FALL | 2019

WHERE CURES BEGIN.

insideSalk

Stopping a killer

TARGETING PANCREATIC CANCER

CONTENTS

ON THE COVER:

Pancreatic cancer is difficult to detect and treat, in part because of an impenetrable "shield" that forms around the tumor and prevents treatment options from reaching their target.

Dear Friends,

Before concrete was poured into a single mold, Jonas Salk had a clear vision for what he wanted to create when he established the Salk Institute. He dreamed of a unique place where the world's top scientists would collaborate across disciplines in pursuit of answers to some of the most difficult challenges facing humankind. Salk's vision would inform his partnership with architect Louis Kahn to design and build an institute "worthy of a visit by Picasso."

For Kahn, his famous client's vision of how science should be pursued shaped many aspects of his architectural designs for the Institute, from the laboratories free of permanent, internal walls to the chalkboards located in the staircase landings. The iconic courtyard, inspired by Luis Barragán, would serve not only as a destination for reflection, appreciation and inspiring views but also the very practical purpose of drawing scientists out of their labs to interact with one another.

Today, nearly 60 years since the Institute opened its doors, our culture of collaboration is stronger than ever, as detailed in the following pages of *Inside Salk*. We examine the collaborative work of several teams of scientists at Salk tackling some of the most critical issues of our time, including pancreatic cancer and climate change. You'll also hear from one of our newest faculty members, Professor Kay Tye, on her fascinating research into the brain and what drives her passion for science.

"Jonas' foundational principle of collaboration is a defining part of the Institute's culture and success."

In this issue, we also inaugurate a new section in which we profile a staff scientist at Salk. Staff scientists are instrumental to the work that unfolds in the labs at Salk and play an important role in our shared success. Our first profile will introduce you to Travis Berggren, a senior staff scientist who provides institutional oversight for all shared scientific resources at the Institute, including Salk's core facilities, which were established to share and provide access to technologies to further the scientific research done here.

Jonas' foundational principle of collaboration is a defining part of the Institute's culture and success. Collaboration, more so now than ever, is the future of scientific discovery. Scientific researchers, community partners, and passionate supporters share a vision of a world where the answers to conquering cancer, mitigating climate change, preventing Alzheimer's and tackling other challenges are within reach. Together, we can make strides to a better and healthier world for all of us.

Sincerely,

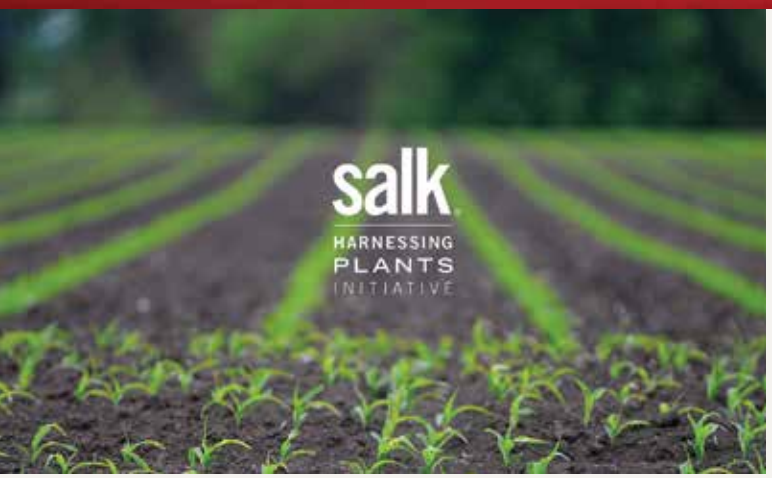
Rusty

Fred H. Gage
President

IN THE NEWS

SALK INSTITUTE INITIATIVE TO RECEIVE MORE THAN $35 MILLION TO FIGHT CLIMATE CHANGE

Joanne Chory



TED

WATCH | www.salk.edu/chory201908

The Salk Institute's Harnessing Plants Initiative to combat climate change using plants, led by Professor Joanne Chory, executive director of the initiative, will receive funding of over $35 million from more than 10 individuals and organizations through The Audacious Project, a highly competitive program housed at TED. The collective commitments represent one of the largest gifts to a single project in the Institute's history.

"We are overjoyed with this strong show of support for the Harnessing Plants Initiative from donors through The Audacious Project," says Chory, who is also director of Salk's Plant Molecular and Cellular Biology Laboratory. "Plants have evolved over time to be an ideal vehicle for carbon capture and storage. If we can optimize plants' natural ability to capture and store carbon, we can develop plants that not only have the potential to reduce carbon dioxide in the atmosphere (negative emissions) but that can also help enrich soils and increase crop yields."

"If we can optimize plants' natural ability to capture and store carbon, we can develop plants that not only have the potential to reduce carbon dioxide in the atmosphere but that can also help enrich soils and increase crop yields."

JOANNE CHORY

Professor and Director of the Plant Molecular and Cellular Biology Laboratory

The Harnessing Plants Initiative Leadership Team—which includes Salk faculty Wolfgang Busch, Joseph Ecker, Julie Law and Joseph Noel—aims to use a combination of cutting-edge technologies to turbocharge plants' ability to capture and store in their roots larger amounts of carbon from the atmosphere and keep it buried in the ground for hundreds of years. Chory led the Institute's involvement with The Audacious Project and was instrumental in the Harnessing Plants Initiative being chosen to receive this support. A Howard Hughes Medical Institute investigator and a recipient of the 2018 Breakthrough Prize and the 2018 Gruber Genetics Prize for her work in plant biology, Chory presented the key elements of the initiative in a nine-minute speech before an audience of 2,000 people attending the TED annual conference in Vancouver, British Columbia, on April 16, 2019. (A video of Chory's talk has over 1 million views online.)

The key to the initiative's plan lies in a substance called suberin (one form of suberin is cork), a naturally occurring, carbon-rich substance found in plant roots that resists decomposition.

By understanding and improving several genetic pathways in plants, the Salk team will develop plants that grow bigger and more robust root systems containing an increased amount of suberin, enabling the plants to absorb larger amounts of carbon from the atmosphere and bury the carbon-rich suberin deep in the soil.

By influencing the genes that control those traits and then combining those characteristics in a single plant, the team will develop Salk Ideal Plants™, which will be tested in a state-of-the-art climate-simulation facility at Salk that is able to mimic environmental conditions almost anywhere on Earth. This facility will allow the scientists to uncover the genetic traits that help plants survive in stressful environments—in the past, present and future.

Once they have developed ways to increase suberin in model plants, the Salk team will transfer these genetic traits to six prevalent crop plants. In addition to mitigating climate change, the additional carbon in the soil will make the soil richer in organic matter and make the plants more resilient to stress caused by climate change, prompting better crop yields and more food for a growing global population. In a related but distinct project, the team will also focus on restoration of coastal plants that constitute some of the most powerful carbon sinks on the planet. Restoring these systems will allow coastal plants to thrive and store more carbon while also reinvigorating fisheries; rejuvenating coral reefs; and aiding in coastal-restoration efforts.

"Rising global temperatures are among the top challenges facing humanity today, and we are extremely grateful to The Audacious Project donors for their generous support of Salk's bold approach to meeting this unprecedented challenge," says Rebecca Newman, vice president of External Relations at Salk. "We have no doubt that this funding will ensure these visionary scientists have the critical resources needed to implement this truly audacious initiative over the next five years."

Donors through The Audacious Project include the Clara Wu and Joe Tsai Foundation, Chris Larsen and Lyna Lam, Lyda Hill Philanthropies, Genevieve and Steve Jurvetson, Rosamund Zander and Hansjörg Wyss for the Wyss Medical Foundation, Joe Gebbia and Isabelle Boemeke, and others.

"Social entrepreneurs masterfully combine their ingenuity with the issues that they care about most to move the needle towards a better world," says Anna Verghese, executive director of The Audacious Project, which aims to take on the world's biggest and most urgent challenges. "Salk's innovative approach to tackling climate change has been hiding in plain sight—in the biology of the plants that surround us—and we're excited to help put their bold plan into action."

Aging— A look from the inside out

READ

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

CELL METABOLISM
06/2019

How old are your organs? To scientists' surprise, organs are a mix of young and old cells

Vice President, Chief Science Officer and Professor Martin Hetzer, first author Rafael Arrojo e Drigo and colleagues discovered that the mouse brain, liver and pancreas contain populations of cells and proteins with extremely long life spans—some as old as the organism itself. The team's methods could be applied to nearly any tissue in the body to provide valuable information about the lifelong function of nondividing cells and how cells lose control over the quality of proteins and cell structures during aging.

WATCH | www.salk.edu/hetzer201908

REDOX BIOLOGY
02/2019

Native California medicinal plant may hold promise for treating Alzheimer's

The medicinal powers of aspirin, digitalis and the anti-malarial artemisinin come from plants. Members of the lab of Professor David Schubert, including senior author Pamela Maher and first author Wolfgang Fisher, discovered a potent neuroprotective and anti-inflammatory chemical in a shrub native to California that may lead to a treatment for Alzheimer's disease.

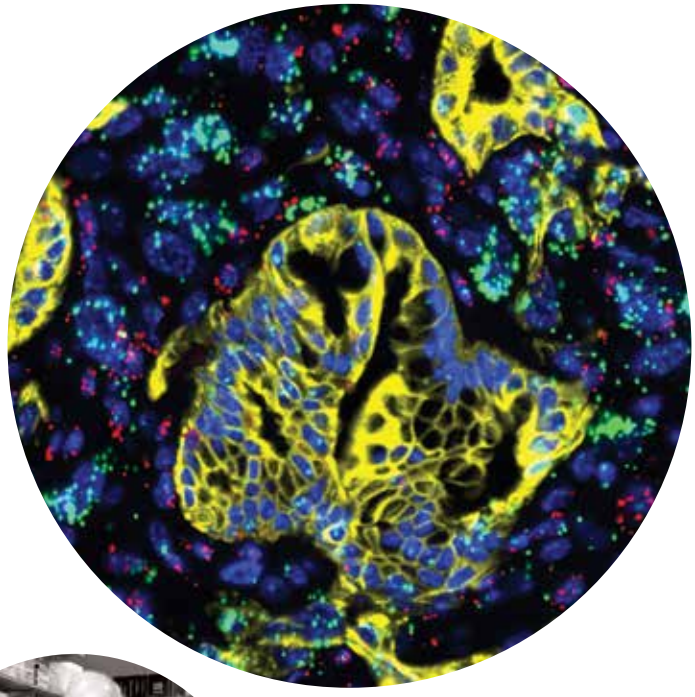
NATURE MEDICINE
02/2019

Putting the brakes on aging

Professor Juan Carlos Izpisua Belmonte, co-first author Hsin-Kai Liao and colleagues developed a novel CRISPR/Cas9 genome-editing therapy that can suppress the accelerated aging observed in mice with Hutchinson-Gilford progeria syndrome, a rare genetic disorder that also afflicts humans. The treatment provides insight into the molecular pathways involved in accelerated aging, as well as how gene therapy can be used to reduce toxic proteins.

WATCH | www.salk.edu/belmonte201908

CANCER



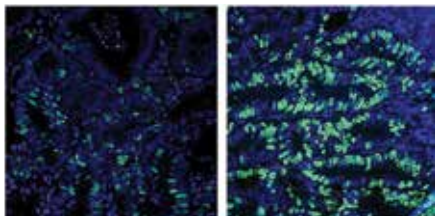
LIF (green), expressed mainly in activated pancreatic stellate cells, is shown along with immune cells (purple) and cancer cells (yellow) in pancreatic cancer tissue.

NATURE
04/2019

NEW STUDY TARGETS ACHILLES' HEEL OF PANCREATIC CANCER

Advanced pancreatic cancer is often symptomless, leading to late diagnosis after metastases have spread throughout the body. Additionally, tumor cells are encased in a protective shield, a microenvironment conferring resistance to many cancer drugs. Professor Tony Hunter, first author Yu Shi and an international team of collaborators uncovered the role of a signaling protein, LIF, that may be a useful biomarker to help diagnose pancreatic cancer more quickly and efficiently than current screenings methods.

WATCH | www.salk.edu/hunter201908



Colon cancer growth, as measured by the number of dividing cells shown in green, is dramatically increased when the FXR-regulated gene network is disrupted by specific bile acids or a high-fat diet.

SALK SCIENTISTS UNCOVER HOW HIGH-FAT DIETS DRIVE COLORECTAL CANCER GROWTH

CELL
02/2019

Deaths from colorectal cancer in people under 55 are increasing. A new study led by Professor Ronald Evans, with first author Ting Fu and collaborators, suggests that high-fat diets fuel colorectal cancer growth by upsetting the balance of bile acids in the intestine and triggering a hormonal signal that lets cancerous cells thrive. The findings could explain why colorectal cancer is being seen in younger people growing up at a time when high-fat diets are common.

WATCH | www.salk.edu/evans201908

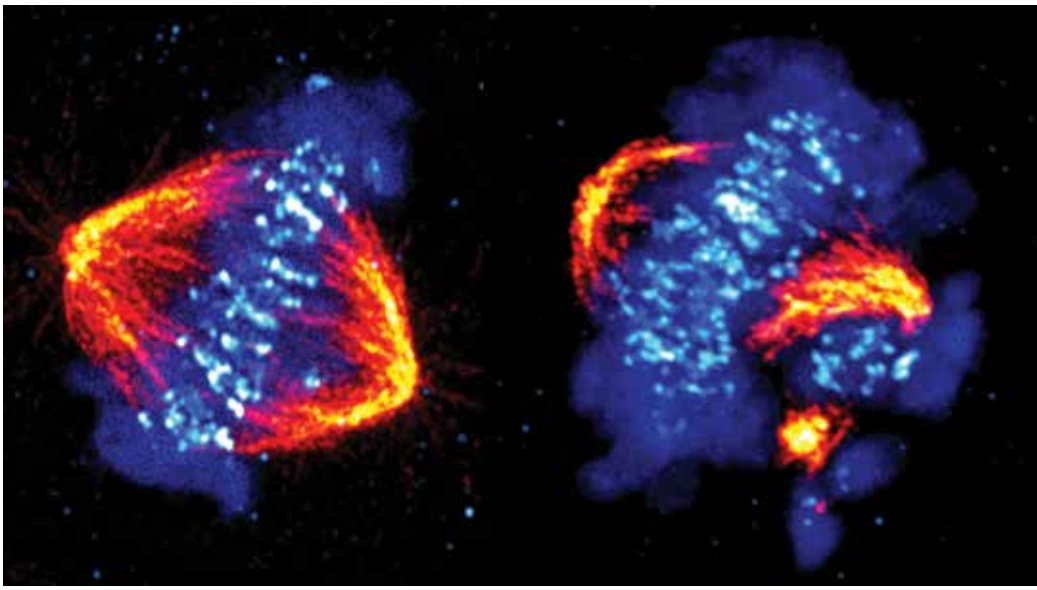
GENES & DEVELOPMENT 04/2019

NEW ROLE FOR A DRIVER OF METASTATIC CANCERS

Metastatic cancers are notoriously difficult to treat and often deadly. Professor Katherine Jones, first author Seung Choi and colleagues revealed a new role for a protein called CDK12. By analyzing the role of CDK12 in protecting cells from chemotherapy, the team discovered a new group of genes that controls cancer-cell metabolism. CDK12 works with another protein, mTORC1, to control the process of translation—an important step in creating a new protein within the cell. This finding points to a potential new metastatic drug target.

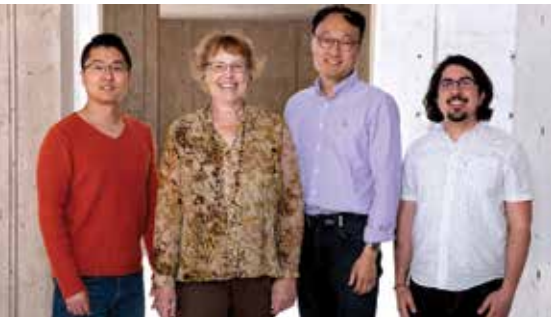
"We've discovered a new translation pathway that nobody knew existed, which is used by a lot of the factors that are involved in cell division—specifically, separating the chromosomes."

KATHERINE JONES



Left: The process of cell division, called mitosis, showing structures called microtubules (orange) pulling the chromosomes (blue) to opposite sides, called spindle poles, of the cell. CDK12 is critical for proper chromosome alignment and progression through mitosis.

Right: Without CDK12 the chromosomes become misaligned and detach from the spindle poles.



From left: Seongjae Kim, Katherine Jones, Seung Choi and Thomas Martinez.

NEUROSCIENCE

HOW ATTENTION HELPS THE BRAIN PERCEIVE OBJECTS

eLIFE
02/2019

Scientists have long theorized that attention to a particular object can alter perception by amplifying specific neuronal activity and suppressing the activity of other neurons (brain "noise"). Professor John Reynolds, first author Anirvan Nandy and collaborators confirmed this theory by showing how too much background noise from neurons can interrupt focused attention and cause the brain to struggle to perceive objects. The findings could help improve designs for visual prosthetics.

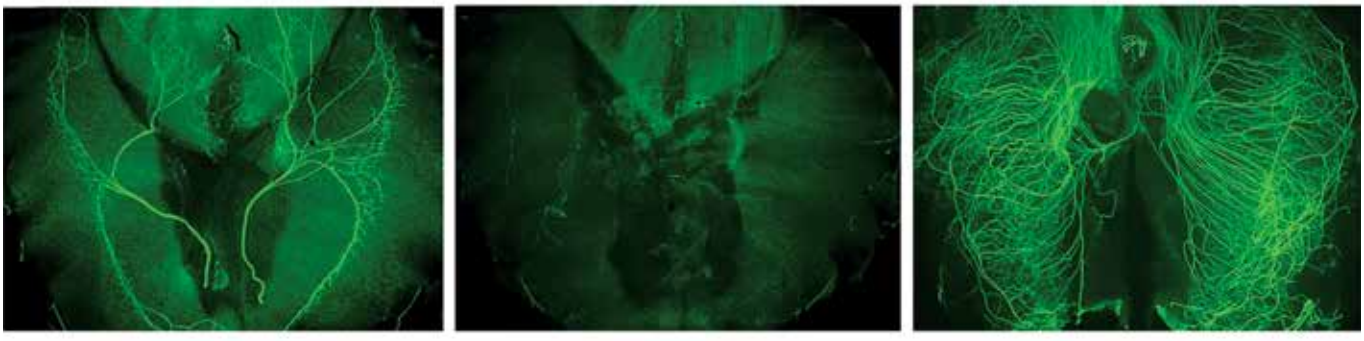
JOHN REYNOLDS

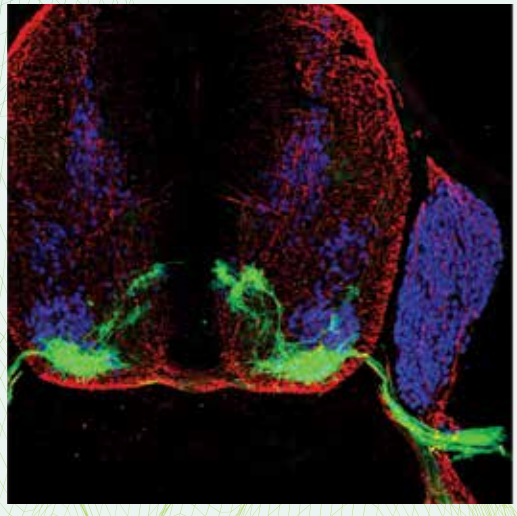
PLOS Genetics
03/2019

GUARDIANS OF THE SYNAPSE: SCIENTISTS IDENTIFY A NEW ROLE FOR NERVE-SUPPORTING CELLS

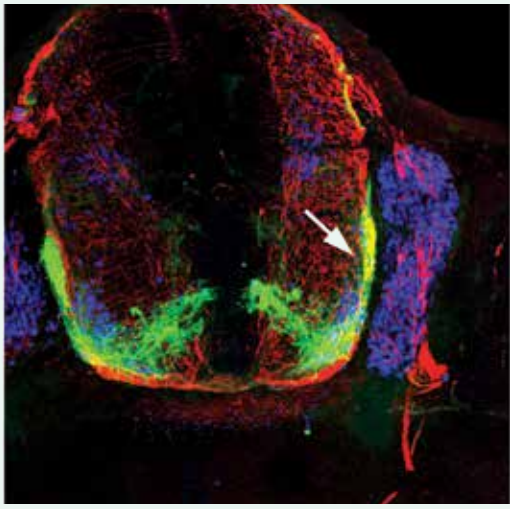
Left: mouse nerves show tight bundling and orderly patterning facilitated by normal Schwann cells. Middle: Nerves without Schwann cells but with acetylcholine experience degeneration from the blood-clotting protein thrombin. Right: Nerves lacking both Schwann cells and acetylcholine are unable to individually bundle axons but do not undergo axon degeneration.

Salk Professor Kuo-Fen Lee, first author Thomas Gould and collaborators found that a blood-clotting protein can unexpectedly degrade nerves—and discovered how nerve-supporting glial cells, including Schwann cells, provide protection from this degradation. The findings show that Schwann cells protect nerves by blocking the blood-clotting protein as well as other potentially destructive enzymes released by muscle cells. The work could have implications for diseases as diverse as amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease and schizophrenia.





Motor neurons (green) exit the spinal cord (red) and enter the periphery of the body to connect with muscles.



Motor neurons (white arrow) without the guidance of p190 are trapped within the spinal cord.

LIKE MOUNTAINEERS, NERVES NEED EXPERT GUIDANCE TO FIND THEIR WAY

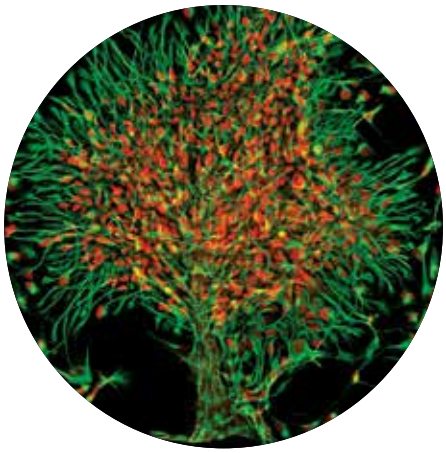
NEURON
03/2019

Similar to the dozens of Sherpas who guide hikers up treacherous Himalayan mountains to reach a summit, the nervous system relies on elaborate timing and location of guidance cues for neuronal axons—threadlike projections—to successfully reach their destinations in the body. Professor Samuel Pfaff, first author Dario Bonanomi and collaborators discovered how neurons listen for directions and simultaneously filter out inappropriate instructions to navigate tricky cellular environments.

"These results provide mechanistic insight into the unimagined complexity that cells use to communicate with one another."

SAMUEL PFAFF

NEUROSCIENCE



A stylized microscopy image of forebrain neural progenitor cells from chimpanzees. The image represents the work's potential for offering insights into the evolution of the primate tree of life.

Image credit: Salk Institute/Carol Marchetto/ Ana P.D. Mendes

UNCOVERING THE EVOLUTION OF THE BRAIN

eLIFE
02/2019

What makes us human, and where does this mysterious property of "humanness" come from? President and Professor Rusty Gage, along with co-first author Carol Marchetto and colleagues, developed a strategy to more easily study the early development of human neurons compared with the neurons of nonhuman primates. The research offers scientists a novel tool to construct an evolutionary tree of multiple primate species to better understand the evolution of the human brain.

WHY ANTIDEPRESSANTS DO NOT WORK FOR EVERYONE

MOLECULAR PSYCHIATRY
1/30/2019, 3/22/2019

In two recent editions of *Molecular Psychiatry*, Gage, first author Krishna Vadodaria and collaborators showed why selective serotonin reuptake inhibitors (SSRIs), a common treatment for major depressive disorder that increases the neurotransmitter serotonin, do not work in some patients. The discoveries could help lead to more personalized treatments for depression as well as other psychiatric conditions, such as bipolar disorder and schizophrenia.

From left: Amy Le, Kelly Heard, Rusty Gage, Krishna Vadodaria and Carol Marchetto.

In the first study, published in January, the researchers created neurons from skin cells from patients whose depression did not show signs of improving with SSRIs. The team discovered that these patient-derived neurons became hyperactive when serotonin levels increased, compared with cells derived from healthy individuals or those who respond to SSRIs.

In March, a second paper by the group demonstrated that neurons from SSRI-resistant patients had longer neuron projections than did neurons from SSRI-responders, along with low levels of key genes involved in forming brain circuits.

Left: Healthy plant.
Right: Plant with defects in chloroplast and leaf development due to abnormal chloroplast RNA editing from MORF2 overexpression.

From left: Jianyan Huang, Xiaobo Zhao and Joanne Chory.

"If we understand how plants respond to stress, then perhaps we can develop a way to increase their resistance and keep food production high."

JOANNE CHORY

EDITING OF RNA MAY PLAY A ROLE IN CHLOROPLAST-TO-NUCLEUS COMMUNICATION

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES
04/2019

When experiencing stress or damage from various sources, plants use chloroplast-to-nucleus communication to regulate gene expression and help themselves cope. The lab of Professor Joanne Chory, with first author Xiaobo Zhao, found that GUN1—a gene that integrates numerous chloroplast-to-nucleus retrograde signaling pathways—also plays an important role in how proteins are made in damaged chloroplasts. The results provide new insight into how plants respond to stress, which may help biologists breed plants that can better withstand environmental stressors.

HOW TO STOP A KILLER

New approaches to pancreatic cancer research

Dannielle Engle has a deeply personal interest in finding a way to diagnose pancreatic cancer early: Her father and her uncle died of it. Now an assistant professor in Salk's Regulatory Biology Laboratory, Engle was an undergraduate at Northwestern University when her father was diagnosed with pancreatic cancer 15 years ago. For a little while, his treatment—surgery and then a two-drug chemotherapy regimen—seemed to have been successful. But the cancer returned, and this time it didn't go away.

Engle, who was very close to her father, says he was one of the lucky ones: He lived for 14 months after his initial symptoms became apparent, versus the typical 4-6 months following diagnosis.

This year, around 57,000 people are expected to be diagnosed with pancreatic cancer and 46,000 will die from it, according to the American Cancer Society, making it one of the deadliest cancers.

Part of the problem in treating pancreatic cancer is that it's hard to detect. In the case of Engle's father, the cancer had been growing quietly for five years before it was diagnosed. One reason for a late diagnosis is that many of the early symptoms of pancreatic cancer—digestive issues, back pain, jaundice—are associated with numerous other health problems, including diabetes and a condition called pancreatitis, in which the pancreas is inflamed.

Another reason this cancer is so hard to defeat is that the pancreas, a smartphone-sized abdominal gland that releases digestive juices into the intestine and releases hormones (such as insulin) into the bloodstream, is difficult to image due to its location in the body.

Once pancreatic cancer is diagnosed, surgery is an option, but only if the cancer has not metastasized.

That's why the Salk Institute has made pancreatic cancer a focus in its Conquering Cancer Initiative, a dedicated research effort that was launched in spring 2018 to tackle five of the deadliest cancers. In addition to pancreatic cancer, Salk faculty are using a variety of research innovations to reveal insights into brain, lung, ovarian and triple-negative breast cancers.

One of the deadliest cancers:

57,000

Americans are expected to be diagnosed with pancreatic cancer in 2019

46,000

of those people will die from it

Source: American Cancer Society

"At Salk, our goal is to push boundaries and come up with ideas that other places don't envision. Simply said, innovation and insight let us go where others have not gone."

REUBEN SHAW

Finding a needle in a haystack

The effort harnesses Salk's National Cancer Institute-designated Cancer Center in the hope that the approaches—ranging from new models of treatment to unexpected collaborations across disciplines and international boundaries—will facilitate better treatments not just for these cancers but for all cancers.

On May 28, 2019, Salk's Cancer Center launched a bold effort in which Salk labs are facilitating international translational alliances to seek a cure for pancreatic cancer. Salk labs are already making headway, as milestone discoveries have appeared in numerous journals and led to four trials using novel approaches.

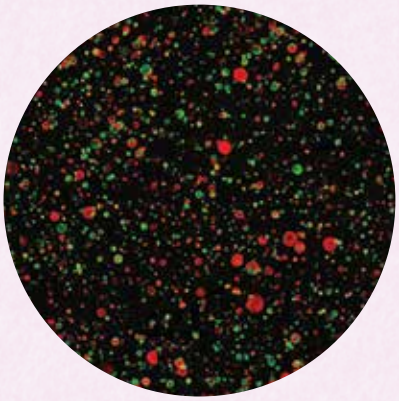
"At Salk, our goal is to push boundaries and come up with ideas that other places don't envision," says Reuben Shaw, the director of the Salk Cancer Center and the William R. Brody Chair. "Simply said, innovation and insight let us go where others have not gone."

"We take on the toughest challenges because those breakthroughs lead to so much more," says Ronald Evans, director of Salk's Gene Expression Laboratory. "Beyond the lab bench, Salk has built a network of clinical collaborators, enabling us to transform discovery into treatment. We're at an inflection point for pancreatic cancer research, in which momentum and pace are moving faster than ever before, leading to innovative treatments even for the most advanced forms of the disease."

Watching her father deal with pancreatic cancer made Engle want to work on developing methods of early detection for the disease. As a graduate student, she conducted research in the lab of Salk faculty member Geoffrey Wahl. Now, as head of her own lab, she develops pancreatic cancer organoids, which can be grown from a sliver of tumor the thickness of a human hair.

These organoids may well be game changers for pancreatic cancer research. Engle is using organoids to test diagnostic methods and treatments. (See sidebar, "Pancreatic organoids" and this issue's "Analysis" to learn more about organoids.)

One of Engle's diagnostic approaches focuses on a carbohydrate called CA19-9. Levels of this sugar are elevated in the blood of pancreatic cancer patients. When people are responding to therapy, the levels decrease, making CA19-9 a valuable indicator of therapeutic effectiveness. Unfortunately, levels are also elevated in pancreatitis, and telling the two conditions apart is difficult. Cancer researchers, Engle among them, think that CA19-9 could be a useful biomarker for early pancreatic cancer detection, if the sugar could be better understood.



Tumor organoids (green) and normal organoids (red).

Image credit: Cold Spring Harbor Laboratory/Tuveson Lab/ Dannielle Engle

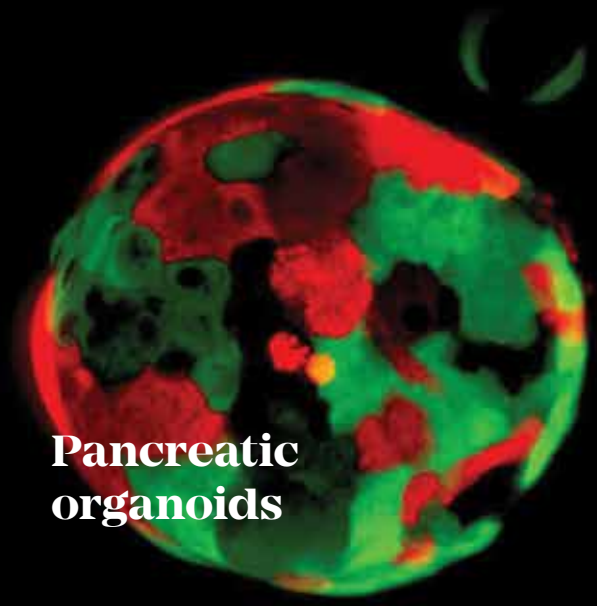
CA19–9 is a sugar molecule that is elevated in both pancreatitis and pancreatic cancer. Unfortunately, this similarity makes early detection difficult.

"Looking for biomarkers is the age-old problem of looking for a needle in a haystack," Engle says. "The blood contains signals not just from the pancreas but from every tissue in the body. So 99.9 percent of your time as a researcher is spent trying to exclude signals that are not relevant. In other words, you spend most of your time in the hay."

Engle is seeking to change that. In June, she published a groundbreaking paper in the journal *Science*, in which she discussed using organoids and mouse models to reveal that CA19-9 is not merely correlated with pancreatitis and pancreatic cancer but can actually contribute to both conditions. Her research suggests that the sugar has the potential to act as either an accelerator or a brake for both cancer genes and tumor-suppressor genes. In addition, she showed that using antibodies to block CA19-9 reversed pancreatitis and made pancreatic cancer less aggressive, which could buy patients valuable time, during which other therapies may work.

Engle is working to develop a large collection of organoids derived both from healthy pancreata and from inflamed or cancerous pancreata in order to compare the types and come up with biomarker candidates for use in developing diagnostic blood tests.

Her lab will also be able to use the organoids for drug testing and analysis of tumors' genetic vulnerabilities.



Pancreatic organoids

Image credit: Cold Spring Harbor Laboratory/ Tuveson Lab/Dannielle Engle

Organoids are simplified, miniature versions of organs, used for research and, in particular, to model disease (see this issue's "Analysis" to learn more about organoids).

Engle is building a repository of pancreatic organoids, derived from both healthy and cancerous tissue, to enable her team to identify differences between the two tissue types—especially at different stages of cancer development—that could be used for diagnostic or therapeutic purposes.

The Engle lab has more than 100 self-renewing pancreatic cancer organoids, most of which are grown from tumor biopsy tissue, which means they have the exact genetic profile of the cancer patient from whom they are derived. Understanding genetic variations in tumors could be a powerful tool in advancing treatments and a cure for the disease.

Breaking down cancer's *shield*

Evans has developed a chemically engineered form of vitamin D that is able to penetrate the normally impenetrable fibrotic shell, creating vulnerabilities that drugs or the immune system can exploit.

Evans, the Gene Expression Laboratory director who talked about being at an inflection point in pancreatic cancer research, also has a familial connection to cancer: His father died of glioblastoma, his brother died of leukemia, and his sister died of kidney cancer.

Initially, Evans, who also holds the March of Dimes Chair in Molecular and Developmental Biology, didn't set out to work on cancer at all, much less pancreatic cancer. The Salk professor and Howard Hughes Medical Institute investigator is an authority on hormones, molecules that carry messages throughout the body. He is known for discovering a large family of molecules called nuclear receptors, some of which respond to steroid hormones, such as vitamins A and D.

In 2013, Evans' lab was profiling hundreds of cell types to map the location of every nuclear hormone receptor and to perhaps yield something about their function. The team noticed that, unexpectedly, there were very high levels of vitamin D receptors in liver stellate cells. Vitamin D receptors act as sensors for organ injury and respond by telling other liver cells to produce fibrous proteins (similar to scar tissue) to heal the wound. Evans wondered why there were so many vitamin D receptors in stellate cells.

The team's follow-up experiment revealed an answer: The receptor acts as a molecular "on-off" switch, controlling liver fibrosis in a hormone-dependent fashion. Without vitamin D, inflammation and scarring are relentless. With vitamin D, inflammation and scarring resolve and the wound heals. The 2013 study, which was published in the journal *Cell*, was exciting not only for its implications for liver fibrosis and liver cancer—but because the pancreas also has stellate cells, suggesting an unexpected role for the vitamin D receptor in the development and treatment of pancreatic cancer.

It turns out that the pancreas treats cancer cells as an injury needing to be healed, so it sounds the inflammatory alarm,

From left: Tony Hunter, Dannielle Engle, Ronald Evans, Reuben Shaw and Susan Kaech

"Staying ahead of the curve, we already have two more discoveries that are on their way to the clinic. This reinforces the idea that 'knowledge is power,' as well as that pancreatic cancer is treatable."

RONALD EVANS

summoning various immune cells and fibroblasts that trigger the fibrotic response. Together, these cellular components form an impenetrable tangle—the stroma—which, ironically, functions as a shield for the tumor, hiding and protecting it from immune cells and therapeutic drugs. This wall of scar tissue surrounding the tumor is one of the main reasons pancreatic cancer is so difficult to treat.

Described in 2014, again in the journal *Cell*, Evans' lab found that inflamed pancreatic stellate cells had higher levels of vitamin D receptors than did normal pancreatic stellate cells. When the researchers gave synthetic vitamin D to mice that had inflamed pancreases, the vitamin again appeared to act as a switch, calming the cells' inflammatory signaling and allowing them to return to a normal, uninflamed state. Given those promising results, the team was eager to try their vitamin D therapy in the tumor environment.

They found that administering the vitamin D analog along with chemotherapy in a mouse model of pancreatic cancer enabled those mice to live 50 percent longer than mice receiving only chemotherapy. The reason was dramatic: In calming the inflammation, the vitamin D analog opened up the normally impenetrable fibrotic shell, allowing chemotherapy drugs and tumor-seeking immune T cells to find and attack the tumor.

The vitamin D receptor is what Evans refers to as a "master regulator," controlling about 250 genes involved in cellular communication, immunity and other functions. But pancreatic tumors degrade vitamin D, essentially making tumors into wounds that cannot heal. However, the chemically engineered form of vitamin D that Evans uses enables it to penetrate the tumor environment without becoming degraded.

"Vitamin D is literally a hormone activated by light," says Evans. "So, when cancer prevents it from functioning, the tumor is able to stay hidden and in the dark, figuratively speaking. That's where our vitamin D analog therapy comes in, acting like liquid light. It flips all the cellular switches the cancer had reprogrammed and sheds new light on the disease, so to speak. The tumor begins to regress, creating vulnerabilities that drugs or the immune system can exploit."

Salk pancreatic cancer research led by Evans has clinical-trial alliances with Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, City of Hope, UC San Diego's Moores Cancer Center, the University of Pennsylvania and others. In fact, Evans' vitamin D analog is currently in human clinical trials, and one patient, Stephen Bigelsen, believes it saved his life. The New York City-based physician was diagnosed with stage IV metastatic cancer in 2016. Surgery wasn't even an option. Bigelsen and his wife, Susan, heard about the experimental vitamin D therapy from his medical team at Weil Cornell Medical Center and decided to try it. About one month into the combination treatment of vitamin D plus chemotherapy, when his first blood tests showed improvement, he began to have hope. Within a year, his cancer was completely gone. Today, Bigelsen serves as a pancreatic cancer patient advocate, educating others about the disease.

"Though it is one case, and more research needs to be done, it is dramatic and proves that new and effective therapies can make their way from the Salk bench to the patient's bedside," Evans says. "Staying ahead of the curve, we already have two more discoveries that are on their way to the clinic. This reinforces the idea that 'knowledge is power,' as well as that pancreatic cancer is treatable."

Disrupting cancerous communication

American Cancer Society Professor Tony Hunter also has made progress in dismantling the wall around pancreatic tumors by focusing on the communication between tumor cells and stellate cells.

Researchers already knew that noncancerous cells are helping to create the pancreatic stroma, but they weren't sure how.

"A tumor is basically a new type of tissue, and in every tissue, cells talk to one another," says Hunter, who holds the Renato Dulbecco Chair at Salk. "We wanted to understand what they were saying."

Hunter's team began by using cell cultures to analyze all of the proteins that stellate cells were exporting, and the team found that inflamed pancreatic stellate cells were producing a protein called LIF (short for leukemia inhibitory factor). LIF was already known for its role in helping embryonic stem cells maintain their full developmental potential, but LIF is usually not present in adults. What, then, was it doing in adult pancreatic stellate cells?

Further experiments in a mouse pancreatic cancer model revealed that LIF was helping tumor cells grow. When LIF was blocked by administering an antibody, tumor growth slowed, giving chemotherapy drugs a chance to work. Equally exciting was the lab's finding that LIF levels in patients were significantly correlated with pancreatic tumor progression and response to chemotherapy. This suggests that LIF, like CA19-9, holds promise as a biomarker for pancreatic cancer stage and treatment response.

The team published their findings in the journal *Nature* in April 2019, and a clinical trial testing an antibody against LIF is now being conducted by a biotech company in Toronto, in partnership with Celgene Corporation and Stand Up To Cancer.

Tapping the body's own defenses

The Evans and Hunter labs' approaches to breaching the stroma allow chemotherapy drugs to access tumors, but Salk Professor and NOMIS Chair Susan Kaech is hoping to make a person's own immune system do the work of chemotherapy, without the toxicity of those types of drugs, as part of a rapidly evolving field known as cancer immunotherapy.

"Immunotherapy is a new form of cancer treatment that is revolutionizing the way we're using drugs. The goal is to stimulate our immune system to identify and defeat cancer cells in a 'seek and destroy' way," says Kaech, director of Salk's NOMIS Center for Immunobiology and Microbial Pathogenesis.

Immune T cells are activated when we encounter a pathogen, like bacteria or a virus, forming a molecular memory of it so that the next time we're exposed, our bodies can quickly mount an efficient response. Even though cancer is not a foreign pathogen, cancer mutations can make otherwise normal cells look foreign to our immune system, allowing T cells to recognize and attack them. Unfortunately, pancreatic cancer doesn't have as many mutations as other cancers, which means it's harder for our immune system to recognize. In addition, the impenetrable barrier of the stroma prevents even immune cells that recognize the tumor from accessing it.

Kaech is working to change that. She discovered that tumors cause immune suppression, in part, by quashing the metabolism of T cells. Just as people aren't as productive if they're hungry, T cells can't function properly if a tumor is hogging all of the available nutrients. Her work suggests that efforts to starve tumors may actually hurt immunity in the process because of the way tumors and immune cells influence each other metabolically.

Kaech is also working to identify how other types of immune cells might be recruited to fight cancer. Although T cells can't penetrate the stroma, immune cells called macrophages can. But macrophages—cells that "eat" other cells by breaking them down—can also make the tumor environment immunosuppressive. By better understanding how various immune cells are regulated, Kaech aims to improve immunotherapy techniques.

Tackling cancer from all angles

If cancers have underlying commonalities, so do Salk's cancer researchers. Salk's collaborative model, which brings together researchers from a variety of biological backgrounds, may be the best way to make progress in the search for effective therapies not only for pancreatic cancer but for all of the hardest-to-treat cancers.

"Salk attracts scientists who have big, bold ideas and want to make a difference," Engle says. "It doesn't matter how wild your idea is. You can make it happen at Salk, even if that means reinventing who you are as a scientist or adopting a new approach that nobody's ever tried before. This is one of the only places in the world where you can do that."

As part of the Conquering Cancer Initiative, the pancreatic cancer research team has taken the first step to expand the program into an international translational alliance that will allow discoveries from Salk to have worldwide impact.

"What we learn about pancreatic cancer gives us powerful tools to help fight other deadly cancers," Evans says. "We're a small institute, but our goal is to tackle big problems. The harder they are, the bigger the reward when you find a solution. And I feel optimistic that with pancreatic cancer we will find solutions, with a goal for the cure."

CONQUERING CANCER SUMMIT 2019

On May 28, Salk supporters came to the Institute for an update on the Conquering Cancer Initiative and to learn about progress in pancreatic cancer research. Keynote speaker Lisa Niemi Swayze, widow of actor Patrick Swayze, spoke about her late husband's battle with pancreatic cancer, and CCI Advisory Committee Chair Tim Schoen moderated a panel that included Salk Cancer Center faculty Ronald Evans, Tony Hunter and Dannielle Engle. Salk President Rusty Gage and Cancer Center Director Reuben Shaw emceed the evening.

WATCH | www.salk.edu/pancreatic-cancer201908

OBSERVATIONS

KAY TYE

Breaking down the brain

Kay Tye, the newest addition to Salk's faculty, is a burst of energy who can chat about everything from the mysteries of the brain to the intricacies of a breakdance move. You might find her brushing off sand from her wetsuit after surfing near a pod of dolphins, or having an "intellectual jam session" with one of her lab members in her study overlooking the Pacific.

Before arriving at Salk, Tye was an associate professor at the Massachusetts Institute of Technology (MIT), where she also received her bachelor's degree before studying at UC San Francisco and Stanford University. The recipient of numerous awards and recognitions—including the NIH Director's Pioneer Award, Society for Neuroscience's Young Investigator Award and *MIT Technology Review's* list of 35 Innovators Under 35—Tye is investigating the neural circuit basis of social and emotional processing. Her research will help us better understand why we are the way we are and what drives social interactions, which may have implications for anxiety disorders, addiction and depression.

Inside Salk sat down with Tye to discuss her roundabout journey to science, her passion for mentorship, and her love of life outside the lab.

Tell us about your path to becoming a globally renowned neuroscientist. How did you decide on a life of research?

KT: My parents were scientists and professors at Cornell University. Ithaca is lovely but remote, so I was interested in going to college anywhere else. I chose MIT, one of the few schools I got into that my parents deemed acceptable over Cornell.

However, I had some discouraging training experiences as an undergraduate, so I took a year off after school and backpacked around Australia. There, I lived on a remote farm that was 500 kilometers from the nearest paved road. After that, I was a yoga instructor, which I really enjoyed doing, but I had a moment when I realized that I could give the same class over and over again and no one could tell the difference. I wanted to feel like what I'd done in the past mattered, and that what I'm doing matters.

Science is incredible in that way: Not only do you build upon what you've done in the past, but everyone else can build on your past work as well, so you feel the impact of your work as it influences others.

I decided to go to graduate school at the University of California, San Francisco. I had a really tough time in my first year of graduate school and was on the verge of dropping out. That's when my PhD mentor, Patricia Janak, along with my mom, helped me to not give up.

It's hard to imagine that you were on the verge of dropping out of graduate school, given how successful you are today. How did you hit your stride?

KT: It was a big adjustment to go back into the academic atmosphere after living in a tent on the beach for months. I felt like I wasn't good enough. Now that I'm where I am, it's really obvious to me that this is the path I was supposed to take, but there were so many times when I almost didn't continue and worried I couldn't keep up with everyone else. I had done three rotations, but the lab I liked didn't choose me, and I was devastated. I did an extra rotation and connected with Patricia Janak, who turned me from a puddle of tears into a functioning, competent scientist. She believed in me and helped me unearth my strengths. At the same time, my mom was like, "You need to do a little less whining and a little more working." It was that combination of tough love from my mom and patient nurturing from my PhD adviser that helped me grow into a professional. By the second year of grad school, I was completely convinced that science was my calling. It was a dramatic turnaround.

That is a great example of how important mentorship is. Is your mom a big inspiration?

KT: Some of the challenges that I faced as an undergrad were very specific to my gender, but I was fortunate to benefit from very strong female role models throughout my life. My mom is my biggest role model in that regard. She was glad that her first name—Bik, a Chinese name—is ambiguous here. She once told me that people were surprised when she showed up to meetings, because they'd thought she was a man. She felt that helped her career. When I was growing up, she'd tell me I didn't have to choose between a family and a career, and that women can do anything men can do.

Many of my female colleagues have dealt with balancing family and career in different ways. I've always been proud to be a very committed parent—right now, of a six-year-old and a three-year-old. My daughter was probably the youngest person to ever attend a Gordon Research Conference; I took her when she was 6 weeks old. And of course, none of this would have been possible without having a wonderful and supportive partner, my husband, Jim Wagner.

Now that you are leading a lab at Salk, how do you approach mentorship?

KT: The mentor-mentee relationship is sacred, and academia is one of the last professions that uses a mentor-mentee model.

Over time, I learned that whoever asks the most questions learns the fastest, and you can't be afraid of looking stupid when you're in pursuit of knowledge. If you worry about that, you're just going to impede your learning. I try to convey that as a mentor. Another thing I learned as a manager is that you should hire people that you are excited about working with.

The most important thing about being a good mentor is constantly applying effort to becoming a better mentor. Every mentee is different, and every mentee's needs will change as they develop. Nobody's perfect, but if you really care about people's well-being and their future, that's your guide star as a mentor. Are you going to be perfect? There's no such thing. It's like how people are nervous about being good parents: There will be some mistakes, but you love your kids and you'll figure it out together.

What big questions do you hope to explore at Salk?

KT: One big-picture question I'm exploring is, how do we process emotional value—or valence—and change that? For example, you hear a song at a party, and some people get really excited, while other people hate that song. I want to understand how you assign valence to something you've never seen before

and how you change the way you assign it when you've seen it many, many times but in different contexts.

Another big question I'm really interested in is how the brain represents social homeostasis—that is, how do our brains determine if we have the right amount (quality, quantity, nature) of social contact? How do we sense when we need more "me" time versus feel lonely? What controls the motivation to seek social contact?

Related to this, I'm also interested in how groups of individuals know their place in a hierarchy. Humans are capable of creating and maintaining many different types of social hierarchies and social structures. For example, you come into a new sports team, and it doesn't take that long to figure out who's the leader, right? And the leader might not be the person assigned that role; it might actually be someone else. But you pick up those cues and figure it out.

Social processing encompasses a huge part of our brain. We don't really even know how much yet or what the complete circuits are. We have some nodes that are probably involved, but we really have no good handle on how the brain performs many of its everyday social functions, like integrating rank information with gesture recognition to determine if behavior is "socially appropriate."

How does exploring the neural circuits of social processes build on your previous work on addiction and reward circuitry?

KT: Our previous work focused primarily on emotional processing and how we assign positive or negative valence to things in the world around us. We have also published on social reward and motivation to seek social contact when isolated.

In modern society, a lot of our happiness and pain comes from social stimuli. It might be an email. It might be someone's offhand comment. It might be road rage. It might be workplace politics or relationships with our family. Understanding how we process straightforward stimuli—hunger, for example—is important, because if we don't know that, then a complex problem like how to interpret that nuanced offhand comment would be impossible.

There are a lot of different components that are feeding into it: past experiences and associations with this individual; identification of your relative rank to this individual's relative rank; extrapolating what the potential consequences of this would be. It's interesting that we care so much about an interaction that has almost no bearing on our survival. Why do we let something that is almost certainly not going to kill us upset us so much? These are some of the questions we want to explore.

Speaking of social interactions, you mentioned you were involved in the breakdancing scene. Tell us more about that.

KT: I used to be really into breakdancing. I got serious about it in grad school, entered competitions and did shows for the Warriors. Windmills—where you roll along your shoulders—was the hardest move I mastered. That wooden boom box on my shelf is a prize for being the best "B-girl" in a breakdancing battle. It definitely was a huge part of my life, but that was a long time ago. I haven't been a part of the competitive scene since I had kids.

What hobbies do you have now?

KT: I've recently taken up surfing since moving to San Diego. I'm pretty obsessed with it right now. It makes me feel so alive. I go a few times a week with lab members just right here by Salk. We've seen dolphins and seals stealing our waves. I still do yoga a couple times a week, and I've started horseback riding again. I also love running in the canyons by my house. In general, I need a lot of activity. It's good for your brain to change states and stay flexible. And of course, everybody knows that exercise promotes neurogenesis.

It sounds like San Diego is agreeing with you! Of all the places to build your lab, why did you choose Salk to launch this next phase of your career?

KT: Well, just look around! From the first time I came here, I thought to myself, "Why don't I live here? Why can't this become my reality?" It is just so beautiful. It is hard not to feel inspired walking into work every day. I totally love San Diego, and have become a San Diego evangelist, trying to convince everyone I love to move here.

But in all seriousness, I found myself craving freedom, and what's the point of "success" if I don't have freedom? Giving good scientists freedom to pursue their scientific interests and go in whatever direction that they want—that is a great model. That's what drew me to Salk.

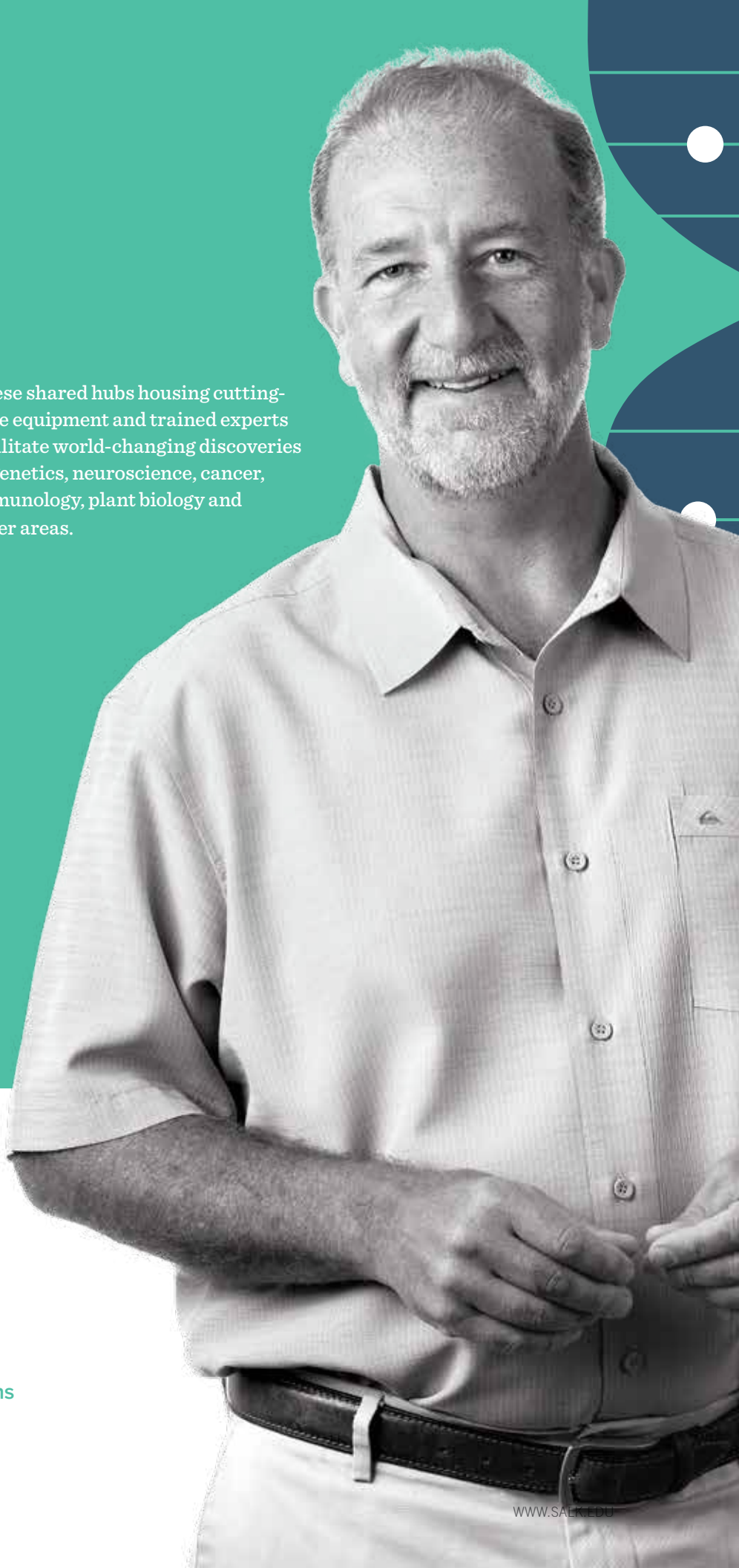
While there are things I will miss about being at a degree-granting institution, everything takes time...and I found myself drowning in administrative, departmental, teaching, advising and other types of work that pulled me away from the actual scientific research. That's the part I love the most, and Salk's model of clearing your schedule to allow you to focus on your research is refreshing.

Working at the intersection of biology and technology

Diving into biological research—systems, cells, proteins and DNA—requires the technology to see the unknown and chart the complex and often evasive inner workings of systems. Emerging technologies allow scientists to reveal the microscopic, construct new research models and analyze an immense amount of information.

Travis Berggren bridges this intersection of biology and its ever-evolving need for technology by overseeing shared resources, most notably Salk's "cores."

These shared hubs housing cutting-edge equipment and trained experts facilitate world-changing discoveries in genetics, neuroscience, cancer, immunology, plant biology and other areas.



INSIGHTS

Travis Berggren

Executive Director of Research Operations

DAY-TO-DAY

In his current role as the executive director of research operations, Berggren provides institutional oversight for all shared scientific resources at the Institute, including animal research, more than a dozen scientific cores and other scientific resources. These efforts enable Salk labs to draw upon state-of-the-art technology and expertise. He also develops interinstitutional partnering agreements for access to additional scientific resources, helping to facilitate scientific discoveries at Salk and beyond.

PATH TO SALK

A San Diego native, Berggren was a curious child who always wanted to understand how things worked. In school, he gravitated toward organic chemistry and earned his undergraduate degree from the University of California San Diego. From there, Berggren worked in the lab of Salk's Wylie Vale in 1993-95 to bridge biology and chemistry, focusing on honing chemistry techniques for analyzing DNA. That is also where he met his future wife (Jennifer Black, MD). Together they moved to the University of Wisconsin-Madison for his PhD, where early work on the human genome project and emerging biomolecular analytical techniques led Berggren into the field of human embryonic stem-cell research.

He studied alongside pioneers in the field of stem-cell biology before returning to Salk in 2007 to establish the Institute's first open-access stem-cell core-research facility. In subsequent years, Berggren helped to launch or renovate core resources in the areas of biophotonics, next-gen sequencing and bioinformatics. "I've been so lucky to work with an amazing group of bright and motivated researchers here at Salk," says Berggren.

LEISURE TIME

Berggren has been an avid recreational cyclist since the age of 13 and has recently become passionate about commuting on an electric bike, which puts his 32-mile round trip in the same time frame as driving. He also bikes for Salk's Pedal the Cause, a local effort to raise funds supporting cancer research. And, like many native San Diegans, Berggren loves being outdoors. At the beach, he favors a surf kayak, a device that is exactly what it sounds like: a kayak made to surf the waves. In addition, he often spends weekends camping with his three daughters, aged 16, 13 and 7.

INSPIRATION

"Currently, the field of stem-cell research is creating exciting new ways to study human diseases, to promote regeneration and improve the outcomes of aging," Berggren says. "Another fascinating line of study is how to better understand neurodegeneration, dementia and Alzheimer's using cutting-edge tools. Stem-cell technology in particular allows us to, for the first time, study some of the early developmental processes for these diseases within cell-based model systems. For example, the stem-cell core has been helping researchers make relatively new tools called organoids. Most cell cultures are done in a two-dimensional cell-culture dish, but we know that human biology happens in three dimensions. Being able to create these three-dimensional organoids that can represent certain types of brain, kidney or heart tissue is starting to open up extensions of how this human stem-cell technology can replicate human biology." (See this issue's "Analysis" to learn more about organoid technology.)

FUN FACT

Growing up in San Diego has its perks: Before he left for graduate school, Berggren put his name on a years-long wait list for a boat permit in a popular area of town. Eleven years later, through a call on his parents' landline, he was granted a permit to use the much-coveted beach bar at Mission Bay for his 16-foot Hobie Cat.

LONG VIEW

"The fields of genomics and genome sequencing have quickly advanced and become powerful and complicated," Berggren says. "That has blown me away in a lot of ways. There were a lot of people that thought once we were able to sequence the first human genome, suddenly we would have so many answers. But what sequencing did is create a framework and scaffolding to allow us to dig into the fine inner workings of how genes, genomes and gene expression are controlled and how they influence how biology functions. You combine that technology with the revolutions we've seen in gene editing and microscopy—as well as ancillary technologies like mass spectrometry and metabolomics that have really come into their own in the last decade—and it's a very, very exciting time to be doing biological research."

ANALYSIS

WHAT ARE ORGANOIDS?

Organoids, sometimes referred to as mini-organs, are three-dimensional collections of cells that mimic features of human tissues. These tiny, pale spheres are revolutionizing the way scientists study health and disease.

Many disease models involve growing a single layer of cells adhering to the surface of a flat dish. While helpful, this 2D approach is limited—it does not capture the complexity of a layered, sophisticated system like the brain. Organoids better mimic a diverse group of cells interacting with one another in a three-dimensional space and offer new insights into human biology.

To develop an organoid, scientists typically begin with skin cells from living humans. A mix of proteins then cues the skin cells to revert to pluripotent stem cells, giving them the ability to develop into virtually any type of tissue. A second concoction of proteins signals which type of cell to become—heart cells or pancreas cells, for example. Scientists can also develop organoids directly from tissue, such as a biopsy.

The use of this technology has surged over the last decade, with Salk scientists leading the way in developing larger, more advanced organoid tissues, such as brain organoids. Therapies for neurological disorders, like Alzheimer's, schizophrenia, autism and depression, have lagged behind, in part, because the human brain is a complex organ that is not easily accessed. Even when a drug shows promise in animal models, it often does not work for humans. Although the technology is still a long way from fully representing a human organ, organoids offer an unprecedented model for studying biological processes and unlocking new possibilities for diagnostic and therapeutic research.

TESTING DRUG EFFICACY

Organoids could be used for drug screening to identify new drugs and reveal how and why groups of patients might respond to certain therapies.

PERSONALIZED MEDICINE

Because organoids contain the genetic makeup of an individual, this technology could be used to provide personalized treatment plans.

TISSUE TRANSPLANTS

Salk researchers are developing organoid models of the brain, pancreas, kidney, liver and other tissues. One day, organoids may be used to grow healthy, genetically matched populations of cells to replace diseased or dysfunctional cells to treat—or even cure—diseases such as Parkinson's, Alzheimer's, pancreatic cancer and liver disease.

FASTER DISCOVERIES

Scientists can more quickly and affordably generate organoids, which speeds up the rate of scientific discovery and decreases the reliance on animal models and patient studies.

ACCESSIBILITY

Some organs are difficult to study due to their location in the body; the human brain is especially difficult, because researchers must rely on postmortem tissue or invasive techniques.

Brain organoids are allowing scientists to observe, as never before, how neurons grow and communicate with one another.

ACCURACY

The lab of Joseph Ecker found that 3D brain organoids more closely resemble a real brain in structure and function compared with the widespread 2D models used in the lab setting. In addition, the lab of Rusty Gage developed a way to enable organoids to receive blood flow and grow larger, providing a more accurate representation of the microenvironment of a real brain (see "Resolution," next page).

CANCER INSIGHTS

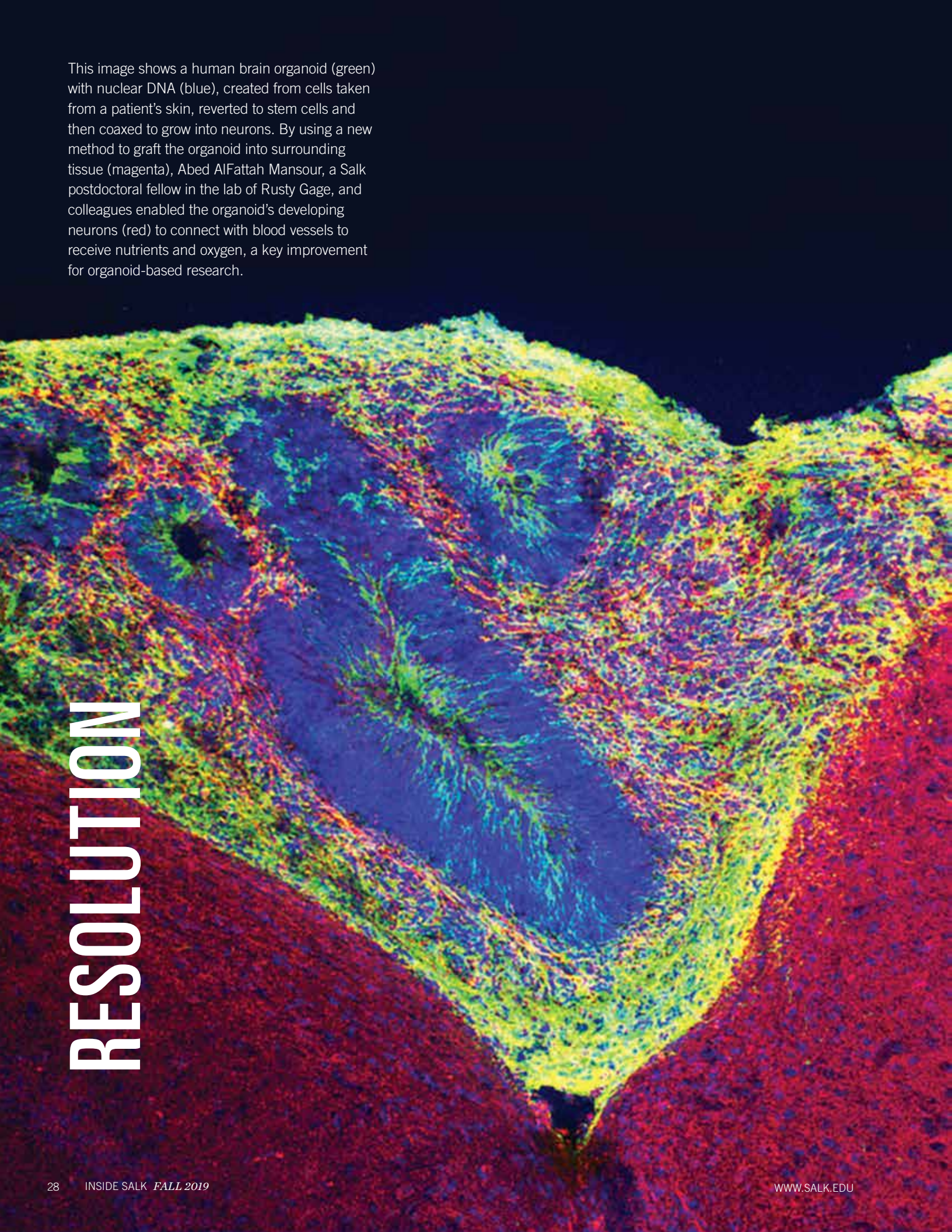
Junko Ogawa, a senior research associate in Tony Hunter's lab, is using brain organoids to reveal insights into glioblastoma. Several labs at Salk are using organoids to explore cancer in other parts of the body as well (see this issue's "Frontiers" article for more).

Learn more about how organoids work:

WATCH | www.salk.edu/organoids

RESOLUTION

This image shows a human brain organoid (green) with nuclear DNA (blue), created from cells taken from a patient's skin, reverted to stem cells and then coaxed to grow into neurons. By using a new method to graft the organoid into surrounding tissue (magenta), Abed AlFattah Mansour, a Salk postdoctoral fellow in the lab of Rusty Gage, and colleagues enabled the organoid's developing neurons (red) to connect with blood vessels to receive nutrients and oxygen, a key improvement for organoid-based research.



Groundbreaking Salk discoveries *on the go!*

PODCAST ANNOUNCEMENT

Launching this fall, **Where Cures Begin** is the official podcast of the Salk Institute for Biological Studies. In each episode, co-hosts Allie Akmal and Brittany Fair interview Salk scientists about their bold research efforts and learn about their lives outside of the lab. The first season will share conversations with President and Professor Rusty Gage, Professor Joanne Chory and Assistant Professor Dannielle Engle to name a few. Join us to hear about advancements in neuroscience, using plants to fight climate change, developing cures for cancer, mastering our circadian clock and more.

The podcast will be available on **iTunes, Google Play** and anywhere you listen to podcasts.

To learn more, visit **Salk.edu/podcast.**

LAUNCHING FALL 2019

Rusty Gage *on the advances of science*

Joanne Chory *on using plants to fight climate change*

Tony Hunter *on decades of cancer research*

Nicola Allen *on the mysteries of astrocytes*

Dannielle Engle *on fighting pancreatic cancer*

Eiman Azim *on the neuroscience of movement*

Ken Diffenderfer *(staff scientist) on the technology of stem cells*

Emily Manoogian *(postdoctoral fellow) on circadian clocks*

salk®
Where cures begin.

Graziana Gatto

Graziana Gatto grew up in the small farming town of Ceraso (which translates to cherry tree) in southern Italy, among orchards of olive trees and terra-cotta-roofed houses. Ceraso lies within the Cilento National Park, an area known for buffalo mozzarella, Greek temples and the Mediterranean diet.

Gatto shared a passion for cooking with her grandmother; every Sunday, they diced eggplants and yellow onions, chopped fresh basil and grated Parmesan cheese to prepare mouthwatering lasagna and parmigiana.

Many of Gatto's family friends were doctors, so, while in high school, she decided to shadow a physician to see whether she had a passion for medicine. Although she enjoyed witnessing how to puzzle out a tricky diagnosis, she realized she wanted to focus on conducting research to find new approaches for treating and curing diseases. Gatto moved to Naples to pursue a master's degree in medical biotechnology. She quickly adapted to her new life in the city—tasting tantalizing foods and attending the many concerts and shows that the city had to offer became staples in her life. She also fell in love with travel, which led her to Munich, Germany, where she pursued her PhD at the Max Planck Institute of Neurobiology.

Munich is an international hub for science, and Gatto was able to meet researchers from around the world, including Salk Professor Martyn Goulding, a pioneer in deciphering the neuron types involved in movement and pain sensation. At a conference, they discussed his research at the Salk Institute and, serendipitously, an opening in his lab.

"Salk scientists value collaboration, and there is always a nice flow of ideas between labs and disciplines, which allows for constant discussion and scientific advancement," Gatto says. "This environment brings forth new perspectives, so it was an easy decision to join Salk for my postdoctoral fellowship."

In 2014, Gatto joined the Goulding lab to examine how various sensations, such as pain, itching or touch, are differentiated by the nervous system and how the spinal cord generates the appropriate motor response.

"The big challenge right now is to accurately identify what each neuron is responsible for in the spinal cord," Gatto says. "Knowing how the spinal cord functions in health can help us develop more-targeted therapies, for example, for neuropathic itch or phantom limb syndrome."

Gatto also wanted to pursue a novel project developing a technique to activate neurons during running and jumping. Winning the 2017 Salk Women & Science Special Award provided her with funding to commence the project. She hopes this basic research will lead to the development of treatments for people with amyotrophic lateral sclerosis, neuropathy or a spinal cord injury.

Outside of her own work, Gatto has a passion for scientific engagement and has immersed herself in Salk's Education Outreach program. Each summer, she mentors a high school student through the Heithoff-Brody High School Scholars Program, a paid eight-week internship in a Salk laboratory.

"The students we have had in the lab are extremely smart, and it has been a pleasure helping them develop scientific skill sets and watching them pursue their own STEM careers after working in a Salk lab," Gatto says.

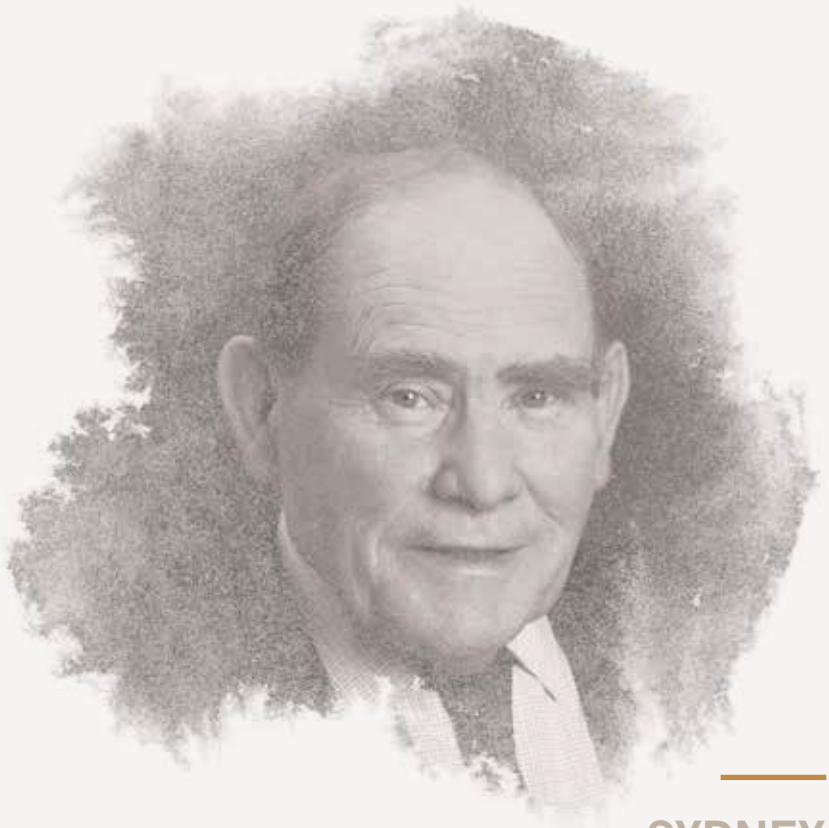
Despite her full-time work and mentorship in the lab, Gatto is still able to find time to unwind by cooking the Italian meals she learned from her grandmother. She aims to start her own lab to continue her research on how the spinal cord shapes movement, and she looks forward to sharing her Italian cuisine with her future team.

NEXT GEN

Gatto has a passion for scientific engagement and has immersed herself in Salk's Education Outreach program.

"Salk scientists value collaboration, and there is always a nice flow of ideas between labs and disciplines, which allows for constant discussion and scientific advancement."

IN MEMORIAM



SALK MOURNS THE PASSING OF NOBEL LAUREATE AND SALK DISTINGUISHED PROFESSOR EMERITUS SYDNEY BRENNER

SYDNEY BRENNER

1927-2019

Nobel Laureate and Salk Distinguished Professor Emeritus Sydney Brenner passed away on April 5, 2019, in Singapore, at the age of 92. Over the course of six decades, Brenner shaped the modern understanding of the genetic code.

"We at Salk join countless other scientists and researchers around the world in mourning the passing of Sydney Brenner," says Salk President Rusty Gage. "Along with raising the field of molecular biology to maturity, Sydney was a generous and dedicated mentor, colleague and friend. He was an inspiration to generations of scientists, and he will be greatly missed."

"We all owe much to Sydney. With his passing, we have lost a great scientist and a good friend," says Salk Professor Terrence Sejnowski.

"Sydney Brenner was a luminary, a 'once in a lifetime' scientist. We at the Salk Institute were entertained and enthralled by his wit and wisdom," adds Salk Professor Ronald Evans. "His research inspired my career. He will be remembered in perpetuity for his brilliant discoveries that ushered in a new era of science and a new generation of scientists."

Brenner joined the Institute as a Distinguished Professor in 2000 and was awarded the Nobel Prize in Physiology or Medicine in 2002, along with H. Robert Horvitz and John Sulston, for "discoveries concerning genetic regulation of organ development and programmed cell death," according to the Nobel Foundation. The team pioneered research using the translucent microscopic worm *Caenorhabditis elegans* as a model system for linking genetics, cell division, organ formation and cell death. Their discoveries laid the groundwork for making *C. elegans* a major model organism in research. Today, thousands of researchers use *C. elegans* for their studies, and Brenner was honored in 2007, when a closely related nematode—*C. brenneri*—was named after him.

"Sydney Brenner was a luminary, a 'once in a lifetime' scientist. We at the Salk Institute were entertained and enthralled by his wit and wisdom."

RONALD EVANS

Salk Professor

Over the course of six decades, Brenner shaped the modern understanding of the genetic code.

Born in Germiston, South Africa, in 1927, Brenner earned degrees in medicine and science from Johannesburg's University of Witwatersrand in 1947 before moving to Oxford University in 1952 to pursue his PhD in physical chemistry. While at Oxford, he became engrossed in DNA and developmental genetics research. He joined the University of Cambridge in 1956 and shared an office with future Nobel Laureate Francis Crick for nearly 20 years.

In 1961, in partnership with Crick, Brenner demonstrated that the genetic code for proteins uses a series of three nucleotides to code for a single amino acid. He further showed that certain combinations of triplet nucleotides called "nonsense" or "stop" codons (a phrase he coined) halt protein creation during translation.

Around this time, Brenner also co-discovered the existence of messenger RNA (mRNA), one of the molecular intermediates between DNA and proteins, and demonstrated that the nucleotide sequence of mRNA determines the order of amino acids in proteins. This work led to his first Lasker Award in Basic Medical Research; he later received a second Lasker Award in honor of his outstanding lifetime achievements.

In 1976, Crick left Cambridge to join the Salk Institute, and Brenner joined him once again, in 1981, as a nonresident fellow. In 1992, Brenner was appointed to the Scripps Research Institute, located less than a mile from Salk. Brenner and Crick were reunited at Salk in 2000. In 2001, Brenner coauthored an autobiography titled, *My Life in Science*. He also helped to establish a number of scientific institutes, including in Japan and Singapore.

"Sydney was a dear friend and uber-mentor," says Gene Yeo, a former researcher at Salk and a professor at UC San Diego, who worked with Brenner (and whose father, Philip Yeo, developed with Brenner a number of scientific institutes in Singapore). "We will miss him terribly."

Brenner is survived by his children Belinda, Carla and Stefan.

IN MEMORIAM

A TRIBUTE TO
AUDREY GEISEL

1921-2018

The Salk Institute and the greater San Diego community lost a good friend late last year. Audrey Geisel, the fun-loving, dedicated philanthropist who was a founding Symphony donor and attended every year until the last few due to declining health, passed away at age 97 on December 19, 2018.

Born Audrey Stone in Chicago on August 14, 1921, she went on to graduate from Indiana University and have an early career as a nurse. Geisel and her first husband, Dr. E. Grey Dimond, and their two daughters moved to San Diego in 1960.

She later married Theodor Geisel, more famously known as Dr. Seuss, in 1968.

Geisel was a generous supporter of numerous charitable organizations and causes. She and Theodor Geisel were long-

Geisel's positive nature and advocacy for the arts and sciences ensures that her influence lives on—both in San Diego and beyond.

time La Jolla residents who valued art and ventures that benefitted humanity. There is no better evidence of the latter than her creation of the Audrey Geisel Chair in Biomedical Science, established at Salk in 2012, which was first held by Professor Edward Callaway and is now held by Professor Gerald Shadel.

"She was a generous person with a warm and loving soul," says Rebecca Newman, Salk's vice president of External Relations. "She did so much for the Institute that we would not have been able to accomplish otherwise and her imprint on our success will be seen for years to come. She only supported institutions she truly believed in, so it is a real honor for Salk to count her as one of our great benefactors."

Geisel, who was friends with Institute founder Jonas Salk and his wife, famed artist Françoise Gilot, cherished her support of Salk. She was a founding donor to the President's Club and founding member, in 1978, of the Women's Association of the Salk Institute, which helped increase awareness about the importance of basic research and provided support for the Salk Scholars Fund.

"One thing that she hated to miss was a good party and the Symphony at Salk is one of the great ones," says Judith Morgan, a Salk supporter, friend of Geisel and author of *Dr. Seuss and Mr. Geisel*. "I shall miss her."

Longtime Salk supporters Irwin and Joan Jacobs agree, sharing that it was always special to see Geisel at Symphony.

"We met Audrey shortly after we came here in 1966 and it was a pleasure to be with her because she had such a bubbly and welcoming personality," Salk Trustee and Board Chair Emeritus Irwin Jacobs says. "It was always fun to meet her at Symphony at Salk and talk about the music."

In addition to supporting Salk, she gave to other local organizations including UC San Diego (the main campus library is named for Audrey and Theodor Geisel), The Zoological Society of San Diego, Scripps Institution of Oceanography, the La Jolla Playhouse and the Old Globe Theatre, among many others.

"I had the wonderful experience of working with Audrey and Ted Geisel for over forty years," says Claudia Prescott, Dr. Seuss Foundation president. "They meant a great deal to me and I learned so much working side by side with them."

A thoughtful and conscientious donor, Geisel met regularly with her associates. Karen and Don Cohn (a Salk trustee) recall Geisel's notoriously early breakfast meetings fondly, noting how Geisel would pull up in her Cadillac—complete with personalized "Grinch" license plates—to conduct business at one of La Jolla's iconic restaurants.

"You would meet her at 7:30 a.m. and had to have a pink grapefruit and breakfast before conducting business," Karen Cohn says. "Then you would make your request to her and she would usually say yes. It was always an honor to have her involved in a project."

"Audrey was such a strong force, with a great sense of humor," Don Cohn adds. "She had a purpose and she exercised it beautifully."

Geisel's positive nature and advocacy for the arts and sciences ensures that her influence lives on—both in San Diego and beyond.

"She was a generous person with a warm and loving soul. She did so much for the Institute that we would not have been able to accomplish otherwise and her imprint on our success will be seen for years to come."

REBECCA NEWMAN

Vice President of External Relations of the Salk Institute

SPOTLIGHT

SALK PROMOTES TWO LEADING SCIENTISTS IN THE FIELDS OF INFECTIOUS DISEASE AND NEUROBIOLOGY

Janelle Ayres and Tatyana Sharpee were each promoted to the rank of full professor after the latest round of faculty reviews determined they are scientific leaders who have made original, innovative and notable contributions to biological research. The promotions were based on recommendations by Salk faculty and nonresident fellows and were approved by President Rusty Gage and the Institute's Board of Trustees.

JANELLE AYRES

Janelle Ayres is a molecular and systems physiologist who uses evolutionary theory and microbes to understand how all of our physiological systems and our brains interact with each other to promote optimal health. Ayres, who is a professor and head of the Molecular and Systems Physiology Lab, as well as a professor in the Gene Expression Laboratory, member in the NOMIS Center for Immunobiology and Microbial Pathogenesis and holder of the Helen McLoraine Developmental Chair, studies how our physiologies are regulated by microbes. She seeks to understand how the mechanisms by which microbes promote health represent a relatively unexplored aspect of host-microbe interactions, and provide an opportunity to discover new, dynamic biological processes in health and disease. Her work has potential translational applications for treating a wide array of diseases, including infectious and inflammatory conditions, and for promoting healthy aging. She recently showed that giving dietary iron supplements to mice enabled them to survive a normally lethal bacterial infection and resulted in later generations of those bacteria being less virulent, thereby eliminating the risk of future infections.

In addition to being a Searle Scholar, Ayres has received a Ray Thomas Edwards Foundation award, a Blavatnik National Award for Young Scientists, a DARPA Young Faculty Award and, most recently, she received $3.5 million through a National Institutes of Health Pioneer Award, $1 million from the W.M. Keck Foundation and $1.8 million from the NOMIS Foundation for her novel research on host-microbe interactions and physiological health.

TATYANA SHARPEE

Tatyana Sharpee conducts her research as part of the Computational Neurobiology Laboratory, where her team focuses on understanding the basic principles of how our brains work and adapt to their environment. Through this, she hopes to find new ways for the diagnosis and treatments of neurologic and psychiatric disorders. Sharpee recently applied new mathematical methods to show that organizing odor molecules based on how often they occur together in nature reveals a coherent map in terms of our perception of odors. Additionally, the team uncovered ways that the brain parses patterned visual stimuli, such as natural scenes, and provided the theoretical framework for understanding how different cell types work together and divide various tasks among themselves.

Sharpee is a fellow of the American Physical Society, as well as a McKnight Scholar, a Sloan Scholar and a Searle Scholar. She is also a recipient of a National Science Foundation CAREER award. Last year, her group received a major international grant to study how the brain processes complex sounds, such as speech and music.

KAY TYE HONORED WITH ENDOWED CHAIR

Salk Professor Kay Tye has been named to the Wylie Vale Chair in recognition of her contributions and dedication to advancing science through research.

Tye joined the Salk Institute on April 1, 2019, from the Department of Brain and Cognitive Sciences, Picower Institute for Learning and Memory, at the Massachusetts Institute of Technology (MIT). At Salk, she is a member of the Systems Neurobiology Laboratory, where she leads a team using a wide variety of cutting-edge techniques to better understand the brain circuitry underlying emotion and motivation. Her discoveries help to inform more targeted and effective treatments for a multitude of brain disorders.

The Wylie Vale Chair was established by Liz Keadle, a Salk Trustee who once worked in the laboratory of the late Salk Professor Wylie Vale. For more than 40 years, Vale conducted groundbreaking research at the Salk Institute.

Kay Tye

PATRICK HSU NAMED AN *MIT TECHNOLOGY REVIEW* 2019 INNOVATOR UNDER 35

Helmsley-Salk Fellow Patrick Hsu has been named to *MIT Technology Review's* prestigious annual list of Innovators Under 35. Every year, the magazine recognizes a list of exceptionally talented technologists whose work has great potential to transform the world.

Patrick Hsu

Joanne Chory

JOANNE CHORY RECEIVES PRINCESS OF ASTURIAS AWARD

Salk Professor and HHMI Investigator Joanne Chory has received the 2019 Princess of Asturias Award for Technical and Scientific Research, alongside biologist Sandra Diáz, for research that has major implications for the fight against climate change. The prestigious award comes with €50,000 ($56,800) and a sculpture designed by artist Joan Miró. The award, which was established in 1980, will be presented by the king of Spain in a ceremony in the city of Oviedo.

Diana Hargreaves

DIANA HARGREAVES NAMED PEW-STEWART SCHOLAR FOR INNOVATIVE CANCER RESEARCH

Diana Hargreaves, an assistant professor in Salk's Molecular and Cell Biology Laboratory, has been named a 2019 Pew-Stewart Scholar for Cancer Research as part of a partnership between the Pew Charitable Trusts and the Alexander and Margaret Stewart Trust. Scholars each receive $300,000 over four years to support their work focused on a better understanding of the causes, diagnosis and treatment of cancer.

Edward Callaway

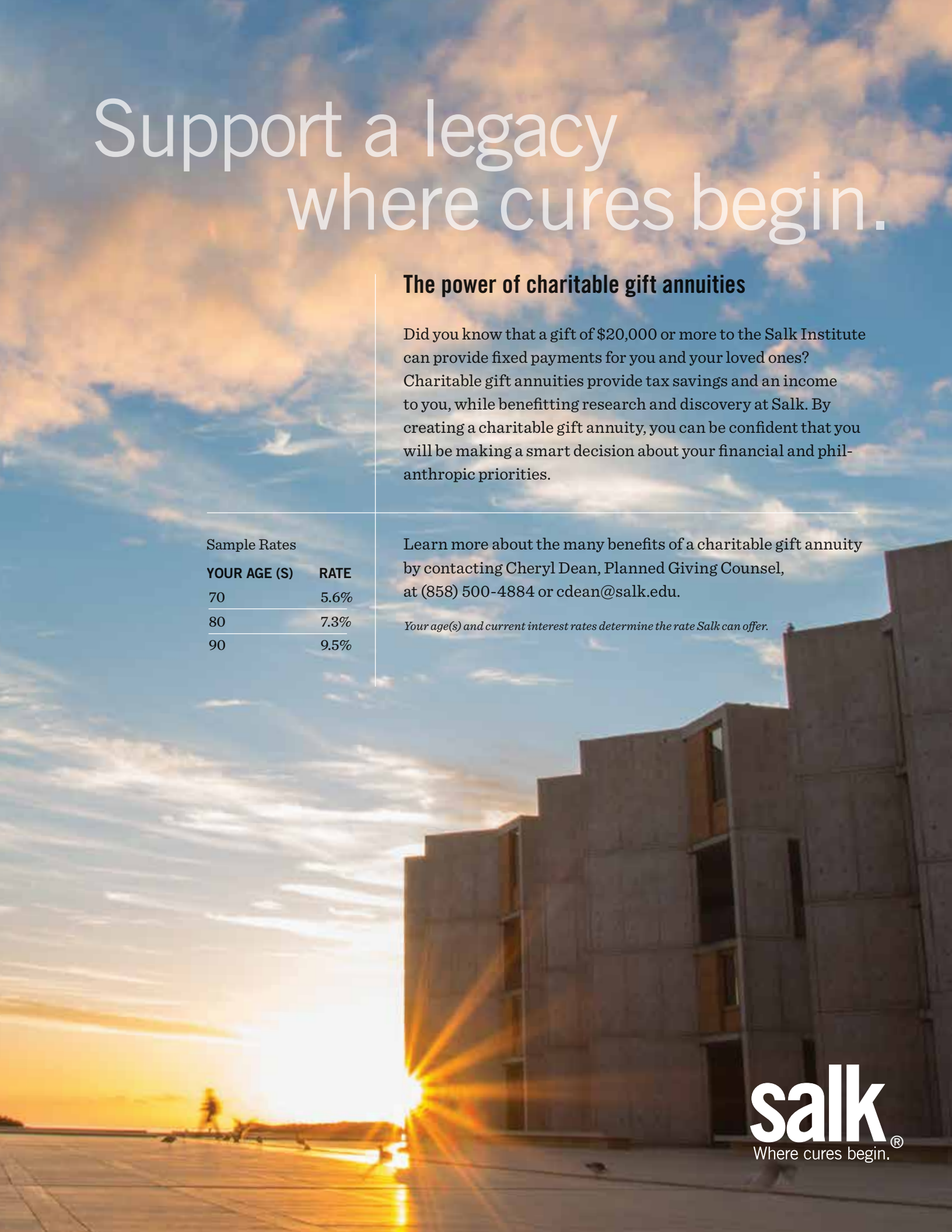
EDWARD CALLAWAY ELECTED TO NATIONAL ACADEMY OF SCIENCES

The National Academy of Sciences (NAS) has announced that Salk Institute Professor Edward Callaway is one of 100 new members to be elected to the NAS, in recognition of their distinguished and continuing achievements in original research. The election is considered one of the highest honors accorded to a U.S. scientist.

Gerald Joyce

GERALD JOYCE NAMED TO ROYAL SWEDISH ACADEMY OF SCIENCES

Professor Gerald Joyce has been elected to the prestigious Royal Swedish Academy of Sciences as a foreign member. Joyce is known for his work on deciphering the origins of the code of life and understanding how RNA can help target diseases.



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.

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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.

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EVENTS

Sonia Shah

A DECADE OF DISCOVERY

On April 10, the Salk Institute celebrated the 10th anniversary of the NOMIS Center for Immunobiology and Microbial Pathogenesis. The anniversary symposium, titled "The Power Within – Harnessing Our Immune System for Better Health," brought together experts in immunology, virology and infectious diseases, including the Center's director, Professor Susan Kaech. As part of this celebration, the symposium featured the inaugural Melvin Cohn Lectures and Awards as well as a keynote presentation by Sonia Shah, author of *Pandemic: Tracking Contagions, from Cholera to Ebola and Beyond.*

From left: Danyte Mockus-Valenzuela, Olivia Valenzuela, Vytautas R. Mockus and Michael Valenzuela

From left: (front row) Kay Chung, Rusty Gage, Juliana Capitanio; (back row) Amanda Phillips Yzaguirre, Shijia Liu, Nikki Lytle, Wenrong He (missing awardee from photo: Jessica Haley)

LEICHTAG AND HPI AT SALK

Supporters of Salk's Harnessing Plants Initiative gathered on May 2 at the Leichtag Foundation Commons to celebrate the $35 million endorsement by The Audacious Project of Salk's unique solution to use the power of plants to fight global climate change. (See this issue's "In the News" section for details.)

Joanne Chory and Tasha Boerner Horvath

Susan Kaech

From left:
Suzanne Bourgeois, Michel Nussenzweig,
Susan Kaech and Björn Lillemeier.

Tatyana Sharpee

SALK WOMEN & SCIENCE HONORS AWARD DONORS AND RECIPIENTS ALIKE

The spring Women & Science event on March 13 celebrated the generosity of two Salk professors emeritae, Suzanne Bourgeois and Ursula Bellugi. Bourgeois established the Suzanne Bourgeois Women & Science Fund to advance the work of female Salk faculty while the Salk Trailblazer award was renamed in honor of Bellugi, who established an endowed fund to support those who have pioneered changes within the STEAM fields. At the event, Salk Professor Tatyana Sharpee gave a talk and fifteen scientists were awarded travel or professional development grants, while seven received Women & Science Special Awards. Three students were also recognized.

From left: Tony Kranz, Lawrence Sherman,
Wolfgang Busch and James S. Farley

EVENTS

MUSIC SERIES ENDS ON A HIGH NOTE

The Salk Science & Music Series concluded its season on April 28, 2019, with a presentation by Assistant Professor Sung Han, who spoke about his research on the neurological underpinnings of pain, and music by the Brubeck Brothers Jazz Quartet. This was the second time the Brubeck Brothers have performed at Salk to a sold-out crowd. The 2019-2020 season will open on November 3.

Tickets will go on sale September 3 at ***music.salk.edu****.*

Sung Han

A MENTOR AND MENTEE PERSPECTIVE ON RESEARCH

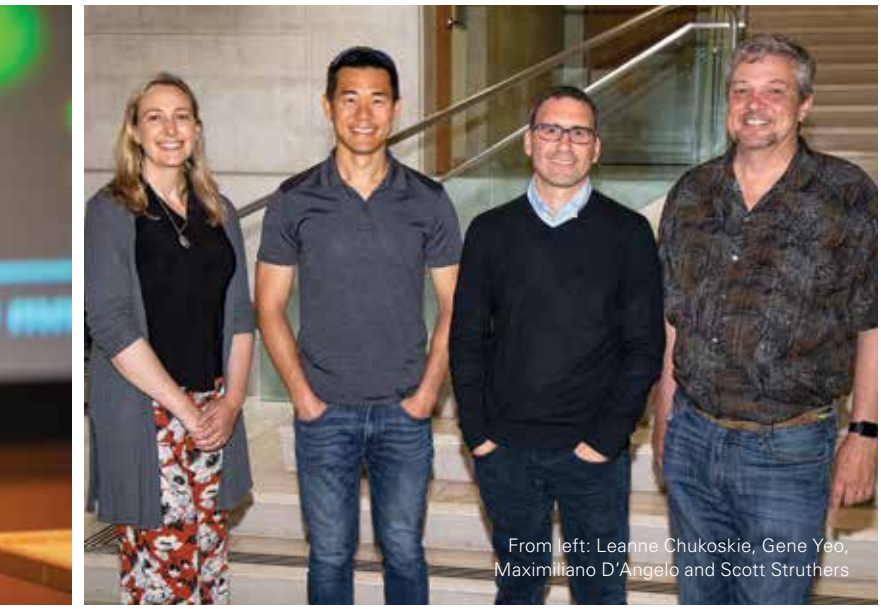
Salk Professor Geoffrey Wahl and Assistant Professor Dannielle Engle, who trained in Wahl's lab as a graduate student, described their journeys to become scientists and their approach to tackle one of the most difficult public health problems we face today: cancer. They offered a unique perspective behind the scenes of the mentor/mentee relationship essential to encourage young scientists and shared their work in identifying vulnerabilities in breast and pancreatic cancer.

Geoffrey Wahl and Dannielle Engle

EDUCATION OUTREACH HOSTS BOOTH ON EXPO DAY

Salk's Education Outreach program participated in the 11th annual STEM Festival of Science and Engineering EXPO Day at Petco Park on March 2, 2019. Booth volunteers like Joanne Wang (left) showed visitors how to extract DNA, completing over 500 extractions throughout the day. The Festival attracts tens of thousands of science enthusiasts each year. Salk Education Outreach is proud to be a founding member of the celebration.

Brubeck Brothers



From left: Leanne Chukoskie, Gene Yeo, Maximiliano D'Angelo and Scott Struthers

SALK ALUMNI RETURN TO CAMPUS

Salk welcomed alumni back to campus on June 5, 2019, for an engaging discussion and opportunity to connect with both familiar and new faces. The Society of Research Fellows (SRF) introduced four Salk alumni panel speakers—Leanne Chukoskie, Maximiliano D'Angelo, Scott Struthers and Gene Yeo—who shared their experiences about pursuing both academic and industry career paths. Afterwards, alumni and current Salk scientists enjoyed hors d'oeuvres while reconnecting.

INSTITUTE COUNCIL SEES A LOT OF HEART

The fifth annual meeting of the Salk Institute Council was held on May 1, 2019, with a keynote address by Beth Sirull, president of the Jewish Community Foundation, who shared how community foundations engage, educate and inspire generations of givers. Salk ambassadors and philanthropic leaders heard updates on scientific initiatives, witnessed beating heart cells under a microscope in the Stem Cell Core, and toured the state-of-the-art plant growth chambers.

Every cure begins with you.

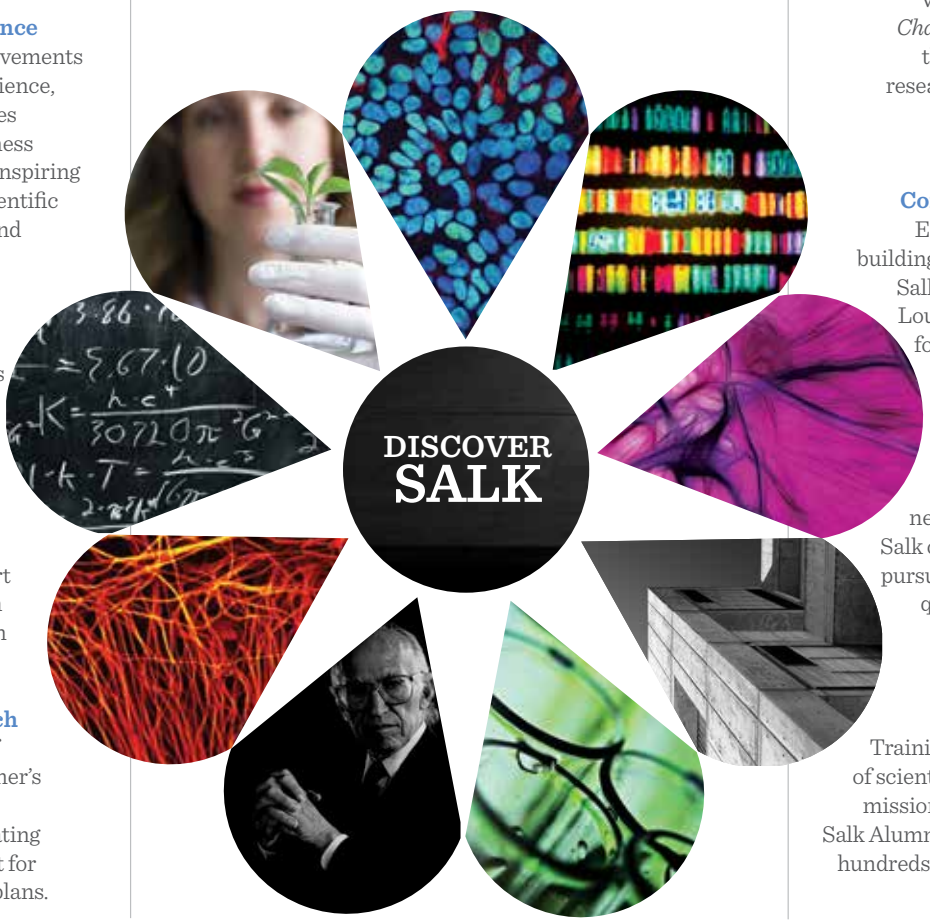
Salk giving programs offer a range of ways to get involved. Learn about Salk science and support vital research.

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.**

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La Jolla, California 92037-1002
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CALENDAR

OCTOBER

02 Back to Basics

23 Salk Women & Science Fall Event

NOVEMBER

03 Salk Science & Music Series
featuring Fei Fei Dong

JANUARY

12 Salk Science & Music Series
featuring Alessio Bax and Lucille Chung

MARCH

08 Salk Science & Music Series
featuring Per Nyström & Karen Joy Davis

MAY

03 Salk Science & Music Series
featuring Anderson and Roe

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