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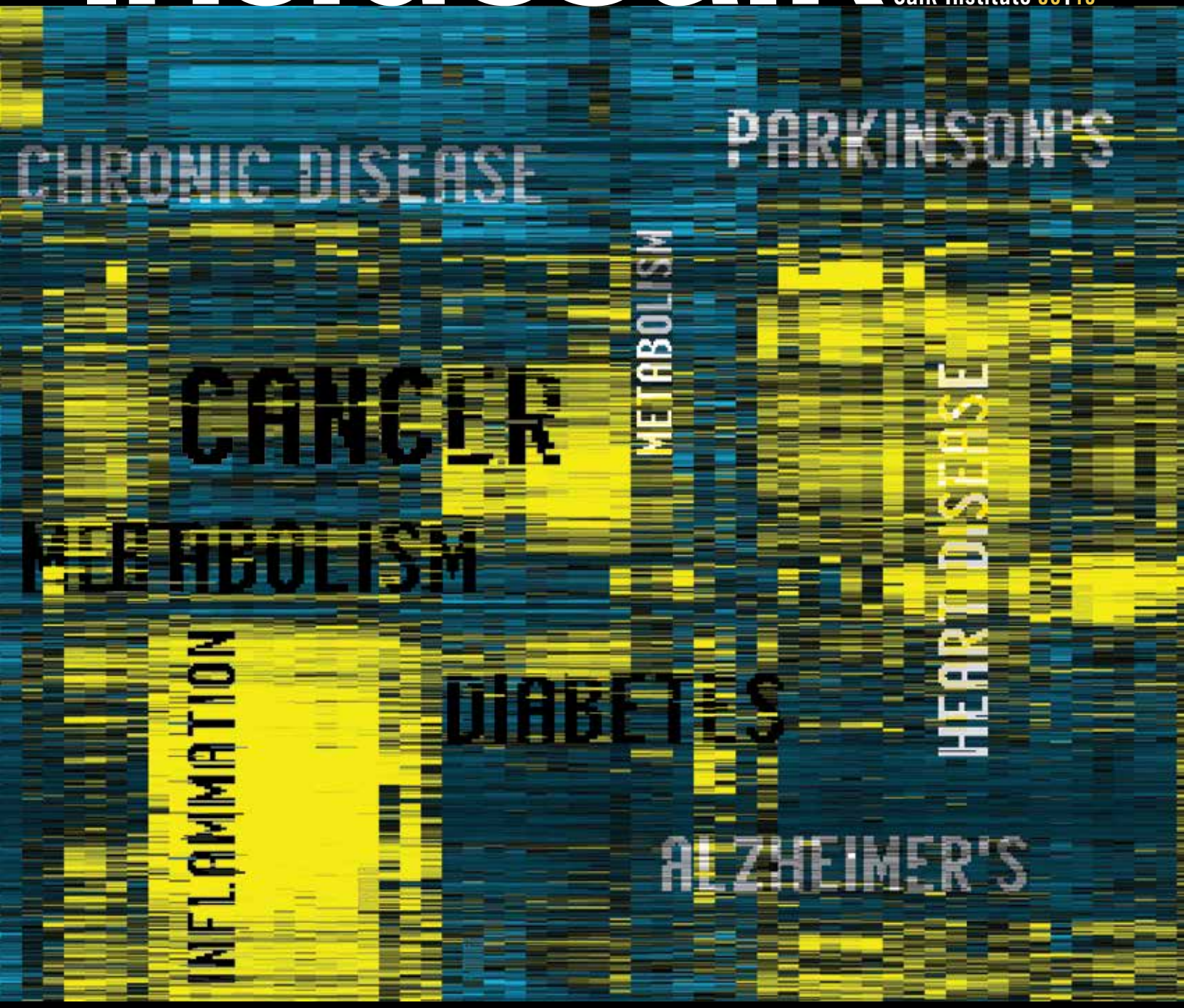

The Helmsley Center for Genomic Medicine

Decoding Chronic Disease

August 2013
Inside Salk

One on one with…Ron Evans

Next generation: Dinorah Morvinski

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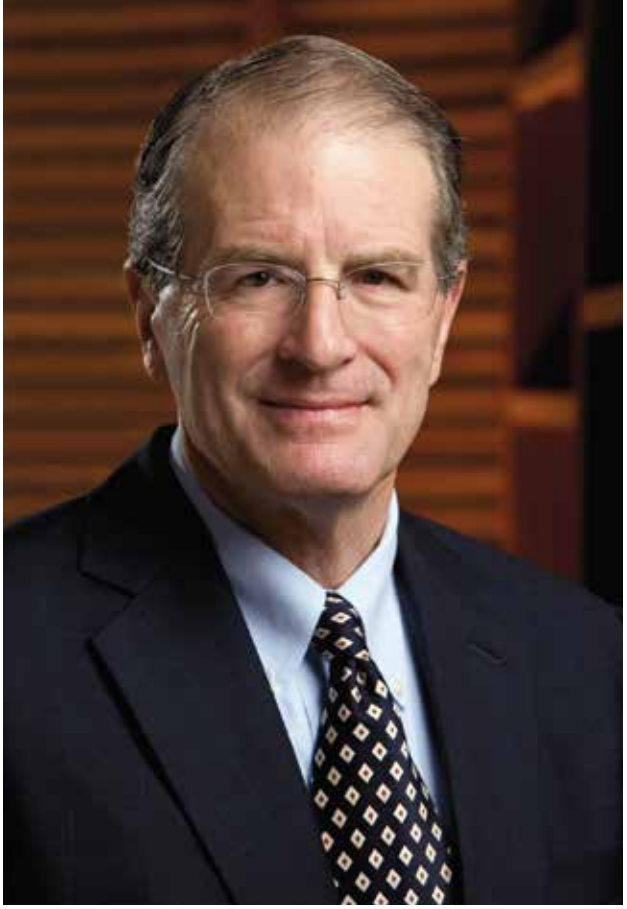


William R. Brody

Dear Friends,

AT OUR RECENT NEW YORK SALKEXCELLERATORS EVENT, AN attendee suggested the public might pay more attention to science, if only it were more like the clothing company Hermès. "They come out with something new and sexy every year," said the fashionable guest.

It may sound surprising, but the analogy to fashion is quite apt. In the future, we will no longer have one-size-fits-all treatments for illnesses such as cancer. As our cover story explains, the aim of genomic medicine is to enable the new era of bespoke therapies, also known as personalized or precision medicine. Often, differences in responses to medical interventions are caused by the genetic makeup of the patient. Many drugs work by interrupting or boosting particular processes in cells, but those processes are the result of a chain of events that involve many different proteins and enzymes. A patient may lack a receptor that a drug targets, or (more fortunately) have one that makes it even more effective. With further discoveries, both the patient's genome or, in the case of cancer, a tumor's genome, will be analyzed to design individually targeted therapies.

Indeed, even now the conduct of basic biomedical research is recognizably similar to the fine craftsmanship of an atelier, rather than a mass production line. Here at Salk, small teams of extraordinarily creative, highly trained and enormously hardworking individuals strive together to perfect the tiniest details. Our laboratory heads, such as **Ron Evans**, the subject of our "One-on-one" feature, provide opportunities and training for graduate students and postdoctoral researchers. These are the leaders of the next generation of science, many of whom, like cancer specialist **Dinorah Morvinski**, profiled in this issue, have already made significant contributions.

The amount of work and time required for basic biomedical research is why we appreciate all the more that you, our readers and contributors, are joining us on our journey to discoveries. We thank you for your curiosity and your generosity. While it may be hard to convince you that science is sexy, we do come out with extraordinary discoveries almost every day of the year. Stay tuned, the best is yet to come.

Thank you for your continued support and commitment.

William R. Brody

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

ON THE COVER
This "heat map" depicts gene expression from 100 different cell types. The resulting pattern indicates how strongly a gene is being expressed (yellow is higher, blue is lower, black is in the middle). By helping scientists quickly see how different genes are expressed and interact, such maps offer scientists clues about the mechanisms behind cellular processes and diseases. Image courtesy of Chris Benner.

DECODING CHRONIC DISEASE

The Helmsley Center for Genomic Medicine

Salk scientists use genome mapping, bioinformatics and powerful computers to study chronic diseases and find new therapies.

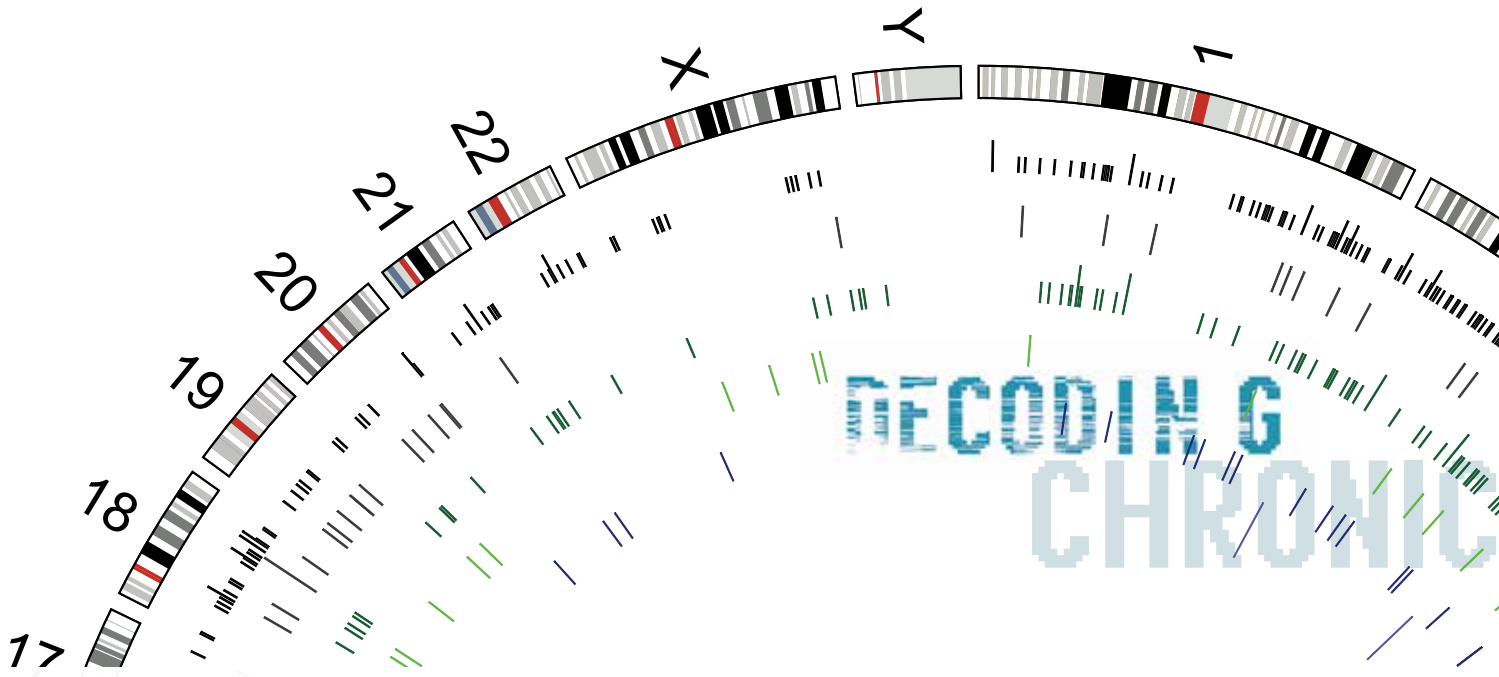
Inder Verma, professor in the Laboratory of Genetics, and Manching Ku of the Genome Sequencing Core Facility

ON THE SURFACE, CHRONIC DISEASES SUCH as cancer, diabetes and Parkinson's look very different. Each has its particular symptoms, prognosis and therapies, and scientists have tended to study each disease in isolation, searching for the particular key that will unlock its mysteries.

Deeper down, however, these diseases have much in common. In recent years, scientists have discovered that certain genetic programs are involved in all chronic illnesses, suggesting that these programs might serve as targets for treating multiple diseases. In particular, many chronic diseases involve inflammation, the body's first defense against stressors such as disease and injury. When inflammation becomes chronic, due to long-term stresses such as infections, toxins or obesity, it can damage cells and organs, leading to clinical illness.

The Salk Institute's new Helmsley Center for Genomic Medicine, launched in January with a $42 million gift from the Leona M. and Harry B. Helmsley Charitable Trust, was established to study these links between chronic diseases, with a focus on the role of chronic inflammation. The center's three major programs—cancer, stem cell and metabolism research—are focused on deciphering the common molecular and genetic mechanisms that go awry in chronic illness.

One of four major scientific initiatives of the Campaign for Salk, the Institute's first major fundraising campaign, the Genomic Medicine Initiative is leveraging new technologies that allow scientists to map the entire human genome—the DNA sequences containing the blueprint for human life. In addition to a core



facility for genomic sequencing, the Helmsley Center includes a bioinformatics core devoted to managing and analyzing the massive amounts of data produced by sequencing machines. Other new facilities allow researchers to study the molecules that make up cells' biochemical machinery and to produce potential new drugs that can be tested in cellular and animal models. The center also supports postdoctoral researchers through the Helmsley Fellows Program, as well as a monthly Helmsley Symposium, where Salk scientists discuss their research in an open forum.

genome allows us to pinpoint these changes in the genome and determine when they occur in the process.

Tracking down such mutations is crucial to providing personalized treatments for cancers and other diseases, says Xia. Through sequencing a donor's genome, doctors will be able to diagnose the genetic problems underlying a disease and determine the most precise and effective treatments. This is already taking place with disorders that have clear and relatively simple genetic links—for example, with certain forms of breast cancer—but whole-genome sequencing offers the possibility

> **"The ability to sequence an organism's genome offers an unprecedented window into what's happening in our cells and how those processes impact our health."**
>
> **—INDER VERMA**

Already, the center is allowing Salk scientists to greatly expand on their research into the genomic underpinnings of disease, generating ideas for new scientific directions and building on the promise of past findings. "The ability to sequence an organism's genome offers an unprecedented window into what's happening in our cells and how those processes impact our health," says **Inder M. Verma**, one of the center's lead researchers and holder of the Irwin and Joan Jacobs Chair in Exemplary Life Science. "When you combine this with the other new core facilities and expertise, you have an incredibly powerful platform for studying the role of stress and chronic inflammation in disease."

In one line of research, Verma's laboratory has developed mouse models of lung cancers to study the links between cancer and inflammation. Using these animal models, they are exploring how the same biochemical players that protect the body by controlling the inflammation response of cells can be hijacked by genetic mutations involved in the development of cancer. Whole-genome sequencing allows them to observe the changes in the genome and in gene expression as a cancer progresses.

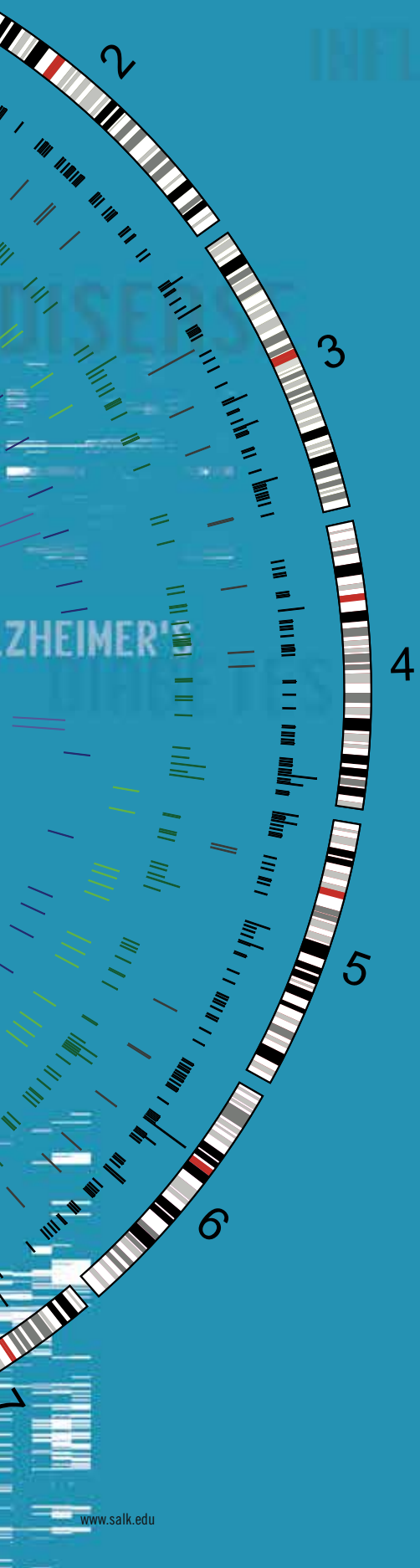
"For a cell to become cancerous, a sequence of several genetic mutations must occur," says **Yifeng Xia**, a postdoctoral researcher in Verma's laboratory who works on the project. "Sequencing the entire

of doing the same for more complex disorders that may involve multiple genetic mutations.

In the past, Salk researchers sent their cellular samples as far as China to be sequenced and wouldn't get the results back for weeks. Thanks to the Helmsley Center's new genomic sequencing core, they now have in-house access to the latest technology.

The Helmsley Center is also allowing Salk to recruit scientists with expertise in bioinformatics, who use powerful computers and statistical modeling to analyze and manage the genomic data produced by the sequencers. "The technologies are critical, but you also need great people to work with the data—it has become an entirely new field of science," says **Ronald M. Evans**, holder of the March of Dimes Chair in Molecular and Developmental Biology and co-lead researcher of the center. "We often look at the genetic signatures from healthy versus unhealthy tissue to determine what's different at the genomic level. To find those signatures, you have to set up the experiments so they produce the right kind of data, and you need expertise in computational analysis to comb the data for answers."

Evans's laboratory is combining whole-genome sequencing with technology to pinpoint genes that control inflammation. "The genome



The technologies that drive genomic medicine

When a clinician gives a patient a prognosis based on genomic research, it's the tip of a very large technical iceberg. Backing up the analysis are years of laboratory research based on gene sequencers and other specialized tools and techniques.

DNA sequencing (whole genome)

Whole-genome sequencing maps the sequences of nucleotides that make up the genetic code stored in DNA. Understanding the genomes of other species is essential to the biomedical research at Salk that underlies successful therapies. In clinical settings, the genomes of patients may be compared to a baseline "normal" human genome to see if there are any mutations or variations that the patients have in common. In personalized medicine, a person's genome might be analyzed to determine whether a particular drug could work within his or her body.

RNA sequencing (gene expression)

While DNA sequencing provides a static view of all the letters in our genome, RNA sequencing offers a dynamic glimpse at how that genomic blueprint actually controls cellular function. RNA sequencing detects what genes are turned on or off, which provides insight into how diseases disrupt the genomic programs that normally keep us healthy. For example, Salk scientists use RNA sequencing to examine the patterns and changes in gene expression as a tumor grows.

Bioinformatics (computational analysis techniques)

One of the greatest challenges of genomics is trying to sort through raw sequencing data, which can run to trillions of letters, to find useful information. It's like trying to find one phrase in all of the books in the Library of Congress. Specialists in bioinformatics, such as **Chris Benner**, director of the Integrative Genomics and Bioinformatics Core, combine a background in computer science with knowledge of biology to mine the data using computer code that seeks out patterns. In addition, they develop new algorithms to solve specific research questions, as well as make "missing piece" predictions about molecular structures.

Laboratory modeling of disease

Disease causes change at the cellular level, and scientists have long hoped to track the progression of these changes throughout the course of an illness. Salk researchers now have the ability to study diseases in animal models, which is far faster and more affordable than studying humans. They can also take skin or blood cells from patients with diseases such as autism, Parkinson's or hemophilia and convert them into stem cells, which can then be differentiated into any cell type. This will allow them to follow the entire cycle of disease progression, yielding insight into both drug development and when best to target therapies in individual patients.

Advanced imaging of disease

Equipment to visualize tumors in different organs, such as MicroCT to visualize tumor size, PET imaging to track tumor usage of glucose, and bioluminescence to track tumor growth in labeled cells, are all critical tools in the cancer researcher's arsenal. They are now available for use with laboratory mice, allowing scientists to track therapeutic responses in the best mouse models for human cancers.

Salk researchers Apua Paquola and Jennifer Erwin

is the control center for our cells, and it adapts to stress to keep us healthy," Evans says. "However, when that stress is persistent, the genome's adaptation leads to chronic inflammation and persistent illness. We are integrating multiple technology platforms to find delinquent genes and develop drugs that can reset the genome to a healthy state. This is where the Helmsley Center therapeutic core comes in. When we have an idea for resetting the genome, we can generate molecules to test as potential drugs."

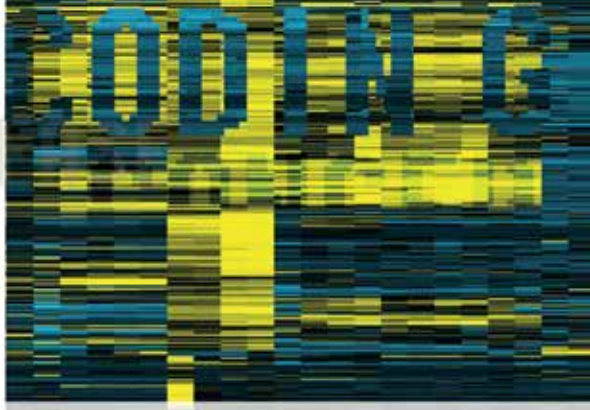
In one project, the Evans team is exploring how long-term inflammation results in liver fibrosis, an excessive accumulation of tough, fibrous scar tissue found in people with chronic liver diseases. The causes of fibrosis include chronic hepatitis virus infection, excess alcohol consumption and obesity. With the help of high-throughput sequencing, **Ning Ding**, a postdoctoral fellow on Evans's team, recently discovered that a synthetic form of vitamin D, calcipotriol (a drug already approved by the FDA for the treatment of psoriasis), deactivates the genetic switch governing the fibrotic response in mouse liver cells, suggesting a potential new therapy for liver fibrosis.

Evans's lab has already begun working with the laboratories of Salk professors **Marc Montminy**, Salk's J.W. Kieckhefer Foundation Chair, and **Greg Lemke**, the Françoise Gilot-Salk Chair, to further develop this disease model. "A prominent part of the vision for the Helmsley Center is to help those of us working in different areas to collaborate more seamlessly," says Evans.

Fibrosis occurs in a wide range of body tissues—heart, lungs, intestines, skin—and Evans is exploring ways to leverage his research on liver fibrosis to understand other types of fibrotic disease. Another postdoctoral researcher on his team, **Mara Sherman**, has found that fibrosis is a particularly powerful driver of inflammation of the pancreas, known as "pancreatitis," which if not controlled, progresses to pancreatic cancer.

Evans's laboratory and other Salk laboratories are adapting sequencing machines to map more than just the DNA code. With rapidly evolving technology, scientists can determine which genes are active in a cell at any given time—a process known as gene expression—and can chart an extra code of chemical markers on DNA known as the epigenome. Computational technology developed at the Salk can overlay maps of DNA sequences with those of the epigenetic code, as well as measurements of gene expression, to produce a three-dimensional view of our cellular machinery in action.

Fred H. Gage, also a lead researcher in the Helmsley Center and holder of the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases, is combining these sequencing approaches with stem cell research to study chronic neurological conditions, such as schizophrenia, autism and Parkinson's disease. Gage and his team reprogram skin cells from patients with these disorders to become induced pluripotent stem cells (iPSCs), then coax these cells into becoming neurons. This overcomes hurdles to obtaining neurons from patients' brains and allows the investigators to study the cells in the laboratory.



The Helmsley Center for Genomic Medicine

Decoding Chronic Disease

> "A prominent part of the vision for the Helmsley Center is to help those of us working in different areas to collaborate more seamlessly."
>
> —RON EVANS

By using this iPSC technology to generate neurons and other brain cells, known as glia, from Parkinson's patients, Gage and his team are investigating the role of inflammation in the disease. "The primary risk factor for Parkinson's disease is aging, and we know that inflammation in the brain increases dramatically when people get older," Gage says. "It's clear that inflammation plays a role, but we don't know the precise mechanisms that lead to the neuron death seen in Parkinson's. It could be that the neurons become more sensitive to inflammation or that the glia malfunction to damage the neurons."

Sequencing the genomes of iPSC-derived neurons shows what genes are regulated differently in Parkinson's patients, which may provide targets for drugs that prevent or reverse the disease. The scientists are also exploring whether it is possible to measure brain-related inflammation through a simple blood test, which might provide an early warning that a person is at risk of Parkinson's. In that case, drugs to reduce that inflammation could help head off the disease.

In another line of research, Gage and his team want to know whether these neurological disorders are linked to so-called "jumping genes," bits of DNA known as retrotransposons that move freely about the genome. "This is the dark matter of the genome," says Gage. "This movement of DNA sequences may explain why people with ostensibly similar genetic profiles have a very different disease history."

In some sets of identical twins, for instance, one twin will develop schizophrenia while the other remains healthy. Also, twins might respond differently to the same drug. By comparing the twins' genomes, Gage's team is discerning what genetic differences explain these variations in health and drug responses. "There's so much we don't know about retrotransposons," says **Jennifer Erwin**, a postdoctoral researcher in Gage's lab. "We are trying to figure out how many copies of these genes there are in the genome, how often they move and where they are located. Once we know those basics, we will have a better idea of their role in neurological disorders."

If genomic medicine at Salk is a marriage between the best molecular biology research and powerful bioinformatic and computational approaches, Erwin and her husband, **Apua Paquola**, a staff scientist in Gage's lab, could be the poster children for the Helmsley Center. Erwin's specialty is molecular genetics, focusing on gene expression and cell culture, while Paquola has a computer engineering background and a doctorate in bioinformatics.

Combining their expertise, the couple is studying the role of jumping genes in Rett syndrome, a rare neurodevelopmental disease that affects mostly girls and is considered one of the autism spectrum disorders. Already Gage's lab has shown that people with the syndrome have more movement of genetic material in their DNA, a groundbreaking study that provided the first evidence of a link between genomic instability and a mental disorder.

"Now we want to find out whether this instability is related to a defect in neurons or glia to explain the symptoms of the syndrome," Paquola says. "The genome is a big, complicated place, but now we've got the right people and the right tools to make much more rapid advances in understanding the relationship between the genome and diseases."

The H.A. and Mary K. Chapman Charitable Foundations: Making a difference

GENE SEQUENCING IS THE FUNDAMENTAL quantitative tool of genomic medicine. A sequencer is similar to a computer, in the sense that it can run different types of sequencing analyses (see page 7). Thanks to a generous contribution from the H.A. and Mary K. Chapman Charitable Foundations, which has allowed the Salk Institute to acquire these cutting-edge devices, Salk scientists are able to explore highly innovative genomic medicine projects and receive results in a much shorter time.

The H.A. and Mary K. Chapman Charitable Trust and The Mary K. Chapman Foundations are the legacy of the late H. Allen and Mary K. Chapman, known for their philanthropy and their loyalty to Oklahoma, where Mary was born and H. Allen spent most of his life.

H. Allen Chapman, born only 12 years after Oklahoma achieved statehood, was an independent oil and gas producer who directed his giving toward educational and medical ends. Mary Chapman retired from nursing after her marriage but retained a nurse's priorities by concentrating her charity on human health and welfare.

Their generosity continues under the stewardship of trustees Donne Pitman and Jerry Dickman. The foundations' gift combines the Chapmans' interests by providing technology that will advance cures for human disease and serve as a training tool for the next generation of biomedical researchers.

From left: Bruce Steel (representing BioMed Realty), Faye Wilson, Darlene Shiley, T. Denny Sanford, Joan Jacobs, Irwin Jacobs, Keith James (Ferring Pharmaceuticals)

Salk celebrates campaign milestone

AS MILESTONES GO, THE ONE THAT THE INSTITUTE CELEBRATED on June 7 was especially noteworthy: more than $200 million raised toward the Campaign for Salk's $300 million goal. Some 125 guests, including donors, trustees, faculty and friends, were on hand to mark the occasion, which also feted newly appointed chairholders and the donors who endowed the chairs, as well as others who have made exceptionally generous investments in Salk's future.

The evening was, as board chair **Irwin Jacobs** noted in his opening remarks, "an opportunity to honor the many amazing and loyal friends of the Institute for their generosity and participation in Salk's first-ever campaign."

Those honors began with recognition of trustee **Ted Waitt's** leadership and the Waitt Family Foundation's 2008 gift establishing the Waitt Advanced Biophotonics Center, which was the catalyst for the campaign. New signage for the center was revealed on the Southeast Building, reflecting the role of Waitt and the foundation.

Also unveiled was a wall honoring donors who have contributed $100,000 or more to the campaign and another acknowledging Jonas Salk Circle donors, who have given at least $1 million to unrestricted endowment for the Institute. The names of the three latest chairs established through the Jacobs Chair Challenge were also added to the existing wall recognizing the chairs. It was particularly poignant when **Elizabeth Keadle**, who endowed one of the chairs in memory of the late **Wylie Vale**, in whose lab she trained, took the podium with Vale's widow, Betty, following a video tribute to the longtime Salk faculty member, who died last year.

Just before a sumptuous dinner, **Beverly Emerson**, **Christopher Kintner** and **Paul Sawchenko**, appointees to the chairs, were presented, underscoring the extraordinary impact the campaign is already having on Salk science.

"The evening was an opportunity to honor the many amazing and loyal friends of the Institute for their generosity and participation in Salk's first-ever campaign." – IRWIN JACOBS

Irwin Jacobs and Hailey Waitt

From left: Bill Brody, Edwin Hunter and Irwin Jacobs
Seated: Bev Emerson

Beverly M. Emerson

Beverly M. Emerson is the inaugural holder of the **Edwin K. Hunter Chair**, established by the Olive Tupper Foundation, the Chambers Medical Foundation, the Jenkins Family Charitable Institute, and the Joe W. and Dorothy Dorsett Brown Foundation. Mr. Hunter is a dedicated supporter of Salk and has served as the Chair of Salk's Annual Tax Seminar since 2010.

Emerson, professor in the Regulatory Biology Laboratory, studies the behavior of genes, notably how they are switched on and off during normal development and during the development of cancer. She explores the molecular mechanisms underlying the cellular response to stress and seeks to find new ways to more easily turn on and off genes that maintain normal tissue function. This work is important for discovering new strategies for repairing or eliminating damaged cells that contribute to cancer and other diseases.

From left: Bill Brody, Richard Atkinson and Irwin Jacobs
Seated: Chris Kintner

Christopher R. Kintner

Christopher R. Kintner has been appointed the inaugural holder of the **Rita and Richard Atkinson Chair** established by the Atkinsons "to recognize outstanding individuals who are making fundamental contributions to the advancement of science that will impact human health."

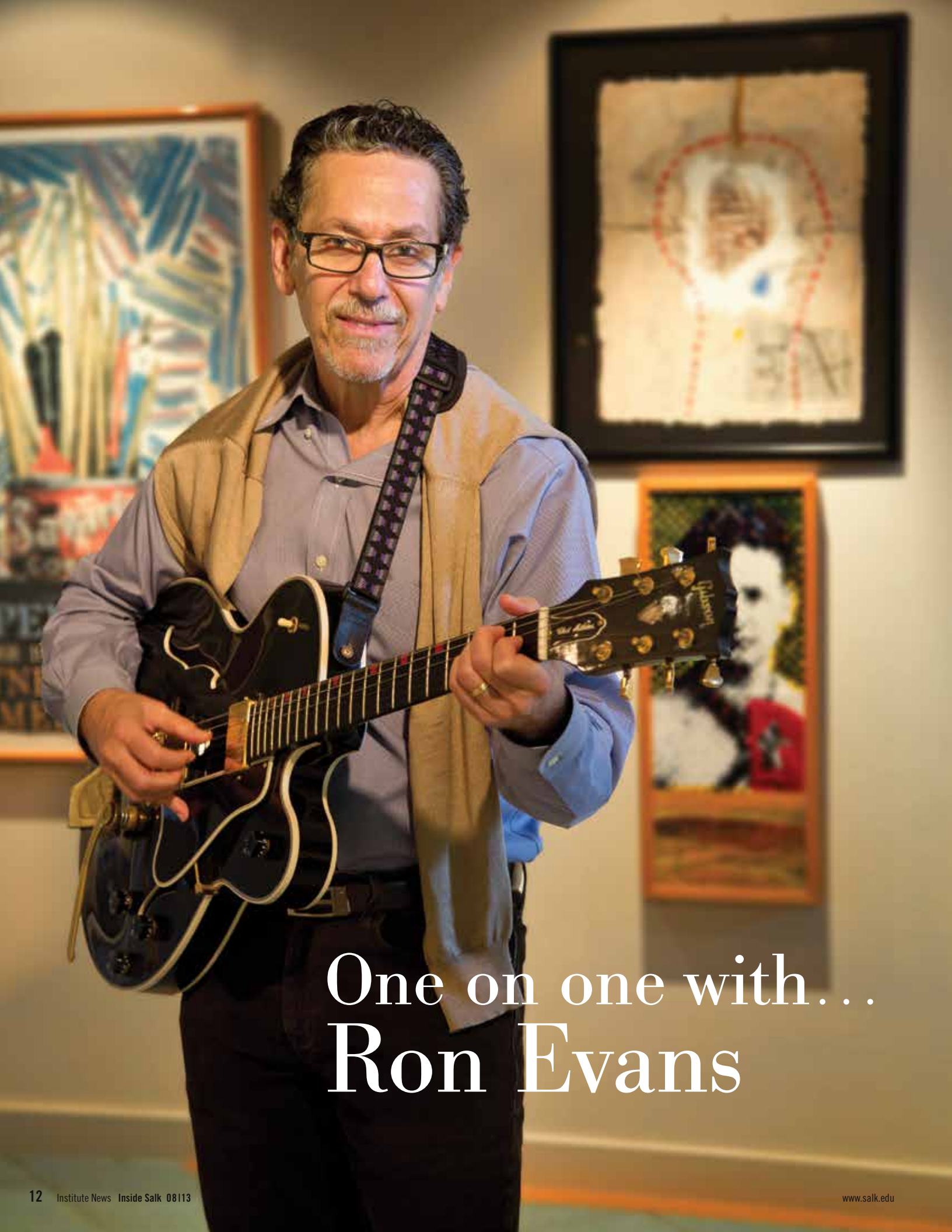
Professor in the Molecular Neurobiology Laboratory, Kintner studies the molecular events that occur in the formation of the nervous system during embryonic development. His research focuses on the development of cells with motile cilia, finger-like projections that beat and move fluid in organs such as the lungs. He studies the genes that are required to form motile cilia and enable cells to orient cilia to beat in the same direction. Analyzing these key genetic pathways of normal development and differentiation of stem cells will advance knowledge about ciliopathies and lung diseases that affect cilia function and will ultimately help prevent or treat human birth defects.

From left: Bill Brody, Liz Keadle, Betty Vale and Irwin Jacobs
Seated: Paul Sawchenko

Paul E. Sawchenko

Paul E. Sawchenko was named the inaugural holder of the **Wylie Vale Chair** established by Liz Keadle, a loyal Salk donor who once worked in the laboratory of the late Salk professor. "Supporting the work of brilliant Salk researchers in Wylie's memory is an honor that allows me to contribute in some small way to the advancement of science," said Ms. Keadle.

Sawchenko, professor and head of the Laboratory of Neuronal Structure and Function, studies how the brain is organized to enable us to respond adaptively to stresses of different sorts, ranging from everyday life events that produce fear and anxiety to immune system challenges resulting from sickness or inflammation. He and his colleagues seek to define the complex networks of brain cells that allow us to cope with specific insults and to identify the molecules that mediate communication between cells within each network. Because stress contributes to the development of many neurodegenerative diseases, including age-related disorders such as Alzheimer's, these studies are paving the way for more effective management of these conditions.



One on one with…
Ron Evans

RONALD M. EVANS, HOLDER OF THE MARCH OF DIMES Chair at Salk, is best known for discovering a family of receptors found on the nucleus of cells, an advance that's helping to explain the complex molecular systems that are the basis of human physiology.

As one of the lead researchers in the Institute's new Helmsley Center for Genomic Medicine, Evans has teamed up with other Salk scientists to explain how the biological programs coded for in the genome orchestrate our biological rhythms and how glitches in this programming lead to disease.

We caught up with Evans to ask him about the new Helmsley Center, his penchant for embracing cutting-edge technologies and his gift for making the complicated seem simple.

The Helmsley Center for Genomic Medicine has a strong focus on providing Salk scientists with access to the latest research technologies. Why is this such a large part of the vision for the center?

The Helmsley Center is about an idea and technology that enables ideas. Technology drives science by letting us ask new questions, which in turn lead to new answers. With the ability to sequence an entire genome—whether that of the fruit fly or a human—we suddenly had tools needed to study complex systems like organ physiology, inflammation and chronic illness. And more of those tools are being developed every day, such as high-throughput sequencers, bioinformatics, genome engineering and atomic resolution microscopy. The secret is being able to generate and manipulate massive amounts of data in a rapid fashion. Of course, having technology is no guarantee. Machines do not design experiments. To access the real power of the technology, you have to ask the right questions.

Have you always been an early adopter of new research technologies?

I was exposed early in my career to what were, for the time, really advanced technologies. First it was RNA sequencing, then DNA cloning and then DNA sequencing. That was all in the '70s and was followed by genetic engineering of animals in the early '80s. I learned that you either create it, adopt it quickly or you will be steamrolled. You need to operate at the cutting edge. When I started, there were no biotech companies like Life Technologies or Illumina that provided you with ready-made tools, so we had to make all the reagents and build many instruments ourselves. We were doing DNA sequencing in 1975 before 99 percent of the world was doing it. At Salk, we began engineering the first transgenic mice in 1982. Forward thinking tends to push you forward, and once you get used to that, you get bored if you're not at the frontier. The Salk is the exact right place for pushing the frontier.

Does that extend to your personal life as well?

I've always been into very high-fidelity audio equipment. My brother and I used to build receivers, amplifiers and shortwave radios and set up media rooms with the equipment we built. I really enjoyed working out the electronics. I don't build those systems anymore because the components now are all solid-state electronics that don't work well with the old style of do-it-yourself fabrication. But we do have a remote-controlled audiophile sound and media system in our house set up to be controlled in any room through an iPad. It's ridiculously complicated, but fun.

Many of the young researchers trained at Salk have gone on to become leaders in their areas of science. What characteristics do you need to be a successful scientist?

Being comfortable with taking risks is important. When you're working inside the box, there is a lot more information. You know what's safe and what's not. But outside the box there is less information and more danger. You have to develop good instincts and have confidence that the problem is big enough to overcome all the challenges. Francis Crick is a great example of how you can be so ahead of your time, so far out of the box, that it can be very risky. After discovering the structure of DNA, Francis came to Salk to study consciousness, which at the time was an audacious idea. Many scientists at the time questioned whether consciousness was an appropriate problem and, if so, what would be the technical challenges needed to make a breakthrough. Francis was far ahead of his time, but he set the field in motion.

Do you have any burning scientific questions that current technologies are incapable of answering?

For Watson and Crick, the question was about the structure of the gene. In my era the question became "How is the gene controlled?" and more generally, "What is the mechanism that controls and coordinates the activity of large gene networks?" The nature of gene regulation is very challenging, yet it lies at the heart of normal physiology. When crippled, it is the source of chronic disease. I'm also very curious about the origins of genes. For instance, we know that many genes in our bodies came from primitive organisms like bacteria, mold and yeast. But I work on nuclear hormone receptors, which aren't found in those organisms. Nuclear receptors are integral to human physiology, but where did they come from? Where did we get the genes that tell our cells to produce them? If we could solve that mystery, we'd know a lot more about who we are and how we interact with our environment.

You have a knack for speaking about science in a way that's clear and engaging. Is that something you've cultivated?

I've worked at it. Good presentations take effort. It's one thing to do science and completely another to be able to communicate it. Working in the laboratory is kind of like working in an elaborate kitchen: you're mixing, spinning and making recipes. It's very detailed, and when you tell people what you did, it's easy to get caught up in the description of what you did without tasting the food. Many scientists aren't comfortable talking about their work to nonscientists, in part because the simpler you make it, the more difficult it is to do. But simplifying is important, because that's when you realize the essence of what you've done. That's when you bring the meal together and try to make it smell good, look good and taste good. It's important, but it's not easy.

Is there anything else you'd like to get better at?

I never picked up computer programming, and that interests me. While I do not like the process of writing (because it is difficult), I would like to write a book about the origin of physiology, behavior and the complex biology that makes us humans. In this case, starting is the hardest part. In regards to relaxing, I love playing the guitar, I like the craftsmanship in well-made guitars, and I like the techniques of playing (but mostly for myself and not for groups). While I like big challenges, I am not very efficient. I am easily distracted—by people, by Google, by just about anything. I keep my lab dynamic, and that gives my team room to be creative and ready for surprises. I like seeing the people in my lab take their discoveries and move on to develop their own research programs around the world. And I like bringing in new people and letting them follow their intuition. Truth is, I thrive on chaos.

Singing sensation Katharine McPhee to headline 2013 Symphony at Salk

MULTI-TALENTED SINGER KATHARINE MCPHEE will step into the spotlight as the headliner for the 18th annual "Symphony at Salk—A Concert under the Stars," performing with the San Diego Symphony and acclaimed guest conductor Thomas Wilkins.

The Institute's signature gala, Symphony at Salk, is a one-of-a-kind concert experience, where audience members take in spectacular sunset views over the Pacific Ocean as they enjoy a gourmet dinner and watch the evening's performance. It is one of the cultural highlights of summer in San Diego and sells out every year. Funds raised from the event directly support the Institute's leading-edge scientific research and award-winning community education programs.

McPhee, an acclaimed singer and popular actress from the NBC television series "SMASH," gained fame as a standout contestant on the fifth season of the Fox reality show "American Idol," where she impressed audiences and judges alike with her stunning voice. She was quickly signed to RCA Records, where her first single, "Somewhere Over the Rainbow/My Destiny," debuted at number two on Billboard's Hot Singles Sales chart. Her self-titled debut album followed in 2007, and in 2009, McPhee garnered a Young Hollywood Award for Best Female Vocalist. She spent 2010 touring the country with her album *Unbroken*, which included the hit single "Had It All."

Individual tickets are on sale for $250 and can be purchased online on the Symphony at Salk website or by calling 858-597-0657. Sponsorship packages are also available and range from $2,500 to $75,000. For additional ticket or sponsorship information, please visit www.salk.edu/symphony or email symphony@salk.edu.

Katharine McPhee

AUGUST 24, 2013 | 18TH ANNUAL SYMPHONY at SALK, *a concert under the stars*

Salk Institute honored with historic gift from family of the late Francis Crick

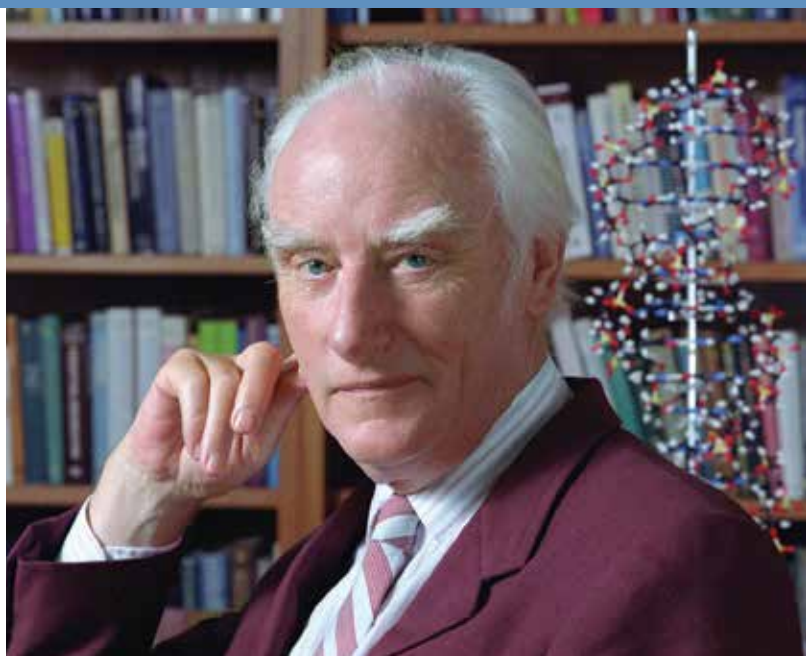
MICHAEL CRICK, THE SON OF THE LATE NOBEL LAUREATE AND SALK faculty member, **Francis Crick**, has generously donated to the Institute half of the proceeds from the sale of a 1953 letter in which the elder Crick describes to his young son his recent discovery of the structure of DNA.

On April 25, 1953, Crick and James Watson published a historic letter in *Nature* that described the DNA double helix, which concluded with the famous understatement that the structure "suggests a possible copying mechanism for genetic material." Crick, Watson and Maurice Wilkins would later share the 1962 Nobel Prize in Physiology or Medicine for the discovery.

But before Crick told the world about DNA, he wrote a letter to his 12-year-old son Michael, then at boarding school. The letter was signed with paternal affection, "Lots of love, Daddy," but the contents are considered the first complete written description of the structure and mechanism of DNA, including a hand-drawn picture by Crick. Of the picture, he commented to his son, "the model looks much nicer than this."

The letter sold April 10 at Christie's auction house to an anonymous bidder for a record price of close to $6 million. The previous record holder was an Abraham Lincoln letter that sold for $3.4 million in 2008.

"Francis Crick was for many years a deeply beloved member of the Salk faculty, who pushed himself and his colleagues to ask profound scientific questions," said Salk Institute President **William R. Brody**. "The Salk Institute is enormously grateful for having had the privilege to know and work with Francis, and that Michael has chosen to honor his father's memory in this way."



Francis Crick

> **"Francis Crick was for many years a deeply beloved member of the Salk faculty, who pushed himself and his colleagues to ask profound scientific questions."**
>
> **– WILLIAM R. BRODY**

James Watson spoke to a standing-room-only crowd in the Frederic de Hoffmann Auditorium.

Salk hosts James Watson to celebrate 60th anniversary of DNA discovery

ON THE EVE OF THE 60TH ANNIVERSARY OF THE DISCOVERY OF DNA, James Watson addressed Salk faculty, staff and guests on his new approach to cancer research.

"James Watson is the most famous scientist in the world," said **Ronald Evans**, holder of Salk's March of Dimes Chair in Molecular and Developmental Biology, as he introduced Watson. Evans disclosed that he'd just asked Watson to autograph his own copy of *The Double Helix*, Watson's best-selling memoir of the quest to understand DNA.

In 1962, Watson shared the Nobel Prize in Physiology or Medicine with long-time Salk Institute faculty member **Francis Crick** and Maurice Wilkins of King's College, London, for describing the double-helix structure of DNA, a discovery that laid the cornerstone for modern molecular biology. The fourth scientist who contributed to the discovery, Rosalind Franklin, had died of uterine cancer before the prize was awarded.

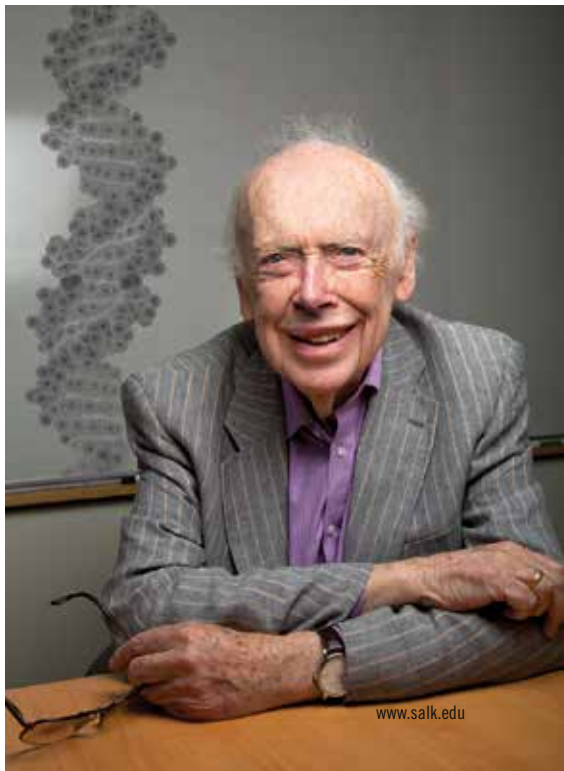
Watson, Chancellor Emeritus of the Cold Spring Harbor Laboratory, has described his research on cancer as "among my most important work since the double helix." He presented a provocative series of questions based on his review of the literature on cancer, especially studies on metformin, known as a diabetes drug, which he has been taking to keep his prostate cancer in check.

At one point, the lecture nearly turned into a private discussion between Watson and **Reuben Shaw**, an associate professor in Salk's Molecular and Cell Biology Laboratory and researcher in the Institute's new Helmsley Center for Genomic Medicine. Shaw had a paper in the journal *Cancer Cell*, which showed that a derivative of metformin decreased the size of lung tumors in mice and increased the animals' survival. "Unfortunately, for Cold Spring Harbor, you didn't accept our job offer!" Watson joked.

In his closing remarks, Evans, who has helped to spearhead Salk's efforts on metabolic diseases and aging research, cautioned, "Most Americans are under-exercised." By contrast, the 85-year-old Watson is a testimony to healthy aging. "I've exercised strenuously for the past twenty years," he said. "If I hadn't, I probably wouldn't be giving this talk."

> **"I've exercised strenuously for the past twenty years. If I hadn't, I probably wouldn't be giving this talk."**
>
> **– JAMES WATSON**

James Watson



President Barack Obama greets Terry Sejnowski at the White House.

Neuroscientist Terry Sejnowksi attends White House announcement of collaborative BRAIN Initiative

THIS PAST APRIL, PRESIDENT OBAMA launched the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. One of the initiative's scientific leaders is the Salk's own **Terry Sejnowski**, who joined the president for the official announcement at the White House.

According to Sejnowski, despite reports in the popular press that the intent of the initiative is to map the entire human brain, its real goal is much more fundamental and practical. "We are at a point where we can develop the tools to map entire circuits, first in invertebrates and eventually in mammals," he says. "This is the start of the million neuron march."

Sejnowski says BRAIN could ultimately help reduce the overwhelming costs for treatment and long-term care of brain-related disorders, which Price Waterhouse Coopers estimated at $515 billion for the United States alone in 2012.

"Many of the most devastating human brain disorders, such as depression and schizophrenia, only seem to emerge when large-scale assemblies of neurons are involved," says Sejnowski. "Other terrible conditions, such as blindness and paralysis, result from disruptions in circuit connections. The more precise our information about specific circuits, the more we will understand what went wrong, where it went wrong, and how to target therapies."

BRAIN's focus on tool development dovetails with Salk's Dynamic Brain Initiative, which is also extending the boundaries of knowledge of the brain, spinal cord and peripheral nervous system. Salk is home to several pioneering tool builders, among them **Edward M. Callaway**, who modified a rabies virus to trace neuronal connections in the visual system, and **Axel Nimmerjahn**, who has invented tiny, wearable microscopes to see into the brains of laboratory mice.

Summing up his excitement over the promise of BRAIN, Sejnowski says, "Imagine how it must have felt to be a rocket engineer when Kennedy said we would reach for the moon. You know there's an almost unimaginable amount of hard work ahead of you—and yet you can't wait to get started."

BRAIN INITIATIVE BRAIN RESEARCH THROUGH ADVANCING INNOVATIVE NEUROTECHNOLOGIES

"This is the start of the million neuron march."

– TERRY SEJNOWSKI

Stephen Smith, Professor of Molecular and Cellular Physiology of the Stanford University School of Medicine

The Waitt Advanced Biophotonics Center holds second annual symposium

MUCH OF THE PUBLIC FRUSTRATION WITH THE SLOW PROGRESS of science may come from our textbooks, which illustrate most ideas as simple cartoons. For example, the synapse of a neuron, where one neuron passes a signal to another, is usually shown as a small bulb which releases tiny bubbles (called vesicles) that float across a channel to dock in another small bulb. How hard can it be to cure a disease, if all it takes is knowing that a few bubbles cross between two bulbs?

The reality is a level of complexity that astonishes even professional scientists, as shown during the Salk's recent Waitt Advanced Biophotonics Center's (WABC) Second Annual Symposium. "It was the best conference I've been to in the last year, in terms of the new information I learned," says **Terry Sejnowski**, Salk's Francis Crick chair.

Organized by Salk faculty members **Martin Hetzer** and **Axel Nimmerjahn** and Biophotonics Core Facility Director **James Fitzpatrick**, the symposium brought together an all-star scientific line-up of specialists in topics ranging from the molecular mechanisms of gene expression to the effect of neural vasculature on microstrokes. "What they all have in common is the desire to understand the three-dimensional architecture of single molecules and cellular systems and how it relates to biological function," says Hetzer, WABC's faculty director and the Jesse and Caryl Philips Foundation Chair.

Consider that textbook cartoon of a neuron. According to symposium speaker Stephen Smith of Stanford University, it's now known many vesicles dock at places other than synapses. Additionally, the vesicles themselves, which appear in the flat gray-scale of older electron micrographs to be bubbles of just one substance, have been revealed by newer techniques to be pin cushion-like structures of hundreds of proteins.

"A piece of cerebral cortex the size of a large grain of sand may contain several billion synapses," says Sejnowski. "It's a multi-dimensional problem that's beyond what a human can calculate." His own talk described his lab's use of computer simulations to model the subcellular architecture and physiology of neurons and their synapses, as well as bacteria.

With its *tour de force* demonstrations of the insights gained from advanced scientific methods, the symposium reinforced the message of President Obama's BRAIN Initiative to push forward with new tools and techniques, says Sejnowski, an advisor to the initiative.

Says Fitzpatrick, "At whatever scale you're working on, the complexity of biological systems is nearly overwhelming. Yet we firmly believe that with the right tools, it's not intractable."

From left to right: Clodagh O'Shea, John Reynolds and Tatyana Sharpee

Salk promotes three outstanding scientists

THREE SALK FACULTY MEMBERS RECEIVED WELCOME NEWS IN mid-April: all were promoted, based on recommendations by their faculty colleagues and by the Institute's non-resident fellows.

John Reynolds, in the Systems Neurobiology Laboratories, was promoted to full professor. His research explores the fundamental nature of the computations that are carried out by the neocortex, including those that enable us to attend to sensory stimuli. He seeks to understand how and why these computations fail in brain disease—research that is essential to developing treatments for disorders in which attention and vision are impaired, such as visual agnosia, Balint's syndrome, visual neglect, attentional aspects of autism, schizophrenia and Alzheimer's disease.

Clodagh O'Shea, of the Molecular and Cell Biology Laboratory, was promoted to associate professor. O'Shea is an expert on oncolytic viruses—viruses that can only reproduce in cancer cells. Such viruses offer a novel and potentially self-perpetuating cancer therapy: each time a virus infects a cancer cell and successfully multiplies, the virus ultimately kills the cancer cell by bursting it open to release thousands of viral progeny. The next generation seeks out remaining tumor cells and distant micro-metastases but leaves normal cells unharmed. O'Shea is at the forefront of this cutting-edge technology.

Tatyana Sharpee was also promoted to associate professor. Working in the Computational Neurobiology Laboratory, she studies the brain's operation in a natural sensory environment, formulating theoretical principles of how it processes information. Using methods from physics and information theory, Sharpee and her colleagues are developing statistical methods that can help identify how the brain can rapidly recognize objects despite variations in their position relative to us. This work may eventually lead to better prostheses for patients whose object recognition has been impaired as a result of a stroke or neurodegenerative disease.

Can't wait for the next issue of *InsideSalk?*

Sign up for our free new monthly e-newsletter, "Salk Central," to learn about the latest Institute news and discoveries in Salk science as they happen! To sign up, just visit www.salk.edu/news/enewsletter.php

Joanne Chory
Professor and Director
Plant Molecular and Cellular Biology Laboratory
Howard Hughes Medical Institute Investigator
Howard H. and Maryam R. Newman Chair in Plant Biology

Joanne Chory feted in Paris celebration of Women in Science

Salk plant biologist **Joanne Chory** was honored in Paris, France, with a larger-than-life photo on the Avenue des Champs-Élysées. The commemoration was a part of the 15th anniversary celebration of the L'Oreal–UNESCO For Women in Science program. In 2000, Chory was the first North American laureate to be inducted into the organization.

Founded in 1998, the L'Oreal–UNESCO For Women in Science partnership was created to recognize and promote remarkable women who have contributed to scientific progress on every continent and to promote scientific advances worldwide. More than 1700 women in 110 countries have subsequently received support from the program.

Board of Trustees welcomes business leader Sanjay Jha

AT ITS APRIL MEETING, THE SALK BOARD of Trustees unanimously approved the election of **Sanjay Jha** to its ranks. Jha is the former chairman and chief executive officer of Motorola Mobility and previously served as the co-chief executive officer of Motorola. Under his leadership, the struggling company was transformed into a powerhouse in the mobile phone market, primarily due to his decision to take a huge risk on the Android smart phone. He stepped down as CEO in May 2012, after Google acquired Motorola Mobility.

Prior to joining Motorola, Jha held a variety of positions at Qualcomm after joining the company as a senior engineer in 1994. He was promoted to vice president of engineering in 1997, and in 1998, he became senior vice president of engineering. In 2002, Jha led the formation of Qualcomm Technologies & Ventures, where he managed both the technology investment portfolio and the new technology group as senior vice president and general manager. He also served as president of Qualcomm CDMA Technologies, Qualcomm's chipset and software division, during a period of rapid growth. Jha became executive vice president of Qualcomm and president of Qualcomm Flarion Technologies in 2003 and was named chief operating officer in December 2006.

"Sanjay's extraordinary record of success as a leader in technology and business makes him a valuable addition to our board," said board chair **Irwin M. Jacobs**. "His wide-ranging curiosity, experience and professional expertise will provide valuable support as we further expand the Institute's scientific impact."

Jha holds a Ph.D. in electronic and electrical engineering from the University of Strathclyde in Scotland. He received his B.S. in engineering from the University of Liverpool in England.

"Sanjay's extraordinary record of success as a leader in technology and business makes him a valuable addition to our board."

– IRWIN M. JACOBS

Salk welcomes the community to Step into Discovery

Institute hosts first ever 5K walk and open house

ON APRIL 13, SALK OPENED ITS CAMPUS TO THE COMMUNITY IN a way it never had before by hosting Step into Discovery day, presenting the inaugural 5K Walk for Salk and Explore Salk, a wellness event and open house that offered exclusive tours of the Institute's science labs.

The morning began with a health and wellness fair, with sponsors such as Scripps Health and Sharp HealthCare providing free health screenings to guests. More than 700 people then took part in the 5K Walk for Salk in support of basic research, beginning their trek in the Institute's famed courtyard.

Following the Walk for Salk, 500 additional people arrived at the Institute for the Explore Salk component of the event. The eager guests toured labs, visited with researchers and attended science talks. It was a unique opportunity for the community to interact with scientists and understand how basic research is the first major step in discovering new therapies and cures for challenging diseases. In addition to the tours and talks, there were opportunities for children to learn about plant biology, the brain and DNA at hands-on science booths.

Step into Discovery

walk for salk Where cures begin

explore salk Tours, activities, talks

» Visit here to view the photo gallery

www.salk.edu/jun13

Annie Onanong Chivatakarn (center), a research associate from the Gene Expression Laboratory, helps two San Diego students with an interactive lab experiment as part of Salk's annual March of Dimes High School Science Day.

March of Dimes High School Science Day introduces students to research careers

FORTY-NINE SALK SCIENTISTS IN 18 LABS HOSTED APPROXIMATELY 200 students and teachers from 21 schools on March 3, for the 23rd annual March of Dimes High School Science Day. The event was anything but a numbers game. Participants took part in engaging hands-on laboratory experiences and enjoyed a group lunch; afterward, Salk professor **Fred "Rusty" Gage** gave a presentation about the uses for induced pluripotent stem cells.

While attendee comments about the event were universally positive, for some students, a half-day behind the scenes at the Institute may have changed their educational and career plans. "Great, great, great way to spend a Saturday!" said a student from the California Academy of Mathematics and Science afterward. "I've known I wanted to work in medicine, and this amazing journey opened my horizons to the expansive careers in science."

Added a participant from Steele Canyon High School: "This was an amazing experience! I think everyone 'on the fence' about their college plans should experience this."

Rusty Gage gives a fascinating lecture to the auditorium filled with students.

Geoff Wahl (center) and Bianca Kennedy (right) join Congressman Scott Peters at the press conference to raise awareness about sequestration.

Congressman Scott Peters fights federal cuts to research funding

CONGRESSMAN SCOTT PETERS, AN ARDENT SUPPORTER OF FEDERAL funding for scientific research, held a press conference at Salk on February 20, calling on lawmakers to avoid sequestration.

Salk scientist **Geoffrey Wahl**, a professor in the Gene Expression Laboratory, and **Bianca Kennedy**, a patient advocate and breast cancer survivor, joined the congressman to express their concern over sequestration as well—a potential cut of $2.5 billion to the National Institutes of Health's (NIH) budget.

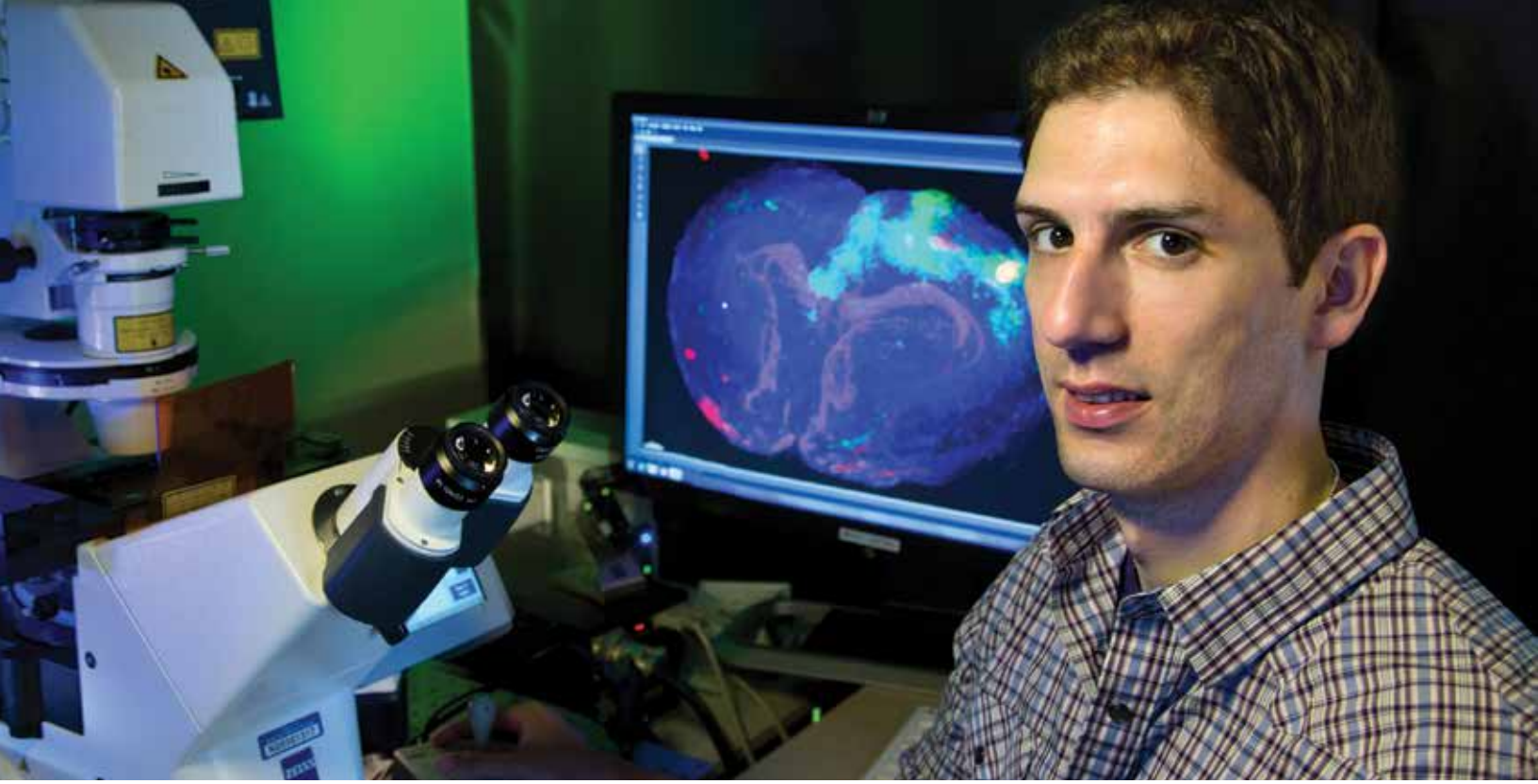
Wahl said that any funding cuts would cripple the scientific landscape and have an adverse impact on cancer research. "Instead of calling it sequestration, call it amputation," he said. "You get to choose which of your limbs you want to lose because that's what it's going to be."

NIH funds one third of all biomedical research conducted in the U.S. and supports 432,000 jobs across the country. Locally, sequestration could cost San Diego's science and technology sector about 4,200 jobs and $290 million in funding.

According to Wahl, in the past, 25 percent of all grant proposals were funded. "That would fund all the research you could possibly need to do," he noted. "In recent years, that has been reduced to 7 percent and will suffer even further as a result of the sequestration."

> "Instead of calling it sequestration, call it amputation."
>
> – GEOFF WAHL

» Watch the video
www.salk.edu/jun13/video3



Jamie Kasuboski

Salk scientist wins 2013 Andor Insight Award

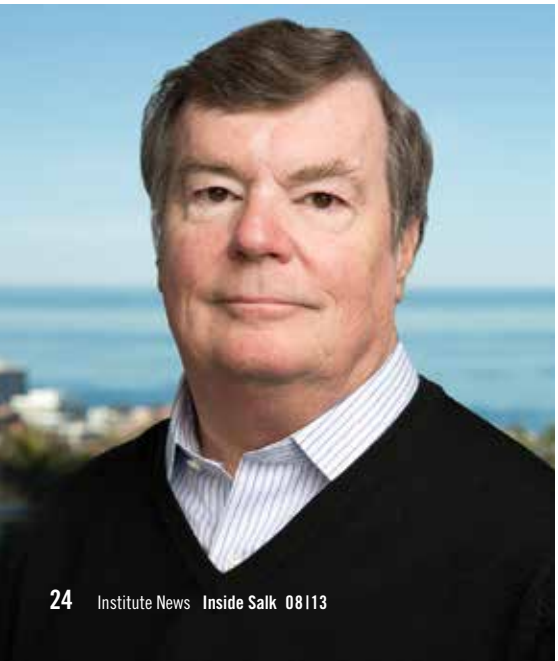
JAMIE KASUBOSKI, A LIGHT MICROSCOPY specialist in the Waitt Advanced Biophotonics Center Core facility, was the recipient of an Andor Insight Award in this year's scientific imaging competition, one of three winners selected out of 90 submissions.

Andor Technology, a world leader in scientific imaging, spectroscopy solutions and microscopy systems, launched the international contest four years ago to reward visually stunning and scientifically captivating images, spectra, graphics and movies. The winners are chosen by a panel of expert judges who focus on recognizing the cutting-edge work carried out by researchers using Andor equipment or Bitplane software in the fields of physical and life sciences imaging.

Kasuboski's winning entry was titled "Whole Mouse Brain 3D Reconstruction." It was the result of a collaborative project with fellow Salk scientist **Marina Garrett** from the Systems Neurobiology Laboratories of **Edward Callaway** to provide an innovative 3D modeling method for neuronal wiring to better probe and understand neuronal networks. It shows in extraordinary detail an Imaris 3D reconstruction of a mouse brain, including proteins and neuron structure. Later analysis counted which regions of the brain contained specific cell types, providing a vivid insight into the wiring of the brain.

"The visual impact and scientific value of this year's entries clearly highlights the cutting-edge work being carried out by researchers using our products," says Andrew Dennis, Andor's director of product management. "The judges' selection of winners provides an interesting insight into the significance and detail of the researcher's work across multiple scientific disciplines."

» View winning entries
www.theinsightawards.com/#!/entries



Daniel C. Lewis honored at Fairleigh Dickinson Charter Day celebration

SALK TRUSTEE DANIEL C. LEWIS WAS HONORED AT FAIRLEIGH DICKINSON UNIVERSITY'S 24th Annual Charter Day on Friday, June 7, for distinguishing himself as an outstanding leader in his profession and community.

Lewis earned an MBA from Fairleigh Dickinson University in 1976 and received a PINNACLE Award from the university in 2009. A well-known leader in the global transportation, defense and aerospace industries, Lewis served as president and as senior vice president at Booz & Company, the renowned global management consulting firm, with a career spanning over 30 years.

In March 2012, Lewis and his wife, Martina, established the Daniel and Martina Lewis Chair at Salk, which is currently held by **Geoffrey Wahl**, professor in the Institute's Gene Expression Laboratory. Lewis also joined the Salk Board of Trustees in 2012. In addition to serving on Salk's board, he serves as a trustee for Fairleigh Dickinson and is on the dean's executive council for the College of Technology at Purdue University.

Daniel C. Lewis

Irwin M. Jacobs awarded 2013 IEEE Medal of Honor

IRWIN M. JACOBS, QUALCOMM COFOUNDER and chair of Salk's Board of Trustees, was honored with the IEEE (Institute of Electrical and Electronics Engineers) 2013 Medal of Honor, the highest award bestowed by the organization. The IEEE is the world's largest professional association dedicated to advancing technological innovation and excellence for the benefit of humanity. The organization paid tribute to Jacobs extraordinary accomplishments and also presented 19 medals and recognitions to other leading technologists at the IEEE Honors Ceremony held on June 29 in San Diego.

Jacobs, an IEEE Life Fellow, was selected for the honor in recognition of his leadership and essential contributions to digital communications and wireless technology. He oversaw Qualcomm's revolutionary innovations in Code Division Multiple Access (CDMA), a technology fundamental to today's 3G mobile wireless standards.

Since 1917, the IEEE awards program has recognized technical professionals whose exceptional achievements and outstanding contributions have made a lasting impact on technology, society, the engineering profession and humanity. Recipients of the awards, who are chosen through peer nomination and approval, are honored as the most influential members in their chosen field.

Irwin M. Jacobs

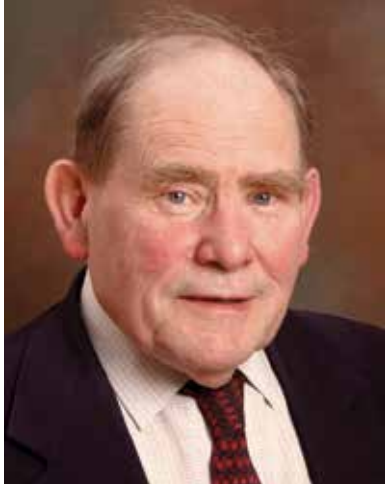
Fred Gage

Fred Gage recipient of 2013 George A. Miller Prize in Cognitive Neuroscience

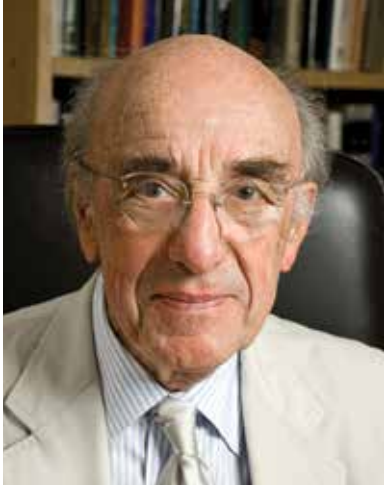
FRED GAGE, PROFESSOR IN SALK'S LABORATORY of Genetics, was named this year's winner of the George A. Miller Prize in Cognitive Neuroscience. Recipients of the honor are acknowledged for a career of "distinguished and sustained scholarship and research at the cutting edge of cognitive neuroscience," and for "extraordinary innovation and high impact on international scientific thinking." The Cognitive Neuroscience Society established the award in 1995 to honor Miller, whose many theoretical advances greatly influenced the discipline of cognitive neuroscience.

Gage delivered the George A. Miller Lecture on April 13, at the 20th annual meeting of the Cognitive Neuroscience Society, discussing his research on the adult central nervous system and how it can adapt to the environment over time. His work may lead to methods of replacing or enhancing brain and spinal cord tissues lost or damaged due to neurodegenerative disease or trauma.

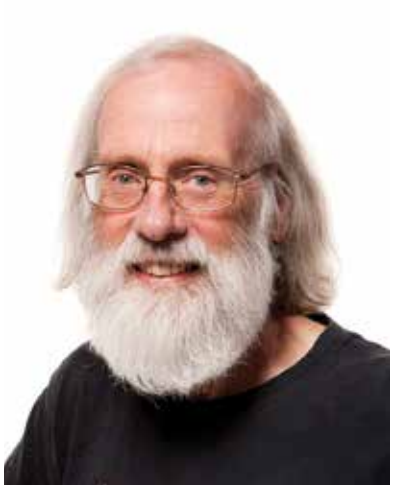
Cognitive Neuroscience Society



Sydney Brenner



Roger Guillemin



Tony Hunter

Geoffrey M. Wahl

American Association for Cancer Research appoints Salk scientists to inaugural class of fellows

THE AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR), the world's oldest and largest professional organization dedicated to accelerating scientific progress to prevent and cure cancer, selected four Salk scientists and two of the Institute's nonresident fellows to be inducted into its first class of fellows of the AACR Academy.

"Membership in the fellows of the AACR Academy will be the most prestigious honor bestowed by the American Association for Cancer Research," says Margaret Foti, chief executive officer of the AACR.

Distinguished professors and Nobel laureates **Sydney Brenner** and **Roger Guillemin**, and faculty members **Tony Hunter**, a professor in the Molecular and Cell Biology Laboratory and director of Salk Institute Cancer Center, and **Geoffrey M. Wahl**, a professor in the Gene Expression Laboratory, were honored at a special ceremony on April 5, at the National Museum of Women in the Arts in Washington, D.C.

Salk nonresident fellows and Nobel laureates **David Baltimore** and **Elizabeth H. Blackburn** were also named to the academy.

"It is a great honor to have a team of our scientists chosen for the inaugural class of the AACR fellows and is indicative of the deep commitment and impact of our research in fighting cancer," says Salk president **William R. Brody**.

The AACR Fellows Academy is a separate entity within the American Association for Cancer Research, and only individuals who have made exceptional contributions to cancer and/or cancer-related biomedical science are eligible for election. It was created to recognize and honor distinguished scientists whose major scientific contributions have propelled significant innovation and progress against cancer.

The inaugural class of fellows includes 106 individuals, to symbolize the age of the organization upon establishment of the academy. Future classes of fellows will consist of no more than 11 individuals, in honor of the founding members of the American Association for Cancer Research.

Salk scientist elected to American Academy of Arts and Sciences

TERRENCE J. SEJNOWSKI, PROFESSOR AND HEAD OF SALK'S COMPUTATIONAL Neurobiology Laboratory, has been elected a fellow of the American Academy of Arts and Sciences, one of the nation's most prestigious honorary societies. It is a distinction awarded annually to global leaders in business, government, public affairs, the arts and popular culture, as well as biomedical research.

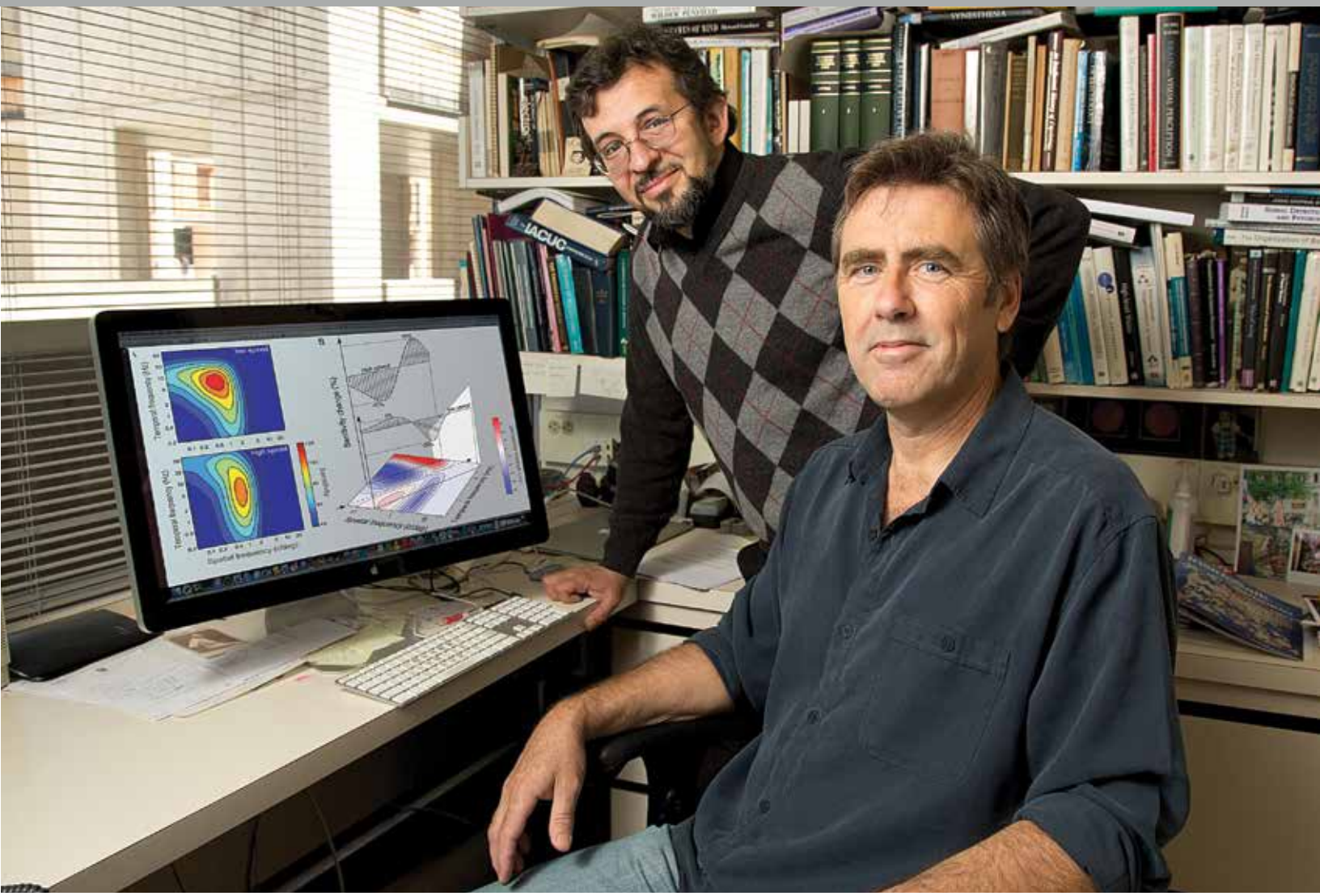
Sejnowski is world renowned as a pioneer in the field of computational neuroscience, and his work on neural networks helped spark the neural networks revolution in computing in the 1980s. His research has made important contributions to artificial and real neural network algorithms and to applying signal processing models to neuroscience.

He is the 12th scientist from Salk to be inducted into the academy and will share the honor with 198 new members of the 2013 class, which includes Nobel Prize winner Bruce A. Beutler, philanthropist David M. Rubenstein, astronaut John Glenn, actor Robert De Niro and singer-songwriter Bruce Springsteen. The honorees will be formally inducted into the academy on October 12, 2013, at its headquarters in Cambridge, Massachusetts.

"Election to the academy honors individual accomplishment and calls upon members to serve the public good," says academy president Leslie C. Berlowitz. "We look forward to drawing on the knowledge and expertise of these distinguished men and women to advance solutions to the pressing policy challenges of the day."

Terrence J. Sejnowski

Discovery Roundup



From left: Sergei Gepshtein and Thomas D. Albright

Despite what you may think, your brain is a mathematical genius

AFTER HOURS OF DODGING DANGEROUS DRIVERS, YOU FINALLY arrive at a quiet mountain retreat, gaze at a pristine lake and congratulate yourself for having "turned off your brain."

But actually, according to **Thomas D. Albright**, an expert on how the visual system works, you've just given your brain a whole new challenge. "You may think you're resting," he says, "but your brain is automatically assessing the spatiotemporal properties of this novel environment—what objects are in it, are they moving, and if so, how fast are they moving?"

The dilemma is that our brains can only dedicate so many neurons to this assessment. "It's a problem in economy of resources," says **Sergei Gepshtein**, a computational neuroscientist and staff scientist in Albright's lab. "If the visual system has limited resources, how can it use them most efficiently?"

Albright, Gepshtein and **Luis A. Lesmes**, a specialist in measuring human performance and former Salk postdoctoral researcher now at the Schepens Eye Research Institute, proposed an answer in a study published in *Proceedings of the National Academy of Sciences* that may reconcile the puzzling contradictions in many earlier studies.

Previously, scientists expected that extended exposure to a novel environment would make you better at detecting its subtle details, such as the slow motion of waves on that lake. Yet those who tried to confirm that idea were surprised when their experiments produced contradictory results. "Sometimes people got better at detecting a stimulus, sometimes they got worse, sometimes there was no effect at all, and sometimes people got better, but not for the expected stimulus," says Albright.

The answer came from asking a new question: What happens when you look at the problem of resource allocation from a system's perspective? It turns out that something's got to give, and the team's study details the computations the visual system uses to accomplish the adaptation.

"It's as if the brain's on a budget; if it devotes 70 percent here, then it can only devote 30 percent there," says Gepshtein.

"Simply put, it's a tradeoff," Albright adds. "The price of getting better at one thing is getting worse at another."

Discovery Roundup

Salk scientists develop drug that slows Alzheimer's in mice

ACCORDING TO THE ALZHEIMER'S ASSOCIATION, MORE THAN 5 million Americans are living with Alzheimer's disease, the sixth leading cause of death in the country. Despite years of research, there are no disease-modifying drugs for the condition. Current FDA-approved medications, including Aricept, Razadyne and Exelon, offer only fleeting short-term benefits for patients and do nothing to slow the irreversible decline of brain function that characterizes the disease.

A drug developed by scientists in the lab of **David Schubert**, however, reverses memory deficits and slows Alzheimer's disease in aged mice following short-term treatment. The findings, published in *Alzheimer's Research and Therapy,* may pave the way to a new treatment for Alzheimer's disease in humans.

In developing the drug, known as J147, Schubert and his colleagues bucked the trend within the pharmaceutical industry, which has focused on the biological pathways involved in the formation of amyloid plaques, the dense deposits of protein that characterize the disease. Instead, the team used living neurons grown in laboratory dishes to test whether their new synthetic compounds, which are based upon natural products derived from plants, were effective at protecting brain cells against several pathologies associated with brain aging. From the test results of each chemical iteration of the lead compound, they were able to alter their chemical structures to make them much more potent.

To test the efficacy of J147 in a much more rigorous preclinical Alzheimer's model, the team then treated mice using a therapeutic strategy that they say more accurately reflects the human symptomatic stage of Alzheimer's. Administered in the food of 20-month-old genetically engineered mice, at a stage when Alzheimer's pathology is advanced, J147 rescued severe memory loss, reduced soluble levels of amyloid, and increased neurotrophic factors essential for memory after only three months of treatment. In a different experiment, the scientists tested J147 directly against Aricept, the most widely prescribed Alzheimer's drug, and found that it performed as well or better in several memory tests.

Although J147 appears to be safe in mice, the next step will require clinical trials to determine whether the compound will prove safe and effective in humans, and Schubert and his team are currently seeking funding for such a trial.

» Watch the video
www.salk.edu/jun13/video1

Salk scientists developed J147, a synthetic drug shown to improve memory and prevent brain damage in mice with Alzheimer's disease.

How the brain keeps track of similar but distinct memories

THE PROCESS OF TAKING COMPLEX memories and converting them into representations that are less easily confused is known as pattern separation. Computational models of brain function suggest that the dentate gyrus, a subregion of the hippocampus, helps us perform pattern separation of memories by activating different groups of neurons when an animal is in different environments. Previous laboratory studies, however, found that the same populations of neurons in the dentate gyrus are active in different environments and that the cells distinguished new surroundings by changing the rate at which they sent electrical impulses—a discrepancy that perplexed neuroscientists.

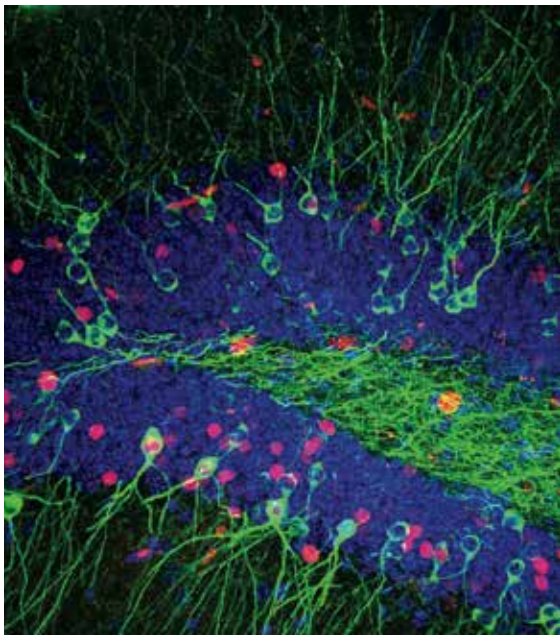
A team of scientists led by **Fred H. Gage** has now discovered how the dentate gyrus helps keep memories of similar events and environments separate.

"Every day, we have to remember subtle differences between how things are today versus how they were yesterday—from where we parked our car to where we left our cellphone," explains Gage. "We found how the brain makes these distinctions, by storing separate 'recordings' of each environment in the dentate gyrus."

Gage's team compared the functioning of the mouse dentate gyrus and another region of the hippocampus, known as CA1, using laboratory techniques for tracking the activity of neurons at multiple time points. What they found was that the dentate gyrus and CA1 subregions functioned differently. In CA1, the same neurons were active during the learning and retrieval of memories. In the dentate gyrus, however, distinct groups of cells were active during learning episodes and retrieval, and exposing the mice to two subtly different environments activated two distinct groups of cells in the dentate gyrus.

"This finding supported the predictions of theoretical models that different groups of cells are activated during exposure to similar, but distinct, environments," says postdoctoral researcher Wei Deng. "This contrasts with the findings of previous laboratory studies, possibly because they looked at different subpopulations of neurons in the dentate gyrus."

In clarifying how the brain stores and distinguishes between memories, the discovery, reported in *eLife*, may also help identify how neurodegenerative diseases such as Alzheimer's rob people of these abilities.



Salk researchers discovered how the brain keeps track of similar but distinct memories. This microscope image shows neural activity in the dentate gyrus, a subsection of the hippocampus where distinct groups of cells were active during the learning episodes (green) and memory retrieval (red).

Smoke signals: How burning plants tell seeds to rise from the ashes

IN THE SPRING FOLLOWING A FOREST FIRE, TREES THAT SURVIVED the blaze explode in new growth, and plants sprout in abundance from the scorched earth. For centuries, it's been a mystery how seeds, some long dormant in the soil, know to push through the ashes to regenerate the burned forest.

But a team led by **Joseph P. Noel** and **Joanne Chory** has now cracked the mystery behind this fundamental "circle of life." In addition to explaining how fires lead to regeneration of forests and grasslands, their findings, reported in the *Proceedings of the National Academy of Sciences,* may aid in the development of plant varieties that help maintain and restore ecosystems that support all human societies.

"This is a very important and fundamental process of ecosystem renewal around the planet that we really didn't understand," explains Noel. "Now we know the molecular triggers for how it occurs."

"What we discovered," Chory adds, "is how a dying plant generates a chemical message for the next generation, telling dormant seeds it's time to sprout."

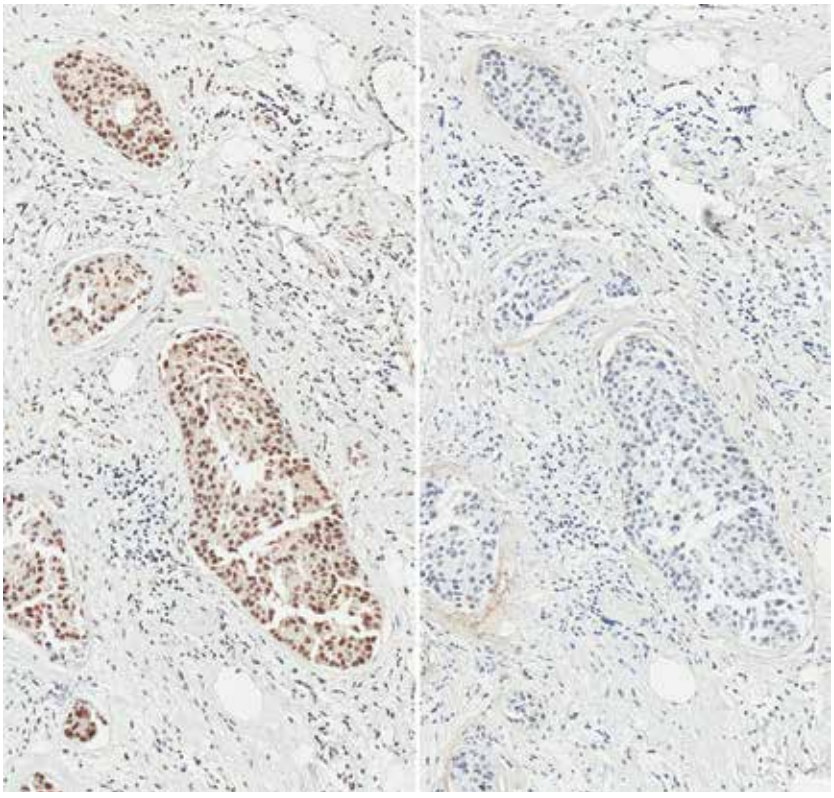
In previous studies, scientists had discovered that chemicals known as karrikins are created as trees and shrubs burn during a forest fire, and they remain in the soil after the fire, ensuring that the forest will regenerate. This new study sought to uncover exactly how karrikins stimulate new plant growth. First, the Salk researchers determined the structure of a plant protein known as KAI2, which binds to a karrikin in dormant seeds. Then, comparing the karrikin-bound KAI2 protein to the structure of an unbound KAI2 protein allowed the team to speculate how KAI2 allows a seed to perceive karrikins in its environment.

The chemical structures they solved revealed all the molecular contacts between a karrikin and KAI2. The study also showed that when a karrikin binds to the KAI2 protein, it causes a change in its shape, which may send a new signal to other proteins in the seeds. These other protein players, together with karrikin and KAI2, generate the signal causing seed germination at the right place and time after a wildfire.

More research is needed to understand exactly how the change in shape of the KAI2 protein activates a genetic pathway that regulates germination, says Chory. "But," she notes, "this finding is an absolutely critical step in understanding this genetic program and how plant ecosystems, forests and grasslands renew themselves."

Discovery Roundup

Beverly M. Emerson



The image to the right shows in brown color the activation of TGFß signaling (left) and p53 levels (right) in a breast biopsy from a patient diagnosed with ductal carcinoma in situ and invasive carcinoma. TGFß1 deactivates the main pathway directing the response to chemotherapeutic drugs, and cellular stress, suggesting a potential new therapy to prevent early stages cancers progression and drug resistance.

Protein preps cells to survive stress of cancer growth and chemotherapy

A TEAM OF SCIENTISTS IN THE LAB OF BEVERLY M. EMERSON has uncovered a survival mechanism that occurs in breast cells that have just turned premalignant—cells on the cusp between normalcy and cancers—which may lead to new methods of stopping tumors. In their study, published in *Molecular Cell,* the group reported that a protein known as transforming growth factor beta (TGF-ß), considered a tumor suppressor in early cancer development, can actually promote cancer once a cell drifts into a precancerous state. The discovery—a surprise to the investigators—raises the tantalizing possibility that with novel treatment, some cancers might be prevented before they even develop.

TGF-ß molecules are secreted proteins found in most human tissues. They play a number of different biological roles, including controlling cell proliferation and inflammation and assisting in wound healing. The prevailing dogma in cancer research is that TGF-ß signaling keeps cells from morphing into cancer, explains **Fernando Lopez-Diaz**, a researcher in Emerson's lab who spearheaded the study.

The researchers conducted the study to learn exactly how TGF-ß and p53, a known tumor suppressor, interact in cancer development, examining premalignant as well as cancer cells from breast and lung tumors and matching normal and premalignant breast cells from healthy women. No matter how many different ways they did their experiments, the team found that TGF-ß can interfere with cells' damage responses in premalignant or cancer cells.

"The bad face of TGF-ß emerged within just a few cell divisions away from normality, allowing cells to avoid death," Lopez-Diaz says.

This newfound immortality explains many oncologic mysteries, he says. One is that it sheds light on how premalignant and early cancer cells are able to withstand the assault of chemotherapy and other treatments. It may also explain why 77 percent of breast cancers have a normal p53 gene, and it further suggests a way that cancer cells can use both to metastasize and survive the journey to organs where they set up a new home.

Agents designed to inhibit TGF-ß are already being tested against cancers that have spread, says Emerson. "This study offers both significant insights into early cancer development and a new direction to explore in cancer treatment," she adds. "It would be fantastic if a single agent could shut down both advanced cancer and cancer that is primed to develop."

> **"This study offers both significant insights into early cancer development and a new direction to explore in cancer treatment."** – BEVERLY M. EMERSON

Salk researchers chart epigenomics of stem cells that mimic early human development

Joseph R. Ecker

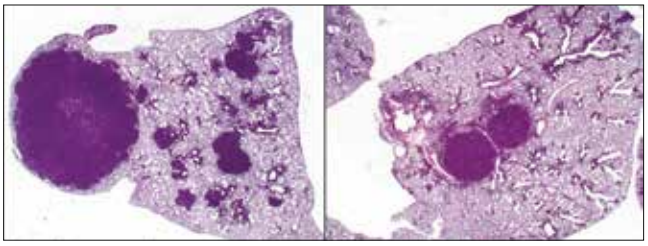
SCIENTISTS HAVE LONG KNOWN THAT control mechanisms known collectively as "epigenetics" play a critical role in human development, but they did not know precisely how alterations in this extra layer of biochemical instructions in DNA contribute to development. Now, in the first comprehensive analysis of epigenetic changes that occur during development, published in *Cell*, a multi-institutional group of scientists, co-led by **Joseph R. Ecker**, has discovered how modifications in key epigenetic markers influence human embryonic stem cells as they differentiate into specialized cells in the body.

Scientists have established that the gene expression program encoded in DNA is carried out by proteins that bind to regulatory genes and modulate gene expression in response to environmental cues. Growing evidence now shows that maintaining this process depends on biochemical processes that alter gene expression as cells divide and differentiate from embryonic stem cells into specific tissues.

Epigenetic modifications—collectively known as the epigenome—control which genes are turned on or off without changing the letters of the DNA alphabet (A-T-C-G), providing cells with an additional tool to fine-tune how genes control the cellular machinery.

In their study, Ecker and collaborators from several prominent U.S. research institutions examined the beginning state of cells, before and after they developed into specific cell types. Starting with a single cell type, the team followed the cells' epigenome from development to different cell states, looking at the dynamics in changes to epigenetic marks from one state to another. They found that sections of the DNA that activate regulatory genes, which in turn control the activity of other genes, tend to have different amounts of the letters "C" and "G" of the DNA alphabet, depending on when these regulatory genes are turned on during development. On the other hand, genes active in more mature cells whose tissue type is already determined tend to be CG-poor and regulated by DNA methylation. The results suggest that distinct epigenetic mechanisms regulate early and late states of embryonic stem cell differentiation.

"Epigenomic studies of how stem cells differentiate into distinct cell types are a great way to understand early development of animals," says Ecker. "If we understand how these cells' lineages originate, we can understand if something goes right or wrong during differentiation. It's a very basic study, but there are implications for being able to produce good-quality cell types for various therapies."



Salk scientists found that the diabetes drug phenformin was effective at reducing tumor size in mice with lung cancer. The image on the left shows tumors (dark purple) treated with a placebo) compared to those treated with phenformin (right).

» Watch the video
www.salk.edu/jun13/video2

Diabetes drug could hold promise for lung cancer patients

OVER THE PAST DECADE, GROWING evidence that cancer and metabolism are connected has emerged from a number of laboratories, including that of **Reuben Shaw**. Although scientists are still working to identify what tumors might be most responsive and which drugs most useful, Shaw and a team of scientists have recently found that phenformin, a derivative of the widely used diabetes drug metformin, decreased the size of lung tumors in mice and increased the animals' survival. The findings, reported in *Cancer Cell*, may give hope to the nearly 30 percent of patients with non-small cell lung cancer (NSCLC) whose tumors lack LKB1 (also called STK11).

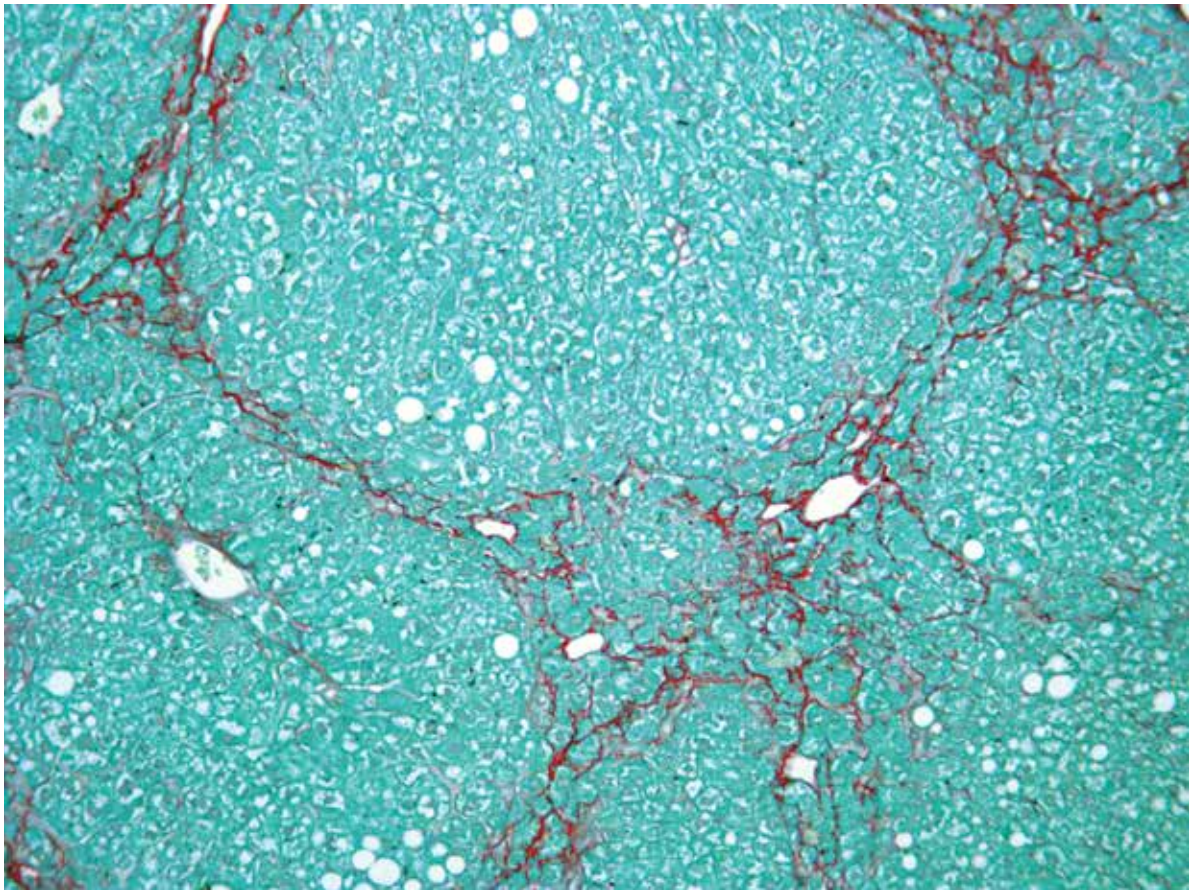
The LKB1 gene turns on a metabolic enzyme called AMPK when energy levels of ATP, molecules that store the energy we need for just about everything we do, run low in cells. Cells that lack LKB1 are unable to sense metabolic stress and initiate the process to restore their ATP levels following a metabolic change. As a result, they run out of cellular energy and undergo apoptosis, or programmed cell death, whereas cells with intact LKB1 are alerted to the crisis and correct their metabolism.

This knowledge led Shaw and his group to a class of drugs that lower cellular energy levels by attacking the power stations of the cell, called mitochondria. Metformin and phenformin both inhibit mitochondria; however, phenformin is nearly 50 times more potent. In the study, the researchers tested phenformin as a chemotherapy agent in genetically engineered mice that lacked LKB1 and had advanced-stage lung tumors. After three weeks of treatment, they saw a modest reduction in tumor burden in the mice.

In further testing on mice with earlier stage disease, Shaw, in collaboration with **David Shackelford** (a former postdoctoral researcher in Shaw's lab who is now at UCLA's David Geffen School of Medicine), found that early phenformin treatment increased survival and slowed the progression of tumors lacking LKB1. It had no significant benefit for tumors with alterations in other lung cancer genes, however.

The work provides proof of principle and a basis to initiate human studies. If enough clinicians who believe in investigating phenformin can be organized, then phenformin as an anti-cancer agent could be a reality in the next several years.

Discovery Roundup



This image shows mouse liver tissue with fibrosis (red), a type of scarring caused by chronic liver diseases and injuries. Salk researchers found that a drug already approved by the FDA for the treatment of psoriasis deactivates the switch governing the fibrotic response in mouse liver cells, suggesting a potential new therapy for fibrotic diseases in humans.

Sunshine hormone, vitamin D, may offer hope for treating liver fibrosis

THERE ARE CURRENTLY NO EFFECTIVE DRUGS FOR LIVER fibrosis, the accumulation of tough, fibrous scar tissue that occurs in most types of chronic liver diseases. Existing therapeutic approaches, which treat the symptoms of liver disease, do not stop liver fibrosis from progressing.

Researchers led by **Ronald M. Evans**, however, have recently discovered that a synthetic, hormonally active form of vitamin D, calcipotriol (a drug already approved by the FDA to treat psoriasis), deactivates the switch governing the fibrotic response in mouse liver cells, suggesting a potential new therapy for fibrotic diseases in humans. Their study, which was reported in *Cell,* focused on a star-shaped "stellate" cell in the liver that serves as a beacon for damage. When called into action, stellate cells produce fibrotic proteins in an attempt to heal an injury. Under chronic stress, localized fibrosis expands, eventually leading to cirrhosis, increased risk of liver cancer and even the need for a liver transplant.

The Evans lab discovered a genetic switch through which vitamin D–related ligands such as calcitriol can put the brakes on fibrosis. "Preclinical results suggest the 'vitamin D brake' is highly efficacious and led us to believe that the time is right to consider a trial in the context of chronic liver disease," says Evans.

Previous studies have shown a physiologic role for vitamin D in liver function, says **Ning Ding**, a research associate in Evans's group, but he notes that it was the discovery of high levels of vitamin D receptor (VDR) in the stellate cell that led the team to consider it as a possible off switch for liver fibrosis.

In liver diseases where the underlying cause cannot be cured, progression to cirrhosis is currently inevitable in some people. What Evans's team has discovered is that by acting on the genome, VDR can simultaneously defend against multiple fibrotic activators. This is important because many different pro-fibrotic signaling pathways converge on the genome to affect their fibrotic response. Their discovery suggests a potentially safer, more effective strategy capable of neutralizing these multiple convergent fibrotic triggers.

The **next** generation:

Putting the "super" in super-mom!

Dino Morvinski balances parenting with cutting-edge cancer research

DINORAH "DINO" FRIEDMANN-MORVINSKI IS A TELENOVELA-watching**,** cake-baking mother of three who also happens to be working on a cure for brain cancer.

Morvinski, a postdoctoral researcher at the Salk Institute, shrugs off her stereotype-busting life. "I'm just normal," she says. Despite her disclaimer, quite a few people find her ability to juggle competing demands on her time extraordinary. "I'm amazed that anyone with three young children can be so focused and energetic," says her mentor, Salk professor **Inder Verma**.

Verma and Morvinski recently published a paper in *Science* describing their fundamental discovery about glioblastoma multiforme (GBM), an aggressive cancer with an extremely poor prognosis. The disease was named for the brain's glia cells, non-neuronal brain cells that are essential for brain health.

Research into genetics, however, has begun to suggest that cancers may not always originate from the types of cells for which they are named. GBM had already been found to originate from neural stem cells, immature cells that could develop into any type of cells in the brain. That was a hint that the glia/glioblastoma assumption needed to be re-examined. Morvinski, along with Verma, holder of the Irwin and Joan Jacobs Chair in Exemplary Life Science, decided to confirm whether GBM truly did start in glia cells.

Morvinski's research was greatly aided by conversations with **Fred "Rusty" Gage**, who holds the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease and who has done pioneering research on neural stem cells, overturning the conventional wisdom that the brain did not grow new cells.

"That's the wonderful thing about Salk—everything is open," says Morvinski. "You have someone who's a giant in his field, and all you have to do is knock on his door. It's incredible that we have this community."

Morvinski found GBM in glia, as well as in neural stem cells, but unexpectedly, also in mature adult neurons. Speaking together, the scientists realized they'd been looking at only part of a far bigger idea. They wondered, says Morvinski, "if glia, neural stem cells, and mature neurons can all be the cell of origin—maybe *any* cell in the brain could be?"

More than a year's worth of experiments later, they worked out the complete story. Glioblastomas can originate when a mature cell, such as a neuron or a glial cell, genetically sets itself back to the state of a stem cell, as part of the transformation process to become a cancer cell. Unlike mature cells, in this state cells can proliferate—growing wild as tumors.

The team's results explain why tumors recur. It isn't merely that a surgeon left behind some malignant tissue or that chemotherapy wasn't

From left: Coby, Gail, Lian, Dinorah and Millie

fully effective. The profound problem is that apparently transformed and differentiated cells contain within themselves the genetic trigger to revert to proliferating cells.

"What it tells us is that it's not just a question of better targeting chemotherapies, but of discovering what is it that makes a cancer cell revert to a stem cell–like state and block that," says Morvinski. She and her colleagues are currently performing a new series of experiments to find the answer.

Altogether it took nearly four years to produce the *Science* paper, an example of the tenacious patience required for world-class science—and that patience is a good explanation for why science is not incompatible with Morvinski's other job as a mother of three children under the age of 11.

Granted, she admits, it isn't easy. She copes by being extremely organized. "When you know you have only nine hours, you have to be focused," she says. "You lay out your experiments, and you know whom you need to question." Another important factor is the flexibility that Verma's lab offers, as well as the scientific and technical support in his laboratory and the Salk Institute.

But there's something else that contributes to balance. "Not everything can be science," she says. "I also need my own Dino time. I love baking cakes for my kids, and I also love watching Argentinian *telenovelas*. My friends say, 'You'll burn your neurons watching those things!' I say, 'I just need an hour where I don't need to use my brain!'"

Most importantly, she emphasizes, she and her husband Coby fully support each other. "When you have kids and you want to do science, you need a 50 percent partner—that's my secret," she says. "It's not that I do everything alone!"

They met in Israel, after Dino left her native Uruguay, where she'd received one of the country's first degrees in biochemistry. "Uruguay is still the third world for science; to advance you have to go abroad," she says. "I studied at the Weizmann Institute, where coincidentally, Inder had also trained."

They take turns with their children and even with their careers. Originally a telecommunications engineer, Coby moved to America for Dino"s career, and now she's staying in America longer than originally planned while he finishes his Ph.D. in business administration at UCSD's Rady School of Management. They plan to return to Israel, where she already has professorship offers, to raise their family.

"I never expected I would wind up working in brain cancer," she says. "But I love what I do, and if you ask the right questions, everything is open to you—and that's what science is—learning to ask the right questions. You just need the freedom to pursue the answers. Inder gave me that freedom in his lab, and there's no limit."

> **"That's the wonderful thing about Salk—everything is open,You have someone who's a giant in his field, and all you have to do is knock on his door. It's incredible that we have this community."**
>
> **– DINO MORVINSKI**

The Cancer Genome Atlas

EVERY HUMAN BEING IS BORN WITH A genome: the millions of letters of DNA that contain short sequences called genes. Cancers, too, have genomes, which determine how they will develop and interact both with a patient's tissues and with therapeutics. Genes are ultimately translated into proteins, which regulate function and communication in cells. Many proteins are shaped like puzzle pieces, into which other proteins—and drug molecules—fit. If a cancer lacks a certain gene, the protein will never be made, and the molecules of an anticancer drug will have no place to anchor. This is only one example of the intricate interactions between genes and cancer.

In order to have a roadmap to these interactions, the National Cancer Institute and National Human Genome Research Institute created the Cancer Genome Atlas, an ongoing repository of the genomes of various subtypes of cancers. The ultimate promise of genomic medicine is that a doctor will receive the genomes of both the patient and the tumor and use them to customize an effective course of treatment. In order for that promise to be fulfilled, scientists depend on the atlas, which Morvinski used for her glioblastoma studies. "It's like what the map of Mars is for NASA," says Verma. "It's an ongoing collaboration among hundreds of scientists that points the direction for future explorations."

The audience shares a laugh at the third annual Salk Women & Science event.

Women & Science shines spotlight on plant biology

THE THEME WAS PLANT BIOLOGY ON March 19, when more than 70 female business and community leaders gathered for the Institute's third Women & Science event. Showcasing research being conducted by female Salk faculty, the afternoon program was a rare opportunity for attendees to learn about discoveries that may shape the future of food and fuel production.

Following a welcome by **Catherine Rivier**, professor emerita of the Clayton Foundation Laboratories for Peptide Biology, **Joanne Chory**, professor and director of the Plant Molecular and Cellular Biology Laboratory, gave a talk titled "Seven billion and counting: How do we feed and fuel the planet?" In addition to discussing her lab's research on plants' signaling pathways, which enable them to detect changes in sunlight, she spoke about her team's efforts to discover the molecular triggers that control plant growth, which has the potential to vastly improve agriculture yields.

Julie Law, a new assistant professor in the Plant Molecular and Cellular Biology Laboratory, then described her work to elucidate the mechanisms by which epigenetic modifications are translated into stable expressions—an area of plant biology that is poorly understood and that impacts gene regulation, imprinting, genome activity and development.

The 2013 Women & Science program is generously underwritten by Union Bank. For more information on the Women & Science program, contact **Betsy Reis**, director of donor relations, at 858.453.4100 x1426 or by email at breis@salk.edu.

From left: Attendees Linda Stouffer and Crystal Sargent enjoy a discussion after the lecture.

salk women & science

Where cures begin.

» Watch the video

www.salk.edu/jun13/video4/

From left to right: Salk alumni Beth Anne Baber, Philip Low, Anthony Craig and William Alaynick

First Annual Alumni Mixer features Salk scientists, past and present

SALK ESTABLISHED A NEW TRADITION ON MAY 14 AT THE Institute's first-ever Alumni Mixer. The special evening included a panel discussion for Salk postdocs and graduate students featuring Salk alumni William Alaynick, Beth Anne Baber, Anthony Craig and Philip Low. Afterward, faculty, alumni, postdocs and graduate students enjoyed poster sessions on Salk's current research and remarks from this year's Alumni-Faculty Fellowship recipient, research associate **Kevin Curran**.

Curran, who works in **Sreekanth Chalasani**'s Molecular Neurobiology Laboratory, presented his early stage work in behavioral neurobiology—specifically, the cellular and genetic mechanisms of behavior using *C. elegans*, a small invertebrate model system. The ability for an organism to respond appropriately to a stressful or potentially harmful situation, such as facing a predator, is critical to the survival and wellbeing of the organism. In humans, malfunctions in this neurobiological process lead to costly and debilitating diseases, such as panic attacks and post-traumatic stress disorder.

"I consider myself very fortunate to be awarded the Alumni-Faculty Fellowship," Curran explained. "This type of 'high risk/high reward' project is often overlooked with traditional government funding. In the coming year, the fellowship will allow me to conduct a drug screen in order to further identify the molecular pathways that modulate threat avoidance behavior."

> "It's our hope that Salk alumni and current scientists can continue to build meaningful connections around our shared experience of the Institute."
>
> – CHRIS KINTNER

The significance of the inaugural event was not lost on the attendees. "It's our hope that Salk alumni and current scientists can continue to build meaningful connections around our shared experience of the Institute," noted **Chris Kintner**, a professor in the Molecular Neurobiology Lab and faculty chair of the event.

Training the next generation of scientists is central to Salk's mission. Approximately 235 postdocs from over 50 countries work in Salk labs, and 100 percent of contributions to the Alumni-Faculty Fellowship Fund will support a research associate each year. To learn more about the Salk Alumni program, visit www.salk.edu/alumni.

Save the date for the next **Alumni Mixer** on June 26, 2014.

Kevin Curran, who was awarded the 2013 Alumni-Faculty Fellowship, with last year's recipient Seung Choi

salkexcellerators

Salkexcellerators on both coasts discover the cutting edge of science

It's a group without boundaries—a bicoastal gathering of men and women from across the professional spectrum, who share an appreciation for fine cuisine; a preference for friendly, easygoing networking opportunities; and most especially, a passion for science and the Salk Institute.

As their name suggests, the Salkexcellerators, who range from professionals in the arts and entertainment industries to the legal and financial sectors (and everything in between), are helping to sustain excellence and accelerate the pace of discovery at the Institute. At the same time they enjoy regular Salkexcellerators get-togethers with their colleagues and friends, they are making a profound difference through their annual commitment, which funds fellowships for postdocs at Salk. It's a powerful combination and one that promises to have an enduring impact on scientific discovery.

This past spring, the Salkexcellerators enjoyed special events in New York and La Jolla, where they socialized, networked, savored gourmet food and learned about the leading-edge science their support is helping to propel forward.

From left: Pam Westbrook, John McCormick, Len Hedge and Mike Lowe

From left: Dan Meader, Laing Rikkers, Jim Harries, Allison Stratton and John Rikkers

San Diego **Salk**ex**cell**erators

SOME 60 MEMBERS OF THE SAN DIEGO SALKEXCELLERATORS gathered at the Salk Institute on May 15 to network, visit with friends and enjoy a presentation by **Fred "Rusty" Gage**, a professor in the Laboratory of Genetics and the holder of the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease. In his lecture, "Modeling Psychiatric Disease with Human Stem Cells," Gage explained how his lab has studied human neurological and psychiatric diseases in vitro using human stem cells. The revolutionary technique involves obtaining skin cells from affected individuals. Then, through genetic reprogramming, these cells are altered to produce induced pluripotent stem cells, which are cultured and differentiated into neurons. Since these cells carry the same genetic code as the skin cells they originated from, they also carry the disease, creating in a dish a small-scale model of a diseased brain and providing an opportunity to study the biological factors behind psychiatric and neurological diseases.

Get Involved

Salkex**cell**erators are community members committed to supporting scientific discovery at Salk. Join us at events throughout the year in La Jolla and New York City, including private receptions and scientific presentations with Salk's renowned scientists. One hundred percent of contributions to the **Salk**ex**cell**erators Fund provide annual fellowships to gifted postdoctoral scholars. For more information, please visit www.salk.edu/salkexcellerators or call (858) 453-4100 x1405.

New York **Salk**ex**cell**erators

THE OWNER OF NEW YORK'S EXCLUSIVE MEMBERS-ONLY NORWOOD Club describes it as "a home for the curious." And that quality was very much in evidence at the New York Salkexcellerators gathering there on April 22. The event drew an eclectic audience of 60 to the Greenwich Village venue, a perfectly preserved 1847 mansion that is on the National Register of Historic Places.

The program featured **Greg Lemke**, a professor in the Molecular Neurobiology Laboratory and holder of the Francoise Gilot-Salk Chair. Lemke studies the regulation of signaling networks that control immune system function. In his presentation, titled "The Sorcerer's Apprentice: Taming Viruses and Autoimmune Disease," he discussed how in the absence of regulation, a biological system is akin to the mythical sorcerer's apprentice, setting in motion a chain of events over which it has no control. This can lead to the development of autoimmune diseases such as lupus, multiple sclerosis and rheumatoid arthritis, as well as contribute to infection by West Nile, influenza and dengue viruses. Fortunately, a corollary to Newton's Third Law of Motion (for every action, there is an equal and opposite reaction) is also true within biology—the ability to turn a biological response on is always coupled with a means for turning it off—and Lemke explained to the rapt audience how these lifesaving mechanisms work.

Salk's 41st Annual Tax Seminar for Private Foundations

NOW IN ITS 41ST YEAR, SALK'S ANNUAL TAX SEMINAR FOR Private Foundations was held this past May at The Lodge at Torrey Pines. The three-day program is a much welcome annual event for the non-profit community, with its expert discussions of tax law, governance, and management for private, family and community foundations.

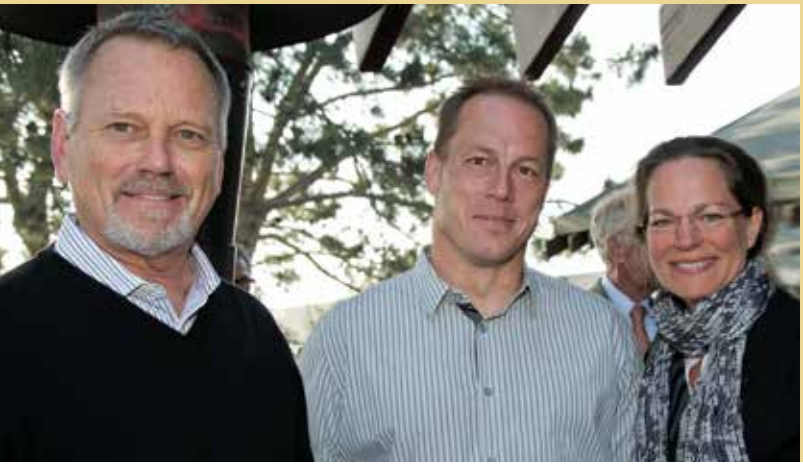
Among the program's highlights was a panel discussion mediated by Seminar Chairman and Salk donor Edwin K. Hunter, who garnered the participation of numerous community foundation directors from across the country. Panelists Adrienne Vargas and BH Kim from The San Diego Foundation, Alice Parkerson from the Greater New Orleans Foundation, and Trish Worthington from the Park City Community Foundation discussed their community foundations and successful philanthropy. In his Friday keynote speech, Bob Kelly, president and CEO of The San Diego Foundation, addressed partnerships between private foundations and community foundations.

Not all the experts in attendance were tax specialists. On Thursday afternoon, Salk faculty members **Tom Albright**, **Beverly Emerson**, **Clodagh O'Shea** and **Sam Pfaff** gave presentations on their research to the seminar's participants, who enjoyed an afternoon of engaging science talks (the temptation of great golfing weather notwithstanding).

"The event is our way of giving back to donors and friends of Salk," says **Seth Schechter**, Salk's Executive Director of Foundation Relations. "We are always delighted by their participation, and honored to be of service to the non-profit community."

From left: Edwin K. Hunter, Chair of the Tax Seminar, and Salk President Bill Brody.

From left: Mark Collins, Glenn Foundation for Medical Research, Inc.; Salk scientist Jan Karlseder and Lily Collins



From left: Adrienne Vargas, The San Diego Foundation; BH Kim, The San Diego Foundation; Alice Parkerson, Greater New Orleans Foundation; Trish Worthington, Park City Community Foundation

Back to Basics on metabolism

SALK SUPPORTERS GATHERED FOR THE latest Back to Basics lecture on April 3, which featured **Marc Montminy**, professor in the Clayton Foundation Laboratories for Peptide Biology, and **Satchidananda Panda** of Salk's regulatory Biology Laboratory.

Montminy kicked off the event by sharing his lab's latest research on metabolism. His lecture ranged from general information about the human diet and activity over millennia to today's growing obesity epidemic. Panda followed with a talk on circadian rhythms and their complex implications for diet and metabolism. Both presentations captivated the enthusiastic audience and prompted a lively question and answer session.

Audience member Harry Anthony (left) engaged in an animated conversation with Satchidananda Panda at the Back to Basics reception

Members of WASI on a tour of the Institute.

Fifty years later, the Institute remembers its first support organization

WHEN JONAS SALK RELOCATED TO SAN Diego from Pittsburgh more than half a century ago, local citizens grateful for his discovery of the polio vaccine were eager to help his fledgling research enterprise succeed. During the Salk Institute's 1962 groundbreaking ceremony, Sally Cohn, wife of a prominent local rabbi who spoke at the event, approached Salk to suggest a women's auxiliary—a volunteer group that, typical of the day, would provide support through various fundraising activities and augment the seed funding from the March of Dimes. From those modest origins, a tradition of philanthropy was born, setting the stage for decades of community investment and involvement in the Salk Institute, as well as today's robust network of support activities.

Cohn's brainchild came into being on May 17, 1963, when she led the first meeting of the Women's Association for the Salk Institute (WASI), as the new organization was called. Bernice Layne Brown, wife of California governor Edmund G. "Pat" Brown (and mother of the state's current governor, Jerry Brown) and Dorothy Mae Dail, wife of San Diego mayor Charles Dail, became honorary members, with Dail also serving as treasurer. In time, the group morphed into the Salk Institute Association (SIA), diversifying its membership to include men.

By its tenth anniversary, the SIA had raised nearly $250,000, providing grants to graduate students and purchasing much-needed scientific equipment. Members also conducted tours of the Institute, ran the gift shop and helped create two of Salk's longstanding traditions: High School Science Day (now named in honor of the March of Dimes, a continuing supporter) and Symphony at Salk, launched through the leadership of Betty Vale (wife of the renowned late Salk faculty member Wylie Vale). It was SIA members who served the food and wine at the inaugural Symphony at Salk. "I worked so hard, I felt I was back in college," recalls Peggy Matthews, a former retail promotions director who also headed public relations for the SIA and coordinated fashion show fundraisers.

While the opportunity to help support one of the world's great research institutions more than compensated for their hard work, SIA members also treasured the opportunity to get to know one of the pivotal figures of the 20th century, Jonas Salk. "I had the honor of going through Dr. Salk's papers after he passed away," says former SIA president Ottilie Baer. "In a building at the back of the parking lot, known as the bungalow, there were stacks and stacks of filing cabinets and drawers. We went from one room to another to make three piles: one for the Institute, one for the family and one for the university across the street."

Today, the SIA, now disbanded, remains a fond memory of an earlier time. Former SIA volunteers still gather for luncheons, where they keep up with each other and Salk news. Many continue to visit the Institute to assist with special events and architectural tours and to ensure Salk's future as Partners in Research supporters—donors who have included the Institute in their estate plans.

Their greatest legacy, however, is both less tangible and more enduring: the robust foundation they created for the ongoing philanthropic support of the Institute. Today's Campaign for Salk may be the Institute's first-ever capital campaign, but it owes an indisputable debt to that pioneering group of visionary volunteers who began meeting 50 years ago. Captivated by the idea of a revolutionary new basic science research institute, they set about providing many of the resources it needed. Subsequent fundraising successes—and the transformative discoveries they have helped facilitate—literally would not have been possible without the indispensable groundwork that the men and women of the Salk Institute Association laid for the future.

Salk Science LEADS TO DISCOVERIES.

IMPACTING HUMAN HEALTH BEGINS AT THE SALK.

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

Get INVOLVED

FRIENDS OF SALK

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

SALKEXCELLERATORS

Salkexcellerators are community members in San Diego and New York City who share a commitment to supporting scientific discovery at Salk. Members receive invitations to private receptions and scientific presentations by Salk scientists on the most critical health-related issues of the 21st century. Engagement ranges from $500 to $5,000.

PRESIDENT'S CLUB

Contributions at the President's Club level ($2,500-$25,000) are allocated to the area of greatest need and make it possible for us to recruit and retain top-tier scientists, acquire the latest technology, and fuel innovative research initiatives; all of which provide extraordinary opportunities for discovery.

Engagement at the President's Club level ensures you will enjoy unique opportunities to interact with Salk's renowned scientists and receive an invitation to the annual holiday luncheon with Salk's President.

CHAIRMAN'S CIRCLE

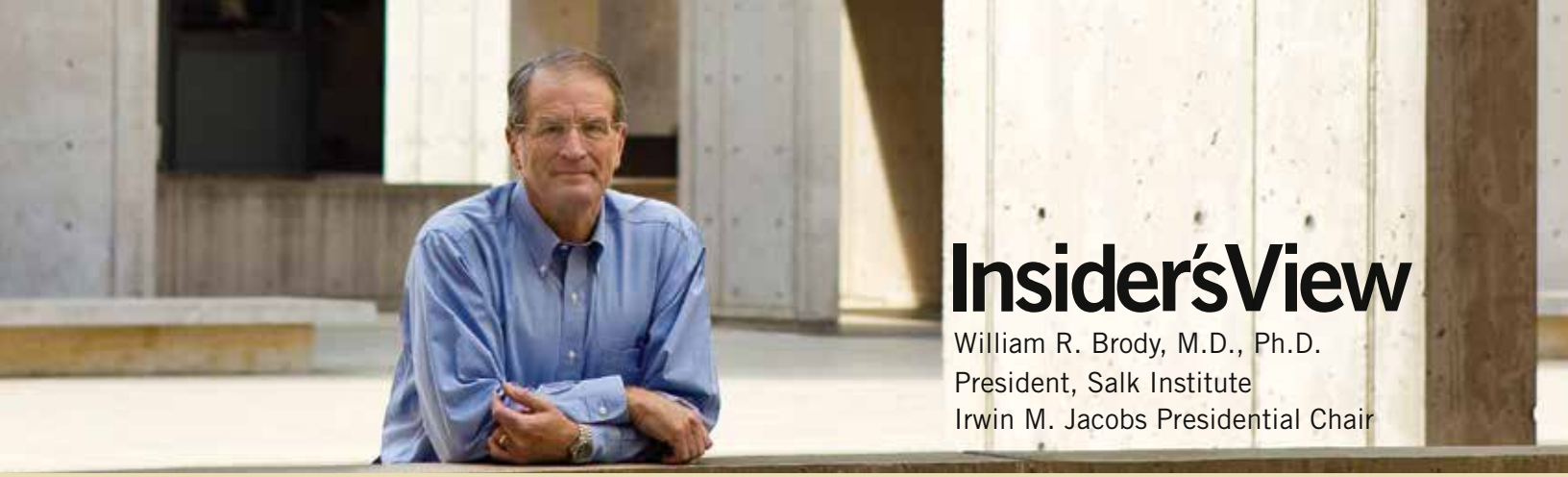
Chairman's Circle visionary donors support the Institute's mission with unrestricted annual gifts of $25,000 and above. Their generous support fills a vital need for the Institute by providing the world's finest minds in science with the resources to pursue discoveries at the frontier of human knowledge.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



Insider's View

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

FASTER CURES COME FROM FASTER DISCOVERIES

The first decade of the 21st century witnessed a dramatic drop in the number of new drugs approved by the U.S. Food and Drug Administration, a decline that some attribute to more stringent requirements imposed by the FDA. While this observation may be partly correct, the fact is that the beginning of the millennium was a watershed for drug development. This was in large part thanks to rapid advances taking place in basic science laboratories, such as those at the Salk Institute.

As scientists discovered specific drug targets, usually genes or proteins that ran amok in disease states such as cancer or diabetes, pharmaceutical and biotech companies began to rely less on the traditional shotgun approach to finding new treatments. Instead they focused on taking advantage of the explosion of information coming from basic science laboratories. With better intelligence in hand, they could more predictably target the errant molecule with a chemical or antibody.

As many of these precision therapeutics now make their way through the pipeline, I believe we will see a wealth of new drugs that have amazingly powerful results. A number of them will be used to treat diseases for which good therapies are lacking, such as lung cancer, melanoma and autoimmune disorders. The ability to treat these difficult diseases will have a tremendous impact on people's health and on society.

At Salk, we are ramping up to help usher in this new era of targeted drugs. The recent grant to create the Helmsley Center for Genomic Medicine is greatly enhancing our ability to conduct interdisciplinary research that helps identify the genetic basis for chronic diseases across the spectrum, from diabetes to cancer to neurologic disorders to diseases of aging. The center will look for common threads that may underpin a number of seemingly unrelated chronic diseases. Perhaps equally exciting, these new tools for finding targets allow Salk scientists to participate in the translation of their discoveries into clinical treatments on a much greater scale than was heretofore possible.

The Helmsley Center will speed the pace of basic research, which is crucial to Salk's mission. That's because faster discoveries beget faster cures—and cures change lives.

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Salk **Calendar**

OCTOBER

2 **Back to Basics**
6 **Salk Science & Music Series**
30 **New York Salkexcellerators**

NOVEMBER

5 **Women & Science Reception**
10 **Salk Science & Music Series**
13 **San Diego Salkexcellerators**

DECEMBER

5 **President's Club Luncheon**

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Symphony at Salk

with special guest artist

Katharine McPhee

AUGUST 24, 2013

18TH ANNUAL SYMPHONY at SALK, *a concert under the stars*