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InsideSalk

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THE SALK INSTITUTE FOR BIOLOGICAL STUDIES
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Decoding the Rosetta Stone of Autism Spectrum Disorders

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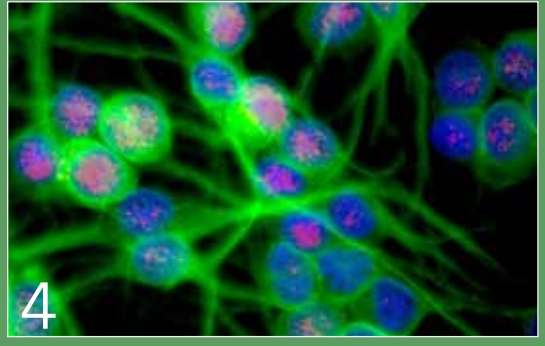
» Symphony at Salk Sets New Fund Raising Record

February 2011
Inside Salk



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Autistic neurons. Photo by Carol Marchetto.

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Dear Friends,

IN LATE OCTOBER WE COMPLETED OUR OFFICIAL 50th anniversary celebrations with an energizing, thought-provoking symposium on the present and future of the life sciences. The three-day meeting featured presentations by two dozen of the world's leading scientists, who examined the near and far horizons of cancer research, neuroscience, immunology and virology, plant sciences, stem cell and developmental biology and metabolism research.

Opening keynote speaker **David Baltimore**, a Nobel Laureate who was one of the Salk's first resident researchers in the 1960s, spoke about witnessing the original construction and recalled working within the new Louis Kahn buildings with their intentional flexibility. The architecture "inspires its denizens to greater heights of creativity," said Baltimore, now a Salk Non-Resident Fellow. "I never cease to be awed by the buildings and the science within."

The symposium was the ideal way to wrap up the first 50 years of Salk science—by appreciating who we are and what has been accomplished here and by foreshadowing the decades of discovery ahead. I must thank professor **Inder Verma** for organizing this gathering of so many of the finest scientific minds, who represent research areas that are especially meaningful to the Salk.

At the culminating dinner event, we awarded the coveted Salk Institute Medals in Science and Public Service to two distinguished individuals—**Robert Roeder** of Rockefeller University and our own extraordinary board chair, **Irwin M. Jacobs**. Roeder is an acclaimed biochemist who studies the way genes are turned on and off in healthy cells and how gene expression breaks down in diseases like cancer. And Irwin, as you already know, is one of the most public-spirited people in America. **Jonas Salk** would have been immensely proud to recognize these men in this fashion.

Now, as we surge into our next half-century, we open this latest issue of *Inside Salk* with a report of astonishing findings by professor **Fred Gage**. He and his team discovered that in patients with Rett syndrome, the most physically disabling of the autism spectrum disorders, so-called jumping genes are given free rein to move about the genome of brain cells. Usually forced to stay put, these mysterious mobile DNA elements start inserting extra copies of themselves into random stretches of DNA, reshuffling the genome of neurons and possibly contributing to the baffling symptoms of the disease.

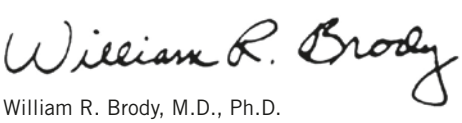
In a related study, Gage collaborated with colleagues from the University of California, San Diego, and successfully replicated autism in the lab with the help of human induced pluripotent stem (iPS) cells derived from patients with Rett syndrome. Their trailblazing experiments gave scientists an unprecedented view of autism by revealing that Rett neurons form fewer connections with other brain cells and that some of the symptoms are reversible, raising the hope that one day, autism may turn into a treatable condition.

William R. Brody

> **"I never cease to be awed by the buildings and the science within."**
>
> **– David Baltimore**

Professor Gage's discovery compels us to wonder about what lies ahead in neuroscience and in each of the disciplines so ably populated by the gifted scientists of the Salk. To that end, Salk faculty and the colleagues who joined them at the recent symposium submitted their written predictions for research advances in the next 25 years.

Those predictions have been collected and placed in a time capsule that now resides in my office, to be opened in 2035. Let's look forward to reading them and evaluating their prescience together.



William R. Brody, M.D., Ph.D.
Irwin M. Jacobs Presidential Chair

Unlocking the **Mystery of Autism**

From left to right: Carol Marchetto, Fred H. Gage, Alysson Muotri

Fred H. Gage uses Rett syndrome as a "Rosetta Stone" to learn more about the biology underlying autism, one of the biggest medical puzzles of our time.

THE PICTURES OF HER FIRST BIRTHDAY party show a smiling little girl, excitedly reaching for the candles on her cake. A year later, she is unable to sit up or grasp with her fingers. Rett syndrome, a devastating brain disorder, has thrown her development into reverse.

Triggered by a tiny genetic flaw, the rare disease afflicts girls almost exclusively. The symptoms start to emerge just as they are beginning to walk and talk. Seemingly out of the blue, normal development slows down, and eventually the infants regress, progressively losing speech and motor skills. Toddlers who used to bask in their parents' attention often become withdrawn and anxious and avoid eye contact. Instead of reaching for toys, they wring their hands over and over again, leading researchers to classify Rett syndrome as one of the autism spectrum disorders. But unlike most forms of autism, which have no single known cause, almost all cases of Rett syndrome can be traced to defects in a single gene known as MeCP2.

"Because of similar symptoms and shared genetic links, Rett syndrome is sometimes considered a 'Rosetta Stone' that can help us to understand other developmental neurological disorders such as autism and schizophrenia," says **Fred H. Gage**, a professor in the Salk's Laboratory of Genetics and holder of the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases.

In two recently published landmark papers, he and his team reported on some startling discoveries that are bound to change the way people think about psychiatric disease. One features "jumping genes," the other "autistic" brain cells in a dish.

Gage had long been interested in so-called L1 retrotransposons, restless bits of DNA that can freely move about the genome, earning them the nickname "jumping genes." Almost all of them are marooned at a permanent spot by mutations rendering them dysfunctional, but in humans a hundred or so are free to paste copies of themselves into random stretches of DNA.

In fact, over past millennia, so many copies have squeezed themselves into the human genome that they now make up 17 percent of a cell's DNA. While most of them have landed in a genomic no-man's land, once in a while, a retrotransposon can insert itself close enough to a functional gene to disrupt its function and cause disease. For example, L1 insertions created the mutations underlying hemophilia and Duchenne muscular dystrophy.

One of the best documented and arguably most beautiful examples of retrotransposons wreaking havoc on a gene's function is the merle coat pattern, which gives Australian shepherds their characteristic patchy coat and stunningly blue eyes. The merle patterning was born when aretrotransposon slipped into SILV, a gene important in mammalian pigmentation.

Most retrotransposons are active in sperm and eggs, explaining how new insertions can be passed on to succeeding generations. But until recently, scientists had no clue that these restless genes might be active elsewhere. Then last year, Gage and his team demonstrated that L1 retrotransposons are on the move in the human brain. They add hundreds of extra copies to the genome of neurons, randomly rearranging our mental structure.

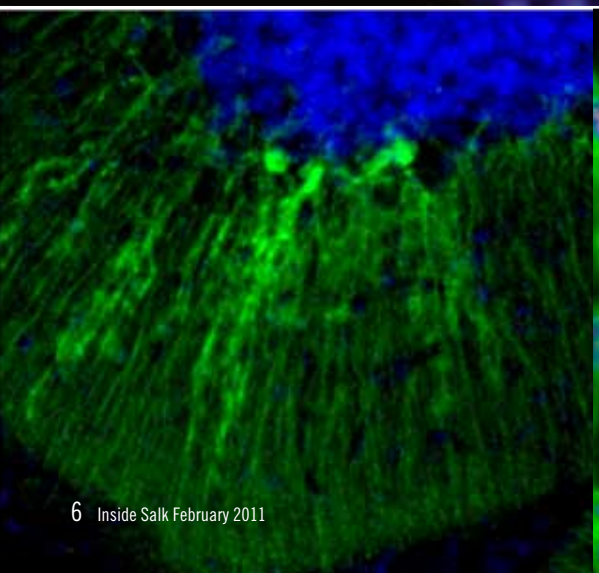
He believes that the addition of these so-called mobile elements is a potential mechanism to create the neural diversity that makes each person unique. "It could also help explain the differences in identical twins," he says. "Even though they are clones, they have their own personalities."

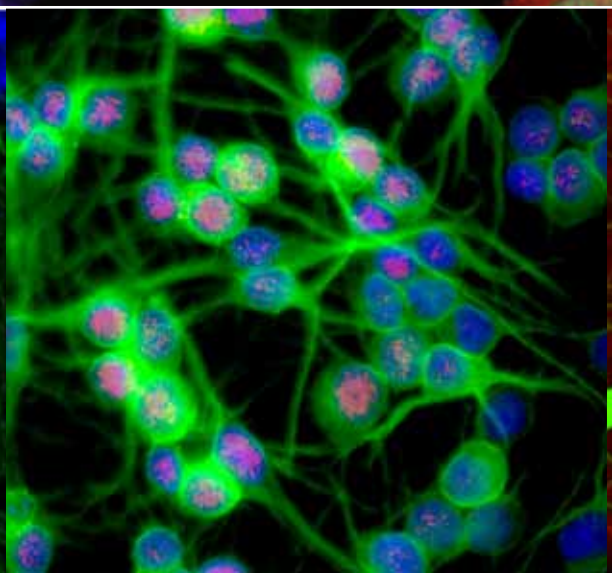
But what if the reshuffling goes wrong? There is a fine line between spawning variety in our minds and eroding the foundation of our mental architecture. "Mobile elements can't just be let loose in the brain; their activity has to be strictly controlled," says Gage.

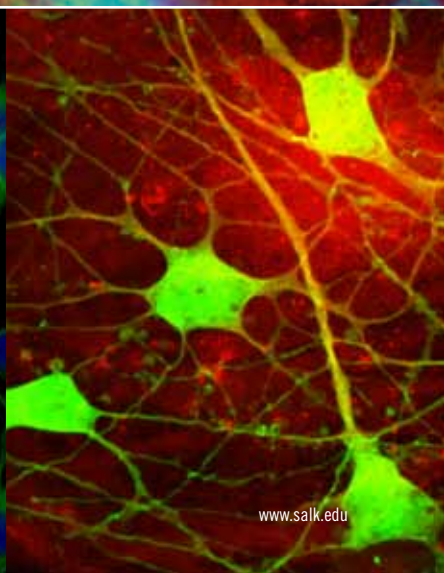
Maybe not surprisingly, L1 elements are only active during a short window of time: the early stages of brain cell development. Once brain stem cells are committed to spending the rest of their lives as neurons, for example, the L1 elements will cease mobility.

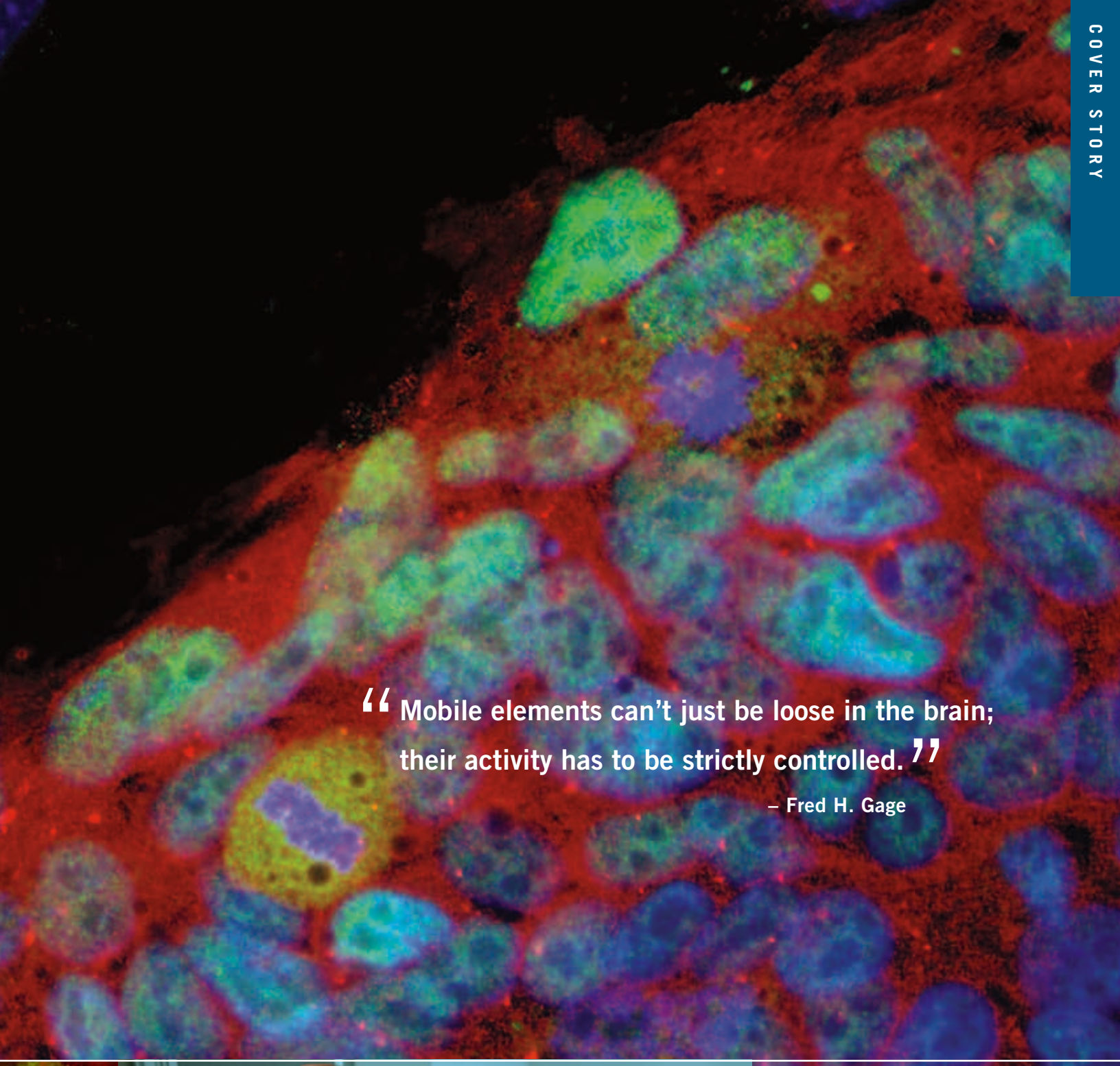
"In my mind, this restricted time frame immediately raised the question of how this process is regulated and what happens when it is derailed," explains **Carol Marchetto**, a postdoctoral researcher on the Gage team. She and her husband, **Alysson Muotri**, Ph.D., who started his career in the Gage lab and now leads his own research group at the University of California, San Diego School of Medicine, decided to look for the answer.

Their attention was quickly drawn to MeCP2. It is one of several so-called methyl-CpG-binding proteins, which are best known as gene silencers. They turn off genes by binding to nearby regulatory regions of DNA. Not only is MeCP2 protein incredibly abundant in neurons, it also binds to a stretch of DNA that is known to control the activity of L1 retrotransposons.

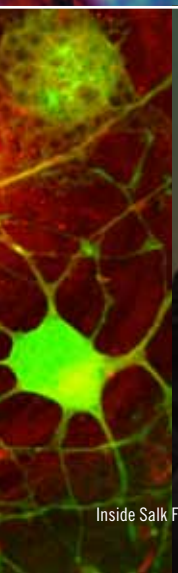


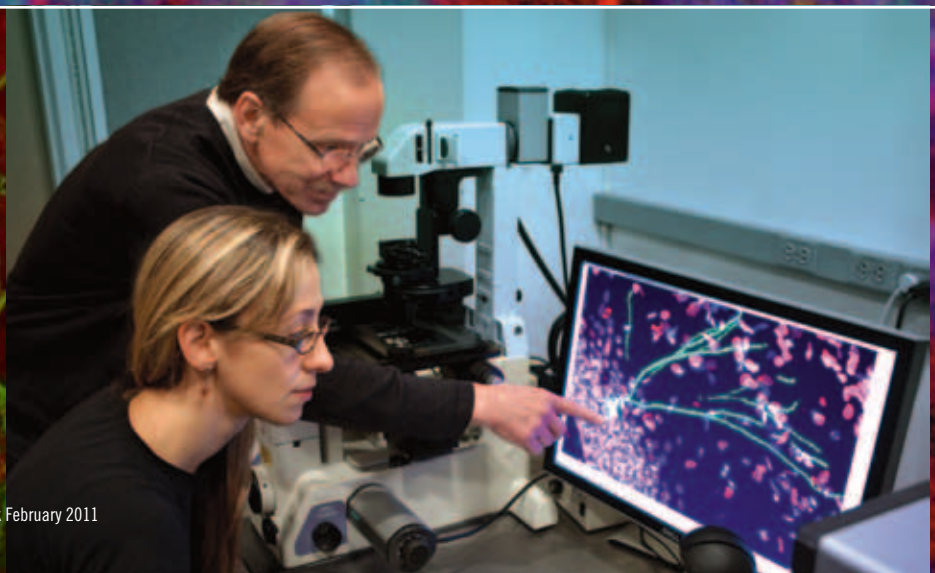


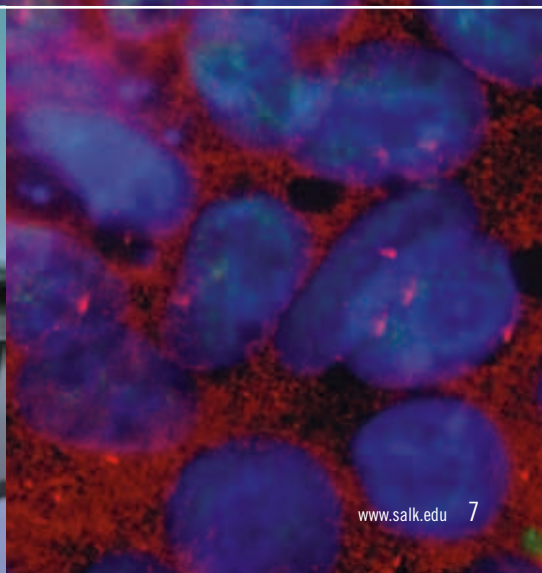


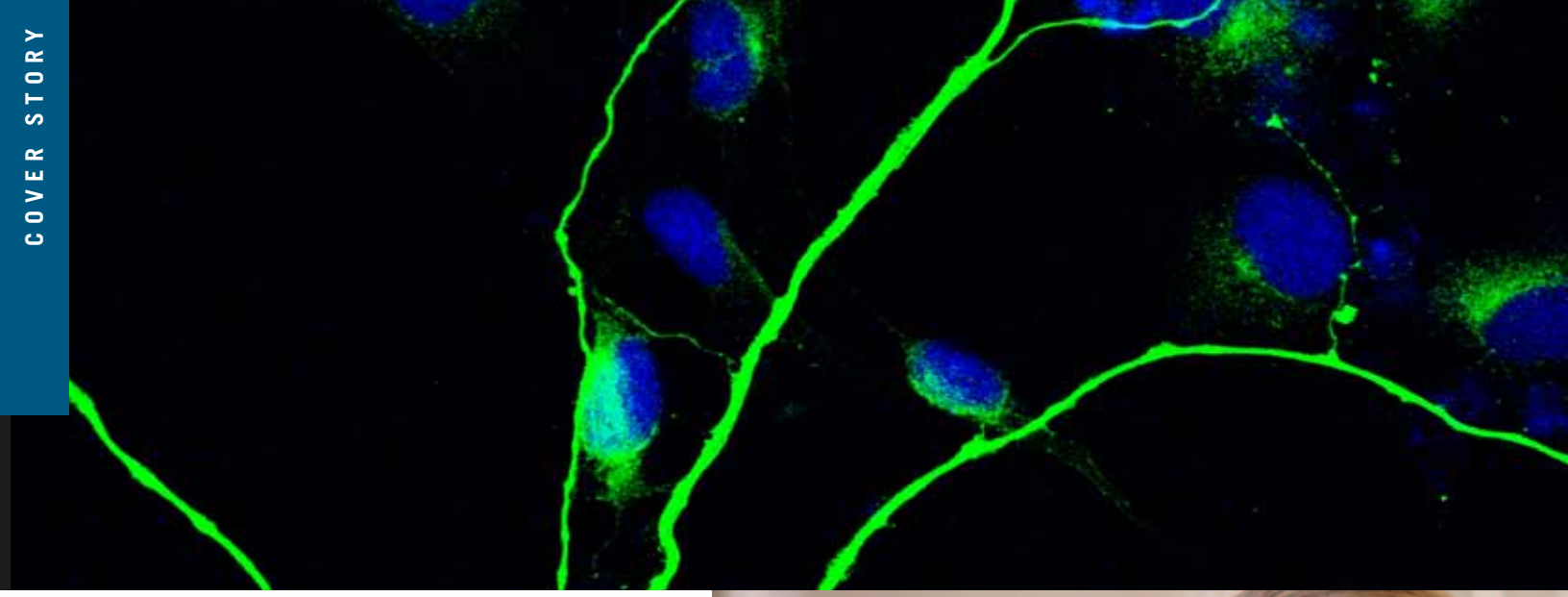


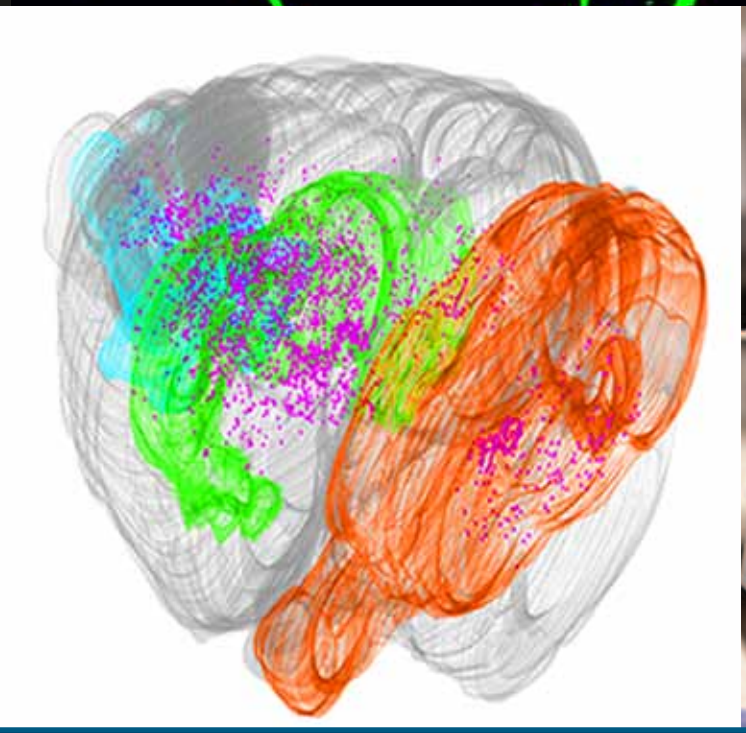
> “Mobile elements can’t just be loose in the brain; their activity has to be strictly controlled.”
>
> – Fred H. Gage











What if?

When Marchetto and Muotri discovered a few years ago that mutations in MeCP2 had been linked to Rett syndrome, they couldn't help but think, *What if unregulated jumping genes played a role in neurological disorders?*

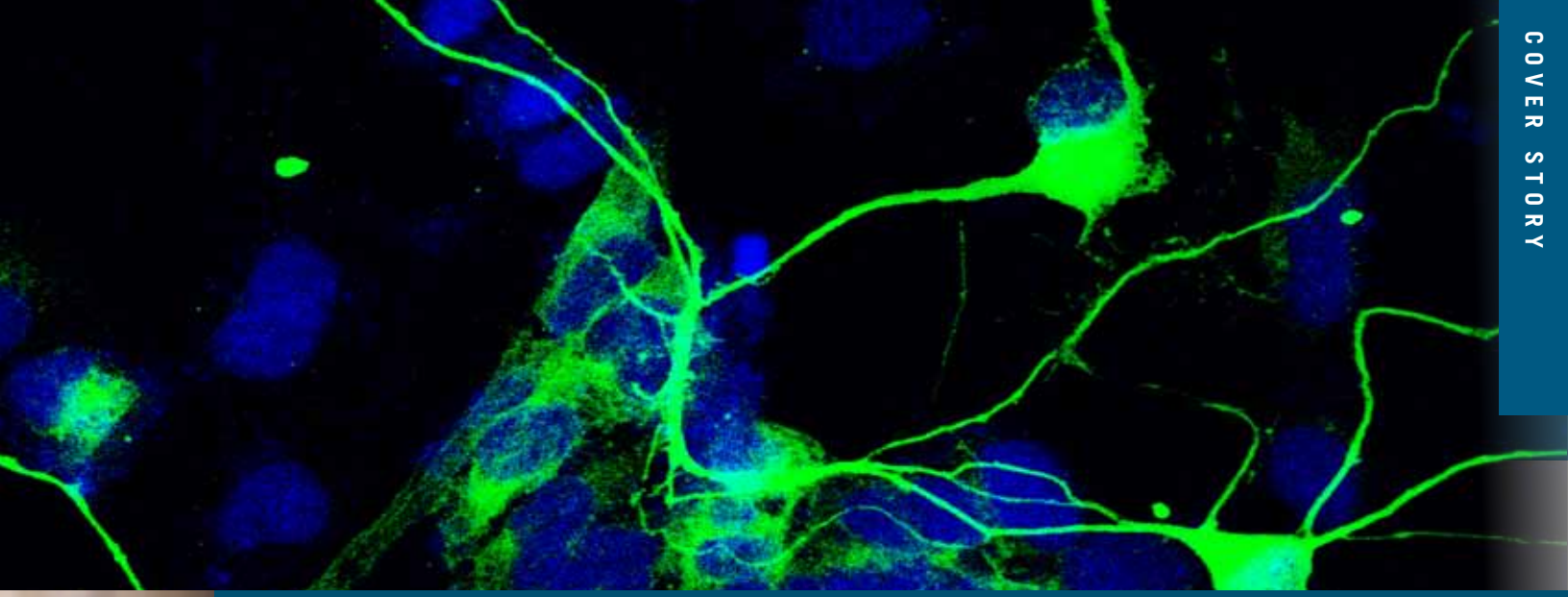
First, the researchers wanted to know whether MeCP2 interfered with the ability of an artificial L1 element to move around in cultured neuronal stem cells. To find the tiny mobile sequence in a sea of genomic DNA, they added to it a molecular tracer—a green fluorescing protein—that lit up the host cell whenever a copy had broken free and migrated to a new spot.

And sure enough, without MeCP2, the cells lit up like a beacon, giving away the presence of roving L1 copies. With MeCP2 around, nothing much happened. What's more, in the brains of mice that had been engineered in the same way, L1 activity increased up to six-fold compared to normal control mice.

Intrigued, Marchetto and Muotri wondered whether the same was happening in the brain cells of patients with Rett syndrome. To find out, they first generated so-called induced pluripotent stem (iPS) cells derived from Rett patients. They started with skin biopsies taken from affected individuals and a healthy control. By exposing the skin cells to four reprogramming factors, they turned back the clock, triggering the cells to look and act like embryonic stem cells.

When Marchetto introduced the modified L1 element and coaxed the iPS cells down the developmental path leading to neurons, she found that the mobility in cells derived from Rett patients was almost twice as high as that in normal cells.

Making an artificial element jump in a Petri dish was one thing, but what about endogenous L1 retrotransposons that make their home in brain cells of patients with Rett syndrome? To search for evidence that mutations in MeCP2 set endogenous L1s free as well, Gage's team developed a new technique that allowed them to detect the minute increase in DNA content caused by the additional copies inserted into the genome.



> **"There is certainly a genetic component to Rett syndrome and other psychiatric disorders, but it may not be the only thing that's relevant. Somatic insertions and alterations caused by L1 elements could play a significant but underestimated role in other neurodevelopmental diseases because they are hard to detect."**
>
> **– Alysson Muotri**

Opposite left: L1 retrotransposons are particularly active in the cerebellum (shown in green), which plays an important role in motor control. Magenta dots represent brain cells with new L1 insertions.

Opposite right: Carol Marchetto

"A single L1 retrotransposon, which is only about 6,000 base pairs long, resembles the proverbial needle in a haystack, when compared to the 3 billion base pairs of the human genome," says Marchetto.

The painstaking search paid off. The researchers found what they had been looking for: the number of L1 copies in the brains of Rett patients was significantly higher than in the brains of non-affected individuals.

"This is the first time that we can show a connection between genomic stability and a mental disorder," says Gage. But he cautions that the high rates of neuronal transpositions in MeCP2-deficient mice and Rett patients may be a consequence, rather than the cause, of the disease.

"Nonetheless, new somatic insertions, especially during early developmental stages, may play a role at later stages of the disease and could explain the baffling variability of autistic symptoms observed in Rett syndrome patients," he adds.

Since MeCP2 abnormalities have been linked to autism and other mental disorders, the insights gained from studying this gene may be relevant beyond Rett syndrome.

"There is certainly a genetic component to Rett syndrome and other psychiatric disorders, but it may not be the only thing that's relevant," says Muotri. "Somatic insertions and alterations caused by L1 elements could play a significant but underestimated role in other neurodevelopmental diseases because they are hard to detect."

The only way to find out is to decrease the activity of L1 elements in mouse models and to see whether that changes the animals' behavior. "If it does, we can then search for drugs that modulate L1 activity in humans," says Gage.

> “Being able to study Rett neurons in a dish allowed us to identify subtle alterations in the functionality of the neuronal circuitry that we never had access to before.”
>
> – Fred H. Gage

Autism in a dish

The ability to obtain iPS cells from patients’ skin cells and to differentiate them into the cell type damaged by the disease gave Marchetto and Muotri a first glimpse at the connection between hyperactive jumping genes and Rett syndrome.

In a separate study, recently published in the journal *Cell*, they used these cells to replicate autism in the lab and study the molecular pathogenesis of the disease.

In the past, scientists had been limited to studying the brains of people with autistic spectrum disorders via imaging technologies or postmortem brain tissues. Both of these strategies are limited, however, and do not allow the researchers to perform experiments in live human neurons.

“It is quite amazing that we can recapitulate a psychiatric disease in a Petri dish,” says Gage. “Being able to study Rett neurons in a dish allowed us to identify subtle alterations in the functionality of the neuronal circuitry that we never had access to before.”

At first, Rett-derived iPS cells were indistinguishable from their normal counterparts. It was only after Marchetto had patiently coaxed the iPS cells to develop into fully functioning neurons—a process that can take up to several months—that she was able to discern differences between the two.

Neurons carrying the MeCP2 mutations had smaller cell bodies and a reduced number of synapses and dendritic spines—specialized structures that enable cell-to-cell communication—as well as electrophysiological defects, indicating that things start to go wrong early in development.

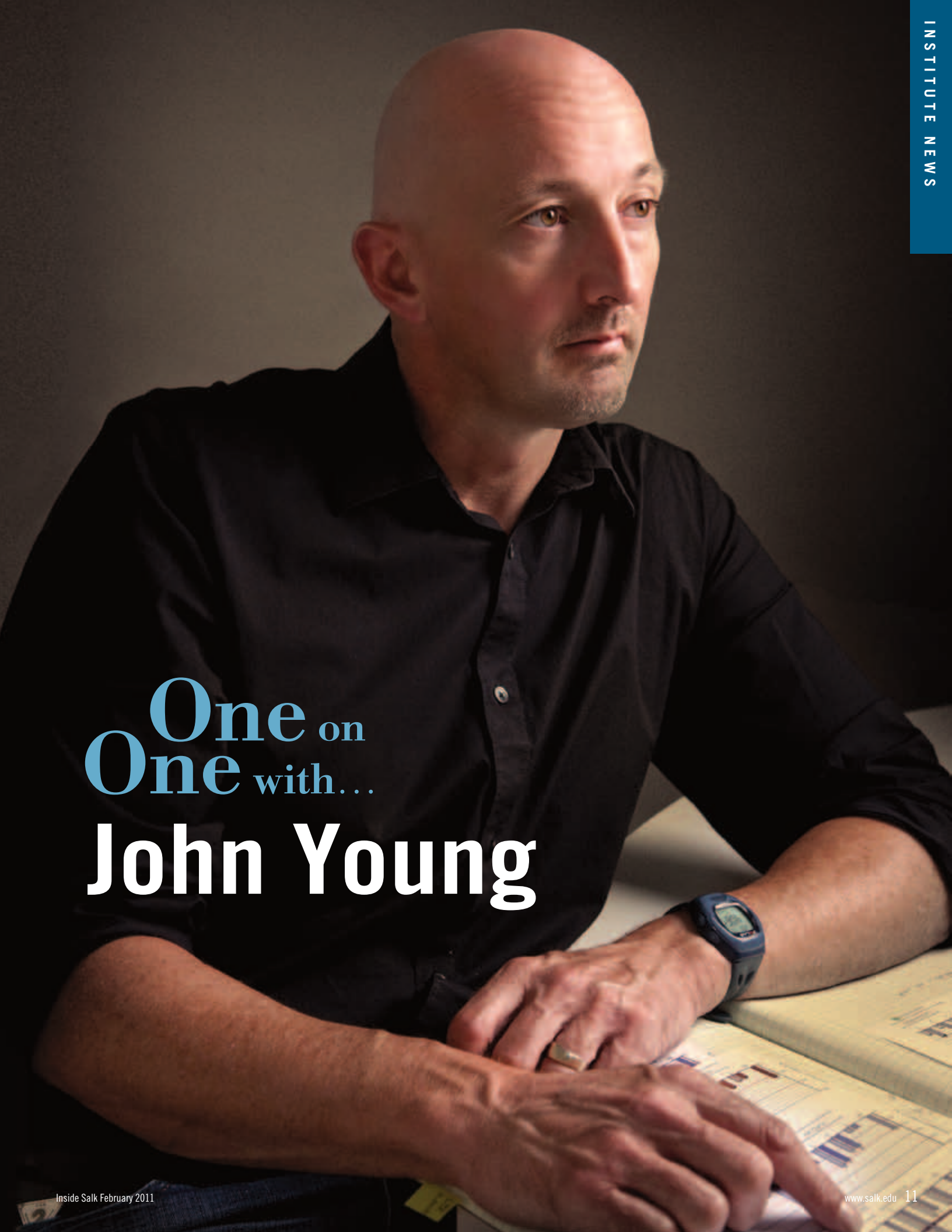
“Mental disease and particularly autism still carry the stigma of bad parenting,” says Muotri. “Our results show very clearly that autism is a biological disease that is caused by a developmental defect directly affecting brain cells.”

When the researchers treated the diseased cells with a drug that was able to alleviate some of the autism symptoms in mice, the abnormalities in the neurons were reversed. “This finding suggests that the autistic phenotype is not permanent and could be at least partially reversible,” says Gage.

Because children don’t often develop Rett syndrome until they are six to 18 months old, the discovery suggests there may be a window of opportunity for early diagnosis and preventive therapies before the disease develops.

Often it’s hard to test autism treatments in animals because it’s difficult to see the physical manifestations of the disorder; researchers can’t observe the impaired social interactions and communication that are the hallmarks of the disease in humans.

“We now know that we can use disease-specific iPS cells to re-create mental disorders and start looking for new drugs based on measureable molecular defects,” says Muotri.



One on One with...
John Young

Intensity and determination. Whether he is probing the complexities of AIDS viral infection or bicycling through Death Valley, the words seem to capture **John Young**'s operating style.

Young is the linchpin of the Salk's small but growing immunology and microbial pathogenesis program (supported by federal research grants and private gifts, including $18 million from the Nomis Foundation). Last summer the National Institutes of Health awarded Young and colleagues a $21 million program grant to study the fundamental science underlying early HIV-1 infection. He now runs his hand-picked multidisciplinary team, coordinating 13 researchers at seven institutions across the country.

What does the public need to understand about conquering the AIDS virus; why is the virus so hard to tame after all these years of research?

An effective vaccine has been difficult to develop, in part because we don't yet know enough about how to stimulate the correct protective response. The AIDS virus is very variable, constantly changing. We now realize that we need to fundamentally understand the repertoire of immune responses required for an effective vaccine.

There is also the public perception that the retroviral therapies, often referred to as drug cocktails, have made HIV a treatable disease, and that is mostly true in developed countries. Because of these therapies, HIV-infected individuals can now have normal lifespans. But the constantly evolving nature of the virus, emerging drug resistance and toxic side effects of the therapies are all serious concerns.

One of the purposes of our new federal program grant is to identify parts of infected human cells that could be new drug targets because, unlike the evolving virus, existing cellular structures are not changing.

And what does all that mean to the public?

It means we have quite a way to go before we have HIV totally under control. And it means sexually active people, particularly in high-risk groups, should think seriously before they engage in unprotected sex or needle-sharing. There's a complacency about HIV infection today that is just not appropriate.

» WEB EXTRA

2008 study by John Young ranked most-cited paper in the Fast Moving Front of Molecular Biology & Genetics. www.salk.edu/insidesalk/young

What drew you to the U.S. for your scientific career?

I studied biochemistry as an undergraduate at the University of Dundee. I had just started my Ph.D. program in Britain at the Imperial Cancer Research Fund when I had the chance to go to the U.S. for a conference. At the time, Harold Varmus (Nobel Laureate and former director of the National Institutes of Health) was at UCSF, studying the retroviruses linked to AIDS and cancer. He was the best in the world, and there was a waiting list of people wanting to work for him. I spent an afternoon talking with him, and he agreed then to hire me as a postdoc, two-plus years later, when I finished my degree. I got some fellowships, then faculty positions at UCSF, Harvard, and at the University of Wisconsin–Madison. When the Salk position opened up in 2003, I moved back to California, and I haven't looked back since.

Would you make the same choices today?

Yes, there are still great resources for doing science in the U.S. And the Salk was the place for me. Here, a scientist is not stuck in a single intellectual track. If opportunities present themselves in other disciplines, there are world experts in these areas just down the hall, and you can scientifically redefine yourself. The Salk culture encourages transformation—here you are not boxed in.

How did you first become interested in life science research?

There were no scientists in my family. I developed an interest in science when a very good junior high school biology teacher opened my eyes. He shared his fascination with understanding how biological systems function. My parents encouraged me to be a medical doctor, but that wasn't for me.

Teachers are so important. I pay close attention to my kids' teachers. Luckily, today kids have access to so many more resources that they can almost inspire themselves. But they still need good role models.

What keeps you passionate about science?

The thrill of discovery! You know, there is a lot of disappointment in science. Sometimes you have to drag yourself in to the lab—when experiments don't work, or when manuscripts or grant proposals are

continued on next page...

John Young (seated) is presented with the Nomis Foundation Chair by Irwin Jacobs, chairman of Salk's Board of Trustees.

rejected. You have to develop a strong resilience. This is a tough discipline, especially in the current funding climate. But when a member of my team walks into my office with a hot result, all of these concerns evaporate.

I also love the energy of my trainees. As a more senior scientist, I now have intellectual progeny—a network of people around the world making a difference in what we know about biology and contributing to biotechnology and pharma. That legacy is very satisfying.

What have the two wonderful gifts from the Nomis Foundation meant to you and your research at the Salk?

The gifts created a core of scientific research in immunology that did not exist here before, with the development of new programs, better laboratory space and, recently, the hiring of two outstanding young investigators as neighbors. Both of them study how the immune response develops and is controlled. We have joint group meetings, and on a day-to-day level our interactions broaden the scope of scientific discourse here, and have created momentum. The gifts have also allowed us to establish the Nomis Center, which involves 11 different research groups at the Salk holding monthly meetings and initiating collaborations in immunology and microbiology. The additional Nomis resources, including an endowed chair, which I have just been awarded, provide crucial funds for us to explore new avenues of research.

And what does John Young do to keep himself sane?

Salsa dancing with my lovely wife Marianne, and spending time with each of my three children. I'm teaching myself to play the guitar at the moment. It is very therapeutic. I go home and strum for an hour, several nights a week, and really enjoy it.

Also, I recently took up extreme endurance bike riding. Sam [Pfaff, good friend and Salk faculty colleague] and I train for months for these day-long mountainous bike rides, which can be up to 130 miles long, with more than 15,000 feet of elevation gain. These rides and all of the training that goes along with them are a welcome release from the day-to-day demands of our work and really help to clear our minds. We encourage each other to push harder, all the while discussing science, the Institute, our families and anything else that comes to mind.

Salk Institute Elects Leaders in Medicine and Corporate Law to Board of Trustees; Names World-Renowned Cell Biologist Non-Resident Fellow

THE BOARD OF TRUSTEES OF THE SALK INSTITUTE unanimously voted to elect **Benjamin H. Lewis** and **Faye H. Russell** as new members during its November 19 meeting in La Jolla.

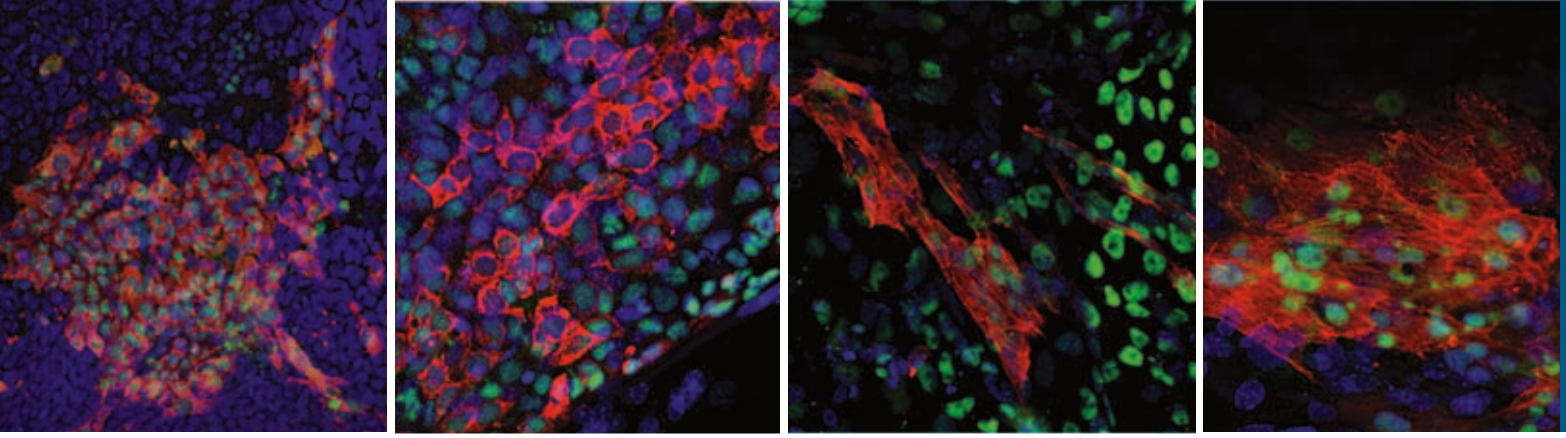
The Salk Institute also named world-renowned cell biologist **Jennifer Lippincott-Schwartz** to join its faculty as a Non-Resident Fellow.

Benjamin H. Lewis is an associate clinical professor of medicine at Columbia University and an attending physician at Columbia University Medical Center, New York–Presbyterian Hospital in New York. Lewis has devoted his career to the prevention of cardiovascular disease with particular focus on the increased use of lifestyle approaches, medical therapies, and noninvasive, nonradioactive techniques—in particular, ultrasound—for the diagnosis and management of heart disease patients.

The Salk board of trustees also elected lawyer Faye H. Russell. A partner in Latham & Watkins' North San Diego office, she assists emerging growth companies in developing and executing acquisition and licensing strategies. She also advises businesses on public and private equity and debt financings, including initial public offerings and venture financings. Russell is a frequent lecturer on intellectual property issues, investor relations, public and private financings, shareholder relations, and general corporate governance, and has been recognized as one of the top 50 IPO lawyers nationwide.

Jennifer Lippincott-Schwartz, an investigator at the National Institute of Child Health and Human Development at NIH in Bethesda, MD, studies the dynamic nature of cells and their organelles. Known for continually pushing the boundaries of the visible world, Lippincott-Schwartz is a leading force in the development of superresolution imaging. Her group introduced photoactivation localization microscopy (PALM), which, for the first time made it possible to track single molecules in living cells. The current head of the Section on Organelle Biology in the Cell Biology and Metabolism Branch at the NICHD, she has been elected to the National Academy of Sciences and the National Institute of Medicine and is a fellow of the American Association for the Advancement of Science.

"I am pleased to welcome Dr. Lippincott-Schwartz, Ms. Russell, and Dr. Lewis to the Salk Institute," said Institute president **William R. Brody**. "Their deep understanding of the importance of basic research will help us expand our vision and guide us as we undertake new and important priorities."



Salk "Dream Team" Pierces Pancreatic Cancer's Defenses

WHEN THE WHO'S WHO OF THE ENTERTAINMENT INDUSTRY gathered for the second Stand Up 2 Cancer (SU2C) celebrity-studded telethon this fall, three Salk researchers—**Geoff Wahl**, **Ronald Evans** and **Tony Hunter**—were among the evening's stars.

They are an integral part of the pancreatic cancer "Dream Team," which has been awarded $18 million by SU2C to combat pancreatic cancer in new ways. Wahl compares the concept behind the dream teams to the Manhattan Project: "You put people with different backgrounds together to solve a bigger problem."

And pancreatic cancer has been a largely intractable problem. It is one of the deadliest forms of cancer, with 94 percent of patients dying within five years of their diagnosis—a statistic that has barely budged over the past 40 years.

One of the obstacles to successful treatment of pancreatic cancer is a dense fibrous shell, which makes it difficult to deliver chemotherapeutic drugs to the tumor. Wahl, who heads the Salk arm of the pancreatic cancer team, and his colleagues at the Institute are trying to devise strategies to break through the wall where the tumor is hiding.

"The idea is to target the armor of the cancer rather than the cancer itself," says Wahl. "Once the defenses are breached, we can use commonly used drugs to directly attack tumor cells."

Trying to hit multiple targets, other team members focus their energies on personalized treatments and cutting off the tumors' fuel supply. Daniel D. Von Hoff, at the Translational Research Genomics Institute in Phoenix, AZ, who initiated the pancreatic cancer dream team, is searching for genetic alterations in individual patients' tumors to develop treatments based on those genetic signatures. Craig Thompson at the University of Pennsylvania Cancer Center is developing tests using advanced imaging techniques to determine what nutrients pancreatic cancer cells require to fuel their growth and survival.

The multi-pronged approach is paying off: the first clinical trial is already under way. "There are many people out there who depend on us," says Wahl. "We really don't have time to waste."

VIDEO LINK

www.standup2cancer.org/su2c/about_us/scientific_dream_teams

In October, the SU2C pancreatic cancer "Dream Team" gathered at the Salk Institute to discuss their groups' progress and future directions.

Left to right:

Front row: Rajesh Kumar, Bart Kamen, Liz Campbell, Cassandra Lucas, Dan van Hoff, Anna DeJesus-DeCosta, Helen Cai, Ron Evans, Ti Dause, Scott Schleiber

Middle row: Mara Sherman, Michael Downes, Dan Laheru, Kim Wood, Mike Barrett, Barbara Vance, Roz Walker, Jeff Nieves

Back row: Jurre Kamphorst, Michelle Duff, Mark Wade, Geoff Wahl, Ning Ding, Zhu Wei, Tony Hunter, Rich Posner, Sandra Rosewell

From left to right: Irivng Weissman, Joseph Goldstein, Jacqueline Mervaille, Larry Swanson, Susumu Tonegawa, Rudolf Jaenisch, Robert Wurtz, Elliot Meyerowitz, David Baulcombe, Rusty Gage, Robert Roeder, Patrick Delavault, Ron Evans, Yves Christen, Didier Trono, Tony Hunter, Dan Littman, Inder Verma, Bruce Spiegelman, Terry Sejnowski, Tamas Horvath, Susan McConnell, Sue Deeley, Ursela Weiss, Ruslan Medzhitov

Scientific Symposium and Salk Institute Medals Presentation Mark End of 50th Anniversary

IT WAS THE PERFECT FINALE TO THE SALK INSTITUTE'S 50TH anniversary celebration: a three-day symposium that feted the Institute's entire reason for being: world-class science. Titled "Biological Complexity: Emerging Concepts and Trends," the October 27–29 event brought together the Salk faculty and some of the most distinguished scientists in the world, capped by an awards dinner featuring presentation of the Salk Institute Medals for Public Service and Research Excellence.

"We had a marvelous three days with 25 talks that were absolutely worthy of the 50th anniversary of the Salk Institute," observed **Inder Verma**, a professor in the Laboratory of Genetics and holder of the Irwin and Joan Jacobs Chair in Exemplary Life Science, who chaired the symposium planning committee and the selection committee for the public service medal. "**Joanne Chory** [director of the Salk Plant Molecular and Cellular Biology Laboratory and holder of the Howard H. and Maryam R. Newman Chair] said most of the presenters were the rock stars of their science, and that's exactly who they were," he added.

Qualcomm cofounder **Irwin Jacobs**, who chairs the Salk board of trustees, received the Salk Institute Medal for Public Service for his leadership and philanthropy, which have literally been reshaping the San Diego region and the world beyond.

"Throughout his life, Dr. Jacobs has demonstrated that rare combination of intellectual curiosity, raw talent, hard work and the ability to imagine doing things differently," noted Salk president **William R. Brody**, in presenting the award. "These are the personal gifts that made him a successful innovator, educator and businessman and are the same ones that then propelled him to become one of the most influential civic leaders and philanthropists in America today."

Upon accepting the medal, Jacobs said, "The medal will be very special, but being part of the Institute—the ability to interact with everyone here at Salk—is what's really exciting for me."

After explaining the science behind gene transcription, **Tony Hunter**, American Cancer Society Professor and holder of the Frederick W. and Joanna J. Mitchell Chair, presented the Salk Institute Medal for Research Excellence to **Robert G. Roeder**, the Arnold and Mabel Beckman Professor at The Rockefeller University, whose pioneering investigations into how genes are transcribed into RNA have revolutionized our understanding of gene expression. Over the past four decades, Roeder has made seminal discoveries and purified a series of large protein complexes containing over 100 different proteins used for the critical process of transcribing DNA into RNA copies—discoveries that have profoundly influenced everyone who works on gene expression in mammalian cells.

"There's little doubt that the identification and the functional characterization of such a large group of proteins all dedicated to the crucial task of regulated RNA synthesis represents the most outstanding biochemical achievement of the last 40 years and perhaps of the last century," declared Hunter, who chaired the selection committee.

For his part, Roeder acknowledged the extraordinary vision of Jonas Salk in founding the Salk Institute, as well as the seminal contributions of the fellows and staff over the years in bringing it to its current pinnacle of scientific distinction. "This of course makes this award all the more meaningful," he said, "and I'm personally thrilled and deeply honored to accept it on behalf of the outstanding young colleagues who over four decades have helped me toward my original goal of understanding the molecular basis of gene control in animal cells."

The first Salk Institute Medals, which were designed by Paloma Picasso, daughter of Francoise Gilot-Salk, Jonas Salk's widow, were presented in 2005.

Salk Researcher Awarded Julius Axelrod Prize

STEPHEN F. HEINEMANN, A PROFESSOR in the Molecular Neurobiology Laboratory and holder of the Salk Institute Council Endowed Chair in Genetics, has been awarded the Julius Axelrod Prize during the annual meeting of the Society for Neuroscience.

The prize, named after Nobel Laureate Julius Axelrod, who discovered the actions of neurotransmitters in regulating the metabolism of the nervous system, recognizes exceptional achievements in neuropharmacology and exemplary efforts in mentoring young scientists.

Heinemann, a past president of the Society for Neuroscience, is best known for his work on the identification and characterization of nicotinic and glutamatergic receptors, which are essential to communication between brain cells, learning, and memory. During his career of more than 30 years, Heinemann has mentored many students who have gone on to secure key academic positions worldwide.

Pharmaceutical and biotechnology companies are currently using discoveries made in Heinemann's lab to develop drugs for stroke, epilepsy, Parkinson's and Alzheimer's diseases, as well as mental conditions such as nicotine addiction, depression, and schizophrenia.

Heinemann is a member of the National Academy of Sciences, the National Institute of Medicine, and the American Academy of Arts and Sciences, and has received the Bristol-Myers Squibb Distinguished Achievement in Neuroscience Research Award and the McKnight Award for Research.

Radiological Society of North America Awards Gold Medal to Salk President Brody

"BILL BRODY IS A RARE COMBINATION of scientist, clinician, engineer, statesman, business leader, educator and concert pianist," said Hedvig Hricak, 2010 president of the Radiological Society of North America (RSNA). "He is not only a highly cultured individual, but also a warm, wise and fiercely loyal friend to the institutions he has led and to the individuals that stood by his side in his many fields of endeavor. His vision has propelled into preeminence every entity that he headed."

In a tradition that originated in 1919, gold medals are presented each year to individuals who have rendered exemplary service to the science of radiology and who have received unanimous approval by the RSNA board of directors.

Joseph Ecker Honored by the Genetics Society of America

THE GENETICS SOCIETY OF AMERICA HAS SELECTED JOSEPH R. ECKER, professor and director of the Genomic Analysis Laboratory at the Salk Institute as the recipient of the George W. Beadle Award for outstanding contributions to the community of genetics researchers.

The award is named after Nobel Laureate George W. Beadle, whose experiments established the linkage between biochemistry and genetics, setting the groundwork for the development of molecular biology.

Ecker is recognized for the body of work he has developed in studying *Arabidopsis thaliana*, a flowering mustard weed and model organism. He was a driving force within the multinational Arabidopsis Genome Sequencing Committee, a team that sequenced the *Arabidopsis thaliana* genome three years ahead of the scheduled ten, and with colleagues has developed new gene scouting techniques. Ecker made national headlines last December when TIME magazine ranked the study, in which his lab mapped the epigenome of two human cell types for the first time, the No. 2 most important scientific finding of 2009.

Ecker has been elected to the National Academy of Sciences and has served as the president of the International Society for Plant Molecular Biology. His long list of awards and honors include the John J. Carty Award for the Advancement of Science, the Martin Gibbs Medal, and the Kumho Science International Award in Plant Molecular Biology.

Cancer Researcher Tony Hunter Honored with Mitchell Chair, Lauded by Colleagues

Tony Hunter, Jamie Simon and Hunter's lovingly decorated alter ego.

AT AN ACADEMIC EVENT ACCOMPANIED BY WARM WORDS AND obvious collegial affection, **Tony Hunter** became the inaugural holder of the Frederick W. and Joanna J. Mitchell Chair, created in memory of their daughter Marian Mitchell through a $2 million gift by the estate of Frederick W. Mitchell.

The endowed chair was established under the Joan Klein Jacobs and Irwin Mark Jacobs Senior Scientist Endowed Chair Challenge, which augments the Mitchell estate's gift with an additional $1 million. The Jacobses officially presented the Mitchell chair to Hunter on August 16 at a late afternoon reception in his honor.

Hunter, an American Cancer Society Professor and a senior scientist in Salk's Molecular and Cell Biology Laboratory, directs the Institute's NCI-designated Cancer Center. He is widely known at the Institute for his scientific generosity and willingness to collaborate.

"Tony is an incredibly committed and passionate scientist whose name is synonymous with scientific excellence," said **Joanne Chory**, chair of the Salk faculty. "In his nearly 40 years at the Institute, he has published 458 papers that have been cited nearly 80,000 times," Chory said.

"Tony is also a scientist's scientist," she continued. "He offers very thoughtful feedback and sage advice."

Hunter, who first joined the Salk as a postdoc in 1971, studies how cell proliferation and division is regulated, and how mutations in genes that regulate proliferation lead to cancer. He has made significant research contributions in the area of signal transduction—how signals that stimulate or rein in cell division are routed—discovering a new type of enzyme, called tyrosine kinases, whose activity triggers cells to divide.

Signal transduction is involved in almost every aspect of normal cell development, and minor defects cause a cell to start growing uncontrollably and turn cancerous. Such mutations are the underlying cause of most pediatric cancers. His lab continues to study signal transduction and its roles in normal and abnormal cell development.

The white-bearded and nearly always casually dressed Hunter has garnered international acclaim for his research. He is a member of both the National Academy of Sciences and a fellow of the Royal Society of London. He holds the 2006 Robert J. and Claire Pasarow Award for Cancer Research; the 2005 Wolf Prize in Medicine, Israel's top recognition for achievements in the interest of humanity; the 2004 Louisa Gross Horwitz Prize, a leading national award for scientific achievement; and Japan's 2001 Keio Medical Science Prize.

Walter Eckhart and **Inder Verma** lauded Hunter for his tremendous ability to collaborate with colleagues at the Salk and around the world. Also emphasizing Hunter's "keen powers of observation" as an experimentalist, Verma said, "The Salk is very lucky to have someone like Tony."

Hunter's wife, Jenny Price, and their sons, Sean and James, were on hand to witness the tributes. **Reuben Shaw**, speaking on behalf of the Salk's junior faculty, presented Hunter with the gift of a "sculpture" depicting Tony in a water-rafting pose. (Hunter is well known for his outdoor adventures.)

Shaw said that as a young Cornell University undergraduate of 19 studying signal transduction in a laboratory, he first became aware of Tony Hunter and his seminal work in the field. Today, as a junior colleague of the famous scientist, he recognizes Hunter's "consummate knowledge and generosity toward colleagues everywhere."

In brief acceptance remarks, the characteristically low-key Hunter thanked all of his lab managers, graduate students and postdocs "who did all the work." And he noted that, based on his British lineage, he is "coincidentally, one eighth Mitchell," wryly suggesting that Mitchell blood could be a requirement for future holders of the Mitchell chair.

Launched in 2008 with a $10 million matching fund, the Jacobs Chair Challenge encourages and enables donors to create prestigious, permanent chairs in support of senior faculty members at Salk. At the reception **Irwin Jacobs** called it "a great honor and personal privilege" to present the chair to Hunter.

Robert H. Wurtz Gerald R. Fink

NRFs Wurtz and Fink Win Gruber Foundation's Prizes

SALK INSTITUTE NON-RESIDENT Fellows **Robert H. Wurtz**, an NIH distinguished investigator, and **Gerald R. Fink**, a professor of genetics at the Massachusetts Institute of Technology (MIT), have been awarded the 2010 Prize of The Peter and Patricia Gruber Foundation for their pioneering work in cognitive neuroscience and yeast genetics, respectively.

Regarded as one of the founders in his field, Wurtz has been studying the physiology of the visual system, showing that single neurons in the brain can process visual information. His work has inspired the research of many others in the broad field of cognitive neuroscience. As a result, scientists now have a deeper understanding of how the brain processes the sensory signals that underlie perception and the control of movement.

Leading the list of Fink's groundbreaking contributions was his development of yeast transformation, a now commonly used technique that allows scientists to introduce genetic material (DNA) from another organism into living yeast cells so that the expression and hereditability of the introduced DNA can be studied.

Today, not only is yeast used to study the genetic dissection of basic cellular processes in other organisms, including humans, but it is also used as a kind of mini-factory to produce medically important products, including insulin and vaccines.

Nobel laureates Renato Dulbecco and Roger Guillemin

Salk Establishes the Renato Dulbecco Chair in Genomics and the Roger Guillemin Chair in Neuroscience with $6 Million Gift from Irwin and Joan Jacobs

A $6 MILLION GIFT FROM IRWIN JACOBS, CHAIRMAN OF THE SALK'S BOARD of trustees, and his wife, Joan Klein Jacobs, will be used to create the Renato Dulbecco Chair in Genomics and the Roger Guillemin Chair in Neuroscience.

"Joan and I are particularly pleased to establish these chairs to recognize our two resident Nobel Prize winners, Drs. Dulbecco and Guillemin, for their incredible achievements in science and research, for the leadership they have provided over the years at Salk, and for the legions of scientists they continue to mentor and inspire," said Jacobs.

Renato Dulbecco, a founding fellow and president emeritus of the Salk Institute, conducted seminal research that provided the first clue to the genetic nature of cancer. He was jointly awarded the 1975 Nobel Prize in Physiology or Medicine for discoveries concerning the interaction between tumor viruses and a cell's genetic matter. In 1986, Dulbecco initiated the idea of studying all human genes, helping to launch the worldwide Human Genome Project.

Roger Guillemin, a distinguished professor and former president of the Institute, won the Nobel Prize in 1977 for discoveries that laid the foundation for brain hormone research. Considered the founder of the field of neuroendocrinology, Guillemin is a scientific pioneer whose work has led to treatments for disorders ranging from infertility to diabetes to pituitary tumors.

"The creation of each chair will pay permanent tribute to the extraordinary research contributions of these two remarkable scientists," said **William Brody**, Salk president. "The central roles played by Dr. Dulbecco in genomics and Dr. Guillemin in neuroscience have built a legacy of leadership and innovation that will remain embedded in the Institute now and for years to come."

> "A successful restoration should preserve the past as well as prepare a building for the future." –Tim Ball

Plant operators **Josefino Vermillo** (standing) and **Joe Price** in the central plant's production level, look forward to a better work environment in the new control room that will be constructed this year.

Salk Institute Launches Infrastructure Renewal and Expansion Project

IN 1960, WHEN JONAS SALK AND Louis Kahn collaborated to create the Salk Institute, they insisted that the facilities should be an inspiration to all who work and visit the campus—a design that would connect the best of both the scientific and artistic worlds. Motivated by a desire to mix his vision with modern technology, Kahn used concrete, glass and wood to form the distinctive exteriors of the buildings, while designing the laboratories around a radical new concept that, among other things, integrated mechanical and electrical services within the structural layout.

Fifty years later, the iconic architecture continues to inspire, but inside, the once cutting-edge infrastructure is showing its age. The outdated operating systems are inefficient and costly to run by today's standards, and repairs and maintenance have become a constant issue. These challenges, combined with the specter of energy shortages and rising utility rates, have made it increasingly important to develop an energy-efficient and cost-effective solution to updating the buildings' infrastructure

Consequently, the Institute launched a comprehensive infrastructure renovation and expansion project in August 2010, designed to position its labs for the research needs of the 21st century.

The project, which will be done in phases over an 18-month period, involves replacing the components of the mechanical and electrical systems that are inoperable or at the end of their useful life and expanding them to accommodate current and future needs of the Institute.

"Preserving the historic spaces and character of the Salk while converting the facilities into sustainable buildings with innovative technologies and alternative energy solutions presented a host of complex challenges," said **Tim Ball**, senior director of Facility Services, who is coordinating and overseeing the project. Because research activity takes place 24 hours a day in the laboratories, the construction has required carefully choreographed timing as vital operating systems are taken offline and immediately set up with temporary substitutes until the permanent equipment is installed and up and running. "Basically, it's like performing a heart transplant on a patient while he is still awake," remarks Ball.

Despite the ambitiousness of this huge undertaking, the benefits to the Institute will be enormous once it is completed in April 2012, with nearly $550,000 of yearly savings in operational expenditures. The installation of a 500 kW solar array on the buildings' rooftops will produce electricity at a cost roughly 30% lower than what SDG&E charges. The project also puts the Salk in line with its desired goals for reducing energy consumption, while extending the life of essential services for another 40 years.

"Not only are we showing leadership by being good stewards of the environment; the energy conservation and improved efficiency will lower our operating costs and result in savings that can be used to support the labs and research," emphasizes Ball. What is more, he adds, the careful planning and design will also allow for adaptation to any new forthcoming "green" technologies down the road.

"A successful restoration should preserve the past as well as prepare a building for the future," he says—a sentiment that Louis Kahn and Jonas Salk would undoubtedly have embraced.

» WEB EXTRA

Watch a video explaining how it will be done.
www.salk.edu/insidesalk/infrastructure

Rita Coblentz Bronowski and Jacob Bronowski

Rita Coblentz Bronowski

RITA COBLENTZ BRONOWSKI, 92, WIDOW OF SALK Founding Fellow **Jacob Bronowski**, died September 2 at the Pacific Palisades, CA home of her daughter, Judith Bronowski.

The British-born sculptor was best known locally as a San Diego arts patron who was a founding member of the revived La Jolla Playhouse and a leader of the San Diego English-Speaking Union.

At the Salk she is also remembered as the supportive spouse of the scientist-philosopher-poet who moved to La Jolla in 1964 to be part of the fledgling Institute. And in the decades after his death in 1974, she also worked to keep Bronowski's legacy alive.

Jacob Bronowski may be best known for creating the groundbreaking public television series "Ascent of Man." But Bronowski, both a mathematician and humanist, was part of Jonas Salk's first select group of internationally renowned researcher-scholars from a wide variety of disciplines who formed the core of the Institute in its earliest days.

The couple had four children: Lisa Jardine, a noted British historian; Judith Bronowski, a filmmaker; Nicole Bronowski Plett, an arts writer, critic and editor; and Clare Bronowski, a Los Angeles attorney.

Salk Colleagues Remember Glen Evans, a Pioneer in Synthetic Biology

GLEN EVANS, A MULTI-TALENTED SCIENTIST AND FORMER SALK faculty member, died September 6 of multiple systems atrophy (MSA), a rare, incurable degenerative neurological disease.

Evans, 57, spent 11 productive years on the faculty at the Salk (1983-94), much of that time contributing to the national Human Genome Project.

"Glen was a talented and energetic scientist who was deeply committed to improving human health," recalled **Walter Eckhart**. "He was particularly talented at applying modern technology to important biological problems."

Always reaching for the next biomedical frontier, Evans had a keen understanding of "big science" and the processes to accomplish it, said **Joanne Chory**.

He established a federally funded gene sequencing center at Salk, running a large group even as a junior professor. Chory also recalls that Evans seemed particularly driven, even by the high-achieving standards of the Salk Institute. His chromosome 11 mapping center (started at the Salk in 1990) completed its work two years ahead of schedule.

Joseph Ecker did not overlap with Evans, but vividly remembers the scientist and his work from their occasional interactions regarding genome biology. Evans had a longstanding collaboration with scientists from General Atomics that was "very innovative...and way ahead of his time."

"Glen was on the leading edge of developing technology for gene synthesis," Ecker said. "He was a brilliant guy, extremely creative...and he was one of the founders of the field of synthetic biology."

Ecker said Evans developed and used lots of robotic systems well before it was commonplace to do so. "I saw his technology in action and thought, he can move mountains," Ecker recalled.

Evans earned a BA in biology from UCSD in three years and then became the first graduate of the university's combined M.D.-Ph.D. program, earning a medical degree and doctorate in chemistry in six years.

Glen Evans

He cofounded Nanogen Inc., which became a Nasdaq-listed San Diego biotech company focusing on diagnostic chip development, and started Egea Biosciences, one of the first synthetic biology companies to create novel pharmaceuticals (later acquired by Johnson and Johnson).

After learning that he suffered from MSA in 2005, he founded the Evans Foundation for Molecular Medicine (evansfmm.org) to support MSA research education and care for others with the disease. At the time of his death, in lieu of flowers, his family suggested donations to the foundation.

Discovery Roundup

Ticking of Cellular Clock Reverberates Throughout the Landscape of Aging

LIKE CATS, HUMAN CELLS HAVE A FINITE NUMBER OF LIVES. Once they divide a certain number of times, they change shape, slow their pace, and eventually stop dividing—a phenomenon called "cellular senescence." Biologists know that a cellular clock, composed of structures at the chromosome end known as telomeres, records how many "lives" a cell has expended. Until recently, however, they had not yet defined how the clock's ticking signals the approach of cellular oblivion.

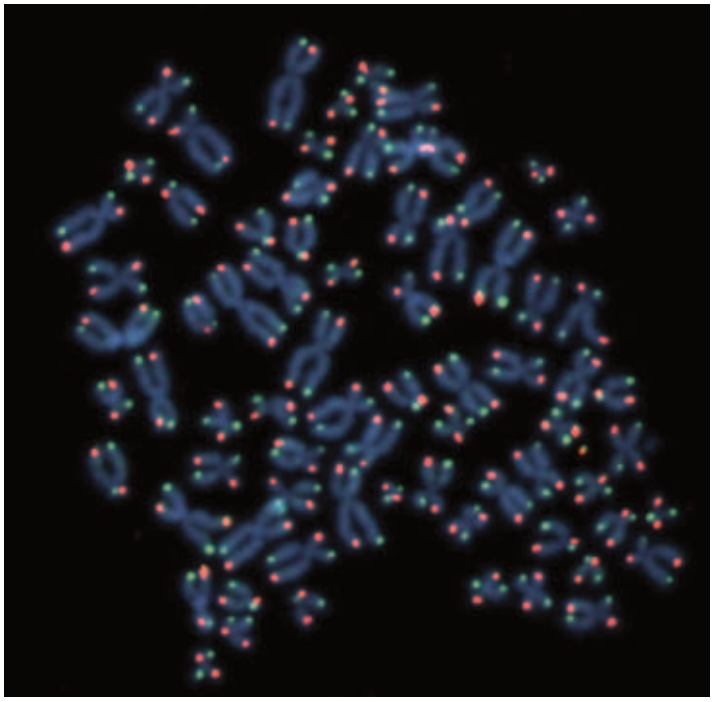
In a study published in *Nature Structural and Molecular Biology*, a team led by **Jan Karlseder** reports that as cells count down to senescence and telomeres wear down, their DNA undergoes massive changes in how it is packaged—changes that likely trigger what we call "aging."

"Prior to this study we knew that telomeres get shorter and shorter as a cell divides and that when they reach a critical length, cells stop dividing or die," said Karlseder. "Something must translate the local signal at chromosome ends into a huge signal felt throughout the nucleus. But there was a big gap in between."

Karlseder and his group began to close that gap by comparing levels of proteins called histones in young cells—cells that had divided 30 times—with "late middle-aged" cells, which had divided 75 times and were on the downward slide to senescence, which occurs at 85 divisions. Histone proteins bind linear DNA strands and compress them into nuclear complexes, collectively referred to as chromatin.

To their surprise, Karlseder's team found that aging cells simply made less histone protein than young cells do. "These proteins are required throughout the genome, and therefore any event that disrupts this production line affects the stability of the entire genome," explains postdoctoral fellow **Roddy O'Sullivan**, the study's lead author.

The team then undertook exhaustive "time-lapse" comparisons of histones in young versus aging cells and confirmed that marked differences in the abundance and variety of histones were evident at every step as cells moved through cell division.



Telomeres, shown here in red and green at chromosome ends, keep track of the number of times a cell has divided.

Comparisons of histone patterns in cells taken from human subjects—a nine- versus 92-year-old—dramatically mirrored the histone trends seen in cell lines. "These key experiments suggest that what we observe in cultured cells in a laboratory setting actually occurs and is relevant to aging in a population," says Karlseder.

Natural Compound Shows Promise Against Huntington's Disease

FISETIN, A NATURALLY OCCURRING compound found in strawberries and other fruits and vegetables, slows the onset of motor problems and delays death in three models of Huntington's disease (HD), according to researchers in the Cellular Neurobiology Laboratory. HD is an inherited disorder that destroys neurons in certain parts of the brain and slowly erodes victims' ability to walk, talk and reason.

One of the intracellular signaling cascades affected by the disease is the so-called Ras/ERK pathway, which is particularly important in brain development, learning, memory and cognition. In earlier studies, senior staff scientist **Pamela Maher** had found that fisetin exerted neuroprotective and memory-enhancing effects through activation of the Ras/ERK signaling pathway. Because the pathway is known to be less active in HD, she thought fisetin might prove useful in the condition.

Maher and her team began their study by looking at a nerve cell line that expresses a mutant form of the protein huntingtin, implicated in HD. Without treatment, about 50 percent of these cells will die within a few days. Adding fisetin, however, prevented cell death. The researchers then tested fisetin in fruit flies overexpressing mutant huntingtin in neurons in the brain. The affected flies don't live as long as normal flies and also have defective eye development. When they were fed fisetin, however, the flies maintained their life span and had fewer eye defects. Finally, Maher and her team tested fisetin's effects in a mouse model of HD. HD mice develop motor defects early on and have much shorter life spans than normal control animals. When Maher and her team fed them fisetin, the onset of the motor defects was delayed, and their life span was extended by about 30 percent. Fisetin was not able to reverse or stop the progress of the disease, but the treated mice retained better motor function for longer and lived longer.

Maher's findings suggest that the compound may be able to slow down the progression of Huntington's disease in humans and improve the quality of life for those who have it. While she cautions that it won't necessarily be effective for people already in advanced stages of the disease, for those in the early stages or who are presymptomatic, fisetin might help.

Retooling the Common Cold Virus to Target Cancer Cells?

A NOVEL MECHANISM THAT ADENOVIRUS uses to sidestep the cell's suicide program could go a long way toward explaining how tumor suppressor genes are silenced in tumor cells and pave the way for a new type of targeted cancer therapy, according to a study published by **Clodagh O'Shea** in the journal *Nature*.

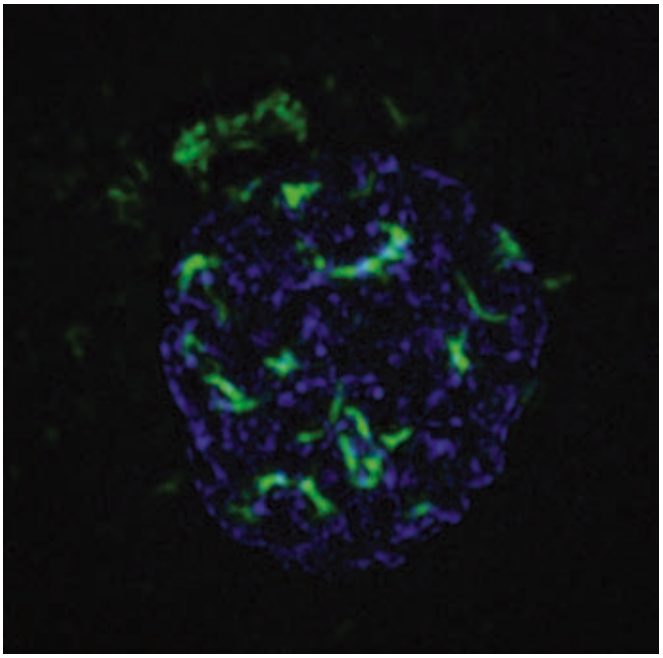
When a cell is under stress, the tumor suppressor p53 springs into action, activating an army of foot soldiers that initiate a built-in "autodestruct" mechanism to eliminate virus-infected or otherwise abnormal cells from the body. Not surprisingly, the p53 tumor suppressor pathway is inactivated in almost every human cancer, allowing cancer cells to escape normal growth control mechanisms. Yet there is still no rationally designed targeted cancer therapy to treat patients based on the loss of p53.

"All of the targeted therapies we have are based on small molecules that inactivate oncogenes, but cancer is not solely caused by the gain of growth-promoting genes," says O'Shea, an assistant professor in the Molecular and Cellular Biology Laboratory. "The loss of tumor suppressors is just as important. The big question is how do you target something that's no longer there?"

Adenovirus seemed to provide the answer. It brings along a viral protein that binds and degrades p53 in infected cells. But if deprived of the protein, adenovirus should only be able to replicate in p53-deficient tumor cells. Then, each time it bursts open the host cell to release thousands of viral progeny, the next generation of viruses is ready to seek out remaining cancer cells while leaving normal cells unharmed. "This makes adenovirus a perfect candidate for oncolytic cancer therapy," says O'Shea.

Yet to everybody's surprise, patient responses did not correlate with the p53 status of their tumors. Intrigued, she and her team followed up on this unexpected finding. They quickly realized that the protein was only half of the story.

It turned out that adenovirus brings along another protein, which neutralizes the p53 checkpoint through a completely different mechanism. Instead of inactivating p53 directly, the tiny protein modifies chromatin, the dense histone/DNA complex that keeps everything neatly organized within the cell's nucleus. These modifications cause parts of chromosomes to condense and bury the regulatory regions of p53 target genes deep within. With access denied, p53 is powerless to pull the trigger on apoptosis.



» WEB EXTRA

Listen to Clodagh O'Shea as she talks about her research.
www.salk.edu/insidesalk/oshea

The tiny adenovirus protein known as ORF3 (shown in green) clears the way for adenovirus replication by creating "zip files" of genes that help the cell defend itself against the virus. O'Shea hopes to exploit this finding to create adenoviruses that selectively destroy cancer cells.

Discovery Roundup

Fly Stem Cells on Diet

A STUDY LED BY SALK ASSISTANT PROFESSOR LEANNE JONES revealed that stem cells can sense a decrease in available nutrients and respond by retaining only a small pool of active stem cells for tissue maintenance. When, or if, favorable conditions return, stem cell numbers multiply to accommodate increased demands on the tissue, her team reported in the journal *Current Biology*.

Elucidating the mechanisms by which hormonal signaling influences stem cell behavior under normal conditions and in response to stress provides important insights into the activities of stem cells in regenerative medicine, during wound repair, and in individuals experiencing metabolic stress.

"Tissues that are maintained by stem cells respond to adverse environmental conditions by reducing the overall number of stem cells, as well as the activity of those stem cells, but maintain them in such a state that they can respond quickly and effectively once the nutritional conditions become more favorable," says Jones.

Stem cells, with their defining characteristics—extensive proliferative potential and an ability to give rise to one or more specialized cell types—are common in early embryos. But by adulthood, only a few stem cells remain, tucked away in their own private niches. They have, nonetheless, retained a remarkable capability: they can operate at a "steady state" to maintain and repair tissues.

When food becomes scarce, animals may go through a period of reduced metabolism to allocate limited resources and maintain tissue homeostasis. In addition, a number of animals, such as those that hibernate, experience a decrease in metabolic rate as part of their normal cycle.

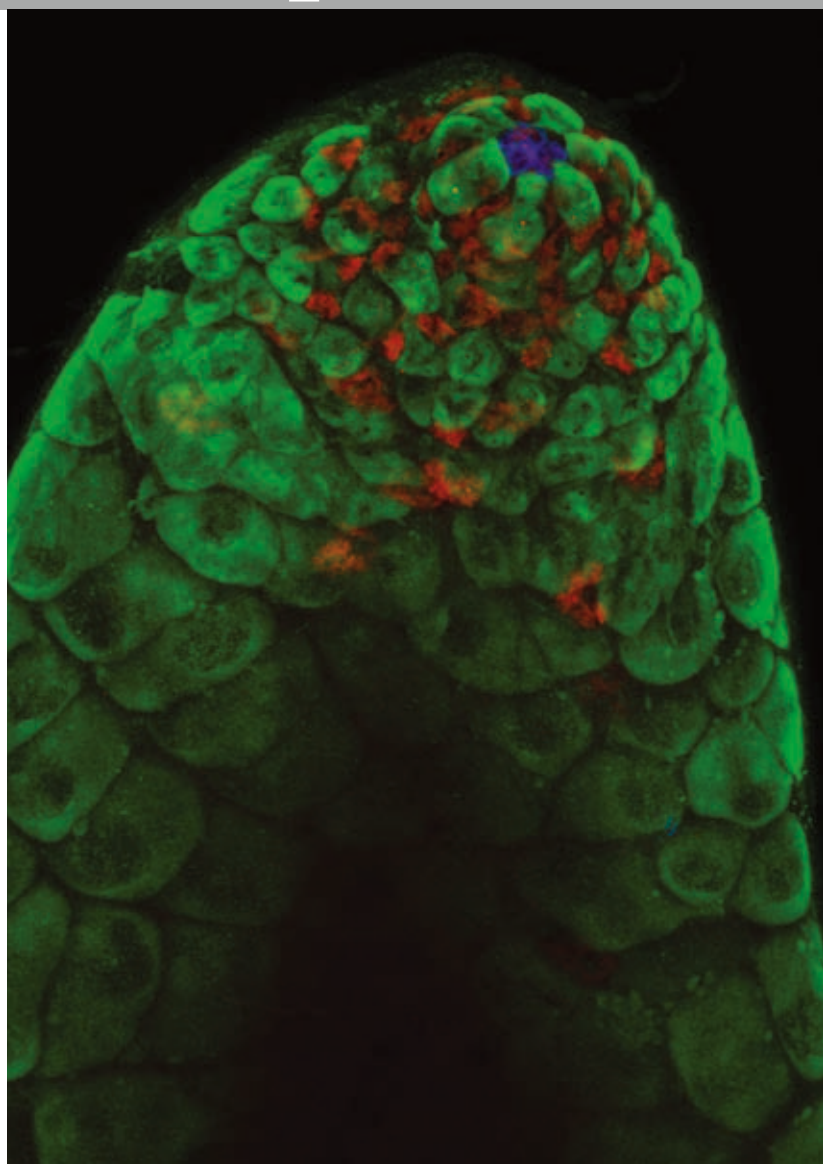
"But very little was known about the effect of chronic changes in metabolism on adult stem cells and the tissues that they maintain," says Jones.

To learn more, the researchers addressed the effects of nutrient availability by feeding their flies a "poor," proteinless diet for several weeks. As a result, the levels of circulating insulin-like peptides plummeted and the number of stem cells in the flies' testes and intestines started to decline. Upon re-feeding, insulin-like peptide expression and stem cell count recovered quickly.

Jones and her team think it likely that the link between hormonal signaling and stem cell response will turn out to be important not only for nutrient deprivation but also for other situations where a body's metabolism might be altered.

"One may think of how tissue homeostasis is modified in a situation when the body cannot accurately monitor or utilize available nutrients—for instance, in the case of a person who is diabetic," says Jones.

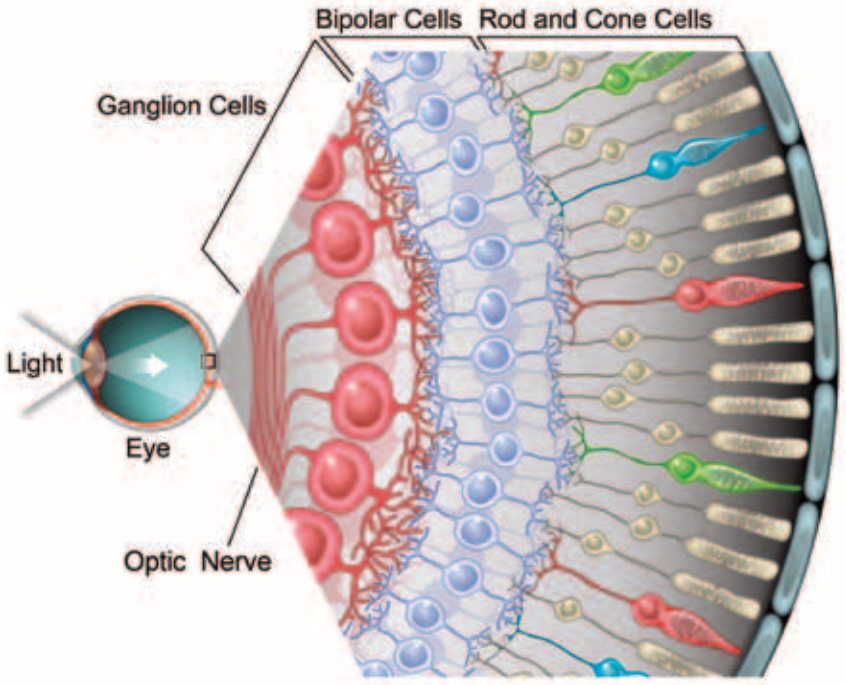
"Further investigating the relationship between nutrient availability and stem cell behavior may also lead to clues for why people who are overfed or malnourished are prone to develop metabolic diseases or cancers, in which cells fail to differentiate properly," adds postdoctoral researcher and co-first author **Lei Wang**, Ph.D.



"In starved flies there are fewer stem cells and they divide slower," says Wang. "However, a small pool of active stem cells remained even after prolonged starvation."

An intriguing question arising from the study is whether an extreme shift in a patient's eating habits could be considered an element of a treatment.

Color Vision Goes Full Circuit



BY COMPARING A HIGH-RESOLUTION VISUAL input with the electrical output of the retina, **E.J. Chichilnisky** and his team were able to draw the first cell-by-cell circuit diagram of the retina, helping to explain how our brains perceive color.

Their measurements, published in the journal *Nature*, not only reveal computations in a neural circuit at the elementary resolution of individual neurons but also shed light on the neural code used by the retina to relay color information to the brain.

"Nobody has ever seen the entire input-output transformation performed by complete circuits in the retina at single-cell resolution," says senior author Chichilnisky, an associate professor in the Systems Neurobiology Laboratories. "We think these data will allow us to more deeply understand neuronal computations in the visual system and ultimately may help us construct better retinal implants."

Visual processing begins when photons entering the eye strike one or more of the 125 million light-sensitive nerve cells in the retina. This first layer of cells, which are known as rods and cones, converts the information into electrical signals and sends them to an intermediate layer, which in turn relays signals to the 20 or so distinct types of retinal ganglion cells, the neurons that carry visual signals to the brain.

It is known that color perception arises from the comparison of signals from different types of cones, but how these inputs are combined by ganglion cells has been less clear. The diagrams put together by Chichilnisky and his colleagues demonstrate how individual cones connect with complete populations of retinal ganglion cells, providing input-output maps of the retina at unprecedented resolution and scale that help to resolve an age-old debate.

Melanopsin Looks on the Bright Side of Life

BETTER KNOWN AS THE LIGHT SENSOR that sets the body's biological clock, melanopsin also plays an important role in vision: Via its messengers—so-called melanopsin-expressing retinal ganglion cells, or mRGCs—it forwards information about the brightness of incoming light directly to conventional visual centers in the brain, **Satchin Panda** and his collaborators reported in *PLoS Biology*.

"Millions of people worldwide suffer varying degrees of blindness because of rod and cone degeneration or dysfunction, but many of them can still perceive differences in brightness," says Panda, an assistant professor in the Regulatory Biology Laboratory. "Melanopsin-expressing RGCs typically survive even complete rod and cone loss and could explain the light responses under these conditions," he adds.

Melanopsin, a photopigment that measures the intensity of incoming light, is fundamentally different from the classical rod and cone opsins, which help us see. For one, it is much less sensitive to light and has far less spatial resolution—characteristics that fit perfectly with this light sensor's primary function of signaling changes in ambient light levels to the brain throughout the day.

"The density of mRGCs in the retina is too low for any meaningful resolution but if we could express melanopsin in a greater number of cells, we might be able to increase resolution to a point that allows blind people to safely navigate their environment," he says.

15th Annual Symphony at Salk, Starring Legendary Entertainer Liza Minnelli, Raises Over $1 Million for Research

IT WAS AN UNFORGETTABLE NIGHT OF OLD SCHOOL SONG AND dance as the incomparable Liza Minnelli took to the stage for the 15th annual Symphony at Salk, held August 28 in the Theodore Gildred Court.

The evening's festivities began with a champagne reception in the spectacular clifftop courtyard, which was still accented with sculptures left behind from April's *Chihuly at the Salk* exhibit. Before the concert, many guests socialized and perused the items offered in the Symphony at Salk Opportunity Drawing, while others attended an architecture and science talk in the Frederic De Hoffman Auditorium (see sidebar, opposite page). The reception and lecture were followed by a gourmet dinner specially prepared by award-winning chef Jeffrey Strauss, owner of the critically acclaimed Pamplemousse Grille.

Under the direction of returning guest conductor Thomas Wilkins, the San Diego Symphony helped build the excitement by playing a lively series of Broadway standards that included pieces by George Gershwin and Cole Porter. But from the moment Minnelli took the stage, she owned the evening.

Her versatility shone through as she alternated between somber ballads and animated dance numbers, pouring raw emotion into every song and charming the audience with her exuberance and energy. For the finale, Minnelli belted out her signature song, "New York New York," and then delighted the crowd with a touching encore, "Every Time We Say Goodbye," accompanied by her longtime collaborator, pianist and Grammy-winning composer Billy Stritch.

Most significantly, the sold-out event set a new record, attracting more than 800 people and generating more than $1 million to benefit Salk scientific research and educational outreach programs.

» WEB EXTRA

To see more images from the Symphony at Salk event, visit: www.salk.edu/insidesalk/symphony2010

Scott Magic

Greg Lemke

Symphony at Salk: Talking about Science and Architecture

NEARLY 100 SYMPHONY AT SALK GUESTS convened in the Frederic De Hoffmann Auditorium to attend a fascinating two-part lecture on science and architecture, presented by Salk scientist **Greg Lemke** and architect **Scott Magic**. Magic, owner of Scott Magic Architecture and an adjunct faculty member at the NewSchool of Architecture, started things off with a slide show and discussion titled "Building Art for Science—Architecture as an Instrument for Community." Lemke, a professor in the Molecular Neurobiology Laboratory, followed with a compelling presentation on new discoveries in immune system regulation, explaining how these findings suggest novel therapies for autoimmune disease. The talks were followed by lively Q&A sessions with a fully engaged and enthusiastic audience.

From left: Irwin and Joan Jacobs, Sandrine Berlanger and John Henry Felix, Marvin and Tina Simner, David and Linda Hale, Robert and Susan de Rose

Mary Jane Salk, John and Anne Codey

Salk Institute Receives Over $15 Million from Helmsley Trust to Support Collaboration with Columbia University for Stem Cell Research

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES WILL SHARE A $15.15 million grant from the Leona M. and Harry B. Helmsley Charitable Trust with Columbia University Medical Center to advance stem cell research.

The three-year grant will establish a collaborative program to fast-track the use of induced pluripotent stem (iPS) cells to gain new insight into disease mechanisms and screen for novel therapeutic drugs.

"Stem cell research is of immense importance to the future of biomedical research and will have a major impact in treating and preventing devastating diseases," said **Fred H. Gage**, professor in the Laboratory of Genetics at the Salk Institute and holder of the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases. "The funding from the Helmsley Trust will accelerate and deepen our research efforts in stem cell biology, already an area of strength at the Salk Institute. In addition, this funding allows researchers at the Salk to join forces with outstanding researchers at Columbia University in a synergistic enterprise that will bring stem cell research closer to fulfilling its promise," he added.

The ability to reprogram adult human cells into iPS cells, which by all appearances look and act like embryonic stem cells, creates a unique opportunity to study human disease in revolutionary ways. After taking a few skin cells from patients, researchers can generate iPS cells and differentiate them into the type of tissue where a disease is manifest.

Along with Gage, Salk scientists **Inder Verma** and **Juan Carlos Izpisúa Belmonte** will develop a stem cell bank of well-characterized iPS cells derived from patients suffering from debilitating neurological, cardiac and hematological conditions. These cell-based models of disease will allow investigators from both institutions to screen at Columbia tens of thousands of chemical compounds to uncover novel drug therapies for thus far untreatable diseases. The grant will create a pipeline of new models and molecules that will start from individual patients and create new avenues back to the clinic.

"The Helmsley Trust is showing great vision by investing in two scientific groups operating at the leading edge of stem cell research," said Salk Institute president William R. Brody. "We are deeply grateful to the trustees and look forward to a very fruitful collaboration with our Columbia University colleagues."

All of us at the Salk Institute celebrate 50 years of discovery made possible through your generosity.

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Salk **Calendar**

FEBRUARY 2011

1–2 **Adler Symposium**

9 **Waitt Advanced Biophotonics Center Grand Opening**

16 **salkexcellerators - *San Diego***

17 **Dulbecco Lecture**

26 **High School Science Day**

MARCH 2011

16 **Salk in the City Luncheon - *San Diego***

APRIL 2011

6 **Diabetes Roundtable**

27 **salkexcelleratorsNY**

28 **Salk in the City Luncheon in New York**

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Employee Council wants to thank everyone who came out November 19 to cheer the walkers participating in the Susan G. Komen 3-day for the Cure. There was plenty of pink EVERYWHERE! Maria Mitra, who works in the Salk's accounting department participated in the walk.