

# InsideSalk

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# SEEDS OF CHANGE





# August 2015

## Inside Salk



One on one with... Beverly Emerson



Next generation: Laura Tan



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### 3 EXECUTIVE MESSAGE

#### FEATURES

### 4 Seeds of change

### 12 One on one with... Beverly Emerson

### 15 Next generation: Laura Tan

#### DISCOVERY ROUNDUP

### 18 Izpisua Belmonte garners international attention for string of major discoveries

### 20 Immune system-in-a-dish offers hope for "bubble boy" disease

### 21 Food for thought: Master protein enhances learning and memory

### 22 Salk scientists reveal epigenome maps of the human body's major organs

### 23 Vital step in stem cell growth revealed

### 24 Walking on ice takes more than brains

### 25 Brain cells capable of "early-career" switch

### 26 How the brain balances risk-taking and learning

#### INSTITUTE NEWS

### 27 A commanding presence

### 28 Vicki Lundblad elected to National Academy of Sciences Joseph Ecker and Dennis O'Leary elected to American Academy of Arts & Sciences

Ronald Evans receives Frontiers in Science Award

### 29 Pew Charitable Trusts names Nicola Allen a Pew Scholar in the Biomedical Sciences

Joanne Chory elected to American Philosophical Society

Esteemed neuroscientist and entrepreneurial leader  
elected to the Salk Institute Board of Trustees

### 30 Salk recruits human geneticist Graham McVicker

### 31 Community discovers world of science at Explore Salk

### 32 Women & Science: An evening of celebration and education

### 33 Hatch, Chang garner first Women & Science awards Trustee Richard Heyman addresses Salk alumni

### 34 Sibylle Szaggars Redford unveils environmental artwork at Salk

### 35 Back to Basics lecture links neuroscience with architecture

Samuel Pfaff shares exciting new discoveries  
with Salk supporters in New York City

### 36 43rd Annual Tax Seminar for Private Foundations held in May

Inaugural meeting of Salk Institute Council offers  
a new way to engage with the Institute

### 37 Music Series: 2015-16

### 38 INSIDER'S VIEW

#### CALENDAR

Back Cover

# Dear Friends,

WITH CALIFORNIA'S DROUGHT PERPETUALLY IN THE HEADLINES, it's an opportune time to note the advancements made by Salk scientists who specialize in plant biology. The feature story in this issue of *Inside Salk* reveals how teams in the labs of **Joanne Chory** and **Joseph Noel** are identifying some of the tools, such as genetic variations and molecular mechanisms, that plants use to adapt to environmental challenges. Theirs is vitally important work that too often does not receive the spotlight. But a burgeoning global population combined with the disruptive changes to our climate means that such work is critical to human survival.

I might add that one of the oldest trees in the world—a 5,000-year-old specimen that has withstood many droughts, along with pests, disease and erratic changes in climate—continues to survive here in California. It's living—and thriving—proof there is hope for plants and for us.

You'll find that advancements in neuroscience comprise many of our other recent discoveries. **Martyn Goulding** has mapped circuitry in the spinal cord that facilitates balance; **Dennis O'Leary** demonstrated the amazing plasticity of neurons; **Ronald Evans** identified a metabolic protein that impacts both physical and mental activities; and **Sreekanth Chalasani** added to our understanding of how chemical signals influence risk-taking behaviors. **Juan Carlos Izpisua Belmonte**, who earned publication in three top biomedical journals—*Cell*, *Nature* and *Science*—in the space of a few weeks, devised a method to eliminate the transmission of mitochondrial disease and tied the aging process to deterioration of DNA packaging.

Additional recent achievements at Salk include **Inder Verma's** development of an "immune system-in-a-dish" that offers hope for those with blood disorders, and **Kathy Jones'** investigation into a cellular pathway that directs the growth of stem cells, a process that is key to regenerative therapies.



William Brody

The volume and significance of these advancements speak to the level of science taking place here at the Institute. It is work that is recognized beyond our walls, and I'm proud to congratulate **Dennis O'Leary** and **Joseph Ecker** on their election to the American Academy of Arts and Sciences; **Vicki Lundblad** to the National Academy of Sciences; **Joanne Chory** to the American Philosophical Society; and **Nicola Allen** on being named a Pew Scholar. Our investigators strive to be at the very forefront of science and I hope you'll find, as I do, that their stories make for inspiring reading. 📖

*William R. Brody*

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



## ON THE COVER

Regions around the world are experiencing drought and desertification due to climate change. Plant biologists at Salk are discovering ways to help plants—and us humans—adapt to new environmental extremes.

*Plants have adapted to  
Earth's extremes.  
Can they help humans  
adapt to climate change?*

# Seeds of Change

HIGH IN THE WHITE MOUNTAINS OF CALIFORNIA, anchored to a rocky slope by its gnarled roots, is a tree older than Methuselah.

Now knotted and twisted with age, the tree sprouted from seed hundreds of years before the Egyptians built the great pyramids. It was roughly 3,000 years old when Julius Caesar was born and 4,000 years old when Genghis Kahn ruled the Mongol Empire. The ancient arbor, a bristlecone pine, predates its famous California neighbor, "Methuselah," another bristlecone named after the Bible's longest-lived man and once thought to be the oldest tree in the world.

Over its 5,064-year lifespan, the pine has experienced droughts as bad, if not worse, than the one currently parching California and other parts of the American West. It has lived through long snowy winters, insect invasions, lightning storms, raging forest fires, torrential rains—a litany of ordeals. The tree's life is an epic tale, but what can we humans learn from a weathered old tree? Perhaps the most poignant lesson is this: to stay in one place requires remarkable flexibility. To survive is to adapt.

"With our nomadic tendencies, we rely on our mobility for our survival," says **Joanne Chory**, director of Salk's Plant Molecular and Cellular Biology lab. "If our current location gets dicey, we can make tracks for another. For plants, though, location is destiny. Because of this, they have developed a wide range of tools for adjusting to whatever their environment throws at them."

It is these tools, a range of genetic programs, molecular devices and versatile chemistry plants deploy like the blades of a Swiss Army knife, that Chory and other Salk plant biologists are intent on cataloging and describing. In this quest, they are propelled by curiosity, the scientist's driving force. But another powerful motivation is necessity—the need to ensure the longevity of *Homo sapiens*.

Jianyan Huang observes seedlings grown in a high-light chamber. Her research could help develop new high-light tolerant crop varieties.







California's bristlecone pines are some of the oldest trees in the world.

## Crunch Time for Farmers

To understand what's at stake, it helps to consider that the global human population recently topped 7 billion and is expected to reach 10 billion in just 35 years. This population crush equates to crunch time for farmers. More people means surging demand for the myriad of products plants provide, from food on the table to the shirts on our backs. United Nations experts predict that agricultural yield must double in the next two decades to meet the demands for natural resources. And as the pressure on farms constantly increases, weather patterns are increasingly inconstant. Thanks to global climate changes, some regions are experiencing extreme drought and desertification, while others are experiencing violent storms and flooding.

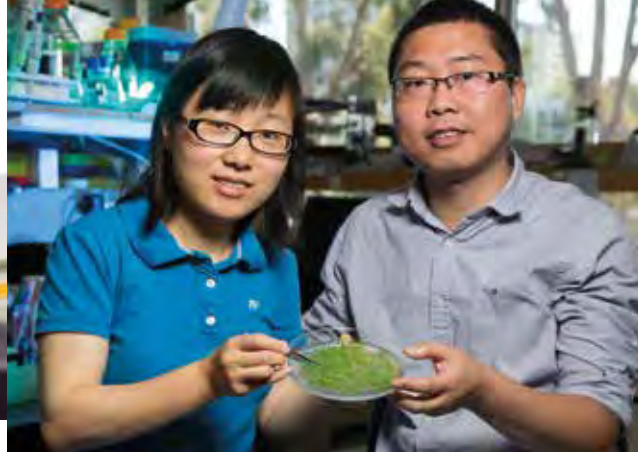
"In California right now, everyone's focused on the drought, and for good reason, but water stress is only one kind of stress plants experience," says Chory, who is also a Howard Hughes Medical Institute Investigator and holder of Salk's Howard H. and Maryam R. Newman Chair in Plant Biology. "These old bristlecone pines, exposed on the side of a mountain, have seen extremes of all sorts—really hot, really cold, lots of water, no water.

"Agricultural crops grow in more moderate conditions," she adds, "but they still have to cope with various kinds of stressors, and farmers have to make sure they plant the right varieties for the climate, or they'll end up with a poor yield or dead crops. With rapid climate change, a great challenge is for our agricultural practices to keep up with environmental extremes."

This is where science can help. One of the great breakthroughs in science was the discovery that when farmers breed for certain desirable characteristics, they are selecting for certain genetic patterns. A recent study published in the journal *Cell*, for instance, identified a specific gene, *COLD1*, that confers cold tolerance to domesticated rice grown in Japan, where temperatures can be too chilly for wild rice species. Finding a gene that helps a plant survive cold stress helps explain what was going on under the hood as farmers drove rice cultivation further north. It might also help in the development of new varieties of cold-tolerant rice or convey cold tolerance to other crops through genetic engineering.

As Chory points out, a single plant can experience a range of extremes over its lifetime, or even over the course of a year. **Joseph Noel**, another Salk plant biologist and longtime collaborator with Chory, notes that there are trade-offs in a plant's ability to tolerate certain types of stress.

"A plant that is highly drought resistant isn't going to grow as well in a rainy year," says Noel, holder of Salk's Arthur and Julie Woodrow Chair and also a Howard Hughes Medical Institute



Jianyan Huang and Xiaobo Zhao explore how plants cope with stress from excess light and heat.

Investigator. "Ideally, a farmer would be able to look at the climate forecast for the upcoming growing season—which have gotten much more accurate—and pick a crop variety that's optimized for the predicted weather. It would work sort of like getting a yearly flu shot, where the vaccines are developed based on informed predictions. It won't work all the time, but on average, you'd come out with better results and more sustainable crop yields."

## Plants, Proteins and Possibilities

In a new line of research, Noel's lab is exploring a related concept: how plants respond to subtle variations in drought. Specifically, he's studying a plant hormone called abscisic acid (ABA) that, among other things, turns on a plant's emergency response program during drought. When the roots sense the soil is drying out, they release ABA, which travels through the stems to the leaves. There, the hormone closes the stomata, the openings in the leaves that exchange oxygen for carbon dioxide. This conserves the plant's water stores, as water vapor can escape from the open stomata. Scientists knew that ABA signaled the stomata to close by flipping molecular switches known as PYR/PYL receptors, 14 varieties of which are found in *Arabidopsis thaliana*, a mustard plant that serves as a model for plants in laboratory research. Initially, scientists thought the interactions seemed to be all-or-nothing in that ABA bound all versions of the receptor, switching them all on when it was present. In recent studies however, Noel's team believes they've uncovered a more complex relationship, one in which alternate forms of the ABA bind some, but not all, of the PYR/PYL receptors, and bind some receptors more tightly than others.

"Looking at this through the lens of evolution and adaptation, it could mean that this gives you a range of different responses to dry soil," says Noel. "We thought the ABA drought response function was an on-off switch, but maybe it's more like a dimmer switch, where you can dial in a precise response to water stress. Back to that idea of precision agriculture: the farmer could pick the appropriate variety of plant based on its ABA profile and match it to climate forecasts."

In another project, **Charisse Crenshaw**, a postdoctoral researcher in Noel's lab, has teamed up with Salk Associate Professor **Tatyana Sharpee**, an expert in computational biology and neuroscience, to study the flexibility of a plant's genome in responding to its environment. Plants have apparently repurposed a few basic protein designs to serve multiple functions, exploiting a biochemical phenomenon called "promiscuity."

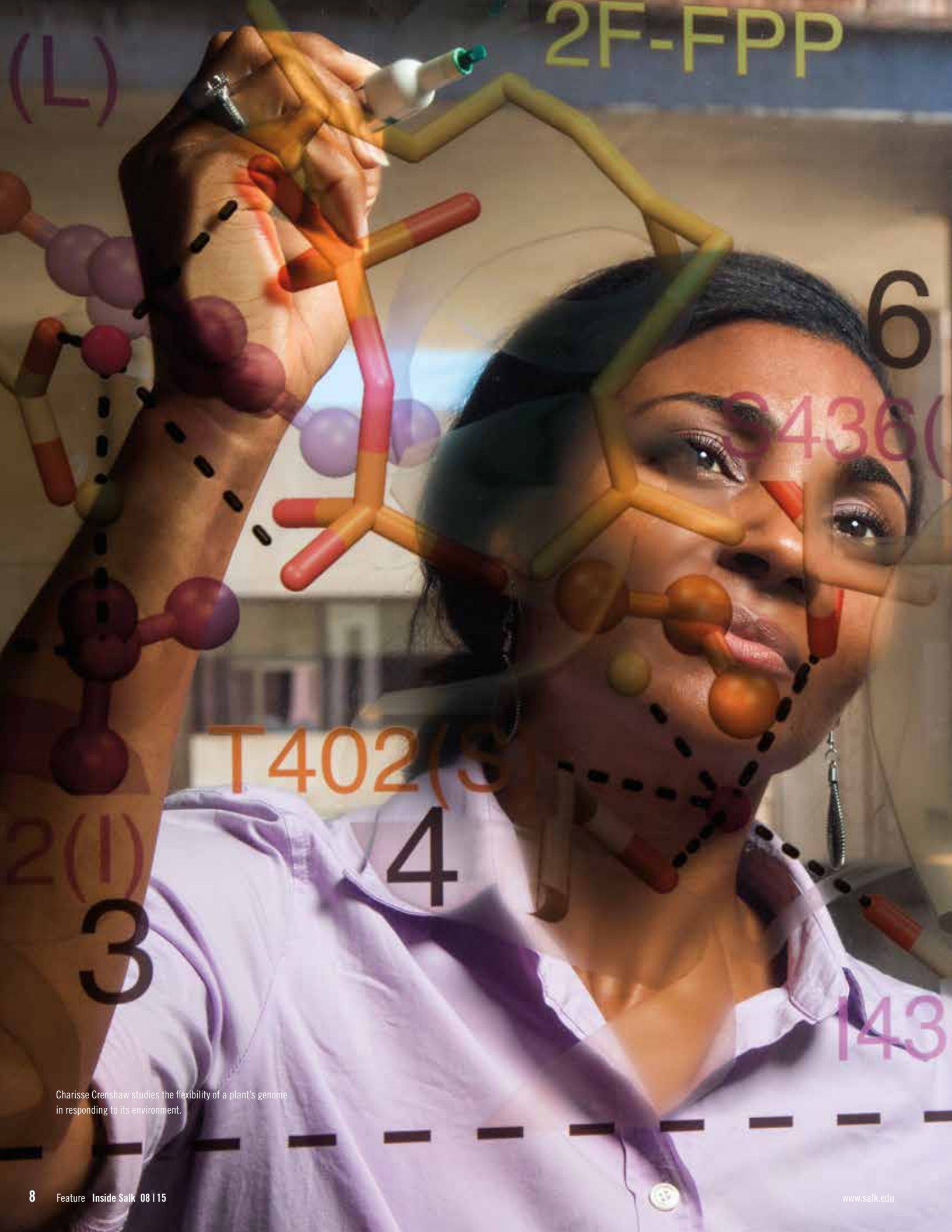
Crenshaw's focus is on the largest class of natural products, called terpenoids, which are responsible for plant defenses and a





Joanne Chory





Charisse Crenshaw studies the flexibility of a plant's genome in responding to its environment.





Joseph Noel



Tatyana Sharpee

number of other functions, including generating aromas that attract bees or deter plant-eating organisms. Oranges, for instance, produce a terpenoid called valencene that smells like...well, oranges. Terpenoids also give mint and lemongrass their distinctive scents. Small changes in the genes responsible for a subclass of terpenoids, known as terpene synthases, allow these enzymes to output diverse chemicals that protect the plant against a range of different foes, including bacteria, fungi and insects. Crenshaw hopes to shed light on the origins, evolutionary history and driving forces responsible for this vast diversification of function.

Crenshaw and Sharpee study a terpene synthase from tobacco called 5-epi-aristolochene synthase (TEAS) that helps generate a natural antibiotic, capsidiol, to protect the plant from mold during wet periods. The plant generates TEAS based on instructions in its DNA, and variations in that gene among different plants result in terpene synthases with different shapes. The plants produce versions of TEAS that best help them defend themselves in their local environment. In other words, plants have learned how to combat antibiotic resistance long before we humans even knew antibiotics existed. In the laboratory, Crenshaw and colleagues generated 500 versions of TEAS by mixing and matching mutations that were identified in nature much like others have identified specific mutations in various human cancers. Tweaking the DNA code altered the sequence of amino acids, which in turn changed the enzyme's properties when the long chain of amino acids folds into a three-dimensional structure. When Crenshaw tested the heat tolerance of the different TEAS mutants the results were surprising.

Working with Sharpee and University of California, San Diego graduate student Jonatan Aljadeff to apply theoretical models borrowed from physics to analyze the data, Crenshaw found that many combinations of the mutations she introduced had modest effects on the thermal stability of the molecules. For instance, most of the proteins were stable up to 40 degrees Celsius (or 104 Fahrenheit), within some range. But this wasn't always the case. Some of her tiny tweaks led to huge shifts in thermal stability, with some of the proteins capable of withstanding temperatures of up to 53 degrees Celsius (127 Fahrenheit).

"Most variations of TEAS have similar characteristics, so it's almost as if there is a mechanism keeping the thermal stability of the protein close to the status quo," she says. "But then you've got these occasional non-linear effects that pop up, where the proteins are stable at temperatures way outside of the norm. So, resilience to even higher temperatures can be accessed through relatively few DNA sequence mutations. And this is possible without plants losing their ability to synthesize critical natural chemicals used for protection and improved growth."

"I'm really interested in exploring what's possible," Crenshaw adds. "The potential in the plant genome to adapt to wide variations in climate is vast. I believe this is the power and promise of understanding plant evolution to help us adapt to changing climates across the globe."

### Some Like it Hot

Crenshaw's quest to plumb the possible is really an extension of something humans have been doing for thousands of years. Because we have always relied on plants for our survival, it's a good bet that we humans have eaten (or gingerly tasted) every plant we've encountered. Many of those we liked, we've modified to our tastes. In the case of the wild cabbage, for instance, humans selecting for different desirable characteristics turned a single species, *Brassica oleracea*, into a smorgasbord of crops that includes broccoli, cauliflower, kale and Brussels sprouts. Corn is another prime example. Corn has long been a food staple in the Mexican culture of the Baja California region near the Salk Institute. The modern corn used by Mexican families to make tortillas and tamales is a far cry from the primitive maize plant, which produced a single, spindly cob covered in tiny kernels. First domesticated 10,000 years ago by ancient farmers, millennia of artificial selection have produced the robust, completely domesticated varieties that produce multiple large cobs per plant—each covered in juicy, pea-sized kernels.

In other cases, plants we use for food didn't need any coaxing to survive—even when we moved into less than hospitable climates. Those Mexican families mentioned earlier also eat wild prickly pear cactus. This thorny emblem of the desert is a great example of a plant that can survive in an extreme environment. In addition to being dry, deserts are also extremely hot and sunny, and as a result cacti and other desert plants are fine-tuned to these conditions. These adaptations are the result of millions of years of natural selection, but what if domesticated crop varieties could be conferred similar properties through traditional breeding or genetic engineering? If so, it might improve crop yield during hot, dry climate swings or allow crops to be introduced to new regions—for example, wheat could be grown in a more arid climate than is now possible. The first step to answering the question is to untangle the molecular pathways and genes that are activated when a plant is stressed by heat and high light—exactly the challenge that Joanne Chory's team is currently tackling.

In the cells of a plant's leaves, organelles known as chloroplasts are responsible for photosynthesis, the conversion of light energy into chemical energy necessary for the plant to survive. The energy captured is used to convert carbon dioxide from the air into high-energy compounds like glucose and starch. One of the byproducts of





*Arabidopsis* seedlings growing in a petri dish.



photosynthesis is oxygen, which is released as a waste product and creates the atmosphere we oxygen-breathing creatures require to roam the Earth.

Because chloroplasts are so essential to a plant's survival, it is critical for a cell to be informed about their functional state and for the cell's nucleus, its control center, to operate in concert with the chloroplasts. The nucleus contains the majority of the plant's DNA, but the chloroplasts also contain a short strand of DNA. Chloroplasts were once independent microorganisms, but somewhere along the line were incorporated into plant cells. Chloroplasts contain about 117 genes, 87 of which are code for proteins involved in directing chloroplast function.

In previous groundbreaking research with *Arabidopsis*, Chory's team discovered how the nucleus and chloroplasts communicate about the production of the photosynthesis machinery. Parts of the system are built in the chloroplast and other parts are built in the nucleus, but the final molecular complexes are assembled in the chloroplasts. They found that signals sent from the chloroplasts to the nucleus helped coordinate this complex process. In another study, Chory and her collaborators identified a gene that is a key player in signaling between the chloroplasts and nucleus. That discovery laid the groundwork for exploring precisely how plants respond to stress, since coordinating cellular responses to protect and repair chloroplasts is critical to a plant's survival. It also suggested an avenue for augmenting a plant's resilience to environmental stressors.

More recently, **Jesse Woodson**, a staff scientist in Chory's lab, has identified a mechanism in plant leaves that tells cells to recycle chloroplasts damaged by extreme heat, light or other stressors. By removing the damaged chloroplasts, this system theoretically prevents the entire cell from dying.

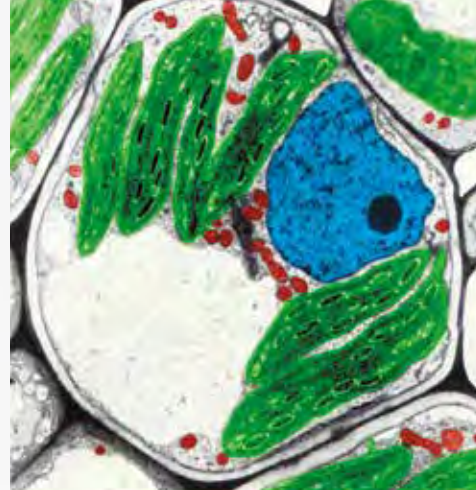
"Maintaining an existing cell takes less energy than generating an entirely new one, so this could be a damage control strategy for plants," says Chory.

In another ongoing line of research, **Xiaobo Zhao**, a postdoctoral researcher in Chory's lab, found that a certain gene mutation made plants more sensitive to heat stress. He is now exploring whether amplifying the expression of the normal form of the gene might make plants more heat resistant. "One goal is to identify the entire pathway by which plants respond to heat stress," Zhao says. "There are general stress mechanisms that are triggered by a number of different stressors, whether it's a cold snap or a hungry insect, but we think we've found a gene that is specifically involved in heat stress. We are also hoping to find ways to control a plant's heat response, so it could grow efficiently in hotter climates, and this gene is a promising lead."

## A Bright Future

On a related front, the Chory lab is searching for a switch that controls plants' response to light intensity that is especially high. Plants have evolved to Earth's particular light cycle and to the light conditions found at the longitude and latitude they call home. Farmers often grow crops that originate in climates that are very different from that of their farms. In places like Australia, Africa, Mexico and the southwestern United States crops have to contend with sunlight that is particularly intense—more intense than many plants need or can withstand.

"When there is more light than the plant needs, the excitation energy exceeds the capacity of the photosynthetic apparatus, which results in a buildup in leaves of reactive oxygen molecules such as hydrogen peroxide," says **Jianyan Huang**, the postdoctoral researcher leading the study. "These molecules trigger a stress response to the high light conditions. If the plant's response isn't adequate, the excess reactive oxygen can damage the plant—for instance, damage to chloroplasts and the loss of chlorophyll results in the leaves turning pale, a phenomenon known as bleaching."



Chloroplasts (green), the living solar panels within a plant cell, can be damaged by extremes of temperature and light.

One way a plant responds to extreme light conditions is to put the brakes on its photosynthesis system. When reactive oxygen molecules start to build up, the plant cells reduce the size of the light-harvesting complex in chloroplasts to relieve the oxidative stress. It's akin to removing the solar panels from your roof on an extremely sunny day to prevent damage to your house's electrical system.

In ongoing experiments, Huang is trying to identify molecules that trigger the high light stress response by activating certain genetic programs in plant cells. She's screening a collection of 2,000 *Arabidopsis* transcription factors, proteins that control which genes are turned on or off. She has identified a number of possible candidates from the collection, and she's currently testing to see whether they are capable of activating genes known to be involved in the high light stress response. Her experiments have turned up some promising results, including identifying several proteins that appear to switch on the high light response. Similar to Zhao's work, her findings could lead to a way to develop agricultural crops that can be farmed in places where high light periods are a threat.

"Our work in *Arabidopsis* and other model organism plants sets the stage for identifying the same genes and molecular pathways in crops," says Chory. She notes, for example, discoveries made in *Arabidopsis* have been instrumental in the development of tomatoes rich in carotenoids, naturally occurring pigments that give vegetables their yellow, orange, and red hues. In addition to providing color, carotenoids such as beta-carotene, lycopene, lutein and zeaxanthin are important dietary nutrients. Another variety of tomato developed separately contains high levels of anthocyanins, plant pigments that are antioxidants and have been shown to extend life in mice with cancer. Tomatoes high in anthocyanins are more purple than red—owing to the bluish color of the anthocyanin molecules.

Scientists in academic institutions and biotech companies are also working to develop drought-tolerant crops, both through traditional crossbreeding and through genetic engineering. For instance, the Drought Tolerant Maize for Africa project has generated 153 new varieties of drought-tolerant maize. In early field trials, these varieties yielded 30 percent more under drought conditions compared to commercially available varieties under normal rainfall conditions. Another project, organized by the African Agricultural Technology Foundation in Nairobi hopes to have a transgenic variety of drought-resistant maize available for African farmers as soon as 2016.

"At Salk, we're not in the business of developing new crops, but we find the genes and pathways that are responsible for the stress response and which can be leveraged to improve agriculture," says Chory. "The more we know about the plants we rely on, the more resilient we humans will be as a species. Change is coming, that much you can be sure of. The big question is how we will respond." ■■■



# One on One with... Beverly Emerson



**E** NORMOUS FOSSILS IN GLASS CASES AND A DUO of plastic dinosaurs adorn biologist Beverly Emerson's study at the Salk Institute. Though the décor may seem unrelated to Emerson's study of processes that underlie cancer, the fossils and dinosaurs have common themes with the deadly disease: evolution and diversity in nature.

Rather than viewing tumors as originating from a single mutated cell that goes awry, Emerson looks at how cancer develops its own diverse "society" (a tumor) that is stubbornly resistant to threats such as chemotherapy.

Emerson came to the Salk Institute in 1987, where she has made seminal discoveries showing how enzymes can remodel chromosomes in normal cells or how this process goes awry to allow cancer to thrive. Her current efforts are focused on combating early cancers (such as breast cancer) and managing the cellular diversity that is required for drug resistance in established tumors. Emerson also has a personal interest in health, particularly around the philosophy of food and self care.

## What was your path to becoming a scientist?

When I was young, I wasn't interested in science. I wanted to be a boxer or an artist. My dad was both, as well as a diesel mechanic, but I never quite grasped how engines worked. Instead, I was my father's sparring partner. Due to Dad's excellent coaching, I retired undefeated at age 8!

After retiring from the ring, I continued my artistic endeavors by painting and wood carving. As an undergraduate at the University of California, San Diego, a class on molecular biology riveted my attention to science, saving me from a career as a mediocre artist. I was struck by the elegance of how genes were regulated and the logic of transcriptional and biological circuitry, like a machine itself. Those concepts have hooked me ever since.

My dad taught his children to be freethinking and not tolerate bullying, while my mom was very optimistic and thought everything was possible. Each parent had a great sense of humor and neither liked hierarchy. I carried these traits into science: follow your own path and don't look for others' approval, as well as a belief that everything will work out, even if there are long downtimes for experiments to succeed.

### Do you feel a connection between art and science?

Every successful scientist I know is also highly creative in an artistic way. The best scientists see not only the importance and significance of what they're doing, but also the beauty of it. It doesn't have to be uncovering a major principle. Just finally understanding a small question or achieving a little yet vexing technical feat has a beauty to it.

People think of science as being very dry, but meticulous and repetitious experiments are the medium scientists have to use: it is their particular paintbrush or musical instrument. When you make a discovery, the beauty of it is thrilling. They call that the "aha" moment, but it's more than that. There's a sense of the aesthetic in one's discovery and in nature.

### Why is cancer so drug resistant?

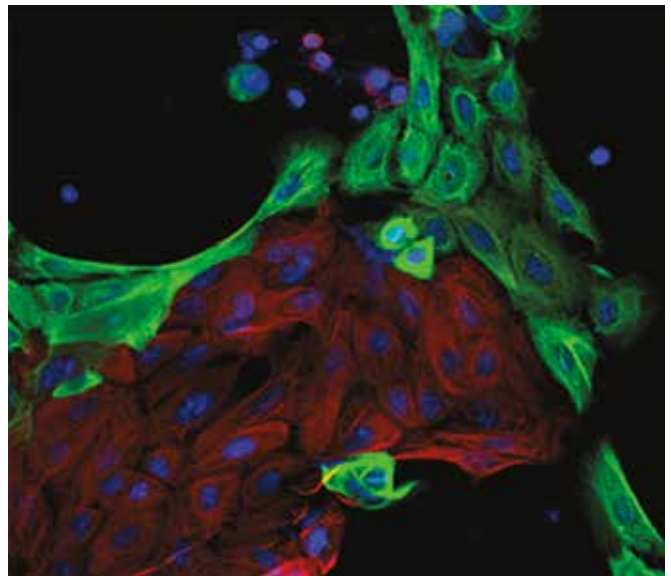
When we keep challenging cells without killing all of them with one chemotherapy drug, cancer develops a specific mechanism to survive. This is like if a town has a flood every week—eventually, the survivors adapt and learn to become expert swimmers. Now, if you're hit with unexpected threats—for cells, a cocktail of chemotherapy drugs, or for people, a natural disaster—there are usually still some that remain because cells and people are diverse in their capabilities to maximize survival.

We liken drug resistance to evolution. Our studies and those of others show that nature has programmed cells to be diverse to ensure survival in harsh conditions. I had trouble wrapping my head around this because, while there is beauty in nature striving for life at every level, drug-resistant metastatic cancer cells are our enemy. Somehow, nature is not distinguishing between the driving force for normal cells versus cancer cells to survive.

### How are cancer cells like "angry, ostracized people?"

A simple way to think about cancer is that it starts from a single, mutated cell that takes on a life of its own and begins to metastasize. But perhaps a more accurate view is that cancer exists as part of a community within a larger ecosystem. A damaged cell can sit in your body forever and never wreak havoc. It's when the relationship between one cell and its community breaks down that the formation of tumors begins.

Some of the first genes to go awry in cancer are those that control the ability of cells to contact each other, called cell adhesion. Now, if you're a stressed cell and lose contact with your neighbors, you have a very



Immunostaining shows the organization of different types of normal human mammary cells, which will be compared against precancerous and tumor-causing cells.

different relationship with your environment. Like an angry person that's been ostracized from a community, that cell forgets its social contract in a sense and begins to act erratically.

One area of cancer that we do not understand that relates to this "community" of the body is the higher-order communication between our overall physiology and control of metastasis. Some patients with cancer, for example, simply waste away (cachexia), as if the higher-order operating system had made the calculation for the body to give up. This mind-body relationship to one's health is a poorly understood area but worth exploring.

### How do you de-stress?

I love to snorkel in Cancun and recently tried the flying trapeze—it was a lot of fun. I enjoy travel, from eating a giant gelato in Italy, hiking in New Zealand, getting a camel kiss in Jordan and riding a yak in the Himalayas. At home, I regularly cycle, go to the gym and take our large, loveable but unruly dogs hiking in nearby canyons as a courtesy to our neighbors.

Aside from those activities, I have recently focused on a holistic approach to food in the last few years. What started as a scientific interest in reading all the strange stuff listed on food labels and seriously wondering how this was affecting my epigenome grew into an ethical philosophy for me.





“The best scientists see not only the importance and significance of what they’re doing, but also the beauty of it.”

**When did you start to think more deeply about food and consumption?**

On a trip to D.C. about ten years ago, I walked by a poster that opened my eyes to the conditions in which factory farm-raised animals are kept. That was an epiphany for me and greatly raised my compassion and awareness about the connection between ethical treatment of animals, contamination-laced produce, artificial foods and diet-based human disease. I never thought I’d be interested in food books, but I started to read about corporate-controlled food politics in books like *What to Eat* by Marion Nestle and *In Defense of Food* by Michael Pollan.

I also was inspired by *French Women Don’t Get Fat* by Mireille Guiliano whose central message is to give yourself lots of variety, take the time to buy and prepare only the best stuff, and bother to put a flower on the table just for you. In this way, grocery shopping can become a reflection of a life philosophy.

In the end, we still don’t understand why some people are able to overcome disease—like cancer—and others don’t. We rely on our bodies to take care of ourselves so we must treat our bodies with respect.

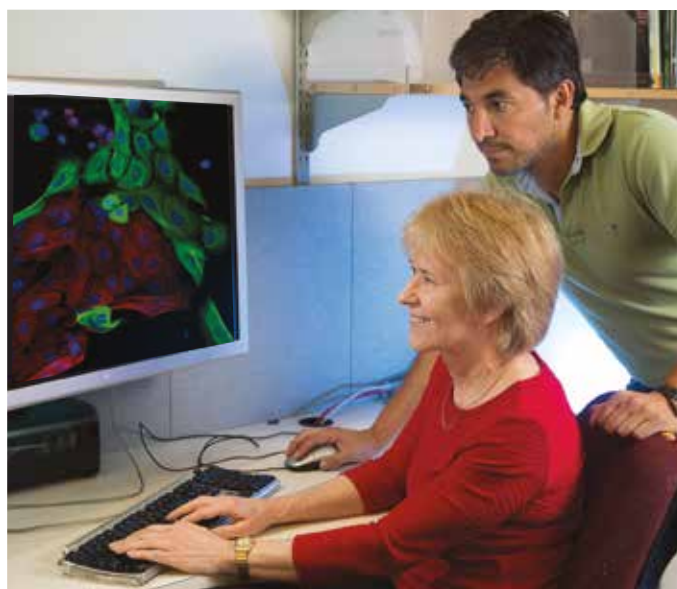
**You’ve mentored dozens of young scientists. What knowledge do you try to impart to them?**

Being a mentor has been both my greatest joy and my greatest frustration. You see some people who have intelligence and work hard, but are held back from reaching their full potential by fear: either fear of failure or of peer review upon completion of their project. It’s a given that to be a successful scientist you need several traits: intelligence, dedication, perseverance, optimism, willingness to accept criticism. You quickly learn as an advisor that the best people have all of these qualities and I am just cultivating them for that extra mile.

My own mentors—Peter Geiduschek from when I was a UCSD undergraduate, Robert Roeder during my graduate work at Washington University and Gary Felsenfeld from my postdoctoral studies at the NIH—were almost as important to me as my parents in influencing my growth and development.

**You’ve given several talks on women in science. What are your thoughts on the landscape today?**

I think things are better for women and minorities, but the culture still needs to improve. In general, it’s easy to be generous to a person junior



Beverly Emerson and Fernando Lopez-Diaz

to you, but the glass ceiling really comes into play when women reach higher levels. At these levels, the more enlightened leaders willingly step aside and remove barriers to elevate qualified and deserving individuals who are underrepresented. The “boys’ club” culture at a professional level is an embarrassing anachronism.

My advice to women scientists is not to put up with the glass ceiling. If your institute or company isn’t providing you with opportunities for fair advancement, go to another organization. Sometimes—and this is the case for all scientists—you have to take a step back from the daily grind of grants and papers to look at the system you operate in and see if it’s good for you and serves your best interests.

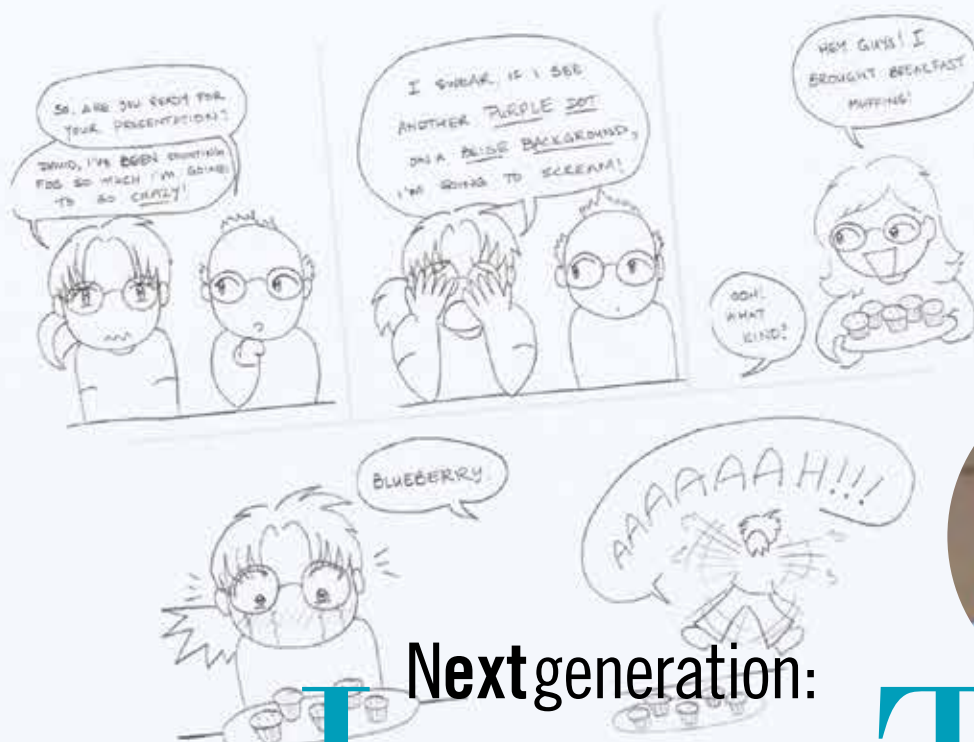
**Any parting thoughts to living the life of a scientist?**

In my own experience, I can delineate three stages to becoming a scientist. The first is embracing the culture: I observed as a naive undergraduate in Dr. Geiduschek’s lab how no sacrifice was too great for the good of one’s experiment. I was very impressed by the dedication of people who routinely came back to the lab at 2 a.m. to optimize their experiment.

The second phase of becoming a scientist is as a graduate student, when you are becoming a journeyman who masters the craft of being an accomplished experimentalist. This often requires doing things over and over for years to learn to solve a problem rigorously.

Thirdly, once you’ve mastered your craft, you develop self-confidence and judgment. Not only can you do the experiments at this point, you can figure out which problems are worth exploring. As a postdoc at the NIH and later a faculty member, I learned to trust and follow my passion.

Ultimately, living the life of a scientist has been a wonderful journey of self-discovery and a golden opportunity to share my professional life with many outstanding people. ■■■



# Next generation: Laura Tan

WHEN LAURA TAN GOT A REQUEST to present a two-minute elevator pitch on her work to faculty and high-end donors, she got a little nervous. When she heard that actor/director Robert Redford and Salk Board Chair Irwin Jacobs were expected to be in the audience, she got excited.

"It was really, really fun," says Tan, a research associate in the Laboratory of Neuronal Structure and Function led by **Paul Sawchenko**. "With two minutes, you really can't get into detail. You are giving a teaser trailer like a movie, just giving little snippets so they come talk to you afterwards."

As it turned out, Jacobs and Redford missed Tan's talk—which included a PowerPoint slide of Fort Knox to represent how impenetrable the brain can be—but rather than be crestfallen, Tan channeled her customary ebullience into the rest of the evening. Several attendees—people she would probably not have met otherwise—approached her to learn more about her work on how the brain perceives and processes stress signals. And she did get to chat with Jacobs and Redford at the evening reception, where Redford requested meeting the postdoctoral researchers.

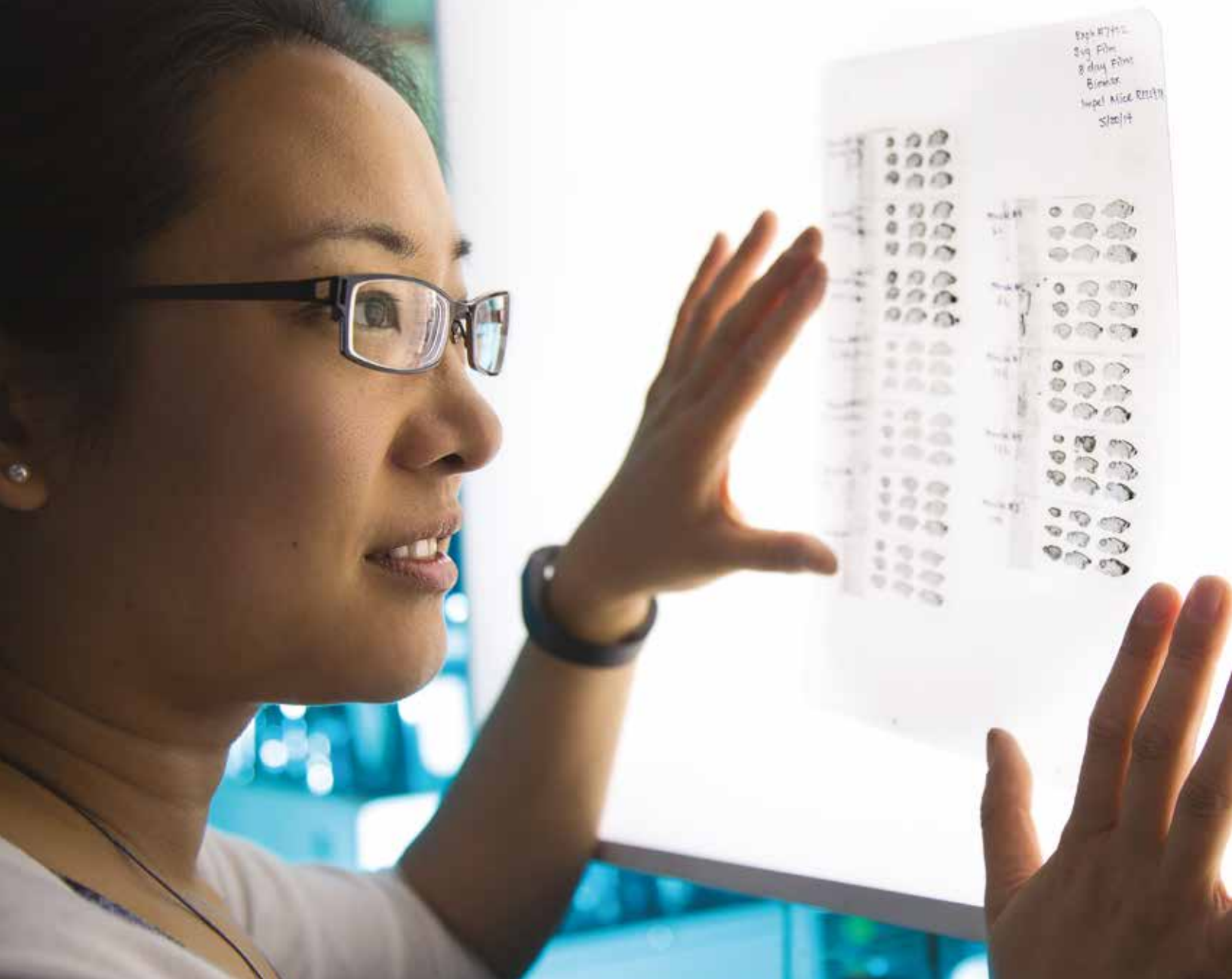
"It's kind of nice to be a rock star in research for two minutes," says Tan. Game to try anything—be it stopping a fast break in lacrosse or lending her alto to a choir—Tan is fueled in

part by the three cups of coffee she drinks every day and in part by an insatiable curiosity for what makes the brain tick, particularly when it's under siege by stress. For the past year, she has turned her considerable energy to studying stress and its effect on Alzheimer's disease.

One of the problems with treating Alzheimer's is that drugs have difficulty crossing the blood-brain barrier, a highly selective fortress that keeps pathogens out of the brain by separating circulating blood from the brain's extracellular fluid in the central nervous system. That makes delivering a beneficial central nervous system drug in a pill or blood injection difficult, as it has to flow through the entire body with perhaps little, or none, of the drug getting into the brain. It can create toxicity problems along the way, affecting the liver, heart, digestive tract and more. And the stress receptor Tan is targeting exists outside of the brain as well, creating more complications for treatment.

If the brain is like Fort Knox, says Tan, the rest of the body is like the Kentucky countryside. "We could go in with planes and tanks to try and get to the gold in Fort Knox, but it would destroy most of Kentucky in collateral damage, which is extraordinarily bad because I like bourbon," she jokes. "In this metaphor, drugs designed for the brain can destroy the body and never even reach their target."





Tan is investigating alternative ways of delivering drugs that block corticotropin-releasing factor (CRF) receptors that are both efficacious and targeted to the brain and that do not require invasive procedures (such as brain surgery) for the treatment and prevention of Alzheimer's disease.

"We are using a sneaky Ocean's 11 approach where we are coming in through the back door," Tan says. "We are going with a smaller team. We are getting in and out with the gold without destroying anything outside."

To accomplish this, Tan uses an intranasal administrator, similar to an asthma inhaler, to deliver drugs precisely to the upper olfactory region of the nasal cavity in her mouse models. Neurons in the mucous membrane that lines the nasal cavity send their axons through the skull to the brain, the same pathway that gives humans their sense of smell. Using this non-invasive route, Tan and her colleagues have been able to show that it can transport lower doses of drugs—in this case, a compound that binds to one receptor—across the blood-brain barrier, thereby sparing peripheral tissues from exposure.

"CRF was discovered at Salk in **Wylie Vale**'s lab in 1981," Tan says. "The fact we are pursuing this feels organic. It's a very Salkian thing to do."

Tan, 33, hails from Mississauga, the sixth largest city in Canada. Her father, a chemical engineer, and her mother, a social worker, never pushed her toward a science career, but she was inspired by her uncle, Larry Tan, who discovered the first acellular vaccine for pertussis. The vaccine contains cellular material but not whole-cell bacterium to invoke an immune response to create antibodies in the patient.

Tan always thought she would be a medical doctor until her senior year at the University of Toronto when she got her first taste of lab life and was hooked. Up to that point, she felt her studies had been all about memorizing and regurgitating information.

"We do that here, too, but I feel we are creating the knowledge," Tan says. "I don't have to be the encyclopedia, but I do have to use the encyclopedia and then apply it to what I'm doing. I like science because I get to ask the questions I want to ask."

Characteristically, Tan plunged head first into the sprawling 50,000-student experience of the University of Toronto. In addition to biology and humanities coursework, she organized an intramural sports program, playing on more than 100 teams. The "Laura A. Tan Award" was created to honor her contribution to athletics at the college.

“She is the kind of individual who enlivens a workplace, embodying a most rare combination of scholarly acumen, a strong work ethic and social conscience.”

—Paul Sawchenko



Image courtesy of Anna Scipione

networking opportunities for researchers and volunteering for a plethora of other Institute events. Almost immediately upon arriving at Salk, she answered an internal bulletin board ad to join a softball team formed by **Inder Verma**'s lab. She encouraged her three colleagues to follow suit.

“We knew nobody in that lab. We just showed up and suddenly, we are all the best of friends,” she says. “So much so that everyone thinks I’m in the Verma lab.”

To relieve the stress she gets from studying stress, Tan also doodles. Many of her cartoons have a central theme of her in the lab being menaced by chocolate chip cookies and muffins, which bear a striking resemblance to a stain she employs when counting cells—the background is beige and the cells are dark brown.

“I was terrified of chocolate chip cookies for awhile,” she says.

Sawchenko describes Tan as a “true Renaissance woman,” a highly creative and productive scientist who is also an accomplished athlete, chef and chorister with a schedule that exhausts him just thinking about it.

“From day one, she has been the unquestioned leader of my laboratory group, heading up not only collegial interactions within our group and between our lab and others at the Institute, but also spearheading such activities as our participation in science outreach to local high school students and holiday food collection drives,” Sawchenko says. “She is the kind of individual who enlivens a workplace, embodying a most rare combination of scholarly acumen, a strong work ethic and social conscience.”

At the Institute, Tan has learned that she likes, and is good at, mentoring the newer researchers. She embraced recruiting volunteers for Explore Salk earlier this year, taking her cue from another research associate, **Amy Rommel**.

“I always think of her as my prototype,” she says. “It’s like, ‘If I can be a little bit more like Amy, I’m doing okay.’”

Beyond the bench, Tan’s life is equally full tilt.

She plays defense for the San Diego Lacrosse Club at nearby Doyle Park during the summer and at tournaments in Los Angeles, Las Vegas, Arizona and Hawaii, among other places. She discovered the club on Facebook and has been playing with the all-woman team since the day after she arrived in town. Tan also sings as an auxiliary member with Sacra/Profana, an eclectic local choir that frequently accompanies the San Diego Symphony, including for its Summer Pops concert paying tribute to Broadway shows such as *Wicked*, *Rock of Ages* and *Les Misérables*. And in her spare time, she bakes. Chocolate milk stout cupcakes with peanut butter buttercream are her signature sweet.

Four years into her time at Salk, Tan still marvels at her good fortune. “There is something about being surrounded by good people and the building itself,” she says. “Sometimes, I come in to work and give the Salk walls a pat as if to say, ‘Hey, hi friend. Nice to see you.’” 🐾

Graduating with distinction in zoology/biology with a minor in classical civilizations, Tan remained at the University of Toronto to earn her PhD in neuroscience. She did her doctoral studies under David Lovejoy, a former Salk postdoctoral researcher in Vale’s lab.

When she began casting her net for a postdoctoral position, Tan was initially attracted to Europe. Then fate intervened in the form of an advisor who told her, “If you want culture, go to Europe. If you want science, you go to the United States.”

Taking that advice to heart, Tan reached out to Salk, and Sawchenko specifically because of his reputation as a good mentor and his mastery of anatomy.

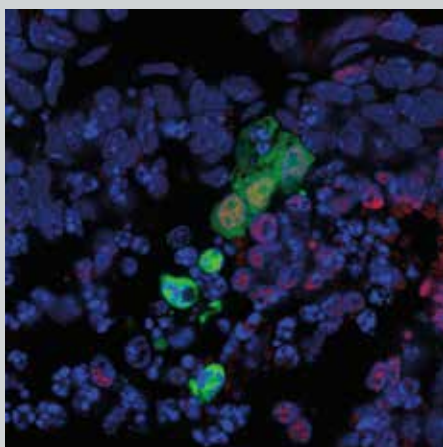
“It was such a good fit,” she says. “I remember emailing Paul and getting a response back in three hours. That was one of the greatest feelings.”

Tan joined Salk in 2011 and slipped into Institute life like a hand into a glove—organizing





## Izpisua Belmonte garners international attention for string of major discoveries



A novel type of human stem cell is shown in green integrating into the surrounding cells of a nonviable mouse embryo. The stem cell holds promise for one day growing replacement functional cells and tissues.

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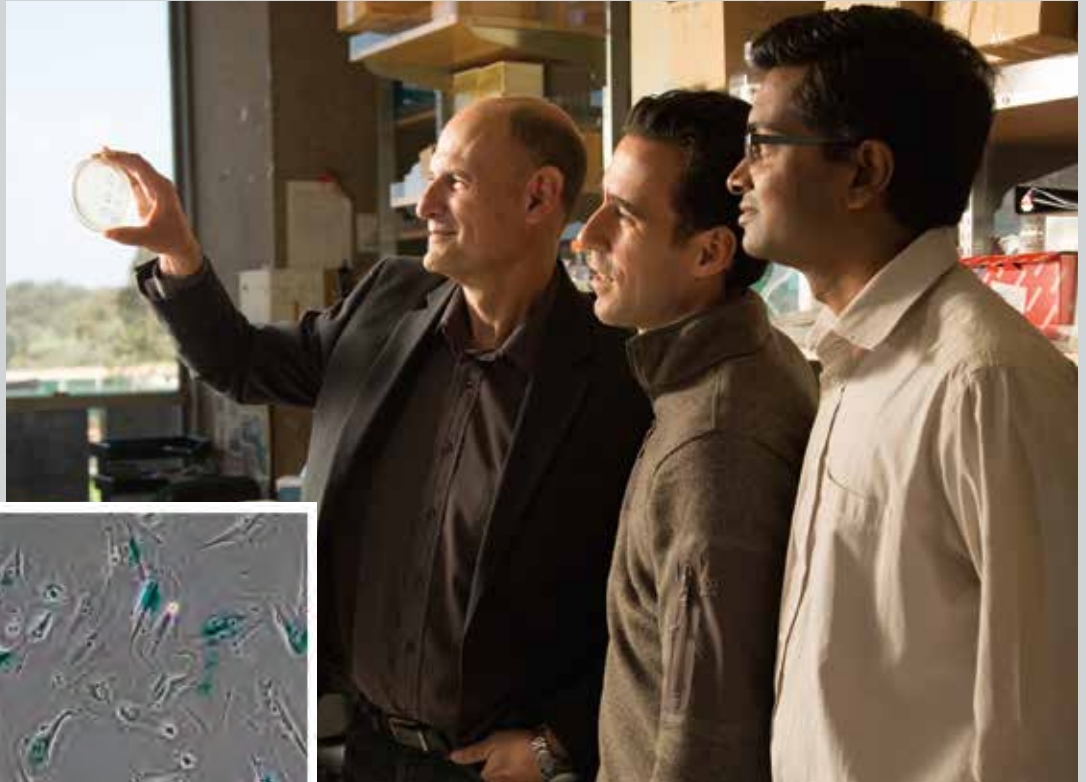
**SALK PROFESSOR JUAN CARLOS IZPISUA BELMONTE AND HIS RESEARCH** team received worldwide media attention earlier this year for a string of groundbreaking discoveries reported in top science journals.

The papers, which shed light on fundamental problems in aging, mitochondrial disease and regenerative medicine, were covered in *TIME* magazine, *The Washington Post*, *Scientific American*, *New Scientist* and *The Guardian*, to name just a few.

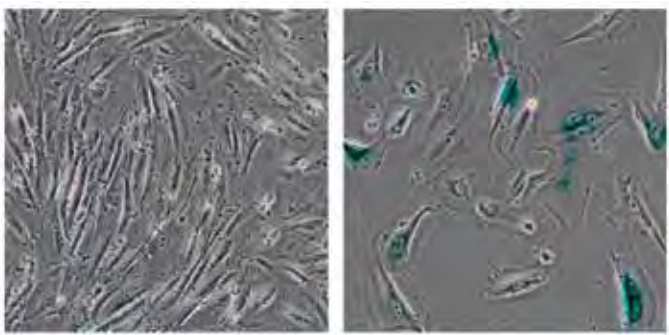
The first of the discoveries to be announced was published April 23 in *Cell*. In that paper, the scientists reported a new method of preventing the transmission of mitochondrial diseases in mice using gene-editing technologies.

For thousands of women around the globe carrying a mitochondrial disease, having a healthy child can be a gamble. This set of diseases affect mitochondria, tiny powerhouses that generate energy in the body's cells and are passed exclusively from mother to child.

Women wishing to prevent their children from inheriting mitochondrial diseases have typically relied on preimplantation genetic diagnosis to pick the healthiest embryos, but that is no guarantee of having a healthy baby. In a mouse study, Izpisua Belmonte's lab developed a simple technique to eliminate mitochondrial mutations from eggs or early embryos, which has the potential to prevent babies from inheriting mitochondrial diseases.



From left: Juan Carlos Izpisua Belmonte, Alejandro Ocampo and Pradeep Reddy



This image shows normal human cells (left) and cells that are genetically modified to model Werner syndrome (right), which show signs of aging.

“Currently, there are no treatments for mitochondrial diseases,” says Izpisua Belmonte, a professor in Salk’s Gene Expression Laboratory and holder of the Roger Guillemin Chair. “Our technology may offer new hope for mitochondrial disease carriers.”

In the second study, detailed later the same month in *Science*, the lab focused on Werner syndrome, a genetic disorder that causes people to age more rapidly than normal. People with the disorder suffer age-related diseases early in life, including cataracts, type 2 diabetes, hardening of the arteries, osteoporosis and cancer, and most die in their late 40s or early 50s.

By studying Werner syndrome, the team found that the aging process for humans is tied to the deterioration of tightly packaged bundles of cellular DNA. The discovery could eventually lead to methods of preventing and treating age-related diseases such as cancer, diabetes and Alzheimer’s.

In early May, the team reported in *Nature* the discovery of a novel type of pluripotent stem cell—cells capable of developing into any type of tissue—whose identity is tied to their location in a developing embryo. This contrasts with stem cells traditionally used in scientific study, which are characterized by their time-related stage of development.

The researchers dubbed this new class of cells “region-selective pluripotent stem cells,” or rsPSCs for short. The rsPSCs were easier to grow in the laboratory than conventional human pluripotent stem cells and offered advantages for large-scale production and gene editing (altering a cell’s DNA), both desirable features for cell replacement therapies.

Collaborating with the labs of Salk Professors **Joseph Ecker** and **Alan Saghatelian**, the Izpisua Belmonte team performed extensive

characterization of the new cells and found rsPSCs showed distinct molecular and metabolic characteristics as well as novel epigenetic signatures—patterns of chemical modifications to DNA that control which genes are turned on or off without changing the DNA sequence.

“The region-selective state of these stem cells is entirely novel for laboratory-cultured stem cells and offers important insight into how human stem cells might be differentiated into derivatives that give rise to a wide range of tissues and organs,” says **Jun Wu**, a postdoctoral researcher in Izpisua Belmonte’s lab and first author of the *Nature* paper. “Not only do we need to consider the timing, but also the spatial characteristics of the stem cells. Understanding both aspects of a stem cell’s identity could be crucial to generating functional and mature cell types for regenerative medicine.”



Jun Wu and Juan Carlos Izpisua Belmonte





From left: Tushar Menon, Inder Verma and Amy Firth

## Immune system-in-a-dish offers hope for “bubble boy” disease

Salk researchers have been able to grow patient-derived, healthy cells in the lab, coming a step closer to treating fatal blood disorders

**FOR INFANTS WITH SEVERE COMBINED** immunodeficiency (SCID), something as simple as a common cold or ear infection can be fatal. Born with an incomplete immune system, kids who have SCID—also known as “bubble boy” or “bubble baby” disease—can’t fight off even the mildest of germs. They often have to live in sterile, isolated environments to avoid infections and, even then, most patients don’t live past a year or two. This happens because stem cells in SCID patients’ bone marrow have a genetic mutation that prevents them from developing critical immune cells, called T and Natural Killer (NK) cells.

Now, Salk researchers have found a way to, for the first time, convert cells from X-linked SCID patients to a stem cell-like state, fix the genetic mutation and prompt the corrected cells to successfully generate NK cells in the laboratory.

The success of the new technique suggests the possibility of implanting these tweaked cells back into a patient so they can generate an immune system. Though the new work, published March 12, 2015 in *Cell Stem Cell*, is preliminary, it could offer a potentially less invasive and more effective approach than current options.

“This work demonstrates a new method that could lead to a more effective and less invasive

treatment for this devastating disease,” says senior author **Inder Verma**, Salk professor and American Cancer Society Professor of Molecular Biology. “It also has the potential to lay the foundation to cure other deadly and rare blood disorders.”

Previous attempts to treat SCID involved bone marrow transplants or gene therapy, with mixed results. In what began as promising clinical trials in the 1990s, researchers hijacked virus machinery to go in and deliver the needed genes to newly growing cells in the patient’s bone marrow. While this gene therapy did cure the disease at first, the artificial addition of genes ended up causing leukemia in a few of the patients. Since then, other gene therapy methods have been developed, but these are generally suited for less mild forms of the disease and require bone marrow transplants, a difficult procedure to perform on critically sick infants.

To achieve the new method, the Salk team secured a sample of bone marrow from a deceased patient in Australia. Using that small sample, the team developed the new method in three steps. First, they reverted the patient cells into induced pluripotent stem cells (iPSCs)—cells that, like embryonic stem cells, have the

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ability to turn into any type of tissue and hold vast promise for regenerative medicine.

“Once we had patient-derived stem cells, we could remove the genetic mutation, essentially fixing the cells,” explains one of the first authors and Salk postdoctoral researcher **Amy Firth**.


The second innovation was to use new gene editing technology to correct the SCID-related genetic deficiency in these iPSCs. To remove the mutation, the researchers used a technology called TALEN (similar to the better known CRISPR method). This set of enzymes act as molecular scissors on genes, letting researchers snip away at a gene and replace the base pairs that make up DNA with other base pairs.

“Unlike traditional gene therapy methods, “we aren’t putting a whole new gene into a patient, which can cause unwanted side effects,” says **Tushar Menon**, another first author and Salk postdoctoral researcher. “We use TALEN-based genome editing to change just one nucleotide in one gene to correct the deficiency. The technique is literally that precise.”

The third step of the work was to prompt the cells to proliferate into the vital immune system cells—not an easy task, but one that could offer a potentially unlimited supply that can be transplanted back into patients at intervals. To do this, the researchers collaborated with scientists at the University of California, Los Angeles, to use a concoction of nutrients and other factors that would encourage the iPSCs to generate NK cells.

And they succeeded. These corrected cells-in-a-dish did indeed develop mature NK cells.

Next, the team is working on reproducing the other vital immune components, T cells. So far, they have prompted the iPSCs to turn into the precursors of T cells, but have not yet been able to coax them to maturity.

“Ultimately, we hope these efforts will help lead to the ‘holy grail’ in the field: the ability to create stem cells from iPSCs capable of generating all types of blood and immune cells,” says Verma, who also holds the Irwin and Joan Jacobs Chair in Exemplary Life Science. The ability to generate the corrected blood stem cells themselves could yield a one-time treatment that would ultimately replenish functioning cells throughout a patient’s whole life. 

## Food for thought: Master protein enhances learning and memory

Salk scientists discover a single protein that energizes both muscles and the brain

**JUST AS SOME PEOPLE SEEM BUILT TO RUN MARATHONS AND HAVE** an easier time going for miles without tiring, others are born with a knack for memorizing things, from times tables to trivia facts. These two skills—running and memorizing—are not so different as it turns out.

Salk scientists and collaborators have discovered that physical and mental activities rely on a single metabolic protein that controls the flow of blood and nutrients throughout the body, as reported in the journal *Cell Metabolism*. The new study could point to potential treatments in regenerative and developmental medicine as well as ways to address defects in learning and memory.

“This is all about getting energy where it’s needed to ‘the power plants’ in the body,” says **Ronald Evans**, director of Salk’s Gene Expression Laboratory and senior author of the new paper, published April 7, 2015. “The heart and muscles need a surge of energy to carry out exercise and neurons need a surge of energy to form new memories.”

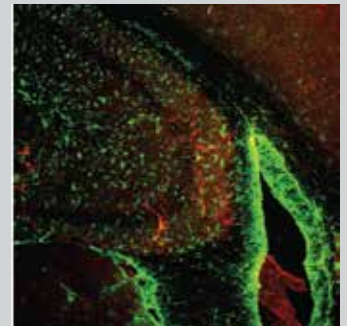
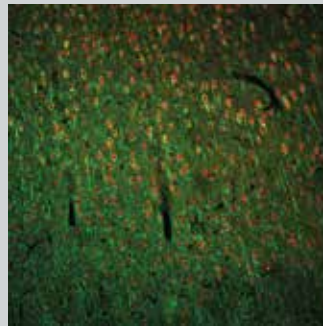
Energy for muscles and brains, the scientists discovered, is controlled by a single protein called estrogen-related receptor gamma (ERR $\gamma$ ). Evans’ research group has previously studied the role of ERR $\gamma$  in the heart and skeletal muscles. In 2011, they discovered that promoting ERR $\gamma$  activity in the muscles of sedentary mice increased blood supply to their muscles and doubled their running capacity. ERR $\gamma$ , they went on to show, turns on a whole host of muscle genes that convert fat to energy.

Thus, ERR $\gamma$  became known as a master metabolic switch that energized muscle to enhance performance. Although studies had also shown that ERR $\gamma$  was active in the brain, researchers didn’t understand why—the brain burns sugar and ERR $\gamma$  was previously shown to only burn fat. So the team decided to look more closely at what the protein was doing in brain cells.

By first looking at isolated neurons, **Liming Pei**, lead and co-corresponding author of the paper, found that, as in muscle, ERR $\gamma$  activates dozens of metabolic genes in brain cells. Unexpectedly, this activation related to sugar instead of fat. Neurons that lacked ERR $\gamma$  could not ramp up energy production and thus had a compromised performance.

“We assumed that ERR $\gamma$  did the same thing throughout the body,” says Evans. “But we learned that it’s different in the brain.” ERR $\gamma$ , they now conclude, turns on fat-burning pathways in muscles and sugar-burning pathways in the brain.

Evans and his collaborators noticed that ERR $\gamma$  in live mice was most active in the hippocampus—an area of the brain that is active in producing new brain cells, is involved in learning and memory and is known to require




Salk researchers and collaborators discovered that physical and mental activities rely on a single metabolic protein, ERR $\gamma$ , which controls the flow of blood and nutrients throughout the body. In this image, ERR $\gamma$  is shown (stained red) in the hippocampus, the area of the brain largely responsible for memory. The new work could point to a way to enhance learning.

lots of energy. They wondered whether ERR $\gamma$  had a direct role in learning and memory. By studying mice lacking ERR $\gamma$  in the brain, they found a link.

While mice without the protein had normal vision, movement and balance, they were slower at learning how to swim through a water maze—and poor at remembering the maze on subsequent trials—compared to mice with normal levels of ERR $\gamma$ .

“What we found is that mice that are missing ERR $\gamma$  are basically very slow learners,” says Pei. Varying levels of ERR $\gamma$  could also be at the root of differences between how individual humans learn, he hypothesizes. “Everyone can learn, but some people learn and memorize more efficiently than others, and we now think this could be linked to changes in brain metabolism.”

A better understanding of the metabolism of neurons could help point the way to improved treatments for learning and attention disorders. And possibly, revving up levels of ERR $\gamma$  could even enhance learning, just as it enhances muscle function. 



# Salk scientists reveal epigenome maps of the human body's major organs

This new atlas of human organ epigenomes provides a starting place to understand the role of chemical markers in development, health and disease

**FOR MORE THAN A DECADE, SCIENTISTS HAVE HAD A WORKING** map of the human genome, a complete picture of the DNA sequence that encodes human life. But new pages are still being added to that atlas: maps of chemical markers called methyl groups that stud strands of DNA and influence which genes are repressed and when.

Now, Salk scientists have constructed the most comprehensive maps yet of these chemical patterns—collectively called the epigenome—in more than a dozen different human organs from individual donors (including a woman, man and child). While the methylation does not change an individual's inherited genetic sequence, research has increasingly shown it has a profound effect on development and health.

"What we found is that not all organs we surveyed are equal in terms of their methylation patterns," says senior author **Joseph Ecker**, professor and director of Salk's Genomic Analysis Laboratory and codirector of The Center of Excellence for Stem Cell Genomics. "The signatures of methylation are distinct enough between organs that we can look at the methylation patterns of a tissue and know whether the tissue is muscle or thymus or pancreas." The new data was published June 1, 2015 in *Nature*.

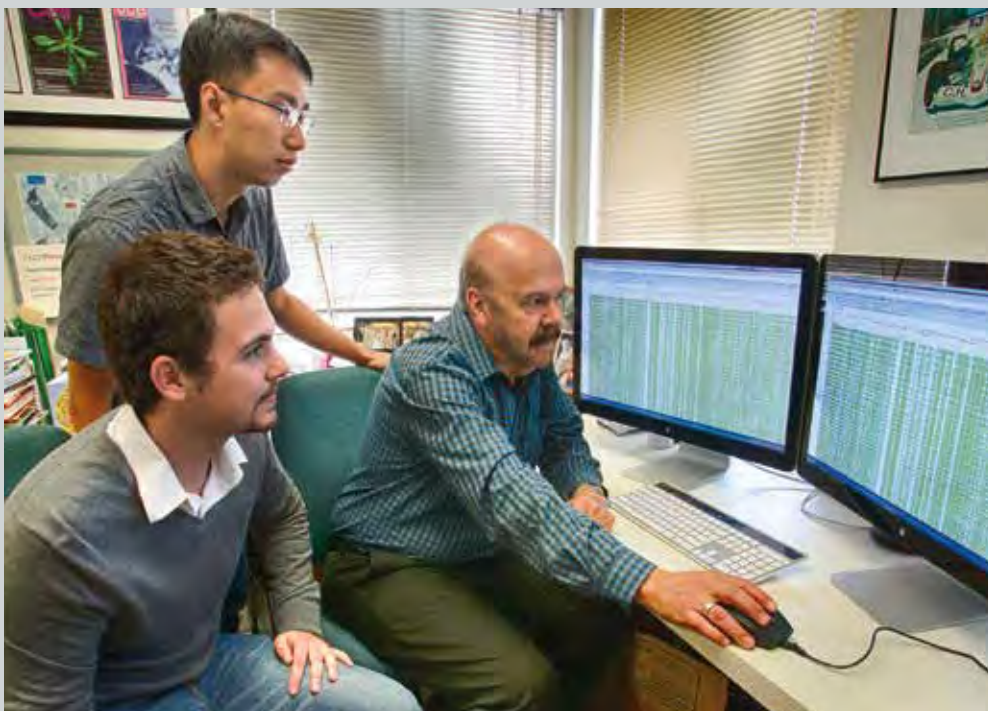
While the genome of an individual is the same in every cell, epigenomes vary since they are closely related to the genes a cell is actually using at any given time. Methylation marks help blood cells ignore the genes required to be a brain or liver cell, for instance. And they can vary over time—a change in a person's age, diet or environment, for instance, has been shown to affect methylation.

"We wanted to make a baseline assessment of what the epigenome, in particular DNA methylation, looks like in normal human organs," says Ecker, who is also a Howard Hughes Medical Institute and Gordon and Betty Moore Foundation investigator. To do that, the scientists collected cells from 18 organs in 4 individuals and mapped out their methylation profiles.

As expected, the patterns aligned somewhat with genes known to be important for a cell's function—there was less methylation close to muscle genes in cells collected from muscle, for instance. But other aspects of the new maps were surprising. The researchers detected an unusual form of methylation, called non-CG methylation, which was thought to be widespread only in the brain and stem cells. Researchers don't yet know the function of that non-CG methylation in adults, but hypothesize that it may suggest the presence of stem cell groups in adult populations. Another surprise was how extensively organs differed from each other in the degree of genome-wide methylation.

The new results just scratch the surface of completely understanding DNA methylation patterns—there are dozens more organs to profile, numerous unknowns about what shapes and changes the epigenome, and questions about whether different cells—even within a single organ—vary in their methylation patterns.

"You could imagine that eventually, if someone is having a problem, a biopsy might not only look at characterizing the cells or genes, but the epigenome as well," says Ecker. ■■■



From left: Matthew Schultz, Yupeng He and Joseph Ecker

“You could imagine that eventually, if someone is having a problem, a biopsy might not only look at characterizing the cells or genes, but the epigenome as well.”

— Joseph Ecker

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Kathy Jones and Conchi Estarás

## Vital step in stem cell growth revealed

Salk scientists' finding could aid regenerative and cancer therapies

**STEM CELLS, WHICH HAVE THE POTENTIAL** to turn into any kind of cell, offer the tantalizing possibility of generating new tissues for organ replacements, stroke victims and patients of many other diseases. Now, scientists at the Salk Institute have uncovered details about stem cell growth that could help improve regenerative therapies.

While it was known that two key cellular processes—called Wnt and Activin—were needed for stem cells to grow into specific mature cells, no one knew exactly how these pathways worked together. The details of how Wnt and Activin influence each other, published April 30, 2015 in *Molecular Cell*, offer guidance for improving stem cell therapies. The new work also reveals more about certain cancers that arise when these processes go astray, for example, when the Wnt signaling step becomes inappropriately reactivated, as happens in most colon cancers.

“We found that the mechanisms of these two pathways are complementary and activate the transcription, or turning on, of about 200 genes essential for stem cells to differentiate,” says **Kathy Jones**, senior author of the paper and Salk professor in the Regulatory Biology Laboratory. These genes are among the first steps that prompt stem cells to begin to change, or differentiate, into specific tissues, particularly ones that will eventually form the digestive and respiratory tracts, including intestines, lung, pancreas, thyroid and liver.

The researchers found that Wnt loads up the cellular machinery needed to begin the copying and activation of genes. Activin, meanwhile, boosts the process further: it increases the speed and efficiency by which the cellular machinery moves to copy the gene. Whereas Wnt treatment alone enhances the expression of developmental genes by a factor of 20-fold, further treatment with Activin boosts the signal to 150-fold or higher, says Jones. The team also found that the order of the signaling is equally important, because Activin could not turn on these genes unless the cells were first exposed to the Wnt signal.

“Wnt gets the ball rolling and Activin amplifies the signal,” says **Conchi Estarás**, first author of the paper. “This is a particularly clear example of how two different pathways, working through two different mechanisms, can cooperate to activate the same genes.” The new finding adds to a growing picture that the transcription process is much more dynamic than previous thought.

“Now we understand stem cell differentiation at a much finer level by seeing how these cellular signals transmit their effects in the cells,” adds Jones. “Understanding these details is important for developing more robust stem cell protocols and optimizing the efficiency of stem cell therapies.”

When they looked closer at the genes that both pathways activated, researchers were surprised to find that the pathways were further

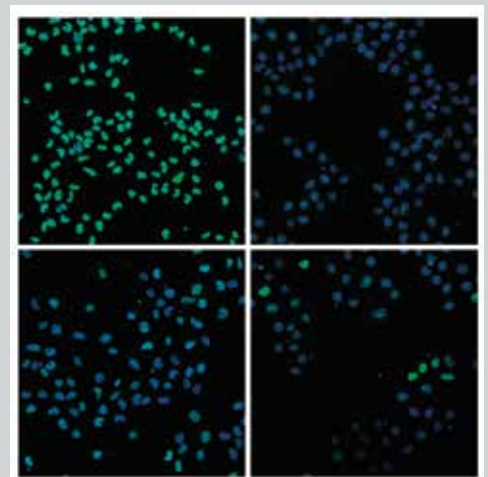
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connected to a third process, which is known to control tissue growth and organ size. The central protein in this new pathway, called Yap, acted specifically at these genes to counteract the effects of the Activin.

“The opposing effects of Activin and Yap are exerted at a late step in transcription, the elongation phase,” says Jones. “We don’t know very much about how the signaling networks in normal or cancer cells specifically affect the elongation stage of transcription, so it was a real bonus to find that it is targeted by two pathways in stem cells.”

Both the Wnt and Activin signaling processes operate differently in cancer, compared to stem cells. Wnt, in particular, is turned on very early in human colon cancer in nearly 90 percent of cases. The aberrant behavior of the Activin process, meanwhile, is tied to the metastasis of many cancers.

“There is great interest in developing transcription-based inhibitors of the Wnt pathway, because these would have strong anticancer activity for many tumor types,” says Estarás. “Because the environments of stem cells and cancer cells are quite distinct, and different target genes are involved, it will be interesting to see how the synergy and regulation that we have defined in stem cells operates in the cells of a tumor.”



In early-stage cell nuclei (blue), developmental genes (green) must be turned on for the cell to develop. When the two cellular processes, Wnt and Activin, work together (upper left), genes are activated to a much greater degree than when neither process is active (upper right). When just a single pathway is active (Wnt, lower left, Activin, lower right), only a few genes are turned on.



# Walking on ice takes more than brains

Salk scientists discover how a “mini-brain” in the spinal cord aids in balance

## WALKING ACROSS AN ICY PARKING LOT IN

winter—and remaining upright—takes intense concentration. But a new discovery suggests that much of the balancing act that our bodies perform when faced with such a task happens unconsciously, thanks to a cluster of neurons in our spinal cord that function as a “mini-brain” to integrate sensory information and make the necessary adjustments to our muscles so that we don’t slip and fall.

In a paper published January 29, 2015 in the journal *Cell*, Salk Institute scientists map the neural circuitry of the spinal cord that processes the sense of light touch. This circuit allows the body to reflexively make small adjustments to foot position and balance using light touch sensors in the feet.

The study, conducted in mice, provides the first detailed blueprint for a spinal circuit that serves as a control center for integrating motor commands from the brain with sensory information from the limbs. A better understanding of these circuits should eventually aid in developing therapies for spinal cord injury and diseases that affect motor skills and balance, as well as the means to prevent falls for the elderly.

“When we stand and walk, touch sensors on the soles of our feet detect subtle changes in pressure and movement. These sensors send signals to our spinal cord and then to the brain,” says **Martyn Goulding**, senior author and Salk professor. “Our study opens what was essentially a black box, as up until now we didn’t know how these signals are encoded or processed in the spinal cord. Moreover, it was unclear how this touch information was merged with other sensory information to control movement and posture.”

Every millisecond, multiple streams of information, including signals from the light touch transmission pathway that Goulding’s team has identified, flow into the brain. One way the brain handles this data is by preprocessing it in sensory way stations such as the eye or spinal cord. In the case of touch, scientists have long thought that the neurological choreography of movement relies on data-crunching circuits in the spinal cord. But until now, it has been exceedingly difficult to precisely identify the types of neurons

involved and chart how they are wired together.

In their study, the Salk scientists demystified this fine-tuned, sensory-motor control system. Using cutting-edge imaging techniques that rely on a reengineered rabies virus, they traced nerve fibers that carry signals from the touch sensors in the feet to their connections in the spinal cord. They found that these sensory fibers connect in the spinal cord with a group of neurons known as ROR $\alpha$  neurons, named for a specific type of molecular receptor found in the nucleus of these cells. The ROR $\alpha$  neurons in turn are connected by neurons in the motor region of the brain, suggesting they might serve as a critical link between the brain and the feet.


When Goulding’s team disabled the ROR $\alpha$  neurons in the spinal cord using genetically modified mice developed at Salk, they found that these mice were substantially less sensitive to movement across the surface of the skin or to a sticky piece of tape placed on their feet. Despite this, the animals were still able to walk and stand normally on flat ground.

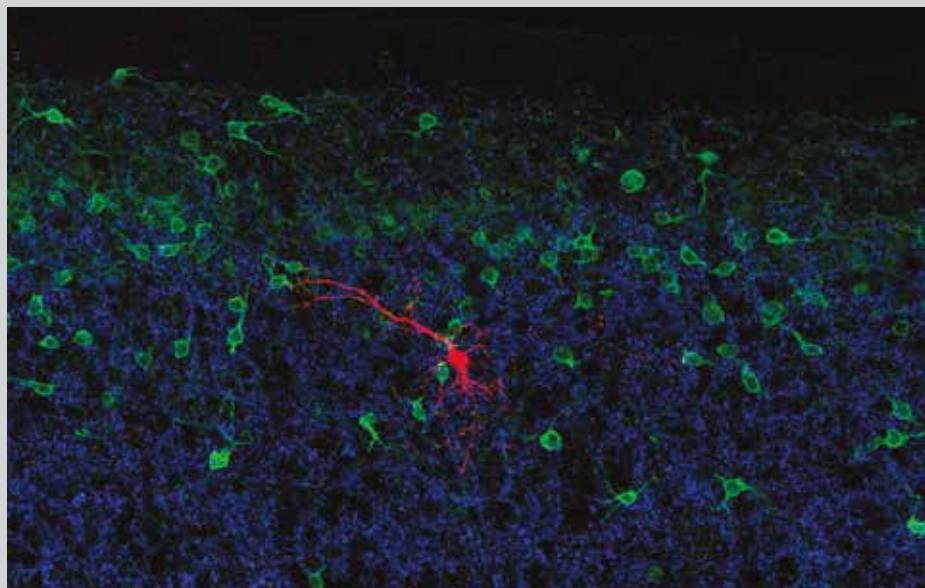
However, when the researchers had the animals walk across a narrow, elevated beam, a task that required more effort and skill, the

animals struggled, performing more clumsily than animals with intact ROR $\alpha$  neurons.

The scientists attribute this to the animals’ reduced ability to sense skin deformation when a foot was slipping off the edge and respond accordingly with small adjustments in foot position and balance—motor skills similar to those necessary for balancing on ice or other slippery surfaces.

Another important characteristic of the ROR $\alpha$  neurons is that they don’t just receive signals from the brain and the light touch sensors, but also directly connect with neurons in the ventral spinal cord that control movement. Thus, they are at the center of a “mini-brain” in the spinal cord that integrates signals from the brain with sensory signals to make sure the limbs move correctly.

The team’s study represents the beginning of a new wave of research that promises to provide precise and comprehensive explanations for how the nervous system encodes and integrates sensory information to generate both conscious and unconscious movement. 



Salk researchers mapped neural circuits in the mouse spinal cord that process light touch signals from the feet, a critical function for fine motor tasks, such as walking on ice. The red cells are ROR $\alpha$  neurons, which merge signals from neural fibers coming from the brain and limbs (both colored blue).

## Brain cells capable of “early-career” switch

Salk scientists find a single molecule that controls the fate of mature sensory neurons

**SCIENTISTS AT THE SALK INSTITUTE HAVE DISCOVERED THAT** the role of neurons—which are responsible for specific tasks in the brain—is much more flexible than previously believed.

By studying sensory neurons in mice, the Salk team found that the malfunction of a single molecule could prompt the neuron to make an “early-career” switch, changing a neuron originally destined to process sound or touch, for example, to instead process vision.

The finding, reported May 11, 2015 in *PNAS*, will help neuroscientists better understand how brain architecture is molecularly encoded and how it can become miswired. It may also point to ways to prevent or treat human disorders (such as autism) that feature substantial brain structure abnormalities.

“We found an unexpected mechanism that provides surprising brain plasticity in maturing sensory neurons,” says the study’s first author, **Andreas Zembrzycki**, a senior research associate at the Salk Institute.

The mechanism, a transcription factor called *Lhx2* that was inactivated in neurons, can be used to switch genes on or off to change the function of a sensory neuron in mice. It has been known that *Lhx2* is present in many cell types other than in the brain and is needed by a developing fetus to build body parts. Without *Lhx2*, animals typically die in utero. However, it was not well known that *Lhx2* also affects cells after birth.

“This process happens while the neuron matures and no longer divides. We did not understand before this study that relatively mature neurons could be reprogrammed in this way,” says senior author **Dennis O’Leary**,

Salk professor and holder of the Vincent J. Coates Chair in Molecular Neurobiology. “This finding opens up a new understanding about how brain architecture is established and a potential therapeutic approach to altering that blueprint.”

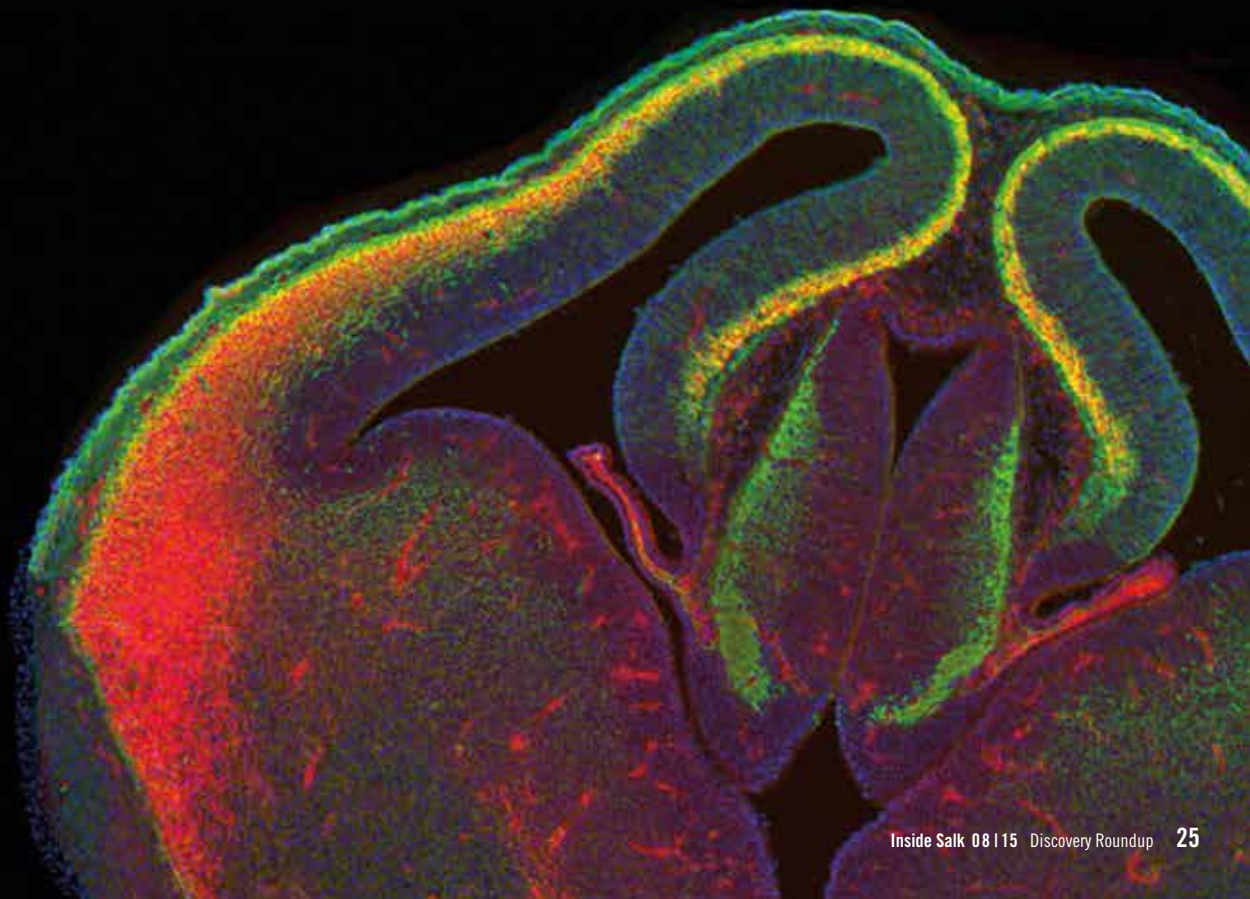
Scientists had believed that programming neurons was a one-step process. They thought that the stem cells that generate the neurons also programmed their functions once they matured. While this is true, the Salk team found that another step is needed: the *Lhx2* transcription factor in mature neurons then ultimately controls the fate of the neuron.

In the mouse study, the scientists manipulated *Lhx2* to make the switch in neuronal fate shortly after birth (when the mouse neurons are fully formed and considered mature). The team observed that controlling *Lhx2* let them instruct neurons situated in one sensory area to process a different sense, thus enlarging one region at the expense of the other. The scientists don’t know yet if targeting *Lhx2* would allow neurons to change their function throughout an organism’s life.

“This study provides proof that the brain is very plastic and that it responds to both genetic and epigenetic influences well after birth,” says O’Leary. “Clinical applications for brain disorders are a long way away, but we now have a new way to think about them.” ■■■

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» [View the photo gallery at: www.salk.edu/insidesalk/0815/oleary](http://www.salk.edu/insidesalk/0815/oleary)





## How the brain balances risk-taking and learning

Salk scientists discover a learning circuit in worms that gives clues to human behavior

**IF YOU HAD 10 CHANCES TO ROLL A DIE,** would you rather be guaranteed to receive \$5 for every roll (\$50 total) or take the risk of winning \$100 if you only roll a six?

Most animals, from roundworms to humans, prefer the more predictable situation when it comes to securing resources for survival, such as food. Now, Salk scientists have discovered the basis for how animals balance learning and risk-taking behavior to get to a more predictable environment. The research reveals new details on the function of two chemical signals critical to human behavior: dopamine—responsible for reward and risk-taking—and CREB—needed for learning.

“Previous research has shown that certain neurons respond to changes in light to determine variability in their environment, but that’s not the only mechanism,” says senior author **Sreekanth Chalasani**, an assistant professor in Salk’s Molecular Neurobiology Laboratory. “We discovered a new mechanism that evaluates environmental variability, a skill crucial to animals’ survival.”

By studying roundworms (*Caenorhabditis elegans*), Salk researchers charted how this new circuit uses information from the animal’s senses to predict the environment and prompt the worm to move to a new location if needed. The work was detailed April 9, 2015 in *Neuron*.

The circuit, made up of 16 of the 302 neurons in the worm’s brain, likely has parallels in more complex animal brains, researchers say, and could be a starting point to understanding—and fixing—certain psychiatric or behavioral disorders.

“What was surprising is the degree to which variability in animal behavior can be explained by variability in their past sensory experience and not just noise,” says **Tatyana Sharpee**, associate professor and co-senior author of the paper. “We can now predict future animal behaviors based on past sensory experience, independent of the influence of genetic factors.”

The team discovered that two pairs of neurons in this learning circuit act as gatekeepers. One pair responds to large increases of the presence of food and the other pair responds to large decreases of the presence of food. When either of these high-threshold neurons detects a large change in an environment (for example,

the smell of a lot of food to no food) they induce other neurons to release the neurotransmitter dopamine.

Dumping dopamine onto a brain—human or otherwise—makes one more willing to take risks. It’s no different in the roundworm: stimulated by large varieties in its environment, dopamine surges in the worm’s system and activates four other neurons in the learning circuit, giving them a greater response range. This prompts the worm to search more actively in a wider area (risk-taking) until it hits a more consistent environment. The amount of dopamine in its system serves as its memory of the past experience: about 30 minutes or so and it forgets information gathered in the time before that.

While it’s been known that the presence of dopamine is tied to risk-taking behavior, how exactly dopamine does this hasn’t been well understood. With this new work, scientists now have a fundamental model of how dopamine signaling leads the worm to take more risks and explore new environments.


“The connection between dopamine and risk is conserved across animals and is already known, but we showed mechanistically how it works,” says Chalasani, who is also holder of the Helen McLoraine Developmental Chair in Neurobiology. “We hope this work will lead to better therapies for neurodegenerative and behavioral diseases and other disorders where dopamine signaling is irregular.”

Interestingly, the scientists found that the high-threshold neurons also lead to increased signaling from a protein called CREB, known in humans and other animals to be essential to learning and retaining new memories. The researchers showed that not only is the presence

of CREB important to learning, but the amount of CREB protein determines how quickly an animal learns. This surprising connection could lead to new avenues of research for brain enhancements, adds Chalasani.

How did researchers test all of this in worms exactly? They began by placing worms in dishes that contained either a large or a small patch of edible bacteria. Worms in the smaller patches tended to reach the edges more frequently, experiencing large changes in variability (edges have large amounts of food compared to the center). Worms on the large patch, however, reached the edge less frequently, thereby experiencing a generally stable environment (mainly an area with constant food).

Using genetics, imaging, behavioral analysis and other techniques, researchers found that when worms are on small patches, the two pairs of high-threshold neurons respond to the greater variation and give a signal leading to increased dopamine. When worms in these smaller patches (and higher dopamine) were taken out and put into a new dish, they explored a larger area, taking more of a risk. Worms from the larger patches, however, produced less dopamine and were more cautious, exploring just a small space when placed in a new area.

Additionally, when the protein CREB was present in larger amounts, the team found that the worms took far less time to learn about their food variability. “Normally the worms took about 30 minutes or so to explore and learn about food, but as you keep increasing the CREB protein they learn it faster,” says Chalasani. “So dopamine stores the memory of what these worms learn while CREB regulates how quickly they learn.” 



*C. elegans*

» View video: [www.salk.edu/insidesalk/0815/chalasani](http://www.salk.edu/insidesalk/0815/chalasani)

“You have been, Roger Guillemin, one of these distinguished ‘soldiers of science’ that Bonaparte wished to recognize when he established the Legion of Honour.”

— Jean-Pierre Changeux



## A commanding presence

**ROGER GUILLEMIN, A SALK PROFESSOR AND NOBEL LAUREATE WHO** pioneered the study of brain chemistry, was presented with France’s highest accolade—the rank of Commander in the Legion of Honour—during a ceremony this spring at the Salk Institute. In bestowing the medal created by Napoleon Bonaparte in 1802 to recognize civilians and soldiers, neuroscientist Jean-Pierre Changeux of the Collège de France and Pasteur Institute in Paris praised Guillemin, 91, before an assemblage of dozens of Guillemin’s family members—including his wife, Lucienne—and friends and colleagues.

“You have been, Roger Guillemin, one of these distinguished ‘soldiers of science’ that Bonaparte wished to recognize when he established the Legion of Honour,” Changeux said. “Through your scientific achievements and your many discoveries, you have played a key role in illustrating the excellence of scientific research, but most of all, as a French scientist working abroad, in fostering scientific collaboration and friendship between the United States and France.”

Colleagues attending the ceremony echoed the sentiment, describing Guillemin as a “national treasure” for both countries.

Guillemin, a native of Dijon, France, earned his medical degree in 1949 from the University of Lyon. He joined Salk in 1970 and received the 1977 Nobel Prize in Physiology or Medicine for his work with hypothalamic hormones. His work introduced a new class of substances proven to be important for the regulation of growth, development, reproduction and responses to stress.

Changeux characterized Guillemin as “the founder of a new science called neuroendocrinology” and said his work led to major medicinal advances including the understanding of thyroid diseases, infertility and juvenile diabetes.

After the presentation, Guillemin expressed his gratitude in French before thanking his family and Salk colleagues, many of whom, including the late **Wylie Vale**, he had worked with for more than 45 years. He concluded his remarks, to a standing ovation, with “Let’s close this unique event in the French tradition with a glass of champagne.” 🍾



## Vicki Lundblad elected to National Academy of Sciences

### PROFESSOR VICKI LUNDBLAD IS ONE OF 84 NEW MEMBERS

elected to the National Academy of Sciences (NAS) this year. The election is considered one of the highest honors accorded a U.S. scientist. Lundblad's recognition brings the number of Salk faculty elected to the NAS to 14.

Lundblad, the Becky and Ralph S. O'Connor Chair and professor in the Molecular and Cell Biology Laboratory, seeks to understand how the ends of chromosomes determine how many times a cell can divide. Her early work showed that these chromosome ends, called telomeres, act as a cellular timekeeper by shortening with each cell division. Fortunately, there is a way around this countdown: an enzyme called telomerase rebuilds these eroding telomeres and allows cells to divide indefinitely.

Lundblad's group pioneered the discovery of the key subunits that make up this telomerase enzyme, using the yeast *Saccharomyces cerevisiae*—the same yeast used to make wine and bread—as their



From left: Beverly Emerson, Roger Guillemin and Vicki Lundblad

experimental system. This simple single-celled organism has also allowed Lundblad and her colleagues to subsequently uncover numerous insights about what dictates when and where telomerase acts inside the cell. 📊

## Joseph Ecker and Dennis O'Leary elected to American Academy of Arts & Sciences

### PROFESSORS JOSEPH ECKER AND DENNIS O'LEARY

have received the prestigious honor of being elected to the American Academy of Arts and Sciences (AAAS) class of 2015. AAAS is one of the nation's most prominent honorary societies. There are 197 accomplished leaders from academia, business, public affairs, the humanities and the arts accepted to this year's class. Its members include winners of the Nobel Prize and Pulitzer Prize; MacArthur and Guggenheim Fellowships; and Grammy, Emmy, Oscar and Tony awards. Ecker and O'Leary bring the number of Salk scientists elected as members of AAAS to 16. The new class will officially be inducted during a ceremony in October.

Ecker is director of Salk's Genomic Analysis Laboratory and a Howard Hughes Medical Institute and Gordon and Betty Moore Foundation investigator. He has made many distinguished contributions to the fields of genomes/epigenomes of plant and human cells, particularly for the development of new tools that enable genome-wide analyses. He also holds the Salk International Council Chair in Genetics.

O'Leary, a professor in Salk's Molecular Neurobiology Laboratory, holds the Vincent



Dennis O'Leary



Joseph Ecker

J. Coates Chair in Molecular Neurobiology. O'Leary tackles questions about brain development in order to better understand the genes and molecules which not only help neurons form and find their place in a developing brain, but also play key roles in neural function and health throughout life. 📊



## Ronald Evans receives Frontiers in Science Award

**RONALD EVANS, PROFESSOR AND DIRECTOR** of Salk's Gene Expression Laboratory, is the recipient of the 2015 Frontiers in Science Award. The award is presented to an individual who has demonstrated exemplary contributions to their individual profession or area of expertise.

A Howard Hughes Medical Institute investigator, Evans is known for his work on nuclear receptors and


the mechanism of hormone signaling, which is crucial to understanding body physiology and the treatment of diseases. His work on the isolation of the genes encoding hormone receptors revealed how they help control sugar, salt, calcium and fat metabolism as well as reproductive physiology. 📊



## Pew Charitable Trusts names Nicola Allen a Pew Scholar in the Biomedical Sciences


**NICOLA ALLEN, ASSISTANT PROFESSOR IN THE** Molecular Neurobiology Laboratory, has received the honor of being named a Pew Scholar in the Biomedical Sciences. She is one of only 22 researchers in biomedical sciences to receive the honor this year. She joins the ranks of more than 600 outstanding scientists who have been selected as Pew scholars in the 30 years since the program's inception.

Allen's research investigates the role of astrocytes in reinforcing the brain's ability to learn new tasks and

make sense of its environment. Astrocytes are the most abundant cells in the brain and play critical roles in regulating neuronal function. During her postdoctoral fellowship, Allen identified molecules that astrocytes use to guide the formation of neuronal connections in the developing mammalian brain. She has extended this work to analyzing the critical period of development when newborns rewire their brains in response to the stream of visual input. 

## Joanne Chory elected to American Philosophical Society

**JOANNE CHORY, PROFESSOR AND DIRECTOR OF THE PLANT MOLECULAR** and Cellular Biology Laboratory, has received the prestigious honor of being elected to the American Philosophical Society (APS). The APS is an eminent scholarly organization of international reputation, which promotes useful knowledge in the sciences and humanities. This country's first learned society, the APS has played an important role in American cultural and intellectual life for over 250 years.

For more than 25 years, Chory has used *Arabidopsis thaliana*, a small flowering mustard plant, as a model for plant growth. She has pioneered the use of molecular genetics to study how plants respond to their environment and has made major discoveries surrounding how plants sense light and make growth hormones. 



Joanne Chory with her husband, Stephen Worland, and children, Joe and Katie

## Esteemed neuroscientist and entrepreneurial leader elected to the Salk Institute Board of Trustees


**IN APRIL, THE SALK INSTITUTE BOARD OF** Trustees elected two new members to the Board: neuroscientist Thomas Jessell and Daniel Tierney, co-founder of GETCO (now KCG), a technology-enabled market making firm.

"Tom and Dan bring outstanding records of scientific expertise and entrepreneurial success to Salk," said **Irwin M. Jacobs**, chairman of the Salk Institute Board of Trustees. "We are greatly pleased to have them join our Board of Trustees."

Jessell has been a Howard Hughes Medical Institute (HHMI) investigator since 1985, and a Salk Institute Non-Resident Fellow since

2001. He is also the Claire Tow Professor in the Department of Neuroscience and the Department of Biochemistry and Molecular Biophysics at Columbia University. His research explores the link between the assembly and organization of neural networks and the behaviors they encode. He is examining these issues through an analysis of circuits that control movement.

Tierney currently serves as a board member and advisor at KCG Holdings, Inc. After stepping down from the co-CEO role at GETCO in 2012, Tierney became the founder and president of his family office, Wicklow Capital. He now spends

most of his time investing in other entrepreneurs and helping them turn their visions into reality. 

**"Tom and Dan bring outstanding records of scientific expertise and entrepreneurial success to Salk."**

— Irwin M. Jacobs





## Salk recruits human geneticist Graham McVicker

### EXPANDING ON ITS LEADERSHIP IN

genetics, the Salk Institute is pleased to announce the appointment of **Graham McVicker** as an assistant professor in the Integrative Biology Laboratory and in the Laboratory of Genetics.

"Graham is a forward-thinking researcher with an impressive background in developing and harnessing innovative techniques to help unravel the human genome," says **Rusty Gage**, professor in the Laboratory of Genetics. "Understanding and analyzing human genetic diversity is crucial to both science and medicine, and Graham's breadth of expertise in computing and genetics will spur important innovations in these areas."


McVicker will join the Salk Institute in January 2016. He seeks to understand how human genetic variation affects molecular processes in the cell and contributes to disease.

Geneticists have cataloged millions of genetic differences between individuals, but it is difficult to determine which of them affect human traits such as height, blood pressure and disease risk. McVicker has begun to tackle this problem by developing powerful statistical and computational approaches to analyze the human genome and determine the molecular function of individual genetic variants.

McVicker is particularly interested in genetic variants that affect chromatin. Chromatin is the molecular packaging that organizes DNA and regulates access to the genome, which helps control which genes are turned on in specific cells. Genetic variants that affect chromatin are likely to be important for many human diseases and the McVicker laboratory will focus specifically on those that affect chromatin in immune cells. By understanding these variants and linking them to disease risk, his laboratory will illuminate why some individuals are more susceptible to autoimmune and infectious diseases.

"I plan to push the boundaries of quantitative genetics and use genetic variation as a tool to understand the molecular processes that

underlie human disease," says McVicker. "I am excited to join the world-renowned faculty at the Salk Institute, where I will have the intellectual freedom, resources and collaborations to make important contributions in these areas."

McVicker earned his BS from the University of British Columbia in computer science and PhD from the University of Washington in genome sciences, where he studied how selection and mutation shape genetic variation in primate evolution. More recently, he conducted postdoctoral research at the University of Chicago, Stanford University and the Dana-Farber Cancer Institute, where he developed new methods for genetic mapping of molecular quantitative traits. 

**"Graham is a forward-thinking researcher with an impressive background in developing and harnessing innovative techniques to help unravel the human genome."**

— Rusty Gage



# Explore Salk

Tours, activities, talks

## Community discovers world of science at Explore Salk



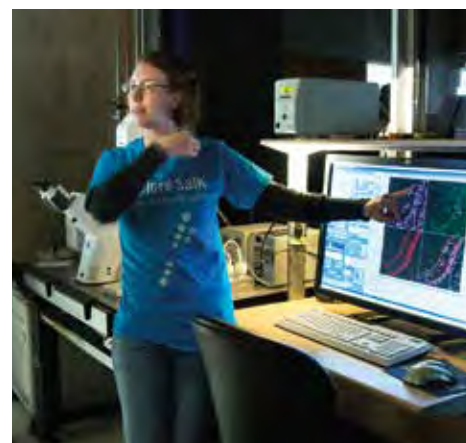
Eric Topol

**ON APRIL 11, THE SALK INSTITUTE** ONCE again opened its doors to the local community for its third annual Explore Salk event. Approximately 1,000 people—from science enthusiasts and Salk supporters to families eager to get a peek inside the world-famous laboratories—visited and spent hours exploring the campus.

Explore Salk included a number of hands-on activities for young attendees, while older participants toured labs and science booths to learn about cutting-edge research. Visitors also had the opportunity to learn about the Salk education outreach programs and were treated to a number of scientific talks. Assistant Professor **Saket Navlakha** spoke about his fascinating research on using lessons

in biology to solve technology problems. Eric Topol, director of the Scripps Translational Science Institute, chief academic officer at Scripps Health and a professor of genomics at The Scripps Research Institute, presented highlights from his recent book, *The Patient Will See You Now: The Future of Medicine is in Your Hands*, to a packed auditorium.

Explore Salk is organized and staffed by Institute employees, scientists, family and friends—a volunteer effort that demonstrates their passion for scientific discovery. In praising their contribution and the event's continued success, **Rebecca Newman**, vice president of External Relations, hailed it as “a unique experience that is not replicated anywhere else in San Diego.”







From left: Clodagh O'Shea, Emily Hatch and Amy Rommel

**salk** women  
& science  
Where cures begin.

## Women & Science: An evening of celebration and education

**TWO FEMALE SALK RESEARCHERS HAVE BEEN NAMED THE FIRST** grant recipients of the Salk Women & Science Special Awards Initiative. Nearly 200 people attended a celebratory event sponsored by BioMed Realty on March 24.

The event kicked off with Dress for Success San Diego, an organization committed to providing job preparation services to low-income women striving for self-sufficiency. Among the many donations Salk received for the drive were 280 dresses and suits, 31 pairs of shoes, 36 purses and more than 100 items of jewelry and accessories.

At the event, Salk researchers **Emily Hatch** and **Christina Chang** were named the 2015 inaugural Postdoctoral Fellowship Recipient and the Graduate Student Fellowship Recipient, respectively.

The awards were created to provide funding to female scientists conducting high-risk research projects. A \$100,000 fundraising goal established in October 2014 was exceeded before the spring Women & Science event, thanks in part to generous initial gifts from Elizabeth Keadle, Carol and John Gallagher of the Gallagher Charitable Fund, Lyn Nelson, Hoyle Cohen Women's Practice, and Lynne Rosenthal and Patti Silver of the Leo S. Guthman Fund.

On the heels of the inaugural Initiative's success, **Joanne Chory**, director of the Salk's Plant Molecular and Cellular Biology Laboratory, pledged the first lead gift for the 2016 grant program "in honor of the 111 women in PBIO-C who enriched my life over the past 27 years." In the nearly three decades Chory has been mentoring young scientists, 44 percent of them have been women.


Before the recognition ceremony, the evening's host, Associate Professor **Clodagh O'Shea**, took the stage to thank attendees for their philanthropy and their growing ranks. Marveling at the mainly female

congregation, she said, "This is the first time I've seen more women in the audience at a scientific talk than men. Let's celebrate that."

Citing double-digit statistics that illustrate the gap still existing between men and women in scientific academia, O'Shea said that is why the Salk Women & Science program is "important to preserve." She expressed gratitude for the opportunities afforded not only her, but also the young women in the field today.

**Amy Rommel**, a postdoctoral research associate in Professor **Inder Verma's** Laboratory of Genetics, then proceeded to captivate the audience with a talk about her research efforts on glioblastoma, one of the most lethal forms of cancers.

Current treatment of glioblastoma combines surgical removal of the tumor, administering toxic chemicals and depriving the tumor of nutrients, Rommel explained. Unfortunately, tumor cells have mechanisms to overcome these attacks. One mechanism of adaptation, previously published in a study from the Verma lab, suggests glioblastoma has the ability to convert some of its tumor cells into functional vascular cells. Rommel's work proposes novel strategies to treat glioblastoma by reverse engineering the mechanism the tumor is already using—reprogramming the tumor-initiating cells back to their "normal" non tumor-initiating state.

Now in its third year, Salk Women & Science was created to engage the community in biological science and technology through presentations such as Rommel's. For more information on the program, visit [www.salk.edu/womenandscience](http://www.salk.edu/womenandscience) or contact **Betsy Reis**, director of Donor Relations, at (858) 453-4100 x1426 or [breis@salk.edu](mailto:breis@salk.edu). 

» View video: [www.salk.edu/insidesalk/0815/womenandscience](http://www.salk.edu/insidesalk/0815/womenandscience)

## Hatch, Chang garner first Women & Science awards

**RESEARCH ASSOCIATE EMILY HATCH, WHO WORKS IN THE MOLECULAR and Cell Biology Laboratory led by Professor **Martin Hetzer**, has been named the inaugural Postdoctoral Fellowship Recipient of the Salk Women & Science Special Awards Initiative.**

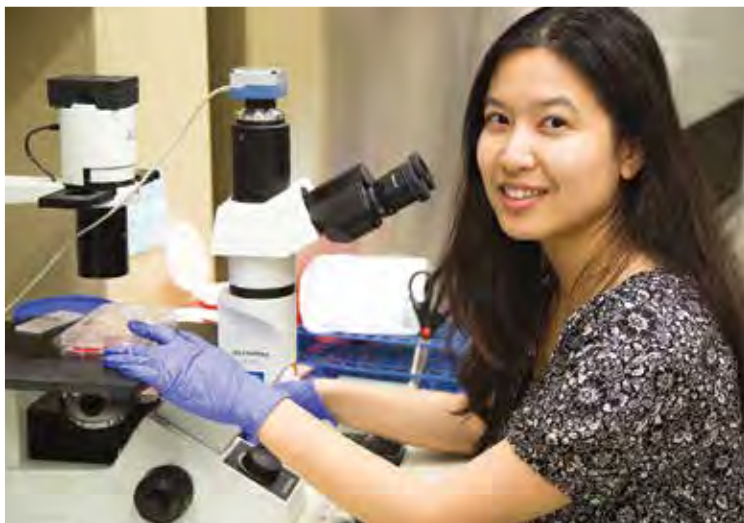
Hatch earned her bachelor's degree in biology from Williams College in 2003, and her PhD in 2011 from Stanford University, where she successfully studied various aspects of centriole duplication. She joined the Salk Institute in 2011, focusing her work on the nuclear envelope dynamics in mammalian cells. In 2013, she published a landmark paper in *Cell* in which she addressed a question centering on the mechanism of chromothripsis, a recently identified process by which chromosomes fragment and undergo massive rearrangement.

"Emily has a great personality and scientifically she is remarkably mature," Hetzer wrote in his nomination of Hatch. "She is driven by scientific passion in its purest form and also by the desire to work on cancer-related questions."

**Christina Chang**, a graduate student in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis led by **Ye Zheng**, was named the Graduate Student Fellowship Recipient for 2015.

Currently attending the University of California, San Diego to earn her PhD, Chang joined Zheng's lab in 2011 to work on a new project that originated from collaboration between the labs of Zheng and **Ronald Evans**. Her research focuses on the molecular mechanism involved in the differentiation of T helper 17 cells, a recently identified subset of T lymphocytes.

"Christina has the genuine curiosity that propels her to constantly ask the right questions and seek answers through her own efforts," Zheng wrote in his nomination letter. "She has also presented her work at multiple meetings and conferences with very positive feedback. I can already see her on the trajectory of becoming an exceptional scientist in the future." 📊



Christina Chang



From left: Richard Heyman, Liz Keadle and Greg Lemke

## Trustee Richard Heyman addresses Salk alumni

### BIOTECH ENTREPRENEUR AND RECENTLY

elected Salk trustee Richard Heyman, PhD, spoke at the Institute's annual alumni mixer in June. He was well suited for the role: Heyman is also a Salk alumnus, having once worked as a postdoctoral researcher in the lab of **Ronald Evans**, professor and director of the Gene Expression Laboratory.

Salk's Alumni Program helps connect some 3,500 researchers who trained at the Institute before going on to important positions at facilities all over the world.

Five years ago, Salk established the Alumni-Faculty Fellowship Fund raising enough funds every year to grant a fellowship to a postdoctoral researcher. Both alumni and current Salk faculty contribute to the fund.

To learn more about the Salk Alumni program, visit [www.salk.edu/alumni](http://www.salk.edu/alumni) or contact **Megan Shockro** at (858) 453-4100 x1405 or [mshockro@salk.edu](mailto:mshockro@salk.edu). 📊



Guests mingling at Salk's annual Alumni event





From left: Irwin Jacobs, Sibylle Szaggars Redford, Joan Jacobs and Robert Redford

## Sibylle Szaggars Redford unveils environmental artwork at Salk


**MULTIMEDIA ARTIST SIBYLLE SZAGGARS REDFORD** shared selections from her series “The Shape of Color & The Way of the Rain” at an April reception at the Institute attended by Salk supporters, trustees and invited guests. Wife of renowned actor and filmmaker Robert Redford—who featured the Salk Institute in last year’s *Cathedrals of Culture* documentary film project—Szaggars Redford exhibits her work throughout the world to raise awareness of humanity’s impact on the environment. The pieces, which were created by exposing pigment to rain, were displayed through May, with 30 percent of all sales generously donated to the Salk Institute. 📺





## Back to Basics lecture links neuroscience with architecture

**IN MARCH, OVER 200 PEOPLE GATHERED ON THE** Salk campus to hear **Thomas Albright**, professor and director of the Vision Center Laboratory and holder of the Conrad T. Prebys Chair in Vision Research, present a Back to Basics lecture. In an engrossing talk that prompted much discussion during the reception that followed, Albright explained how what neuroscientists are learning can help architects design buildings optimally suited for the humans inside them. Informed architects can manipulate light, sound, texture and space to design, for example, hospitals that promote healing or schools that enhance learning.

Audiences continue to grow for these biannual lectures that invite the public to hear about the dynamic research performed at the Salk Institute. There is no cost to attend. For more information about the next Back to Basics event, which will be held Tuesday, September 22, 2015, please contact **Jennifer Rothrock** at (858) 500-4881 or [jrothrock@salk.edu](mailto:jrothrock@salk.edu). 

## Samuel Pfaff shares exciting new discoveries with Salk supporters in New York City


**IN APRIL, SAMUEL PFAFF, PROFESSOR** in the Gene Expression Laboratory, Howard Hughes Medical Institute investigator and holder of the Benjamin H. Lewis Chair, traveled to New York to share his most recent discoveries in neurodegenerative disease. Trustee Mary Jane Salk hosted the event. Françoise Gilot, artist and widow of Jonas Salk, was among the attendees.

Pfaff's team investigates how nerve cells form and how they wire up correctly, focusing on fetal development of the spinal cord. His lab hopes to eventually harness these "embryonic pathways" to repair or augment the central nervous system. He and his team are building on their discovery that just a handful of critical genes direct the complex



neuron wiring programs in early brain development, information that could lead to novel treatments for those with spinal cord injury or neurological disorders such as amyotrophic lateral sclerosis (ALS).



For more information on scientific presentations in the New York region, please contact **Megan Shockro** at [mshockro@salk.edu](mailto:mshockro@salk.edu) or (858) 453-4100 x1405. 





Tax Seminar attendees and representatives from the Joe W. and Dorothy Dorsett Brown Foundation at the Marine Room dinner



Representatives from the Marshall Heritage Foundation and Legacy Foundation with Samuel Pfaff and Eric Brunstad

## 43rd Annual Tax Seminar for Private Foundations held in May

**THE 43RD ANNUAL TAX SEMINAR FOR PRIVATE FOUNDATIONS**, hosted by the Salk Institute, returned to La Jolla May 11-13. The event, held at the Estancia La Jolla Hotel & Spa, drew a series of nationally known lecturers and authors who provided insights on foundation tax law, management, finance and governance. The seminar covered everything from the complexity of changes in tax law to new ideas and perspectives for foundation leaders.

Edwin Hunter, chairman of the event and president of Hunter, Hunter & Sonnier, says, "No seminar in the private foundation universe offers a more distinguished or capable faculty."

Randall Munroe, the tax seminar keynote speaker and creator of the webcomic *xkcd*, offered an entertaining talk based on his nonfiction best seller, *What If?: Serious Scientific Answers to Absurd Hypothetical Questions*. Munroe, a former NASA roboticist, spoke to a nearly full house in Salk's Conrad T. Prebys Auditorium and followed up his presentation with a book signing for attendees. The seminar concluded that evening with an outdoor supper reception in the courtyard. 📖

## Inaugural meeting of Salk Institute Council offers a new way to engage with the Institute

**THE INAUGURAL MEETING OF THE SALK INSTITUTE COUNCIL**, HELD May 12-14, attracted a roster of more than 50 attendees who gathered to learn more about the Institute. Salk Institute Council co-chairs Rich Heyman and Diana Kalman, along with faculty liaison **Reuben Shaw**, put together an exciting and robust program focusing on the continuum of Salk science from the early visionary years to the present and beyond.

The mission of the Council is to advocate on behalf of Salk science by focusing on leadership development and fundraising through the meaningful engagement and active participation of its members.

The meeting kicked off with "Bio 101" by Salk's award-winning Education Outreach team, **Ellen Potter** and **Dona Mapston**, who focused on the basic science underlying the various research areas represented by Salk scientists. Additionally, nine Salk faculty members as well as postdoctoral researchers gave presentations on topics ranging from breakthroughs in science to creativity and the intersection of disciplines. Chief Financial Officer **Kim Witmer** and Vice President of External Relations **Rebecca Newman** also presented an insider's view of Salk's operational strategy. Finally, Salk Board of Trustees Chairman Irwin Jacobs closed the meeting with an inspiring talk about his career in innovation as well as why he was drawn to Salk.

The program offered many opportunities such as these for participants to take a behind-the-scenes peek at the inner workings of the Institute. In addition to the access attendees were granted to the Institute's scientists



Institute Council Co-Chairs Diana Kalman and Rich Heyman

and Salk community, there was also an opportunity to tour Salk's Stem Cell Core and Waitt Advanced Biophotonics Center Core.

**Claudia Ehrlich**, senior director of External Relations and staff liaison for the Council, noted, "The meeting offered many ways for attendees to engage with the innovative work being done at Salk, from the science to the business and leadership. Our hope is they all came away invigorated and inspired to deepen their engagement with the Institute." 📖



## 2015–2016 SEASON

BE AMAZED AND INSPIRED



**SUNDAY, OCTOBER 11, 2015**

**VADYM KHOLODENKO, piano**  
Gold Medalist, 2013 Van Cliburn Competition

“His masterful performance astonished us with the power and beauty of his playing...It was the kind of magical performance that made you hold your breath.”

— *Peninsula Reviews*



**TONY HUNTER**  
Professor, Molecular and Cell Biology Laboratory



**SUNDAY, FEBRUARY 21, 2016**

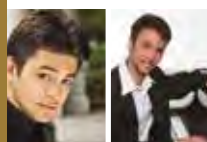
**CICELY PARNAS, cello**  
Winner, Young Concert Artists Competition

“Self-possessed Parnas is musically poised...this was artistry that cannot be taught; the musician simply owns it.”

— *The Washington Post*



**BEVERLY EMERSON**  
Professor, Regulatory Biology Laboratory



**SUNDAY, NOVEMBER 8, 2015**

**ASI MATATHIAS & VICTOR STANISLAVSKY**  
violin and piano

“...with virtuosic flair and technique to burn, Asi Matathias and Victor Stanislavsky performed a riveting recital.”

— *San Diego Arts*



**JANELLE AYRES**  
Assistant Professor, Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis



**SUNDAY, MARCH 20, 2016**

**JULIA BULLOCK, soprano**  
Winner, Young Concert Artists Competition

“Ms. Bullock wielded her elegant, richly hued voice to alluring effect...ravishingly visceral.”

— *The New York Times*



**GEOFFREY WAHL**  
Professor, Gene Expression Laboratory



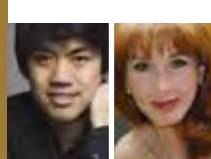
**SUNDAY, JANUARY 24, 2016**

**Jazz Legend VICTOR GOINES**  
Victor Goines Trio

“...reaffirms that lyrical grace and technical bravura can co-exist beautifully.” — *Chicago Tribune*



**SREEKANTH CHALASANI**  
Assistant Professor, Molecular Neurobiology Laboratory



**SUNDAY, APRIL 24, 2016**

**SEAN CHEN & KAREN JOY DAVIS**  
Duo piano concert

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

— *L.A. Music Examiner*

“Ms. Davis’ performance was unique and assured... displayed sparkling brilliance and technical accuracy”

— *The London Times*



**JULIE LAW**  
Assistant Professor,  
Plant Molecular and Cellular Biology Laboratory





# Insider's View

William R. Brody, MD, PhD

President, Salk Institute

Irwin M. Jacobs Presidential Chair

## The Second Green Revolution

**IN 1968, I REMEMBER BEING SCARED OUT OF MY** wits reading the best-selling book by Stanford ecologist Paul Ehrlich, *The Population Bomb*. Professor Ehrlich's logic was impeccable: he said the global population would double by 2005 (to about 7 billion in actuality) and that the world would run out of food, causing mass starvation and deaths.

When 2005 came, Ehrlich's predictions on population growth proved remarkably accurate, but not his warnings of global-scale starvation. Where was the food shortage? As it turned out, Ehrlich's calculations hadn't factored in important developments in the growth of the food supply that would help food production keep pace with the burgeoning human population.

In fact, what happened was the Green Revolution, a period of dramatic growth in the world food supply kicked off by Norman Borlaug, an American plant biologist who developed strains of wheat that were much higher yielding and disease resistant than the status quo. In addition, the introduction of advanced agricultural practices worldwide provided a tremendous increase in productivity not thought feasible when Ehrlich made his doomsday prediction.

Borlaug launched the Green Revolution and was joined in this effort by many other scientists who introduced similar innovations in agriculture production.


Agricultural innovations allowed wheat production to increase from 800 pounds per acre in the 1950s to over 6,000 pounds per acre by the late 1960s. For his work, Borlaug received the Nobel Peace Prize and is credited with saving millions of lives from starvation.

Today, young ecologists are beginning to write books similar to *The Population Bomb*. Although the world population growth is slowing, so is the growth of agricultural productivity, and climate change is already tipping regions around the world into drought.

We need visionary plant biologists who can develop a much deeper understanding of how plants react to environmental stress and what can be done to protect existing species or create new ones that are more tolerant of heat, drought and disease.

Unfortunately, at the moment, the field of plant biology is seriously underfunded. Yes, I know that getting National Institutes of Health grants is difficult, but for plant biology the scene is even bleaker. NIH typically only funds plant biology grants where there is a link to the understanding of human diseases, while the National Science Foundation budget for plant biology has been woefully inadequate for decades.

Private philanthropy is helpful—the Gordon and Betty Moore Foundation teamed with the Howard Hughes Medical Institute to fund faculty scholars in plant biology—as was illustrated when Salk professor **Joseph Ecker** received one of these generous awards. But we need to raise awareness among the general public that funding plant science is just as important as funding cancer research.

We need to kick-start the Second Green Revolution. The well-being of our children and grandchildren will likely depend upon innovations to protect and grow our food sources. 

# 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](http://www.salk.edu/support) or call (858) 453-4100 x1405.

## Get Involved

### FRIENDS OF SALK

Unrestricted gifts, in any amount, provide funding where it is most needed and allow our scientists to conduct critical early-stage research. Contributors up to \$2,500 receive *Inside Salk* magazine and invitations to annual events at the Institute.

### 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.

### PRESIDENT'S CLUB

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 to \$25,000 enjoy unique opportunities to interact with our scientists in the lab and receive Salk publications.

### CHAIRMAN'S CIRCLE

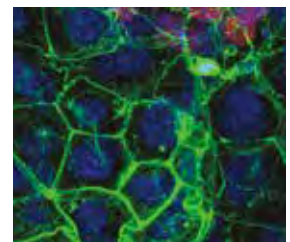
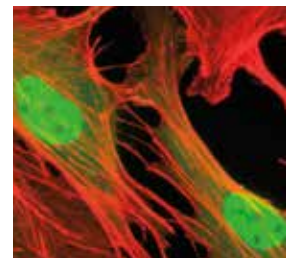
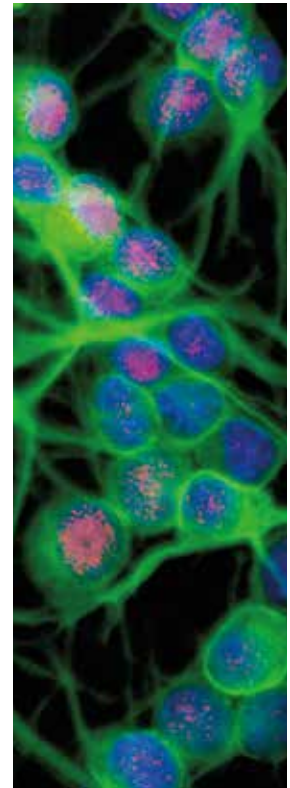
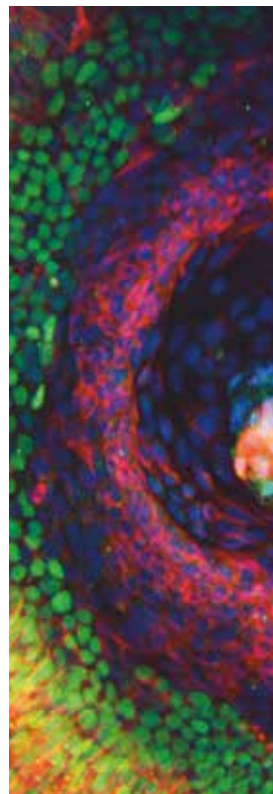
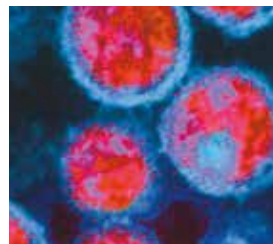
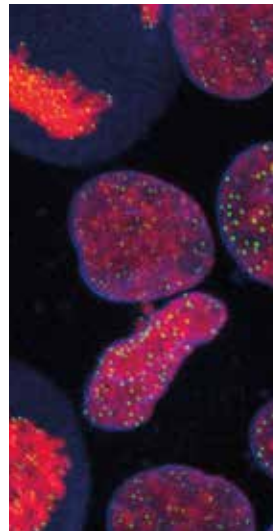
Chairman's Circle visionary donors support the Institute's mission with unrestricted annual gifts of \$25,000 and above. Their generous support fills a vital need for the Institute by providing the world's finest minds in science with the resources to pursue discoveries at the frontier of human knowledge. 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.



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Where cures begin.





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**Salk Institute for Biological Studies**

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There are many ways to support Salk. For detailed information on opportunities, please email [giving@salk.edu](mailto:giving@salk.edu) or call (858) 550-0472

## Salk Calendar

### SEPTEMBER

- 22 Back to Basics Lecture
- 24 San Diego Salkexcellerators private dinner

### OCTOBER

- 11 Salk Science & Music Series  
featuring Vadym Kholodenko
- 28 San Diego Salkexcellerators private reception  
and scientific presentation

### NOVEMBER

- 8 Salk Science & Music Series  
featuring Asi Matathias & Victor Stanislavsky

### DECEMBER

- 2 Salk Women & Science



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