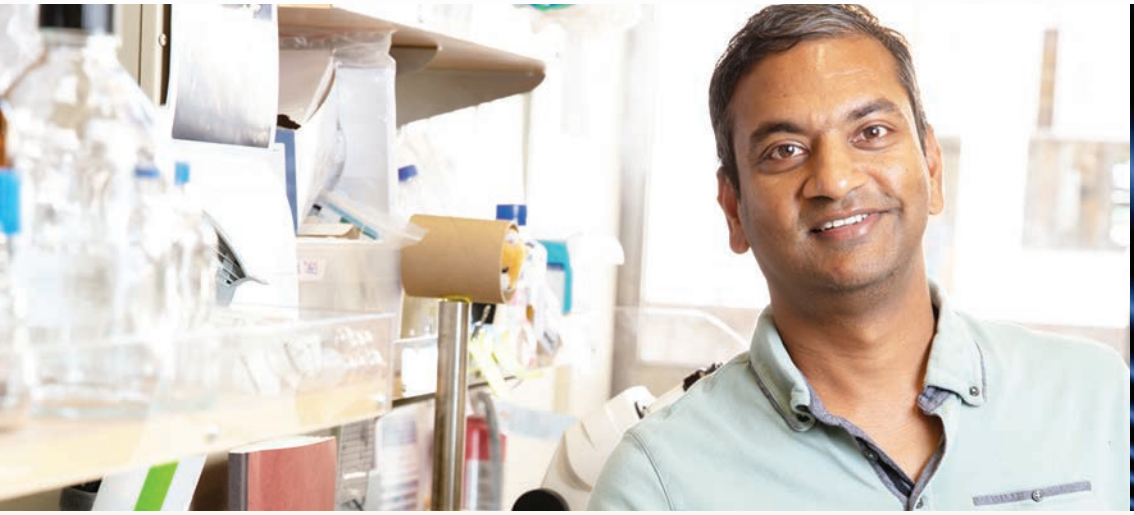
JUAN CARLOS IZPISUA BELMONTE:
Studying transgenerational epigenetic inheritance by developing an epigenetically modified mouse

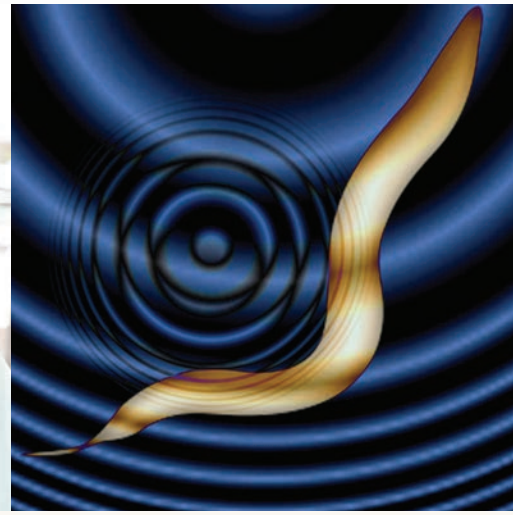
DAVID SCHUBERT AND ANTONIO CURRAIS:
Discovering novel drug candidates for treating Alzheimer's disease using a unique screening assay for mitochondrial dysfunction

Janelle Ayres

JANELLE AYRES AWARDED $1.8 MILLION BY NOMIS FOUNDATION FOR NOVEL RESEARCH ON MECHANISMS TO PROMOTE HEALTH

Associate Professor Janelle Ayres has been awarded $1.8 million over two years by the NOMIS Foundation to study health as an active process in which microbes—including the trillions of microorganisms that call the human body home—initiate interactions that promote the health of the host. Her project, "Harnessing Physiological Health to Treat Disease," will integrate concepts from evolutionary biology, physiology, host-microbe interaction and ecology to establish a new conceptual framework and approach in which scientists can mechanistically understand what it means to be healthy and can thus understand how to apply this knowledge to treat diseases





Sreekanth Chalasani

SREEKANTH CHALASANI ADVANCES ULTRASOUND TECHNOLOGY FOR NEUROLOGICAL THERAPY

Salk scientists are using sound waves to control brain cells—a technique dubbed sonogenetics.

Associate Professor Sreekanth ("Shrek") Chalasani, who pioneered the idea of using ultrasonic waves to stimulate neurons and coined the term "sonogenetics," will participate in the Defense Advanced Research Projects Agency's ElectRx program, with the aim of taking his lab's work to the next level with $750,000 in new funding. Sonogenetics has the potential to replace pharmaceutical drugs or invasive surgical treatments for neurological conditions like epilepsy, Parkinson's disease or post-traumatic stress disorder.

NICOLA ALLEN RECEIVES $2.5 MILLION CHAN ZUCKERBERG INITIATIVE EARLY CAREER AWARD

Associate Professor Nicola Allen has received a five-year, $2.5 million Ben Barres Early Career Acceleration Award from the Chan Zuckerberg Initiative (CZI) as part of a nearly $52 million effort launching the CZI Neurodegeneration Challenge Network to understand the underlying causes of disorders such as Alzheimer's, Parkinson's, Huntington's disease and ALS. Allen will study the role of astrocytes (support cells in the brain), which could reveal details about potential causes of—and treatments for—dementia.

Nicola Allen

SAKET NAVLAKHA RECEIVES CAREER AWARD FROM NSF

Assistant Professor Saket Navlakha has received a CAREER award from the National Science Foundation (NSF), totaling more than $1 million over the next five years, to study the naturally occurring algorithms in biological systems, such as the branching of a tree root, and compare the network design strategies and optimization principles to that of developing neurons in the brain.

Saket Navlakkha

Ronald Evans

RONALD EVANS NAMED 2018 AAAS FELLOW

Salk Professor and Howard Hughes Medical Investigator Ronald Evans has been named a 2018 fellow of the American Association for the Advancement of Science (AAAS), the world's largest general scientific society, for his discoveries on steroid- and orphan-receptor signaling. The receptors Evans discovered are primary targets in the treatment of breast cancer, prostate cancer, pancreatic cancer and leukemia, as well as osteoporosis and asthma.

SALK SCIENTISTS RECEIVE $1 MILLION IN LATEST ROUND OF BRAIN INITIATIVE GRANTS

Professor John Reynolds, assistant professor Saket Navlakha and postdoctoral fellow Robert Henley (Ecker lab) have received funds totaling over $1 million in direct costs in the latest round of grant-making from the National Institutes of Health BRAIN Initiative. The transagency effort aims to arm researchers with revolutionary tools to fundamentally understand the neural circuits that underlie both the healthy and the diseased brain.


Support a legacy
where cures begin.
The power of charitable gift annuities
Did you know that a gift of $20,000 or more to the Salk Institute can provide fixed payments for you and your loved ones? Charitable gift annuities provide tax savings and an income to you, while benefitting research and discovery at Salk. By creating a charitable gift annuity, you can be confident that you will be making a smart decision about your financial and philanthropic priorities.
Sample Rates
YOUR AGE (S) RATE
70 5.6%
80 7.3%
90 9.5%
Learn more about the many benefits of a charitable gift annuity by contacting Cheryl Dean, Planned Giving Counsel, at (858) 500-4884 or cdean@salk.edu.
Your age(s) and current interest rates determine the rate Salk can offer.
salk®
Where cures begin.

EVENTS

SALK SCIENCE & MUSIC SERIES PLAYS ON

The Salk Science & Music Series continued with two more events from the current season's exciting lineup. On December 9, 2018, guests were treated to the beautiful sounds of pianist Alessio Bax and to a scientific talk on genetics by Assistant Professor Graham McVicker. Attendees were also able to fall in love with the music of cellist Amit Peled and pianist Karen Joy Davis on February 24, 2019—albeit a little late for Valentine's Day. Professor Jan Karlseder discussed the science of telomeres at the performance.

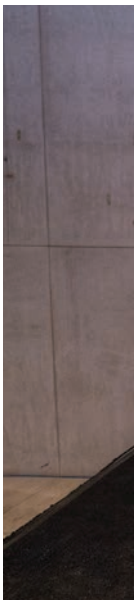
*One more **Science & Music event** in the 2018-19 season remains, which will showcase Salk's Sung Han and the Brubeck Brothers Jazz Quartet, on April 28. Tickets are available at **music.salk.edu**.*

SALK HONORS WOMEN & SCIENCE DONORS

Donors to the Salk Women & Science program attended an event on December 11, 2018, honoring their generosity and partnership in supporting Salk's women of science. President Rusty Gage provided introductory remarks before the 2018 awardees showcased their research projects. Assistant Professor Diana Hargreaves emceed the event. In total, 19 awards were given out in 2018, thanks to those who donated to the Salk Women & Science program. Tina Simner made a generous leadership gift that launched the 2018 fundraising effort, alongside honorary chair Linda Chester.

Tina Simner, Salk Design and Discovery Event Chair and Kathleen DelGiorno

Reuben Shaw



Graham McVicker

Alessio Bax

From left:
Diana Hargreaves, Joani Nelson,
Barbara Donnell, Mei Lai and Shefali Krishna

Rosemary Straley
and Nasun Hah

From left: Dan Lewis (Board Chair),
Clodagh O'Shea and Rusty Gage

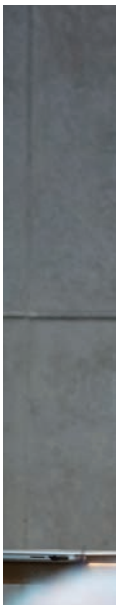
CELEBRATING SALK'S CANCER CENTER AND CLODAGH O'SHEA

On November 15, 2018, more than 80 people, including faculty, donors and Board members, celebrated the 45th anniversary of the Salk Cancer Center, one of only seven National Cancer Institute-designated cancer centers in the country. The event also fêted Salk Professor Clodagh O'Shea, who was named the inaugural holder of the Wicklow Chair. In addition to remarks from O'Shea and Cancer Center Director Reuben Shaw, previous directors Walter Eckhart and Tony Hunter were honored for their service to Salk, while comedian Tim Lee provided the evening's entertainment.

EVENTS

PRESIDENT'S CLUB LUNCHES WITH ALAN SAGHATELIAN, LEARNS ABOUT NEW POSSIBILITIES IN MEDICINE

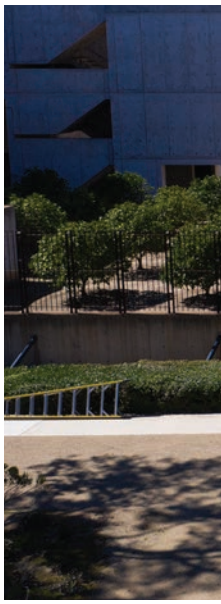
On December 4, Salk's President's Club members enjoyed a private lunch with Professor Alan Saghatelian, whose research touches on virtually all areas of human biology. Specifically, he seeks to improve human health by focusing on bioactive metabolites and peptides to identify potential therapeutic opportunities. The President's Club is open to donors who annually contribute $2,500 or more to Salk's scientific research.



Nicola Allen

MARCH OF DIMES HIGH SCHOOL SCIENCE DAY ANOTHER SUCCESS

On Saturday, February 23, high school students and their teachers from throughout San Diego converged on Salk to learn alongside Salk's world-class faculty. This half-day annual event sparks high school students' interest in careers in science and research. Attendees spoke with researchers, took lab tours and enjoyed a keynote presentation. The Anne and Neal Blue High School Science Fund generously supports this popular program.



Samuel Pfaff

SALKEXCELLERATORS DIVE INTO BRAIN-SCIENCE INNOVATIONS

Salkexcellerators are community members in San Diego and New York City who share a commitment to supporting scientific discovery at Salk. On February 6, the group came together for an evening with Professor Samuel Pfaff and Associate Professor Nicola Allen to discuss the fundamentals of neuroscience and the pathways that promote disease—key areas in Salk's efforts to innovate new therapies for a number of illnesses, including Alzheimer's and Parkinson's diseases.

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
For nearly half a century, Salk has offered programs to inspire—and launch—the next generation of scientists, Salk's Education Outreach program includes a Mobile Science Lab, Heithoff-Brody 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.**

salk®
Where cures begin.

Rusty Gage
President

Rebecca Newman
Vice President, External Relations

Steven Johnson
Chief Communications Officer

Kristina Grifantini
Director, Scientific Communications
and Media Relations

Allie Akmal
Media Relations Manager

Andrew Young
Development Communications Writer

Brittany Fair
Science Writer

Liz Hincks
Director of Electronic and
Graphic Communications

John McDonagh
Senior Web Developer

Stephanie Harada
Web Designer

Chris Keeney
Photographer

Aaron Howard
Video Communications Manager

Sara Jacobsen
Graphic Designer

Visit the Salk Institute at **www.salk.edu.**

Inside Salk is published by the Salk Institute for Biological Studies. Please send comments to communications@salk.edu or contact the Communications Department at (858) 453-4100 x1371.

Inside Salk is printed on recycled paper.

MIX
Paper from responsible sources
FSC® C013371

salk®
Where cures begin.

NONPROFIT ORG.
U.S. POSTAGE
PAID
PERMIT NO. 611
SAN DIEGO, CA

Salk Institute for Biological Studies
10010 N Torrey Pines Rd
La Jolla, California 92037-1002
Telephone: (858) 453-4100
www.salk.edu

CALENDAR

APRIL

28 Salk Science & Music Series

MAY

15 Salkexcellerators Lecture

28 Conquering Cancer Summit:
Progress In Pancreatic Cancer

JULY

24 Salk Women & Science

AUGUST

24 Symphony at Salk

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

VISIT US ONLINE AT: inside.salk.edu

Salk Institute has received the highest rating 8 consecutive times from Charity Navigator, the nation's foremost charity evaluator.

CHARITY NAVIGATOR
★★★★
Four Star Charity

Follow us on:
@salkinstitute