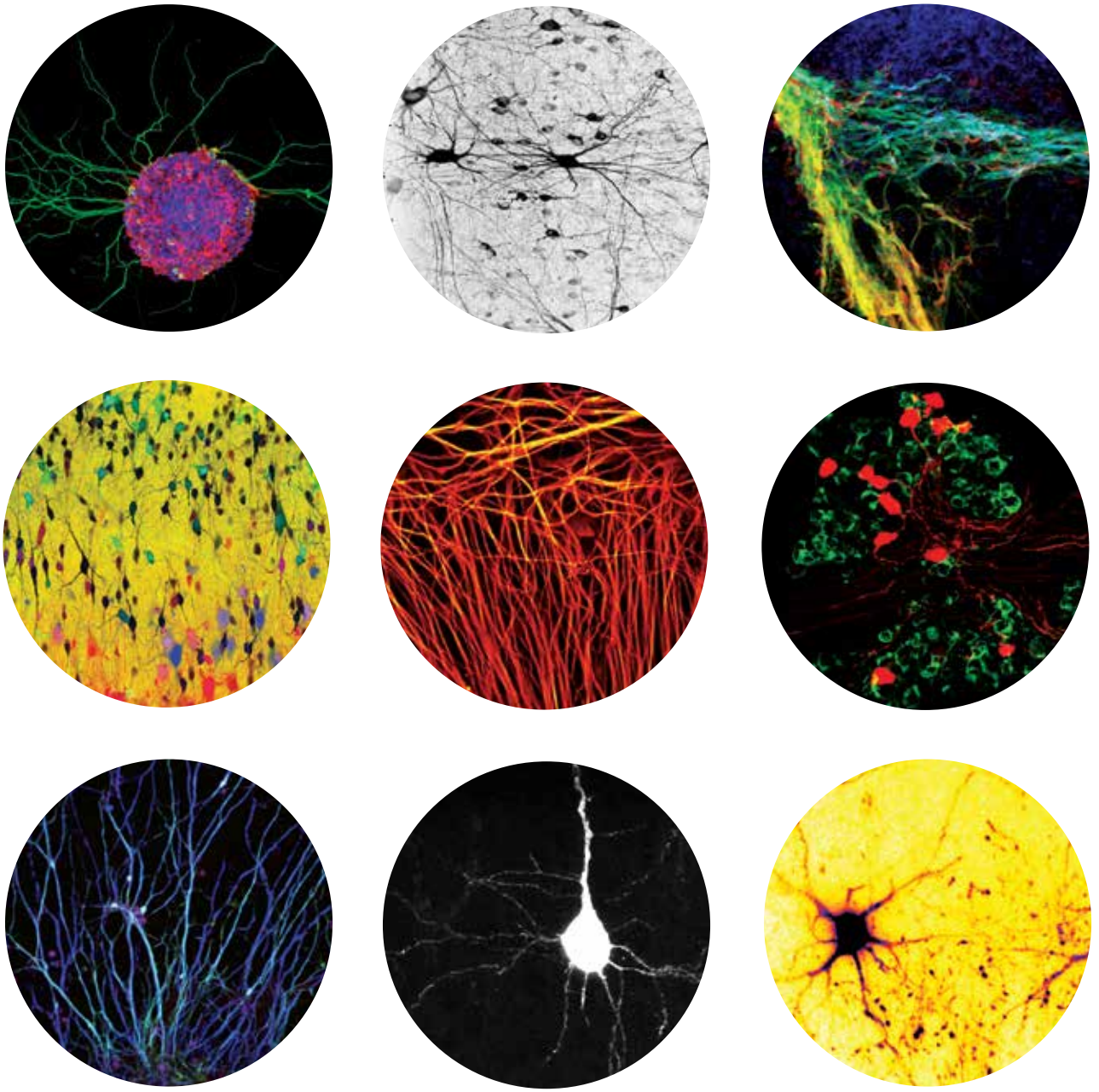
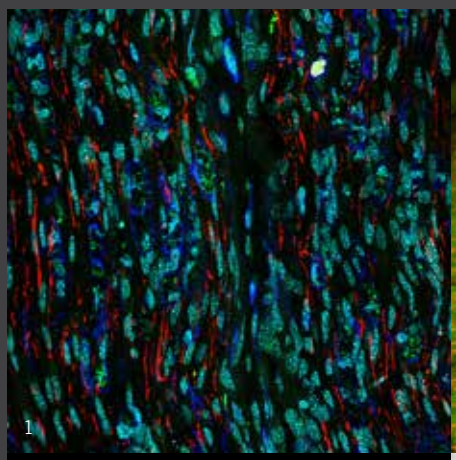
SUMMER | 2017

WHERE CURES BEGIN.

insideSalk

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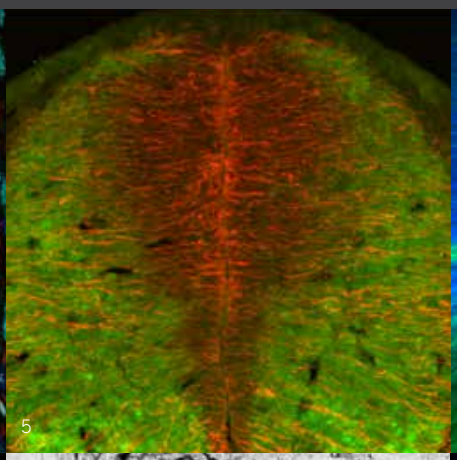
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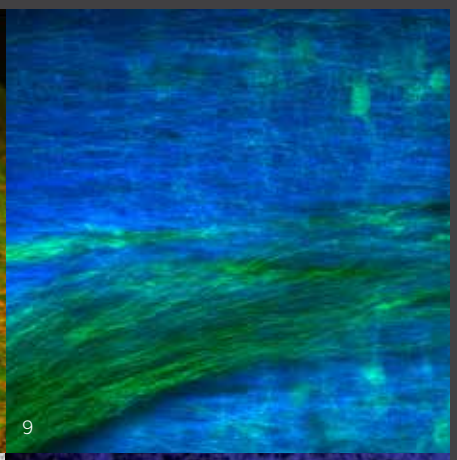
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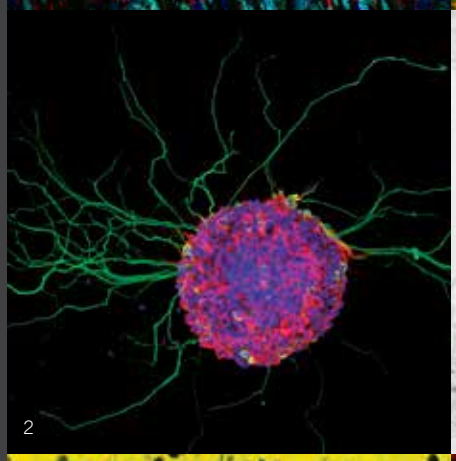
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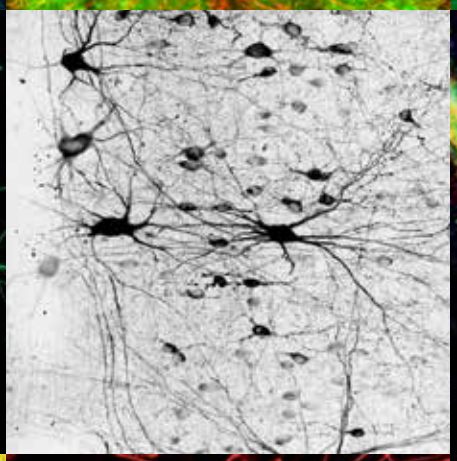

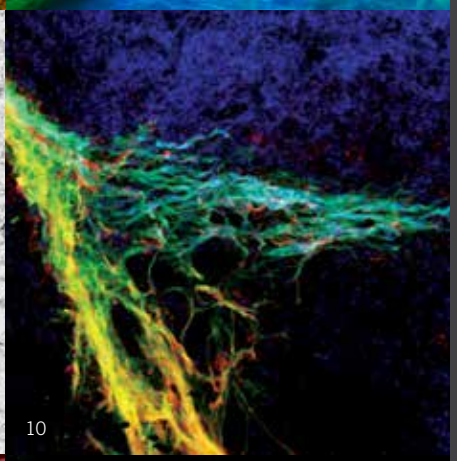
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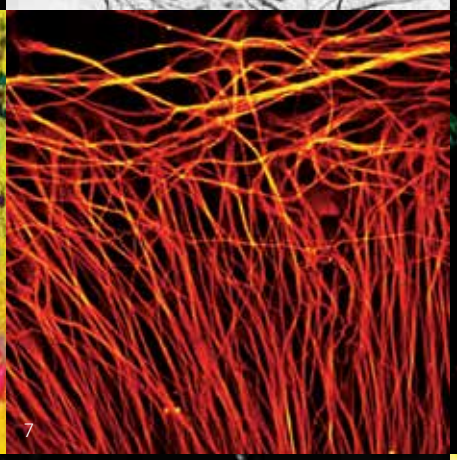
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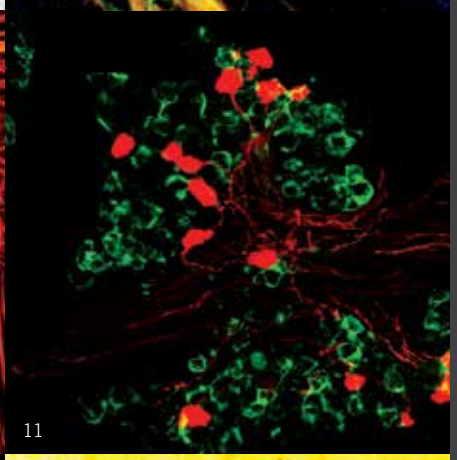
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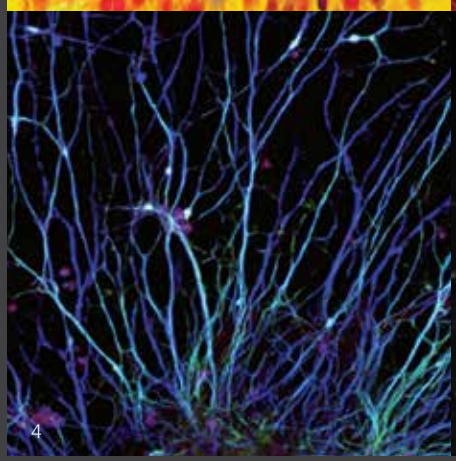
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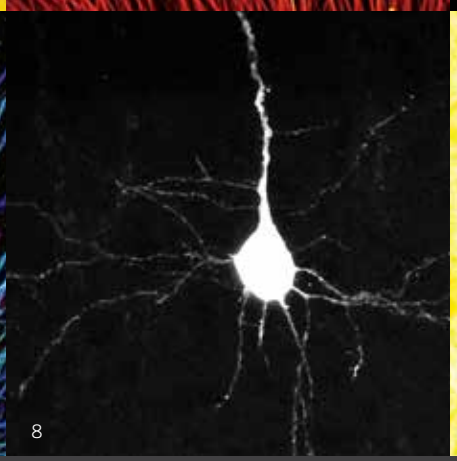
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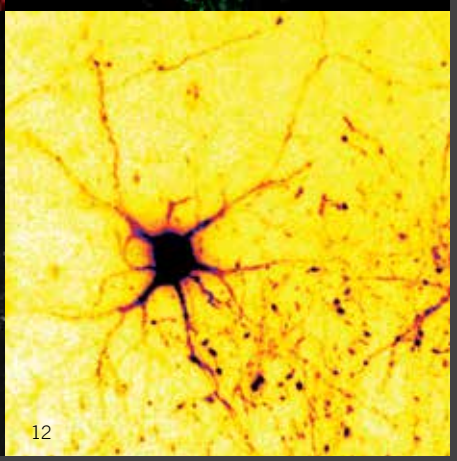
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Untangling the Mysteries of the Spinal Cord

1 Response to injury in a nerve

2 A cluster of embryonic stem cells that have become neurons extending long axons

3 Characterization of synaptic connections within the spinal cord

4 Fasciculated axons growing from a neurosphere

5 Radial fiber pattern within the neural tube

6 Labeling to study neuronal morphology

7 Sensory neuron culture revealing vast axonal growth

8 A pyramidal neuron

9 Genetically labeled neurons within the spinal cord

10 Axon growth toward muscle

11 Sensory ganglia

12 Unexpected tiling of V0c interneurons

CONTENTS

ON THE COVER:

Read the full captions on the interior flap of the cover.

ON THE BACK COVER:

Fluorescent labeled motor neurons.

Credit: Courtesy of the Pfaff Lab

PRESIDENT'S LETTER

Dear Friends,

As an active hiker, I often ponder the wondrous complexities of human locomotion—the seamless coordination between neural, muscular and skeletal systems that allows bipedal creatures to negotiate all sorts of uneven terrain. So it's of special interest to read about the advances Salk professor Sam Pfaff and colleagues are making in the study of the spinal cord and the related diseases that compromise this ability. This Salk research is an excellent example of how cutting-edge technologies such as high-tech microscopy and gene-editing techniques are helping us unravel biological mysteries.

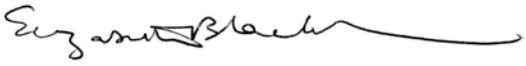
Elsewhere in this issue, several junior faculty members take a well-deserved turn in the spotlight. Diana Hargreaves' knowledge of biochemistry and epigenetic regulation is helping us better understand the cell mutations that lead to cancers, information that should have translational impact for ovarian and other cancers. Eiman Azim, who joined Salk just last year, has received the prestigious Searle Scholar and Pew Scholar awards. The former is given annually to only 15 researchers in the fields of chemical and biological sciences. And innovative and notable work performed by junior faculty members Janelle Ayres and Axel Nimmerjahn has earned them each a promotion to associate professor. The Salk Institute continues to attract the best minds in the world and we're especially proud of our rising stars.

Another star in our midst is research associate Shani Stern in Rusty Gage's lab, who helped develop a highly accurate method for predicting which individuals with bipolar disorder will respond to lithium. Previously, doctors and patients had to endure up to a year of wait-and-see to learn if a patient was one of the 30 percent who would positively respond to lithium therapy. You'll read more about her in our Next Gen article.

I'm pleased to welcome two new Trustees to the Board, both of whom are already making valuable contributions to Salk. Jay Flatley, former CEO of Illumina, provides deep experience in biotechnology and healthcare; and Joon Yun, a physician now heading a prominent investment management firm, advocates strongly for research into the aging process, a field that became a focus in my own career.

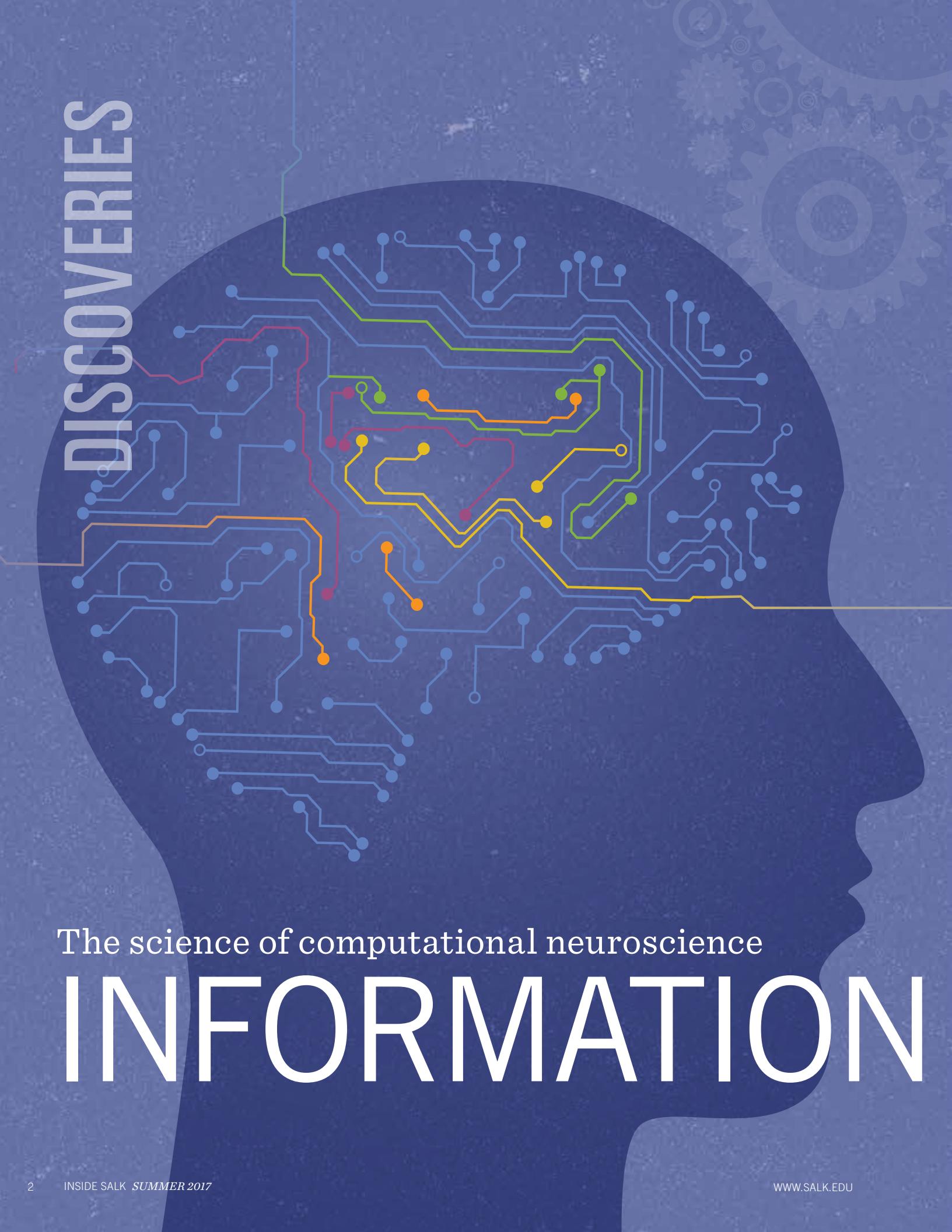
As always at the Institute, science marches on and important discoveries occur daily. It is my honor to lead such a talented, dedicated group and my additional honor to collaborate with Salk's many accomplished and generous supporters.

Sincerely,



Elizabeth Blackburn
President, Salk Institute
Irwin M. Jacobs Presidential Chair

"This Salk research is an excellent example of how cutting-edge technologies such as high-tech microscopy and gene-editing techniques are helping us unravel biological mysteries."



The science of computational neuroscience

INFORMATION

NEURON
06/2017

How cells divide tasks and conquer work

Despite advances in neuroscience, the brain is still very much a black box—no one even knows how many different types of neurons exist. Salk Associate Professor Tatyana Sharpee has used a mathematical framework to better understand how new cell types spontaneously arise and how the various types divide work among themselves. The theory could help reveal how cell types achieve greater efficiency and reliability or how disease results when the division of labor is not as effective.

NEURAL COMPUTATION
02/2017

The Internet and your brain are more alike than you think

Although we spend a lot of our time online nowadays, few of us know about the mathematical algorithms that manage how our content is delivered. But deciding how to route information fairly and efficiently through a distributed system with no central authority was a priority for the Internet's founders, says Salk Assistant Professor Saket Navlakha. He and his coauthor from Yale University show that an algorithm used for the Internet called additive-increase multiplicative-decrease (AIMD) is also at work in the human brain, an insight that improves our understanding of engineered and neural networks and potentially even learning disabilities.

NATURE COMMUNICATIONS
06/2017

How the brain recognizes what the eye sees

If you think self-driving cars can't get here soon enough, you're not alone. But programming computers to recognize objects is very technically challenging, especially since scientists don't fully understand how our own brains do it. How precisely this recognition happens is still a mystery, in part because neurons that encode objects respond in complicated ways. Associate Professor Tatyana Sharpee and Research Associate Ryan Rowekamp have developed a statistical method that takes these complex responses and describes them in interpretable ways, which could be used to help decode vision for computer-simulated vision. The duo analyzed how neurons in a critical part of the brain, called V2, respond to natural scenes, providing a better understanding of vision processing and how the brain works in general.

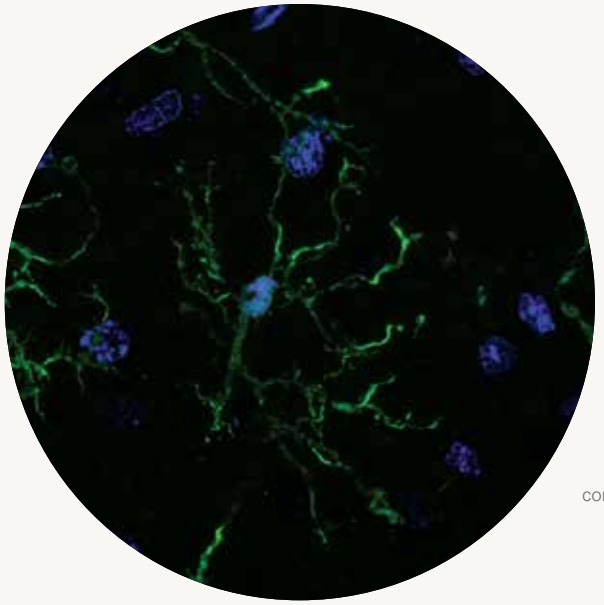
WATCH	http://bit.ly/sharpee201708

READ

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

CALCULATION

NEUROSCIENCE

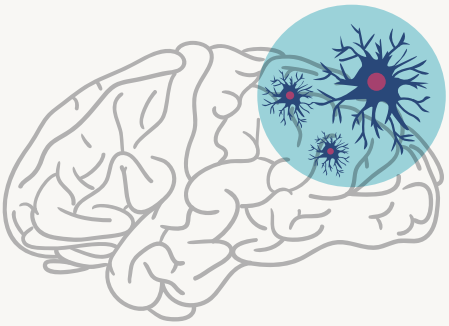


Salk and UC San Diego scientists conducted a vast survey of microglia (pictured here), revealing links to neurodegenerative diseases and psychiatric illnesses.

Credit: Nicole Coufal and Monique Pena

BRAIN'S IMMUNE CELLS LINKED TO ALZHEIMER'S, PARKINSON'S, SCHIZOPHRENIA

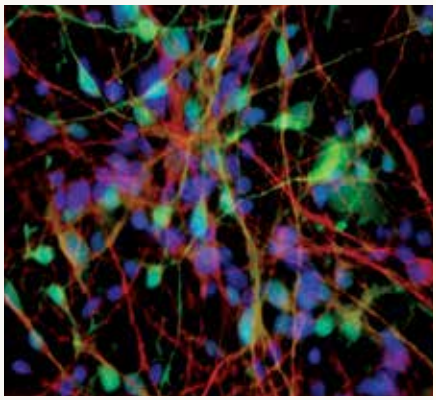
Scientists have, for the first time, characterized the molecular markers that make the brain's front lines of immune defense—cells called microglia—unique. In the process, they discovered further evidence that microglia may play roles in a variety of neurodegenerative and psychiatric illnesses, including Alzheimer's, Parkinson's and Huntington's diseases as well as schizophrenia, autism and depression. Professor Rusty Gage and a collaborator from UC San Diego reported in *Science* on May 25, 2017, that genes previously linked to neurological diseases are turned on at higher levels in microglia compared to other brain cells. While the link between microglia and a number of disorders has been explored in the past, the new study offers a molecular basis for this connection. S

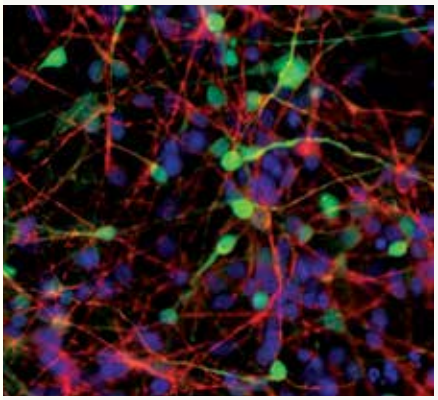


A STAR IS BORN: A LESSER-KNOWN BRAIN CELL TAKES CENTER STAGE

Neurons have long enjoyed the spotlight in neuroscience—and for good reason: they are incredibly important cellular actors. But, increasingly, star-shaped support cells called astrocytes are being seen as more than bit players in the brain's rich pageant. The lab of Rusty Gage reported a new method of deriving astrocytes from stem cells, opening up broad avenues for research into diseases with inflammatory features. The protocol, which is described in the June 6, 2017, issue of *Stem Cell Reports*, offers a faster and more effective way to obtain astrocytes for brain research that could yield breakthroughs for treatments of such diverse conditions as stroke, Alzheimer's or depression. S

The electrical activity of neurons (red/green) from bipolar patients can predict who will respond to lithium therapy. Left, responder; right, nonresponder.





NEW METHOD PREDICTS WHO WILL RESPOND TO LITHIUM THERAPY

For roughly one-third of people diagnosed with bipolar disorder, lithium is a miracle drug, effectively treating both their mania and depression. But once someone is diagnosed, it can take up to a year to learn whether that person will be among the 30 percent who respond to lithium. Salk Professor Rusty Gage, co–first authors Shani Stern and Renata Santos and colleagues report a way to predict, from neuronal firing patterns and with 92 percent accuracy, whether an individual with bipolar disorder will be a lithium responder. The work, which appeared online in *Molecular Psychiatry* on February 28, 2017, validates the lab's 2015 discovery of a cellular basis for the disorder and could benefit not only those who will respond to lithium but also the vast majority who will not, sparing them an ineffective treatment.

READ more about Shani Stern on page 24.

HARD CHOICES? ASK YOUR BRAIN'S DOPAMINE

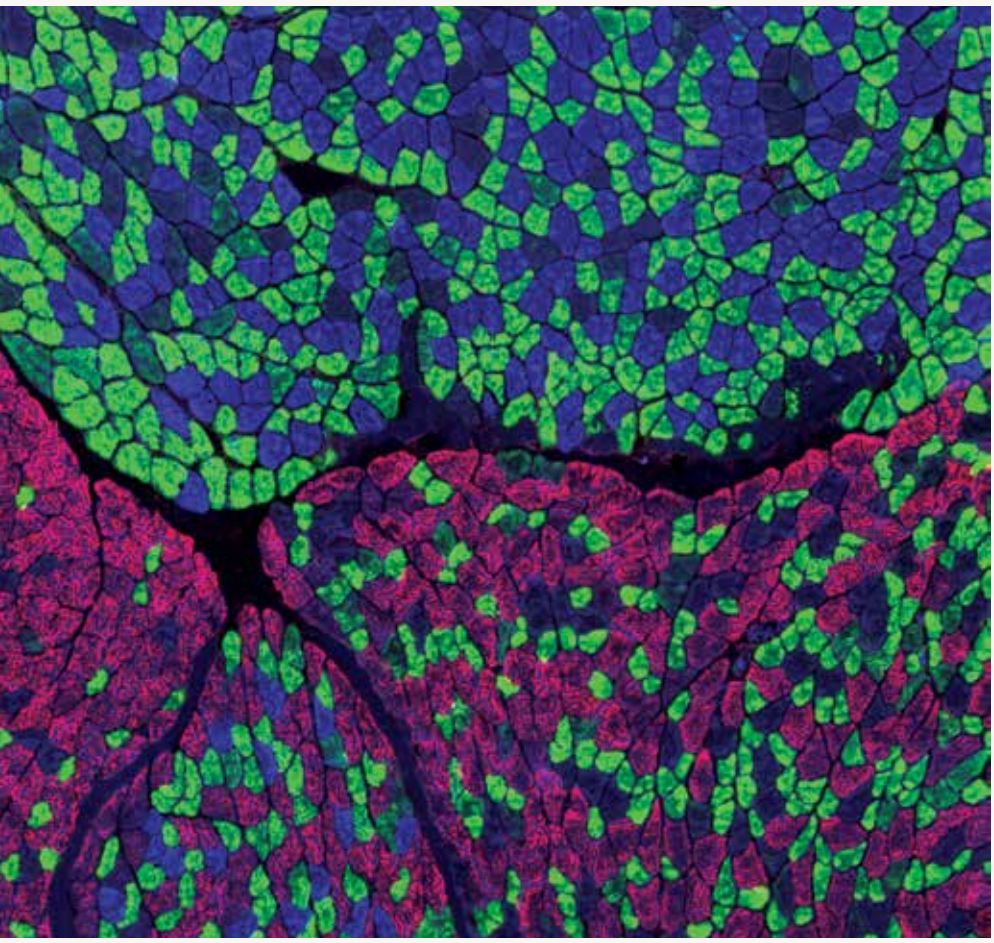
Say you're reaching for the fruit cup at a buffet, but at the last second you switch gears and grab a cupcake instead. Instead of moving left, your hand went right.

Such split-second changes play a major role in diseases that involve problems with selecting an action, like Parkinson's, OCD and drug addiction. In the March 9, 2017, online publication of the journal *Neuron*, Salk Professor Xin Jin, co–first authors Christopher Howard and Hao Li and colleagues report that the concentration of a brain chemical called dopamine governs decisions about actions so precisely that measuring the level in mice right before a decision allows researchers to accurately predict the outcome. The work may open new avenues for treating disorders both in cases where a person cannot select a movement to initiate as well as those in which someone cannot stop repetitive actions.

METABOLISM

"EXERCISE-IN-A-PILL" BOOSTS ATHLETIC ENDURANCE BY 70 PERCENT

Every week, there seems to be another story about the health benefits of running. That's great—but what if you can't run?



Partial view of a mouse calf muscle stained for different types of muscle fibers: oxidative slow-twitch (blue), oxidative fast-twitch (green), glycolytic fast-twitch (red).

For the elderly, obese or otherwise mobility-limited, the rewards of aerobic exercise have long been out of reach. Co–senior authors Ronald Evans and Michael Downes, together with first author Weiwei Fan and colleagues, have built on earlier work by the lab that identified a gene pathway (PPARD) triggered by running. In the current study, which appeared in *Cell Metabolism* on May 2, 2017, the team reported fully activating that pathway in sedentary mice with a chemical compound, mimicking the beneficial effects of exercise. They also found that PPARD encourages fat-burning but suppresses sugar-burning in muscles during exercise, likely to preserve sugar for use by the brain. The work reveals why runners who "hit the wall" experience both physical and mental exhaustion upon using up their ready supply of glucose. S

WATCH | http://bit.ly/evans201708

SALK SCIENTISTS EXPAND ABILITY OF STEM CELLS TO REGROW ANY TISSUE TYPE

When scientists talk about laboratory stem cells being totipotent or pluripotent, they mean that the cells have the potential, like an embryo, to develop into any type of tissue in the body. What totipotent stem cells can do that pluripotent ones can't do, however, is develop into tissues that support the embryo, like the placenta. Salk Professor Juan Carlos Izpisua Belmonte, along with first author Jun Wu and researchers from China's Peking University, discovered a chemical cocktail that enables cultured mouse and human stem cells to generate both embryonic and extra-embryonic tissues. Their technique, described in the journal *Cell* on April 6, 2017, could yield new insights into mammalian development that lead to better disease modeling, drug discovery and even tissue regeneration.

From left: Inder Verma and Suvasini Ramaswamy

DON'T KILL THE MESSENGER RNA

FedEx, UPS, DHL—when it comes to sending packages, choices abound. But the most important delivery service you may not have heard of? mRNA. That's how your DNA sends blueprints to the protein-assembly factories of your cells. Inder Verma and first author Suvasini Ramaswamy, along with industry collaborators, reported the successful treatment of hemophilia B in mice using mRNA to deliver instructions for the clotting protein that is defective in the debilitating bleeding disorder. The therapy, which was described the week of February 13, 2017, in *Proceedings of the National Academy of Sciences*, is a proof of concept that mRNA therapy could be applied to a range of genetic diseases.

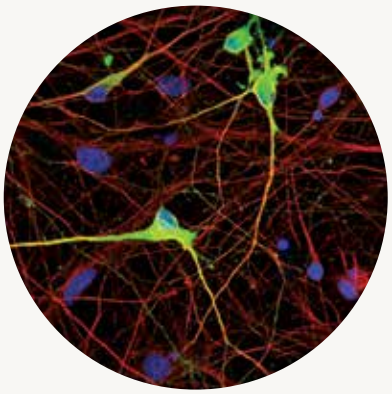
GENETICS

IDENTICAL TWINS, NOT SO IDENTICAL STEM CELLS

In a study published in *Cell Stem Cell* in April 2017, senior author Juan Carlos Izpisua Belmonte and collaborators have shed light on a longstanding question about what leads to variation in stem cells by comparing induced pluripotent stem cells (iPSCs) derived from identical twins. Even iPSCs made from the cells of twins, they found, have important differences, suggesting that not all variation between iPSC lines is rooted in genetics, since the twins have identical genes. The findings help scientists better understand the processes involved in reprogramming cells and the differences between iPSCs and ESCs (embryonic stem cells). The work could also lead to improvements in the way iPSCs are being used for research and therapeutics. S

NOVEL TOOL CONFERS TARGETED AND STABLE EDITING OF THE EPIGENOME

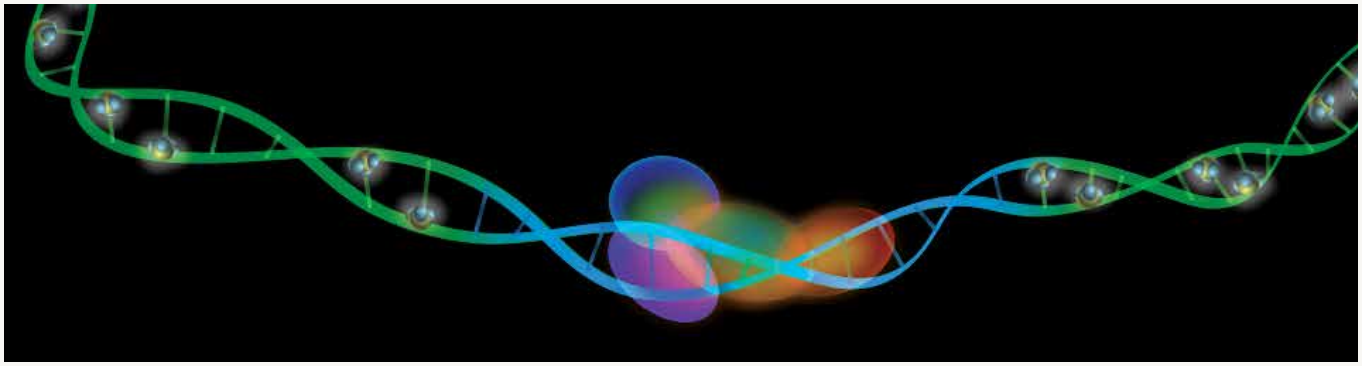
The lab of Juan Carlos Izpisua Belmonte has developed a novel technology to correct disease-causing aberrations in the chemical tags on DNA that affect how genes are expressed. These types of chemical modifications, collectively referred to as the epigenome, are increasingly being considered as important as the genome itself in development and disease. In the May 4, 2017, issue of *Science* the team described how they used the tool to model mutations in tags associated with colon cancer and to restore the proper tags in stem cells derived from people with Angelman syndrome. S



Neurons from Angelman syndrome (AS) patients lack expression of the UBE3A protein due to an epigenetic defect. The new Salk technology restores normal expression of the UBE3A protein in neurons derived from the cells of an AS patient by correcting the aberrant methylation pattern.

WATCH	http://bit.ly/belmonte201718

FINDING OUR WAY AROUND DNA



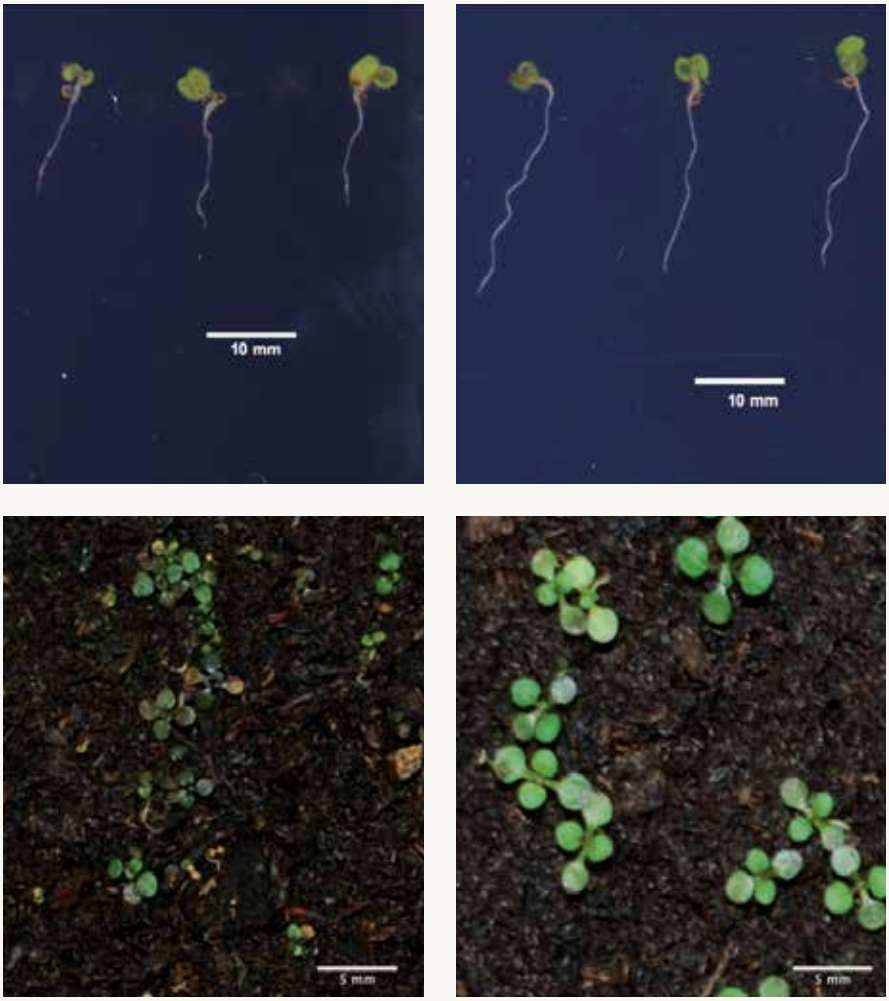
Salk team develops tool that maps functional areas of the genome to better understand disease.

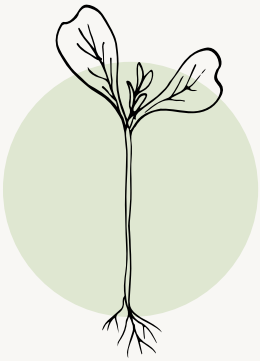
Most of us would be lost without Google maps or similar route-guidance technologies. And when those mapping tools include additional data about traffic or weather, we can navigate even more effectively.

Similarly, Joseph Ecker, first author Yupeng He and collaborators have developed a computational algorithm that integrates two different data types to make locating key regions within the genome more precise and accurate than other tools. The method, detailed during the week of February 13, 2017, in *Proceedings of the National Academy of Sciences*, could help researchers conduct vastly more targeted searches for disease-causing genetic variants in the human genome, such as ones that promote cancer or cause metabolic disorders.

PLANT BIOLOGY

HELPING PLANTS PUMP IRON



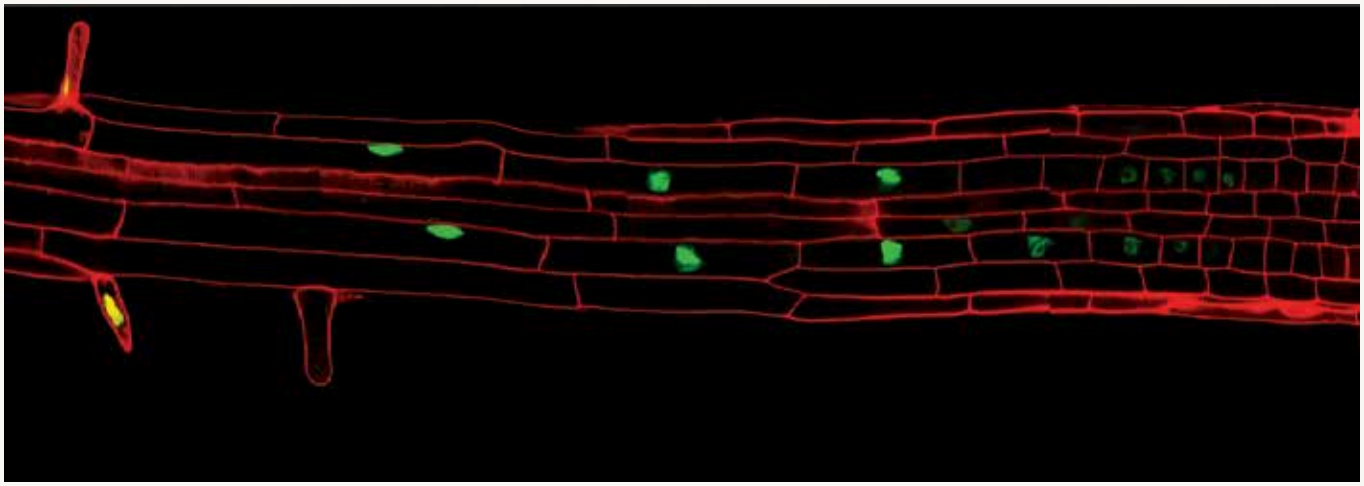


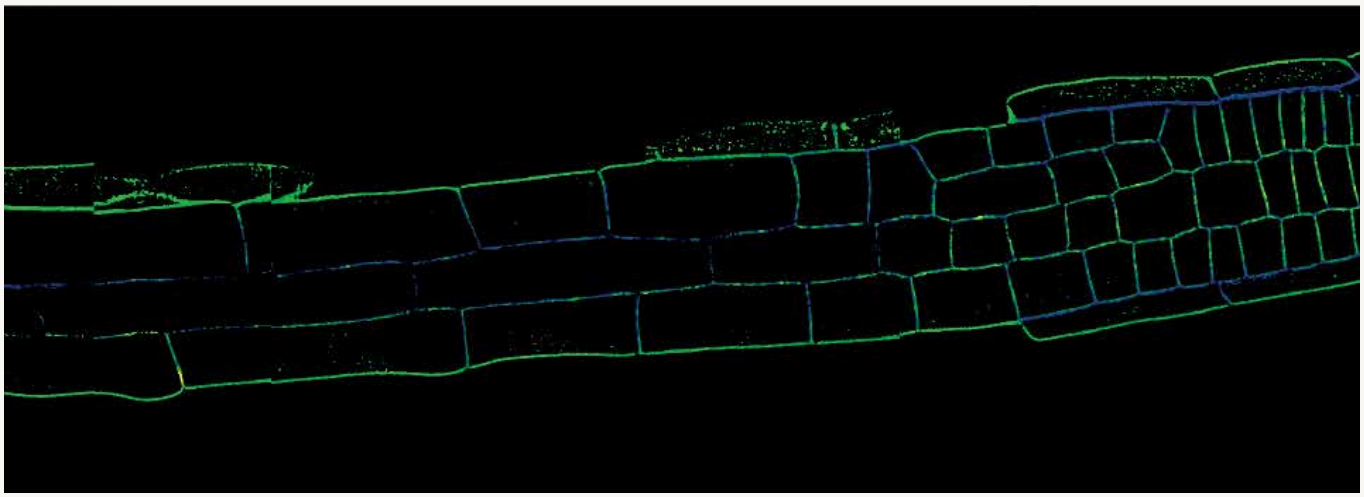
Just like people, plants need iron to grow and stay healthy. But some plants are better at getting this essential nutrient from the soil than others. Associate Professor Wolfgang Busch, first author Santosh Satbhai and collaborators have found that variants of a single gene called *FRO2* can largely determine a plant's ability to thrive in environments where iron is scarce. The work, which appeared in *Nature Communications* on May 24, 2017, could lead to improved crop yields for farmers and richer dietary sources of iron for animals and humans. S

Seedlings (bottom) and roots (top) of *Arabidopsis thaliana* plants reveal that one variant of the *FRO2* gene (right) is better for growth in low-iron conditions than the other *FRO2* variant (left).

In these two images showing different fluorescent markers in the *Arabidopsis* root tip, the upper image indicates auxin signaling (green) in the plant's outer layer (red), while the lower image defines the onset of acidification (blue) important for cellular growth/elongation.

A BETTER DYE JOB FOR ROOTS—IN PLANTS





Just the right chemical is needed to measure exactly how plant roots grow.

Salk's Wolfgang Busch and collaborators have discovered a fluorescent dye that, paired with other imaging techniques, reveals root growth to be influenced by a major plant hormone more than previously thought. The work, appearing in the *Proceedings of the National Academy of Sciences* the week of May 29, 2017, could be useful for many types of plant studies, as well as more fully understanding the hormone auxin, which is instrumental for growth and many other critical plant processes. Insights into auxin could, for example, inform the production of faster-growing crops or help mitigate such effects of climate change as drought or early flowering.

Untangling the Mysteries of the SPINAL CORD

Converging research and innovative technologies are tackling some of the deadliest motor diseases

For an expectant parent, few things are scarier than receiving genetic testing results and finding you're a carrier for spinal muscular atrophy, or SMA, a devastating genetic disease that kills neurons within the spinal cord needed for movement. Those who carry a dysfunctional version of one of two related genes have no symptoms of their own—though they risk passing the full-fledged disease to offspring if their partner is also a carrier. In the majority of children with SMA, the disease is fatal in their first few years of life.

But SMA patients today have a ray of hope. The United States recently approved the first drug for the disease, in a breakthrough that came after nearly 50 years of studies by academic and industry scientists into the genetic and molecular underpinnings of SMA, as well as basic research into motor neurons. These cells are some of the longest neurons in the body, stretching from the base of our spine to the ends of our toes in one continuous span.

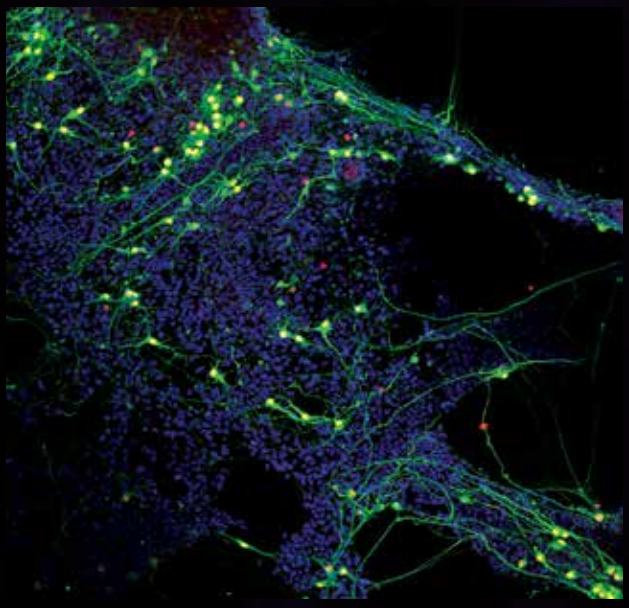
Little is known about why motor neurons are susceptible to degeneration, but recent work has shown that, far from being just an information relay between the brain and the rest of the body, motor circuits in the spine do their own heavy lifting when it comes to sensory perception and movement. Analyzing this motor neuron circuitry has become an important area of research in several Salk labs, with insights not only pointing toward potential cures for movement disorders and spinal injury but also revealing general rules the nervous system uses to process information and compute instructions in other brain regions.

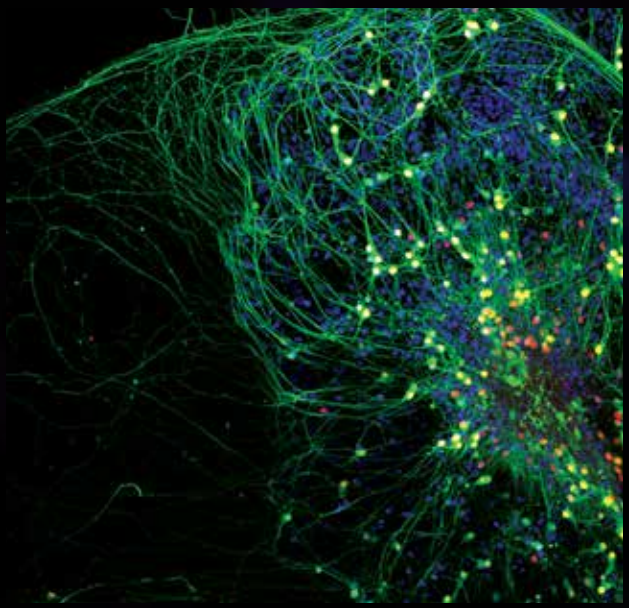
Little is known about why motor neurons are susceptible to degeneration, but recent work has shown that, far from being just an information relay between the brain and the rest of the body, motor circuits in the spine do their own heavy lifting when it comes to sensory perception and movement.

Spinal Muscular Atrophy (SMA)

Below, stains of neurons show mutations that cause the often-fatal spinal muscular atrophy.

All microscopy imagery courtesy of the Pfaff Lab.





"A drug for SMA is one of the great success stories of modern biomedical research and a historic achievement for many reasons," says Samuel Pfaff, Salk professor and holder of the Benjamin H. Lewis Chair. "It is not only exciting to finally have a treatment for this devastating disease of the nervous system, but it provides hope that the continued investment in research on other age-related neurodegenerative diseases such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS) will produce the insights needed to create useful treatments."

A legacy of healing

A history of delving into motor disease is built into the Institute's foundations, starting with its founder, Jonas Salk, who discovered the first polio vaccine. Polio, a virus that invades and destroys motor neurons (leading to infantile paralysis) devastated millions of people worldwide before Salk's vaccine helped to all but eradicate it.

For those unfortunate enough to contract the disease before the vaccine became available, there was a small chance of recovery that showcases the potential of spinal circuitry. Like many other areas in the nervous system, once motor neurons die they are not replaced. But it turns out that the remaining motor neurons after a polio infection will sprout additional connections over the course of several months in an attempt to compensate for the loss. This adaptation allowed many polio patients to recover from some degree of lost motor function over time, depending on the extent of the damage.

The Salk Institute was also home to the late Stephen Heinemann, whose pioneering research on neuro-transmitters laid the groundwork for understanding that many diseases of the brain result from deficits in communication between nerve cells. Heinemann was widely considered one of the world's most accomplished neuroscientists and inspired many at Salk, including Pfaff.

"By targeting the cause of spinal cord diseases we could focus our attention on biologically important processes. That was an 'aha' moment for me."

— Samuel Pfaff | Salk professor

"He once commented that neural diseases are nature's direct way of telling us about molecular pathways and cellular processes that are absolutely critical for the brain," says Pfaff. "Until that time, I considered studies of neural disease too descriptive and inconvenient for my lab's experiments, but this comment made me realize that by targeting the cause of spinal cord diseases we could focus our attention on biologically important processes. That was an 'aha' moment for me."

The complexity of standing and walking

In many ways, the brain and spinal cord are still a black box: an incredibly complex tangle of electrochemical circuitry built and maintained through elaborate networks of molecular and genetic pathways. However, developments in technology, such as imaging, microscopy, stem cell research and others, are yielding rapid new discoveries in the field.

The brain interacts with the world by moving the body through everyday acts like tying a shoe or typing an email, to more impressive accomplishments like hitting a fastball or playing the guitar. During these types of behaviors the brain sends signals to the spinal cord, where intricately organized neural circuits must orchestrate the activity of dozens of muscles to perform smooth and precise movements.

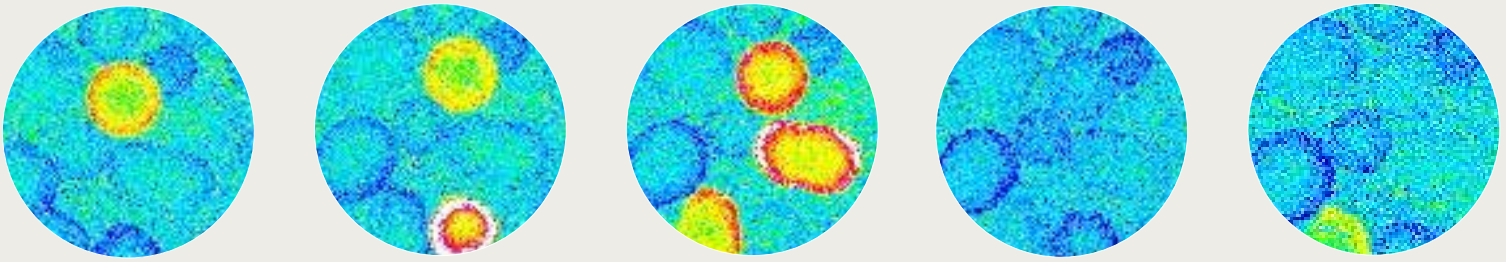
"We are only in the very early stages of understanding exactly how the spinal cord does its job, yet it is abundantly clear that these spinal circuits are particularly vulnerable to neurodegenerative disease and injury," says Assistant Professor Eiman Azim, whose work focuses on understanding neural circuits of movement. "One of the most promising ways to make progress in developing therapies for motor disorders is to have a better understanding of how it all works—by teasing apart the basic organization of motor circuits and defining how they function during normal movement. With this kind of knowledge, we will be in a much better position to understand how motor control can go awry, and how we might be able to intervene to repair circuits and restore function."

One way to do this is to create replicas of pieces of the nervous system, particularly three-dimensional versions of networks. Pfaff created such a system called a circuitoid, a miniature collection of neuron types organized within a petri dish that mimics a functional unit in the spinal cord. First published in 2017 in the journal *eLife*, Pfaff's circuitoids—which fire in a way that mimics the rhythm of stepping—revealed the different ratios of cells needed for locomotion. It had been suspected that different combinations of neurons working in unison played a role in locomotion, but circuitoids revealed the ratio of five types of neurons needed for successful movement.

His lab was able to develop the circuitoids thanks to innovations by other neuroscientists, such as Salk Professor Martyn Goulding, who developed a strain of mice with fluorescent proteins in specific neuron types. The Pfaff team used these mice to isolate hundreds of different stem cell lines and study how stem cells could be converted into an array of different spinal neuron types. With these advances in identifying and labeling spinal neurons, the team could monitor the cells' growth in real time and focus on the cell types they suspected were most important for controlling rhythmic movements, such as stepping, chewing and breathing.

"We found combinations of motor neurons that would allow us to regulate the speed of the cells' electrical bursts, equivalent to controlling the speed of walking," says Pfaff. "This further illustrates that the spinal cord itself isn't just a relay for information, but an important processing center."

The circuitoid system is the first step in studying the computational principles that underlie the complex



regulation needed for movement, he adds. This novel approach of building a neural circuit entirely within a dish is leading others to request Pfaff's cell lines in order to model diseases and study neural interactions.

Scientists have also recently uncovered a "mini brain" in the spine that integrates sensory information from light-touch sensors in the feet and makes the necessary adjustments to our muscles so that we don't slip and fall. Goulding's lab discovered that this cluster of cells in the spine, called RORα neurons, doesn't just receive signals from the brain and light-touch sensors, but also directly connects with neurons in the ventral spinal cord that control movement. This circuit helps us to reflexively make small adjustments to foot position and balance when dealing with a slippery surface, for example. The study, conducted in mice, provides the first detailed blueprint for a spinal circuit that serves as a control center for integrating motor commands from the brain with sensory information from the limbs.

"How the brain creates a sensory percept and turns it into an action is one of the central questions in neuroscience," says Goulding. "Our work is offering a robust view of neural pathways and processes that underlie the control of movement and how the body senses its environment."

Together, all of these advances in revealing the basis of movement and spinal cord circuitry help lead to the next step: repairing dysfunctional movement.

What it takes to rebuild spinal function

It is still a mystery why motor neurons degenerate with seemingly little warning after many decades of life in patients with ALS. Once symptoms appear, typically in people's 40s, they may only have 5 years to live, with most dying within 2 years.

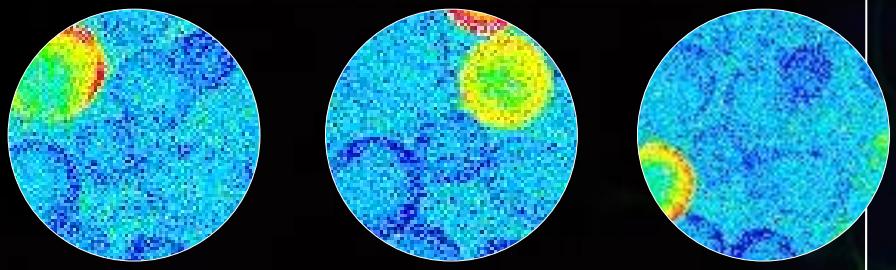
"A diagnosis of ALS is a death sentence with no treatments or cures," says Pfaff. Even though the same motor cells die in ALS as in SMA, a different pathway is at work, potentially due to a combination of genetics and environment.

Despite the grim odds, one tantalizing possible treatment for both ALS and spinal cord injury is on the horizon. Could stem cells—cells that have the potential to grow seemingly unlimited supplies of tissues—be injected into the spine to grow new neurons?

It turns out this isn't as easy as it sounds. Stem cells don't have the same cellular and environmental cues instructing them on what to become in a stable adult body as they would in, for example, a developing fetus. Fresh stem cells introduced into a spinal cord may not develop into the desired cells, or worse, develop into undesirable cells or even cancer. So-called stem cell tourism—where people travel to other countries to have stem cells injected into an area of injury—are incredibly dangerous for precisely those reasons, in many scientists' opinions.

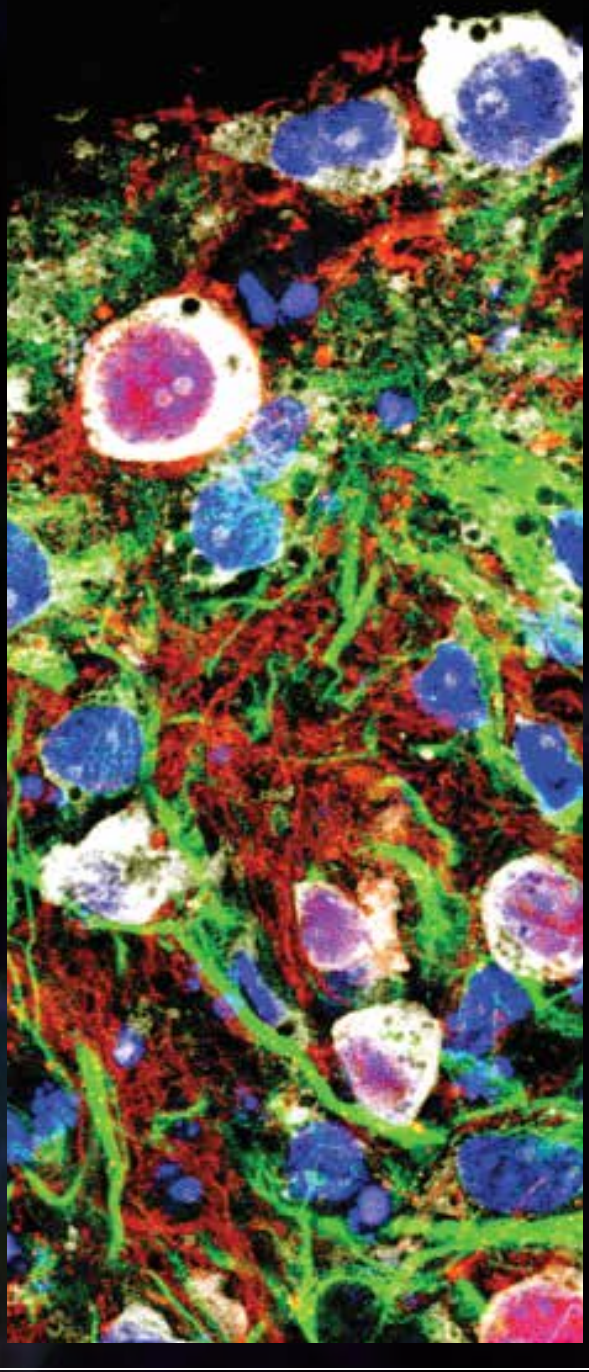
"It's unclear that injection of immature, rapidly dividing cells into the nervous system is a full solution to regenerative medicine," says Pfaff. "If they survive and become neurons, they may make connections with the partners they should, or they may start to make connections with anything and everything. The latter would be a wiring disaster, a short circuit in effect."

Although stem cells have been used in other clinical treatments— such as providing new blood to patients with leukemia—nothing is currently available for motor disease or spinal cord injury, though early clinical trials are under way for a number of stem-cell-based treatments to find methods to safely introduce stem cells. Pfaff's lab, along with researchers at the University of California, San Diego, are part of a bigger project through the California Institute of Regenerative Medicine (CIRM) to develop neural stem cells that can be transplanted into spinal cord patients without the risk of forming tumors. After five



Circuitoids

By creating replicas of pieces of the nervous system, particularly three-dimensional versions of networks, Pfaff was able to create one such system called a circuitoid—a miniature collection of neuron types organized within a petri dish that mimics a functional unit in the spinal cord, pictured left and below.



years of experiments, the team is currently collecting data related to safety measures to present to the FDA in the first step toward obtaining approval for these cells to test in ALS.

"ALS is a disease that's so devasting that the FDA has shown a lot of flexibility in what can be tested," says Pfaff. "It is likely to be the forerunner for testing various innovative stem cell approaches for many kinds of injury and neurological disease, whether stroke, injury, Parkinson's or Alzheimer's."

Pfaff is tackling ALS from several angles. Aside from stem cell therapy, he is exploring supportive cells in the nervous system called glia (in particular a subtype called astrocytes) that research in the field has pointed to as a potential culprit in damaging motor neurons in ALS.

"The transplantation of astrocytes into the spinal cord to promote recovery of motor neurons in disease is an exciting new research area," says Nicola Allen, an assistant professor at Salk who studies glial cells. "For this to be a successful therapy we need to understand the unique features of spinal cord astrocytes, compared to astrocytes in the rest of the brain, to ensure that transplanted astrocytes have the right properties to support spinal neurons."

The lab of Salk Professor Rusty Gage grew astrocytes from human embryonic stem cells (published in *Cell Stem Cell* in 2008) to confirm that dysfunctional human astrocytes turn against their charges and kill off healthy motor neurons. His team found that treating the cultured cells with an antioxidant staved off motor neuron death caused by malfunctioning astrocytes. The work provides insight into the toxic pathways that contribute to the demise of motor neurons in ALS and opens up new possibilities for drug-screening experiments using human ALS in vitro models, as well as clinical interventions using astrocyte-based cell therapies.

In Salk Professor Samuel Pfaff's free time he is an avid cyclist and rides in the annual Pedal the Cause event to raise money for the Salk Cancer Center. Here he is wearing a bicycle jersey featuring his lab's microscopy images.

The measurement of limb joint angles during movement is a typical method used to detect changes in the neural circuitry controlling our limbs. This type of "kinematic" analysis is represented as a series of stick figures.

"We are exploring whether we could replace those harmful glial cells or at least get some normal, healthy glial cells in the environment to slow the disease down," says Pfaff.

Tiny molecules and supportive cells that have a big effect

It turns out that many of the dozen-plus genes associated with ALS—as well as the one associated with SMA—involve the metabolism of small molecular versions of RNAs (short for ribonucleic acids). Most RNAs, which are molecules that help decode the genome, are thousands of amino acids long, but microRNAs are only about 20 long. Pfaff's lab discovered that motor neurons have a unique microRNA called miR-218. By creating mutations in miR-218 they found that the absence of this single small RNA was enough to cause motor neuron degeneration through a series of steps that mimic ALS and SMA.

"This was the smoking gun we had been searching for," says Pfaff. "We believe this could be the convergence point that is affected in many forms of ALS." Pfaff, along with a team of collaborators from UC San Diego and the Weizmann Institute, was recently awarded a grant from Target ALS to further investigate this possibility using compounds to mimic miR-218.

The microRNAs may connect the different factors that lead to ALS—such as the aging process as well as mutations in genes that contribute to the function of microRNA. Pfaff will be collaborating with a local company that specializes in making compounds that mimic microRNAs.

"This could be a very novel therapeutic approach," says Pfaff. "And if this ends up benefiting SMA and ALS, then maybe we need to think about microRNAs in other neurodegenerative diseases." Right now, microRNA therapies are few and far between and mainly associated with tumor treatments.

With the series of exciting developments in motor disease research over the last few years, Pfaff credits the progress to funders like the Marshall Foundation, who provide support for the high-end microscopic equipment that makes visualizing neurons more accessible. Pfaff still has his microscope from when he was 7 years old in his office, worth around $5 and nestled in a brown case smaller than a shoebox. He contrasts that with the million-dollar microscopes he works with regularly. "The toys have gotten more expensive," he says with a smile. But, if it means finding ways to help the hundreds of thousands of people with impaired spinal function, then the price is worth it.

A Closer Look

1 Neuronal labeling within the spinal cord

2 Explant culture of embryonic neurons

3 Embryonic stem cell potency fluctuates with endogenous retrovirus activity

4 Response to injury in a nerve

5 A pyramidal neuron

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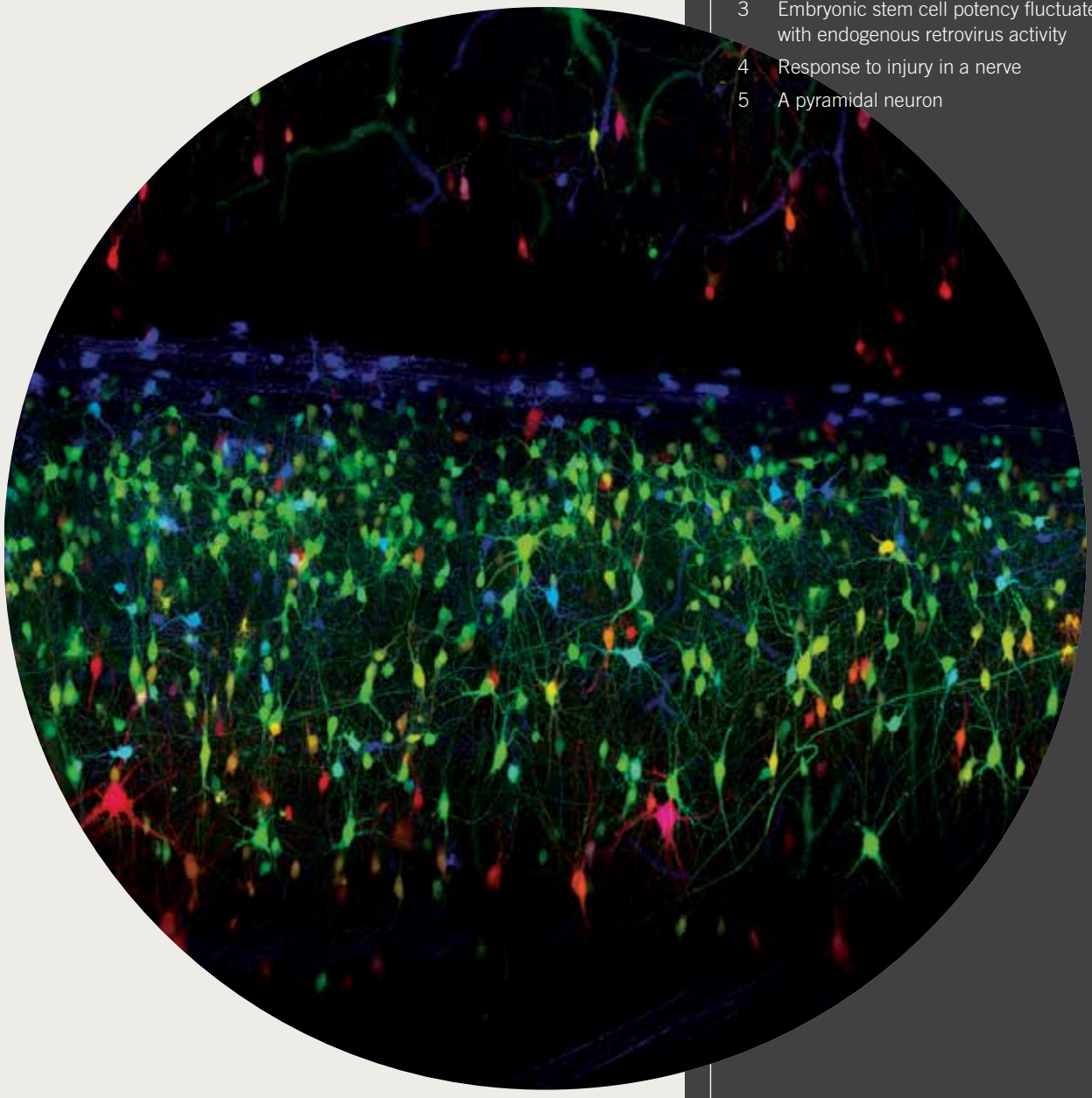

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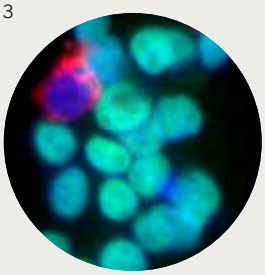

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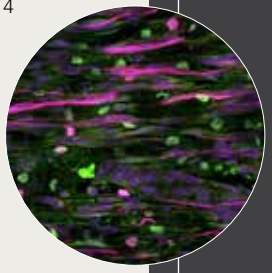

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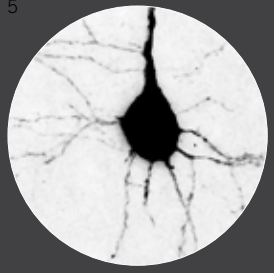


FRONTIERS

An Interview with DIANA HARGREAVES

At a recent Salk event, Diana Hargreaves was talking with some attendees whose grandchildren were looking at colleges. They commented that Hargreaves must have attended a large research university as an undergraduate in order to become a scientist at such an elite institution as Salk. She told them that, actually, she had attended a liberal arts college of only 1,000 students called Haverford. "Really?" they exclaimed. "You're a top scientist and you went to a place like Haverford?" She replied, "It's *because* I went to Haverford!"

Hargreaves doesn't often talk about her undergraduate institution, but it turns out to fit a pattern for the assistant professor in Salk's Molecular and Cell Biology Laboratory: choosing small, intimate environments where, as she puts it, "there's less hierarchy in terms of thoughts and ideas." Her graduate program at Yale University was like that, and it's what she values about Salk.

Inside Salk talked with Hargreaves about why she prefers smaller intellectual environments, what excites her about the science she does at the Institute, and how she thinks about being a woman in science.

What is special about smaller institutions?

Visibility. There's more possibility of having a voice because there aren't 400 people out-voicing you. You're able to contribute. My undergraduate experience was incredibly formative. You're in a classroom with 15 other kids and you're talking directly to the scientist—you're talking to [someone like] Ron Evans! He's spending time with you! Getting your education from someone who has some history with the material is incredibly valuable. It sets the foundation for how to study and learn and be resourceful. All of that foundation is much more important than learning how to pipette—that's vocational. But learning how to think, how to write papers, how to be creative about the questions you're interested in and to develop your own ideas—that's the hard part, but it's incredibly valuable.

Salk is that way, too. The senior faculty are all very approachable. I've had great discussions with Ron Evans and Inder Verma about their fields, and the history at Salk. I talk to Tony Hunter almost every day! Normally junior faculty wouldn't get that kind of access to senior faculty. The environment at Salk really allows assistant professors to thrive.

Were you always interested in science?

I think I was naturally inclined to do science from pretty early on. I had lots of great teachers along the way, but my mom is probably one of the most important role models. She was in one of the country's first MD/PhD programs—she's a pathologist and an academic—and I think that having that visual of her doing it, of making it work—and making it work with a family—as well as giving me lots of encouragement of the "follow your passions" type was really important. It's funny—she started in chemistry, I ended up doing chemistry. She did her PhD on chemotherapy in rats and now I'm in cancer biology.

Is that how you ended up in cancer biology?

I got my undergrad degree in chemistry, but I've always been interested in the basic mechanisms of transcriptional

regulation—asking what the cellular machinery is that tells cells which genes to use, when they should be on and when they should be off. As a graduate student, I began to focus on complexes involved in chromatin remodeling.

[DNA is tightly packaged in bundles called chromatin and, in order for it to be read, it has to be unwound by large protein complexes known as chromatin remodelers or regulators.]

Next-generation sequencing was coming onto the scene, and a couple of years into my postdoc we had this wealth of information just fall into our laps. One of those proteins turned out to be highly mutated in cancer, and it was one of these things you couldn't ignore because the mutation frequency was so large. The *Arid1a* gene, which I study, turns out to be one of the most frequently mutated genes of these complexes, so we've been trying to understand how mutations in that gene affect the process when gene expression is turned on.

Every cell contains the same DNA blueprint, the same instructions. But only parts of the blueprint are used by each cell to confer identity. You can think of the protein complex that I work on as a team of workers reading that blueprint.

So the idea is that when you have mutations in these chromatin regulators, you kind of change the cell identity because you basically pull out the wrong set of instructions. So what was a normal cell takes on different qualities. And in some cases those can be qualities that cancer cells thrive on.

You followed your mom into cancer research—do you talk to her about being a woman in science?

Not really. She never made a big issue of it, which is probably why it never seemed like a huge hurdle for me. She had more of an attitude of, "Why not?" If you find something interesting, get into it. Don't worry about anything that might create obstacles.

So what makes the Salk Women & Science program important to you?

I don't necessarily shy away from discussions of being a woman in science, but sometimes those discussions can psych people out a bit. I think one of the most important things for women scientists is just being present and visible and showing that you're happy and doing the work that you want to be doing. So I would say that if you find something interesting, try it and see how it goes. Don't dwell on the expectation that it's going to be negative. Things aren't changing overnight, but people are definitely trying. That's why I think the Women & Science program is great, because it's important to be visible in a way that's positive.

You're married with two young children. How do you find work-life balance?

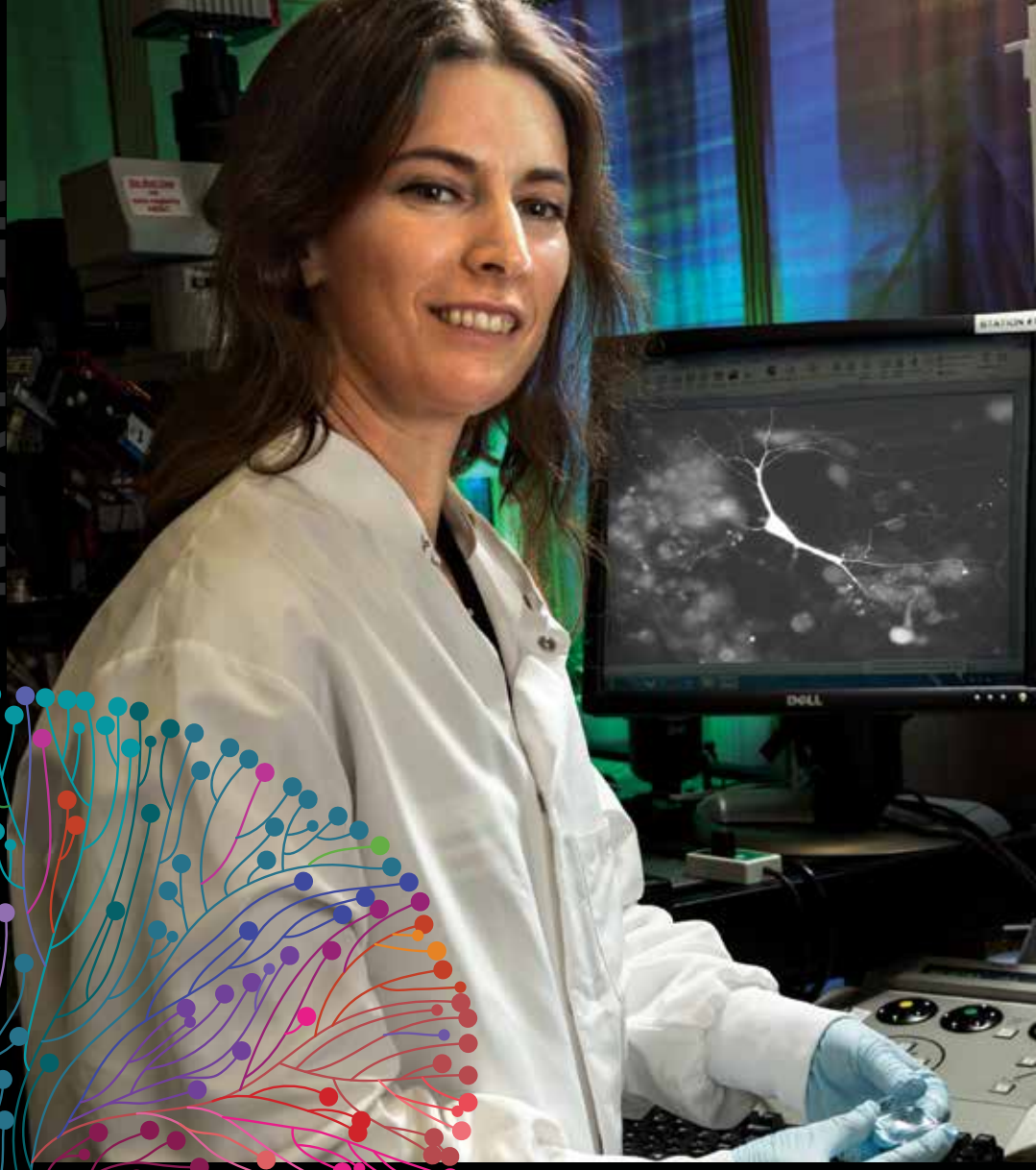
My older boy is four and the younger one is not quite six months. I think everybody's doing well. I have to compartmentalize to get my work done, because I don't have the unlimited hours that I had when I didn't have a family. And so the things that are an immediate priority always rise to the top. On the days I have teaching or administrative duties, I feel like the science can take a hit. It's like, OK, I'm going to have to pick up on that Western blot tomorrow because it's not calling me on the phone!

How do you relax?

I really love hiking and my husband and I have done quite a bit of that. I'm trying to get my boys interested but they're still a bit young. My parents dragged my brother and me hiking all over the place. I did some exciting backpacking trips in my youth, and I'd like my boys to do that as well. San Diego offers a lot of opportunities for it, so you don't have to be a very creative parent!

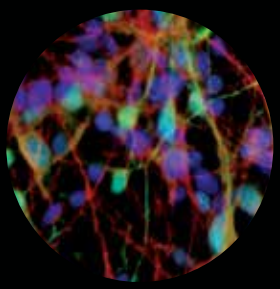
We'll probably do a couple of camping weekends this summer, and I'm looking forward to that.

NEXT GEN



Delving into the best of both worlds with

SHANI STERN



As the only electrophysiologist in the lab, Stern uses her engineering expertise to delve into the biological mysteries that most intrigue her, particularly bipolar disorder.

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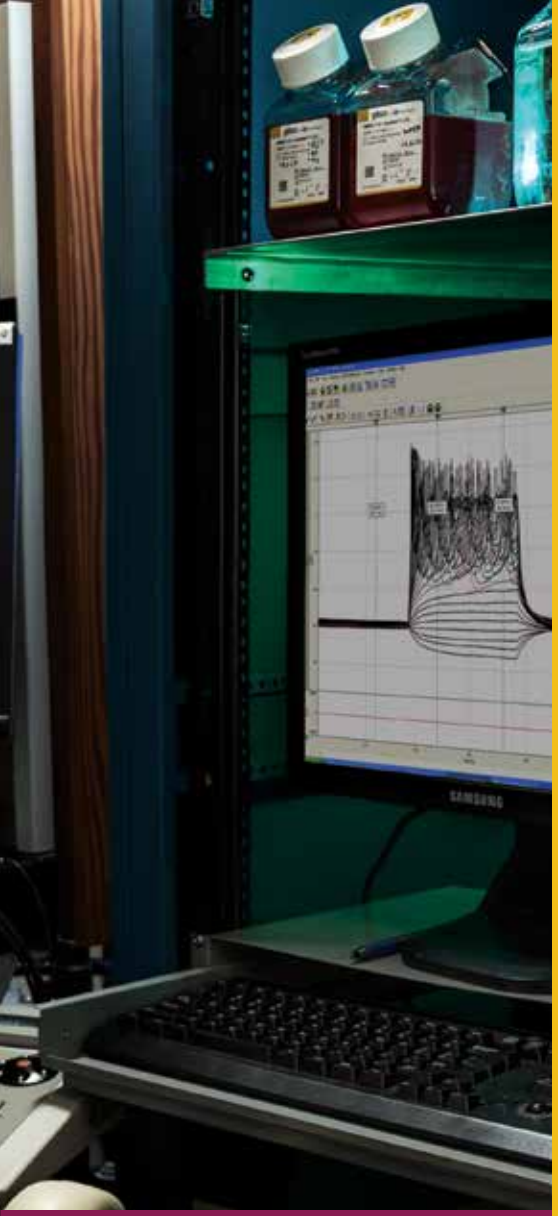

Biology held no interest for her, at first.

As a high school student in Israel, Shani Stern was a math and physics whiz. She got her degree in electrical engineering from Tel Aviv University before starting her requisite service in the Israel Defense Forces where she made the rank of lieutenant.

Stern seemed contentedly destined to follow in the footsteps of her electrical engineer father, and worked as an electrical engineer for a few years for Intel and Motorola designing modem and speech algorithms for cellular phones. Then, she got married and had the first of her four children. Reading about birth and the various sicknesses children get, Stern suddenly became very interested in biology and wondered how the subject had escaped her interest before.

After receiving her PhD in physics from the Weizmann Institute in Israel and collaborating with its neuroscience department, Stern joined Rusty Gage's lab at Salk in 2015 and became a member of the Engman Laboratory for Schizophrenia Research, where she enjoys the best of both worlds. As the only electrophysiologist in the lab, she uses her engineering expertise to delve into the biological mysteries that most intrigue her, particularly bipolar disorder.

With electrophysiology—a method invented in the 1970s that remains to this day the best way to measure the electrical currents through specific ion channels of cells—Stern studies the physiology and altered function of neurons derived from bipolar patients' induced pluripotent stem cells. Using a pipette in which an electrode has been inserted, she is able to barely graze the surface of a cell, apply a minute amount of suction to create a seal so no currents can escape, then rupture the cell membrane to measure its currents and potentials. Stern's expertise in this area makes her a hot commodity, and she is often enlisted by her lab mates to help record their research projects on such disorders as schizophrenia and autism.

This spring, Stern was the first author of a paper reporting the lab's ability to accurately predict whether an individual with bipolar disorder will respond to lithium. One-third of patients diagnosed with bipolar disorder are effectively treated with lithium. However, it can take up to a year of treatment before seeing whether or not a patient is among the 70 percent who do not respond to the drug. The work, published in *Molecular Psychiatry*, reported predicting with over 90 percent accuracy whether an individual will respond to lithium, which could spare patients an ineffective treatment as well as help to better understand the disorder. She has already begun writing another major paper, this one on CA3 neurons in the hippocampus, whose ion channels in bipolar individuals exhibit marked differences from those in people who do not have the disorder.

Stern's leisurely pursuits are anything but. She likes to unwind on weeknights by teaching advanced math to her children, who range from 4 to 15 years. On Sundays, the whole family heads outdoors to hike or visit an amusement park.

Despite the blistering pace she sets for herself, Stern wants at least one more paper on her resume before returning to Israel to start her own lab. "I haven't learned enough," she says. "I am still learning, and I am still having fun."

A Building of Wonders

The Salk Institute, completed in 1965, serves as a globally renowned scientific facility and famed architectural landmark to this day.

The Institute has 2,352 solar panels that supply 500 kilowatts of energy to the Institute each year.

The lab floors are column-free spaces that are 65 feet wide and 245 feet long. The open design provides flexibility for the ongoing configuration, renovation and modernization of labs.

By creating interstitial spaces between each lab floor, Kahn succeeded in confining all the electrical lines, piping systems and ventilation ducts to this area–keeping the laboratories completely open and unobstructed.

The sun sets along the axis of the "River of Life" twice a year, on the spring and fall equinoxes.

Jonas Salk directed the eminent architect Louis Kahn to provide unobstructed laboratory spaces that could be adapted to the ever-changing needs of science. The building materials had to be simple, strong, durable and as maintenance-free as possible, including concrete, teak, lead, glass and steel. Each building contains three floors of laboratory space, interspersed by three levels of interstitial pipe spaces. With its two mirror-image, 6-story-tall buildings that flank a grand courtyard, the Salk Institute, completed in 1965, serves as a globally renowned scientific facility today.

ANALYSIS

Teak panels line the 36 studies in individual towers, which provide a place of quiet contemplation for the professors. The saw-toothed arrangement allows for full views of the ocean and plaza.

Kahn built the outer walls of the laboratory levels out of large, double-strength glass panes, providing an open, airy work environment. Even the underground stories receive natural illumination: he designed a series of light wells for each building to bring daylight into the lower levels.

Architect Luis Barragán suggested the open courtyard of travertine marble would act as a facade to the sky and add to the monumental nature of the building.

Kahn used a "pozzolanic" concrete, which was first formulated by the ancient Romans. It is a volcanic and pumice aggregate added to cement mix, giving the concrete water resistance and a warm, pinkish appearance.

The "River of Life" water feature represents the trickle of knowledge produced by science spilling out into a larger body of discoveries, symbolized by the Pacific Ocean beyond.

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SPOTLIGHT

Salk promotes two dynamic faculty who study the microbiome and neurobiology

JANELLE AYRES

AXEL NIMMERJAHN

Janelle Ayres and Axel Nimmerjahn were each promoted to the rank of associate professor. Ayres, who conducts research in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis, studies how the body controls and repairs the collateral damage generated during interactions with harmful microbes.

Nimmerjahn, who is a member of the Waitt Advanced Biophotonics Center, develops and uses novel imaging approaches to explore the role of glial cells, which carry out critical activities in the central nervous system such as sensing and minimizing damage.

SALK'S WAITT ADVANCED BIOPHOTONICS CENTER PARTNERS WITH IMAGING GIANT ZEISS

From left: James A. Sharp, President, Carl Zeiss Microscopy LLC; Uri Manor, PhD, Waitt Advanced Biophotonics Core Director; Elizabeth Blackburn, PhD, President, Salk Institute; Jacob A. James, Managing Director, Waitt Foundation

The Salk Institute's Waitt Advanced Biophotonics Center and Zeiss, a global company based in Germany that develops cutting-edge optical and optoelectronic technologies, announced a global partnership on June 5, 2017, to accelerate the frontiers of microscopy and imaging technologies. The partnership will enable the Waitt Center to access Zeiss' state-of-the-art technology before it's commercially available. Zeiss will collaborate with Salk scientists to receive critical feedback on challenging imaging needs to further push the boundaries of imaging technologies to new frontiers.

SALK INSTITUTE WELCOMES NEW TRUSTEES JAY T. FLATLEY AND JOON YUN

The Salk Institute Board of Trustees welcomed its newest members, Jay T. Flatley, MS, and Joon Yun, MD. Flatley, as a former CEO of Illumina, brings deep experience in biotechnology and healthcare to bear on his new role at Salk. Yun joins Salk's Board with significant expertise in healthcare and finance. As managing partner and president of investment management firm Palo Alto Investors, LLC, he oversees $2 billion in assets invested in healthcare. Yun is also board-certified in radiology.

Jay T. Flatley

Joon Yun

Salk Professor Tony Hunter (middle) shakes hands with King Carl XVI Gustaf of Sweden

HUNTER AWARDED SWEDISH PRIZE

Salk Professor Tony Hunter traveled to Stockholm, Sweden, to accept the Royal Swedish Academy of Sciences' inaugural Sjöberg Prize for Cancer Research. He was awarded $500,000 as part of the $1 million prize for "groundbreaking studies of cellular processes that have led to the development of new and effective cancer drugs." The prize ceremony was held during the Academy's annual meeting on March 31 in the presence of His Majesty the King and Her Majesty the Queen of Sweden.

CONGRATULATIONS WOMEN & SCIENCE AWARD WINNERS

Ten postdoctoral researchers and graduate students were honored at the third annual Salk Women & Science Special Awards Initiative ceremony. Each received a grant ranging from $10,000 to $20,000 from the funds specifically raised to help support female scientists conducting high-risk research projects.

Salk President Elizabeth Blackburn hosted the March 29 forum, which began with a panel discussion moderated by Rebecca Newman, vice president, External Relations, on the importance of female leadership in science, technology and business. The honorees were: Ceyda Coruh, Graziana Gatto, Claire Geddes, Silvana Konermann, Sara Linker, Hermina Nedelescu, Annie Rathore, Cynthia Reyes, Maya Ridinger and Swati Tyagi.

Ceyda Coruh

Graziana Gatto

Claire Geddes

Silvana Konermann

Sara Linker

Hermina Nedelescu

Annie Rathore

Cynthia Reyes

Maya Ridinger

Swati Tyagi

SPOTLIGHT

Eiman Azim

SALK RESEARCHER EIMAN AZIM NAMED SEARLE SCHOLAR, PEW SCHOLAR

Eiman Azim, assistant professor in Salk's Molecular Neurobiology Laboratory, has been named both a Searle Scholar, which each year is awarded to only 15 researchers in the fields of chemical and biological sciences, and a Pew Scholar in the Biological Sciences. Of the 22 researchers named Pew Scholars, Azim is one of a subset of five selected as Kathryn W. Davis Aging Brain Scholars. The Searle award provides $300,000 to support scientific research for each scholar over the next three years, while the Pew award provides $240,000 over four years "to investigate the world's most pressing health problems." Azim will use the dual awards to explore the function of a set of neural circuits in the spinal cord thought to convey movement-related information.

SALK GARNERS EDC AWARD

The San Diego Regional Economic Development Corporation presented the Salk Institute with the 2017 Duane Roth Renaissance Award at its annual dinner on April 20 at SeaWorld San Diego. Named after the late biotech executive Duane Roth, who was noted for his dedication to life science, the award recognizes an organization for creating outstanding inventions, innovations or breakthroughs that have changed and improved the world. Roth, who passed away in 2013, was vice chairman of California's stem cell agency, the California Institute for Regenerative Medicine, and played a key role in bringing together scientists from Salk, the University of California, San Diego, The Scripps Research Institute, Sanford Burnham Prebys Medical Discovery Institute and other research organizations to create the Sanford Consortium for Regenerative Medicine.

SALK'S RESEARCH CENTER ON AGING RECEIVES ADDITIONAL $3 MILLION AWARD FROM GLENN FOUNDATION FOR MEDICAL RESEARCH

Salk has received a $3 million award from the Glenn Foundation for Medical Research for the second time in 4 years, enabling the Institute to continue investigating the biology of normal human aging and age-related diseases.

The award supports the Paul F. Glenn Center for Biology of Aging Research at the Salk Institute, which was established in 2009 with a $5 million gift from the Glenn Foundation.

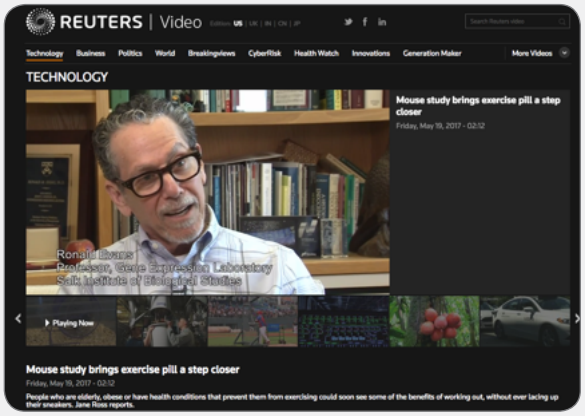
SALK IN THE MEDIA

Over the last few months, Salk President Elizabeth Blackburn was featured on Japan's largest broadcast station, NHK, as well as the Dr. Oz and Tavis Smiley shows. Other Salk scientists were also featured on major outlets this spring, including Ronald Evans (*Reuters* and *Science Friday*), Thomas Albright (*Washington Post*), Satchidananda Panda (BBC World Service and *Korean Herald*), Wolfgang Busch (*Forbes*), Janelle Ayres (*STAT*) and Jun Wu (NBC) .

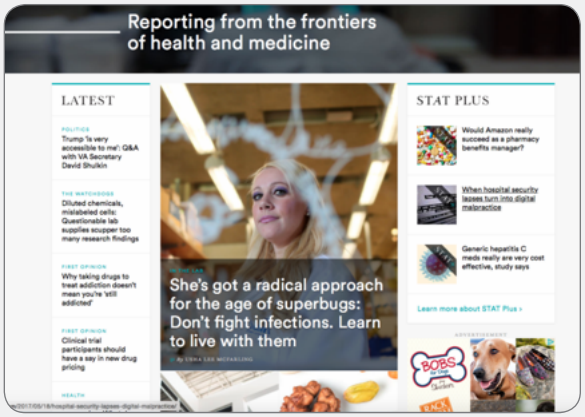
WATCH | bit.ly/media201708

Elizabeth Blackburn on NHK to talk about telomeres.

Jun Wu from Juan Carlos Izpisua Belmonte's lab discusses chimera research on NBC.



Ronald Evans discusses health and metabolism on Reuters.



An in-depth STAT feature showcases Janelle Ayres' work.

EVENTS

salk | EXCELLERATORS

BEING DR. BLACKBURN

Salkexcellerators concluded its season on May 17 with a private reception with Institute President Elizabeth Blackburn, who shared an insider's view of what it is like to lead Salk. Salkexcellerators are the next generation of community members committed to supporting scientific discovery at Salk. The program provides social and educational events throughout the year and supports a fellowship fund for the Institute's postdoctoral researchers.

Read more about the program: www.salk.edu/salkexcellerators

From left: Karen Nicholas, Elizabeth Blackburn, Laing Rikkers, Sandy Mossy and Peter Mossy

RESTORATION REVEALED

After a year of cloaked construction, the scaffolding came down and Salk's newly restored teak window wall assemblies were unveiled June 27 during a special outdoor ceremony. The Institute partnered with the Getty Conservation Institute to develop a preservation strategy that included historical research, on-site condition surveys, analysis of the teak and the repairs.

Opposite page: From left: Jonathan Salk, Elizabeth Shepherd and Irwin Jacobs

MIXING IT UP

Salk alum Suhaila White and Alumni-Faculty Fellowship Fund recipient Jared Smith of the Jin Lab were guests of the annual Salk Alumni Mixer on May 24 at the Institute. The fund was established as a way for today's leaders to help the next generation of scientists at Salk.

Left: Laura Tan, Jared Smith, Emily Manoogian and Amy Rommel
Right: Suhaila White and Salk Professor Geoffrey Wahl

ONE FINAL NOTE

The fourth season of the Salk Science & Music Series concluded with a high-octane jazz performance by the Helen Sung Quartet and a science talk by Assistant Professor Nicola Allen on April 30. The popular series returns for a fifth season on October 22, 2017.

From left: Nicola Allen, Rebecca Newman, Karen Joy Davis and the Helen Sung Quartet

EVENTS

INSTITUTE COUNCIL PRESENTS FOCUSED AGENDA

More than 40 members of the Salk Institute Council convened for the third annual meeting May 2 to discuss Salk science and ways to advance the Institute's mission. This year, led by Salk Board Chair Ted Waitt and 10 faculty members, intensive discussions focused on plant, cancer and microbiome research as well as other areas at the Institute.

BENEFITTING PANCREATIC CANCER RESEARCH

A fundraiser featuring remarks by Salk President Elizabeth Blackburn, and entertainment by rock violinist Lili Haydn and Jon Batiste, bandleader of "The Late Show With Stephen Colbert," was hosted by the William H. Isacoff MD Research Foundation for Gastrointestinal Cancer. Proceeds of the May 6 event at the Intercontinental Hotel in Los Angeles will benefit pancreatic cancer research as well as other areas at the Salk Institute.

From left: Los Angeles Mayor Eric Garcetti, Elizabeth Blackburn and William Isacoff

Back to Basics

BACK TO BASICS—DON'T BE NERVOUS!

Salk Associate Professor Sreekanth Chalasani addressed a full house in the Conrad Prebys Auditorium with his talk "Fear…Prozac and worms" at the March 22 Back to Basics lecture. Chalasani spoke about his lab's research with roundworms to explain how humans have evolved to cope with fear and anxiety. The Back to Basics program offers lay science lectures to the public twice a year. The next lecture will be on September 20, 2017.

TEA AND SCIENCE

More than 20 young girls took tea with author Rachel Ignotofsky during a Salk Women & Science event on May 3 at the Institute. Ignotofsky wrote and illustrated *The New York Times* bestseller *Women in Science: 50 Fearless Pioneers Who Changed the World*, highlighting the contributions of trailblazing women in science, technology, engineering and math, including Salk's first female president, Nobel laureate Elizabeth Blackburn.

From left: Ellen Potter, Ronald Evans, Jon Batiste, Tony Hunter and Jenny Price

Jon Batiste

WHEN SCIENCE AND ART COLLIDE

More than 20 local artists paired with Salk scientists, using their research as inspiration for a multimedia exhibition at the San Diego Art Institute in Balboa Park. Featuring all new works, "Extra-Ordinary Collusion" ran from May 20 to July 2.

EVENTS

MARCHING FOR SCIENCE

More than 200 Salk staffers, trustees and supporters took to the streets with thousands of other San Diegans on Earth Day to raise awareness of the contributions of science to society and the importance of supportive public policy.

The local March for Science stepped off from the San Diego Civic Center downtown on April 22 and was one of nearly 500 such marches held around the globe.

The power of charitable gift annuities

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

Sample Rates

YOUR AGE (S)	RATE
70	5.1%
80	6.8%
90	9.0%

Learn more about the many benefits of a charitable gift annuity by contacting Cheryl Dean, senior director of Planned Giving, at (858) 500-4884 or cdean@salk.edu.

Your age(s) and current interest rates determine the rate Salk can offer.

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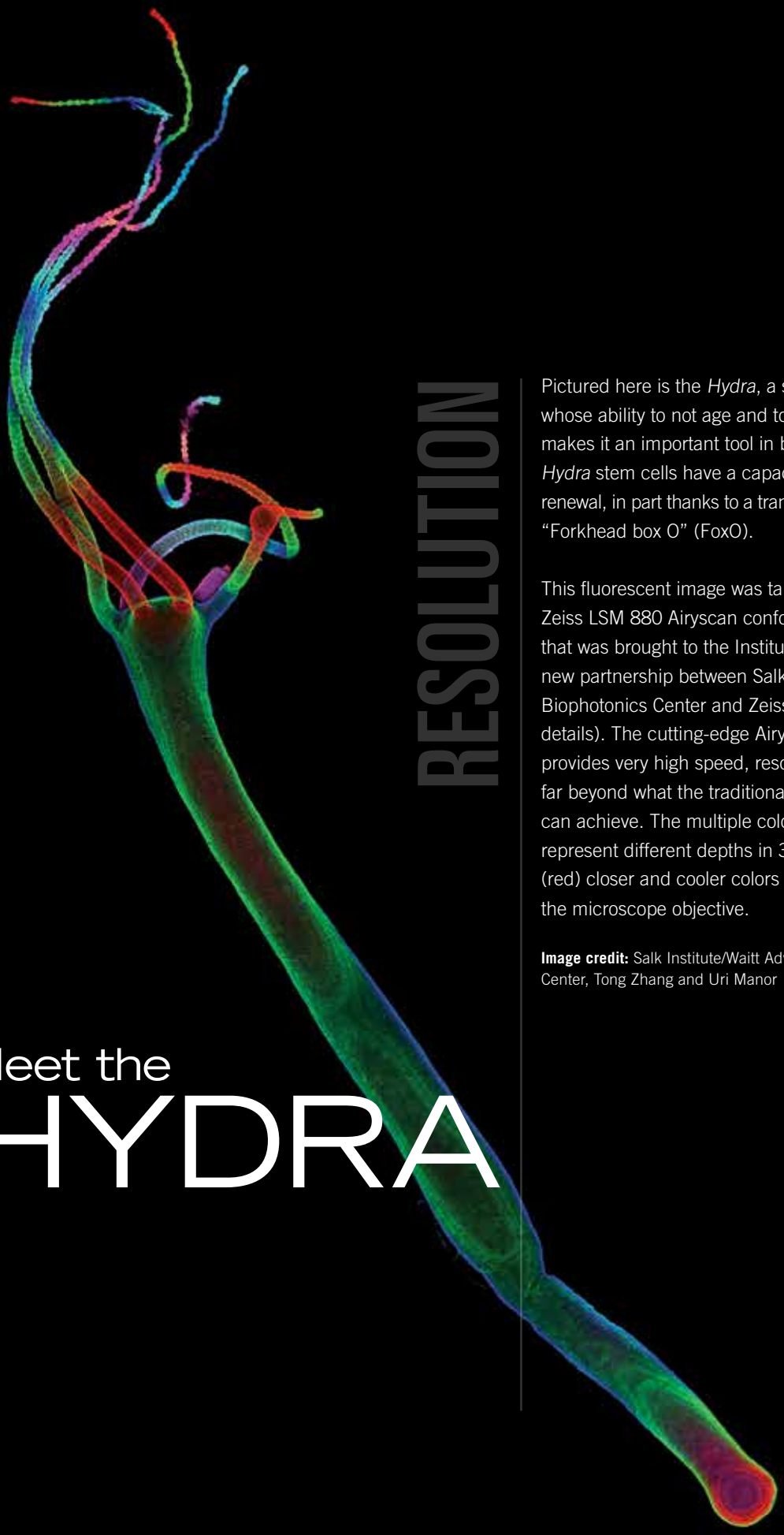


RESOLUTION

Meet the HYDRA

Pictured here is the *Hydra*, a small, freshwater animal whose ability to not age and to regenerate its tissue makes it an important tool in biological research. *Hydra* stem cells have a capacity for indefinite self-renewal, in part thanks to a transcription factor called "Forkhead box O" (FoxO).

This fluorescent image was taken with an inverted Zeiss LSM 880 Airyscan confocal microscope that was brought to the Institute as part of a new partnership between Salk's Waitt Advanced Biophotonics Center and Zeiss (see page 31 for details). The cutting-edge Airyscan microscope provides very high speed, resolution and sensitivity far beyond what the traditional confocal microscope can achieve. The multiple colors in this *Hydra* image represent different depths in 3D, with warmer colors (red) closer and cooler colors (blue) farther away from the microscope objective.

Image credit: Salk Institute/Waitt Advanced Biophotonics Center, Tong Zhang and Uri Manor

PERSPECTIVE

Elizabeth Blackburn
The Power of Knowledge

My favorite scientific heroine, the physicist Marie Curie who was twice a Nobel Prize winner, said something that I have always remembered: "Nothing in life is to be feared, it is only to be understood."

That observation, with its inherent fearlessness, speaks to me at my core as a scientist. It also can be a North Star for our daily lives. Yes, things to fear—indeed, sometimes, outright danger—are all around us, in the risk of injury and loss of material goods and threat of disease. But we possess immense capabilities for surviving these adversities. We have our intellect and our accumulated societal knowledge and our science. So we learn from our setbacks; we adopt new strategies and then go forward.

I think about fearlessness and the triumph of knowledge as I look out across the beautifully refurbished buildings on our Salk campus. The teak window wall assemblies, installed in accordance with Louis Kahn's breathtaking design, have existed for some 50 years in their own dangerous environment of damp marine air, harsh sunlight, termites and an invasive fungus from a recently identified culprit. Some time ago, they began exhibiting many familiar symptoms of disease and aging: failing structural integrity, exterior discoloration and increased vulnerability to pathogens. Thanks to a determined scientific investigation and intervention, however, these panels have been rejuvenated. Their lives have been extended.

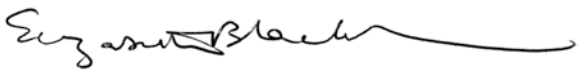
We are very grateful to the Getty Conservation Institute, which in partnership with the Salk Institute, convened a team of experts to examine all 203 teak assemblies and charged them with arriving at a diagnosis for the deterioration and then developing a plan for restoration. This cross-disciplinary team included historians, scientists, architects, engineers and philanthropists—a strategy that mirrors some of Salk's recent successes in elucidating complicated biological systems. For their part, scientists turned to DNA analysis to ascertain that the fungal biofilm blackening the wood was caused by spores from the campus's grove of eucalyptus trees. The Getty's conservation team has since implemented protection against these spores as well as the other damaging elements of the marine environment.

And that leads to my point: we can't eliminate all biological dangers in our world—and we wouldn't want to. Pathogens, despite their link with disease, play an important role on Earth. Within the plant community, for example, it's been proven that pathogens help maintain diversity. And diversity aids long-term species survival. In humans, our immune systems have been challenged over generations to develop different strategies to identify and target the wide variety of pathogens in our daily environment. Therefore, we are better equipped to face future, and continually evolving, dangers.

It all comes back to scientific knowledge. The more we learn about these fungi, bacteria, viruses and cancers, the more readily we can intercept and manage them, and the more successfully we can mitigate the damage they do. Managing pathogens, rather than trying to outright exterminate them, is somewhat of a new paradigm for addressing disease and one that several Salk scientists, always on the leading edge of scientific thought, are advancing. We are moving toward a day when cancers, along with many viral and bacterial diseases, will be identified early and then contained and managed, preventing them from inflicting serious damage on our bodies.

Our environment will always include dangers, seen and unseen. Salk's teak window wall assemblies, refurbished now to a beautiful golden glow, are still surrounded by eucalyptus trees and their infectious spores. But we've provided them with additional defenses. And armed with new scientific knowledge, we can closely monitor them for future signs of disease, before it takes hold and demands emergency remediation.

Let me conclude with what an architect friend of the Institute, Hugh Davies, pointed out to me: when you see someone walk across the Salk courtyard, silhouetted against the sea and sky, they appear larger than life. I think this is more than an optical illusion; being a part of the Salk Institute makes people larger than life. It inspires them to be so. So, as both a scientist and President of Salk, I will heed Marie Curie's words and know that what we may fear can always be understood.



Elizabeth Blackburn | *President, Salk Institute*

Every cure begins with you.

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

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

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

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

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

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

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

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

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

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

Get involved.

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

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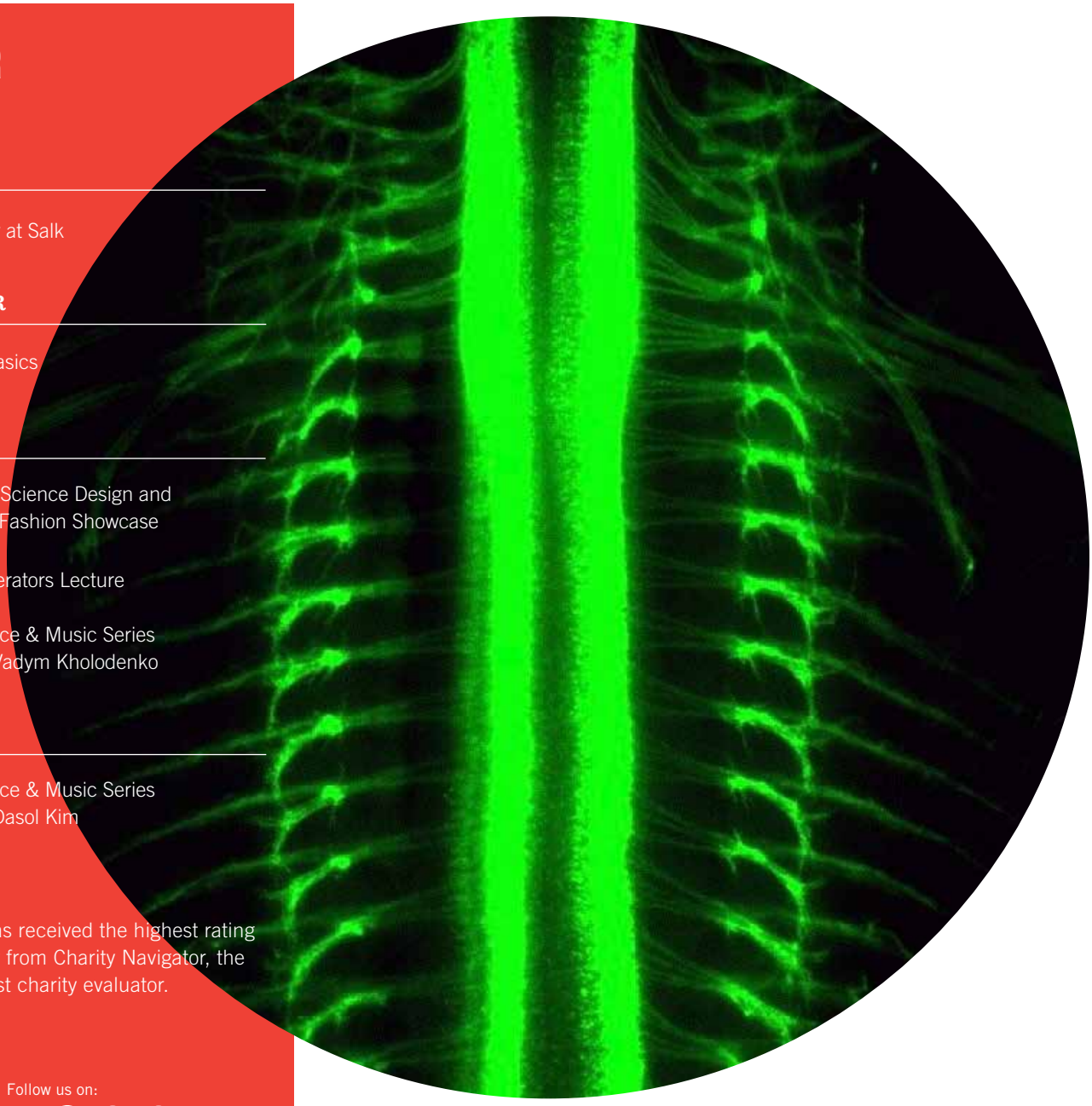

AUGUST

26 Symphony at Salk

SEPTEMBER

20 Back to Basics

OCTOBER

4 Women & Science Design and Discovery Fashion Showcase

11 Salkexcellerators Lecture

22 Salk Science & Music Series featuring Vadym Kholodenko

DECEMBER

3 Salk Science & Music Series featuring Dasol Kim

Salk Institute has received the highest rating 6 years in a row from Charity Navigator, the nation's foremost charity evaluator.

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