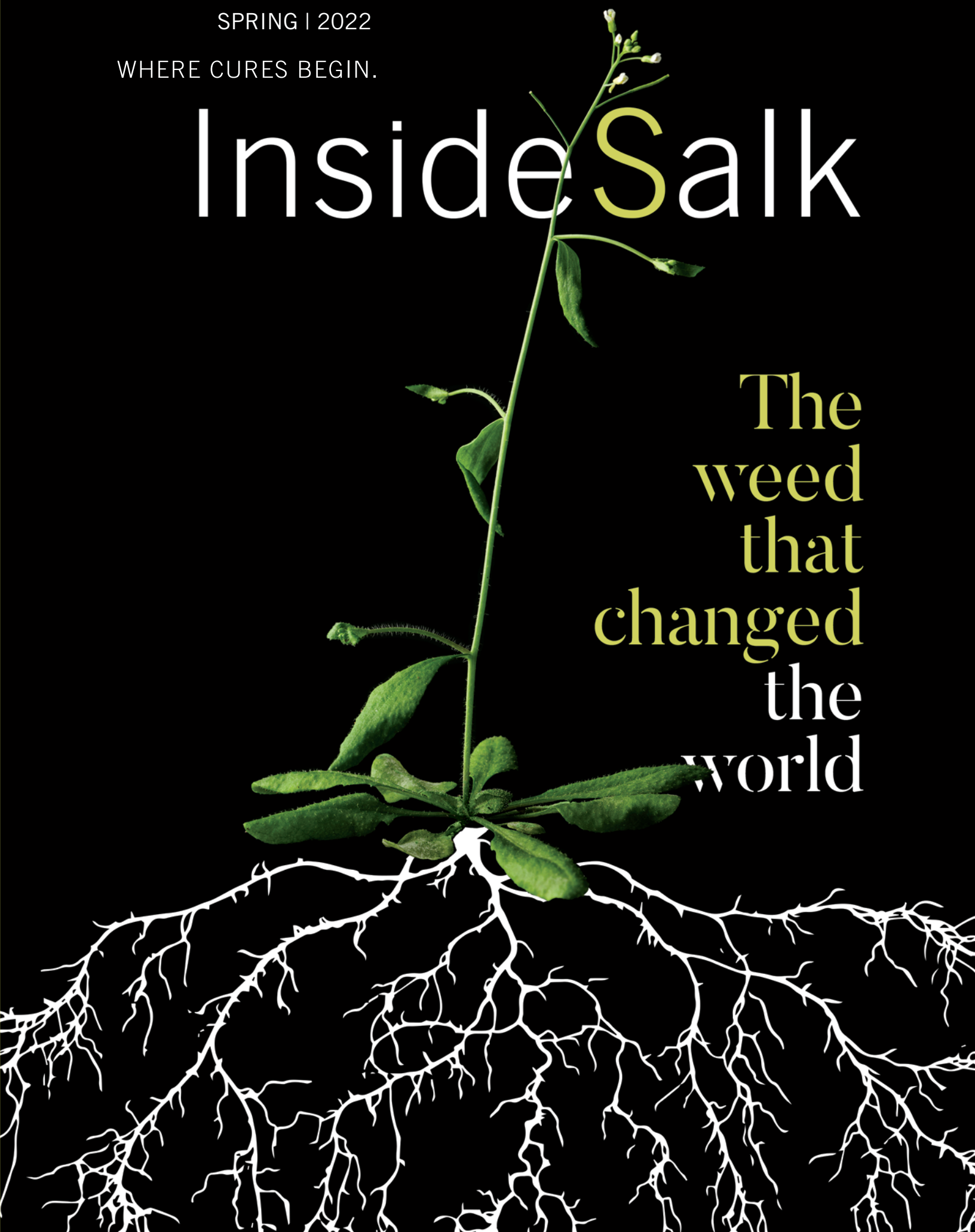
SPRING | 2022

WHERE CURES BEGIN.

InsideSalk



The weed that changed the world

Dear Friends,

Over the past few years, the Salk Institute has embraced a new focus: adaptation for a changing world. To achieve this, we are taking an increasingly holistic approach to research to better protect our health and the health of the planet. As we do so, I can't help but notice that our plant scientists have already begun implementing this approach, allowing for our collective growth well into the future.

That future will undoubtedly include a changing climate, and Salk is fully invested in the effort to help mitigate its damaging effects. As you'll learn in this issue of *Inside Salk*, several of our researchers played early, instrumental roles in sequencing the genome of the plant *Arabidopsis thaliana*, a ubiquitous model organism that has been used to unravel many basic biological functions over the past century. As part of our Harnessing Plants Initiative, researchers are now using those fundamental discoveries to develop resilient plants that can thrive in harsh environments, as well as crops with roots that capture and store excess carbon dioxide from the atmosphere, preventing further damage to our planet.

Indeed, our plant scientists themselves are a model for how a collaborative approach to exploring the foundations of life can often lead to innovative solutions for global problems.

This issue also profiles Associate Professor Kenta Asahina, who shares how insects and humans are similar, including our need for social interaction and the way genetic mutations may cause disease. We also sit down with Senior Staff Scientist Courtney Glavis-Bloom, whose goal of finding new treatments for Alzheimer's disease is motivated by a personal connection, and with Postdoctoral Fellow Helen McRae, who is looking for new ways to use the body's immune cells to fight cancer.

In the following pages we also share more about our vision for the future of science at Salk. Our five-year scientific and philanthropic initiative, the Campaign for the Future: Building a More Resilient World, has launched, thanks to the transformative gift by Joan and Irwin Jacobs (read the Winter 2021 issue of *Inside Salk* for full details). It's undeniable that science and technology are rapidly changing and, as stewards of Jonas Salk's legacy, it is our responsibility to meet the most pressing challenges head-on and to ensure that the next 60 years of Salk science are as impactful to the world as the first 60.

Salk's Campaign is focused on three key elements: people, technology and space. With your support, we can build the centerpiece of this initiative—the Joan and Irwin Jacobs Science and Technology Center—and fulfill each of these areas of priority. The Institute envisions more lab space for discoveries, we intend to outfit the new building with leading-edge technology, and we intend to recruit and retain talented experts in a variety of disciplines—including some disciplines that didn't even exist a decade ago. This is an ambitious effort, but one that will further solidify the Institute's place as a world-renowned research facility for many decades to come.

As summer approaches, I hope you will take the opportunity to learn more about Salk's Campaign for the Future (www.salk.edu/resilient). The Jacobs have generously given the Institute a challenge to raise $200 million to match their $100 million gift by September 30, 2022. Please consider meeting the Jacobs' challenge by supporting Salk's Campaign—and joining us for the next phase of our growth.

Sincerely,

Rusty

Fred H. Gage
President

"It's undeniable that science and technology are rapidly changing and, as stewards of Jonas Salk's legacy, it is our responsibility to meet the most pressing challenges head-on and to ensure that the next 60 years of Salk science are as impactful to the world as the first 60."

The Salk Institute and Lustgarten Foundation form strategic pancreatic cancer research partnership

Pancreatic cancer is the third-leading cause of cancer deaths in the United States. The National Institutes of Health estimates 60,430 people in the US were diagnosed with pancreatic cancer in 2021, and more than 48,000 are expected to die from the disease.

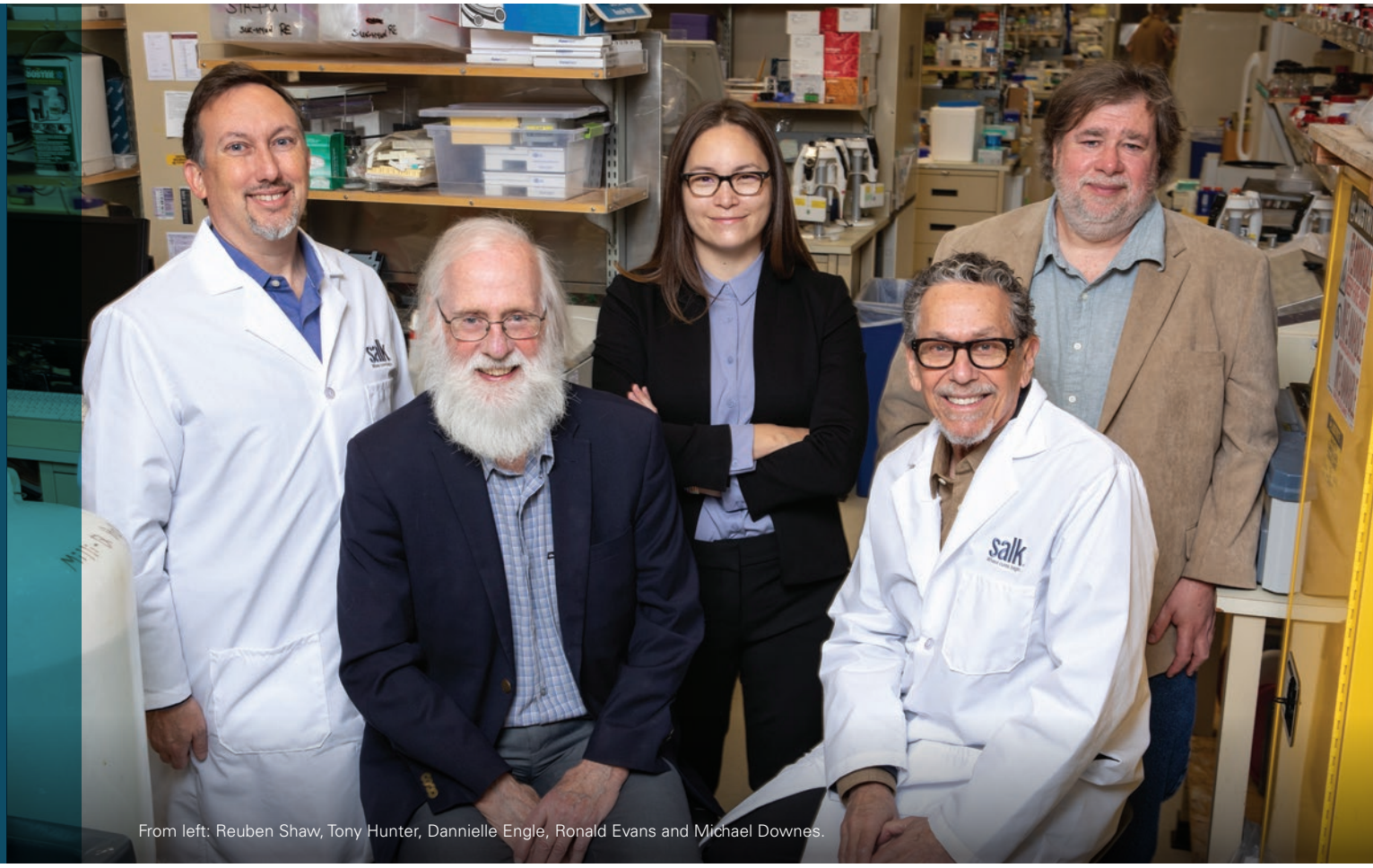
A new partnership is dedicated to changing those odds.

The Salk Institute has partnered with The Lustgarten Foundation, the world's largest private funder of pancreatic cancer research, to identify and validate potential targets for new pancreatic cancer drugs. The partnership, supported by a $5 million grant, is part of the Lustgarten Advancing Breakthrough Science (LABS) Program.

Four co-principal investigators, all prominent researchers in the Salk Dedicated Program in Pancreatic Cancer, are leading the effort: Professors Reuben Shaw, Ronald Evans, Tony Hunter and Assistant Professor Dannielle Engle.

"The Foundation's funding of the Salk Dedicated Program in Pancreatic Cancer is unique because we're committed to funding preeminent pancreatic cancer scientists focused on a single goal," says David Tuveson, the Lustgarten Foundation chief scientist, American Association for Cancer Research president and director of the Cold Spring Harbor Laboratory Cancer Center. "Unlike most funding models, Lustgarten LABS gives scientists at leading research institutions the freedom to build the right team and infrastructure to support the kind of high-risk, high-reward studies required to meet the goal."

In addition to the Salk Institute, the LABS Program includes several other renowned research institutions. Scientists at each of the LABS frequently collaborate, sharing new capabilities and specialized information to further the pancreatic cancer research field and to advance the most promising discoveries in the lab to treat patients in the clinic. The Salk Institute will pursue funding to match the Lustgarten grant of $1 million per year over the next five years.



From left: Reuben Shaw, Tony Hunter, Dannielle Engle, Ronald Evans and Michael Downes.

Meet the Salk researchers exploring unique and understudied areas related to diagnosing and treating pancreatic cancer:

Reuben Shaw, director of the Salk National Cancer Institute-Designated Cancer Center, professor in the Molecular and Cell Biology Laboratory and William R. Brody Chair, explores the role of lipid metabolism.

Ronald Evans, professor in the Gene Expression Laboratory and March of Dimes Chair in Molecular and Developmental Biology, investigates transcriptional and epigenetic targets.

Tony Hunter, American Cancer Society Professor in the Molecular and Cell Biology Laboratory and Renato Dulbecco Chair, will continue his renowned exploration of kinase drug targets.

Dannielle Engle, assistant professor in the Regulatory Biology Laboratory, addresses vulnerabilities in glycans, carbohydrates that coat proteins and cells.

Michael Downes, senior staff scientist in the Gene Expression Laboratory, will oversee the central core facility studying changes in pancreatic cancer and developing new models and therapeutic approaches.

"We are honored to be the first Lustgarten LAB on the West Coast, which really catalyzes the four participating labs to share common equipment and resources as we bring our individual areas of complementary expertise to bear on the collaborative goal of curing pancreatic cancer," says Shaw, lead investigator on the grant.

Salk's discoveries could lead to future therapies for cancer and diabetes

The Salk Institute has long been a driving force in improving human health through basic biological research. Great strides have been made in advancing the efficacy of treatments for diseases such as cancer. Now, promising new discoveries have the potential to deliver better outcomes to patients with colorectal cancer and diabetes.

EDWARD STITES

CELL REPORTS
12/2021

Improving drug options for colorectal cancer patients

A major issue in cancer medicine is matching patients with effective treatments. Although patients with colorectal cancer were among the first to receive targeted therapies, many were ineligible, as their cancer-promoting mutations were believed to cause resistance to certain drugs. Assistant Professor Edward Stites and first author Thomas McFall paired computational models and experimental data and discovered that up to 12,000 additional colon cancer patients could benefit from an existing class of targeted therapies. They hope that clinical trials will highlight the magnitude of these findings and motivate more research on these mutations.

Stites' team found and classified 10 drug-sensitive KRAS mutations (lighter). Also shown are some the drug-resistant mutations (darker).

Credit: *Cell Reports* and the Salk Institute

CELL METABOLISM
01/2022

A new route for regulating blood sugar levels independent of insulin

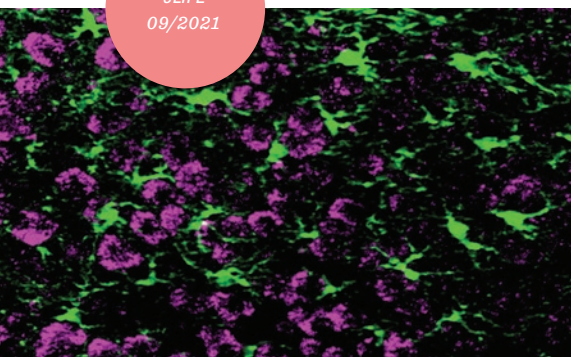
The discovery of insulin 100 years ago opened a door that would lead to life and hope for millions of people with diabetes. Since then, insulin, produced in the pancreas, has been considered the primary means of treating conditions characterized by high blood glucose, such as diabetes. Now, Professor Ronald Evans, first author Gencer Sancar and colleagues have discovered a second molecule called FGF1 that is produced in fat tissue and, like insulin, also potently and rapidly regulates blood glucose. Their finding could lead to the development of new diabetes therapies, and also lays the foundation for promising new avenues in metabolism research.

"Finding a second hormone that suppresses lipolysis and lowers glucose is a scientific breakthrough. We have identified a new player in regulating fat lipolysis that will help us understand how energy stores are managed in the body."

RONALD EVANS

NEUROSCIENCE

eLIFE
09/2021



Astrocytes (green) and neurons (magenta) closely interact in the developing cortex and signal to each other to ensure correct development.

CALL-AND-RESPONSE CIRCUIT TELLS NEURONS WHEN TO GROW SYNAPSES

Brain cells called astrocytes play a key role in helping neurons develop and function properly, but there's still a lot scientists don't understand about how astrocytes perform these important jobs. Now, Associate Professor Nicola Allen and colleagues have found one way that neurons and astrocytes work together to form healthy connections called synapses. This insight into normal astrocyte function could help scientists better understand disorders linked to problems with neuronal development, including autism spectrum disorders.

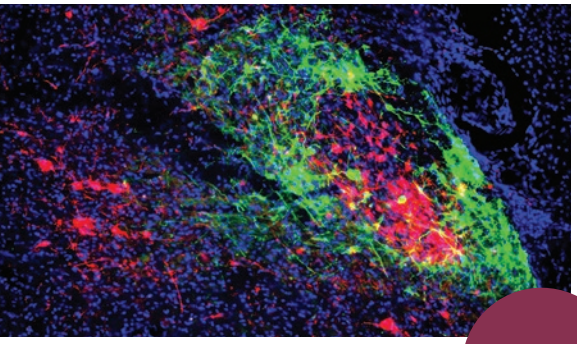
READING THE MIND OF A WORM

PLOS COMPUTATIONAL BIOLOGY
11/2021

Associate Professor Sreekanth Chalasani and colleagues have found a way to look at the brain activity of a worm and tell you which chemical the animal smelled a few seconds before. It sounds like a party trick, but these findings help scientists better understand how the brain functions and integrates information. The goal, of course, isn't to read the minds of worms, but to gain a deeper understanding of how humans encode information in the brain. These findings help scientists unravel what happens when this encoding goes awry in sensory processing disorders and related conditions, such as anxiety, ADHD and autism spectrum disorders.

"C. elegans seems to have attached a high value to sensing salt, using a completely different circuit configuration in the brain to respond. This might be because salt often represents bacteria, which is food for the worm."

SREEKANTH CHALASANI

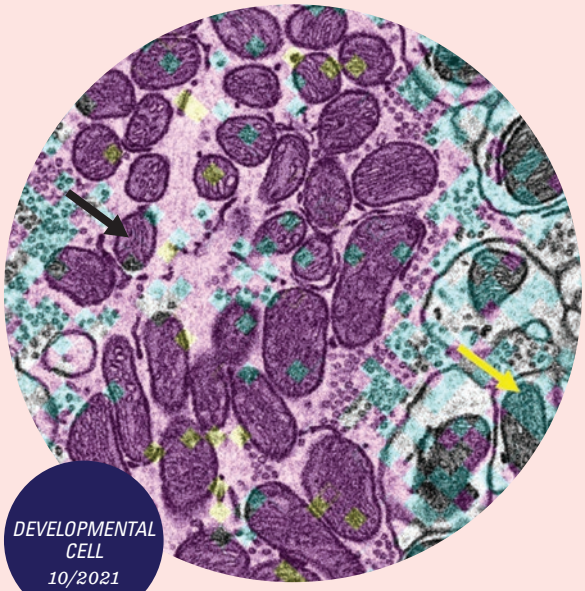


Shell neurons (green) that project to the breathing center and core neurons (red) that project to the pain/emotion center.

NEURON
12/2021

PAIN AND ANXIETY IMPACT BREATHING ON A CELLULAR LEVEL

You're startled by a threatening sound, and your breath quickens; you smash your elbow and pant in pain. Why a person's breathing rate increases dramatically when they're hurting or anxious was not previously understood. Now, Assistant Professor Sung Han, first author Shijia Liu and colleagues have uncovered a neural network in the brain that coordinates breathing rhythm with feelings of pain and fear. The findings contribute to the fields of pain management and psychological theories of anxiety. What's more, the study could lead to development of an analgesic that prevents opioid-induced respiratory depression, the disrupted breathing that causes overdose deaths. See Analysis on page 28.



DEVELOPMENTAL CELL 10/2021

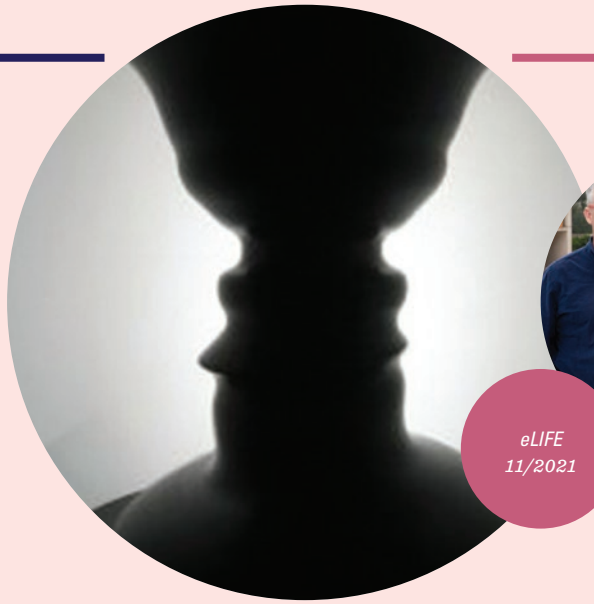
Clusters of long-lived mitochondria in neurons. Older mitochondria (black arrow, in maroon) and younger mitochondria (yellow arrow, in cyan) demonstrating age mosaicism (differential aging) among mitochondria in the brain.

LONG-LIVED PROTEINS IN BRAIN MITOCHONDRIA STABILIZE PROTEIN COMPLEXES

Mitochondria are known as the powerhouses of the cell, generating the energy that's needed to fuel the functions that our cells carry out. Senior Vice President and Chief Science Officer Martin Hetzer, first author Shefali Krishna and colleagues have taken a closer look at how mitochondria are maintained in nondividing cells, such as neurons. The researchers found that many of the proteins in mitochondria last much longer than expected, and that this stability likely protects them from damage. These findings will ultimately help researchers better understand age-related diseases, such as Alzheimer's disease, and offer insights on treatment and prevention.

WHICH SIDE IS WHICH: HOW THE BRAIN PERCEIVES BORDERS

Professor John Reynolds and first author Tom Franken have discovered that neurons deep in the brain's cortex are the first to compute which side of a visual border is an object versus a background. Through recording the activity of neurons in different layers of the cortex, the scientists were able to determine which particular cells were processing this border. Their discovery helps reveal how neurons communicate to supply us with internal representations of the external world. This work also provides researchers with better tools for diagnosing and treating brain disorders, such as schizophrenia.



eLIFE 11/2021

From left: John Reynolds and Tom Franken.

In the classic Rubin's vase optical illusion, neurons in the brain must decide whether the border between black and white belongs to the white area or to the black area, which determines whether you perceive the scene as either a black vase on a white background, or white faces on a black background.

Credit: Talking faces by solsken CC BY-NC-SA 2.0

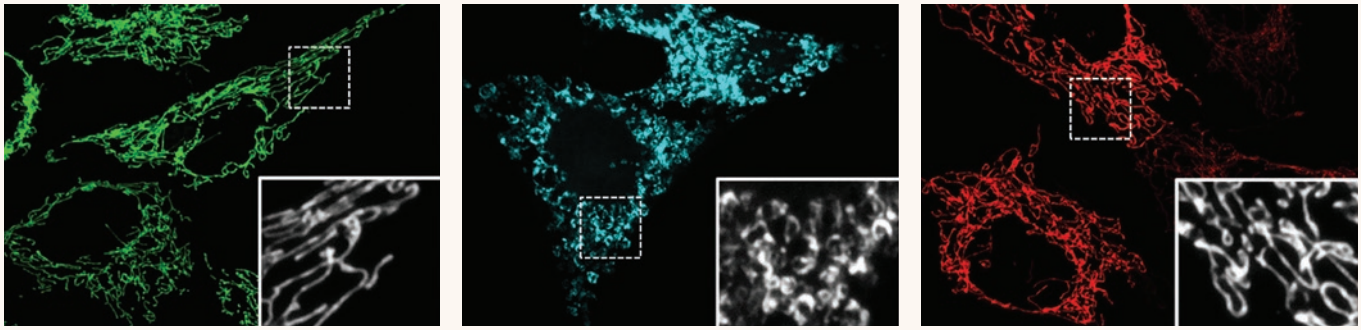
NEUROSCIENCE

NATURE COMMUNICATIONS 02/2022

IN A FIRST FOR "SONOGENETICS," RESEARCHERS CONTROL MAMMALIAN CELLS WITH SOUND

Clinicians treating brain disorders such as Parkinson's disease and epilepsy currently use deep brain stimulation, a process that involves surgically implanting electrodes in the brain, to activate certain subsets of cells. Now, Associate Professor Sreekanth Chalasani, co-first authors Marc Duque, Corinne Lee-Kubli and Yusuf Tufail, and colleagues have pinpointed a sound-sensitive mammalian protein that lets them activate brain cells with ultrasound. Pioneered by Chalasani, "sonogenetics" uses ultrasonic waves to stimulate specific groups of genetically marked cells. The finding paves the way toward non-invasive versions of deep brain stimulation, pacemakers and insulin pumps. See Resolution on page 12.

WATCH | www.salk.edu/chalasani202204



Healthy mitochondria (green); mitochondria showing the effects of oxidative stress (blue); and oxidative stress with cannabinol (red). Insets show higher magnification of the structure of the mitochondria.

ACTIVE INGREDIENT IN CANNABIS PROTECTS AGING BRAIN CELLS

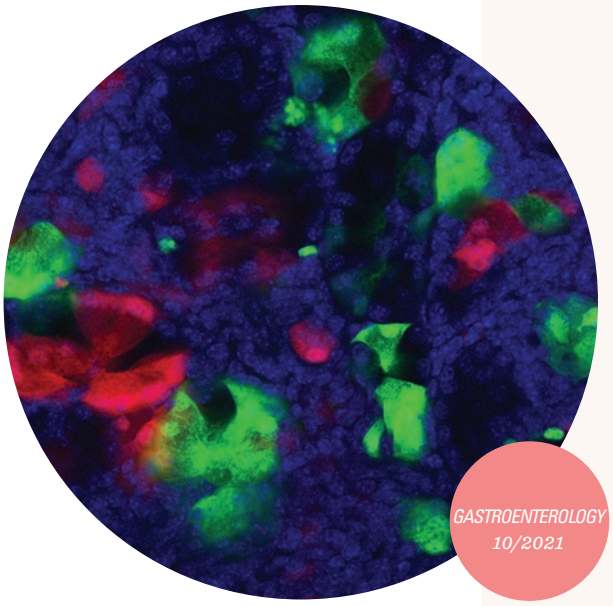
FREE RADICAL BIOLOGY AND MEDICINE 02/2022

Decades of research on medical cannabis has focused on the compounds THC and CBD in clinical applications. But less is known about the therapeutic properties of cannabinol. This molecule is derived from the cannabis plant, is molecularly similar to THC, but is not psychoactive. Now, Research Professor Pamela Maher, first author Zhibin Liang and colleagues have found that cannabinol can protect nerve cells from oxidative damage, a major pathway to cell death. The discovery suggests that cannabinol has the potential to treat age-related neurodegenerative diseases, such as Alzheimer's disease.

PAMELA MAHER

ZHIBIN LIANG

From left: Sammy Weiser Novak, Uri Manor, Geoffrey Wahl, Zhibo Ma, Nikki Lytle and Cynthia Ramos.



Pancreatic acinar cells form a diverse population of new cell types in response to injury, with the potential to limit or drive disease. Acinar-derived clones labeled in red and green.

HOW INJURY TO THE PANCREAS INFLUENCES CANCER DEVELOPMENT

In a study led by Professor Geoffrey Wahl and Vanderbilt Assistant Professor Kathy DelGiorno, first author Zhibo Ma and colleagues found that cells in the pancreas form new cell types to mitigate injury, but then become susceptible to cancerous mutations. Their findings establish a better understanding of the pancreas' healing mechanisms and offer insights into what happens when the process goes awry. Targeting these processes may lead to new treatments for patients with pancreatitis and pancreatic cancer.

PLANT BIOLOGY

The quillwort plant *Isoetes taiwanensis*.
Image credit: Yao-Moan Huang

NATURE COMMUNICATIONS 11/2021

SECRETS OF QUILLWORT PHOTOSYNTHESIS COULD BOOST CROP EFFICIENCY

The humble quillworts are an ancient group of approximately 250 small, aquatic plants that have largely been ignored by modern botanists. While most plants breathe in carbon dioxide (CO_2) during the day, quillworts breathe in CO_2 at night. Now, Research Professor Todd Michael and colleagues have sequenced the first quillwort genome to uncover new insights related to the plant's unique method of photosynthesis. Their discoveries could eventually lead to the engineering of crops that address climate change through more efficient water use and carbon capture.

PLANTS RELY ON THE CLASSY GENE FAMILY TO DIVERSIFY THEIR EPIGENOMES

NATURE COMMUNICATIONS 01/2022

What determines how a cell's genome is regulated to ensure proper growth and development? Turns out, the parts of the genome that are turned on or off in each cell-type or tissue play a major role in this process. Now, Associate Professor Julie Law, first author Ming Zhou and colleagues have shown that the CLASSY gene family regulates which parts of the genome are turned off in a tissue-specific manner. The discovery has the potential to advance many areas in biology, from boosting crop yields in plants to enhancing the efficacy of medical treatments for humans.

JULIE LAW

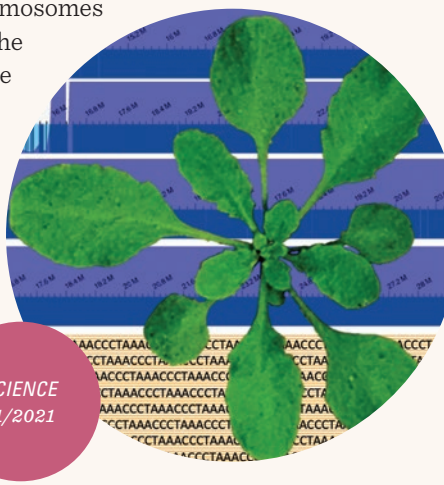
MING ZHOU

STUDY SHINES A LIGHT INTO "BLACK HOLES" IN THE *ARABIDOPSIS* GENOME

TODD MICHAEL

Research Professor Todd Michael and colleagues sequenced the genome of the world's most widely used model plant species, *Arabidopsis thaliana*, revealing new information about a region of its chromosomes called the centromere. The findings provide insights into centromere rapid evolution and the genomic equivalent of black holes. With this approach, scientists will be able to map centromeres from diverse *Arabidopsis* species, and ultimately more widely throughout plants.

SCIENCE 11/2021



The plant *Arabidopsis thaliana*.

Discover your legacy at the Salk Institute

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

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

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

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

Plan your future. We can help you get started.

salk®
Where cures begin.

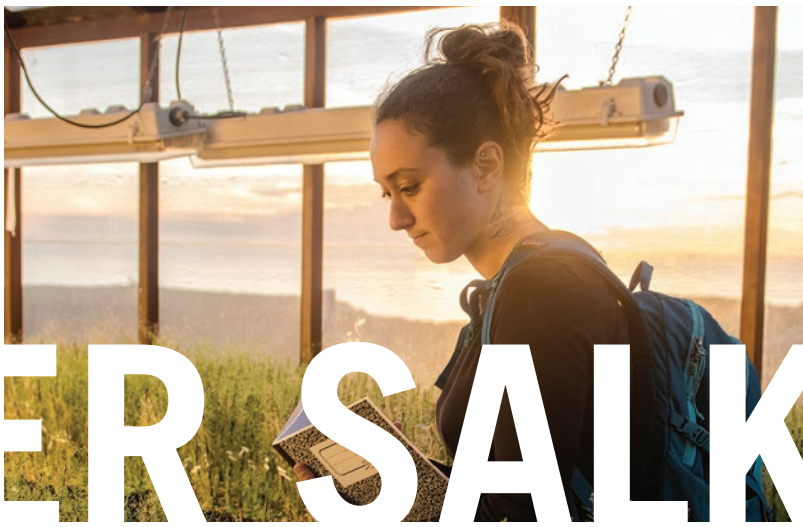
Contact Cheryl H. Dean, Esq., at cdean@salk.edu or 858.500.4884 for help finding the right gift plan.

RESOLUTION

Neurons in a mouse brain are shown here in magenta. The lab of Associate Professor Sreekanth Chalasani made some neurons (white) express the protein TRPA1 so they can be activated by ultrasound in a technique known as "sonogenetics." Sonogenetics is a powerful, non-invasive tool that allows researchers to control brain cells with sound waves. Chalasani coined the term and pioneered this technology, which could one day be used to treat neurological conditions, such as epilepsy and Parkinson's disease.

DISCOVER SALK

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



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

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

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

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

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

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

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

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

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

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

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

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The weed that changed the world

How *Arabidopsis thaliana* became one of the most important tools in science

Around Easter in 1905, a 20-year-old German botany student named Friedrich Laibach picked a small, flowering weed from the bank of the Lahn River near his hometown of Limburg, placing it in a solution of acetic acid for preservation.

Back in the lab at the University of Bonn, Laibach stained the plant's cells with dye and examined them under a microscope, noting that they had only five chromosomes. This excited his advisor, as it was the lowest odd number of chromosomes known to science at the time. (A plant with four chromosomes had been identified the year before.) The plant was *Arabidopsis thaliana* and—although the exact spot where Laibach collected it was paved over for the Autobahn in the 1930s and lost to history—the species has since become firmly rooted in the pantheon of biology's most important research tools.

Today, Laibach is credited with making *Arabidopsis thaliana*, a nondescript member of the mustard family, a model organism: one used to study basic biological functions, which may be applicable more widely. It's a mainstay of plant biology and genetics research owing not only to its small chromosome number but also to its compact size, rapid life cycle and prolific seed generation. In other words, it's relatively fast to sequence the plant's genome, it doesn't take up much lab space and multiple generations can be grown quickly, saving time and resources.

In 2000, *Arabidopsis thaliana* was one of the first organisms—and the first plant—to have its genome sequenced, beating the fruit fly, mouse and human to the punch. The seven-year, $70 million Arabidopsis Genome Initiative (AGI) involved multiple labs in Europe, Japan and the US working together to determine the DNA sequence of all five *Arabidopsis* chromosomes—the exact string of chemical building blocks (known as As, Ts, Cs and Gs) that spell out the plant's genetic code.

Salk Professors Joanne Chory and Joseph Ecker were instrumental in getting the initiative off the ground in the US, rallying influential *Arabidopsis* researchers around the idea, which led to significant funding with the National Science Foundation as the lead agency. (At the time, Ecker was at the University of Pennsylvania; he arrived at Salk in 2000.)

"In the early '90s, it was pretty clear that all of the model organisms at that time—yeast, fruit fly, worm and mouse—were headed toward having their genomes sequenced because it was really challenging to do science otherwise," says Ecker, who directs Salk's Genomic Analysis Laboratory, holds the Salk International Council Chair in Genetics and is a Howard Hughes Medical Institute investigator.

"So, those of us in the *Arabidopsis* community were asking, 'Are we going to let those other groups beat us to sequencing?' We wondered if people would even want to work on plants if there were better tools for other model systems."

After the initiative got underway, Ecker co-led a team of US-based researchers to sequence chromosome 1, the largest of the five *Arabidopsis* chromosomes. The other four chromosomes were sequenced by teams from the US, Japan and the European Union.

Chory, who made a big impact in plant biology with a 1989 paper revealing an *Arabidopsis* mutant that could grow in the dark, was asked to be a member of AGI's scientific advisory committee. "When I first arrived at Salk, we published a paper on a mutant called DET1. This mutant could grow in the dark like a light-grown plant, even though it was not exposed to any light. What was unique about our study was the application of genetic techniques to a problem that had been studied only by plant physiologists. It was the beginning of a huge revelation of how complex the pathways are that allow a plant to respond to light," says Chory, director of Salk's Plant Molecular and Cellular Biology Laboratory, Howard H. and Maryam R. Newman Chair in Plant Biology, and Howard Hughes Medical Institute investigator. "It was really hard to clone [identify] a gene with the tools that we had back then, and no overall sequence."

Deciphering the *Arabidopsis* genome was revolutionary for both plant biology and genetics. Before that, plant biologists who had an interesting mutant had been unable to clone genes to understand the molecular underpinnings (the mechanism) of how a mutation in such a gene could cause a dramatic phenotype—growing in the dark, for example, or tiny leaves. (In genetics, these known mutations are called markers.) The frequency with which the mutations show up together (dark-growing plants with tiny leaves) in the offspring can be used to map the genes relative to each other, although it takes many crosses (breeding plants)—with multiple markers—to get close to the gene of interest. In this way, and with a molecular technique called RFLP analysis, Chory was able to localize the DET1 gene to the top of chromosome 4.

Identifying the gene's chromosome was only the first step; figuring out the sequence and exact location in the genome was another laborious undertaking, which Chory accomplished for DET1 in 1994. In part, this involved

JOANNE CHORY

JOSEPH ECKER

"If we understand all these unique features of plants—the edge cases of how plants have adapted to very specific environments or specific physiologies or very specific architectures—then we can start to use that knowledge to build plants that do the specific things that we need."

TODD MICHAEL

searching a library of DNA fragments for one that overlapped the nearest marker. Then the nonoverlapping end was used to again search the library for another overlapping fragment. Repeated over and over, this process—known as chromosome walking—could eventually reach the gene of interest. Identifying and mapping a single gene within the genome could take a long time.

"I had a headache for six years," says Chory. "It was so much work."

The AGI made it possible for researchers to locate genes much more easily within the *Arabidopsis* genome. They could, for example, look for DNA sequences that are telltale signs of genes. Or they could look for gene sequences already known from other plants and see if they were also present in the *Arabidopsis* genome.

Most importantly, researchers could use a method called plant transformation to identify unknown genes in the genome. One of the keys to this method is a bacterium called *Agrobacterium tumefaciens*, which infects plants. The bacterium does so to randomly insert its own DNA, in the form of a circular structure called a plasmid, into the plant's genome. The bacterial DNA causes the plant to form a crown gall or tumor.

Scientists figured out how to replace the bacterial DNA with custom DNA (known as a T-DNA insertion line), which *Agrobacterium* ferries into the plant. (Viruses are used in a similar way to deliver gene therapies into human cells.) If the T-DNA lands in a gene, it can cause a mutation—for example, a plant that produces petals where the stamens would normally be. Then scientists can locate their T-DNA within the genome and know that it must have landed in a gene related to flower development. They can sequence that region and identify the gene.

With this approach, using hundreds of thousands of T-DNA insertion lines, scientists have managed to identify, to some degree, all of *Arabidopsis*' approximately 28,000 genes.

One of the scientific community's most important T-DNA insertion collections, or sequence-indexed insertion mutant libraries, was created by Ecker and other Salk researchers. These insertions are known as "Salk lines." Younger plant scientists and geneticists may not have heard about Jonas Salk and the polio vaccine, says Ecker, but they're very familiar with Salk lines, which can be ordered from a Salk website. To date, the database has been accessed more than 11 million times, typically 4,000 times per month. Salk also provides seeds to the global *Arabidopsis* research community via two seed banks.

Branching out

The original AGI didn't assemble the entire *Arabidopsis* genome; it left some regions unfinished that were challenging to complete with the methods of the time. These included the centromere, a constricted area near the middle of a chromosome that is important for cell division. Recently, Salk Research Professor Todd Michael collaborated on a project to sequence and assemble the *Arabidopsis* centromeres, which had been hard to do previously because they contain many long, repetitive segments, and earlier sequencing techniques were better suited to deciphering short, variable segments.

An expert in genome sequencing, assembly and analysis, Michael has branched out from *Arabidopsis*. In 2015, he published the first near-complete genome of the drought-tolerant grass *Oropetium thomaeum*, which revealed complete centromere structure for the first time. More recently, his lab sequenced quillworts, small aquatic plants with a unique method of photosynthesis, and *Wolffia*, the world's fastest-growing plant, known colloquially as duckweed. He is also working on a collaboration to sequence the pan-genome of sorghum, one of the top five cereal plants in the world. Sorghum is drought-resistant and grows well on marginal land, making it agriculturally important in a warming world. Although sorghum was initially sequenced a decade ago, scientists want to sequence many more breeding lines and wild relatives. The pan-genome comprises the complete set of genes within a species and allows scientists to accelerate the breeding of new disease-resistant, drought-tolerant and higher-yielding varieties.

Michael's goal in sequencing structurally and functionally unique plants is to discover how genomic differences enable plants to better respond to and exploit their environment. Such knowledge is vital to the Harnessing Plants Initiative, Salk's approach to mitigating climate change by developing crops and wetland plants that can capture excess carbon dioxide from the atmosphere and store it underground in long-lasting roots.

"The holy grail of agriculture is to design plants that do what we want them to do," says Michael. "If we understand all these unique features of plants—the edge cases of how plants have adapted to very specific environments or specific physiologies or very specific architectures—then we can start to use that knowledge to build plants that do the specific things that we need."

Prior to joining Salk, Michael worked for a time at the agricultural biotechnology company Monsanto, where one of his projects was to sequence *Arabidopsis* strains other than the original strain sequenced in the AGI. Just as no two humans (except for identical twins) have exactly the same DNA, different strains of *Arabidopsis* also have slightly different DNA. Some strains may be more drought-tolerant than others or more disease-resistant. Some may bloom earlier or have longer roots. Ecker co-initiated a project with European and American colleagues called the 1,001 Genomes Project to sequence the genomes of many different strains and involved Michael in the effort. (The name was a playful nod to the human genome sequencing community, which had a 1,000 Genomes Project underway.)

Professor Wolfgang Busch, who along with Chory is codirector of Salk's Harnessing Plants Initiative, is one of the leading experts in using a method called genome-wide association studies (GWAS) to find genes and mechanisms that are responsible for plant features in various strains

"The hope is to use genes to engineer crops with more and deeper roots that can store more carbon captured from the atmosphere."

WOLFGANG BUSCH

and has pioneered these approaches for root characteristics. A major component of his success is to use an integrated approach leveraging genetics, genomics and computational approaches along with molecular and cellular biology to learn how root characteristics are encoded in the genetic blueprint of plants.

Over the years, Busch has identified numerous genes using this approach, including a gene that makes roots deeper—a major success for the Harnessing Plants Initiative. The hope is to use genes to engineer crops with more and deeper roots that can store more carbon captured from the atmosphere. He has already taken an important next step in this work, as he is using his arsenal of tools to work on all Harnessing Plant Initiative target crop species. He conducts experiments not only in the laboratory and the greenhouse but also at multiple field locations in the US and South America.

"I started my scientific journey into the systems biology of plant development during my PhD at the Max Planck Institute for Developmental Biology in Tübingen, Germany, in Detlef Weigel's department," says Busch, who holds the Hess Chair in Plant Science. "Detlef had just moved there from Salk, so of course I got immersed in all these stories about the exciting plant science that had been going on at Salk. And then, almost all the mutant lines I worked with were from the legendary Salk T-DNA mutant collection that Joe Ecker had established. Salk was all around me already back then."

JULIE LAW

DNA methylation is a type of epigenetic modification in which a chemical tag called a methyl group is attached to DNA like a Post-it note reminder that says, "Keep off."

Going beyond genes: Epigenetic Post-it notes

Though much of the work of Salk's plant biologists concerns genetics—DNA sequences and the genes they encode—another fraction involves epigenetics, the various mechanisms that turn genes on or off without affecting the underlying DNA sequence. Epigenetic modifications are how different types of cells—root cells, stem cells, leaf cells—can all have the same DNA but function differently.

Associate Professor Julie Law studies epigenetic modifications using *Arabidopsis* because it's such a good model for genetic experiments.

"Mutations that would be lethal in animal cells can be studied effectively in plants," says Law. "And their short life span allows scientists to study the effects of experimental manipulations over multiple generations and collect a large amount of epigenetic information over a short time."

Her work has important implications for the Harnessing Plants Initiative, which may be able to use genetic and epigenetic methods to further increase the carbon storage capacity of plants.

Law's research also has relevance for human health and disease because the same epigenetic processes that are at work in plant cells are also at work in human cells—heart, liver and skin cells all have the same DNA, but they have different functions based on which of their genes are active.

Recently, Law's lab published a study of how genes in the *Arabidopsis* CLSY family (pronounced "classy") control DNA methylation patterns during plant development. DNA methylation is a type of epigenetic modification in which a chemical tag called a methyl group is attached to DNA like a Post-it note reminder that says, "Keep off." Depending on the plant tissue, different CLSY family members take the lead on targeting where DNA methylation is located, and this results in different patterns of DNA methylation in different plant tissues. Given the roles of DNA methylation in keeping the correct set of genomic regions turned off, these findings may open the door to advances in many areas, from boosting crop yields in plants to informing precision medicine in humans.

Joanne Chory and Joseph Ecker clarified another epigenetic mechanism in a 2021 paper showing that shade from close-growing neighbors causes plants to grow taller. The study looked at the role of proteins called transcription factors in activating this growth response. Transcription factors turn genes on or off by binding to DNA. The team worked with mutant *Arabidopsis* seedlings that lacked transcription

"Wetland plants sequester as much as 100 times more carbon per acre than dry land plants, so an important part of our work in the Harnessing Plants Initiative is to study the genes and genomes of wetlands plants to inform increasingly critical wetland restoration efforts."

JOSEPH NOEL

factors called PIFs. When the team grew these plants in simulated shade, the plants without certain PIFs did not elongate or speed up their growth, suggesting that those PIFs are necessary for rapid growth. Further experiments showed that within five minutes of shade onset, the PIF7 protein gets activated and removes an additional epigenetic stop sign called H2A.Z. With the brakes off the growth genes, shaded plants are free to shoot up.

Chory says the work shows how plants respond to subtle environmental changes on the cellular level, as will increasingly occur as plants adapt to global climate changes.

From left: Joseph Noel and Todd Michael don waterproof pants to collect wetland plants for sequencing.

Credit: Spectrum News

Adapting and advancing

Professor Joseph Noel, also a member of Salk's plant biology team, is interested in how plants have already adapted to nearly every ecosystem on Earth by evolving unique ways to make their own specialized products. Although he has employed *Arabidopsis* in the past, he more typically uses biochemistry techniques to study the structure and chemistry of compounds produced by many types of plants.

For example, as part of the Harnessing Plants Initiative, Noel analyzes suberin, the carbon-rich molecule that protects plants from environmental stressors such as drought, floods, disease and salt. It's found in cork as well as cantaloupe rinds and avocado skins. Noel, director of Salk's Jack H. Skirball Center for Chemical Biology and Proteomics, is the lead researcher for the Harnessing Plants Initiative's Coastal Plant Restoration project. This effort aims to develop wetland plants that hold carbon, purify water, preserve land and can thrive in challenging environments around the world.

"People often don't realize the importance of wetlands in addressing climate change," says Noel, who holds the Arthur and Julie Woodrow Chair. "Wetland plants sequester as much as 100 times more carbon per acre than dry land plants, so an important part of our work in the Harnessing Plants Initiative is to study the genes and genomes of wetlands plants to inform increasingly critical wetland restoration efforts."

Noel and Michael routinely don waterproof pants and wade into San Diego's marshes to collect wetland plants to sequence back in the lab.

Sequencing has advanced by leaps and bounds since 2000, when the first *Arabidopsis* genome was published. The AGI was an international collaboration that took seven years and $70 million; today, Ecker can sequence an *Arabidopsis* genome in three minutes for around $16 using a printer-sized machine outside his office. And it will be done more thoroughly that way, he says, because the machine will run through the genome 30 times to ensure high accuracy.

"Now that's a model for success."

From lab to greenhouse to field

The goal of Salk's Harnessing Plants Initiative is to use two of Earth's existing carbon storage mechanisms—plant roots and wetlands—to help mitigate climate change. Salk plant biologists are working hard to optimize crops (Salk Ideal Plants™) to absorb an increasing amount of excess carbon from the atmosphere and store it in the ground, in roots that have increased capacity and can bury the carbon deep.

But to be successful, their research efforts will need to continue to scale up.

In 2016, when Salk plant scientists identified climate change as an important area of research, just four faculty members were studying plants. The labs of Professors Joanne Chory, Joseph Ecker, Joseph Noel and Associate Professor Julie Law had approximately 50 total members. Their labs were in three different buildings (one of which was a trailer), and plants were grown in two scenic but rundown greenhouses perched above the Pacific Ocean at the west end of the campus.

A lot has changed.

Professor Wolfgang Busch and Research Professor Todd Michael joined the plant biology faculty, and together the six labs now have approximately 90 members. Four large (walk-in) and 12 smaller climate-simulation chambers have been constructed in Salk's East Building, allowing the plant team to reproduce the climate of almost any location on Earth. A custom-built seed-planting robot designed by Busch can accomplish in one day what would take a human researcher five weeks. A state-of-the-art, 10,000-square-foot offsite greenhouse allows researchers to rapidly move discoveries from the laboratory into the greenhouse. Small-scale field trials of Salk Ideal Plants™ have begun in several locations across the US and abroad. And the trailer is being retired.

The rapid growth of the Harnessing Plants Initiative program came when Chory was selected as a beneficiary of the 2019 TED Audacious program, which resulted in the Harnessing Plants Initiative program receiving more than $35 million in new donations. The program has gained additional support since then from individual donors, foundations and businesses, including the Bezos Earth Fund, Sempra Energy and Hess Corporation.

But cooling our warming planet is a monumental challenge. Salk will need to add research personnel, emerging technologies and expanded research space.

Last fall, Salk launched the $500 million Campaign for the Future, a philanthropic and scientific campaign to acquire the people, technology and space necessary to expand Salk's research to change the world for the better. In addition to recruiting new faculty and leveraging emerging technologies, the Campaign includes the construction of the Joan and Irwin Jacobs Science and Technology Center on the Salk campus. The Jacobs, longtime Salk supporters for whom the Center is named, will donate $1 for every $2 raised from other sources, up to a $100 million. **The Institute has until September 30, 2022, to meet the match.**

Designed to create research space with the same principles Jonas Salk and architect Louis Kahn applied to the original buildings, the new center will allow the Institute to add scientists from multiple disciplines; expand collaborations between plant scientists, biologists, bioengineers and information theorists; and provide the critical space to work together on the world's most challenging problems.

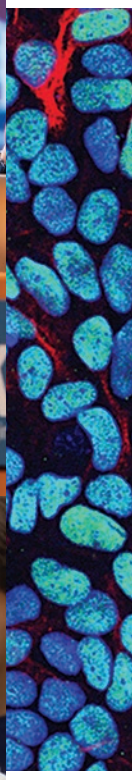
Once completed and fully staffed, the Joan and Irwin Jacobs Science and Technology Center will provide a home for the Center for Plant Biology, one of four Salk Centers of Excellence. It will host meetings between scientists, government officials and agriculture-industry partners, who will be key to scaling up worldwide distribution of Salk Ideal Plants.

If you are interested in learning more about how you can make a difference in our work on climate change, contact Jane Rhett at (858) 453-4100 x1521 or jrhett@salk.edu. Climate change is a global problem that will require solutions from around the globe and participation by all of us.

To learn more about the Campaign for the Future, visit www.salk.edu/resilient.

Salk Education Outreach

Hands-On Science Education



teach
inspire
promote

Jonas Salk founded the Salk Institute with the philosophy that it should both drive scientific breakthroughs and inspire the next generation of elite scientists. Out of Jonas Salk's vision, the Institute's Education Outreach program was born. Its mission is threefold:

To teach
students, teachers and the community about scientific literacy in addition to the role of basic biological research in our world.

To inspire
enthusiasm and interest in advanced levels of science instruction, and particularly in science as a career.

To promote
public awareness of Salk and the value of basic research as it relates to career readiness, critical thinking skills and the development of an informed citizenry.

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Hands-on Science Education

Salk Education Outreach serves San Diego County students, teachers and other community members through its programs: Mobile Science Lab, Heithoff-Brody High School Summer Scholars, March of Dimes High School Science Day, SciChats@Salk and the Ellen Potter Research Connections for Teachers Symposium. These programs are offered at no cost to students, teachers and schools, thereby reducing economic barriers to high-quality STEM education. Over the past 40 years, Salk Education Outreach has delivered innovative, engaging STEM learning experiences to thousands of students—a majority of whom come from underrepresented and underserved communities.

To learn more about Education Outreach, please email **education@salk.edu**.

OBSERVATIONS

KENTA ASAHINA

Flying into the future of technology and innovation

Originally from Chiba, Japan, Associate Professor Kenta Asahina grew up exploring the farmland outside his town with his two brothers in search of insects and plants. Their dad enjoyed taking them to the mountains and national parks, and these experiences inspired Asahina's interest in the natural world from a young age.

Asahina, who holds the Helen McLoraine Developmental Chair in Neurobiology, now studies how genetics impact behavior in fruit flies, as part of Salk's Molecular Neurobiology Laboratory. Although tiny flies may seem a far reach from humans, his work consistently demonstrates the many similarities between insects and humans, including our need for social interaction and how our genes may work in similar ways to cause disease.

Inside Salk *sat down with Asahina to learn about his path to becoming a scientist, his work and his vision for Salk's future.*

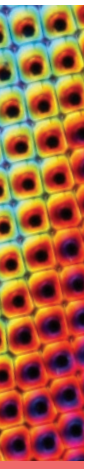
Did you always want to become a scientist?

KA: Actually, no. I didn't really know what the career of a scientist looked like since all of my close relatives were humanities or art majors. But I was very interested in biology, so I followed my passion to pursue zoology at the University of Tokyo. The university has great biology professors and is known for producing excellent scientists, so I was elated to attend. My senior year, I joined a lab to focus on research and studied the molecular biology of honeybees and their social behavior.

From there, I went to Rockefeller University in New York for my PhD. I had never lived outside of Japan before, but the United States is the center of the world's research activity. Although I was far from my family in Japan, moving to the US was one of the best decisions of my life because I was exposed to so many diverse perspectives.

Why did you switch your focus to studying fruit flies?

KA: I found that the genetic tools were very limited in the honeybee model. I realized that if I wanted to pursue more rigorous, cutting-edge research then I would need to switch to a model organism that was more readily used, and with more existing technologies. Using the common fruit fly *Drosophila melanogaster* as a model was a natural choice for me because I was still very interested in studying the behavior of insects. I have an affinity towards insects as these were the kinds of animals I played with as a kid. In my research, one thing I like to do is test how a specific gene and neuron control behavior. So, I was eager to learn about the state-of-the-art neurogenetic techniques available in the fly model.



Why are fruit flies a great model species for studying genes and behavior?

KA: Thanks to a long history of scientists using flies as a genetic model, there are so many powerful genetic resources available to study this animal species. It's not exaggeration to say we can manipulate virtually any gene or neuron in the fly. In addition, the body of a fruit fly is segmented, and their body movement is limited. Thus, you can use computational analysis to easily quantify their behavior, such as courtship and fighting, with high accuracy. Fruit flies also have a short life span of about four to eight weeks, which is a great advantage when studying aging.

And as a member of the San Diego Nathan Shock Center, a consortium of local research institutions, how are you using fruit flies to study aging?

KA: The goal of the Nathan Shock Center is to better understand aging to advance personalized interventions that could increase the number of years of healthy life (health span). I study how genes and neurons lead to the control of social behavior, but I also recently started looking at how social isolation affects long-term health. I was curious to see how social isolation affected aging and life span. Then the pandemic happened, and my work became especially relevant.

And what did you find about social isolation?

KA: Well, it's interesting. We examined the effects of social isolation on male versus female flies to see how their behavior differed. Because flies have neurons that are specific to each sex, in the lab we can make a male fly that has a female brain and vice versa. In other words, in flies, we can dissociate the sex of the brain with the sex of the body. That can be useful for understanding the impact either body sex or brain sex has on life span.

We found that our "normal" or fully female flies live longer than males. Interestingly, the females with male brains do not live as long as the normal females. The male-type brain seems to shorten their life span for some reason, and we want to know what is causing this altered life span. One possibility is that male-specific behaviors, such as mating, or behavioral motivations may be energetically costly. The fact that the brain can influence the life span of animals is very interesting.

Does this finding have any relevance in humans?

KA: It will be interesting to see if this kind of life span flexibility that we observed in the fly also occurs in humans. While food, exercise and sleep are all important for a healthy life, experiments in the fly may tell us something about how mental health can impact health and longevity. Statistically, we do know that social isolation is a health risk factor for many conditions. For example, elderly people who are isolated tend to suffer more, which reduces their life and health spans. Thus, it is critical to better understand how social interactions and mental health play a role in longevity. So, animal models, like flies, can be an inspiring way to look at human health.

"The body of a fruit fly is segmented, and their body movement is limited. Thus, you can use computational analysis to easily quantify their behavior with high accuracy. Fruit flies also have a short life span of only one to two weeks, which is helpful for studying genetic manipulation. This shorter life span is also a great advantage when studying aging."

KENTA ASAHINA

And what can a fruit fly tell us about human brain disorders?

KA: Obviously, flies are not humans, and some diseases do have specific origins in the human brain. But we can use flies to go down to the molecular level to unravel how genes and cells malfunction, causing the problems that can lead to disease. Once we know which genes are involved, we can study their molecular function and their role in cells and tissues, which often does translate to other animals, including humans. It is worth mentioning that genes that govern our sleep cycles were originally found in flies. These molecules control human wakefulness with exactly the same mechanisms as in flies.

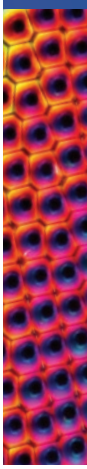
My lab also identified a small fly molecule used for cell-to-cell communications in the brain as a key regulator of aggressive behavior. Surprisingly, this molecule is important for controlling aggression in mice, rats and cats, and there is a study that links aggressive behavioral disorder in humans to the same molecule. The human neuron and the fly neuron may not be the same, but the genes often work in similar ways.

How do genes lead to behavior?

KA: That's an important question! This is one of the biggest challenges in neuroscience today. We can identify gene function and how that impacts individual neurons, but how that translates to an external behavior is difficult to study. And it begs the question, which is more important—nature or nurture? The answer is both! As a geneticist by training, I cannot overemphasize that genes do not determine your fate.

Even if animals have the same genetic makeup, if you raise them in different environments, then they're going to act very differently. But genes also have a major impact because if an animal has a particular gene mutation, then it may respond differently to an environmental change than one without the mutation. Thus, genes play a role in how sensitive we may be to a particular environment. For example, even if someone has a genetic mutation making them more susceptible to a certain cancer, there are a lot of lifestyle changes they can make to help live a long, healthy life.

I believe that scientists need to start taking environmental variability into account. In other words, how nature and nurture interact is a critical question moving forward. Doing this will make the research more complicated, but the findings will be more interesting. And with the fly as a model, we are in a great position to carry out these types of experiments.



How will Salk's Campaign for the Future help with those experimental goals?

KA: Our world is changing quickly, and experiments are getting more complicated and more demanding. Our current technologies limit us from doing the exact experiments we want to do, and we can't just order new devices because they don't yet exist. We need to create new technology to answer new questions. The Campaign for the Future is a $500 million philanthropic and scientific campaign that will reimagine Salk's campus by adding critical laboratory, technology and engineering space to accelerate Salk's innovative research tackling some of the most challenging problems facing humanity.

The Computational and Engineering Center of Excellence in the planned Joan and Irwin Jacobs Science and Technology Center is designed to allow for collaboration between a team of in-house engineers and Salk scientists. For example, I might draw a sketch of what I need specifically for our experiments, then the engineers would make a prototype, which my lab could test and provide feedback for the engineers to create an even better product. This process would allow us to develop cutting-edge, commercially unavailable devices quickly and efficiently. With the new Center, engineers and biologists will be able to work together to invent new devices to keep Salk's research ahead of the curve. If we want to make big improvements in human health, then we need answers as soon as possible.

Shining the spotlight on aging to find a cure for Alzheimer's disease

When Courtney Glavis-Bloom was in high school, her maternal grandparents were diagnosed with Alzheimer's disease.

"I flew out to Texas to see my grandparents with my mom, and we found the turkey that we had sent them for Thanksgiving still in the fridge. It was springtime, so we knew something had to be done," she says.

Her grandparents moved to San Diego and, as their caregiver for many years, Glavis-Bloom saw firsthand how dementia robs individuals of their connections to each other, family and the world.

Now, as a senior staff scientist in the lab of Professor John Reynolds, Glavis-Bloom studies the brain areas and pathways that are affected in aging in the hope of finding a cure for Alzheimer's.

INSIGHTS

Courtney Glavis-Bloom

EARLY LIFE

As a teenager in San Diego's Scripps Ranch neighborhood, Glavis-Bloom balanced a competitive softball career with serving as science team president at La Jolla High School. Her talent as a pitcher got her recruited to Yale University's softball team. However, shortly after arriving, she sustained a career-ending wrist injury.

"Although I was initially devasted by the injury, it was a blessing in disguise," says Glavis-Bloom. "I used to have softball practice twice a day, and the courses I could take were limited because of my schedule. After the injury, I was able to take more science courses and work in three different science labs simultaneously."

PATH TO SALK

At Yale, Glavis-Bloom initially intended to become a veterinarian. However, studying the brain offered another exciting avenue, and Glavis-Bloom shifted her studies to focus on neuroscience.

"The brain is resilient and filled with cells that last our entire lives," she says. "The more I thought about it, the more I became enthralled with learning about the aging brain and cognition."

During her PhD in neuroscience and animal behavior at Emory University, Glavis-Bloom studied a memory center of the brain called the hippocampus and how the brain compensates when this region is injured. She wanted to understand why the brain can adapt to injury early in life but can't compensate enough in old age or in age-related neurodegenerative diseases, such as Alzheimer's. Her work led to a few non-academic positions where she examined how potential therapies could aid cognition in healthy brains and those with Alzheimer's degeneration.

In 2018, a multidisciplinary team of Salk researchers, including Reynolds, was awarded $19.2 million over eight years by the American Heart Association-Allen Initiative to study aging and why the process is the primary risk factor for neurodegenerative diseases. It was a natural fit for Glavis-Bloom to join Reynolds' team as a staff scientist to examine age-related cognitive decline across the life span.

"The collaborative spirit of the Salk community drew me in," says Glavis-Bloom. "And joining the Reynolds lab was a perfect mixture of being able to study cognition as well as the factors that occur during aging that lead to neurodegeneration."

RESEARCH AT SALK

At Salk, Glavis-Bloom is looking at aging across multiple time points to better understand cognition in normal aging, which can help inform age-related disease states. In addition to designing and implementing cognitive tests that detect brain changes with aging, Glavis-Bloom is working with Professor Rusty Gage's lab to transform skin sample cells into neurons to see how they change with age. They're also using high-powered imaging techniques to look at how neurons communicate at various stages across the life span.

"If we don't understand normal aging, then we can't possibly treat age-related disorders," she says. "We want to figure out what the normal cellular and biological underpinnings of aging and cognitive decline are."

DAY-TO-DAY

Although her daily schedule is full of conducting experiments and writing scientific papers, Glavis-Bloom also spends time mentoring aspiring scientists from her lab and the Kavli Institute for Brain and Mind, at Salk and UC San Diego.

"I find it incredibly fulfilling to be able to mentor and teach while pursuing my own scientific goals," she says. "The ultimate goal is to combine moving the science forward while growing the next generation of scientists. The ideas that come from conversations with my mentees are genuine and often drive our science in new and exciting directions."

FUN FACT

Glavis-Bloom dreams of owning a bookstore that would specialize in neuroscience and general science books to help make science accessible to all.

LEISURE TIME

Although she still plays a little softball for fun, Glavis-Bloom now spends most of her free time hanging out with her two children, Emma and Wyatt. She also loves gardening; raised garden beds line her backyard, where her family strives to grow much of what they eat.

LONG VIEW/FUTURE PROJECTS

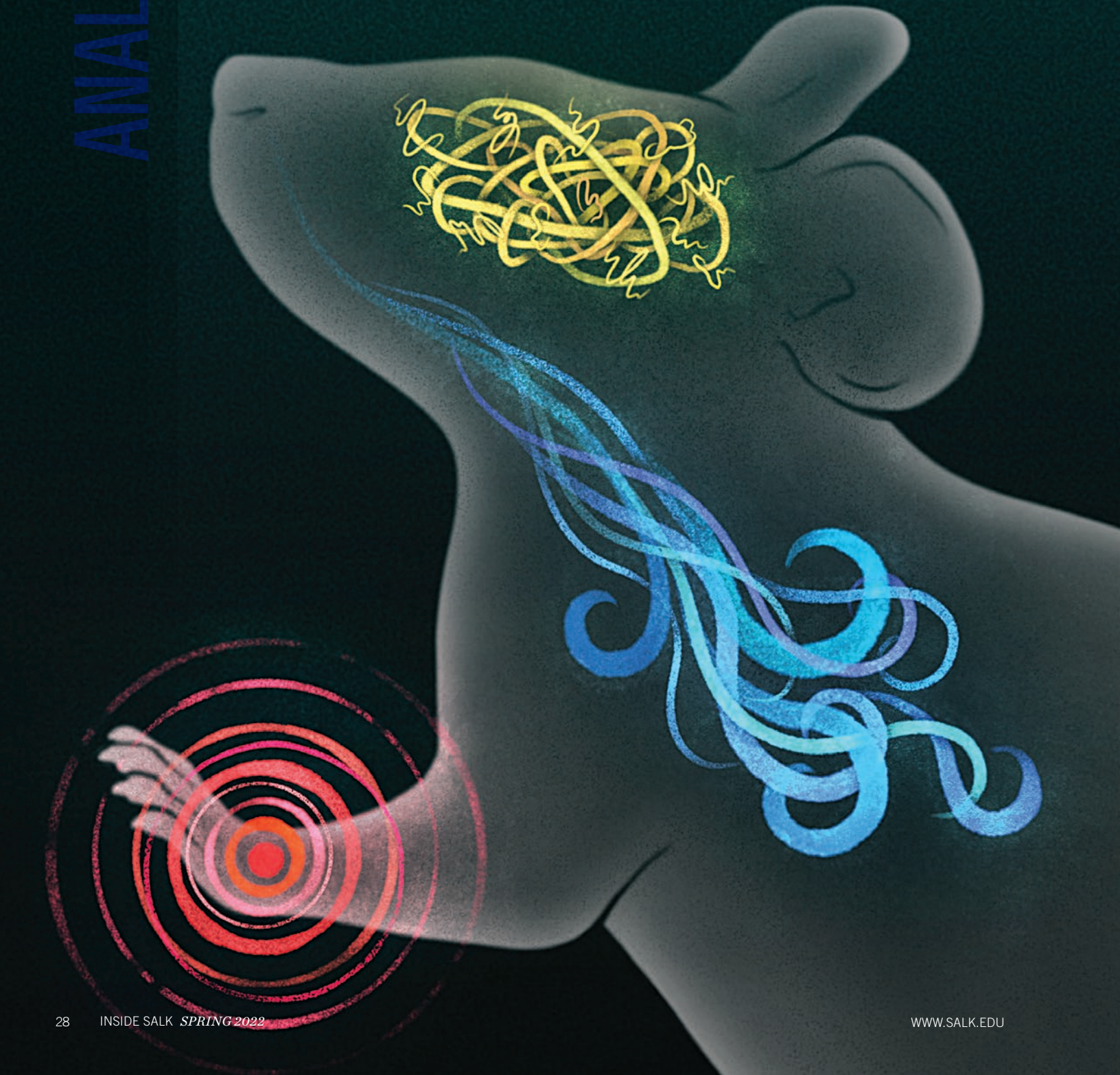
"I think there's hope for the fields of aging and Alzheimer's research. These problems aren't unsolvable, but they're some of the toughest problems in medicine," says Glavis-Bloom. "I think it's going to take large-scale collaborative research to make significant progress." She is hopeful a cure for Alzheimer's will be discovered and available for the next generation.

Breathing can be heavily influenced by pain or internal emotional states, according to a recent study by Assistant Professor Sung Han, first author Shijia Liu and colleagues. The team discovered how a neural circuit coordinates breathing with pain and negative emotions.

In this illustration, breathing is represented by the blue waves flowing along the airway, pain is represented by the red circles centered on the paw, and emotion is represented by the yellow entangled thoughts in the brain. Collectively, this artwork depicts the dynamic coordination of breathing with pain and emotion in mice.

This artwork, by Salk's science illustrator Amy Cao, was selected to appear on the cover of the March 2, 2022, issue of the journal *Neuron* to accompany the Salk team's paper.

Image credit: Salk Institute, reprinted with permission from Cell Press.



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MAY 15 — **ZLATA CHOCHIEVA,** piano

JUNE 12 — **SEAN CHEN,** piano

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DONOR PROFILE

How would you change the world?

These generous supporters gave to Salk's **Campaign for the Future: Building a More Resilient World** in varying amounts, big and small, each crucial and deeply appreciated. The impact of their gifts will be maximized through the generosity of Irwin and Joan Jacobs' match challenge (they will contribute $1 for every $2 donated—up to $100 million—for every new gift), and fully realized once Salk completes construction of the new state-of-the-art, 100,000-square-foot Joan and Irwin Jacobs Science and Technology Center.

In order to accomplish that, we want your partnership as well. Science is a collaborative pursuit, and without your support, Salk could not undertake the bold research needed to understand the biology behind our body's resilience to disease, to stem climate change and to transform the health of the world for the better.

Learn why each of these donors chose to support the Institute's five-year, $500 million vision to expand and accelerate Salk's critical research.

Suhaila White

Suhaila White takes great pride in being a Salk alumna. Her first professional job was at the Institute, where for 14 years she worked as a cancer research assistant in Ian Trowbridge's lab. She left Salk in 2000 only when Trowbridge retired. Since then, White has consistently supported Salk, saying she has a strong obligation to "pay it forward" for the opportunities Salk and Trowbridge provided her.

White contributed to the Campaign in part because she's excited for the new Joan and Irwin Jacobs Science and Technology Center that will house four Centers of Excellence, including one focused on cancer research, her passion.

"I think globally and act locally, keeping in mind that giving to your community makes the most difference."

"I consider Salk my community, so what better way to help my community than to give to this Campaign? I would like to see many people join this Campaign, because the bottom line is that every dollar counts."

SUHAILA WHITE

Carol and John Gallagher

Carol and John Gallagher first heard about Salk's Campaign for the Future at Symphony at Salk last summer and were immediately excited. Carol Gallagher, who serves as the chair of the Salk Women & Science Advisory Committee, says they were discussing how to best support the Campaign when the Jacobs established a match challenge. The Gallaghers didn't delay in making a generous contribution of their own.

"We were thrilled about the plans for the next 60 years of Salk science and the clear vision of how to execute on that," Carol Gallagher says. "If you're considering whether to give, don't delay. Make sure you can get your gift included in this match. Campaigns like this take a lot of hard work and a lot of money, and every gift, no matter the amount, is crucial."

Thomas Grant

Thomas Grant's philanthropic giving is informed by his love of family. The father of a seven-year-old son, Grant lost both his parents to cancer, which prompted him to become an ardent supporter of cancer research.

"I want to be there for my son's future," Grant says. "Health comes first. If you're not healthy, you can't contribute or support your family."

When he learned about Salk's Campaign for the Future and the increased emphasis Salk's vision places on cancer research, he was thrilled to lend his support.

"Salk is our future. They have the best people, are at the cutting edge of research on cancer—and many other ailments—and I truly believe Salk is spearheading scientific breakthroughs that will improve the health of the world," he says.

Paul Naour and Ann Hesselink

Retired behavioral neuroscientist Paul Naour and Ann Hesselink, a financial lawyer, recently decided to take a strategic approach to their giving and focus their support on places and efforts where their donations could make the most impact. Salk made their list, and when they read about the Jacobs' match challenge in a local newspaper they stepped up.

"Giving to the Campaign was an opportunity for us to become a part of a larger picture and ensure that our contribution went further than it would have on its own," Naour says.

The couple says they are eager to see the Institute's campus grow and be enhanced by the Science and Technology Center, and are excited by the scientific discoveries that will result from the increased collaborative possibilities the building will offer.

"We really wanted to be involved in something bigger than ourselves," Hesselink says.

WILL YOU TAKE THE JACOBS' CHALLENGE?

By taking the Jacobs up on their challenge, you can help the Institute build the new, state-of-the-art Joan and Irwin Jacobs Science and Technology Center, where the brightest minds will seek solutions to our most difficult health problems. The Jacobs will match every $2 donated with $1 to fund the cutting-edge new center—and a brighter future for us all. Salk scientists are bold, visionary and committed to making the world a better place. Salk supporters are, too. Together, we can meet any challenge.

www.salk.edu/resilient

NEXT GEN

Helen McRae

Leveraging the body's own immune response for more effective cancer therapies

Less than a year into Helen McRae's graduate degree in medical research, her cousin was diagnosed with lung cancer. "She was in an immunotherapy clinical trial and her tumor appeared to shrink," says McRae. McRae knew little about immunotherapies at the time but learned that unlike traditional cancer treatments that target cancer cells, immunotherapies assist the patient's immune system in fighting the cancer. "Ultimately, it didn't work out, which showed me the promise of this newer approach to cancer treatment, but also how much more research is needed to help it work for more people."

Now a postdoctoral fellow at Salk, McRae researches new ways to control tumor growth by using the body's immune cells. Her goal is to help discover and develop more effective immunotherapies, so that cancer patients will have better treatment options in the future.

Raised in Victoria, Australia, McRae became enthralled with science in high school. "When my older brother told me about evolutionary theory, it sounded so cool!" says McRae, "I wanted to learn more about how our genes evolved and their role in health and disease."

McRae later pursued her bachelor's degree in genetics at the University of Melbourne. She didn't know what a career in science entailed at the time—she was just passionate about learning. She eventually joined a structural biology lab at the Walter and Eliza Hall Institute, where she studied cell-to-cell signaling molecules and a protein involved in preventing programmed cell death. Unfortunately, after only six months she experienced a common peril within academic research: the project ran out of funding, and she could no longer continue her work. Luckily, she found a new research opportunity at the same institution, where she stayed for her PhD work examining the genetic mutations related to blood cell formation disorders, such as leukemia. She valued the ability to collaborate with her colleagues, and Salk's highly collaborative environment is one of the reasons she chose to move to San Diego for her postdoctoral studies.

"I've admired Associate Professor Diana Hargreaves' work since I was in graduate school. She is dedicated to mentoring her trainees and supporting them as they learn new techniques, so when the opportunity arose to join her lab, I couldn't say no," says McRae.

In Hargreaves' lab at Salk, McRae investigates immune cells called macrophages and ways to control them to target cancer. Normally, macrophages help fight off infections. But in tumors, these cells support the growth of cancer cells by promoting blood vessel development and suppressing other anti-cancer immune cells. McRae believes macrophages could be altered to become tumor-fighting cells, which could lead to new types of immunotherapies for cancer patients.

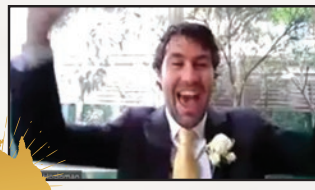
The impact of McRae's work has not gone unnoticed—she has received numerous awards for her achievements in science. Recently, she received the Catharina Foundation Postdoctoral Fellowship, the Tang Prize Foundation Fellowship, the Salk Women & Science Special Award, the American-Australian Association Graduate Fund Scholarship, and the Cancer Research Institute Merck Fellowship.

Though she has thrived at Salk, the transition to San Diego wasn't entirely smooth. Soon after McRae arrived, the coronavirus pandemic reached the US, leaving her separated from her fiancé in Australia. After two years, the couple decided to get married over Zoom. "Although not an ideal situation, it worked out great!" she says. "We had people from all around the world attend the ceremony."

"I've admired Associate Professor Diana Hargreaves' work since I was in graduate school. She is dedicated to mentoring her trainees..."

When travel restrictions finally loosened up, McRae flew back to Australia for an immunology conference, and she was able to see her now-husband for the first time. "We were both wearing masks, so it wasn't quite the rom-com reunion!" she says. "But I was elated that we could finally be together as a married couple." They both now live in San Diego, where they swim, run and occasionally surf.

Although McRae wasn't initially sure where her interest in genetics would lead, it's provided her with incredible opportunities to propel her career and study immunotherapy. "I don't know what's next, but for now I enjoy researching tumor-associated macrophages, in the hopes we can unleash the potential of our immune system to fight cancer."



SPOTLIGHT

SALK PROFESSOR RONALD EVANS AWARDED $1.2 MILLION BY LARRY L. HILLBLOM FOUNDATION TO STUDY A NEW DRUGGABLE PATHWAY THAT COULD HELP TREAT DIABETES

Professor Ronald Evans will receive $1.2 million over four years as part of a Network Grant from the Larry L. Hillblom Foundation to examine a molecular pathway that regulates blood sugar and fat independent of insulin. The research will advance our understanding of type 2 diabetes and could lead to the development of new therapies for treating the disease. Other members of the team include Professors Jin Zhang and Alan Saltiel from the University of California San Diego.

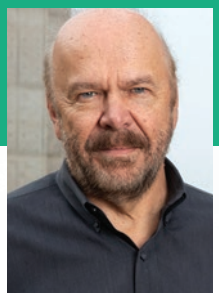
RONALD EVANS

Recently, the Evans lab discovered that a hormone called FGF1 regulates blood sugar (glucose) by inhibiting fat breakdown (lipolysis), and thus simultaneously lowers both blood glucose and fat. This effect is rapid and similar to how insulin works. While insulin acts through a regulatory switch called PDE3, Evans found that FGF1 uses a parallel pathway called PDE4. This finding is important as insulin action is greatly reduced in people with type 2 diabetes. The Evans study further shows that even when insulin action is blocked, FGF1 continues to control both lipolysis and blood glucose levels. Insulin resistance is considered to be a major problem and hard to control, so FGF1 represents a novel target for developing therapies for type 2 diabetes. Now, with funding from the Larry L. Hillblom Foundation, the group will examine the FGF1 pathway in more detail, explore where the pathway is located in the cell, and test how the pathway functions in different forms of diabetes.

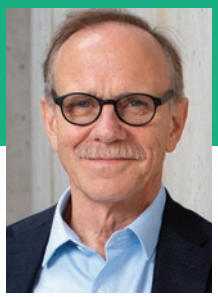
Six Salk professors named among most highly cited researchers in the world

Professors Joanne Chory, Joseph Ecker, Rusty Gage, Satchin Panda, Reuben Shaw and Kay Tye were named to the Highly Cited Researchers list by Clarivate. The list identifies researchers who demonstrate "significant influence in their chosen field or fields through the publication of multiple highly cited papers." Additionally, Ecker appeared in two separate categories: "plant and animal science" and "molecular biology and genetics."

JOANNE CHORY



JOSEPH ECKER



RUSTY GAGE

SATCHIN PANDA

REUBEN SHAW

KAY TYE

DAVID LAWRENCE APPOINTED EXECUTIVE DIRECTOR OF HARNESSING PLANTS INITIATIVE

Salk recently appointed David Lawrence as executive director of the Harnessing Plants Initiative. In the new role, he will oversee program management and administrative support for the project, as well as help deliver real-world applications based on Salk research findings. For example, he will help scale and deploy Salk Ideal Plants™ worldwide—crops that can capture excess carbon dioxide from the atmosphere and store it deep in root systems.

Lawrence has served as chair of the Harnessing Plants Initiative Advisory Committee since 2020. In 2021, he assisted the initiative in developing a science delivery and scaling plan to harness the natural power of plants to rebalance the carbon cycle.

"Dave's familiarity with the Salk Institute, our scientists, staff and collaborators, as well as our aspirations, challenges and opportunities, gives us a running start to help address climate change on a global scale," says Professor Wolfgang Busch, co-director of the Harnessing Plants Initiative and Hess Chair in Plant Science.

DAVID LAWRENCE

JUAN CARLOS IZPISUA BELMONTE

Professor Juan Carlos Izpisua Belmonte tapped for high-profile life sciences position

After nearly 30 years at the Institute, Professor Juan Carlos Izpisua Belmonte will soon lead the San Diego division of Altos Institutes of Science, a newly created life sciences company focused on cellular rejuvenation programming to restore cell health and resilience.

During his time at Salk, Izpisua Belmonte became a world-renowned researcher. Named one of TIME magazine's "50 Most Influential People in Health Care" for 2018, Izpisua Belmonte pioneered gene editing, epigenetic editing and stem cell technologies to better understand how to reprogram and rejuvenate diseased cells. Recently, his lab showed how stem cell therapy might be used to treat type 1 diabetes, boost liver and muscle regeneration and eliminate some of the hallmarks of aging.

"I am thankful for Salk's support during these three decades, which has allowed my lab to pursue innovative areas of scientific research," says Izpisua Belmonte, holder of the Roger Guillemin Chair. "It has been humbling to grow and work beside every member of our Salk community, especially including the more than 300 trainees that have worked in the lab. For me and my wife, Concepcion Rodriguez, the fundamental pillar of my lab, Salk will always remain as some of the most inspiring and happiest memories of our lives."

Left: Izpisua Belmonte working in a Salk Institute lab, 1993.

Above: Ronald Evans and Dannielle Engle

SALK SCIENTISTS RECEIVE THE 2021 ASPIRE AWARD TO STUDY PANCREATIC CANCER

The Mark Foundation® for Cancer Research

Professor Ronald Evans and Assistant Professor Dannielle Engle were granted a 2021 ASPIRE (Accelerating Scientific Platforms and Innovative Research) award to study the cellular and molecular drivers of pancreatic cancer. The $250,000 award, supported by The Mark Foundation for Cancer Research, enables innovative approaches to solving impactful problems in cancer research. The 23 scientists chosen to lead 2021 ASPIRE projects represent disciplines across the spectrum of cancer research at top academic institutions worldwide.

SAN DIEGO NATHAN SHOCK CENTER ANNOUNCES GRANT AWARDEES

NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

Recently, the San Diego Nathan Shock Center of Excellence in the Basic Biology of Aging, a consortium between the Salk Institute, Sanford Burnham Prebys and the University of California San Diego, announced its second-year class of pilot grant awardees. Recipients from six different institutions will receive up to $15,000 to pursue research that advances our understanding of how humans age, with the ultimate goal of extending health span—the number of years of healthy, disease-free life.

The six pilot grant awardees are Leena Bharath, assistant professor at Merrimack College; Shefali Krishna, staff scientist at the Salk Institute; Gargi Mahapatra, postdoctoral fellow at Wake Forest School of Medicine; Chiara Nicoletti, postdoctoral fellow at Sanford Burnham Prebys; Anastasia Shindyapina, instructor in medicine at Brigham and Women's Hospital and Harvard Medical School; and Xu Zhang, research associate at the Mayo Clinic.

EVENTS

SALK WOMEN & SCIENCE 10-YEAR ANNIVERSARY

On December 1, 2021, Salk Women & Science celebrated its 10-year anniversary of engaging women in the community with leaders in biological science and technology.

This year's event was held in honor of Swati Tyagi, a postdoctoral researcher in the Hetzer lab who was tragically killed in June 2021. A Women & Science endowed fund has been established in her name.

In addition, the Salk Women & Science Special Awards were presented. Every year, the awards provide crucial support to graduate students and postdoctoral researchers to pursue high-risk, high-reward research in stages too early to attract traditional funding. The awards support future scientific leaders who will also actively encourage women and girls in science.

2021 SALK WOMEN & SCIENCE AWARDEES

Awardees pictured above starting from left.

Ying Sun
Busch Lab
Identify the genes and regulatory factors that control root growth in legumes—ultimately to optimize roots that capture excess carbon dioxide from the atmosphere

Helen McRae
Hargreaves Lab
Profile epigenomics—chemical changes to the genome—in tumor-associated immune cells called macrophages

Veronica Scerra
Reynolds Lab
Develop new methods to probe changes in synapses—connections between neurons—that could play a role in neurological diseases

Xiaochun Cai
Jin Lab
Discover how two brain regions, the thalamus and striatum, work together to control the way animals perform actions in sequence

Wen Mai Wong
Chalasani Lab
Characterize ultrasound-sensitive proteins from single-celled organisms for use in sonogenetics—a new method for activating cells with sound waves

Katia Troha
Ayres Lab
Determine how amino acid supplementation promotes renal growth to increase survival of infection

Nuttida Rungratsameetaweemana
Sejnowski Lab
Determine how neurons work together to take in sensory information and form a schema—a conceptual picture of a task or environment, which can help shape future learning

Payel Mondal
Towers Lab
Use new light-based tools to inhibit autophagy—the process cells use to remove and recycle their "junk"—and visualize the resulting metabolic changes over time

Suzanne Dufresne
Towers Lab
Investigate how cancer cells can survive and bypass the deletion of autophagy—the way cells remove and recycle their "junk"—in animal models, and how we might treat it

POWER OF SCIENCE: IMPACT OF SALK SCIENCE ON HUMANITY

On December 8, 2021, Ha Nguyen, senior director of the Office of Technology Development, highlighted the past and present successes of translating Salk's scientific discoveries into technologies and interventions that prevent, treat or mitigate some of our most difficult health challenges, to benefit humankind.

WATCH	https://www.salk.edu/powerofscience202112

MELVIN COHN LECTURE ON CONCEPTUAL IMMUNOLOGY

On November 17, 2021, pioneering scientist Ruslan Medzhitov led a thought-provoking lecture on conceptual immunology. Medzhitov is a Sterling Professor of Immunobiology at the Yale School of Medicine. He has made multiple seminal discoveries in the fields of inflammation and immunobiology. A reception was held after the lecture in the Red Brick Courtyard.

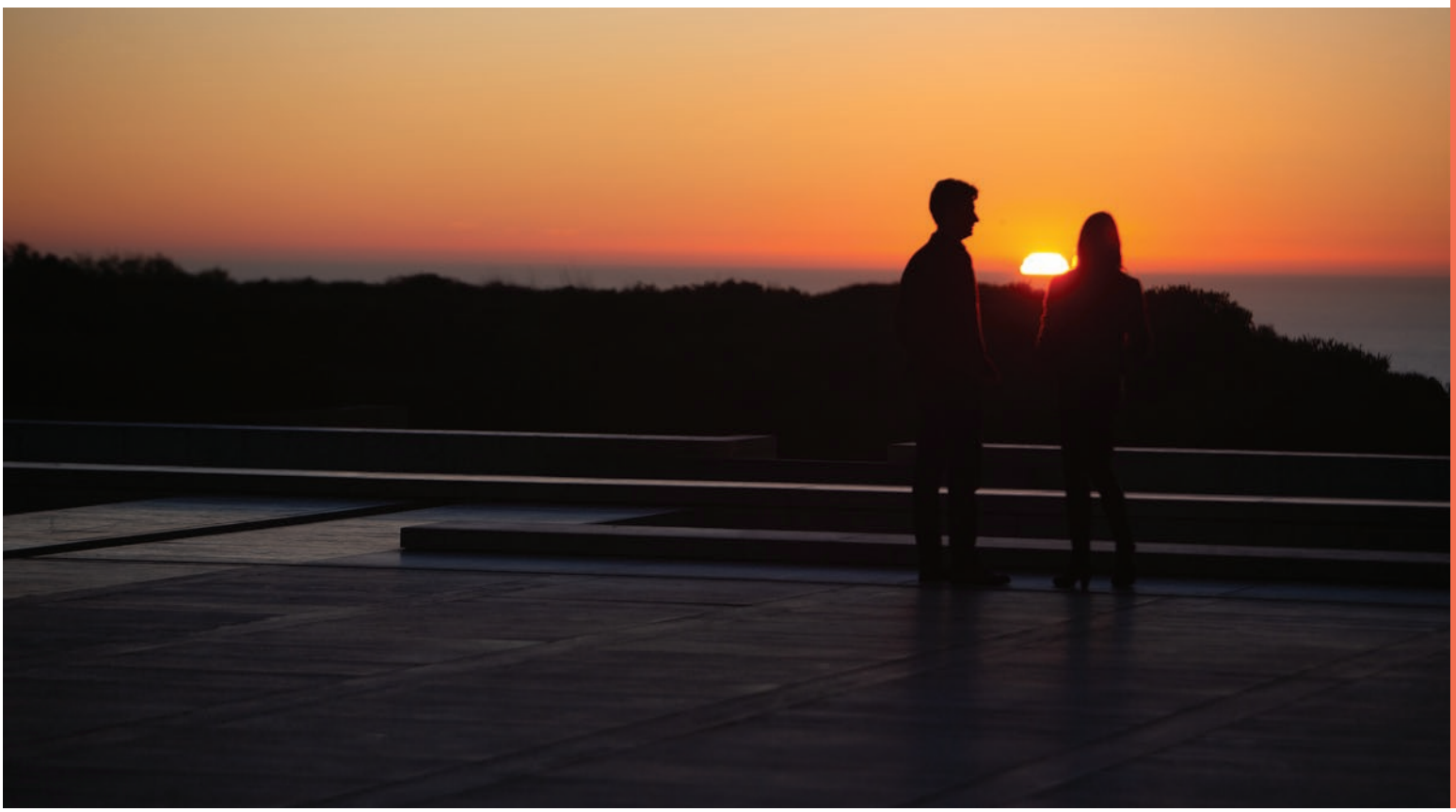
From left: Samuel Redford, Susan Kaech, Dan Chen and Siva Karthik Varanasi.

SALKEXCELLERATORS MIXER

On October 27, 2021, Professor Alan Saghatelian and Postdoctoral Researcher and 2021 Salkexcellerators Fellow Jacob Tremblay shared highlights from their labs with the Salkexcellerators group in an outdoor mixer. Salkexcellerators are the next generation of community members who support scientific discovery at Salk and engage with scientists through a full schedule of activities.

From left: Lisa Cashman, Jane Rhett, Alan Saghatelian and Brian Tauber.

From left: Jacob Tremblay and Dannielle Engle.



salk
Where cures begin.

THE PLACE WHERE IT ALL HAPPENS

For 60 years, the Salk Institute has pursued Jonas Salk's vision of fearless, interdisciplinary science tackling some of the biggest challenges facing humankind. With a legacy of six decades of life-changing discoveries, the Salk Institute has launched the Campaign for the Future:

Building a More Resilient World.

The Campaign, like Salk science, is a bold, collaborative five-year, $500 million vision to expand and accelerate Salk's critical research.

Included in the Campaign is a plan for the new Joan and Irwin Jacobs Science and Technology Center housing four Centers of Excellence focused on plant biology, cancer, healthy aging and computational biology/engineering.

Science is a collaborative pursuit. And you are our partner.

Without your support, Salk scientists could not pursue the bold research needed to understand the biology behind our body's resilience to disease, to stem climate change and to transform the health of the world for the better.

We Invite You to Join Us

Sign up to learn more about how you can accelerate scientific discoveries and you will receive the latest updates, giving opportunities, event invitations and more.

www.salk.edu/resilient