



InsideSalk

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BRAINGAIN

December 2014

Inside Salk



20

One on one with... Robert Redford



22

Next generation: Avani Wildani



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3 EXECUTIVE MESSAGE

FEATURES

- 4 Brain Gain
- 14 Cathedrals of Culture
- 20 One on one with... Robert Redford
- 22 Next generation: Avani Wildani

DISCOVERY ROUNDUP

- 26 One injection stops diabetes in its tracks
- 27 Dynamic duo takes out the cellular trash
- 28 Some stem cell methods closer to "gold standard" than others
- 29 New gene discovered that stops the spread of deadly cancer
- 30 Salk scientists uncover new clues to repairing an injured spinal cord
- 31 Genetic signal prevents immune cells from turning against the body

PHILANTHROPY NEWS

- 32 Salk science leads to discoveries
- 33 2014 Donor Honor Roll

INSTITUTE NEWS

- 67 Stephen F. Heinemann, pioneering Salk neuroscientist, dies at 75
- 68 Charles Stevens receives NSF grant under BRAIN Initiative
 - Tony Hunter receives 2014 Royal Medal in biological sciences
- 69 Salk scientists receive \$3 million for BRAIN Initiative grant
 - Third Salk researcher wins distinguished NIH New Innovator Award
- 70 Salk scientist receives 2014 Ray Thomas Edwards Foundation Career Development Award
 - First appointment in new Salk Fellows Program
- 71 Institute welcomes four new faculty
- 72 Salk Science & Music Series
- 73 Biophotonics symposium makes the invisible visible
- 74 San Diego Salkexcellerators cap off year with lecture on new findings that will aid in stem cell therapies
- 75 Salk's New York supporters gather to learn more about the latest discoveries in aging
- 76 19th annual Symphony at Salk an evening of magical performances
- 78 Back to Basics lecture offers a new perspective on diabetes
- 79 Women & Science lecture gives glimpse of how scientists are using stem cells to model autism spectrum disorder
- 80 High School Scholars share love of science

82 INSIDER'S VIEW

CALENDAR

Back Cover

Dear Friends,

HERE AT THE SALK INSTITUTE, I'M REMINDED DAILY WHAT AN extraordinary place this is. It's not just our groundbreaking discoveries, although those continue to make headlines around the world. It's also our iconic Louis Kahn buildings, which have helped create an environment that nurtures collaboration and innovation. Factor in some of the world's most gifted researchers and you have a formula for brilliant science.

This issue of *Inside Salk* celebrates both the marvelous discoveries that Salk investigators have made in recent months and the campus that has made them possible. Our cover story on neuroscience reveals why we've been renowned in this field for many years. (I share more of my thoughts on this subject in my Insider's View column.) We also have two articles about the architecture that has helped make us who we are—one on Robert Redford's recent film about the Salk buildings and a one-on-one interview with Mr. Redford, which I was privileged to conduct. The film officially debuted in the United States in October, but special friends of the Institute were able to attend a preview in June, with Mr. Redford in attendance. It's a measure of the impact of Louis Kahn's design that the film was the only one in the *Cathedrals of Culture* series to focus on American architecture.

The research taking place in those buildings has yielded some especially significant findings in the last few months. **Kuo-Fen Lee's** group has found a small molecule that may be able to induce damaged nerves to grow and rewire neural circuits. A team led by **Ye Zheng** has discovered a key control mechanism with implications for autoimmune diseases and some types of cancer, and scientists in **Reuben Shaw's** lab have identified a gene responsible for stopping the movement of cancer from the lungs to other parts of the body. **Ronald Evans** and his team have found a protein that may lead to a new treatment for type 2 diabetes. And a multi-site collaboration co-led by **Joseph Ecker** has demonstrated



William Brody

differences between stem cells depending on how they were created, a finding that could improve approaches for developing stem cell therapies and lead to a better understanding of stem cell biology.

On a very sad note, we lost one of our leading scientists when **Stephen Heinemann** died on August 6 after a long, illustrious career. We pay tribute to him in this issue.

As always, it is friends like you who help us sustain our momentum. This issue also includes our annual Donor Honor Roll, which recognizes the men, women and organizations who invest so generously in Salk science. All of us at the Institute are extremely grateful for their confidence in our work. 🏢

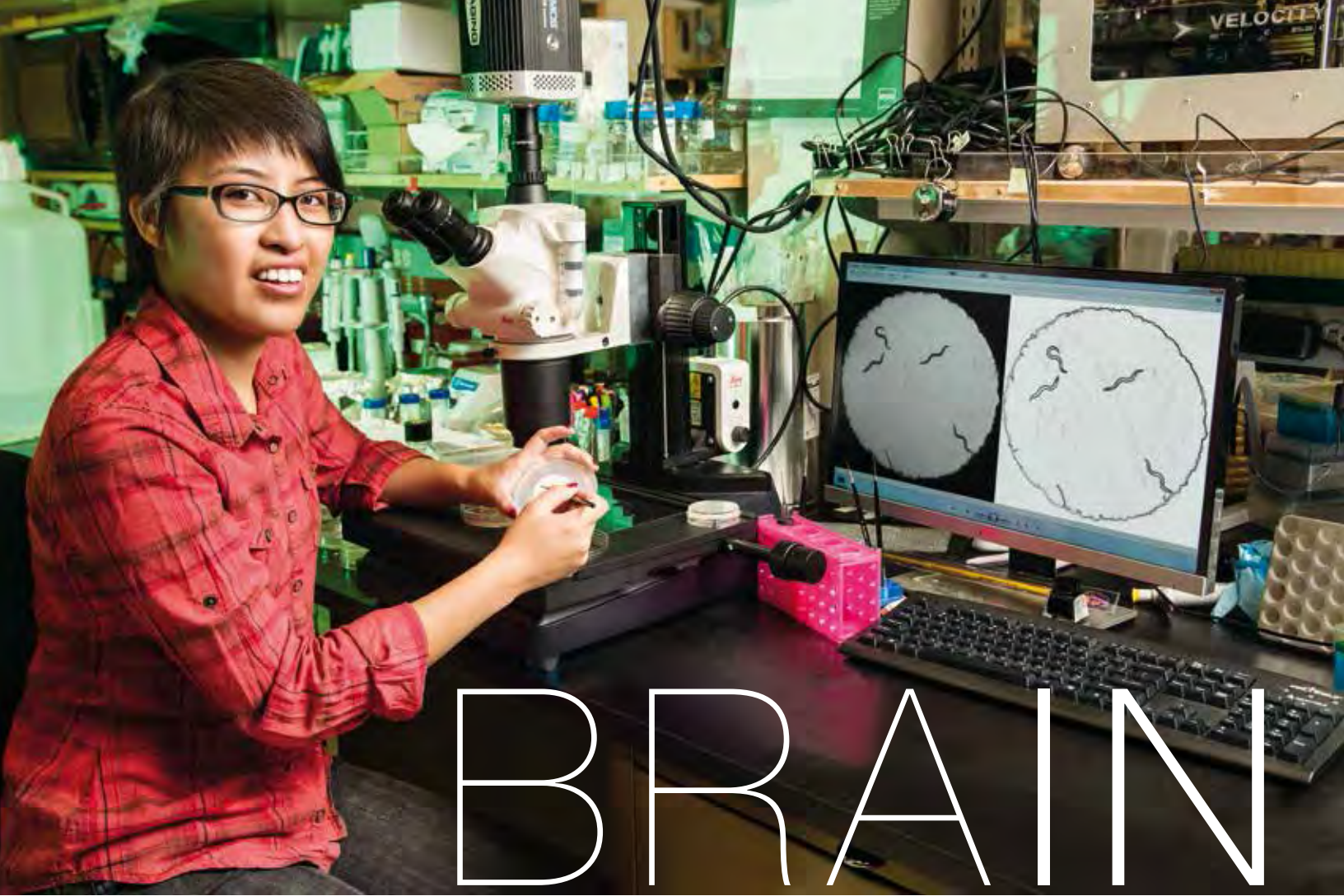
A handwritten signature in black ink that reads "William R. Brody".

William R. Brody, MD, PhD
President, Salk Institute
Irwin Jacobs Presidential Chair



ON THE COVER

This computer-generated image depicts the axons (the outgoing "wires") of two neurons (light gray), communicating with the dendrite (the receiving "wire") of another neuron (blue) using neurotransmitter molecules (yellow). An astrocyte, a cell of another type, wraps its arms (light turquoise) around the neurons. Astrocytes are now thought to play important roles in the formation and maintenance of connections between neurons and are a major area of research at the Salk Institute. The image is based on research by Tom Bartol, Justin Kinney, Dan Keller, Chandra Bajaj, Mary Kennedy, Joel Stiles, Kristen Harris and Terrence Sejnowski.



BRAIN

Kathleen Quach, a graduate student in the Salk laboratory of Sreekanth Chalasani, studies *C. elegans* to learn how its simple nervous system gives rise to complex behaviors.



P. pacificus roundworm (right) biting *C. elegans* roundworm (left)

Always a leader in neuroscience, the Salk Institute is once again at the forefront of a renaissance in brain research, thanks to new talent, big questions and strange allies

GAIN

WATCHING THE TINY WORMS UNDER

Kathleen Quach's microscope glide gracefully around their petri dish, it's hard to imagine their lives are anything but serene. Named in part for their elegant motion—the “elegans” in *C. elegans*—the dozen or so roundworms undulate across a white circle of light, gobbling up *E. coli* bacteria without a care in the world. But life isn't always so carefree for Quach's worms.

“These don't have any predators in with them,” says Quach, pointing to the round dish on the microscope's brightly lit stage. “If a predator worm is nearby, they can back up pretty quickly to get away.”

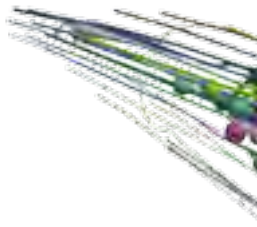
To demonstrate this, Quach, a graduate student in the laboratory of Salk neuroscientist **Sreekanth Chalasani**, goes to a laptop next to

the microscope and pulls up a video she recently shot. In the video, a group of *C. elegans* is joined by a brawnier roundworm, a toothy member of the *P. pacificus* species that proceeds to rush one of the *C. elegans* and nip the smaller worm on its side. Getting the message loud and clear, the *C. elegans* puts itself in reverse, avoiding a fight by wiggling away from the *P. pacificus*.

It's clear from this tempest in a microscopic teapot that roundworms can be both predator and prey. But what's more intriguing are the questions at the center of Quach and Chalasani's research. What, they ask, is the role of aggression and fear in this relationship? How does the roundworm nervous system, one of the simplest in nature, give rise to such behaviors? And what can these tiny creatures tell us about ourselves—about human aggressions and fears,

emotions and behaviors at once necessary for our survival but also sources of great suffering?

In the past, such questions were exceedingly difficult, if not impossible, to answer. But in recent years, neuroscientists have started looking in odd places—Quach and Chalasani's worm brains, for instance—and using unexpected new tools to explain how the human brain works. From studying cells once overlooked as simply “brain glue,” to budding up to rabies virus and pond scum, brain researchers are making rapid progress thanks to unlikely allies. As a result, now perhaps more than ever, Salk scientists exude excitement about the state of neuroscience and their ability to ask big questions—and actually find answers.



TINY CREATURES **BIG IDEAS**

The complexity of the human brain is—pardon the pun—utterly mind blowing. The brain is thought to contain around 86 billion neurons that are wired together to communicate through approximately 100 trillion—yes, trillion—connections called synapses. Each neuron can connect with thousands of other neurons and, to make matters even more complicated, connections are broken and new ones formed constantly.

Given the difficulty of hitting this moving target, one could forgive scientists for just throwing in the towel and seeking a more straightforward pursuit—quantum physics maybe. Fortunately, many have persevered. Over the past century, scientists have made terrific strides in describing the nervous system and explaining how it works, and for the past fifty years the Salk Institute has been in the vanguard of this quest. Beginning with early pioneers—including **Francis Crick**, who turned his focus to the brain after winning the Nobel Prize with James Watson for describing the structure of DNA, and **Sydney Brenner**, who won a Nobel for his work studying neural development in *C. elegans*—Salk scientists have helped lay the groundwork for understanding what makes nervous systems tick in creatures big and small.

Shrek Chalasani decided to go small. Chalasani's studies provide an example of how decades of foundational research on a particular organism—*C. elegans* roundworms in this case—combined with powerful technologies are breathing new life into neuroscience. Seen through the eyes of a scientist, the beauty of *C. elegans* lies in its familiarity. This species of roundworms is one of a handful of creatures dubbed “model organisms,” meaning they have been extensively studied both as the primary representatives of a class of organisms—invertebrates, in the case of *C. elegans*—and as manageable surrogates of more complex organisms.

It was Sydney Brenner who first proposed that the roundworms be used as a model organism in 1963, noting that they are one of the simplest organisms with a nervous system. Since then, the worms have been studied extensively. They were the first multicellular organisms to have their entire genome sequenced, and they are the only creatures whose entire nervous system—302 neurons in total—has been mapped. Charts in hand, Chalasani and his

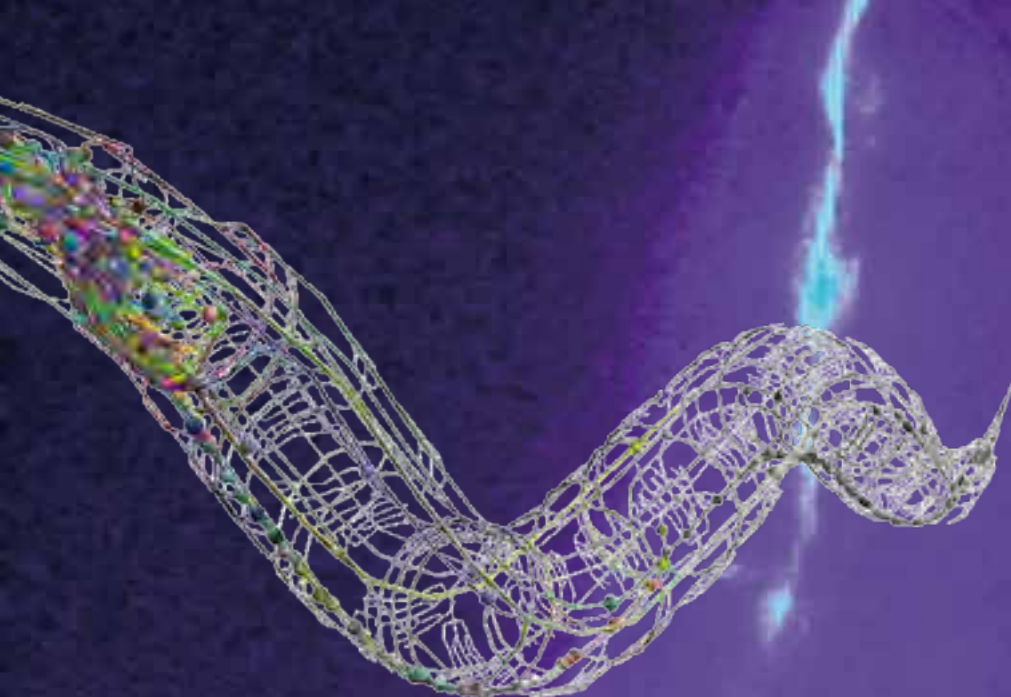
team can now observe exactly what's going on in these compact nervous systems, from the activity of genes to the signals traveling through the worms' neural circuits. For Chalasani, what's most intriguing is how those observations connect with the worms' behavior, particularly in situations where these behaviors align with those of humans and other organisms.

“How do fear, aggression and other behaviors manifest at the very basic level in the nervous system?” asks Chalasani. “Somehow, with just 302 neurons, these worms appear capable of these behaviors—which means they offer an opportunity to map the circuitry of fear and anxiety. Nature likes to repurpose its innovations, so chances are that we're not as different from worms in this respect as we might like to think. What we find in worms will probably tell us a lot about the same behaviors in people.”

At the core of Chalasani's research and that of many of Salk's neuroscience labs, are new technologies that connect the dots between genes, neurons, neural circuits and behaviors. For instance, using genetic engineering, his team was able to breed worms with neurons that glow when calcium levels rise inside the cell, an indication of increased neural activity. This allows the team to observe precisely which neurons light up during a certain behavior. Another technique lets Chalasani turn off genes that code for certain neurotransmitters, molecules that allow neurons to communicate. This helps him and colleagues identify, through a process of elimination, which neurotransmitters stimulate certain behaviors.

“Serotonin is a good example of a neurotransmitter in humans that kicks off a large behavioral change,” Chalasani says. “We know that drugs that increase serotonin levels in our bodies can alleviate anxiety. It's a neurotransmitter found in both worms and humans, so understanding how this system works in the worm might tell us how to better treat anxiety disorders or prevent violent outbursts in soldiers with post-traumatic stress disorder, for example.”

We know exactly how many neurons *C. elegans* possesses and how they connect with one another, but charting the nervous systems of other creatures has proven more challenging. Here too, however, Salk scientists are making rapid progress, thanks to new technologies.



Sreekanth Chalasani

“...understanding how this system works in the worm might tell us how to better treat anxiety disorders or prevent violent outbursts in soldiers with post-traumatic stress disorder, for example.”

—Sreekanth Chalasani

RABIES VIRUS

THE NEUROSCIENTIST'S LITTLE HELPER

At the opposite end of the complexity continuum from *C. elegans*' simple nervous system is the cerebral cortex, the outer layer of the brain of humans and other mammals. It's here that we mammals really shine in terms of neural circuitry and sheer computing power. Each of the two halves of the cortex is divided into four deeply grooved lobes that are subdivided into areas responsible for processing the deluge of information streaming in from our sensory organs. The cortex is also responsible for the higher-level functions that make humans different from roundworms and fruit flies, such as the capacity for language, memory and planning.

A Spaniard named Santiago Ramón y Cajal provided the first glimpses of the astoundingly complex neural architecture of the human cortex more than 100 years ago. Using a technique developed by his contemporary, the Italian scientist Camillo Golgi, he used a silver-based compound to stain individual neurons in slices of brain tissue. This allowed Ramón y Cajal, who'd originally wanted to become an artist before his father pushed him into medicine, to pen beautiful renderings of neurons organized into columns just under the outer surface of the cortex. The drawings illustrated a forest of living circuitry that Ramón y Cajal would call an "impenetrable jungle."

Since he made his observations around the turn of the twentieth century, scientists have been exploring this neural "jungle," hunting for the big game of neuroscience. One of the most sought-after prizes is the "canonical cortical circuit," a pseudo-mythical beast that may only exist in the minds of neuroscientists. The thinking goes that the functional unit of the cortex—its basic hardware, in computer speak—is a circuit composed of about 100,000 neurons, known as the "cortical column." Each of these blocks of cells takes

up a millimeter square under the surface of the cortex and is repeated thousands of times.

"In concept, it's similar to the transistors found in a computer chip," says **John Reynolds**, a professor of neuroscience at Salk who studies how the visual cortex processes information. "The cortical circuit is the basic unit of computation, working in tandem with all the other units to process information, make decisions and produce action and thought."

A "canonical cortical circuit" is an archetype, a theoretical model of real-life cortical circuits. But it's only that, because life is messier than theory. The architecture of the visual cortex, for instance, which is responsible for processing information coming from the eyes, is somewhat different than that of the auditory cortex, responsible for processing data streaming in from our ears. Yet, while different, they are probably riffs on a theme.

"There is a degree of variation in the organization of this circuit across the cortex," Reynolds says, "but based on what we've seen to date, it is a neural circuit motif that is repeated throughout the cortex."

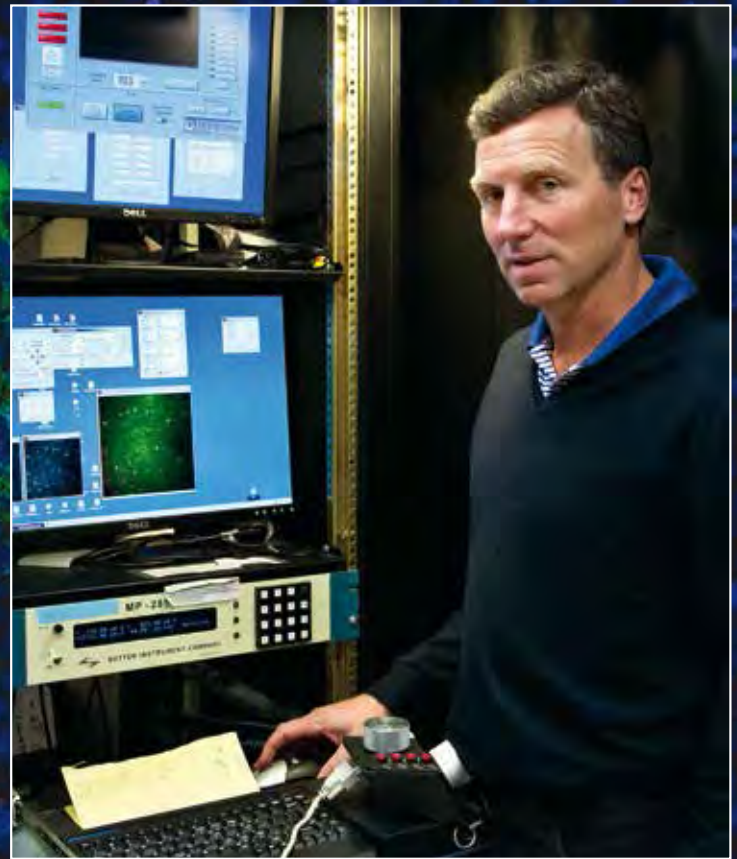
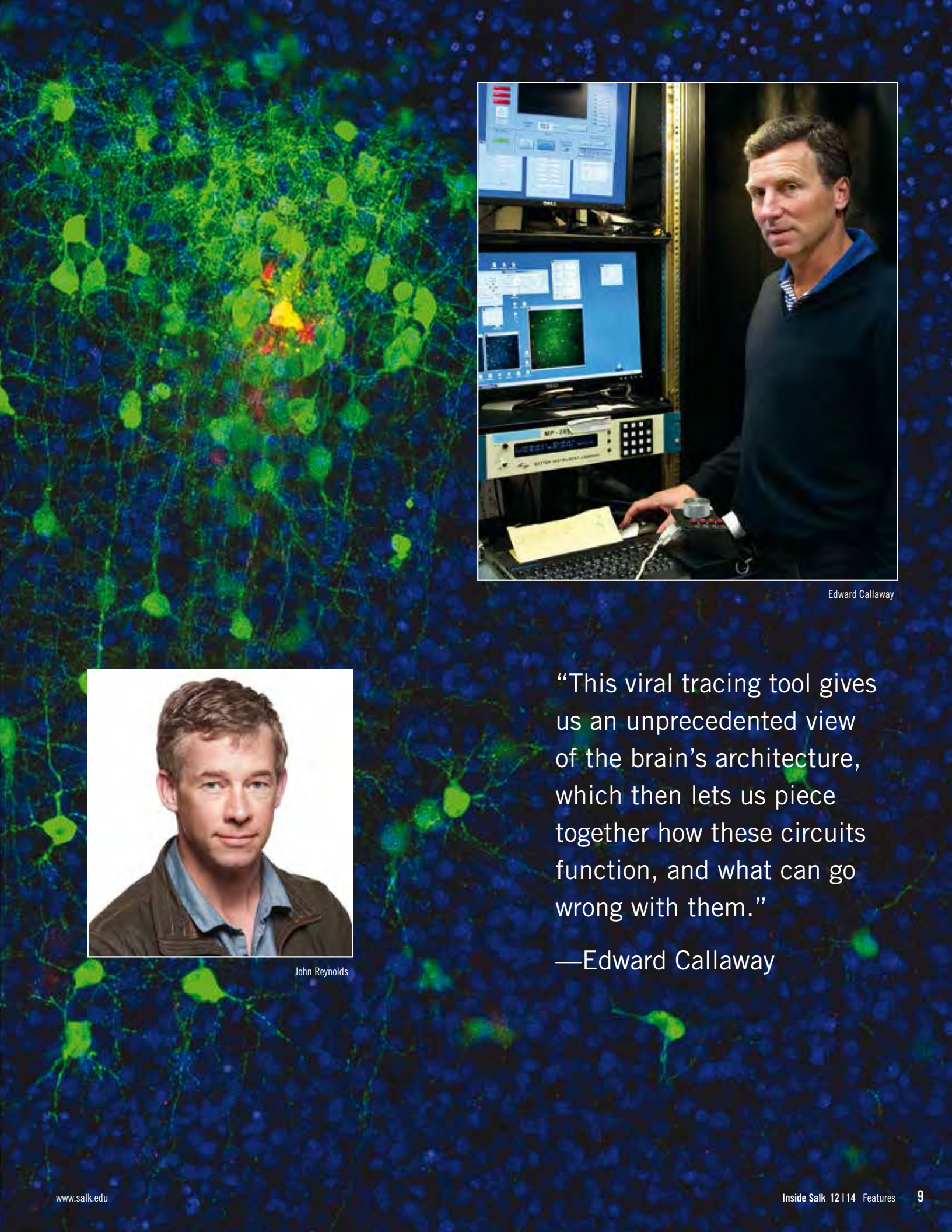
Mapping various real-world examples of these circuits has occupied scientists since Ramón y Cajal first glimpsed them, but the sheer numbers and types of neurons, as well as the difficulty in untangling their webs of connections, has made progress agonizingly slow. Recently, however, neuroscientists have recruited a powerful, if unlikely, ally: the rabies virus. When a rabid animal bites another animal or a human, rabies virus found in the animal's saliva invades nearby nerves in the victim's body, then travels along the fibers of the peripheral nervous system to infiltrate the spinal cord and brain, where it spreads rapidly nerve to nerve, leaving a swath of destruction. The infection leads to terrible symptoms, including anxiety, confusion, paralysis, hallucinations,

agitation and a fear of water. Left untreated, it typically leads to a very unpleasant death within a few weeks.

So where's the silver lining? **Edward Callaway**, a Salk neuroscientist, and **John Young**, a former Salk virologist, wondered whether the virus' remarkable ability to jump between neurons might not be a blessing in disguise. First, the scientists developed a technique for inserting a genetically modified rabies virus into a neuron and allowing the virus to spread only to neurons directly connected to the first infected cell. The researchers combined this with a method of making cells fluoresce under a microscope, so that the original infected cell glows red and the cells it connected to directly glow green. The result was remarkable: like plugging in a Christmas tree for the first time, the branching neurons blazed red and green. The practical application is that scientists can now map brain circuits neuron by neuron, identifying a cell's close connections, then in turn tracing those connections' closest contacts.

Using the technique in mice, Callaway and colleagues have assembled brain-wide maps of neurons that link with the basal ganglia, a region of the brain that is involved in movement and decision-making. Developing a detailed anatomical understanding of this region is important, as it could explain disorders traced to basal ganglia dysfunction, including Parkinson's and Huntington's diseases.

"This was something we've dreamt of having for a long time, and now it's a reality," says Callaway. "Before, we could guess that a cell in a certain position in the cortical column probably connected with certain other cells, but it was really a guess. This viral tracing tool gives us an unprecedented view of the brain's architecture, which then lets us piece together how these circuits function, and what can go wrong with them."



Edward Callaway



John Reynolds

“This viral tracing tool gives us an unprecedented view of the brain’s architecture, which then lets us piece together how these circuits function, and what can go wrong with them.”

—Edward Callaway

THE PERKS OF POND SCUM

If rabies virus seems like a strange bedfellow, another hot technology, dubbed “optogenetics,” owes much to an equally odd contributor—pond scum.

To understand this, recall that electrical signals of a neuron are generated by gates in the neuron’s outer membrane that control whether and how fast the cell fires off electrical impulses. Conveniently enough, similar membrane gates, known as “channelrhodopsins,” are found on the outer surface of a type of pond algae named *Chlamydomonas*. The crucial difference is that the membrane gates of little green pond denizens respond to light, helping the photosynthetic algae swim to a place in the sun.

By inserting the genes from the algae into the neurons of roundworms, fruit flies and mice, scientists were able to generate neurons that incorporated *Chlamydomonas*’ light-sensitive gates into their outer cell membranes. Different colors of lights tell the gates to open or close, allowing researchers to control the activity of the neurons with beams of light.

Whereas Callaway’s viral tracer method helps scientists map neural circuits, optogenetics can tell them what role different neurons play in those circuits. Using beams of light, they turn neurons on or off and see what effect this has on organisms’ nervous systems and behaviors.

A number of Salk labs are now using optogenetics in their research. Callaway and Reynolds, for instance, are using the technology to explore how the brain identifies objects among the clutter of shapes, colors and lines in our visual field. In contrast, their colleagues **Martyn Goulding** and **Samuel Pfaff** use the technology to study motor circuits that connect the brain to the muscles.

“The beauty of optogenetics lies in its speed and specificity,” says Pfaff. “We can modify the activity of neurons almost instantly, which is important because neurons operate on the millisecond timescale. You can perturb the system and immediately see the effect.”

In a recent study, Pfaff used optogenetics to discover neurons, dubbed “synergy encoders,” in the spinal cord that act as middle managers between the brain and muscles. These cells coordinate the many muscles required for walking,

running and other movements, and pinpointing their identity and function is crucial to developing better therapies for diseases and injuries that impair movement.

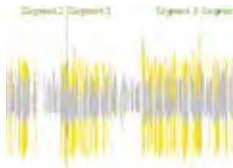
Xin Jin, an assistant professor at Salk, also uses optogenetic techniques to study movement. Jin focuses on a higher center of the nervous system than Pfaff: a region of the brain known as the striatum that serves as a middleman in the flow of information from the brain to the body, linking thought to movement. Imagine, for instance, that you decide to tie your shoe. The nervous system works somewhat like a battleship’s chain of command. The cortex, acting as captain, makes the big picture decision (“tie shoes”) and that order is conveyed to the striatum, the engineering department that manages the sequence of maneuvers: bending down, grabbing the laces, tying the knot. The striatum then tells “synergy encoders” in the spinal cord to orchestrate each of these tasks in the correct order.

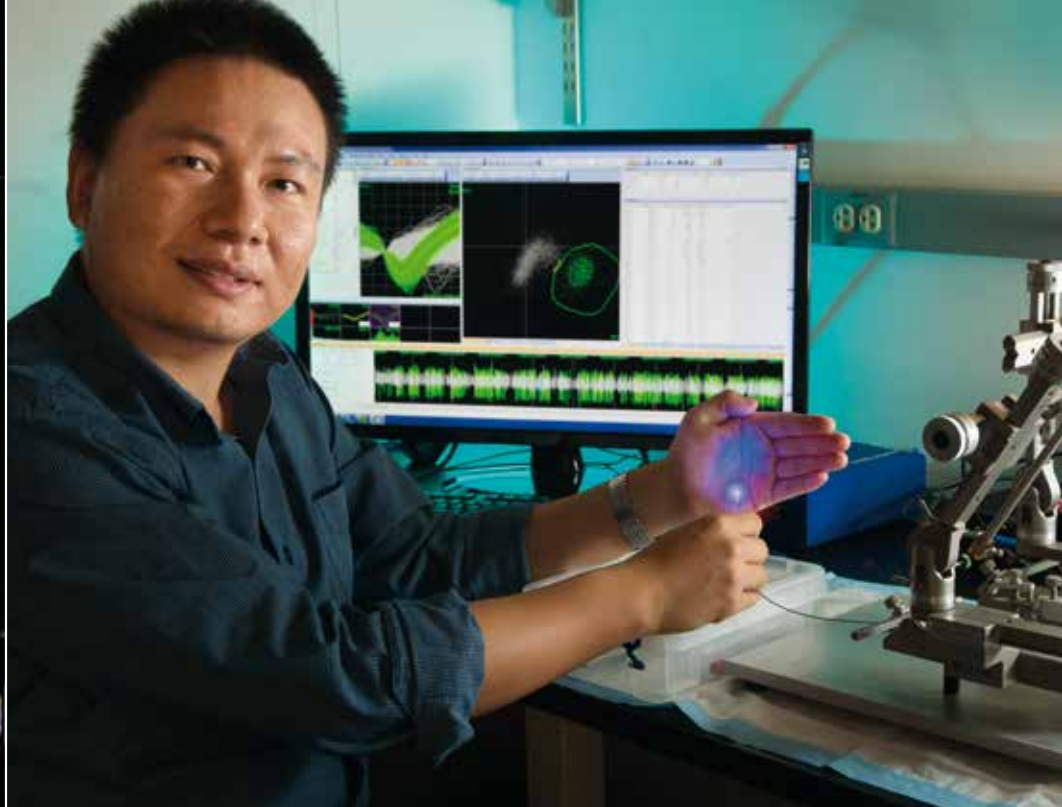
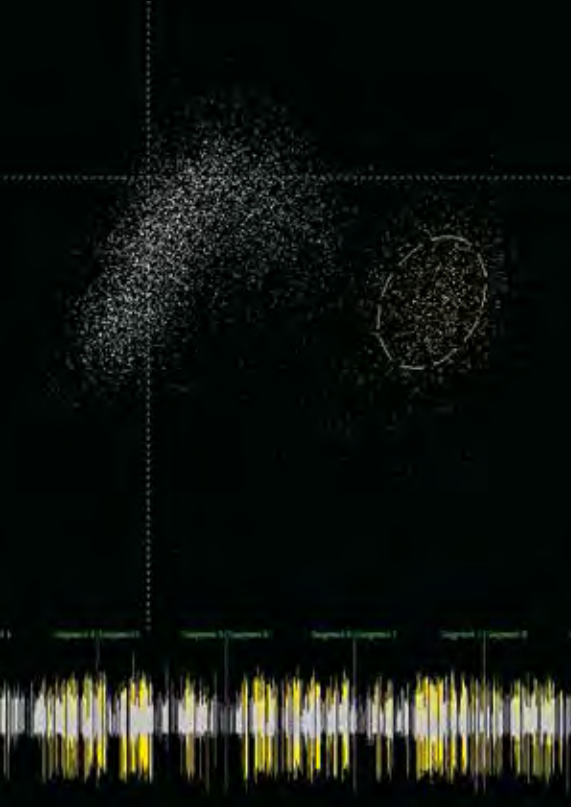
“We want to know how movement is organized, how we drive a car, use a pen or play ping pong,” Jin says. “We’re trying to figure out how these programs are learned and localized in the striatum.”

To study this, Jin’s team created mice with channelrhodopsins incorporated into neurons in the striatum of their brains, then taught the mice to perform complex motor tasks, such as pushing a button a certain number of times. The scientists can then turn different neurons in the striatum on and off to see how this alters the animal’s behavior. For example, turning off certain neurons will cause the mice to forget what they were doing and stop halfway through the task. Turn the neurons back on and the mice go back to pushing buttons.

“This is a part of the brain damaged by neurodegenerative diseases such as Parkinson’s and Huntington’s,” says Jin, “so our hope is that knowing precisely the roles of different kinds of neurons might tell us what’s going on in these diseases.”

The research might also point the way for new therapies for these disorders. “If a disease has damaged one portion of a motor pathway,” Jin says, “you might be able to stimulate neurons further down the circuit, closer to the spinal cord, to initiate sequences of action.”





Xin Jin



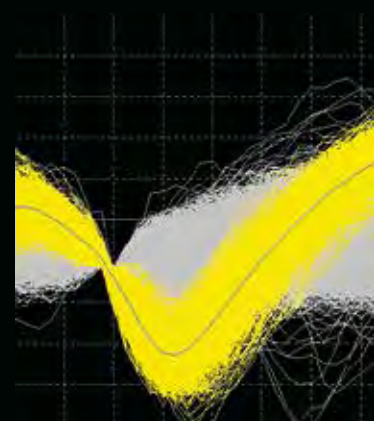
Samuel Pfaff

“If disease has damaged one portion of a motor pathway, you might be able to stimulate neurons further down the circuit, closer to the spinal cord, to initiate sequences of action.”

—Xin Jin



Martyn Goulding



HITTING A MOVING

It wasn't long ago that the adult brain was viewed as a physiologically static organ—as the saying goes, you can't teach an old dog new tricks. In fact, it was only in 1998 that **Fred Gage**, a professor in Salk's Laboratory of Genetics, rocked the neuroscience world by demonstrating that, contrary to existing dogma, stem cells in the adult human brain continue to generate new neurons throughout our lifetimes. Gage's discovery and reams of other research show that throughout our lifetimes our brains actually retain some degree of "plasticity," the general term scientists use to describe the brain's ability to adapt and change.

In another nod to the brain's dynamism, Gage has recently turned to whole-genome sequencing technologies to chip away at another edifice of scientific dogma: that each neuron in a person's brain possesses the same DNA code. In one recent study, Gage and colleagues obtained 100 neurons from three people posthumously. When his team sequenced the genomes of each of the cells, they discovered that as many as 41 percent of neurons had at least one unique, massive deletion or duplication that arose spontaneously, meaning it wasn't passed down from a parent. While it's still too early to say precisely how or why this patchwork of genomic variation arises in the brain, Gage theorizes that this genomic mosaicism might help people adapt to new and unpredicted stimuli encountered over a lifetime or help them cope with unexpected disease by providing flexibility and diversity in defense mechanisms.

Other Salk scientists are attacking another fast-crumbling bit of dogma—that neurons are the only cells important in the brain's vast networks. Roughly half of the cells in the brain are "glia," from the Greek word for "glue," so named because scientists originally saw them as present only to hold other cells in place. It turns out, however, that they play a crucial part in keeping the brain healthy and in managing the trillions of ever-changing synaptic connections between neurons. Instead of playing second fiddle to neurons, they may act more like conductors, coordinating and guiding the brain's symphony of information processing.

Glia serve a number of important roles in the brain. For example, during development astroglia, named for their star-like shape, secrete factors that guide neurons to their proper destinations and allow neurons to make the right connections at the right place. In the adult brain, they shuttle nutrients from the blood vessels to neurons. Another type, oligodendroglia, wrap the axons of neurons in myelin, an insulating material that allows electrical impulses to travel much faster. And microglia act as the watchdogs of the brain, providing the first line of defense against injury or infection and cleaning up dead cells and other waste.

"We know that glia are critical to the brain's health. When something goes wrong with the them, it impacts the neurons and vice versa.



Fred Gage



Nicola Allen



Axel Nimmerjahn

Identifying the Culprit

What can neuroscience tell us about the reliability (or unreliability) of eyewitness testimony in police line-ups? Salk brain researcher **Thomas Albright** recently co-chaired a National Academy of Sciences committee that investigated this very question.

The group proposed best-practices in law enforcement to help address the limits of human vision and memory in eyewitness testimony.



» [View video: www.salk.edu/insidesalk/dec14/eyewitness](http://www.salk.edu/insidesalk/dec14/eyewitness)

TARGET

What we know much less about is what glia do in the healthy brain,” says **Axel Nimmerjahn**, a glia researcher in the Waitt Advanced Biophotonics Center at Salk. A physicist by training, Nimmerjahn develops optical and genetic approaches to study microglia in the brain and miniaturized microscopes to observe how astroglia and neurons interact in the brain during behavior.

Nicola Allen, who joined the Salk faculty just a couple of years ago, focuses on astroglia, which don’t transmit electrical signals of their own, but use chemical signaling to affect nearby neurons. Their “arms,” which project outward from the cells, surround the majority of neuronal synapses.

“I want to know what controls when and where these synapses are formed, and how synaptic connections are modified to allow memories to be stored,” says Allen. “We think astroglia play a crucial role in dictating synapse formation and function via the release of specific proteins that determine the type of synapse that will form and the strength of that connection.”

In previous studies, Allen began to identify the molecular signals between neurons and astroglia and showed that proteins secreted from developing astroglia affect synapse formation. She’s now trying to figure out how these proteins promote connections between neurons, trying to identify other ways astroglia influence synapse formation and maturation. Ultimately, her goal is to understand the role of astroglia in neurodevelopmental disorders—such as autism—that are caused by defects in synapse formation and function. In turn, this will shed light on addressing diseases, such as stroke, by promoting the repair of neural connections following injury.

“This is a terrific time to study the brain,” Allen says. “Technology is really changing how we do neuroscience and the scope of the questions we can ask, and that’s going to help us really make a difference in deciphering how the nervous system operates and how we treat its diseases.” 📺



Terrence Sejnowski

Memory relies on astrocytes, the brain’s lesser known cells

WHEN YOU’RE EXPECTING SOMETHING—LIKE THE MEAL you’ve ordered at a restaurant—or when something captures your interest, unique electrical rhythms sweep through your brain.

These waves are called gamma oscillations and they reflect a symphony of cells—both excitatory and inhibitory—playing together in an orchestrated way. Though their role has been debated, gamma waves have been associated with higher-level brain function, and disturbances in the patterns have been tied to schizophrenia, Alzheimer’s disease, autism, epilepsy and other disorders.

Recently, **Terrence Sejnowski** and his colleagues showed that supportive cells in the brain known as astrocytes may in fact be major players that control these waves. They uncovered an unexpected strategy to turn down gamma oscillations by disabling not neurons but astrocytes—cell types traditionally thought to provide more of a support role in the brain. In the process, the team showed that astrocytes, and the gamma oscillations they help shape, are critical for some forms of memory.

“This is what could be called a smoking gun,” says Sejnowski, head of Salk’s Computational Neurobiology Laboratory and a Howard Hughes Medical Institute investigator. “There are hundreds of papers linking gamma oscillations with attention and memory, but they are all correlational. This is the first time we have been able to do a causal experiment, where we selectively block gamma oscillations and show that it has a highly specific impact on how the brain interacts with the world.”

» **View video:**
www.salk.edu/insidesalk/dec14/sejnowski



ROBERT REDFORD

FILM CELEBRATES **SALK INSTITUTE**

PRODUCED BY



CATHEDRALS OF CULTURE

**A FILM PROJECT IN 3D
ABOUT THE SOUL OF BUILDINGS**

SUNDANCE PRODUCTIONS • RADICALMEDIA • NEUE ROAD MOVIES



WIDELY ACKNOWLEDGED AS ONE OF THE MOST inspirational works of architecture in the world, the Salk Institute was completed in 1965. But did it do what it set out to do? Is it a scientific monastery that nurtures contemplative research? Does it inspire the scientists within its walls to strive to discover the unknown and to solve the seemingly impossible?

That's what director Robert Redford set out to explore when he signed on to participate in a project originated by German filmmaker Wim Wenders called *Cathedrals of Culture*. Wenders challenged himself, Redford and four other directors to each make a short film—not a documentary—revealing the soul of an important building. Could creatively conceived architecture influence both the people within its walls and the work they perform there?

Redford focused on the Salk Institute, the only U.S. building featured in the series of six short films, to answer that question. He began by delving into the relationship between **Jonas Salk**, the scientist, and **Louis Kahn**, the architect who designed the

Institute. He found that the brilliant men, though often differing in their opinions, did manage to create a building that, in Redford's words, "epitomizes a design that understands how dramatically creativity drives discovery."

Upon talking with several of the scientists who work at the Salk Institute, Redford discovered just how much they were influenced on a daily basis by its design. "The connection between them and the building was much deeper than I ever expected," he said in an interview with *Screen*. "I could see that there was an organic relationship: the scientists were part of the building and the building was part of their work."

The six-film *Cathedrals of Culture* series premiered in Berlin earlier this year to critical acclaim. Featured along with the Salk Institute in the series are the Berlin Philharmonic in Germany, the National Library in Russia, Halden Prison in Norway, the Opera House in Norway, and the Centre Pompidou in France. The Salk Institute film premiered in the



Cinematographer Edward Lachman and Director Robert Redford

**“The connection between [the scientists] and the building was much deeper than I ever expected. I could see that there was an organic relationship: the scientists were part of the building and the building was part of their work.”
—Robert Redford**






Redford gives an introduction to the film prior to a private screening at the Salk Institute in June.

United States in October at the Architecture and Design Film Festival in New York. Prior to the New York premier, Redford returned to the Salk Institute in June to share his film, which was shot in 3D and scored by the songwriter and DJ Moby, with a select group of Salk friends and supporters. A panel discussion afterward, led by the film's writer, Anthony Lappé, provided an opportunity for three of the scientists featured in the film—**Tom Albright, Greg Lemke and Clodagh O'Shea**—to talk a little more about what the Institute's architecture means to their work.

"When you walk into the courtyard," Albright explained, "it's as if the curtains are pulled back on the greatest act of nature: the movement of light across the sky and sea. Being surrounded by nature of this magnitude is incredibly compelling. It makes you consider the properties of the world in which we live. And that inspires the work we do here."

Lemke pointed out that the building's open design, one that encourages interaction and collaboration among scientists of varying specialties, was "completely innovative and novel at the time." Now, he noted, it's a model for workspaces all over the world. O'Shea added that it's critical for researchers to "draw on each other's knowledge, to be reminded of the fundamental truths and elements of nature that join all the sciences."

Remarking that the Institute "does feel like a cathedral, a sanctuary apart from market forces," Lappé asked O'Shea if that was important to scientific research. "It's absolutely essential," she replied. "Jonas Salk pursued his dream without any commercial interest or backing. And while it's always hard to take on risky projects like that, you have to persevere. Everything's impossible until it's possible." 



“When you walk into the courtyard, it’s as if the curtains are pulled back on the greatest act of nature: the movement of light across the sky and sea. Being surrounded by nature of this magnitude is incredibly compelling. It makes you consider the properties of the world in which we live. And that inspires the work we do here.”
—Tom Albright



From left: The film’s writer, Anthony Lappé, leads a discussion with three of the scientists featured in the film, Tom Albright, Clodagh O’Shea and Greg Lemke



One on One with...

Robert Redford



Robert Redford and William Brody

When actor, director and producer Robert Redford traveled to La Jolla to share his film honoring the Salk Institute, part of the *Cathedrals of Culture* series headed by German director Wim Wenders, he sat down with Salk President **William Brody** to discuss how art can complement science, and how that seeming incompatibility can lead to surprising discoveries.

How did you come to choose the Salk Institute as the subject of your film?

I think it began with my personal history. I grew up in L.A., surfed off Dana Point. I was around when the Institute was being built. And I have an abiding interest in architecture.

When Wim Wenders called and said, 'I'm picking five people from different countries to each make a 30-minute film about a building that speaks to you,' I immediately thought of the Salk because it tied back to my own history. You see, I had a mild case of polio when I was eleven. I was bedridden for two weeks and I was scared. When the polio vaccine was announced not long after that, it was a huge, huge deal. So choosing the Salk Institute as a building that spoke to me made sense.

What was the next step?

That was deciding how to portray the building. It's very angular, very Euclidean. My ambition was to romanticize the angles, to use 3D and move the camera in a way that softens them.

At the same time, I delved into archival materials to study the relationship between Jonas Salk and Louis Kahn. They were such an interesting pair. I learned that they were very collaborative, sometimes argumentative, but always respectful. They gave to each other. That really underscores Salk's belief that art and science go together. And so the core idea for the film became showing how a spiritual atmosphere is created around a building of science.

Did that play into choosing the soundtrack? I like it, but I was expecting something classical, Beethoven, perhaps. Why Moby?

Because of his abstract approach. There's a spiritual component to his music, yet it's very simple....minimalistic. That's better than something highly orchestrated, I think. The music needed to fit the shape of the building.

It is a beautiful building that visitors come from all over the world to see and yet, they all take the same photo.

Well, it's an iconic photo. You go from structure out across the ocean into space and infinity. You can't get much better than a view into infinity. I remember standing on the beach when I was a kid and looking out across the ocean and thinking how it went all the way to Japan. There was absolutely nothing between me and Japan, and that was so cool.

Many people who come to view this iconic architecture don't know what goes on inside. I think your film personalizes the people inside the building. And that supports one of my objectives: to connect Salk to the broader community.

That's a great objective and I'm happy to help in any way I can. You have no idea how important this project was for me. 🎬







Next generation: Avani Wildani

Lines of code in fuschia, teal and yellow run across a computer screen next to an office window overlooking the ocean at the Salk Institute. Similar colors—glossy teal and purple—streak the brown hair of the young woman who types alternately at a desktop and laptop, both adorned with images of galaxies. Strewn around her desk are tins of tea and half-rolled posters showing illustrations of what look like virtual donuts.

Avani Wildani, a computer scientist in the Computational Neurobiology Laboratory under **Tatyana Sharpee**, is constructing geometric forms from massive amounts of biological data, with the hopes of finding large-scale patterns in nature. By constraining the data in three-dimensional space, representations emerge—shapes like donuts and spheres—that can lead to a better understanding of complex processes.

“I was always interested in what information means for the mind,” says Wildani. “And computer science is the rock I come back to in order to understand that.”

Wildani has juggled interests in biology, computer science and art throughout her life. At age three and under her father’s encouragement, she used the programming language LOGO and an early home computer system, Texas Instruments’ TI99, to program simple lines and shapes. (She still uses a version of that program today to teach basic computer science.) Wildani wanted to be a physician like her father, but she was born with brittle bone disease, a genetic disorder that requires the use of a wheelchair and has resulted in, on occasion, broken fingers from brushing her hair.

Her father realized that the physical demands of medicine wouldn’t be a good fit and steered her toward computer science at a young age.

In grade school, Wildani coded math game programs to help tutor her younger brother (now a medical school student) and her sister (now an artist) and wrote a version of the Paint program on an Apple IIe while in high school. Despite her aptitude in computer science, her interest in biology persisted. But a transformative lecture she attended while a junior in high school planted the seed of more serious interest in computer science.

“The lecturer had some very big questions and he’d get to the answers in just a few steps,” Wildani recalls. “He showed how, given a small, understandable set of commands, he could do pretty much every set of computation there is. That really blew my mind.”

At Harvey Mudd College, she began with a focus on biochemistry and art, but the lecture had made such a deep impression on her she switched to computer science and math at the end of her freshman year.

She started her graduate studies in biological machine learning at the University of New Mexico, where her group correlated massive amounts of data from fMRI studies of schizophrenic patients to reveal four subsets of the disease phenotype (for example, a history of drug abuse in patients resulted in a specific manifestation of schizophrenia). Funding for the project ran out abruptly, so Wildani transferred to the University of California, Santa Cruz to again make a shift: she began to study storage systems, which would later give her a unique perspective on the brain.



In storage systems, Wildani explains, researchers want to increase two abilities: availability—getting the data quickly whenever you want—and reliability—keeping data around when units fail.

“We have a good model for how information should be stored in a large distributed set of computers—how information moves around and is saved even as disks die,” she said. “Since we know how to do this in computers, I started to ask those same questions about the brain.”

It was an unusual idea. Generally, computer scientists try to figure out how principles in biology can help make new computer models, for example, neural networks. But Wildani was interested in also looking in the other direction: asking what computer science can teach

researchers about phrasing biological questions in a different, and potentially helpful, way. While the rest of her classmates went to work for industry jobs in storage, she was drawn to academic research to pursue this and other ideas.

All of her interests—how systems store and process data, biomedicine, machine learning, and even the spatial reasoning in art—culminated in her work at the Salk Institute, where she continues to ask what computer science can teach us about biology and vice versa, particularly in relation to the brain.

“Avani brings a unique and enthusiastic perspective to the field,” says Sharpee, associate professor in Salk’s Computational Neurobiology Laboratory. “Her intelligence and creative synthesis of different facets of computer

science make her well poised to bring a new understanding to biological data.”

In the area of neuroscience, Wildani aims to trace how information moves through the brain. Despite an abundance of experimental biological data, two major challenges emerge: the data tends to be “noisy” (with errors) and also hard to compare, since recording methodologies can vary slightly.

By transforming experimental data into a virtual surface—where each data point is plotted in relation to the other data points in its set—Wildani and other computer scientists are able to minimize noise and get the most out of data that biologists collect.

For example, Wildani is making two sets of maps from vision experiments, tracing the



“This work is a first step toward a better model of object recognition in the brain, which could in turn lead to treatments for visual agnosia, an ailment that prevents stroke victims from being able to recognize objects or faces.” —Avani Wildani

signals from neurons to see which clusters fire in response to different types of images. In one set of maps, she is charting the electrical responses of visual cortex neurons. In the second set, she is charting the stimuli themselves, which consist of nature-based and artificial scenes.

By mapping these sets into shapes, Wildani will be able to compare data within and across experiments to pull out the larger patterns that show how signals are transmitted between single and groups of neurons. “When plotted correctly, connectivity between data points stay the same, allowing us to create shapes that accurately reflect the data when compared across sets,” says Wildani.

A practical application of this work would be to build robots with better machine vision or to develop better treatments for those with vision impairment. “This work is a first step toward a better model of object recognition in the brain, which could in turn lead to treatments for visual agnosia, an ailment that prevents stroke victims from being able to recognize objects or faces,” she says.

The far-out notion of this work would be to reverse-engineer the brain. For example, researchers could establish a crude type of “mind-reading” where, just by looking at the neural spike response, researchers could reconstruct what the stimuli were (e.g., an image of a forest).

The science-fiction concept of deconstructing the brain well enough to transfer consciousness into a virtual reality environment is one idea she enjoys. “It would be so cool if we could ‘upload our brains’ and live entirely in a virtual reality. I would love that,” she says.

Nevertheless, the physical world keeps her busy. A preoccupation with shapes and space diffuse into her hobbies. She uses charcoal and pencils to sketch portraits of family and friends, one way she gives her mind a break. “When I’m drawing, I can relax and zone out on the negative space on the paper. Eventually, a picture comes out of it,” she says.

She is also an avid stargazer, building a telescope from scratch and grinding the mirror herself to get the parabolic shape just right. In addition, she kayaks and enjoys experimenting with classic cocktail recipes (the “Aviation” is her favorite).

Wildani also believes in giving back professionally. She is particularly interested in supporting women in the Science, Technology, Engineering and Mathematics (STEM) fields in two big ways. The first is in her involvement with the Anita Borg Institute’s Grace Hopper conference, an initiative to celebrate women in computer science. She works with the conference to attract younger attendees and to help

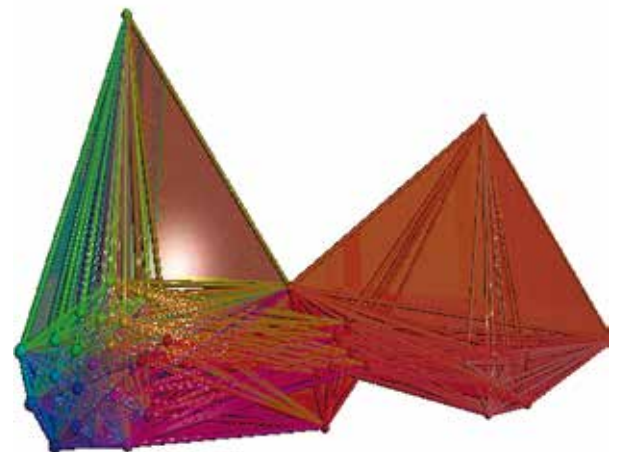
establish early professional support for women starting out in computer science.

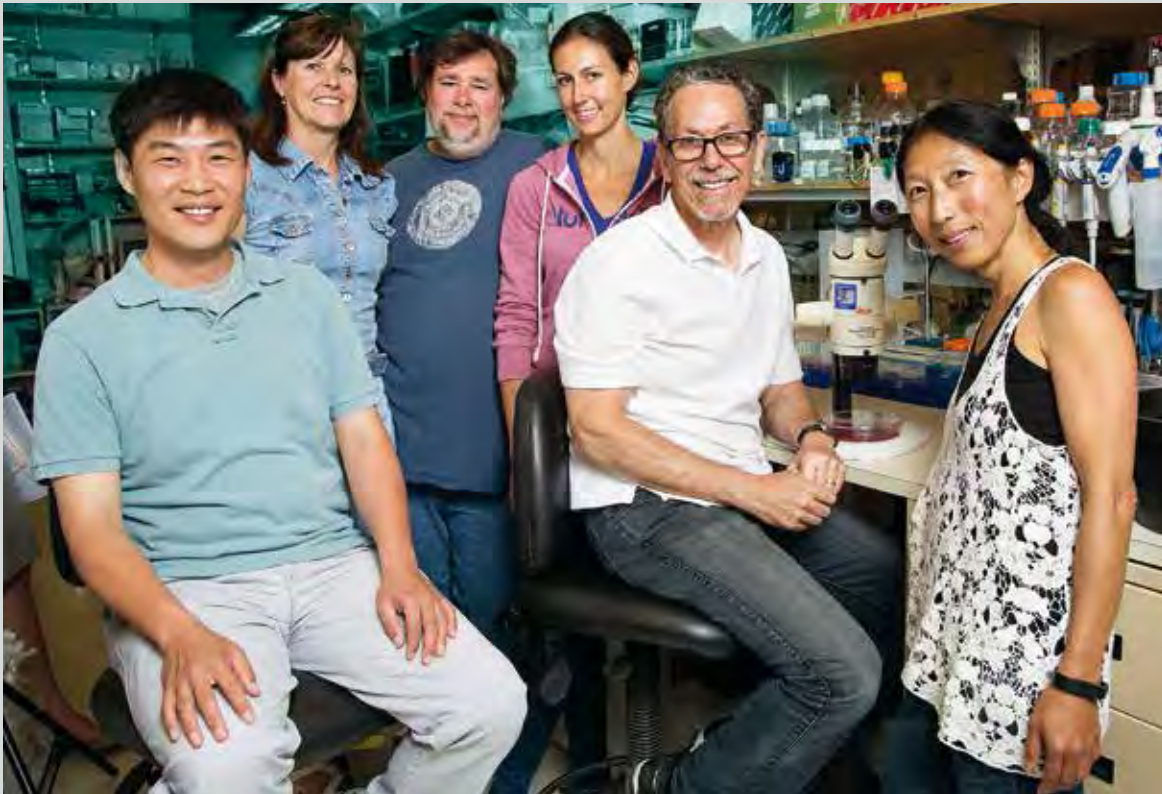
Secondly, Wildani is developing an upcoming website dubbed Project Hypatia, named for the ancient Greek female philosopher and mathematician. The website—open to all genders—will showcase female first-authored papers and encourage multiple reading groups. “By having strong examples to look up to, I hope this site convinces women that they ‘belong’ in the field,” says Wildani. She herself says she has been fortunate to have many female mentors and peers and hopes the website can provide a similarly supportive community.

“It’s important to get young women interested in STEM fields in middle school and high school—that’s a time when we start to lose them,” she says. “But the support needs to continue well into all stages of the career path.”

Wildani has also promoted science to elementary students through the Salk’s Education Outreach program. She was a featured scientist in the program’s SciChat initiative, where researchers give Skype presentations to classrooms throughout San Diego County. For her SciChat, Wildani explained how data from neurons could lead to a way to develop more intuitive robotic vision and answered students’ questions about how objects and animals of all sorts see. Just like the lecture at Harvey Mudd that opened her eyes to the possibilities of computer science, she hopes that promoting science through many different kinds of venues will spark others’ interest.

“I love helping people develop an interest in science and being party to the fascinating questions they come up with,” says Wildani. “I hope to encourage all inquiring minds to tackle problems in the rich boundary between computer science and biology.”





From left: Jae Myoung Suh, Annette Atkins, Michael Downes, Maryam Ahmadian, Ronald Evans and Ruth Yu of the Gene Expression Laboratory

One injection stops diabetes in its tracks

IN MICE WITH DIET-INDUCED DIABETES—the equivalent of type 2 diabetes in humans—a single injection of the protein FGF1 is enough to restore blood sugar levels to a healthy range for more than two days. The discovery, published in the journal *Nature*, could lead to a new generation of safer, more effective diabetes drugs.

The team, led by **Ronald Evans**, found that sustained treatment with the protein doesn't merely keep blood sugar under control, but also reverses insulin insensitivity, the underlying physiological cause of diabetes. Equally exciting, the newly developed treatment doesn't result in side effects common to most current diabetes treatments.

"Controlling glucose is a dominant problem in our society," says Evans, director of Salk's Gene Expression Laboratory and holder of the March of Dimes Chair at Salk. "FGF1 offers a new method to control glucose in a powerful and unexpected way."

Type 2 diabetes, which can be brought on by excess weight and inactivity, has skyrocketed over the past few decades around the world. Almost 30 million Americans are estimated to have the disease, where glucose builds up in the bloodstream because not enough sugar-carrying

insulin is produced or because cells have become insulin-resistant, ignoring signals to absorb sugar. As a chronic disease, diabetes can cause serious health problems and has no specific cure. Rather it is managed—with varying levels of success—through a combination of diet, exercise and pharmaceuticals.

Diabetes drugs currently on the market aim to boost insulin levels and reverse insulin resistance by changing expression levels of genes to lower glucose levels in the blood. But drugs, such as Byetta, which increase the body's production of insulin, can cause glucose levels to dip too low and lead to life-threatening hypoglycemia, as well as other side effects.


In 2012, Evans and his colleagues discovered that a long-ignored growth factor, FGF1, had a hidden function: it helps the body respond to insulin. Unexpectedly, mice lacking FGF1 quickly develop diabetes when placed on a high-fat diet, a finding suggesting that FGF1 played a key role in managing blood glucose levels. This led the researchers to wonder whether providing extra FGF1 to diabetic mice could affect symptoms of the disease.

In the new work, Evans' team injected doses of FGF1 into obese mice with diabetes to assess

the protein's potential impact on metabolism. Researchers were stunned by what happened: with a single dose, blood sugar levels quickly dropped to normal levels in all the diabetic mice.

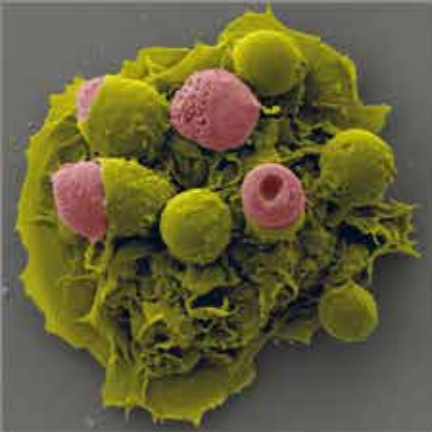
"Many previous studies that injected FGF1 showed no effect on healthy mice," says **Michael Downes**, a senior staff scientist and co-corresponding author of the new work. "However, when we injected it into a diabetic mouse, we saw a dramatic improvement in glucose."

FGF1—even at high doses—did not cause glucose levels to drop to dangerously low levels, a risk factor associated with many glucose-lowering agents. Instead, the injections restored the body's own ability to naturally regulate insulin and blood sugar levels, keeping glucose amounts within a safe range—effectively reversing the core symptoms of diabetes.

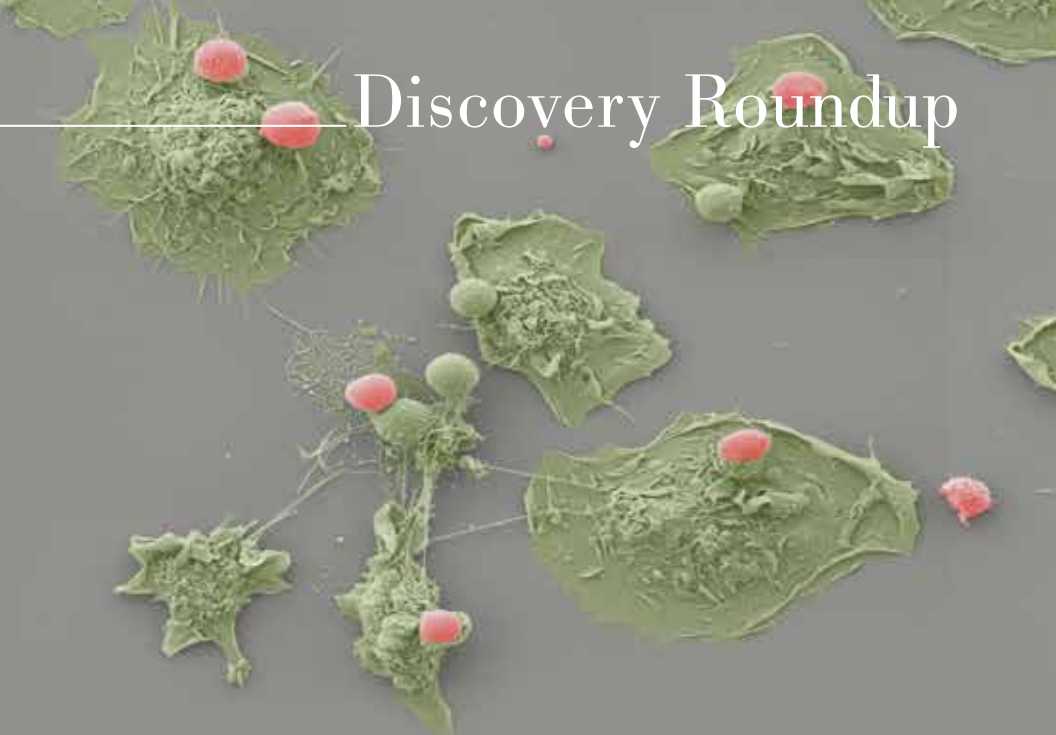
The mechanism of FGF1 still isn't fully understood but Evans' group discovered that the protein's ability to stimulate growth is independent of its effect on glucose, bringing the protein a step closer to therapeutic use. 

» **View video:**
www.salk.edu/insidesalk/dec14/evans

» **View video:**
www.salk.edu/insidesalk/dec14/lemke



In an inflammatory environment (left) and normal environment (right) macrophages (green) engulf dead cells (pink).



Dynamic duo takes out the cellular trash

IN MOST OF THE TISSUES OF THE BODY, SPECIALIZED IMMUNE cells are entrusted with the task of engulfing the billions of dead cells that are generated every day. When these garbage disposals don't do their job, dead cells and their waste products rapidly pile up, destroying healthy tissue and leading to autoimmune diseases such as lupus and rheumatoid arthritis.

Now, Salk scientists have discovered how two critical receptors on these garbage-eating cells identify and engulf dead cells in very different environments, as detailed in the journals *Nature Immunology* and *eLife* this past September.

"To target these receptors as treatments for autoimmune disease and cancer, it's important to know exactly which receptor is doing what. And these discoveries tell us that," says senior author of the work **Greg Lemke**, Salk professor of molecular neurobiology and the holder of Salk's Françoise Gilot-Salk Chair.

The garbage-disposing cells, known as macrophages, have arrays of receptors on their surface, two of which—called Mer and Axl—are responsible for recognizing dead cells in normal environments and inflamed environments, respectively. Mer operates as a "steady-as-she-goes" receptor, clearing out dead cells in healthy tissues on a daily basis. Axl, in contrast, acts as an "all-hands-on-deck" receptor, kicking macrophages into action in inflammatory settings that result from infection or tissue trauma. These inflamed environments have many more dead cells.

"We thought Axl and Mer were doing the same job, and they are: they both recognize a so-called 'eat me' signal displayed on the surface of dead cells. But it turns out that they work in very different settings," says Lemke, whose lab first discovered the two receptors—which, along with a third, make up the TAM family—two decades ago. The receptors have since become a growing focus for cancer and autoimmune research, as well as research in other areas.

In the new work, the researchers found multiple critical differences between Axl and Mer.

"The results were very striking," says **Anna Zagórska**, first author of the *Nature Immunology* paper, which detailed Axl and Mer's two different roles. "In response to many different pro-inflammatory stimuli, Axl was upregulated and Mer was not. In contrast, immunosuppressive

corticosteroids, which are widely used to suppress inflammation in people, upregulated Mer and suppressed Axl."

"Understanding how these two receptors act differently—one during inflammation and one during homeostasis—will allow us to design targeted therapies for a number of autoimmune diseases," says **Erin Lew**, first author of the *eLife* paper, which demonstrated how the two receptors use different molecules—called ligands—to become activated. For both receptors, their ligands must bind to the 'eat me' signal on the surface of dead cells and simultaneously to the receptors to activate the garbage-disposing mechanism of the cell.

The work further details how Axl's ligand, once engaged, is quickly cleaved from the surface of the macrophage. Levels of the free-floating Axl in the blood have turned out to be an accurate, general biomarker for inflammation, quickly showing up in the circulation after tissue trauma or injury.

Next, the researchers are looking into each receptor's activity in more detail. The team is finding that these receptors are unusual in that they have a three-step binding procedure, whereas most cell receptors bind in one step. Exploring and understanding this process will help to lead to more targeted therapeutics for cancers and other diseases in which the receptors are thought to act. [Read more](#)

From left: Greg Lemke, Erin Lew, Anna Zagórska and Paqui Gonzalez of the Molecular Neurobiology Laboratory



Some stem cell methods closer to “gold standard” than others

RESEARCHERS AROUND THE WORLD HAVE TURNED TO STEM CELLS, which have the potential to develop into any cell type in the body, for possible regenerative and disease therapeutics.

Now, for the first time, a team at Salk’s Genomic Analysis Laboratory, along with collaborators from Oregon Health & Science University and the University of California, San Diego, have shown that stem cells created using two different methods are far from identical. The finding could lead to improved avenues for developing stem cell therapies as well as a better understanding of the basic biology of stem cells.

The researchers discovered that stem cells created by moving genetic material from a skin cell into an empty egg cell—rather than coaxing adult cells back into an embryonic state by artificially turning on a small number of genes—more closely resemble human embryonic stem cells, which are considered the gold standard in the field.

“These cells created using eggs’ cytoplasm have fewer reprogramming issues, fewer alterations in gene expression levels and are closer to real embryonic stem cells,” says co-senior author **Joseph Ecker**, co-director of the Center of Excellence for Stem Cell Genomics. The results of the study were published in *Nature*.

Human embryonic stem cells are directly pulled from unused embryos discarded from in-vitro fertilization, but ethical and logistical quandaries have restricted their access. Most commonly, scientists create induced pluripotent stem (iPS) cells by starting with adult cells and adding a mixture of genes that, when expressed, regress the cells to a pluripotent stem-cell state. Researchers can then coax the new stem cells to develop into cells of particular tissues, giving scientists a valuable model for studying human disease in the lab.

Over the past year, a team at OHSU built upon a technique called somatic cell nuclear transfer to transplant the DNA-containing nucleus of a skin cell into an empty human egg, which then naturally matures into a group of stem cells.

Ecker, holder of the Salk International Council Chair in Genetics, teamed up with Shoukhrat Mitalipov, developer of the new technique, and UCSD assistant professor Louise Laurent, to compare the approaches. The team created four lines of nuclear transfer stem cells all using eggs from a single donor, along with seven lines of iPS cells and two lines of



Joseph Ecker, co-director of the Center of Excellence for Stem Cell Genomics

the gold standard, embryonic stem cells. All cell lines had nearly identical DNA content contained within them.

But when they looked closer at the cells, the researchers spotted some differences: the patterns of methylation—chemical flags that are added to genes to control their expression—varied between the cell lines. And when the investigators looked at patterns of actual gene expression—by measuring the levels of particular RNA strands produced by each cell—the differences continued. Once again, nuclear transfer cells had RNA levels closer to embryonic stem cells, making them more accurate for basic research and therapeutic studies.

If researchers can pin down what it is within an egg that drives the production of pluripotent stem cells, they may be able to integrate that knowledge into iPS cell methods to improve stem cell therapy for disease. ■■■

““ These cells created using eggs’ cytoplasm have fewer reprogramming issues, fewer alterations in gene expression levels and are closer to real embryonic stem cells. ”” – JOSEPH ECKER



Focal adhesion complexes (bright green) are typically large and sticky, anchoring a cell into place (left). When the gene DIXDC1 is knocked out, focal adhesion complexes instead become small and numerous, readying cancer cells to move into the bloodstream and become metastatic (right).

New gene discovered that stops the spread of deadly cancer

SCIENTISTS IN REUBEN SHAW'S LAB HAVE IDENTIFIED A GENE responsible for stopping the movement of cancer from the lungs to other parts of the body, indicating a new way to fight one of the world's deadliest cancers.

By identifying the cause of this metastasis—which often happens quickly in lung cancer and results in a bleak survival rate—the researchers are able to explain why some tumors are more prone to spreading than others. The newly discovered pathway, detailed in the journal *Molecular Cell*, may also help scientists understand and treat the spread of melanoma and cervical cancers.

Lung cancer, which also affects nonsmokers, is the leading cause of cancer-related deaths in the country (estimated to be nearly 160,000 this year). The United States spends more than \$12 billion on lung cancer treatments, according to the National Cancer Institute. Nevertheless, the survival rate for lung cancer is dismal: 80 percent of patients die within five years of diagnosis.

“Lung cancer, even when it's discovered early, is often able to metastasize almost immediately and take hold throughout the body,” says Shaw, professor in Salk's Molecular and Cell Biology Laboratory and a Howard Hughes Medical Institute early career scientist. “Now, through this work, we are beginning to understand why some subsets of lung cancer are so invasive.”

To become mobile, cancer cells override cellular machinery that typically keeps cells rooted within their respective locations. Deviously, cancer can switch on and off molecular anchors protruding from the cell membrane (called focal adhesion complexes), allowing cancer cells to begin migration.

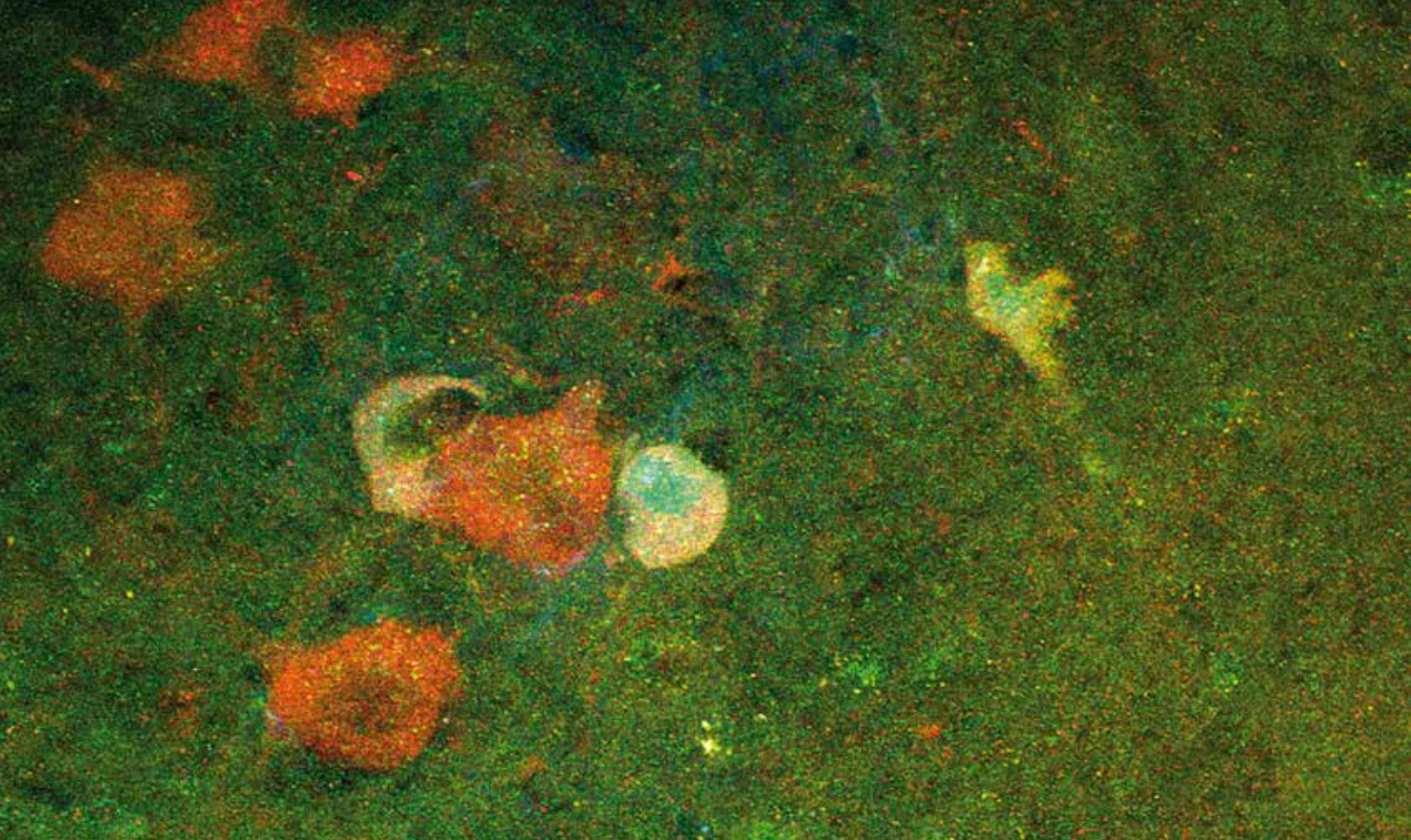
In addition to different cancers being able to manipulate these anchors, it was also known that about a fifth of lung cancer cases are missing an anti-cancer gene called LKB1 (or STK11). Cancers missing LKB1 often spread rapidly through the body. However, no one knew how LKB1 and focal adhesions were connected.

Now, the Salk team has found the connection and a new target for therapy: a little-known gene called DIXDC1. The researchers discovered that DIXDC1 receives instructions from LKB1 to go to focal adhesions and change their size and number. When DIXDC1 is turned on, half a dozen or so focal adhesions grow large and sticky, anchoring cells to their spot. When DIXDC1 is blocked or inactivated, focal adhesions become small and numerous, resulting in hundreds of small “hands” that pull the cell forward in response to extracellular cues, allowing the tumor cells to escape the lungs, survive travel through the bloodstream and dock at organs throughout the body.

Tumors turn off this stay-put signal by either inhibiting DIXDC1 directly or deleting LKB1. The team also found that the addition of DIXDC1 did indeed blunt the ability of cancer cells with low levels of DIXDC1 to be metastatic in vitro and in vivo.

“The good news is that this finding predicts that patients missing either gene should be sensitive to new therapies targeting focal adhesion enzymes, which are currently being tested in early-stage clinical trials,” says Shaw, who is also a member of the Moores Cancer Center and an adjunct professor at the University of California, San Diego. 📺

» [View video: www.salk.edu/insidesalk/dec14/shaw](http://www.salk.edu/insidesalk/dec14/shaw)



The presence of p45 (green staining) and p75 (red staining) indicates that motor neurons increase both p45 and p75 expression after sciatic nerve injury in an animal.

Salk scientists uncover new clues to repairing an injured spinal cord

FROGS, DOGS, WHALES AND SNAILS CAN all do it, but humans and primates can't—regrow nerves after an injury that is. While many animals have this ability, humans don't. But new research from the lab of **Kuo-Fen Lee** suggests that a small molecule may be able to convince damaged nerves to grow and effectively rewire circuits. Such a feat could eventually lead to therapies for the thousands of Americans with severe spinal cord injuries and paralysis.

"This research implies that we might be able to mimic neuronal repair processes that occur naturally in lower animals, which would be very exciting," says Lee. The results were published in *PLOS Biology*.

For a damaged nerve to gain function, its long, signal-transmitting extensions known as axons need to grow and establish new connections to other cells. In a study published last summer in *PLOS ONE*, Lee and his colleagues found that the protein p45 promotes nerve regeneration by preventing the axon sheath (known as myelin) from inhibiting regrowth. However, humans, primates and some other more advanced vertebrates don't have p45.


Instead, the researchers discovered a different protein, p75, which binds to the axon's myelin when nerve damage occurs in these animals. Instead of promoting nerve regeneration, p75 actually halts growth in damaged nerves.

In the new paper, the scientists looked at how two p75 proteins bind together and form a pair that latches onto the inhibitors released from damaged myelin. By studying the configurations of the proteins in solutions using nuclear magnetic resonance (NMR) technology, the researchers found that the growth-promoting p45 could disrupt the p75 pairing.

"For reasons that are not understood, when p45 comes in, it breaks the pair apart," says Lee, holder of the Helen McLoraine Chair in Molecular Neurobiology.

What's more, the p45 protein was able to bind to the specific region in the p75 protein that is critical for the formation of the p75 pair, thus decreasing the amount of p75 pairs that bond to inhibitors released from myelin. With less p75 pairs available to bond to inhibitor signals, axons were able to regrow.

The findings suggest that an agent—either p45 or another disrupting molecule—that can effectively break the p75 pair could offer a possible therapy for spinal cord damage.

One method of therapy could be to introduce more p45 protein to injured neurons, but a smarter tactic might be to introduce a small molecule that jams the link between the two p75 proteins, Lee says. "Such an agent could possibly get through the blood-brain barrier and to the site of spinal cord injuries," he says. The next step will be to see if introducing p45 helps regenerate damaged human nerves. 



Kuo-Fen Lee, professor in Salk's Clayton Foundation Laboratories for Peptide Biology



From left: Xudong Li, Ye Zheng and Yuqiong Liang of Salk's Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis

Genetic signal prevents immune cells from turning against the body

WHEN FACED WITH PATHOGENS, THE IMMUNE SYSTEM SUMMONS

a swarm of cells made up of soldiers and peacekeepers. The peacekeeping cells tell the soldier cells to halt fighting when invaders are cleared. Without this cease-fire signal, the soldiers, known as killer T cells, continue their frenzied attack and turn on the body, causing inflammation and autoimmune disorders such as allergies, asthma, rheumatoid arthritis, multiple sclerosis and type 1 diabetes.

Now, a team led by **Ye Zheng**, has discovered a key control mechanism on the peacekeeping cells that determine if they send a halt signal to the killer T cells. The new research, published in *Cell*, could help develop treatments for autoimmune disorders as well as some types of cancer.

“We discovered a mechanism responsible for stabilizing the cells that maintain immune system balance,” says Zheng, assistant professor and holder of the Hearst Foundation Developmental Chair.

This balance of signaling for the peacekeeping white blood cells—known as regulatory T cells (“Tregs”)—is crucial to normal immune response. Aside from letting killer T cells run rampant, Tregs can conversely send too many cease-fire signals, which causes killer T cells to ignore threatening invasions. For example, some tumors surround themselves with a high density of Tregs transmitting the cease-fire signal to protect themselves from being attacked.

“Tregs are like the surveillance system of the immune response,” says Zheng. “This surveillance system is key to healthy immune reactions, but it can be kicked into overdrive or turned entirely off.”


For about a decade, researchers knew that the key to Tregs’ peacekeeping ability is a gene called *Foxp3*, but they weren’t sure how exactly it worked. Researchers also knew that under certain conditions, Tregs can go rogue: they transform into killer T cells and join in the siege. This change means that they lose the ability to send a ‘halt’ signal and add to inflammation.

In the new paper, Zheng’s lab reports that a particular genetic sequence in *Foxp3* is solely responsible for the stability of a Treg. If they removed the sequence, dubbed CNS2, Tregs became unstable and often morphed into killer T cells—the type of cell they are supposed to be controlling—resulting in autoimmune disease in animal models.

“*Foxp3* safeguards Treg to not become anything else,” says Zheng. “Previously, very little was known on how *Foxp3* did this. We discovered the area of the *Foxp3* gene that determines the stability of Tregs and keeps the immune system balanced.”

Without this specific region in *Foxp3*, Treg cells are much more likely to lose their identity and defect into killer T cells when faced with inflammation and infection, says Zheng.

He adds that recent new drugs on the market or in clinical trials are attempting to disable Tregs in tumors to help the body’s own immune system fight cancer. This new work provides a target for future cancer drugs as well as autoimmune treatments.

“Now we can try to target this region on *Foxp3* to either enhance or reduce the impact of Tregs for treatment of autoimmune disease or cancer, respectively,” Zheng adds. 



In lungs lacking a ‘halt’ signal from regulatory T cells (right), killer T cells and other pathogen fighters accumulate (purple rings) in an excessive immune system response, creating lung inflammation and asthma-like symptoms.

Salk Science Leads to Discoveries

IMPACTING HUMAN HEALTH BEGINS AT THE SALK

Scientific discovery at the Salk Institute is made possible through annual contributions from individuals, organizations, corporations and foundations. Your support will accelerate the pace of breakthroughs in understanding disease and pave the way to new drug therapies. To learn more, please visit www.salk.edu/support or call 858.453.4100 x1405.

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SALKEXCELLERATORS

The Salkexcellerators program is focused on making Salk science accessible to a younger generation of business professionals, entrepreneurs and volunteers. Donors receive *Inside Salk* magazine and invitations to private receptions and lectures with Salk's renowned scientists. Salkexcellerators meet in La Jolla and New York City, and engagement ranges from \$500 to \$5,000.

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President's Club donors fulfill a central role for the Institute and provide the flexibility to respond to Salk's greatest needs. Contributors of \$2,500 – \$25,000 enjoy unique opportunities to interact with our scientists in the lab and receive Salk publications.

CHAIRMAN'S CIRCLE

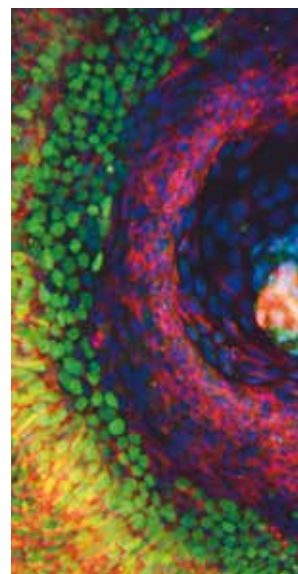
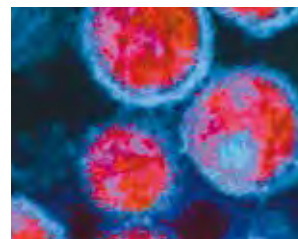
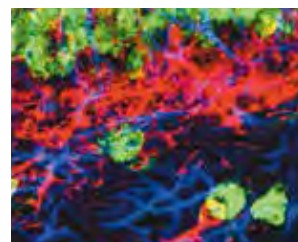
Chairman's Circle visionary donors support the Institute's mission with unrestricted annual gifts of \$25,000 and above. Their generous support fills a vital need for the Institute by providing the world's finest minds in science with the resources to pursue discoveries at the frontier of human knowledge. Donors are invited to exclusive lab tours and special events with senior researchers that provide opportunities to discuss specific areas of interest. Donors receive Salk publications and individual reports on the impact of their gifts.

SPECIAL PROJECTS

If you have a special interest in one of Salk's areas of research, such as cancer, aging, diabetes, neuroscience, genetics, vision or plant biology, you may designate your gift to support investigations in that field. You may also elect to support the work of a young scientist with a fellowship or Salk's education outreach programs. You will be privy to exclusive updates and invitations.

PARTNERS IN RESEARCH

Salk's legacy society, Partners in Research, welcomes those who have included Salk in their estate plans. Charitable gift planning is a powerful way of ensuring your legacy lives on, and it can maximize tax and other financial benefits to you, your family, and the Institute. Partners in Research members receive special communications and are invited to events throughout the year.





Stephen F. Heinemann, pioneering Salk neuroscientist, dies at 75

STEPHEN F. HEINEMANN, WHOSE PIONEERING RESEARCH ON neurotransmitter receptors in the brain helped lay the groundwork for understanding diseases of the brain, died August 6 of complications of kidney failure at Vibra Hospital in San Diego, California. He was 75.

A professor of neuroscience at the Salk Institute, Heinemann focused his research on the molecular mechanisms by which nerve cells communicate with each other at specialized connections known as synapses.

Groundbreaking findings from his laboratory supported the idea that many diseases of the brain result from deficits in communication between nerve cells. He was widely considered one of the world's most accomplished neuroscientists.

"Steve was a giant of twentieth century neuroscience," says **William Brody**, president of the Salk Institute. "His discoveries opened many avenues to better understand the function of the brain and for pursuing new therapies for neurological disorders."

Heinemann was born in Boston on February 11, 1939, to parents Robert B. Heinemann, a secondary school teacher and counselor, and Christel Fuchs Holtzer. He received his first chemistry set from his uncle, Emil Julius Klaus Fuchs, a theoretical physicist who contributed to the development of the atom bomb as part of the Manhattan Project, but later confessed to spying for the Soviet Union.

Heinemann earned a bachelor of science degree from the California Institute of Technology in 1962 and a PhD in biochemistry from Harvard University in 1967. Subsequently, he completed postdoctoral studies at the Massachusetts Institute of Technology and Stanford University School of Medicine.

In 1970, Heinemann was invited to join the core faculty of the Salk Institute, and was among its very first neuroscientists. There, he established the Salk Institute's Molecular Neurobiology Laboratory, a program that by the late 1980s was ranked number one in the world.

Among his many notable achievements, Heinemann and his team identified the genes encoding the major excitatory neurotransmitter receptors in the brain—those that are activated by glutamate and acetylcholine—and figured out how these receptors work.

"His discoveries established the basic molecular rules for how nerve signals are conveyed from one neuron to the next," says **Greg Lemke**, a professor of molecular neuroscience at Salk. "It is difficult to overstate the importance of this science—both for our understanding of how brains process information normally, and for how things can go wrong in neuropsychiatric and neurodegenerative disease."

Heinemann held several patents and was honored by numerous awards in his lifetime. He was a member of the National Academy of Sciences, the National Institute of Medicine, and the American Academy of Arts and Sciences, and was a former President of the Society for Neuroscience. He received the Bristol-Myers Squibb Distinguished Achievement in Neuroscience Research Award and the McKnight Award for Research. In 2010, he was awarded the Julius Axelrod Prize for exceptional achievements in neuropharmacology and exemplary efforts in mentoring young scientists.

He is survived by his wife of 54 years, Ann Reischauer Heinemann; his sons, Nate (Suzi), Danny (Cindy), Quentin (Rachel) and Tad; a daughter, Eden Westgarth (John); sisters Marcia Saunders, Kristel Heinemann, Marianna Holzer and Heidi Holzer; and 12 grandchildren. 🏠🏠

“His discoveries opened avenues to better understand the function of the brain and for pursuing new therapies for neurological disorders.” — WILLIAM BRODY

Charles Stevens receives NSF grant under BRAIN Initiative



CHARLES STEVENS, A PROFESSOR IN THE Salk Institute's Molecular Neurobiology Laboratory, will receive one of 36 Early Concept Grants for Exploratory Research (EAGER) from the National Science Foundation to further research on how complex behaviors emerge from the activity of the brain.

The EAGER program, part of President Obama's \$100 million BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative, aims to uncover how the brain works and potential ways to treat, prevent and cure brain disorders such as Alzheimer's disease, schizophrenia, autism, epilepsy and traumatic injury. The \$300,000 award, announced on August 18, will support short-term, proof-of-concept projects.


"I'm really excited about the opportunity this grant presents because we are exploring a completely new way of looking at how the

brain works," Stevens says. "And if it's correct, it will provide a critical piece of the puzzle."

Stevens will use the funds to investigate the function of the olfactory cortex, hippocampus, cerebellum and basal ganglia, employing a cutting-edge mathematical theory called compressed sensing. He hypothesizes that in these parts of the brain, a critical mass of cells is responsible for representing information. Much like a music or a photo file becomes compressed for storage, neural information is compressed in such a way that only a small portion of the data needs to be readily available for those areas of the brain to function effectively. Stevens speculates that these four regions represent information in similar, but slightly different ways.

At the end of the two-year grant period, he hopes to gain insight into how the brain uses compressed sensing and why. The EAGER



award will also allow Stevens to generate quantitative information, such as the number of cells involved in each area, and other knowledge critical for developing mathematical models of how brain circuits work. 

Tony Hunter receives 2014 Royal Medal in biological sciences

TONY HUNTER HAS BEEN AWARDED THE 2014 Royal Medal for biological sciences by the Royal Society, a fellowship of some of the world's most eminent scientists based in the United Kingdom.

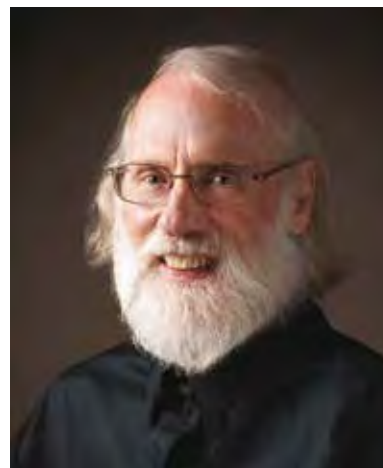
The award recognizes Hunter, director of Salk's NCI-designated Cancer Center, for his significant contributions to the understanding of the chemical signaling that tells cells when to multiply. Signaling networks inside cells are involved in almost every aspect of normal cell development, and mutations that perturb these networks often lead to cancer. Hunter, a fellow of the Royal Society and a member of the National Academy of Sciences, discovered a master "switch" for this growth signaling that ultimately led to the development of a number of new cancer drugs, such as Gleevec for leukemia.


"Tony Hunter's discoveries have changed the landscape for the treatment of cancer and

other related diseases and underscores the importance of basic science," says **William Brody**, president of the Salk Institute. "All of us at the Salk Institute are thrilled that the Royal Society is recognizing Dr. Hunter's groundbreaking discoveries with the award of the Royal Medal."

Each year, the Royal Society, which was founded in 1660 and is the oldest scientific academy in continuous existence, awards three Royal Medals for the most important contributions in the physical, biological and applied sciences.

"I am delighted to have been selected to receive the 2014 Royal Medal of the Royal Society of London, and I am extremely honored to join the scientific luminaries who make up the list of past biological sciences medal winners," says Hunter, who is also an American Cancer Society professor and the holder of Salk's Renato Dulbecco Chair. "It is



a particular pleasure to join my friend and colleague Tim Hunt as a Royal Medal winner, since we worked together as graduate students under Asher Korner in the late 1960s." 

“I am extremely honored to join the scientific luminaries who make up the list of past biological medal winners.”

– TONY HUNTER

Salk scientists receive \$3 million for BRAIN Initiative grant

JOSEPH ECKER, A SALK PROFESSOR AND HOWARD HUGHES MEDICAL Institute investigator, and Margarita Behrens, a Salk staff scientist, have been named recipients in the 2014 round of grants from the National Institutes of Health (NIH) through the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative for leading-edge work in neuroscience. The grant, announced September 30, provides more than \$3 million in funding to the Salk scientists over three years.

The BRAIN Initiative, launched last year, is a Presidential effort to support high-priority research that advances basic neuroscience, with the goal of better understanding the brain, as well as preventing and treating neurological disorders. Four federal agencies—the NIH, National Science Foundation (NSF), Food and Drug Administration (FDA) and Defense Advanced Research Projects Agency (DARPA)—have committed to contributing more than \$100 million in the 2014 fiscal year to support the initiative.

The brain has several cell types, many of which are still not well understood. The new grant will support Ecker and Behrens' labs in constructing a map of the brain that identifies each cell type and how they are connected. In particular, Ecker and Behrens will examine how brain cell formation is influenced by the epigenome, an array of molecules or chemical tags that dot the DNA and regulate the activity of genes. The epigenome, together with the genome, determine the growth and function of all organs, including the brain.



Margarita Behrens and Joseph Ecker

“We are very excited by this additional support from the National Institute of Mental Health to participate in the BRAIN Initiative,” says Ecker, who is also a Gordon and Betty Moore Foundation Investigator and the Salk International Council Chair in Genetics. “We believe our new approach—which utilizes epigenetic differences in brain cell types—will complement existing mapping approaches, ultimately leading to deeper understanding of neurons' identity and functional differences, as well as providing a possible window into brain development and disease.”

Third Salk researcher wins distinguished NIH New Innovator Award



SCIENTISTS AT THE SALK INSTITUTE HAVE scored a rare hat trick with a third assistant professor from the Waitt Advanced Biophotonics Center being named a recipient of the prestigious National Institutes of Health (NIH) Director's New Innovator Award.

Hu Cang will receive the New Innovator Award for 2014, joining the two other Salk researchers who were previous recipients of the prize. The award will provide Cang with \$1.5 million to support his research on cutting-edge microscopy.

The NIH Director's New Innovator Award is a highly selective program with hundreds of researchers from the nation's top scientific institutions competing for the award. Cang, along with a select group of other young investigators, will receive this funding to pursue novel ideas with the potential to have a significant impact on human health.

“We are very proud of Dr. Cang and grateful for NIH's continuing support of young researchers who pursue creative and highly innovative science,” says **William Brody**, president of the Salk Institute. “The ability to see molecular components of cellular structures is crucial to advancing biology and medicine, and his work is expanding the frontiers of microscopy.”

The New Innovator Award will support Cang in his work in developing a “super lens” that sees things far smaller than previously possible. Cang's group has already made a microscope that can focus light down to a smaller point than ever before, letting them track individual proteins on the surface of a cell.

“The fact that three of our junior faculty at the Salk have won this prestigious award speaks to our ability to recruit the very best young scientists and highlights the exceptionally high quality of science that we do here,” says **Martin**



Hetzer, faculty director of the Waitt Advanced Biophotonics Center and holder of Salk's Jesse and Caryl Philips Foundation Chair.

Björn Lillemeier, an assistant professor in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis and **Axel Nimmerjahn**, an assistant professor in the Waitt Advanced Biophotonics Center, received the award in 2012.




Salk scientist receives 2014 Ray Thomas Edwards Foundation Career Development Award

JANELLE AYRES, SALK ASSISTANT PROFESSOR in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis, has been selected to receive the prestigious Ray Thomas Edwards Foundation Career Development Award. Only one three-year grant is conferred annually, aiming to foster the development of a promising early career biomedical researcher in San Diego County and to help him or her make the transition to becoming an independent investigator.

Ayres will receive \$150,000 over three years to support her research into the complex ecosystem of the digestive system. Ayres aims to uncover how the trillions of bacteria in the stomach and

intestines maintain health and wellness, and to better understand, treat and prevent infectious and inflammatory diseases that occur when harmful bacteria take over.

The Ray Thomas Edwards Foundation was established in 1997 to provide financial support for basic research in the biomedical sciences. Funded by an endowment from the late Ray Edwards, the foundation supports a range of programs designed to train and support San Diego's future scientific leaders and provides much-needed resources for young researchers. The foundation has also provided funds to endow the Roger Guillemin and Francis Crick Nobel lecture series at the Salk Institute. 

First appointment in new Salk Fellows Program

THE SALK INSTITUTE HAS LAUNCHED a new initiative called the Salk Fellows Program, which brings scientists from broad disciplines to the Institute to trigger innovation and collaboration.

"Interdisciplinary interactions among the Fellows and faculty will continue to add to our environment of excellence and create future intellectual leaders in the biological sciences," says Salk professor **Inder Verma**, who is, along with professors **Fred Gage** and **Ronald Evans**, currently leading this program.

Most fellows will come directly from a PhD or MD program and have expertise in a wide range of innovative technologies. Their work will have a combination of novelty, originality and risk, factors that often lower the chances of obtaining support through traditional channels. Salk Fellows will be independent group leaders and will be appointed for an initial period of three years, which may be followed by a two-year extension.


Salk's first Fellow in this new program, **Dmitry Lyumkis**, supported by the Helmsley Charitable Trust through the Helmsley Center for Genomic Medicine at Salk, joined the Salk

as a Helmsley-Salk Fellow on July 1 from The Scripps Research Institute.

Lyumkis has made groundbreaking innovations in biological imaging. He uses single-particle cryo-electron microscopy—a cutting-edge technology that enables the visualization of large proteins and protein complexes under near-native conditions—to build three-dimensional models of the imaged objects. The resulting 3D models, which can now be resolved at near-atomic resolution with select specimens, facilitate a better understanding of protein function and sometimes reveal long sought-after clues in structural biology. Last year, the technology unlocked a major clue to an elusive protein on the AIDS virus, helping to pave the way for a potential HIV vaccine.

"At the Salk, I plan to bring this technology to address interesting biological problems



related to cancer and HIV," says Lyumkis. "I am excited to push this technology further in order to address questions that have fundamental relevance in human disease." 

“ Interdisciplinary interactions among the Fellows and faculty will continue to add to our environment of excellence and create future intellectual leaders in the biological sciences. ”

– INDER VERMA

Institute welcomes four new faculty

THE SALK INSTITUTE IS PLEASED TO

welcome a new full professor and three new assistant professors, all exceptional leaders in their respective fields. The new faculty will facilitate innovative and collaborative breakthroughs in understanding human health and disease.

“The Salk Institute’s efforts in groundbreaking and inventive work targeting some of our most pressing research and disease questions will be greatly enhanced by these outstanding researchers,” says Salk President **William Brody**. “We could not be more pleased to welcome such accomplished scientists.”

Alan Saghatelian, whose appointment was announced last fall, joined the Institute on July 1 as a professor in the Clayton Foundation Laboratories for Peptide Biology. Saghatelian’s lab focuses on the biology of metabolites and peptides, two classes of molecules that are extremely important in disease—particularly

diabetes, cancer and autoimmune disease—but are understudied because of technical challenges.

Saghatelian developed new mass spectrometry methods that enable his lab to measure changes in these molecules, which could accelerate the development of novel medicines. Saghatelian plans to integrate these new methods into many areas of research through cross-disciplinary collaborations aimed at discovering new targets for disease therapy. By identifying how key metabolic hormones that control blood glucose levels are processed, for example, Saghatelian and his colleagues developed a drug-like compound that improves blood glucose in mice.

Saghatelian, who comes to the Salk from Harvard University, was previously awarded a Sloan Foundation Fellowship, a Searle Scholars Program Award, a New Innovator Award from the National Institutes of Health and a Burroughs



Wellcome Fund Career Award in Biomedical Sciences. He attended the University of California, Los Angeles for his undergraduate work in chemistry and pursued his graduate degree and postgraduate work at The Scripps Research Institute. [▶](#)

Assistant Professors



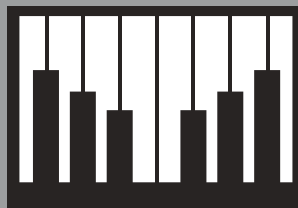
KENTA ASAHINA JOINS THE MOLECULAR Neurobiology Laboratory as an assistant professor. He previously worked with David Anderson at the California Institute of Technology, where he strove to understand the connection between gene functions, the nervous system and social behavior. In particular, his work on aggression in fruit flies with Anderson garnered attention from the *New York Times*. He has won the 2009 BioMed Central Biology Prize and the 2011 JSPS Postdoctoral Fellowship for Research Abroad. At the Salk Institute, he will continue to study the genes and neural pathways that give rise to behaviors, with the hopes of translating findings to therapies for psychiatric disorders. Asahina received his undergraduate degree from the University of Tokyo and his PhD in neurobiology from the Rockefeller University.



DIANA HARGREAVES WILL BE AN ASSISTANT professor in the Cancer Research Center. She is a postdoctoral research fellow in pathology at the Stanford School of Medicine, where she is exploring the tumor suppressor mechanism of several epigenetic regulators recently identified in genome sequencing efforts of primary human tumors. Particularly, she is aiming to uncover how mutations in a complex within a cell’s nucleus contribute to the creation of tumors. At the Institute, she will continue to study the cause and development of human tumors from a biochemical and epigenetic perspective. She is the recipient of fellowships from the National Science Foundation and Helen Hay Whitney Foundation and received her PhD in immunology at Yale University and her undergraduate degree from Haverford College.



SAKET NAVLAKHA IS AN ASSISTANT professor in the Salk Center for Integrative Biology. Navlakha, previously a computer scientist at Carnegie Mellon University, studies “algorithms in nature”—how collections of molecules, cells and organisms communicate, process inputs and coordinate responses to solve problems. He plans to develop collaborations to create biological network analyses that bridge theoretical computer science and systems biology. Navlakha studied as an undergraduate at Simon’s Rock College and Cornell University and received a PhD in computer science focusing on biological networks at the University of Maryland, College Park. In 2013, he received an F32 postdoctoral fellowship award from the NIH.



PLEASE JOIN US AS WE CONTINUE THIS EXCITING JOURNEY INTO OUR SECOND SEASON

SUNDAY, NOVEMBER 2, 2014



ELDAR TRIO

Jazz pianist virtuoso, Eldar Djangirov, returns to San Diego to perform with his Trio

“His command of the instrument is beyond staggering.”

—Bob Doerschuk: *Downbeat Magazine*



TERRENCE SEJNOWSKI

Professor and Laboratory Head, Computational Neurobiology Laboratory

SUNDAY, FEBRUARY 22, 2015



SEAN CHEN

Pianist, 2013 Van Cliburn Crystal Award winner

“Sean Chen has the rare ability to combine poetic musical sensibilities and dazzling technical prowess.”

—Paula Edelstein, *LA Music Examiner*



INDER VERMA

Professor, Laboratory of Genetics

SUNDAY, DECEMBER 7, 2014



RACHEL KUDO & KAREN JOY DAVIS

Duo piano concert, featuring Tchaikovsky's *Nutcracker Suite*

“Kudo is an extraordinary artist who promises to become a legend.” —*El Nuevo Herald*



“Ms. Davis' performance was unique and assured...displayed sparkling brilliance and technical accuracy.” —*The London Times*

TOM ALBRIGHT

Professor and Director, Vision Center Laboratory

SUNDAY, APRIL 26, 2015



CHING-YUN HU

Winner, 2008 Arthur Rubinstein International Piano competition

“Ching-Yun Hu possesses the soul of Chopin.” —*Chopin International Festival, Duzniki-Dzroj, Poland*



JUAN CARLOS IZPISUA BELMONTE

Professor, Gene Expression Laboratory

SUNDAY, JANUARY 25, 2015



GIUSEPPE MENTUCCIA

Winner, 2006 Vittoria Prize from the Accademia Nazionale di Santa Cecilia

“This young pianist has warmth, musical intelligence and an innate electricity.”

—*Talk in New York*



TONY HUNTER

Professor, Molecular and Cell Biology Laboratory

SUNDAY, JUNE 7, 2015



BRUBECK BROTHERS QUARTET

Tribute to Dave Brubeck concert

“Once again the Brubeck Brothers Quartet attains that rarefied level where music is both relaxed and expressive.” —*All About Jazz*



SATCHIN PANDA

Associate Professor, Regulatory Biology Laboratory

TICKETS & INFORMATION:
WWW.SALK.EDU/MUSIC OR 858.453.4100 x2098



From left: James Fitzpatrick and Clodagh O'Shea of the Salk Institute; Alice Ting of the Massachusetts Institute of Technology; Mark Ellisman of the University of California, San Diego; Dan Larson of the National Cancer Institute; Eric Kool of Stanford University; Axel Nimmerjahn of the Salk Institute; Taekjip Ha of the Howard Hughes Medical Institute and the University of Illinois; and Martin Hetzer of the Salk Institute.

Biophotonics symposium makes the invisible visible

ON SEPTEMBER 26, SALK COLLABORATORS and other preeminent scientists gathered for the third annual biophotonics symposium, “Fluorescence and Beyond: Illuminating the Dark World,” presented by Salk’s Waitt Advanced Biophotonics Center to share innovative approaches to biological imaging.

The field of biophotonics isn’t just about making pretty pictures. By pushing the limits of imaging, scientists are able to reveal much about fundamental processes that still elude us. Researchers use cutting-edge imaging techniques to unveil these processes—such as how DNA is packaged or how critical cell receptors function on immune cells—to understand more about diseases like cancer, autism or Alzheimer’s.

Salk researchers—including **Clodagh O’Shea**, **Krishnan Padmanabhan**, **J. Tiago Gonçalves** and **Ying Hu**—discussed how to map, visualize and better understand everything from DNA and the olfactory system to neurons and immune cells. Other speakers included Mark Ellisman of the University of California, San Diego, Alice Ting of MIT, Eric Kool of Stanford University, Luke Lavis of Janelia Farm Research Campus, Taekjip Ha of the University of Illinois at Urbana-Champaign and Daniel Larson of the National Cancer Institute.

The symposium was organized by Salk’s Waitt Advanced Biophotonics Center—particularly **Martin Hetzer**, faculty director; **Axel Nimmerjahn**, assistant professor; and **James Fitzpatrick**, core director. The day was

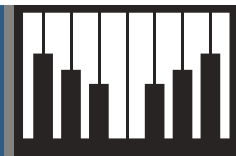
underwritten by the Waitt Foundation and sponsored by Zeiss, Olympus, Leica Microsystems, Nikon, Newport, Spectra-Physics, Coherent, Marine Reef International and Bitplane. [▶▶▶](#)



Mark Ellisman



SALK
SCIENCE &
MUSIC
SERIES



JAZZ PIANIST VIRTUOSO ELДАР DJANGIROV PERFORMED with his trio on November 2 for the first of six concerts in the **Salk Science & Music Series**. This is the second season of the music series, which features performances by some of the hottest established and emerging classical and jazz musicians, as well as riveting talks on the latest scientific discoveries by the Institute’s world-renowned scientists.

Tickets for future Science & Music Series concerts are available at www.salk.edu/music



Jennifer Saga and Martin Smith



From left: Karen Fredrich, Anthony Imbimbo and Shelley Petraglia

San Diego Salkexcellerators cap off year with lecture on new findings that will aid in stem cell therapies

A GROUP OF 60 SAN DIEGO SALKEXCELLERATORS GATHERED at the Salk Institute on May 29 for a private reception and scientific presentation given by **Chris Kintner**, professor in the Molecular Neurobiology Laboratory and holder of Salk's Rita and Richard Atkinson Chair. Kintner discussed research in cilia, the tiny hair-like structures that move fluids through the lungs and brain and have many implications for human health. He also shared some of the discoveries his lab made that will aid in the development of stem cell therapies.

William Brody, president of the Salk Institute, provided an introduction to Kintner's talk and spoke of the rising cost of health care in the United States. Brody, who has written and spoken extensively about health care reform, is a national figure in encouraging innovation and the strengthening of the country's economy through investments in basic research and education.

At the start of the evening, **Rebecca Newman**, Salk's vice president of External Relations, welcomed attendees with an announcement that as of May, the group had raised \$70,000 toward the annual Salkexcellerators

fellowship. Each year, Salkexcellerators award a fellowship to support a Salk postdoctoral researcher.

Salkexcellerators come from various professional industries ranging from biotechnology and engineering to legal and financial. Yet, all have a common interest—supporting science and staying abreast of the latest scientific discoveries. San Diego Salkexcellerators receive invitations to visit the campus throughout the year for lectures, laboratory tours and special events. In March, the group toured the state-of-the-art Waitt Advanced Biophotonics Center with **Axel Nimmerjahn**, holder of the Hearst Foundation Developmental Chair.

For more information about Salkexcellerators, visit www.salk.edu/salkexcellerators or contact **Megan Shockro** at mshockro@salk.edu or (858) 453-4100 x1405. 📄 📱

» **View video:**
www.salk.edu/insidesalk/dec14/excellerators



From left: Mike Doiron, Devra Doiron, George Katakaidis and Mary Katakaidis



From left: John Rikkers and Dan Meador

Salk's New York supporters gather to learn more about the latest discoveries in aging

IN EARLY NOVEMBER, SALK

supporters in the New York area gathered to hear **Martin Hetzer**, professor and holder of Salk's Jesse and Caryl Phillips Foundation Chair. Hetzer, who is director of the Salk Waitt Advanced Biophotonics Center and co-director of the Glenn Center for Aging Research, gave a presentation titled "What Makes the Brain Age?"

Hetzer and his staff in the Molecular and Cell Biology Laboratory are working to unravel the mysteries of aging and related diseases, such as Alzheimer's and Parkinson's. To do this, they home in on the activity of cells and proteins,

particularly on structures that decode the genome. "Our laboratory is focusing on deciphering the structural and molecular organization of the nucleus and the nuclear genome under various developmental and pathological conditions," says Hetzer.

One focus of Hetzer's work is the cell nucleus, where channels and structures can go awry and cause problems in genetic coding, which then lead to disease. For example, he is investigating whether the deterioration of a structure called the nuclear pore complex might initiate or contribute to the onset of certain neurodegenerative diseases,

like Parkinson's. Once scientists have a complete understanding of how some people maintain normal function and ward off disease, Hetzer hopes to bolster genetic and epigenetic mechanisms that protect people as they age.

Salk representatives visit with President's Club, Salkexcellerators, alumni and Friends of Salk in New York City each spring and fall. For more information on Salk programs in Manhattan, please contact **Megan Shockro** at mshockro@salk.edu or (858) 453-4100 x1405. 📞

“Our laboratory is focusing on deciphering the structural and molecular organization of the nucleus and the nuclear genome under various developmental and pathological conditions.” — MARTIN HETZER





19th annual Symphony at Salk an evening of magical performances



William Brody and Maestro Thomas Wilkins

OVER 750 MUSIC LOVERS AND FRIENDS OF THE SALK INSTITUTE descended upon the grounds on August 23 for one of summer's premier events, the 19th annual Symphony at Salk. The Institute's largest fundraiser of the year raised \$820,000 to support science research.

Returning for his tenth consecutive year, Maestro Thomas Wilkins led the famed San Diego Symphony for a program that started off with Gioachino Rossini's overture to his opera *La Gazza Ladra*. The highlight of the evening was a surprise performance on the piano by **William Brody**, president of the Salk Institute, who received a standing ovation after a masterful rendition of *Rhapsody in Blue*.

Joining the symphony on stage for the second half of the program was Emmy-, Tony- and Golden Globe-nominated star Matthew Morrison.



Morrison, who stars in the TV show *Glee*, delighted the audience with classics such as “The Lady is a Tramp” and “It Don’t Mean a Thing (If It Ain’t Got That Swing).”

Before the concert, guests were treated to a gourmet dinner in the Institute’s iconic courtyard, prepared by celebrated chef Jeffrey Strauss, owner of the critically acclaimed Pamplemousse Grille. Symphony at Salk was made possible through the generous support of title sponsor Conrad T. Prebys and Debra Turner along with Audrey Geisel, Joan and Irwin Jacobs, Liz Keadle, Martina and Daniel Lewis, Becky and Ralph O’Connor, Pfizer, and Darlene Marcos Shiley. The stellar evening reaffirmed Symphony at Salk as the premier event of the summer in San Diego. 🏙️

» [View a gallery of photos from the event:](http://www.salk.edu/insidesalk/dec14/symphony)
www.salk.edu/insidesalk/dec14/symphony



From left: Geoff Wahl, Barbara Parker, Irwin Jacobs, Joan Jacobs, Iris and Matthew Strauss



From left: Paul Carpenter, Jim Schaeffer, MT Schaeffer, Steve Bartz and Melinda Richter




Back to Basics
LECTURE SERIES at the SALK INSTITUTE



Back to Basics lecture offers a new perspective on diabetes

MORE THAN 100 FRIENDS OF THE SALK INSTITUTE gathered in the Conrad T. Prebys Auditorium on the afternoon of September 23 for the biannual Back to Basics lecture. **Ronald Evans**, a professor in the Gene Expression Laboratory and holder of the March of Dimes Chair in Developmental and Molecular Biology, delivered the talk, which focused on his work with the FGF1 receptor. In research published in the journal *Nature*, Evans' team found that a single injection of the FGF1 protein was enough to restore blood sugar levels in diabetic mice to a healthy range for more than two days. The discovery could lead to a new generation of safer, more effective diabetes drugs.

Evans' talk captivated the audience and sparked a lively Q&A session followed by a reception. 

The next Back to Basics lecture will be held Tuesday, March 10, 2015. For more information, contact **Jennifer Rothrock** at 858.453.4100 x2068, or jrothrock@salk.edu.

» **View the video of the presentation:**
www.salk.edu/insidesalk/dec14/backtobasics





Carol Marchetto and Ursula Bellugi

salk women & science

Where cures begin.

Women & Science lecture gives glimpse of how scientists are using stem cells to model autism spectrum disorder

CAROL MARCHETTO, A SENIOR STAFF scientist in the lab of Salk professor **Fred Gage**, spoke to a group of about 100 business and community leaders at the Salk Institute's Women & Science event on July 23. Marchetto presented her topic, "Using human pluripotent stem cells to model autism spectrum disorders," following an introduction by **Ursula Bellugi**, professor and director of the Laboratory for Cognitive Neuroscience.

Marchetto explained that scientists have long been limited to studying the brains of patients who had passed away, which doesn't let them fully test and observe neurons' behavior. "When you study postmortem samples, you cannot get any functional information," she says.

By using induced pluripotent cells, however, scientists are able to create simplified models of autism spectrum disorder in the lab. To do this, scientists take cells from a living patient (for example, skin cells), and revert or reprogram those cells to become stem cells. These reprogrammed stem cells can then be coaxed to grow into specific tissues, like neurons, that retain the genetic material of the patient.

"Today, pluripotent stem cells allow scientists to capture a patient's individual genome and enable them to model neurological disorders," Marchetto explains. Scientists will be able to use this method to study other diseases, including schizophrenia, Williams syndrome and bipolar disorders.

This year, Salk is proud to announce the launch of the Salk Women & Science Innovation Grant and Special Awards Initiative. These grant awards will provide critical seed funding for high-risk research projects in stages too early to attract traditional funding. The reality is that too many novel ideas do not receive funding because of the level of risk. Innovation grants and special awards, ranging from \$10,000 to \$100,000, will allow for the development of promising ideas so that they can eventually attract larger grants.

We hope that you will partner with Salk Women & Science by making a gift to the Innovation Grant and Special Awards Initiative. For more information about the Salk Women & Science program, contact **Betsy Reis**, director of Donor Relations, at 858.453.4100 x1426 or email breis@salk.edu.

» **View the video:**
www.salk.edu/insidesalk/dec14/marchetto





From understanding the effect of gene knockout in cells to targeting cellular receptors in brain tumors, students of the Salk High School Scholars Program presented their research projects in September at a VIP reception unveiling the exhibition “Genome: Unlocking Life’s Code” at the Reuben H. Fleet Science Center in San Diego’s Balboa Park. The High School Scholars Program brings students from throughout the San Diego area to the Salk Institute every summer to participate in hands-on laboratory experiences under the mentorship of a Salk scientist.



From left to right: Joshua Sohmer of Steele Canyon High, Brandon Cooper of Patrick Henry High, mentor April Goebel, Maegan Ledwith of Chapparral High, Samantha Hartogs of Canyon Crest Academy, Maria Marcelo of King-Chavez Community High, Ellen Potter, director of Education Outreach, and mentor Amy Rommel.



High School Scholars share love of science

WHEN MARIA MARCELO WAS NINE YEARS OLD, HER GRAND-mother died and the doctors didn't know why. In what proved a pivotal moment in her young life, she decided to become informed in order to aid other people who, like her, might feel helpless when family members were facing health crises.

Today, Maria is poised to become the first in her family to graduate from high school and go on to higher education. And when she applies to colleges this year, she'll have a special qualification on her resume: a summer spent in a Salk Institute laboratory through the High School Scholars Program. Maria, whose biology teacher convinced her that she had what it took to succeed in the program, was so motivated that she commuted two hours on public transportation to come to the Salk Institute every day. As a student from a small downtown San Diego high school, she admits that she originally felt like an underdog who didn't belong in the program. But by the end of eight weeks, which included mentoring by **Amy Rommel**, a postdoctoral fellow in the lab of **Inder Verma**, she says, "I learned to love science. I learned that I am strong and smart enough, and I discovered myself as a scientist."

“ I learned to love science. I learned that I am strong and smart enough, and I discovered myself as a scientist. ” – MARIA MARCELO

Maria was one of ten students who presented their research projects to a packed audience in the Trustees' Room on August 14. Each had spent most of the summer working in a Salk lab, under the mentorship of a Salk scientist, and the event was the culmination of their work. Following welcoming remarks by **Ellen Potter**, director of the Salk's Education Outreach program, and **Dona Mapston**, education specialist, the students took turns at the podium, using PowerPoint slides and their own experiences to explain their highly technical research projects to their families, friends, teachers, Salk staff and lab colleagues. For many, the High School Scholars Program was transformative and has sent them down a new educational and career path.

The event was an inspirational reminder that the Salk's mission is as much about motivating and educating future scientists as it is about making the discoveries that will advance human health. 🏗️



Insider's View

William R. Brody, MD, PhD
President, Salk Institute
Irwin Jacobs Presidential Chair

The 'Decade of the Brain' has finally arrived

EVER SINCE I WAS IN MEDICAL SCHOOL (AS MANY DECADES AGO as the number of fingers on one hand, at least), I have been hearing "this is the decade of the brain," meaning that in the next ten years, scientists will unlock the manifold secrets of the brain.

In the late 1950s, the famous mathematician John von Neumann wrote a book *The Computer and the Brain* in which he pointed out that when we don't understand something—in this case the introduction of digital computers—we use a more familiar term by analogy—i.e., the brain—as a way of making the new concept more understandable. Of course, this analogy is laughable given the relative understanding that scientists and engineers have about the brain versus computers.

Think of the 10 to 100 billion neurons (like transistors) with more than many trillions of connections in the human brain and it is hard to wrap your brain (pun intended) around any ability to understand human perception, awareness, memory and more. For many decades, neuroscientists had to concern themselves with inserting a single electrode into the one of 10 billion neurons and recording the electrical activity of that single cell. All the while, they had little or no clue as to what other neurons might be connected to, controlling or communicating with the neuron under observation. Imagine going into Shanghai, with several billion telephone subscribers, and being given access to one telephone, challenged to come up with the complete wiring diagram of the Shanghai telephone system and how it operates!

So what's different about the current decade and the science behind understanding brain function? A whole lot, to be sure. The most amazing discoveries in how the brain operates have been enabled by technologies:

1. Manipulation of the genome: Scientists can now insert specific genes not only into brain cells, but into particular types of brain cells. These 'inserts' can encode for proteins that mimic human diseases like Alzheimer's and Huntington's diseases and many, many more;

2. Observing the activity of hundreds of neurons (and more): The green fluorescent protein, a protein found in jellyfish in the ocean off the coast of San Diego, emits green light whenever a particular neuron in question is active. Thanks to this technology, scientists can observe hundreds (or more) cells;

3. Stimulating nerve cells with light (optogenetics): Using genes that encode for proteins that absorb light and convert light to electrical signals (analogous to the photosensitive pigments found in our retinal cells), it is possible to stimulate one or many nerve cells selectively;

4. Identifying which neurons are connected to a particular nerve cell of interest: Using a technology developed at Salk by **Ed Callaway** and **John Young**, the rabies virus can be used (safely I might add) to outline which neurons are connecting to a specific neuron of interest;

5. Pluripotent stem cells used to study human neurons: The generation of pluripotent stem cells from patients with neuropsychiatric diseases allows scientists to study brain cells in the laboratory. This is a vehicle to better understand abnormalities in neuronal function;

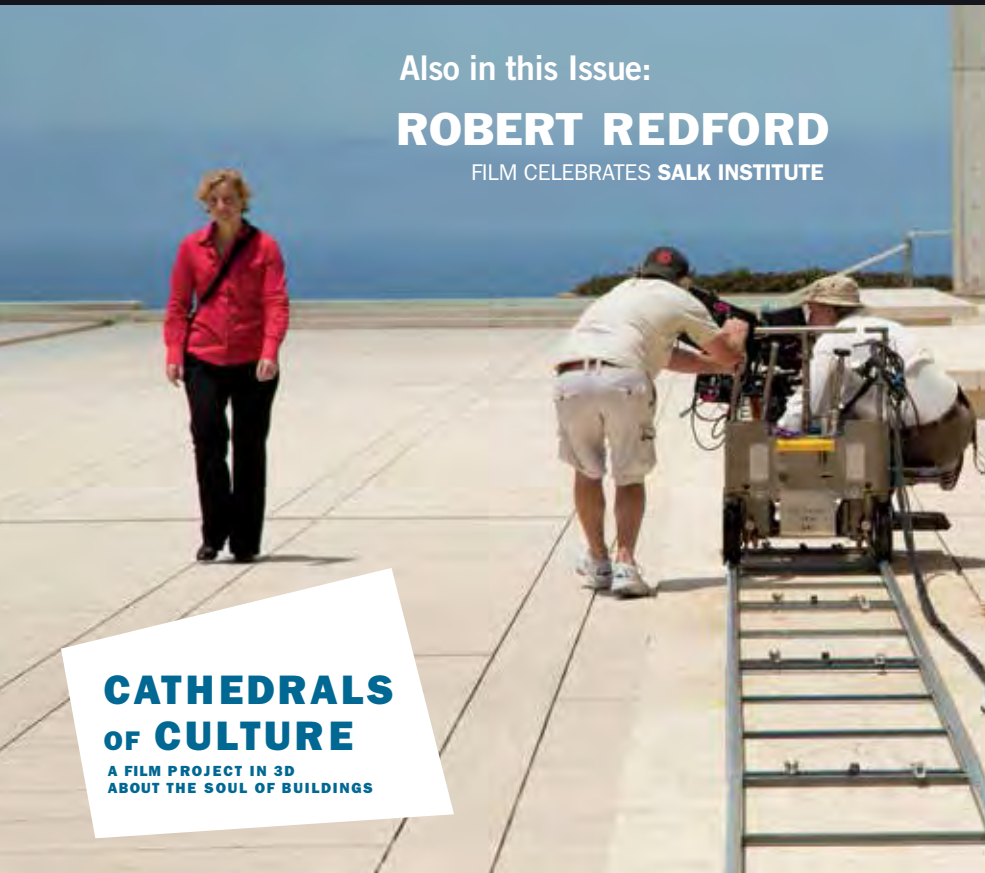
6. Advanced microscopy: At the Waitt Advanced Biophotonics Center, Salk scientists are conceiving of powerful new microscopes that provide previously unheard of capability to carry out the actions outlined above.

With these new tools, scientists are pushing back the frontiers of Alzheimer's, brain cancer, stroke, movement disorders (e.g., Parkinson's), and many more areas, as well as increasing our basic understanding of brain function in health and disease. While I can be certain that the complexity of the brain will not be unraveled at Salk or elsewhere in the next ten years, I am also highly optimistic that the discoveries of the next decade will move the field of neuroscience forward farther and faster than perhaps in the previous 200 years.

It is truly a time of great renaissance for the study of the brain. 📖 📱

There are many ways to support Salk. For detailed information on opportunities, please email giving@salk.edu or call 858.550.0472

Also in this Issue:
ROBERT REDFORD
FILM CELEBRATES SALK INSTITUTE



**CATHEDRALS
OF CULTURE**

A FILM PROJECT IN 3D
ABOUT THE SOUL OF BUILDINGS



Salk Calendar

JANUARY

- 25 Salk Science & Music Series featuring Giuseppe Mentuccia
- 28 San Diego Salkexcellerators

FEBRUARY

- 22 Salk Science & Music Series featuring Sean Chen

MARCH

- 10 Back to Basics Lecture

APRIL

- 11 Explore Salk open house
- 26 Salk Science & Music Series featuring Ching-Yun Hu

MAY

- 20 San Diego Salkexcellerators

JUNE

- 7 Salk Science & Music Series featuring the Brubeck Brothers Quartet