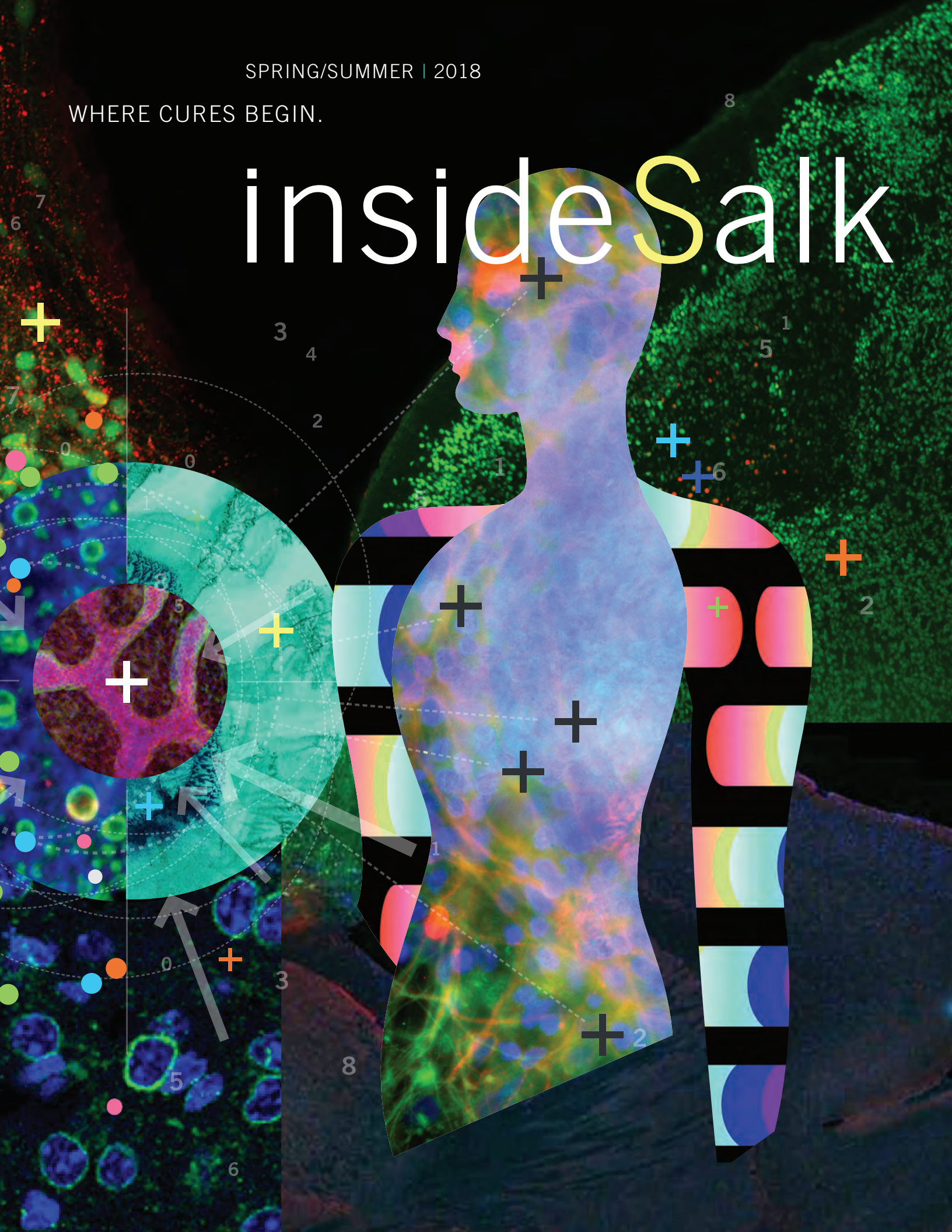
SPRING/SUMMER | 2018

WHERE CURES BEGIN.

insideSalk



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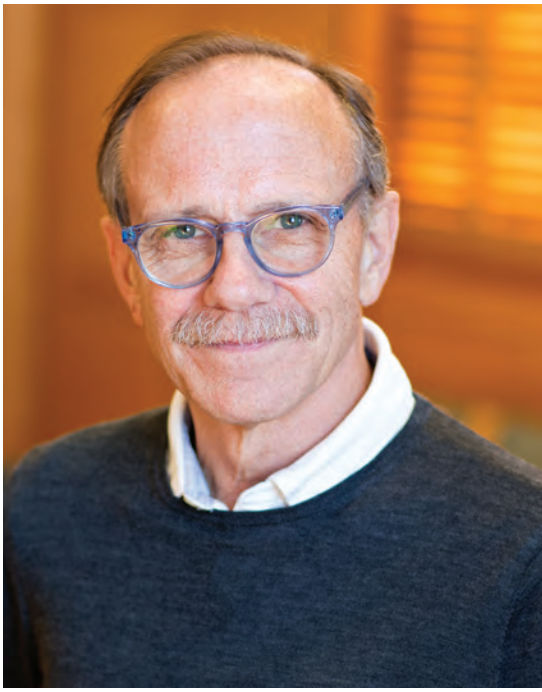
ON THE COVER:

Salk's Conquering Cancer Initiative aims to address the underlying causes of some of the deadliest cancers—pancreatic, brain, triple-negative breast, ovarian and lung.

PRESIDENT'S LETTER



Dear Friends,

Sixty-three years ago, on April 12, 1955, Jonas Salk's polio vaccine was declared safe and effective, marking the beginning of the end for the crippling virus that tragically affected so many children and families. To create a powerful visual reminder of what Salk's team accomplished, the University of Pittsburgh Graduate School of Public Health recently placed on display an "iron lung" donated by our Institute.

For those with horrifying memories of the devastating disease, the infamous ventilation device is likely a stark reminder of dark days that ultimately—and thankfully—were illuminated by the dawn of discovery. For all of us in the scientific community, it is a reminder of the enormous, transformative possibility of our work, and the vital mission of this Institute.

As you're likely aware, the Institute is in the midst of a transition phase and has faced some challenges. True to our nature, we are embracing this season of change, addressing our challenges and seeking to build on the progress we achieved in recent years under the leadership of Dr. Elizabeth Blackburn, one of the great scientific luminaries of our time who will be retiring at the end of the summer.

Rarely has a day gone by when I haven't been reminded about where our core focus must remain; the pace of breakthrough research coming out of this Institute has been truly amazing. In this issue, you'll read more about our exciting new cancer initiative —a multi-pronged approach toward conquering five of the most deadly cancers—and, in the process, seeking to develop entirely new classes of therapies that can be used to treat all cancers.

Recently, a longtime, enthusiastic supporter of the Institute asked me: "why should we care about Salk?" He meant the question honestly and I'm glad he asked it. Because it's a question that's incumbent on all of us to emphatically and constantly answer as stewards of a bold scientific mission and ambassadors of a place where we continue to prove possibility is limitless.

So what's the answer? For me it is this: We care because we are, in effect, brick layers, building foundations and creating critical connections that piece by piece, hand by hand, lead to towering achievements. We care because we are explorers and risk takers who have signed up for the hard work, the seemingly impossible tasks—because we know the rewards. We care because every day we see in our mind's eye an image akin to that iron lung relic, a symbol that declares with Salk, the match was met.

I am very passionate about this Institute and privileged to be serving in this role. Thank you very much for your support.

Sincerely,

Fred H. Gage

Rusty Gage
President

DISCOVERIES

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

READ

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

RESEARCH
AT SALK

NEUROSCIENCE

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

PLANT BIOLOGY

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

GENETICS

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

CANCER

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

MICROBIOME

We are not alone; the human body is home to trillions of bacteria. At Salk, we explore how this community of bacteria helps us stay healthy, and how we might help it fight disease.

REGENERATIVE MEDICINE

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

AGING

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

IMMUNOLOGY

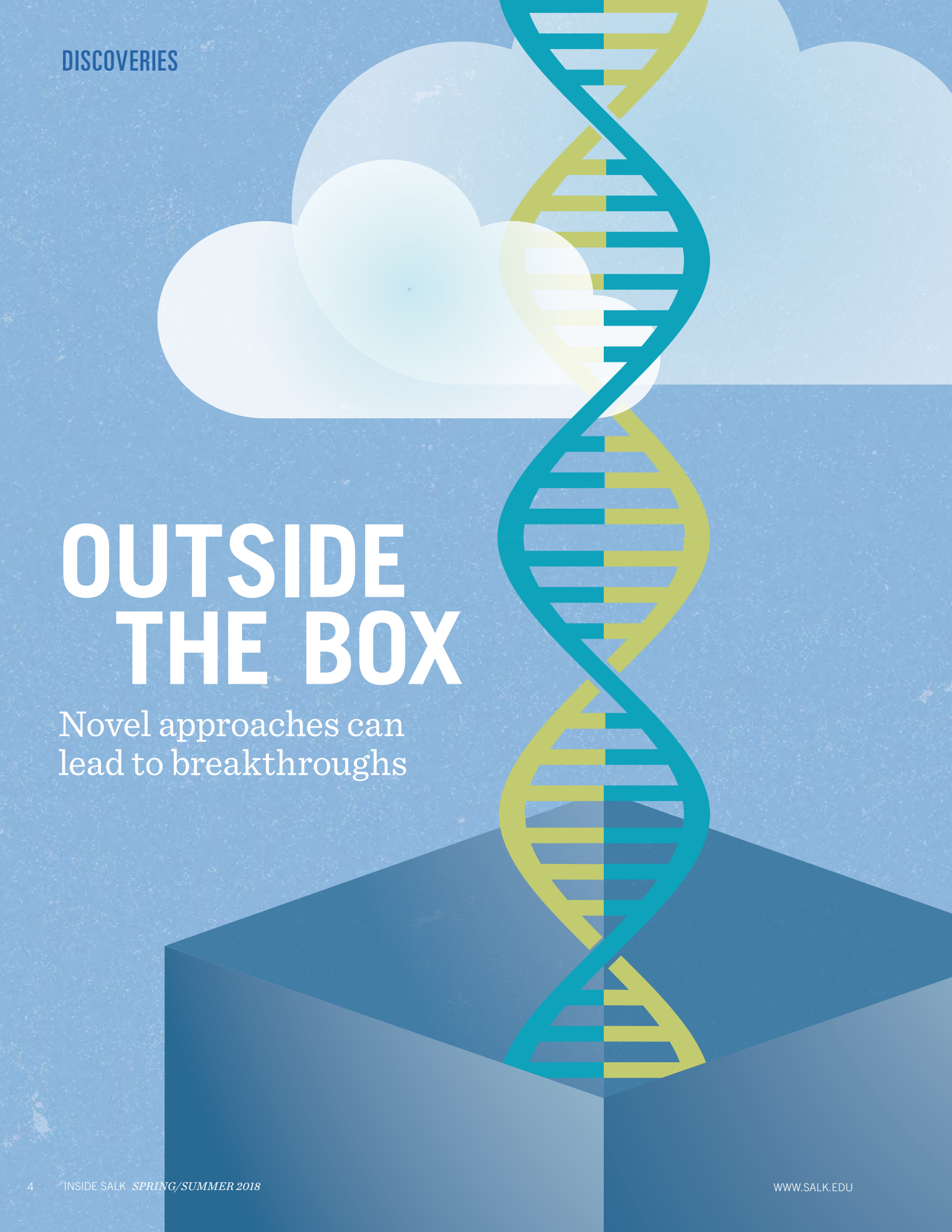
In a world full of dangers, from bacterial infections to cancer, our immune system is our fortress. We study the immune system to boost our ability to fight off numerous diseases.

METABOLISM

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

PROTEIN INTERACTIONS

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



OUTSIDE THE BOX

Novel approaches can lead to breakthroughs

GENETICS

CANCER

CELL
12/2017

Salk scientists modify CRISPR to epigenetically treat diabetes, kidney disease, muscular dystrophy

A research team led by Juan Carlos Izpisua Belmonte, and including co–first authors Hsin-Kai (Ken) Liao and Fumiyuki Hatanaka, developed a new version of the CRISPR/Cas9 gene-editing tool, allowing them to activate genes without creating DNA breaks. This breakthrough could circumvent a major hurdle to using gene editing in the treatment of human diseases. Most CRISPR/Cas9 systems create double-stranded DNA breaks, but many researchers are opposed to creating these breaks in humans because they can cause additional health problems. However, the system developed in the Belmonte lab alters gene expression without actually breaking DNA. The team used this new approach to treat several diseases in mouse models, including diabetes, acute kidney disease and muscular dystrophy. They are now working to improve the precision of their system and apply it to more cell types in the hopes of treating a wider range of human diseases, rejuvenating specific organs and reversing age-related conditions, such as hearing loss and macular degeneration.

WATCH | http://bit.ly/belmonte201805

AS SEEN IN

Los Angeles Times Forbes The Guardian

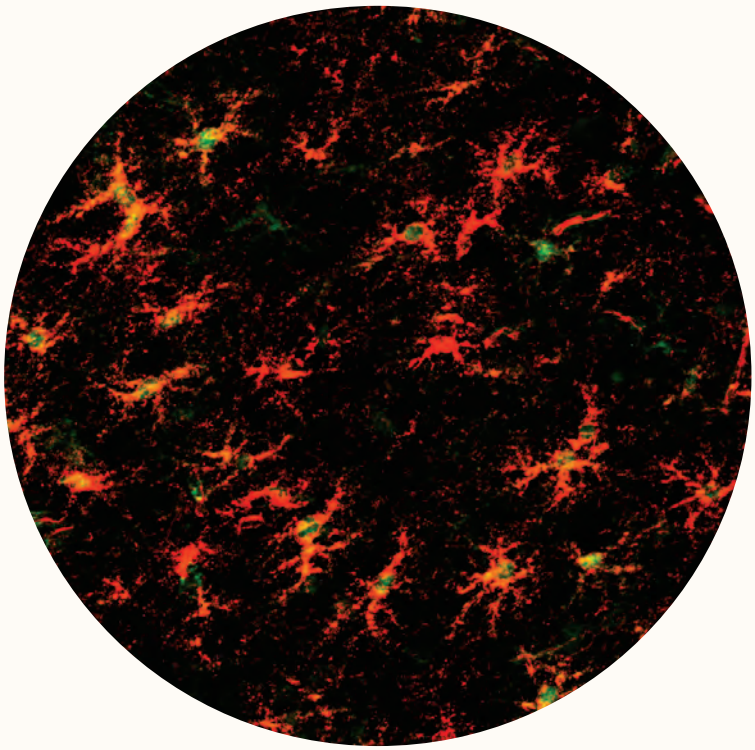
NATURE
01/2018

Salk scientists curb growth of cancer cells by blocking access to nutrients

Research led by Satchidananda Panda, with first author Gabriele Sulli, showed how to curb cancer cell growth by blocking the cells' access to nutrients. The key is the circadian cycle, the intrinsic clock that exists in all living things and helps control when individual cells produce and use nutrients. The team focused on REV-ERBα and REV-ERBβ, proteins that are part of the clock's machinery and modulate cells' ability to synthesize fats and recycle materials. Since cancer cells rely heavily on both of these processes to grow, the researchers thought activating REV-ERBs might slow that growth. Panda's team used two activating drugs on a variety of cancer cells, including T cell leukemia, breast, colorectal, melanoma and glioblastoma. In each line, the drugs were able to kill the cancer cells, but had no effect on healthy cells.

WATCH | http://bit.ly/panda201805

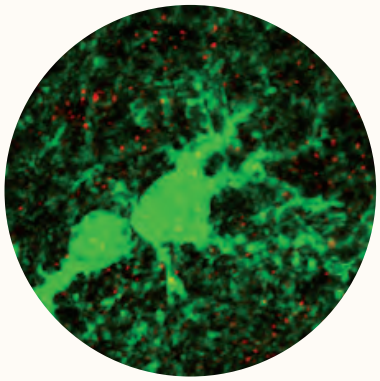
NEUROSCIENCE



Ribosomes in astrocytes are stained red using the ribo-tag method. Green stains indicate the nuclei of the star-shaped support cells.

WHEN THE BRAIN'S SUPPORT CELLS AREN'T SO SUPPORTIVE

Early in human development, neurons make a flurry of connections that are then pruned back to fine-tune the brain. Assistant Professor Nicola Allen and UC San Diego graduate student Matthew Boisvert discovered that genes that get switched on to sever these early connections between neurons are later activated again in support cells called astrocytes. Named for their star-shaped appearance, astrocytes make up one-third to one-half of all brain cells and are critical for neuronal function. By comparing gene expression in astrocytes in adult and aged mouse brains, the team uncovered that a genetic program is reactivated as astrocytes age, causing neurons to lose connection with each other. The discovery, which appeared in *Cell Reports* on January 2, 2018, hints that astrocytes may be good therapeutic targets to prevent or reverse the effects of normal aging. S



Fluorescently labeled astrocytes (large green structures) and neuronal postsynaptic receptors (red).

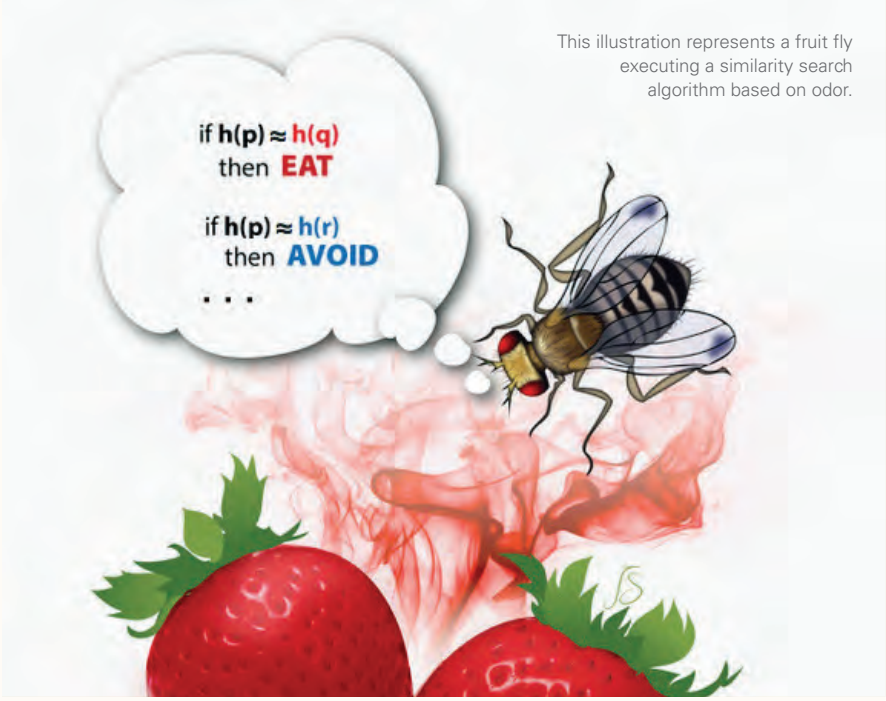
ENSURING GOOD CELLULAR CONNECTIONS IN THE BRAIN

Astrocytes are brain cells that, among other things, help neurons form active connections with each other. The exact mechanism behind this process has been a mystery. Scientists in Nicola Allen's lab have begun to uncover more about these important cells. Allen and first author Isabella Farhy-Tselnicker discovered that astrocytes initiate communication between pairs of neurons by prompting specific changes in neurons through a protein called glypican 4. This protein influences both sending and receiving neurons, helping them make synaptic connections. It may be a target for better understanding neurodevelopmental disorders, such as autism, ADHD and schizophrenia, all of which may result at least partially from faulty communication between neurons. The work was published in *Neuron* on October 11, 2017. S

WATCH	http://bit.ly/allen201805

WHEN YOUR SPINAL CORD TAKES CHARGE

We think the brain masterminds our actions, but a surprising amount of movement-related information is processed in the spinal cord. When we move, motor circuits in the spinal cord are constantly barraged by information from sensory receptors in the skin and muscles, information as varied as what our limbs are doing or what the ground underfoot feels like. This information is critical for actions like walking or standing still. Researchers in Martyn Goulding's lab have solved a long-standing mystery about how spinal cords know when to pay attention to certain pieces of information and when to ignore them. Goulding, first author Stephanie Koch and others, in work published in *Neuron* on December 7, 2017, showed that specific neurons, called RORβ interneurons, inhibit the transmission of potentially disruptive sensory information during walking, allowing for a fluid gait.



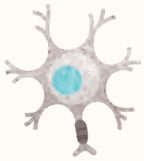
This illustration represents a fruit fly executing a similarity search algorithm based on odor.

FRUIT FLY BRAINS INFORM SEARCH ENGINES OF THE FUTURE

Current computer algorithms find similar items by reducing the amount of information associated with each item. Fly brains do exactly the opposite.

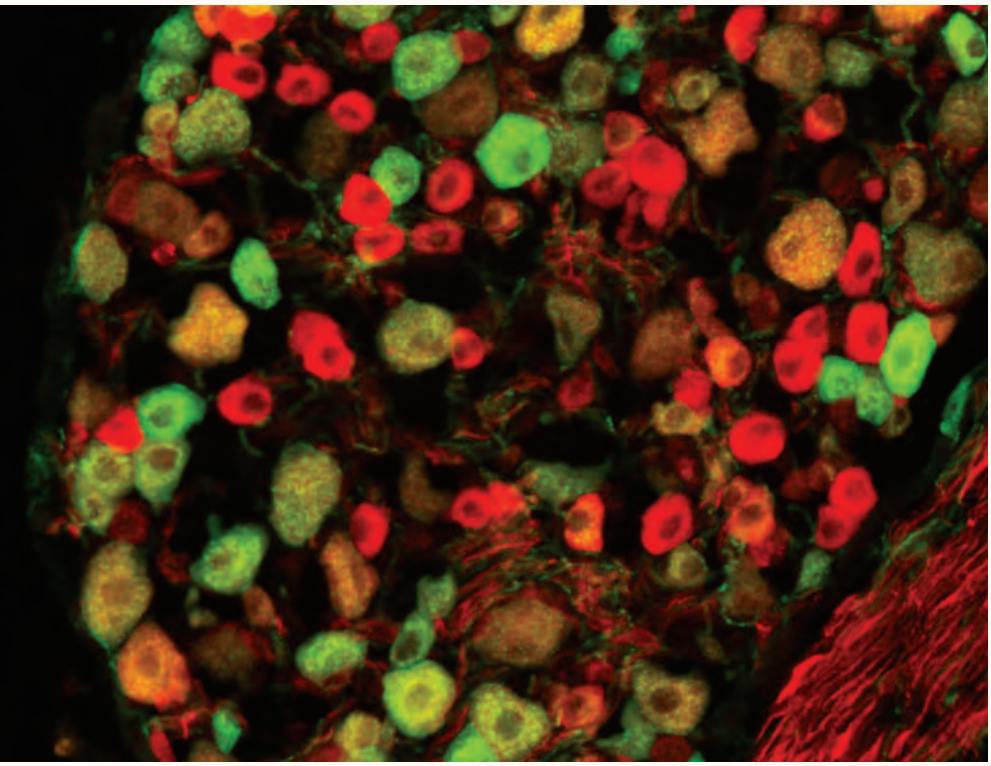
Every day, websites and apps crunch huge sets of information to find data points that resemble each other, such as products that are similar to past purchases. These tasks are called similarity searches, and performing them well—and fast—has been an ongoing challenge for computer scientists. Salk faculty Saket Navlakha and Charles Stevens, together with collaborator Sanjoy Dasgupta of UC San Diego, have shown that fruit fly brains, in their efforts to identify similar odors, may have found a better way to perform similarity searches. Current computer algorithms find similar items by reducing the amount of information associated with each item. Fly brains do the opposite, expanding the amount of information associated with each item, which allows them to better distinguish similar from dissimilar. When the researchers applied this approach of expanding rather than reducing information associated with data to three standard datasets, they found the fly method dramatically improved search performance. They reported their findings in *Science* on November 9, 2017.

WATCH	http://bit.ly/navlakha201805



NEUROSCIENCE

The presence of p75 (green) and Ret (red) together in some sensory neurons suggests that the proteins may interact with each other.



"BUSYBODY" PROTEIN MAY GET ON YOUR NERVES, BUT THAT'S A GOOD THING

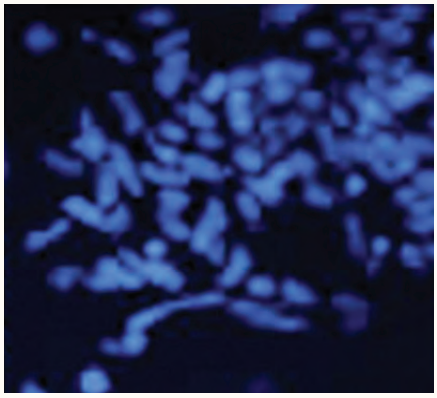
Sensory neurons regulate how we recognize touch and pain as well as body movement and position, but neuroscientists are only now beginning to unravel this circuitry. New research from Kuo-Fen Lee's lab, co–first authored by Zhijiang Lee and Christopher Donnelly, and in collaboration with researchers at the University of Michigan, shows how a protein involved in many different signaling pathways plays a key role in pain signaling in the brain.

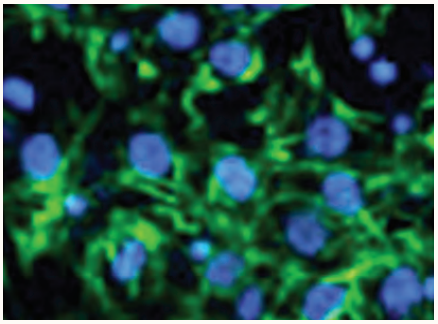
This "busybody" protein, called p75, enhances the survival of proteins that support sensory neurons involved in transmitting pain signals. When p75 is removed, the survival-promoting signal of these proteins is reduced and the neurons that respond to this signal gradually degenerate. These findings could lead to new insights into neurological disorders, as well as spinal cord injuries and other traumas. The work was published on October 17, 2017, in *Cell Reports*.

ALZHEIMER'S DRUG TURNS BACK CLOCK IN CELLULAR POWERHOUSE

The experimental drug J147, a synthetic, modified version of the curcumin molecule found in the spice turmeric, is almost ready for human trials. The lab of Dave Schubert developed J147 while looking for plant compounds that reverse cellular and molecular aging in the brain. Since then, the team has shown J147 reverses memory deficits, drives the production of new brain cells and slows or reverses Alzheimer's disease progression in mice. Now Schubert, first author Josh Goldberg and their colleagues have figured out how J147 works: in a study published in *Aging Cell* on January 9, 2018, they reported that the drug binds to an enzyme called ATP synthase, which is found in our cells' power-generating organelles (mitochondria). The team showed that, by manipulating ATP synthase activity, they could protect brain cells from multiple toxicities associated with aging. Unraveling J147's mechanism of action is a critical step towards clinical trials in humans.

GETTING STRAIGHT TO THE HEART OF THE MATTER IN STEM CELLS





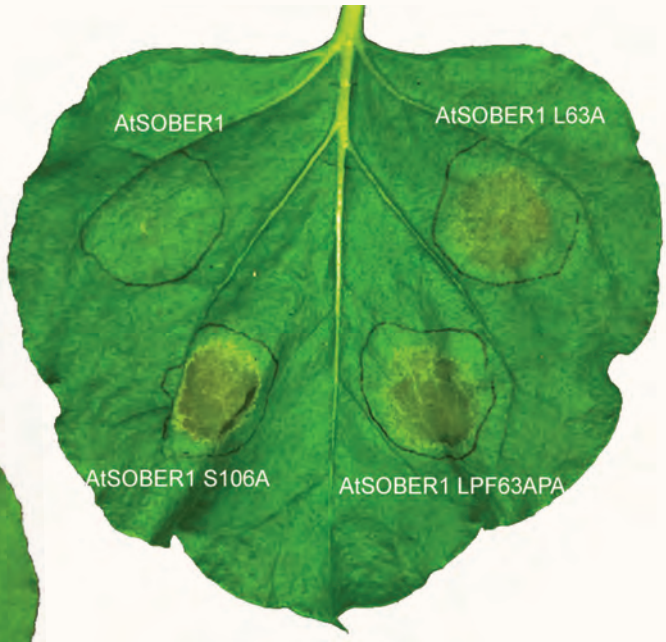
Only hESCs with YAP (right panel) make heart cells (green) in one step. Blue dye marks cell nuclei.

The process by which embryonic stem cells develop into heart cells is complex, involving the precisely timed activation of several molecular pathways and at least 200 genes. Now, Salk Professor Kathy Jones and first author Conchi Estarás, alongside their colleagues, have found a simpler way to go from stem cells to heart cells that involves turning off a single gene, called YAP. The work, which appeared in *Genes & Development* on December 21, 2017, offers scientists a streamlined method to arrive at functioning heart cells (cardiomyocytes) for both research and regenerative therapies.

MULTIFUNCTIONAL PROTEIN CONTRIBUTES TO BLOOD CELL DEVELOPMENT

Researchers in Martin Hetzer's lab found a previously unknown role for a protein called nup98. In addition to helping control how certain molecules move in and out of a cell's nucleus, nup98 helps direct the development of blood cells, enabling immature blood stem cells to differentiate into mature cell types. The team described their discovery in the December 21, 2017, issue of *Genes & Development*. Hetzer, first author Tobias Franks and collaborators found that when perturbed, this differentiation process can contribute to certain leukemias, making nup98 a potential target for new cancer therapies.

PLANT BIOLOGY



LEFT: This illustration depicts a leaf with areas of damage (brown spots) caused by the plant's innate immune response. The superimposed schematic shows SOBER1's three-dimensional structure.

RIGHT: This illustration shows four areas of a tobacco leaf infected with both a bacterial toxin and three mutant versions of the SOBER1 protein. The unmutated version of SOBER1 (upper left) has the healthiest-looking tissue because the plant's tissue-killing immune response against the toxin has been blocked by SOBER1.

SELF-DEFENSE FOR PLANTS

When you see brown spots on otherwise healthy green leaves, you may be witnessing a plant's immune response as it tries to keep a bacterial infection from spreading. Some plants are more resistant to such infections than others. To explore why, Salk scientists Joanne Chory and co–first authors Marco Bürger and Björn Willige studied a plant protein called SOBER1, which had previously been probed in relation to infection, and discovered that, counterintuitively, SOBER1 rendered plants less resistant to infection. The work, which appeared in *Nature Communications* on December 29, 2017, sheds light on plant resistance generally and could lead to strategies to boost plants' natural immunity or to better contain infections that threaten to destroy an entire agricultural crop.

IMMUNOLOGY

IMMUNE CELL POLICING OFFERS INSIGHTS INTO CANCER, AUTOIMMUNE DISEASE

Regulatory T cells (Tregs) are the immune system's traffic cops, instructing other immune cells when to stop and when to go. Research led by Ronald Evans, with first author Nanhai He, has uncovered, for the first time, how a protein called Lkb1 controls Treg survival and function. Lkb1 had previously been shown to play a role in cell metabolism. But until this study, published in *Proceedings of the National Academy of Sciences* during the week of November 6, 2017, investigators didn't know Lkb1 also controls Treg function. They discovered that the Lkb1 pathway provides Tregs with energy, without which the cells are unable to function. Learning how to direct Treg activity could potentially improve cancer immunotherapy and lead to better treatments for autoimmune diseases, such as rheumatoid arthritis and type 1 diabetes.

PROTEIN INTERACTIONS

From left: John Lubin, Vicki Lundblad and Tim Tucey

REVEALING THE BEST-KEPT SECRETS OF PROTEINS

In the bustling setting of the cell, proteins encounter each other by the thousands. Despite the hubbub, each one manages to selectively interact with just the right partners thanks to specific contact regions on its surface. However, these regions have remained far more mysterious than might be expected, especially given decades of research into protein structure and function. Salk Professor Vicki Lundblad and co–first authors John Lubin and Timothy Tucey, now at Monash University, developed a new method to discover which surface contacts on proteins are critical for these cellular interactions. Their approach shows that essential new functions can be uncovered even for well-studied proteins, and has significant implications for therapeutic drug development, which depends heavily on how drugs physically interact with their cellular targets. The paper appeared in the early-access online version of *Genetics* on November 29, 2017.

Glioblastoma Multiforme

Glioblastoma surgery has been likened to lifting a spider web off wet leaves—small pieces stay behind. In addition, glioblastomas tend to have many different mutations, even within a single tumor. This genetic heterogeneity helps them persist, even after multiple treatments. Five-year survival peaks at 10 percent.

Five-year survival peaks at

10%*

for glioblastoma multiforme patients

TARGETING FIVE DEADLY CANCERS

A cancer diagnosis is never good news, but there are five types that are are particularly deadly: pancreatic, ovarian, lung, glioblastoma and triple-negative breast. These cancers are often diagnosed late, can be difficult to remove surgically and rebuff most therapies.

Lung Cancer

Non–small cell lung cancer, the most common variety, tends to be diagnosed late and is often quite aggressive. Surgeons may remove visible tumors, but microscopic cancer can persist. In addition, lung cancers tend to be more resistant to systemic treatments, such as chemotherapy. Around 18 percent of lung cancer patients survive five years.

18%

of lung cancer patients survive five years (if the cancer has spread, survival rate drops to 4%)

Triple-Negative Breast Cancer

While many forms of breast cancer are quite treatable—even curable—triple-negative remains a challenge. These tumor cells lack estrogen, progesterone and HER2 receptors, which are often targeted in breast cancer therapies. Without these targets, patients have fewer therapeutic options. In addition to being more difficult to treat, triple-negative breast cancer can be more aggressive, rapidly spreading to other tissues.

Five-year survival rate for all breast cancers is 90%, but drops for triple-negative breast cancer.

78%

Pancreatic Cancer

Approximately 8 percent of pancreatic patients survive more than five years. Part of the problem is late diagnosis. Pancreatic cancer presents indistinct symptoms, such as abdominal pain, jaundice and weight loss. But the biggest issue is the shell pancreatic tumors build to protect themselves. Similar to scar tissue, this shell thwarts the immune system, as well as chemotherapy and other treatments.

Only

8%

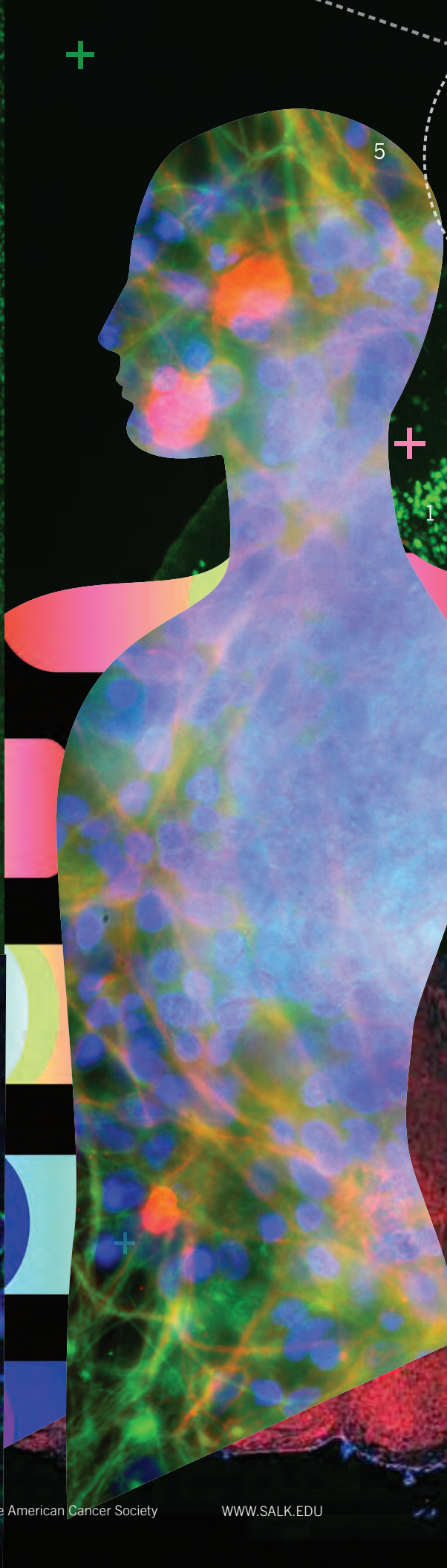
of pancreatic cancer patients survive more than five years

Ovarian Cancer

Like pancreatic, ovarian cancer is often diagnosed late. Early stage ovarian cancer looks a lot like irritable bowel syndrome. By the time many patients are diagnosed, the cancer has already spread. The five-year survival is 46 percent.

The five-year survival rate for ovarian cancer is

46%



*Sources: The National Cancer Institute and the American Cancer Society

TAKING ON THE BIG FIVE

SALK TAKES AIM AT FIVE DEADLY CANCERS

Cancer is not like other diseases. Most conditions have external causes—bacteria, viruses, injury—but cancer comes from inside us. Cells go rogue, divide recklessly, invade other tissues and spread throughout the body. They do things normal cells cannot do.

The word itself evokes fear. Cancer is secretive, terrifying. It grows unobserved, recodes itself to escape treatment and co-opts normal biology to keep growing. To add complexity, cancer is not one disease but many—hundreds, perhaps thousands.

THE SALK INSTITUTE CANCER CENTER

The Cancer Center at the Salk Institute for Biological Studies was established in 1970. Two years later, the Salk Cancer Center became one of the first National Cancer Institute (NCI)-designated basic research cancer centers in the United States. This designation recognizes the Institute's scientific rigor across its laboratory investigations, scientific discoveries and therapeutic cures. The Salk Cancer Center, led by Reuben Shaw, comprises half of the research at the Salk Institute, including 32 faculty members, 199 postdoctoral researchers, 41 graduate students and 101 research assistants.

WHY SALK?

THE LEGACY

The Salk Institute has a long history of making critical scientific breakthroughs in cancer research that have directly resulted in new classes of therapies for cancer, such as the tyrosine kinase inhibitor Gleevec.

THE PEOPLE

Established and recent additions to the Salk faculty have created an environment in which some of the most brilliant minds in their respective fields work with cutting-edge technology in immunology, metabolism, genomics and many other disciplines to battle cancer.

THE APPROACH

At Salk, scientists explore unexpected areas of research and collaborate across fields to uncover foundational knowledge that can lead to new treatments. This culture of innovation and collaboration gives Salk scientists an unparalleled community in which to make life-changing discoveries.

For these and other reasons, cancers are among the most difficult conditions to treat. Nearly 50 years after the United States declared a War on Cancer, it remains the second-leading killer after heart disease and causes untold suffering.

To change that, Salk's NCI-designated Cancer Center—one of the first such centers in America—is launching the Conquering Cancer Initiative. This five-year, $55 million effort will bring together scientists in more than 30 Salk labs to harness new strategies against five deadly cancers: pancreatic, ovarian, lung, brain (glioblastoma) and triple-negative breast. Together, Salk researchers will identify cancer's vulnerabilities and find new methods to attack tumors and leave healthy tissue alone.

"We have historical expertise with making discoveries in these five intractable cancers," says Salk Cancer Center Director Reuben Shaw. "And because they are among the most complex and deadly, if we can make headway against them, we will make advances against many cancers."

Hitting back

Cancers are genetic diseases, and they're exceptionally patient. A tumor may start with a single mutation in a growth pathway, the genes that tell cells to grow and divide. This is a normal function—if you cut yourself, adjacent cells grow faster for a time and heal the wound. But these mutations can eliminate molecular "off" switches, allowing cells to continue multiplying.

By itself, such a variation might not be enough to generate a tumor. The body has excellent defenses, such as the immune system and DNA safeguards. For example, the p53 protein scans for genetic anomalies and shuts down cell division to correct them. If the mistakes can't be fixed, p53 initiates the cell's self-destruct mechanism, a function called apoptosis.

These systems keep mutated cells at bay, but over time—years or even decades—they can fail. Cancer cells learn to fool the immune system into thinking they are normal tissue. Mutations corrupt p53 and other quality-control mechanisms.

Without these safeguards, random mutations appear more rapidly, and some confer survival advantages for tumors. Proteins that initiate apoptosis get shut down. Molecules that pump toxins, such as chemotherapy, out of cells get turned up. Some cancers become virtually invulnerable to current treatments. Eventually, the tumor invades surrounding tissue and spreads throughout the body, a process called metastasis.

But strengths can also be weaknesses. The same mutations that help tumors survive can be targeted for treatment. The key is learning how these cellular mechanisms work—something Salk scientists have excelled at for more than 50 years (see sidebar "Intellectual firepower").

"The Salk Cancer Center aims to push back the boundaries of fundamental understanding of cancer and use that knowledge to develop new therapeutics," says Shaw. "By being bold, by being innovative and by being collaborative, we hope to turn the tide against cancer."

Specifically, Salk's new cancer initiative will focus on five ways to eliminate the disease: cutting the metabolic supply lines that provide fuel to tumors; disrupting the inflammatory barriers protecting cancer cells; decoding cancer's genomics to reprogram malignant cells back to normal; mobilizing the immune system to recognize and attack cancer; and developing sophisticated methods to strike cancer's many vulnerabilities simultaneously. By targeting these five areas, Salk scientists continue the Institute's legacy of discovering foundational biological mechanisms to understand—and ultimately conquer—cancer.

From left: Jonas Salk and Renato Dulbecco

INTELLECTUAL FIREPOWER

Salk has a long history of focusing the best minds on the most difficult problems. Over the years, six Salk faculty have received Nobel prizes, including Renato Dulbecco, who was honored for his pioneering work on cancer.

A Founding Fellow at Salk, Dulbecco won the Nobel Prize in Physiology or Medicine in 1975 for discovering how tumor viruses promote cancer via genetic changes. His work set the stage for much of the cancer research being done today.

Later, Dulbecco pioneered using monoclonal antibodies to identify cells based on their genetic signatures. These antibodies are now routinely used for both research and treatment.

In 1986, Dulbecco called on the scientific community to sequence the DNA in human cells. The Human Genome Project would begin four years later. Dulbecco's work continues to have a major impact on researchers around the world. His legacy inspires the Institute's continuing efforts to defeat cancer.

STRATEGY: 1

CUTTING FUEL LINES

"We need to think about how we use drug strategies to treat each individual patient's subset of cancer. One would be targeted therapeutics, another would be immunotherapy drugs and a third could be taking out the metabolic Achilles' heel. These would be viable strategies with less toxicity."

—**REUBEN SHAW** | Salk Cancer Center Director

Cutting fuel lines

To continue growing, tumors must constantly find new food sources. Scientists have known for more than a century that tumors rewire their metabolisms to get more energy. However, it's only in the past few years they've recognized what a powerful weapon metabolism can be.

Shaw has been investigating this metabolic connection for more than a decade. He discovered that the altered LKB1 gene, which is often mutated in lung cancer, activates a metabolic master switch. This unforeseen connection between cancer and metabolism offered a new therapeutic strategy: hit cancer through its food supply.

Like normal cells, tumors rely primarily on glucose for energy. But cancer always has a backup plan. Should glucose run short, tumors rewire themselves to use the amino acid glutamine for fuel. However, once a tumor commits to a secondary energy source, it can have trouble reversing the process. Healthy cells are more flexible. Shaw and others believe they can take away these sources, one at a time, and gradually force cancer into a corner.

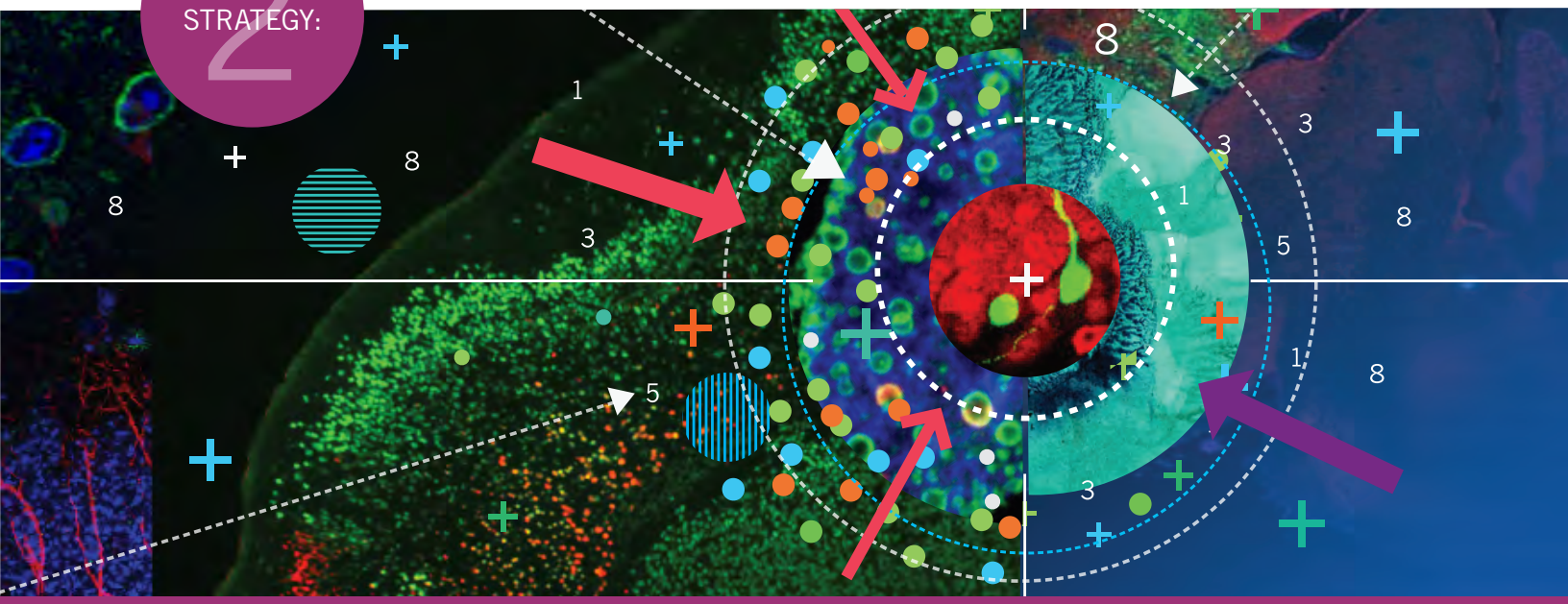
"Normal cells aren't metabolically stressed—they can flip back and forth between using different food sources," says Shaw, who holds the William R. Brody Chair. "Tumor cells are naturally more constrained in their metabolism. You're confining the tumor metabolically (by taking away its energy sources), and when you get it there, you hit the trap door." Another example of tripping metabolic trap doors is by targeting mitochondria, the cells' power stations. "We have discovered that specific cancer gene mutations make cells sensitive to mitochondrial drugs, including the diabetes drug Metformin."

Shaw's metabolic strategy shows great promise and underscores Salk's overall approach: identify cancer's many vulnerabilities and exploit them. Because each patient's disease is different, these approaches can be mixed and matched based on a tumor's genetic profile.

"We need to think about how we use drug strategies to treat each individual patient's subset of cancer," says Shaw. "One would be targeted therapeutics, another would be immunotherapy drugs and a third could be taking out the metabolic Achilles' heel. These would be viable strategies with less toxicity."

STRATEGY: 2

FIGHTING INFLAMMATORY FIRES WITH FIRE



"Pancreatic cancer is like its own ecosystem. Once it's contained in this shell, it's difficult for drugs to reach it. Instead of directly attacking the cancer, we had the idea to attack the ecosystem that surrounds it."

—**RONALD EVANS** | Professor and Director, Gene Expression Laboratory

Fighting inflammatory fires with fire

As cancer develops, the body responds, sending inflammatory signals to fight the invader. Acute inflammation is part of the body's healing process. But if it persists, inflammatory mechanisms can do even more harm.

"Cancer has been referred to by pathologists as a wound that will not heal," says Geoffrey Wahl, a professor in Salk's Gene Expression Laboratory. "The body is trying to restore balance to the cancerous organ, but it can't do that because of all the genetic and epigenetic changes that have led to deranged growth."

Wahl has been studying this interplay between tumors and the body's response systems and has made a startling discovery: in this hyperinflammatory environment, cells change—a lot.

The lab's work led them to a gene called SOX10, which is normally associated with early development. Inflammatory signals intended to heal cancer can turn on SOX10 signals, which can change cells in a variety of ways. Normal cells tend to stay put, but under SOX10's influence, they revert to early, developmental states, becoming mobile and, ultimately, invasive.

These processes play a big role in triple-negative breast cancer, which is even more disorderly than other forms of the disease. In this biological melee, cells lose p53, the quality-control mechanism that helps keep genomes intact.

"Because of this persistent wounding environment, some of these cells start to reprogram themselves," says Wahl, who holds the Daniel and Martina Lewis Chair. "They get reprogrammed into fetal antecedents, which are selected to survive in this chaotic environment."

By illuminating this biology, Wahl hopes to find markers that can differentiate reprogrammed cells from normal tissue. Once these aberrant cells can be separated, they can be selectively targeted.

Inflammation also plays a major role in pancreatic cancer, which creates a protective shell that blocks both immune cells and chemotherapy.

"Pancreatic cancer is like its own ecosystem," says Ronald Evans, professor and director of the Gene

Expression Laboratory and holder of the March of Dimes Chair in Molecular and Developmental Biology. “Once it’s contained in this shell, it’s difficult for drugs to reach it. Instead of directly attacking the cancer, we had the idea to attack the ecosystem that surrounds it.”

Evans’ lab modified vitamin D, transforming it into a molecule that can alter the environment supporting pancreatic cancer’s protective shell. By softening the shell, this modified vitamin D drug makes tumors vulnerable to attacks from the immune system or chemotherapy. The drug is currently in clinical trials in combination with Merck’s immunotherapy Keytruda. The lab recently received a $2.5 million Catalyst grant from Stand Up To Cancer to advance this work.

Tony Hunter, American Cancer Society Professor and holder of the Renato Dulbecco Chair, is one of many researchers collaborating with Evans. Hunter started his career investigating the signaling mechanisms that drive cancer, providing the foundational knowledge for an entirely new class of cancer drugs (see sidebar “From basic discovery to effective treatment”). In this case, his lab is focusing on the cross-talk between pancreatic tumors and their surrounding cells, called stroma.

“Stromal cells produce hundreds of proteins, including LIF, a protein that strongly stimulates tumor cells,” says Hunter. “Tumor cells make their own factors that stimulate the stroma, so it’s reciprocal.”

Hunter is working with a company called Northern Biologics, which has developed an antibody against LIF that will soon enter clinical trials.

FROM BASIC DISCOVERY TO EFFECTIVE TREATMENT

Salk Board Chair Dan Lewis has had chronic myelogenous leukemia (CML) for 10 years. He may have CML for the rest of his life, but he probably won’t die from it. He has a treatment, Gleevec, which transforms CML from a deadly disease into a chronic one.

CML is a unique cancer because it’s caused by a single mutation—a protein fusion called BCR-ABL. ABL is a tyrosine kinase, an enzyme that turns on other proteins by transferring energy packets called phosphate groups—a process called phosphorylation.

Salk Professor Tony Hunter discovered tyrosine kinases almost by accident in 1979. At the time, many researchers thought tumors were caused by viruses. Hunter’s lab was studying two of these viruses, looking for kinase activity generated by the viruses with a technique called electrophoresis. In this common lab procedure, a sample is put on a plate and separated by applying an electrical current. Different molecules (DNA, RNA, proteins and phosphorylated amino acids) move across the plate at different rates, depending on their charge. The results look like rows of small spots along a line.

Hunter expected the experiment to produce a phosphorylated amino acid spot in one of two places and was surprised when it produced a third option. Phosphorylation adds a phosphate group, a cellular energy packet, to a protein, basically turning that molecule on. He redid the experiment with the same results.

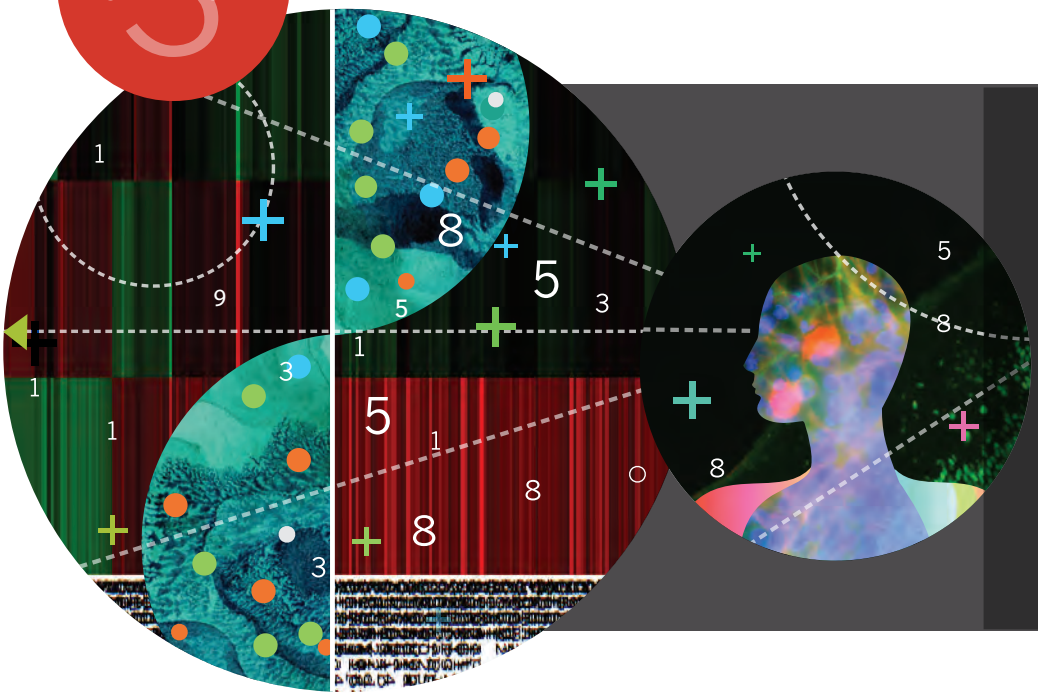
Further study showed he had discovered a tyrosine kinase, which makes phosphorylated tyrosine. Later, he realized that, by using an old buffer with an altered pH, he had inadvertently caused the product of the tyrosine kinase to migrate to a different place. If he had used a fresh buffer, this would have layered the phosphorylated tyrosine under another more common phosphorylated amino acid, and he never would have seen it.

Over time, this serendipitous discovery led to an explosion of work. Researchers discovered tyrosine kinases are integral components in cancer biology—making them excellent therapeutic targets. Pharmaceutical companies have developed a number of inhibitors, including Gleevec, which inhibits the BCR-ABL kinase that causes CML.

Unfortunately, CML is an outlier—most cancers have several molecular drivers—but tyrosine kinase inhibitors have become important anticancer therapies. Combined with immunotherapies and other approaches, they are helping medical science make headway against tumors.

STRATEGY: 3

DECODING CANCER GENOMES



"This gives us a window of opportunity. We can look into how to drug the cancer epigenome. One method is to target the enzymes that place the flags, resetting the epigenome to normal levels, and lowering the activity of cancer-promoting genes."

—**DIANA HARGREAVES**
Assistant Professor, Salk's Molecular and Cell Biology Laboratory

Decoding cancer genomes

When Jonas Salk founded the Institute, he wanted to encourage foundational research to spark new ideas and therapies.

"He had this vision," says Martin Hetzer, professor in the Molecular and Cell Biology Laboratory and Salk's Chief Science Officer. "Let's address the most prominent problems, understand the biology on the deepest level, bring people here who will work across disciplines and let them do what interests them."

This approach produces results. In 1996, American Cancer Society Professor of Molecular Biology Inder Verma was trying to put genes into cells. He realized a neutered HIV virus might be an excellent delivery vehicle. Fast-forward 22 years and the FDA approved Kymriah, a CAR-T therapy.

These customized treatments remove T-cells from a patient's blood, add genes to make them more aggressive against certain blood cancers and infuse them back into that patient. Kymriah, and other CAR-Ts, use Verma's approach to add those all-important genes.

His work has also clarified how the mutated breast cancer gene BRCA1 raises the risk of breast and ovarian cancers and why glioblastoma (GBM) is so difficult to treat. Genetic changes in GBM cells make them resemble embryonic stem cells, meaning they can become virtually any type of brain cell, albeit diseased ones. This acquired trait gives them an enormous survival advantage.

"Every cell in GBM basically becomes a stem cell," says Verma. "Even if the surgeon has removed 99.999 percent of the tumor, what remains will come back."

This adaptability has grave consequences. Oncologists have prescribed a drug called Avastin against GBM, with limited success. Avastin targets the VEGF gene, which helps the body produce new blood vessels, to cut off tumor blood supplies. But GBM adapts.

The tumor develops new blood vessels independent of VEGF, so Avastin is no longer relevant.

But the lab has pioneered a new strategy against glioblastoma. They showed that these tumors express many genes associated with NF-kB, a master switch that turns on many tumor-associated genes. The lab then developed a peptide (a piece of a protein) that can shut down NF-kB's ability to activate these genes and maintain the glioma-inducing stem cells. When GBM mice receive this peptide, they survive for 70 days, compared to 30 days in the controls.

That's the equivalent of 20 years in humans.

Given that most GBM patients live only 14 to 18 months after diagnosis, this could be a huge advance. Verma is forging links with biotech companies to move this potential drug strategy towards the clinic.

Research at Salk has shown that genomes can be modified in many ways. The Hetzer lab studies a process called chromothripsis, in which DNA and its proteins, coiled into packages called chromosomes, get separated from the nucleus and pulverized. The resulting DNA is like a mini-Frankenstein—everything is out of place.

"This monster chromosome is then reincorporated into the main nucleus," says Hetzer, who holds the Jesse and Caryl Philips Foundation Chair. "In most cases, these cells will die, but sometimes it gives cells a growth advantage. Up to 50 percent of bone cancers have chromothripsis."

Jan Karlseder, professor in the Molecular and Cell Biology Laboratory, is investigating telomeres, repeating DNA sequences on chromosomes that keep them from unravelling, kind of like plastic tips on shoelaces. In normal cells, telomeres get shorter with each cell division. When they get too short, a signal tells the cells to self-destruct. Cancer has found a way around this timekeeper, granting these cells a form of immortality.

"By inhibiting telomere maintenance, we can make immortal cancer cells mortal again," says Karlseder, who also holds the Donald and Darlene Shiley Chair. "After a certain number of population doublings, they start to die. It is possible that targeting telomere maintenance could be a fairly universal cancer treatment option." As Karlseder continues to investigate telomere function in healthy and malignant cells, he hopes to identify new molecular targets for treatment. Eventually, selectively modulating telomere maintenance might be used to prevent cancer.

Diana Hargreaves, assistant professor in Salk's Molecular and Cell Biology Laboratory, investigates an emerging scientific discipline to better understand cancer genomes: epigenetics. These patterns of molecular markers on DNA help determine whether a gene is turned on or off. The epigenome is akin to software that tells hardware how to run. It instructs cells containing the same DNA, for example, whether to become muscle or brain or bone tissue. Unfortunately, tumor cells have caught on and harness the epigenome to selectively turn on cancer-promoting genes. In many tumors, the enzymes that place these molecular flags, or regulators, are mutated, giving cancer cells an added advantage. To eliminate cancer without harming normal cells, Hargreaves wants to target these epigenetic regulators.

"This gives us a window of opportunity," says Hargreaves, who holds the Richard Heyman and Anne Daigle Endowed Development Chair. "We can look into how to drug the cancer epigenome. One method is to target the enzymes that place the flags, resetting the epigenome to normal levels, and lowering the activity of cancer-promoting genes."

By focusing on ovarian and gynecological cancers, in which epigenetic enzymes are frequently mutated, Hargreaves' team seeks to understand how these mutations alter gene expression and whether they can be targeted to treat ovarian cancer. In particular, the lab is looking at an epigenetic regulator called the SWI/SNF complex, which unpacks and unwinds DNA from structural proteins to alter DNA accessibility and, in turn, which genes are activated.

The SWI/SNF complex can assume different forms through various combinations of individual subunits. One of these, called ARID1A, is mutated in many solid tumors, including ovarian, bladder and colorectal. By exploring the different activities of these complexes in normal and cancer settings, the lab hopes to identify new ways to target these cancers.

STRATEGY: 4

MOBILIZING THE IMMUNE SYSTEM

"We are looking to uncover the pathways that tumors are using to suppress T-cells, as well as ways to manipulate those to turn suppressed responses into effective responses."

—**SUSAN KAECH** | Professor and Director, NOMIS Center for Immunobiology and Microbial Pathogenesis

Mobilizing the immune system

As cancers evolve, they learn to disable the immune system, sending signals that fool immune soldiers called T-cells, and other components, into thinking tumors are healthy tissue. Drugs called checkpoint inhibitors interfere with those signals, revving up the immune response. It was a checkpoint inhibitor, combined with radiation, that put former President Jimmy Carter's melanoma into remission.

These therapies can be exceptionally effective, but only for around 25 percent of patients, fewer in some cancers. The race is on to better equip the immune system to tackle tumors.

Susan Kaech, professor and director of the NOMIS Center for Immunobiology and Microbial Pathogenesis, is working to understand how tumors evade detection by the immune system and ultimately reverse that process.

"The drugs that stimulate the immune response are having such beneficial effects for patients, we know they are going to be part of, if not the future of, cancer treatment," says Kaech, holder of the NOMIS Foundation Chair. "We are looking to uncover the pathways that tumors are using to suppress T-cells, as well as ways to manipulate those to turn suppressed responses into effective responses."

Kaech is one of Salk's newest faculty, joining the Institute this past summer from Yale University. Her lab seeks to understand how immunity works on the most basic levels. How does immune memory form? Why do T-cells infiltrate some tumors and not others? Can we turn macrophages, cleanup cells that consume and destroy other cells, into cancer killers? How do nutrient-starved regions around tumors affect glucose-hungry T-cells?

If that last question suggests a link to Shaw's work on tumor metabolism, that's no accident. Kaech looks forward to collaborating with Shaw, Evans and others on a variety of projects, uniting different disciplines to get a more complete picture of these diseases and possible therapies.

"I love collaborating and working with researchers who think about problems from different perspectives," says Kaech. "This is the fabric of Salk, and I am very excited to be a part of that."

STRATEGY: 5

RE-ENGINEERING THERAPEUTICS

"The data is enormous, but no one person can look at all those numbers and make sense of them. We are developing computer models to simulate what we think is happening and using these simulations to generate new ideas."

—**EDWARD STITES** | Assistant Professor, Integrative Biology Laboratory

Re-engineering therapeutics

Many new therapies target tumors based on specific mutations. The challenge is figuring out which patients will respond to a particular drug. Salk scientists are working to solve that problem: first, by understanding the mutations in each patient's cancer and the consequences of those mutations, and second, by determining which targeted therapies will do them the most good.

Edward Stites, assistant professor in the Integrative Biology Laboratory, is using math to solve this problem. As a medical doctor, Stites has a unique perspective on both research and treatment. He regularly participates in tumor boards at Moores Cancer Center at UC San Diego Health in La Jolla, where clinicians develop patient-care plans based, in part, on the mutations in their tumor DNA. This helps him identify the most pressing clinical needs for cancer research. His main target is the RAS oncogene, the major mutation in approximately 30 percent of all cancers and 95 percent of pancreatic tumors.

"Scientists have measured almost everything that can be measured about this protein over the past few decades," says Stites. "The data is enormous, but no one person can look at all those numbers and make sense of them. We are developing computer models to simulate what we think is happening and using these simulations to generate new ideas."

Occasionally, this mathematical modeling produces unexpected insights into cancer. Every gene has two copies (alleles), one from each parent. In most patients, only one RAS copy is mutated. For decades, scientists thought the normal copy didn't matter in cancer, but Stites showed the hyperactive mutant copy makes the normal allele more active. Now, scientists are focusing on both alleles to better understand how they interact.

Genes can also be mutated in different ways; RAS has around 20 variations. These various forms can affect which patients respond to treatment. Stites wants to make sure every patient receives the right combination of therapies.

"Right now, there are guidelines for who should get a treatment and who

The Salk Cancer Center comprises half of the research at the Salk Institute and includes 32 faculty members and hundreds more scientists and support staff. For details, please visit: **https://www.salk.edu/cancercenter**

shouldn't," says Stites. "I think those guidelines are mostly right but not quite. There are likely patients who would benefit from a treatment but don't receive it, and there are patients who get a treatment that won't help them. We are using our computational models to better understand the relationship between mutations and response so that patients ultimately receive the right treatment."

Conquering cancer… as a team

Any cell biologist will tell you that a protein's shape impacts its function. The same is true of research institutes. Louis Kahn's iconic architecture is more than just pleasing to the eye—it also helps drive discovery. Salk's design ensures that some of the world's most significant experts in cancer biology, genomics, metabolism, plant biology and many other fields run into each other often, and these courtyard consults make a difference.

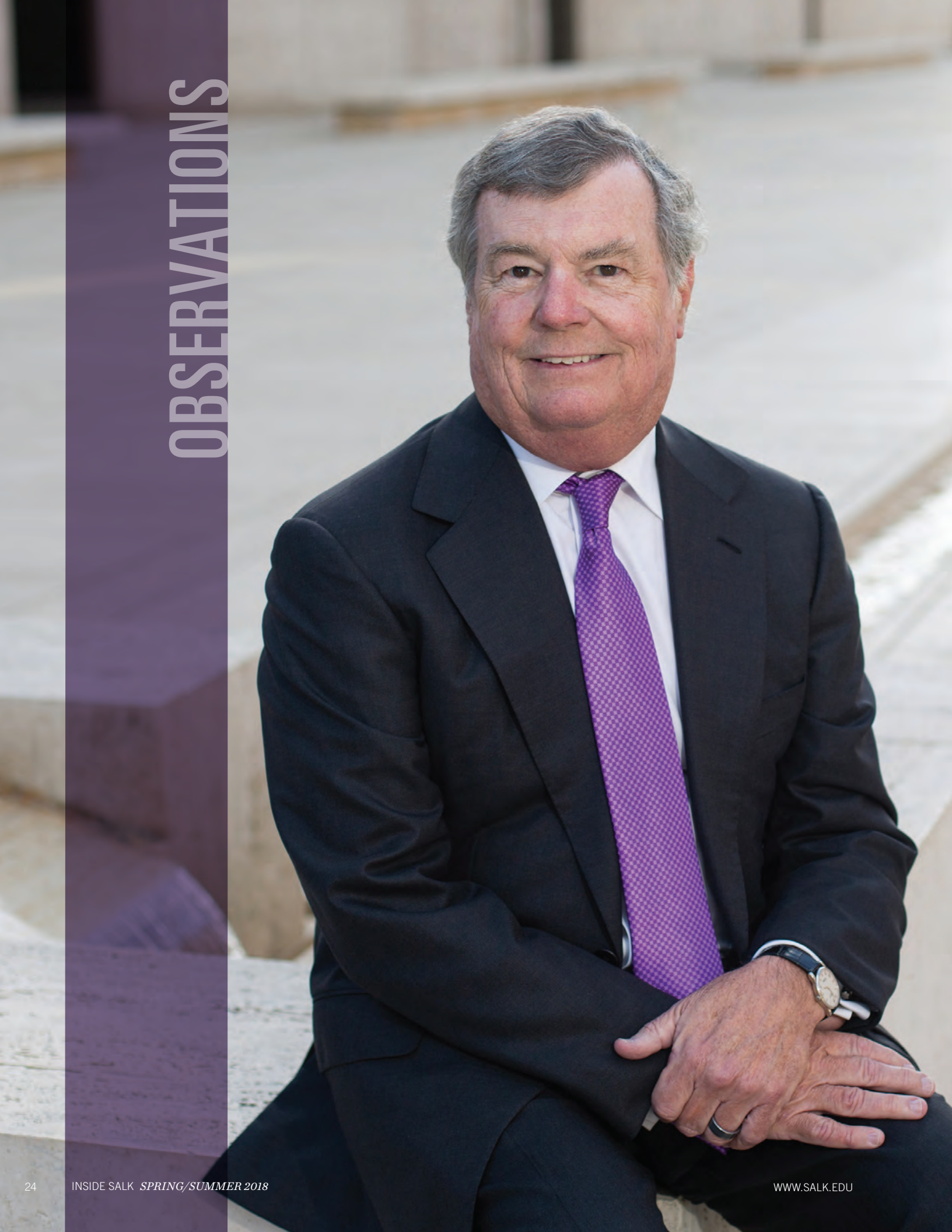
"It's the cross-fertilization of fields that has been the secret to almost all of these breakthroughs at Salk," says Shaw. "If you look at the papers, many of the breakthroughs have been from labs that are physically right next to each other."

Chat with any Salk scientist, from principal investigators to graduate students, and they will inevitably turn to the collaborations that help make them successful.

If there is one universal truth about cancer, it's that the disease is complicated. Successful approaches must attack several mechanisms. This makes collaborations between multiple disciplines to identify cancer's most profound vulnerabilities, as well as the molecules and approaches that will attack them, all the more essential. In addition to collaborating within Salk's walls, Institute researchers will continue to work closely with hospitals, universities, biotechs and pharmaceutical companies to move new agents into the clinic.

"The collaboration that goes on at the Salk is essential to take on a disease as complex as cancer," says Hetzer. "There are so many mechanisms that need to be addressed, and only by throughly understanding them all—in context—can we really get to the root of the problem."

OBSERVATIONS



DAN LEWIS
INTENSE CONNECTION

The Salk Institute has been fortunate over the course of its history to have an extraordinary Board of Trustees deeply committed to advancing the Institute's life-changing scientific mission. But few trustees have had a connection as intensely personal as new Board Chair Dan Lewis, who knows firsthand that cures, indeed, begin with Salk. Thanks to the research of Salk Professor Tony Hunter, the drug Gleevec was born. And thanks to Gleevec, Lewis survived leukemia.

A former president of Booz Allen Hamilton with a distinguished career in management consulting, Lewis has lent his support to the Salk for more than 15 years. Having joined Salk's International Council (now the Salk Institute Council) in 2002, he was elected to the Board in 2012, the same year he and his wife, Martina, established the Daniel and Martina Lewis Chair at the Institute, currently held by Salk Professor Geoffrey Wahl.

Described as precisely the right leader at precisely the right time, Lewis has brought a personal passion, a global perspective and extensive business acumen to the role of Chair as the Institute charts an exciting course forward. A former leader on the World Economic Forum's Aviation, Travel and Tourism Board of Governors, the La Jolla resident has been a frequent lecturer and author on the topic of air transportation strategy and policy, and the environment. And while most of his professional career has focused on aviation, he's most at home on the water—sportfishing the deep blue ocean to catch and release marlin as large as 500 to 700 pounds.

Martina and Dan Lewis

Inside Salk sat down with Lewis to discuss his growing support for Salk over the years and what he envisions for the future of the Institute.

Can you tell us a bit about what drew you to Salk in 2002?

One of my mentors at Booz Allen Hamilton, who joined the firm in 1950, was visiting with me on my deck at home and said: "You know, eventually you will not be President of Booz Allen Hamilton. You will have to come back to La Jolla and you need to do something really important." He pointed over the cliffs and said, "It's right over there." It was the Salk Institute.

Having long been an admirer and supporter of the Institute, in 2002 I joined the Salk Institute Council [formerly the International Council]. Today, as then, it's a very useful and productive organization designed to bring people from around the world closer to Salk and leverage philanthropic efforts. Once I got closer to retirement, then–Board Chair Irwin Jacobs and former President Bill Brody asked me to join the Board. This experience has given me a front-row seat to the world's most astonishing scientific discoveries that are truly life-changing. It's also helped to infuse a great passion for this remarkable place. I've watched in awe the steady flow of groundbreaking discoveries emerging from Salk laboratories, knowing that each has the potential to impact the lives of millions of people for the better. To know I am a part of that is incredibly gratifying.

Speaking of groundbreaking discoveries, in 2006, a cancer diagnosis connected you to the Salk Institute in a much more personal way. Can you speak a bit about your diagnosis and treatment of leukemia?

In 2006, I was diagnosed, to my great surprise, with chronic myeloid leukemia, called CML for short. That leukemia had typically been a three-year death sentence. But thanks to a drug called Gleevec, I am still here today.

I discovered that some of the foundational research that led to Gleevec was done at Salk by Tony Hunter. He uncovered a category of inhibitors called tyrosine kinase inhibitors and that was one of the keys to developing the medical treatment Gleevec, which gave patients a way to live with CML. This is a very personal and tangible example of how basic research into cancer can lead to entirely new kinds of treatments.

While we do very little translational medicine at the Salk, without the knowledge of how biological mechanisms work, there would be no translational medicine. There wouldn't be ways to go from here to there. Gleevec is a perfect example. Tony wasn't investigating cancer when he made his discovery into tyrosine kinase inhibitors. But the discoveries that he and others made in this area led to one of the most successful cancer drugs in the world. This is the great potential of doing the hard work that Salk, and other institutions like ours, do.

During your 32-year career at Booz Allen Hamilton, you developed an impressive track record of leading multidisciplinary teams in transformation efforts, especially in the aerospace industry. What are some impressions from those experiences that you carry with you today?

The first 22 years at Booz Allen Hamilton, I learned my trade and became a senior client officer working with the aviation industry. Broadly speaking, this included interfacing with everyone from the people who made parts, to the airplane builders, to the airlines that flew them, and to the service providers that provided booking systems programs, like Expedia. I immensely enjoyed that work. After 22 years, I was elected to become president of the firm. From that period of time, I worked with 183 partners and 34 offices worldwide, and I was part of the global management consulting business for Booz Allen Hamilton.

I've had the pleasure of working for some of the very largest firms in the aviation industry, both airlines and aircraft manufacturers, such as Boeing. Interestingly, I think there are strong correlations between the Salk Institute and Boeing. Salk has the most remarkable scientists on the planet and their groundbreaking discoveries are becoming an almost daily occurrence. Similarly, Boeing has some of the most fantastic engineers in the world. They developed aircraft and technologies that were unparalleled in their day, from the 747 all the way up to the aircraft that they have today, the 787 and the new 777. It's thrilling to be part of organizations that are creating the future.

Following up on that, are there parallels between how you supported Boeing engineers back then to how you support Salk scientists now?

Absolutely. It takes about seven to 10 years to design an aircraft before it gets to the manufacturing floor. At Salk, we also have a long lead time. The scientists here make new discoveries every day that take us a little bit closer to solving some of the most pressing issues facing humanity. This is foundational research. This is basic research. It's the mechanisms that have to change in order to really resolve chronic illnesses that affect all of humankind. But it takes time, and it takes doing everything possible to support the scientists with the resources and tools they need to make those discoveries.

Salk has a long history of collaborating across disciplines and it's part of the free-flowing way in which science works best. That was also true at Boeing. It wasn't everyone gathered around a drawing board. It was a lot more about making many different components work together so that you could take an airplane from design to production.

That focus on collaboration seems very complementary to Salk's ethos. Would you agree?

Yes. Salk is a very collaborative place and that's what makes science work. It's not always focused on an individual lab and an individual problem. When you can't get that problem solved, you take it to other places and have other people look at it. A classic example of that is Tony Hunter, who has helped Ronald Evans on cutting-edge pancreatic cancer work. Ron had the original scientific discoveries related to mechanisms in pancreatic cancer and he asked Tony to look at his work. Tony looked at it very differently and I think they're making great progress. This is an example of life-changing collaborations.

A lot of organizations talk about collaborating, but it seems like Salk does it well. Why do you think that is?

I think there are a lot of little intangibles that contribute to it. For one, the Salk is inspirational. It's wide open. The scientists can walk out of their lab and meet and talk in the middle of the Institute's courtyard. It's a reinforcing environment that contributes immensely. It's something that you see every day when you walk through the Salk. The other component of success is the people that are drawn here. They truly love this place and they want it to work. They want it to work well. They want to be collaborative and they want to be good stewards of our donors' money. For that money, we want to deliver a truly tremendous value proposition.

As you have been involved with Salk a long time, what would you say makes the Institute unique?

Salk is a scientific treasure. The campus also is an architectural masterpiece; that in and of itself is an inspiration. Louis Kahn's building and Jonas Salk's vision of what this place should be have been celebrated over and over again. What Salk has is an environment that is conducive to doing this kind of very detailed, very difficult foundational research. Support for this type of institute is absolutely critical because it takes a lot of resources to do this work. It takes specialized equipment. It takes very specialized people. It takes very specialized processes to make these discoveries happen.

When you aren't advising on boards, you have a pretty serious marlin fishing hobby. How did that come about?

The work as a management consultant allowed time for a single hobby. I chose sportfishing. This hobby allowed me to completely get away from airplanes, travel and work, at least for little while. I have a boat in Cabo San Lucas, Mexico, and fish as often as I can. I also fish the tournaments, particularly the world-famous Bisbee tournaments. We took the biggest purse in 2014, which happened to be the year that Hurricane Odile hit. The hurricane was terrible, so we raised money to support people who live there to rebuild their homes, which had been completely destroyed.

What is the biggest marlin you ever caught?
A 762-pound blue marlin. Too bad it wasn't for a tournament.

Neuroscientist and self-described history geek Jared Smith wants to boldly go where no one has gone before.

"If this were the 1400s," asks Smith, "and we were Europeans exploring the world, where is the new world?"

For Smith and colleagues in Xin Jin's lab, the answer is simple: the brain. Using an array of sophisticated tools, the team is learning how neurons translate sensory signals into decisions and decisions into actions.

Smith wasn't planning to study neuroscience. He entered his freshman year at Bucknell University, about an hour from his home in Harrisburg, Pennsylvania, intent on chemistry. But a mind-blowing psychology class sent him in a different direction.

"Day one of undergrad, I took a class called 'Distortions of Reality,'" says Smith. "The professor asked: 'Do you think everything you see is exactly the way it is?' I was 18 and, for the first time, I realized my brain completely makes up my reality."

There were more epiphanies along the way. While interviewing for a doctoral program at Penn State, he listened to brain signals for the first time.

"It's a great sound, kind of like Rice Krispies –snap, crackle, pop," says Smith. He was hooked.

After earning his PhD and conducting postdoctoral research at Penn State, he couldn't resist the in-depth brain studies being conducted by Xin Jin at Salk.

"One aspect of our work is looking at how we process sensory information," says Smith, "and how that sensory processing guides our interactions with the outside world; that is to say, how the brain takes that perceptual information and uses it to make decisions."

Smith is studying brain regions in the basal ganglia, which help govern how we both choose and implement specific actions. These regions are linked to schizophrenia, Parkinson's disease and other conditions. Specifically he's investigating a nucleus to the basal ganglia called the striatum, which contains many opioid receptors in dense neural clusters called patches—critical studies, given the ongoing epidemic.

While these biological questions are compelling, the tools Smith and his colleagues in the Jin lab use are just plain amazing. One approach, pioneered by Salk's Ed Callaway, uses an altered rabies virus to map how brain cells share information. Rabies is unique because it jumps across synapses. By modifying it to jump only one synapse, researchers can get a highly detailed view of how neurons interact.

Another approach uses the toxin diphtheria to destroy small numbers of neural cells to determine how they influence animal behavior. The lab can also turn neurons on and off using light, allowing researchers to delineate the different pathways and see how they function in real time.

"Now we have the technology to tease out how brain regions, as well as the types of cells within those brain regions, are talking to each other," says Smith.

At home, Smith likes to play guitar, walk Henry the beagle and spend time with his wife and one-year-old son. He tries to segregate his personal and professional lives, with mixed success.

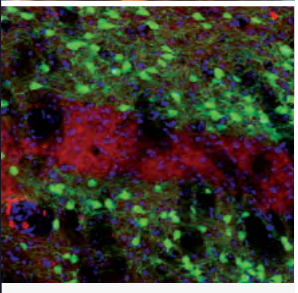
"Much to my wife's dismay, I spend our vacations thinking about the data, worried about how that's going to turn out," he says.

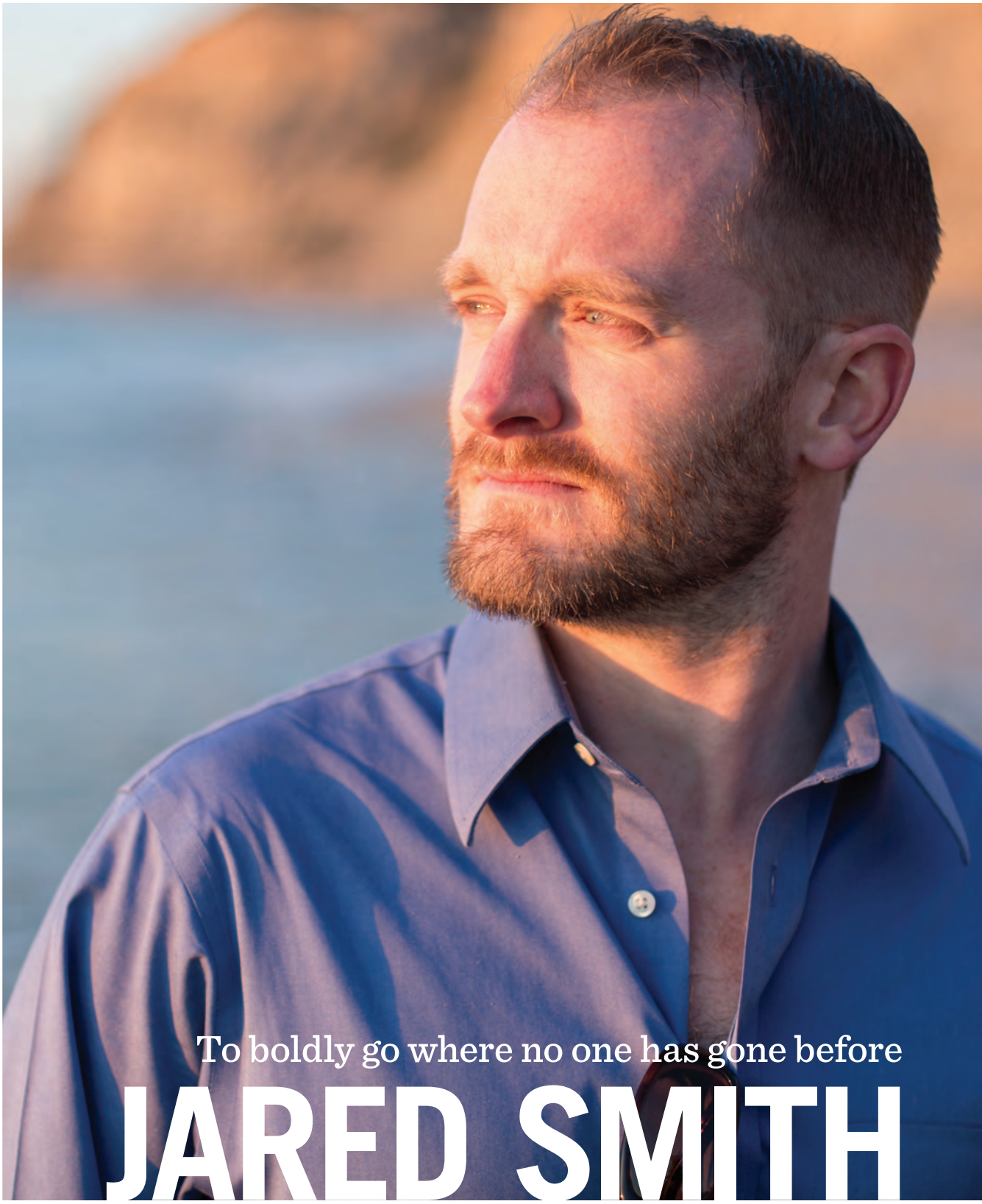
Like all parents, Smith enjoys watching his baby learn to walk—but of course, there's a twist.

"The thing I keep telling myself is to not turn it into an experiment, to spend time really enjoying him," says Smith. "But it's hard not to. Watching him walk was particularly fascinating. I'd done gait analysis in my last postdoc."

Eventually, when Smith runs his own lab, the time spent chasing his toddler may allow him to explore even more complex questions.

"What is the neural basis for curiosity?" asks Smith. "Why are humans wired to go out and explore from the very beginning? Where is that inclination in the brain?"

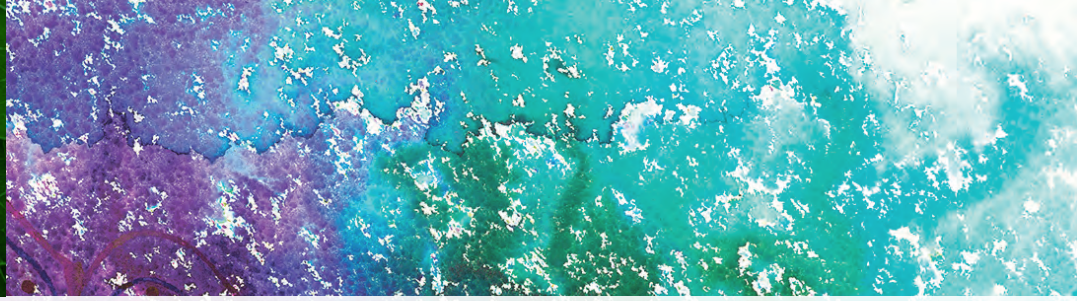




To boldly go where no one has gone before

JARED SMITH

"One aspect of our work is looking at how we process sensory information and how that sensory processing guides our interactions with the outside world; that is to say, how the brain takes that perceptual information and uses it to make decisions."



SPOTLIGHT

The Way of the Rain

On November 17, science and art joined forces as environmental artist Sibylle Szaggars Redford gave a Salk audience a sneak peek of her new project: *The Way of the Rain – Voices of Hope*. The event supported Salk's Harnessing Plants Initiative, an ambitious effort to develop plants that can help reduce greenhouse gases and restore damaged ecosystems.

A powerhouse plant biology team at Salk—Wolfgang Busch, Joanne Chory, Joseph Ecker, Julie Law and Joseph Noel—is focusing on creating plants that more efficiently capture and store carbon. This biology-based solution could reverse lost soil carbon, enhance plant survival and boost crop yields, particularly in agriculturally challenged ecosystems.

Szaggars Redford celebrated the initiative's launch with a multimedia show, featuring Native American flute player Robert Mirabal, Celtic musicians, and Szaggars Redford's own brightly painted organic silk backdrops. Szaggars Redford's husband, actor/director Robert Redford, and Pulitzer Prize–winning poet N. Scott Momaday made guest appearances.

Drawing inspiration from ancient cultures and threatened ecosystems, Szaggars Redford, in collaboration with composer and artist Tim Janis, uses her art to raise environmental awareness and inspire others to take action. The performance combined dancing, singing, narration, poetry and film to create a profound sensory experience. The Salk performance was the first of several, including the official Carnegie Hall premiere on December 1, 2017.

The show highlighted the climate's beauty and fragility, but also pointed to possible solutions, such as the Salk team's efforts to develop plants that can mitigate human disruptions to the carbon cycle. Salk's "ideal plants" will be able to sequester carbon more efficiently than other plants and buy the planet more time as people and governments cope with a growing human population and dramatic climate change.

To read more about the Harnessing Plants Initiative, please visit: www.salk.edu/harnessingplants

Highlights of *The Way of the Rain*, celebrating the launch of the Harnessing Plants Initiative, included sharing the spotlight with both an Oscar winner, Robert Redford, and a winner of the "Oscars of Science" Breakthrough Prize Joanne Chory (top left); appearances by Redford and poet N. Scott Momaday (bottom left); Celtic and Native American musicians (bottom right); and talks by Salk plant biologists (top right).

JOANNE CHORY AWARDED PRESTIGIOUS BREAKTHROUGH PRIZE

One of the world's preeminent plant biologists, Joanne Chory is now leading the charge to combat global warming by developing plant-based solutions. Recently, Chory was awarded a 2018 Breakthrough Prize for her pioneering efforts to illuminate how plants optimize their growth, development and cellular structure to transform sunlight into chemical energy.

Created in 2013 by Silicon Valley luminaries Sergey Brin and Anne Wojcicki, Mark Zuckerberg and Priscilla Chan, and Yuri and Julia Milner, this prestigious award honors top scientists for their achievements in the life sciences, physics and mathematics.

Chory, professor and director of the Plant Molecular and Cellular Biology Laboratory, received the $3 million prize on December 3, 2017, during a televised event at the NASA Ames Research Center in Mountain View, California.

Because plants are rooted in the ground, they must constantly adapt their shapes and sizes to an ever-changing environment. Chory has spent more than 25 years deciphering the mechanisms that help plants achieve this flexibility. She pioneered the use of molecular genetics to understand the mechanisms that help plants respond to their environments, leading to important discoveries that showcased how plants sense light and make growth hormones.

More recently, Chory teamed up with other plant biologists at the Salk Institute to turn their hard-won knowledge into practical solutions to tackle perhaps the greatest challenge facing the planet: climate change. They recently launched the Harnessing Plants Initiative to develop Salk Ideal Plants to help address human carbon dioxide emissions, declining agricultural yields and collapsing ecosystems. These plants may also help meet the rapidly growing human population's burgeoning need for food and other plant products.

"Humanity is at a crossroads," said Chory. "In the coming decades, as the human population increases from 7 billion to 10 billion or more, we are going to put incredible pressure on the planet's ability to support us. Global warming is going to make providing for this population very difficult, if not impossible, and we desperately need ways to remove carbon from the atmosphere. Plants can be a critical part of the solution."

Top: Joanne Chory flanked by the presenters of her Breakthrough Prize, Kevin Systrom, cofounder of Instagram and Kára McCullough, a scientist at the Nuclear Regulatory Commission and Miss USA 2017. Bottom: The prize trophy, designed by artist Olafur Eliasson.

Joanne Chory accepting the Breakthrough Prize.

SPOTLIGHT

SALK SCIENTISTS RECEIVE $1.5 MILLION TO STUDY FIREFIGHTER HEALTH

The lab of Salk Professor Satchidananda Panda and UC San Diego School of Medicine researchers have been awarded a $1.5 million grant by the Department of Homeland Security for a three-year study to see whether restricting food intake to a 10-hour window can improve the health of firefighters, who are at high risk for many chronic diseases because of how shift work disrupts the body's natural rhythms.

Panda, whose laboratory studies the molecular bases of circadian (daily) timekeeping in mammals, previously found that restricting the access of lab mice to food for 8–10 hours a day resulted in slimmer, healthier animals compared to mice that ate the same number of calories around the clock. Preliminary studies in humans suggest similar health benefits of such "time-restricted eating," which does not change the quality or quantity of food, just the time period in which it is consumed.

Sanjay Jha

SALK TRUSTEE SANJAY JHA NOMINATED TO NATIONAL ACADEMY OF ENGINEERING

Salk Trustee and Globalfoundries Inc. CEO Sanjay Jha was nominated to the National Academy of Engineering "for leadership in the design and development of semiconductor technology enabling universal digital access."

Prior to joining Globalfoundries, Jha served as chairman and CEO of Motorola Mobility, which was spun out as an independent public company from Motorola Inc. in early 2011. Before that, he held multiple senior engineering and executive positions over 14 years at Qualcomm Inc., where he ultimately served as executive vice president and chief operating officer (COO). Jha has a PhD in Electronic and Electrical Engineering from Scotland's University of Strathclyde.

Election to the National Academy of Engineering is among the highest professional distinctions accorded to an engineer. The newly elected class will be formally inducted during a ceremony at the NAE's annual meeting in Washington, DC, on September 30, 2018.

SALK RESEARCHERS AWARDED $2.5 MILLION FOR INNOVATIVE PANCREATIC CANCER CLINICAL TRIAL

As part of a multi-institution team, Salk professor and HHMI Investigator Ronald Evans has been awarded $2.5 million by Stand Up To Cancer (SU2C) to help improve immunotherapy for pancreatic cancer. The group will conduct clinical studies to test whether a form of modified vitamin D, developed in Evans' lab, will make the Merck checkpoint inhibitor pembrolizumab (Keytruda®) more effective.

While pancreatic tumors normally rebuff immune T-cells, the modified vitamin D reprograms the tumor microenvironment to allow these cells access. The researchers believe this altered microenvironment, combined with pembrolizumab's ability to take the brakes off T-cells, will spur the immune system to attack and destroy pancreatic tumors.

The award is part of SU2C Catalyst® and is supported by Merck.

From left: Michael Downes and Ronald Evans

Gerald Joyce

GERALD JOYCE NAMED 2017 AAAS FELLOW FOR CONTRIBUTIONS TO SCIENCE

Professor Gerald Joyce has been a named a 2017 Fellow of the American Association for the Advancement of Science (AAAS), the world's largest general scientific society. His work has had a profound impact on our understanding of Darwinian evolution at the molecular level.

Joyce, a professor in Salk's Jack H. Skirball Center for Chemical Biology and Proteomics, is a pioneer of *in vitro* evolution (evolving molecules in a test tube). While DNA is the code for life, its single-stranded counterpart, RNA, shares top billing and has profound effects on development and disease. It's likely that RNA was DNA's ancestor during the early history of life on Earth.

Joyce and colleagues seek to recreate early biomolecules in test tubes, coaxing RNA's building blocks to assemble, replicate and evolve. Although scientists can't know exactly how the first genetic molecules developed 4 billion years ago, recreating plausible facsimiles in the lab may provide insights into early evolutionary processes and lead to synthetic RNA molecules that could potentially treat cancer, immune defects, viral infections and other conditions.

SPOTLIGHT

Roger Guillemin

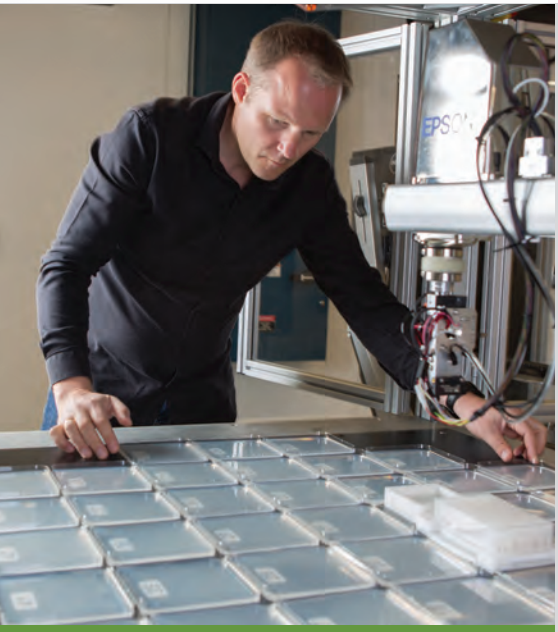
University officials unveil the plaque honoring Guillemin.

ROGER GUILLEMIN'S ALMA MATER RENAMES SPACE IN HIS HONOR

Roger Guillemin received the Nobel Prize in Physiology or Medicine in 1977 for shedding new light on peptide hormones in the brain. To honor him for this and many other accomplishments, the Université de Montréal has renamed the University Assembly Hall to Salle Roger-Guillemin.

An honorary plaque, highlighting Guillemin's exceptional career, has been placed at the entrance.

In 1953, after studying medicine in Lyon, Guillemin defended his doctoral dissertation on endocrinology at the Université de Montréal. Soon after, his career took him to Baylor College of Medicine in Houston. In 1970, Guillemin joined the Salk Institute to head the newly established Laboratories for Neuroendocrinology. Considered the founder of neuroendocrinology, Guillemin is a scientific pioneer whose research led to treatments for many disorders—from infertility to pituitary tumors.



Wolfgang Busch

SEED-PLANTING ROBOT SUCCESSFULLY CROWDFUNDED

Spearheaded by Salk plant biologist Wolfgang Busch, the Institute has successfully completed a $313,840 crowdfunding effort to purchase a fast, seed-planting robot. The campaign exceeded its goal, bringing in more than $334,000 with the help of long-time Salk supporters Larry and Carol Greenfield, who matched the first $150,000 in donations.

The robot brings high-throughput to planting, performing as many experiments in a single day as a human researcher could complete in five weeks. The system transfers seeds with incredibly high precision, conducting the same motions millions of times—without the barriers of fatigue, boredom or other human limitations.

Busch and his team will use the robot to test hundreds of seed and environmental variations in the lab to better understand how plants respond to different environments and other aspects of plant biology. Their ultimate goal is to develop a new generation of plants that can grow in the most challenging conditions.

WATCH | http://bit.ly/robot201805

JOANNE CHORY AND TERRENCE SEJNOWSKI NAMED TO NATIONAL ACADEMY OF INVENTORS

Professors Joanne Chory and Terrence Sejnowski have been elected Fellows of the National Academy of Inventors (NAI). In addition to directing the Salk Institute's Plant Molecular and Cellular Biology Laboratory, Chory is a Howard Hughes Medical Institute investigator and holds the Howard H. and Maryam R. Newman Chair in Plant Biology. Sejnowski heads the Institute's Computational Neurobiology Laboratory and holds the Francis Crick Chair.

NAI Fellows are honored for their prolific spirit of innovation in creating or facilitating outstanding inventions and advances that have made a tangible impact on quality of life, economic development and the welfare of society.

Chory has spent more than two decades studying the mechanisms that allow plants to adapt their shapes and sizes to their ever-changing environments. Sejnowski has helped pioneer the study of neural networks and computational neurobiology. His research aims to discover the principles linking brain mechanisms and human behavior.

Joanne Chory

Terrence Sejnowski

SALK AND INDIVUMED PARTNER TO ADVANCE GLOBAL CANCER RESEARCH

The Salk Institute is partnering with cancer research company Indivumed to secure, preserve and analyze human cancer tissue and annotated clinical data from consenting patients around the world. This collaboration will leverage the most cutting-edge basic and translational research tools to study gene expression, metabolites and many other aspects of tumor biology. Indivumed will provide dedicated resources to help researchers in the Salk Institute Cancer Center retrieve cancer specimens for intense study. Salk and Indivumed will also develop a portfolio of collaborative research projects, developing a global cancer database that includes comprehensive genomic and phenotypic information. Ultimately, this partnership will drive translational research to more rapidly bring new therapies to patients.

Clockwise from top left:
Salk's Chief Science Officer Martin Hetzer, Cancer Center Director Reuben Shaw, Indivumed's Founder and CEO Hartmut Juhl and Managing Director Andrew Deubler.

Chief Science Officer Martin Hetzer adds two key staff positions

KURT MAREK, PHD, NAMED NEW DIRECTOR OF RESEARCH DEVELOPMENT

Expanding the resources available to its faculty through the Office of the Chief Science Officer, Salk announced that Kurt Marek, PhD, has joined as director of research development. In this role, Marek will work closely with the Institute's faculty and leadership to support the advancement of institutional research by enhancing its ability to secure major grants.

Marek has a wealth of training and experience in this area, having most recently served as a deputy director of the Office of Translational Alliances and Coordination for the National Heart, Lung and Blood Institute (NHLBI), where he was instrumental in developing and managing grant programs to support translational research. He also oversaw the NHLBI's support of small businesses performing research and development on innovative biomedical products.

Marek earned undergraduate degrees in biology and humanities from UC San Diego and received his PhD in neuroscience from the University of California San Francisco where he was a Howard Hughes predoctoral fellow. He later studied spinal cord development as a Damon Runyon Cancer Research Fellow at UC San Diego, using genomics to identify new roles for electrical activity in the nervous system and to characterize the underlying molecular mechanisms. He joined NHLBI as an AAAS Science and Technology Policy fellow.

TRICIA WRIGHT, PHD, NAMED FIRST POSTDOCTORAL SCHOLAR ADVISOR

Elevating and expanding its postdoctoral program, Salk announced that Tricia Wright, PhD, has joined the Institute as its first postdoctoral scholar advisor, a newly created position responsible for overseeing the new, dedicated Postdoctoral Office.

With extensive experience in this area, Wright most recently served as the director of the Office of Postdoctoral Affairs for the Indiana University School of Medicine in Indianapolis, where she was responsible for fostering the professional development of approximately 200 postdoctoral trainees through programs, advocacy and resource development. At Salk, she will lead the way in ensuring the Institute's program fulfills its purpose of providing resources and support in myriad areas, including assisting postdocs in obtaining funding, aiding and improving existing career development programs, and identifying strategies and tools to enhance the postdoctoral experience.

Wright earned a BS in biotechnology from Rutgers University and a PhD in genetics and molecular biology from the University of North Carolina at Chapel Hill, and was a postdoctoral associate at Duke University.

SERVICE AWARDS CELEBRATE SALK EMPLOYEES

The Institute honored nearly 60 employees for their dedication and years of service at the annual service awards presentation on February 14. Certificates were presented in five-year increments for service ranging from 10 years to 35 years.

ADDY

FOLIO:

SALK MAGAZINE WINS "ADDY" AND FOLIO AWARDS

Inside Salk, the Institute's thrice-yearly magazine, took first place for overall design, feature design and electronic newsletter in Folio's annual Eddie and Ozzie Awards for media and marketing. The publication also garnered nine honorable mentions, including for full issue, cover design and magazine website: inside.salk.edu

In addition, the magazine has been awarded two silvers and a bronze for publication design by the American Advertising Federation. The American Advertising Awards, informally known as the "ADDYs," are the advertising industry's largest and most representative competition, which recognizes and rewards the creative spirit of excellence in the art of advertising.

THE (NEURO)ANATOMY OF A

DESIGN

1 | *Lights respond to the model's movements, reflecting the cerebellum's role in control of movement and indicating ongoing signaling between nerves.*

2 | *The lighted "cerebellar" controller reflects "convergence" of corrected motor information at the waist. Convergence refers to the entire cerebellar cortex funneling information to a few neurons deeper inside the structure, which amplifies the information to ensure that the motor task is accurate.*

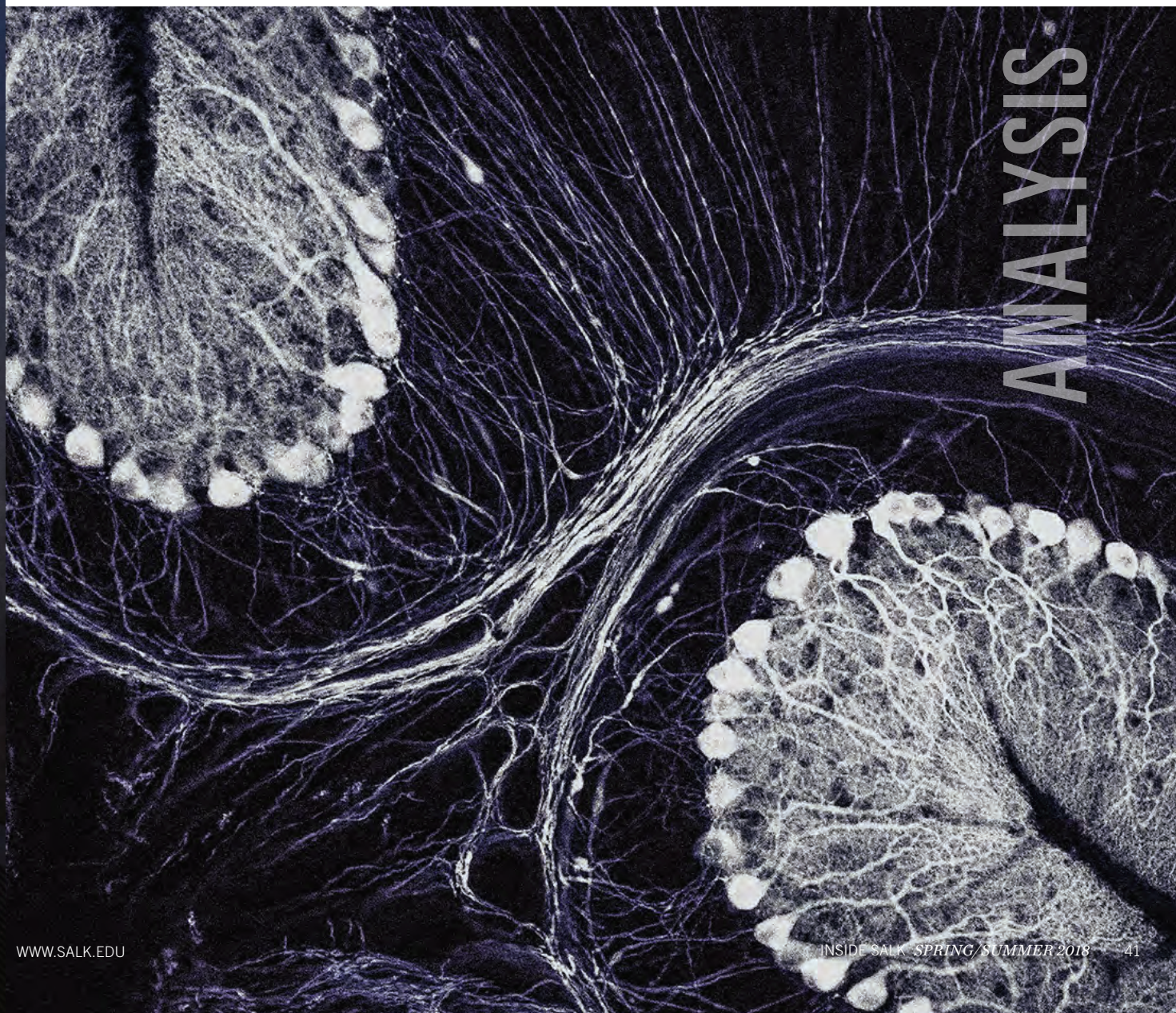
3 | *The flaring of the "cerebellar folds" reflects the brain architecture that coordinates perfect movement.*

4 | *The 3D-printed structure houses a tiny computer and power source that controls the garment's lights, mirroring the neuroanatomy of the cerebellum.*

Photo courtesy of Howard Max

Salk's Women & Science program held its first Design and Discovery Fashion Showcase on October 4, 2017, and featured 13 gowns inspired by Salk microscopy images and created by San Diego Mesa College design students and Salk scientists.

Light Dance was designed by Rachel Merrill, based on the work of former Research Associate Hermina Nedelescu (now a collaborator in the Molecular Neurobiology Laboratory of Assistant Professor Eiman Azim). Nedelescu studies how the cerebellum, a cauliflower-shaped brain structure atop the neck, coordinates perfect movement.



EVENTS

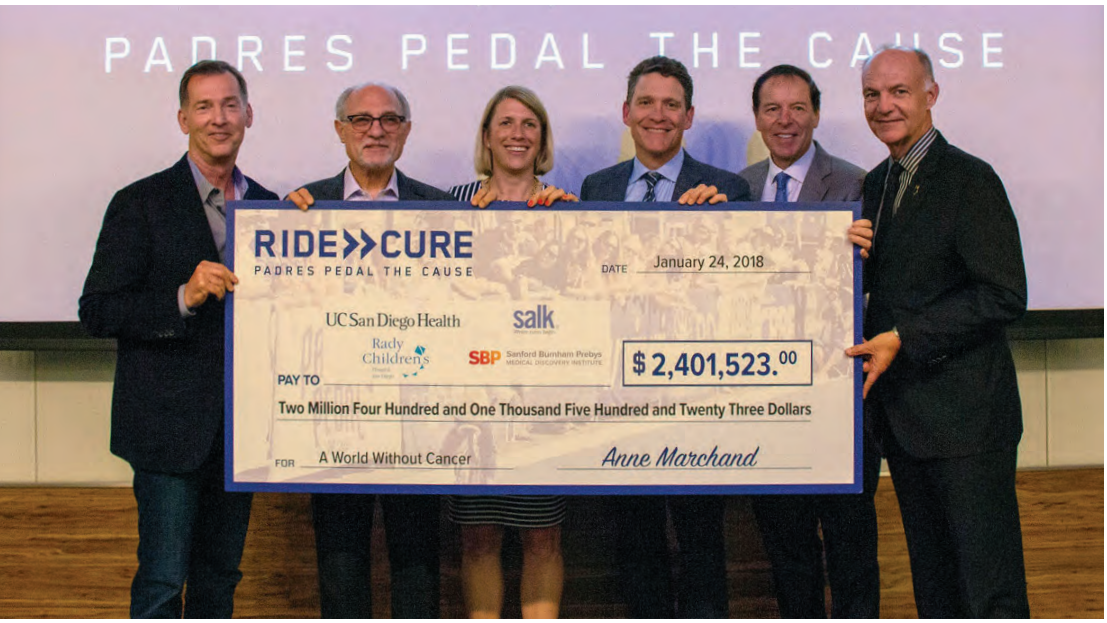
salk | EXCELLERATORS

ENGAGING THE COMMUNITY

Assistant Professor Eiman Azim and neurosurgeon Sharona Ben-Heim, a visiting scientist from UC San Diego, spoke about the neurological basis of movement at the Salkexcellerators' spring forum in February. At the fall forum in October, Associate Professor Wolfgang Busch spoke about his research on root growth.

Salkexcellerators are the next generation of community members committed to supporting scientific discovery at the Institute. The program provides social and educational events throughout the year and supports a fellowship fund for the Institute's post-doctoral researchers.

Eiman Azim



Salk's Geoffrey Wahl (second from left) and representatives of other institutions accept a donation check from Pedal the Cause. Image credit: Pedal the Cause

From left: Sonja Brun and Stephanie Mount of the Shaw lab.

Reuben Shaw


From left: Kevin Sagara, Lisa Cashman and Tony Toranto.

President's Club

SHAW SPEAKS AT PRESIDENT'S CLUB

Professor and Director of the Salk Cancer Center Reuben Shaw addressed the President's Club at its annual holiday luncheon on November 29, speaking about the science behind Salk's plan to defeat five deadly cancers. Contributions at the President's Club level are allocated to the areas of greatest need and make it possible to recruit and retain top-tier scientists, acquire the latest technology and fuel innovative research initiatives.

PADRES PEDAL THE CAUSE

KEEP ON PEDALING

Twenty-six intrepid cyclists from Team Salk Cancer Center participated in the annual Padres Pedal the Cause fundraiser on November 11–12, which raised $2.4 million for cancer research—the most attained in the event's five-year history. The funds will be shared with three other local cancer research centers.

EVENTS

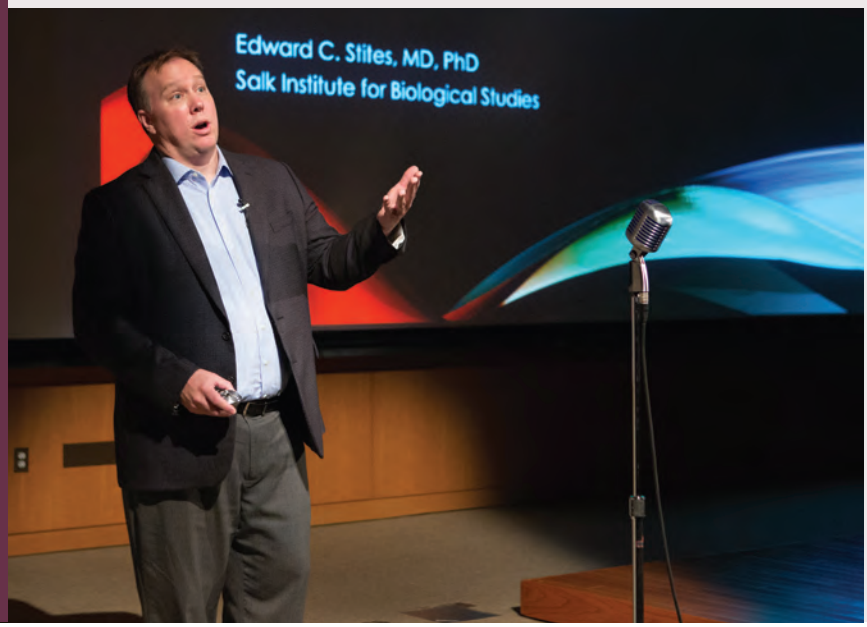
ELLEN POTTER SYMPOSIUM CELEBRATES SECOND YEAR

Salk welcomed more than 30 middle school and high school science teachers to the second annual Ellen Potter Research Connections for Teachers Symposium. The event, named in honor of the Institute's long time Education Outreach director, who retired last year, featured Salk scientists speaking on the theme of "Bench to Bedside," highlighting the challenges of translating biological research into biomedical therapies.

THE PERFECT FIFTH

The fifth season of the popular Salk Science and Music Series continued on December 3 and February 4 with classical performances accompanied by talks from Salk scientists Satchidananda Panda and Tatyana Sharpee, respectively. The season concluded on April 8 with a piano concert by Zlata Chochieva and a talk by Assistant Professor Edward Stites.

From left: Asi Matathias, Gabriel Schwabe and Dominic Cheli.



Edward Stites

Zlata Chochieva

Ellen Potter

From left to right: Dominic Cheli, Larry Greenfield, Karen Joy Davis, Asi Matathias, Carol Greenfield, Gabriel Schwabe, Tatyana Sharpee.

Satchidananda Panda

Dasol Kim

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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.

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CALENDAR

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11 Salk Women & Science

AUGUST

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