

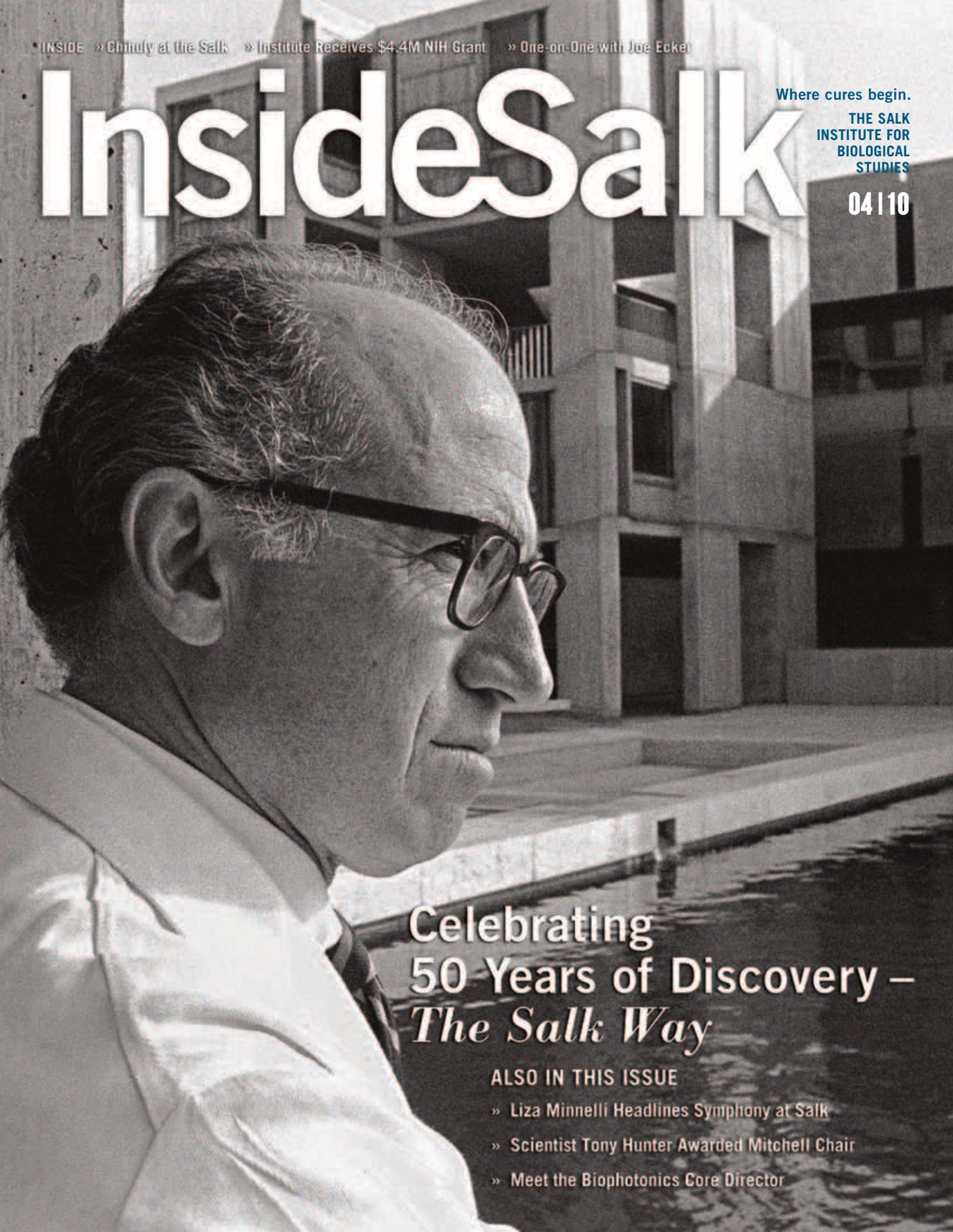
INSIDE » Chiruly at the Salk » Institute Receives \$4.4M NIH Grant » One-on-One with Joe Ecker

InsideSalk

Where cures begin.

THE SALK
INSTITUTE FOR
BIOLOGICAL
STUDIES

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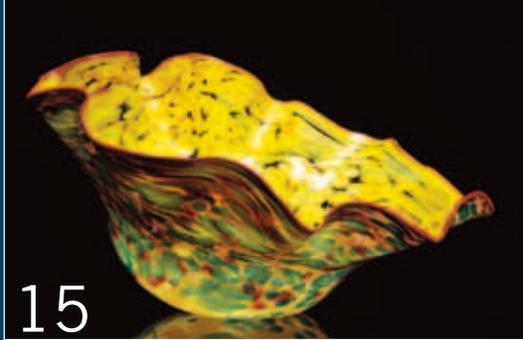


Celebrating
50 Years of Discovery –
The Salk Way

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ON THE COVER

Jonas Salk (1968), photo by Darrel K. Miller.

Image used with permission of the family of Jonas Salk.

Salk's History: A Story Rich in Creativity and Scientific Discoveries

Dear Friends,

I BELIEVE YOU WILL ENJOY READING ABOUT THE SALK INSTITUTE'S rich history of the last half-century in this anniversary-year issue of *Inside Salk*. It is a splendid success story that began with a daring idea by our founder, Jonas Salk, and became a reality that today yields vital scientific discoveries for the benefit of mankind.

Much like the Institute's laboratory spaces, which were designed with flexibility in mind by famed American architect Louis Kahn, research at the Salk has undergone organic evolution and expansion as research interests shifted and new technology appeared. At its core, the Salk science story has always been and continues to be about creativity and unwavering curiosity.

This is what drew a small group of brilliant scientists to the West Coast in the early 1960s to join Jonas Salk as founding fellows in what he described as a "crucible of creativity." Over the next 50 years, Jonas' concept was put into remarkable practice.

Today, a highly collaborative environment in which scientists are free to pursue their boundless questions is what defines the Salk Institute and has established it as a much sought-after place to conduct leading basic biological research.

The Institute's intellectually hospitable atmosphere has prompted many of the best minds in science to make the Salk their permanent home. Many of the young scientists who were appointed to the Salk's faculty in the 1970s are still here, still contributing seminal discoveries that are improving our understanding of human health and disease.

Many of the early discoveries you'll read about in the cover story have led to treatments for cancer, depression, heart disease and reproductive disorders. The impact of some of these landmark findings has also been recognized by the greater scientific community – leading in some cases to Nobel Prizes and many other top honors.

Throughout its history, the Salk is also credited with preparing the next generation of exceptional scientists who will contribute tomorrow's discoveries.

The Salk Institute has grown and firmly cemented its superb reputation since four scientists (Renato Dulbecco, Edwin Lennox, Melvin Cohn and Jacob Bronowski) chose to follow Jonas Salk to La Jolla and establish what many today call a "temple of science" in one of the most idyllic locations in the world.



William R. Brody

“Today, a highly collaborative environment in which scientists are free to pursue their boundless questions is what defines the Salk Institute and has established it as a much sought-after place to conduct leading basic biological research.” – William R. Brody

In the next *Inside Salk* and my next column, I will highlight our most laudable scientific accomplishments, and then close our anniversary year with a look at the very promising future of Salk science. For now, I invite you to learn more about our storied history in the following pages. 📖

William R. Brody

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

Celebrating 50 Years of Scientific Discovery— *The Salk Way*

In the Beginning

JONAS SALK MAY NOT HAVE BEEN FULLY PREPARED FOR THE LEVEL OF instant fame and adulation he received after a much-anticipated press conference in Ann Arbor, Michigan, on April 12, 1955.

The announcement that the polio vaccine he and a team of researchers developed in a Pittsburgh laboratory was deemed safe and effective for humans led to a tsunami of international recognition, including an invitation to the White House and an offer for a ticker-tape parade.

Though Salk and his family proudly attended the White House ceremony where President Dwight Eisenhower thanked him on behalf of the American people, to the amazement of many, he graciously turned down a flashy parade (suggesting the money be used for student scholarships instead). Even more memorably, Salk chose not to patent and profit from the polio vaccine that would protect millions of people.

It would not be the first time Salk's way of thinking appeared unusual – or even provocative. Much like his strategy for developing the polio vaccine, Salk's penchant for addressing and solving problems through unconventional approaches would influence what he was envisioning next: a revered research enclave where some of the world's brightest minds in biological science could freely explore their curiosity in a collaborative and unfettered environment for the benefit of human health.

His vision became a reality in 1960 when Salk – together with a small group of elite scientists (“founding fellows”), seed funding from the March of Dimes, and a gift of 27 acres from the city of San Diego – established the Salk Institute for Biological Studies. He commissioned American architect **Louis Kahn**, challenging him to design “a facility worthy of a visit by Pablo Picasso.”

Completed in 1965 and designated a National Historic Landmark in 1991, the mirror-image laboratory buildings flanked by a sweeping courtyard overlooking the Pacific Ocean is considered among the world's boldest structures by architectural critics. Incorporated in its innovative design was a visionary flexibility that has allowed the interior research space to adapt to five decades of scientific advances.

It is apparent today, as we celebrate the Salk's 50th anniversary, that the brilliant result of the Salk-Kahn partnership is an extraordinary structure that can withstand and can be molded to the evolving conditions required for discovery.





From left to right: Jacques Monod, Gerald Edelman, Melvin Cohn, Leslie Orgel, Robert Holley, Jacob Bronowski, Frederic de Hoffmann, Salvador Luria, Paul Berg, Edwin Lennox, Roger Guillemin

POPULATING THE TEMPLE OF SCIENCE

While basic research has always been at the core of the Institute, Salk envisioned unorthodox collaborations as an approach to solve both biological and social problems. In addition to recruiting several leading scientists in the early years, such as virologist and Nobel laureate **Renato Dulbecco**, physicist **Edwin Lennox** and immunologist **Melvin Cohn**, Salk also brought on mathematician and humanist **Jacob Bronowski**.

Other high-profile collaborators included founding non-resident fellows such as Nobel laureates **Francis Crick** and **Jacques Monod**, and **Leo Szilard**, the physicist who planted the seed for the creation of the Manhattan Project.

"He really wanted to engage people with multidisciplinary backgrounds," says Salk's son,

Peter, who conducted research in his father's lab from 1972-1984. "He was looking for people who were broad in their thinking, comfortable with interdisciplinary work, and taken with the idea of creating an environment where you could relate to individuals on your own level."

Jonas Salk was always inclined to consider the broader implications of his experiments, Peter recalls.

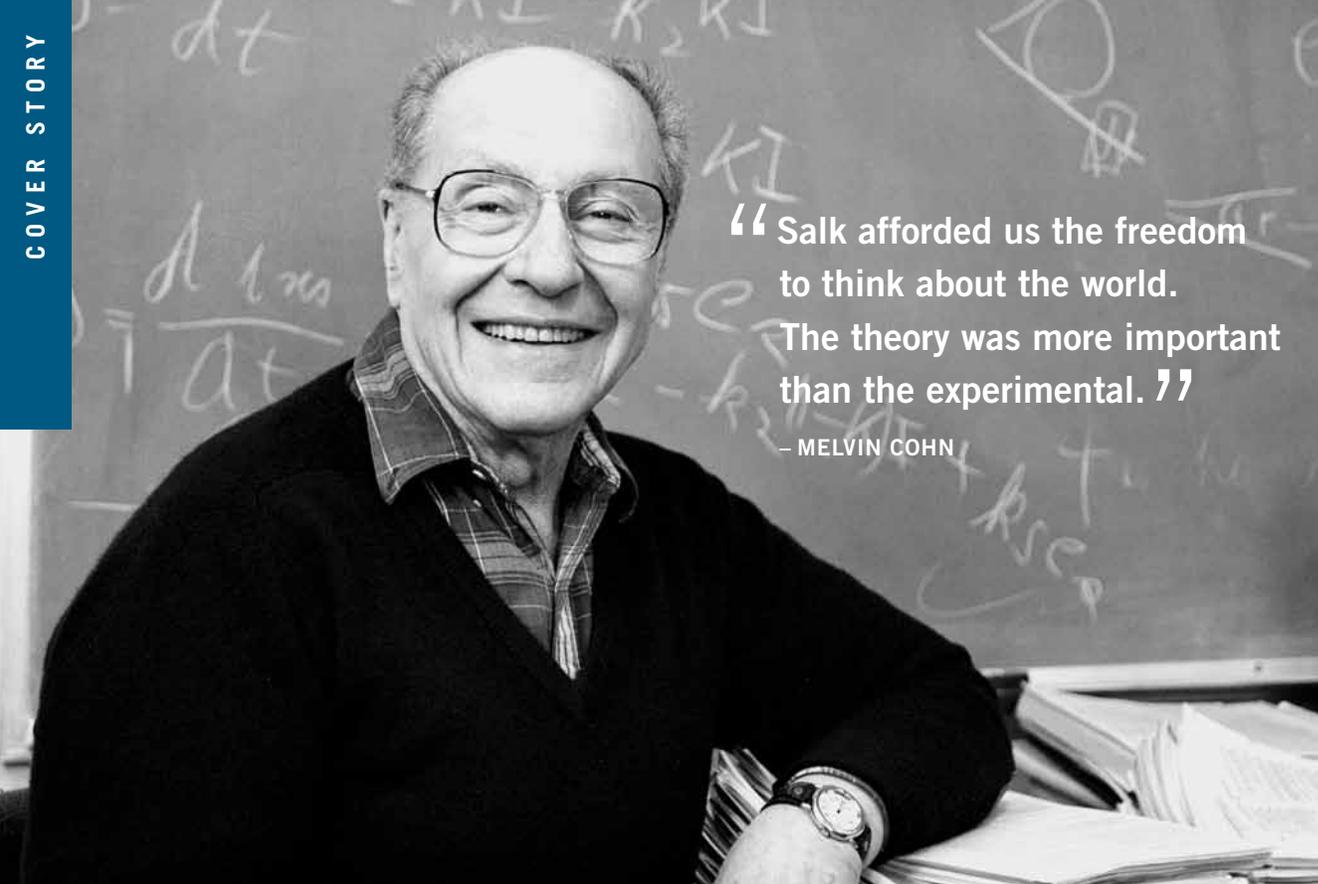
"He applied this way of thinking to his strong interest in human interactions and to the development of the idea for the Institute. I know he saw the Institute from the beginning as an experiment," he says. "And he spent the next several decades as a participant in, and an observer of, that experiment."

FREEDOM TO THINK

There was no question that the Salk Institute offered researchers a unique opportunity, says Cohn, a founding fellow who still conducts research in the Conceptual Immunology Group. "Jonas had a vision for the Institute, and it really inspired the way people thought of it," he says.

What the Institute provided Cohn and the others was the freedom to think and explore some of the most profound questions about life's basic principles – a model that still defines the Salk 50 years later.

In those days, science in the United States was, and still is, largely accomplished at research-intensive universities. Although he had the security of tenure at the Pasteur Institute in



“Salk afforded us the freedom to think about the world. The theory was more important than the experimental.”

– MELVIN COHN

Melvin Cohn

Paris and obtaining grants wasn't an issue, Cohn, like Lennox, had grown tired of splitting his efforts between teaching and conducting research. Prior to arriving to the Institute in 1963, both had turned down appointments at Harvard, Cohn says.

“In order for us to leave that secure situation, we had to have something else we wanted to do. In that sense the Institute was special,” he says. “Salk afforded us the freedom to think about the world. The theory was more important than the experimental, although Renato preferred working in the lab, but it was certainly true of Ed Lennox and myself – and especially a year later when [Chemical Evolution Lab Director] **Leslie Orgel** came to Salk.”

After his arrival, Cohn worked on developing new methodologies of science. Bronowski brought with him eminent philosophers like **Karl Popper**, with whom Cohn engaged in conversations to address such problems. Szilard was interested in both the mechanisms of memory, and the regulation and limitations on use of the atomic bomb.

Lennox's interests were in the practical applications of science, while Dulbecco and Salk worked in the laboratory conducting research with more immediate missions, seeking treatments for cancer and multiple sclerosis. Bronowski, it turned out, was a master at communicating science, which he did extensively in the community and through his internationally acclaimed BBC television series, *The Ascent of Man*. He developed much of the material for the series through the many conversations he had with scientists at the Salk Institute, Cohn says.

“We were an interactive group. It wasn't enough that we had some of the world's most creative minds here,” he says. “Those creative minds had to interact with one another. So we would meet often to talk about our respective scientific problems and interact experimentally, too.”

Collaboration extended into the decision-making process developed by Salk to include three governing bodies: the fellows, the non-resident fellows and the administration.

This organizational and functional model proved essential in the late 1960s when the fellows were discussing ways to expand the Institute's scientific research program. After meetings with the non-resident fellows, it was clear that adding studies in neurobiology was key to the Institute's future – mostly because it offered the strongest opportunities for collaboration with existing scientists at the Institute.

“We really wanted to develop the Institute step-by-step, so in speaking with the non-resident fellows, we specifically agreed that we needed someone who studied the hypothalamus,” Cohn says. “This is how we brought [Nobel laureate] **Roger Guillemin** to the Salk.”

EARLY DISCOVERIES IN NEUROSCIENCE

Guillemin was making a name for himself at Baylor College of Medicine after he and his group had successfully isolated brain molecules that scientists were previously unaware even existed. Although he was not particularly eager to uproot his young family from Houston, Guillemin says the opportunity to continue his work at the Salk was impossible to pass up after his first visit in 1969.

“I'll never forget walking through the eucalyptus grove for the first time and seeing this extraordinary place,” Guillemin says. “I'm still moved today by what I saw. I thought, ‘My God, whatever the offer is, I'll say yes.’ My initial meeting took place when the non-resident fellows were here. I was impressed. Jacques Monod, Francis Crick, Salvadore Luria, Bob Holley – I've never seen so many Nobel laureates in my vicinity. It was extraordinary.”



Jonas Salk and Roger Guillemin

“Not only was the Institute properly started, but it has evolved in the right ways.”

– ROGER GUILLEMIN

Starting in 1970, Guillemin spent the next 20 years as the head of the Laboratories for Neuroendocrinology, where he and his group went on to discover an entire class of neurohormones found to be important for the regulation of growth, development, reproduction and responses to stress. Analogs of somatostatin, one of the brain hormones first identified by Guillemin's lab in 1973, today are used to treat tumors of the pituitary gland and gastrointestinal tract. He received the Nobel Prize for this work in 1977.

Over the decades, new labs have been added to the Institute in appropriately organic fashion as research interests expanded. Today, studies in neuroscience at the Salk Institute, for example, are conducted in nine broad areas of research by at least 24 laboratories – all of which have contributed major discoveries to better understand, and in many cases treat, human disease.

Former Guillemin lab members **Wylie Vale**, who in 1978 formed the Laboratories for

Peptide Biology with **Jean Rivier** and his wife, Salk investigator **Catherine Rivier**, characterized the corticotropin-releasing hormone (CRF) and ultimately three related hormones, which mediate and regulate the responses to stressors impacting the cardiovascular, gastrointestinal and central nervous systems.

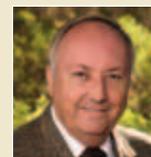
Proof of principle studies using receptor blockers of CRF developed by Jean Rivier and Vale, together with the cloning of the CRF receptor by Vale's group, have led to the development of novel drugs currently being tested to treat major depressive disorder and heart disease.

The Guillemin and Vale/Rivier groups discovered several novel hormones, growth factors and their receptors involved in reproduction and development. Variants of these molecules have led to the development and clinical testing of treatments for reproductive disorders, including precocious puberty, infertility and endometriosis.

Molecular Neurobiology firmly took root at the Salk in the early '70s, but the '80s and '90s marked the blossoming of Systems



Wylie Vale



Jean Rivier



Catherine Rivier

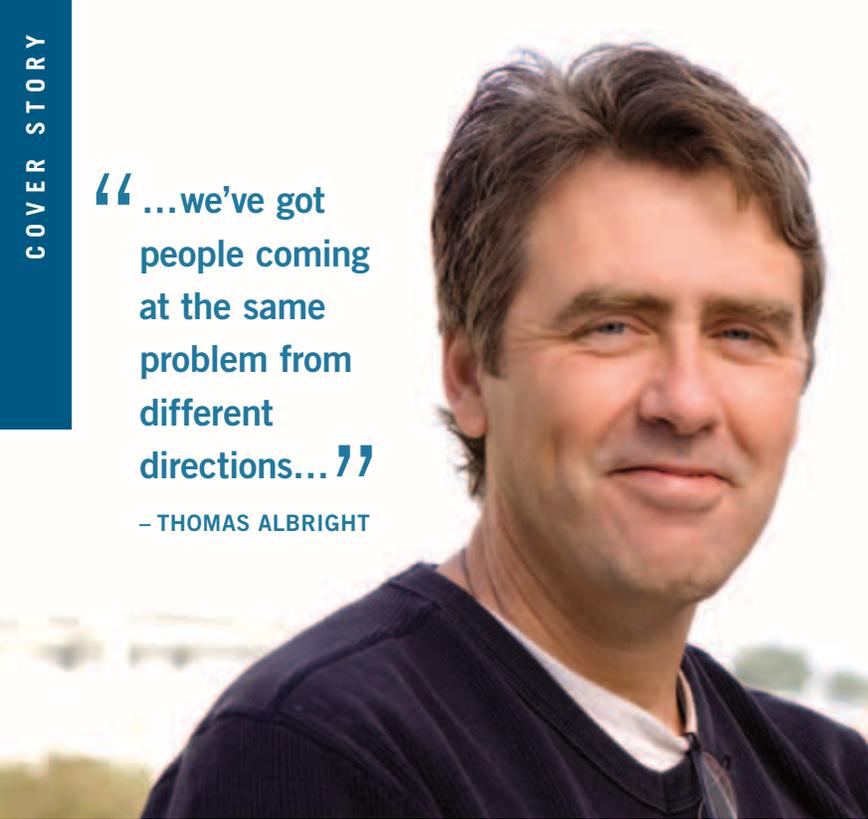
Neuroscience. Neurobiologists **William Maxwell “Max” Cowan**, **Floyd Bloom** and Francis Crick were among the scientists who helped pave the way for this area of research at the Institute.

Cowan had a long association with the Salk – first as a non-resident fellow starting in 1974, along with renowned neurophysiologist **Stephen Kuffler**, and later as a professor beginning in 1980 when he brought with him a few young promising scientists, including **Dennis O'Leary** and **Paul Sawchenko**. Both still conduct research as professors at the Institute.

Cowan later hired **Simon LeVay**, a British neuroscientist who was an early researcher of the visual system as a means to understand brain function. As Cowan left the Institute in 1986 (eventually to lead the Howard Hughes Medical Institute as Vice President and Chief Scientific Officer), **Thomas Albright** joined the Salk in 1987 as a young neuroscientist/physiologist whose lab focused on the visual system and cognition.

“...we've got people coming at the same problem from different directions...”

– THOMAS ALBRIGHT



Thomas Albright

Terry Sejnowski



Ed Callaway



E.J. Chichilnisky



Sascha du Lac



Richard Krauzlis



John Reynolds

At the same time, Crick – a strong supporter of Systems Neurobiology and its role to someday help answer some of the bigger questions regarding behavior and cognition – successfully recruited computational neurobiologist **Terry Sejnowski** in 1989.

Between 1994 and 2000, Albright and Sejnowski brought on board several new assistant professors, each working in a particular area that complements the rest. They include **Ed Callaway**, **E. J. Chichilnisky**, **Sascha du Lac**, **Richard Krauzlis**, **John Reynolds** and **Geoff Boynton**.

Last year, the group launched the Salk Institute Center for Neurobiology of Vision with a \$3.8 million grant from the National Eye Institute of the National Institutes of Health. The designation placed the Salk as one of seven NEI centers focused exclusively on the basic research of vision, and understanding that mysterious eye-brain connection.

“I think one of the great features that makes this program so successful is that we've got people coming at the same problem from different directions,” Albright explains. “It's worked very well because we chose the right people and there isn't any redundancy.

“Researchers in the Vision Center use anatomy, physiology and behavioral analysis to understand the many stages of visual processing, the plasticity of those stages, and the ways they interact with systems for memory and motor control. And then you have Terry, who is a great computational modeler,” he says. “All of these areas ultimately confront questions of mechanism. And one of the most powerful ways of addressing mechanism is through computational modeling.”

Credited with pioneering the field of Computational Neuroscience, Sejnowski's lab today is staffed by an eclectic team– with backgrounds in mathematics, electrical engineering, physics, and even philosophy – that aims to learn how the brain works.

His Computational Neurobiology Laboratory uses computer models based on physiological experiments to make predictions that call for additional experiments to test the model. To date, his group has contributed major breakthroughs in understanding how the brain works and developed powerful algorithms that are used in industry.

Today, the Salk Institute's Neuroscience research program consistently ranks among the top in the world. Last summer, it garnered the top discovery spot in the latest international ranking in the “Neuroscience and Behavior” category by *Science Watch*, a scientific organization that measures the citation impact of research published worldwide.

“Not only was the Institute properly started, but it has evolved in the right ways,” Guillemin observes.

A NEW OPERATING MODEL

The Institute fine-tuned its research focus soon after **Frederic de Hoffmann** came on board, first as chancellor in 1970 before his appointment as president in 1972. Less emphasis was placed on the humanities with the passing of Bronowski while greater efforts were focused on hard-core basic research. This opened the door to additional funding, which the Institute was in great need of at the time, while providing the opportunity to hire bright young researchers.



Suzanne Bourgeois



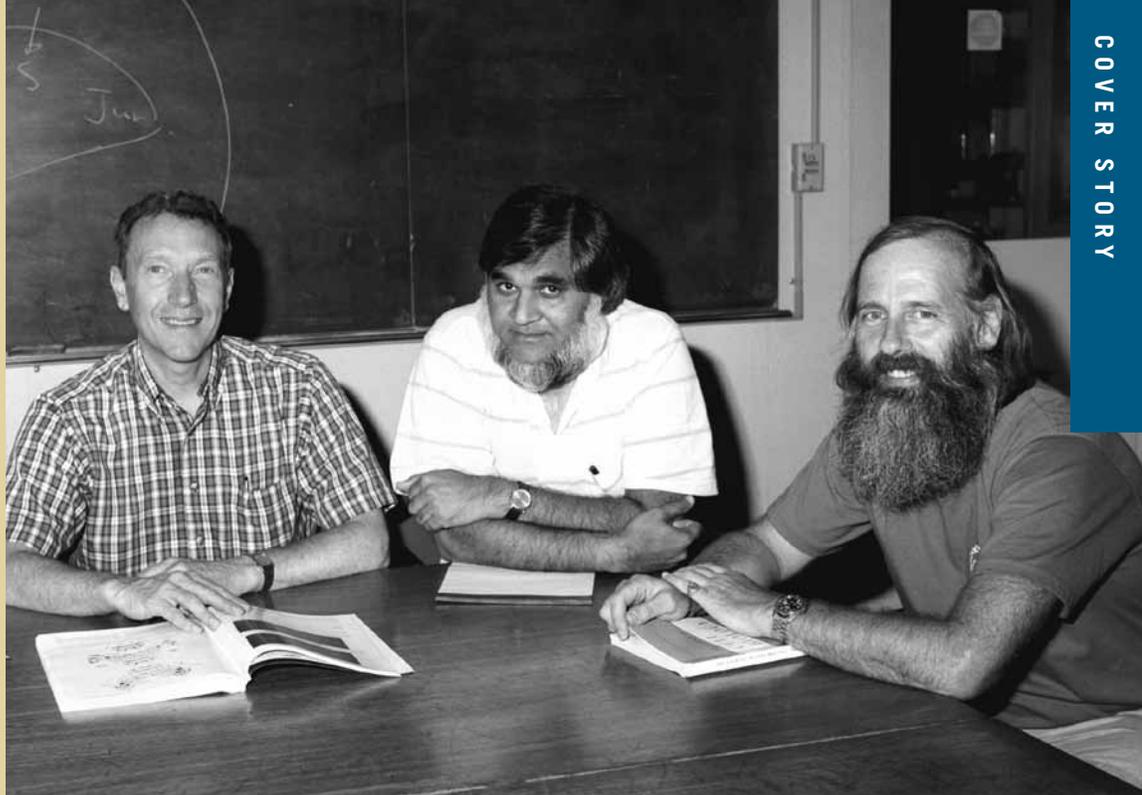
Marc Montminy



David Schubert



Marguerite Vogt



Left to right: Walter Eckhart, Inder Verma, Tony Hunter



Ursula Bellugi



Katherine Jones



Beverly Emerson



Greg Lemke



Geoffrey Wahl



Stephen Heinemann

Under de Hoffman's leadership (1970-1988), the Salk Institute flourished in a new way. An extremely well-connected mathematician/physicist and businessman, de Hoffmann proved to be a strong administrator. The Institute's annual budget grew from \$4.5 million to \$33 million during his 18-year tenure.

Many longtime relationships with individuals and private foundations were forged during this time, the latter reinforced in part by the Salk-hosted tax seminar he created for foundations – now in its 38th year. He also formed the Salk's International Council consisting of worldwide leaders in business and industry who serve as Salk ambassadors.

In 1970 the Institute adopted an academic system to make several junior faculty appointments, beginning with **Walter Eckhart** (Molecular and Cell Biology), **Stephen Heinemann** (Molecular Neurobiology), **Suzanne Bourgeois** (Regulatory Biology), **David Schubert** (Cellular Neurobiology) and **Ursula Bellugi** (Cognitive Neuroscience). Most are still conducting research at the Institute, while all maintain a presence here.

Marguerite Vogt, a longtime Dulbecco collaborator who was also among the faculty appointees, was widely admired for being an influential mentor to younger scientists for more than 40 years at the Salk. Today, faculty promotions are independently approved by the resident faculty and the non-resident fellows to ensure the highest quality among its professors.

After the first appointments, Bourgeois and Eckhart, in particular, were tasked to recruit new members to the faculty. Bourgeois, who contributed early work on regulatory protein-DNA interaction and founded the Regulatory Biology Laboratory at the Salk, was also instrumental in bringing several female scientists to the Institute, including Professors **Kathy Jones** and **Beverly Emerson** in 1986.

Marc Montminy (Laboratories for Peptide Biology), who uncovered a family of genes that act as metabolic switches, joined the Institute that same year, while **Greg Lemke** (Molecular Neurobiology), who studies a group of cellular receptors associated with the immune system, joined one year earlier.

Eckhart's role expanded soon after Dulbecco, in whose lab he worked as a post-doc between 1965-1970, briefly left the Institute in 1972 (after making his landmark discovery that demonstrated how tumor viruses could induce cancer).

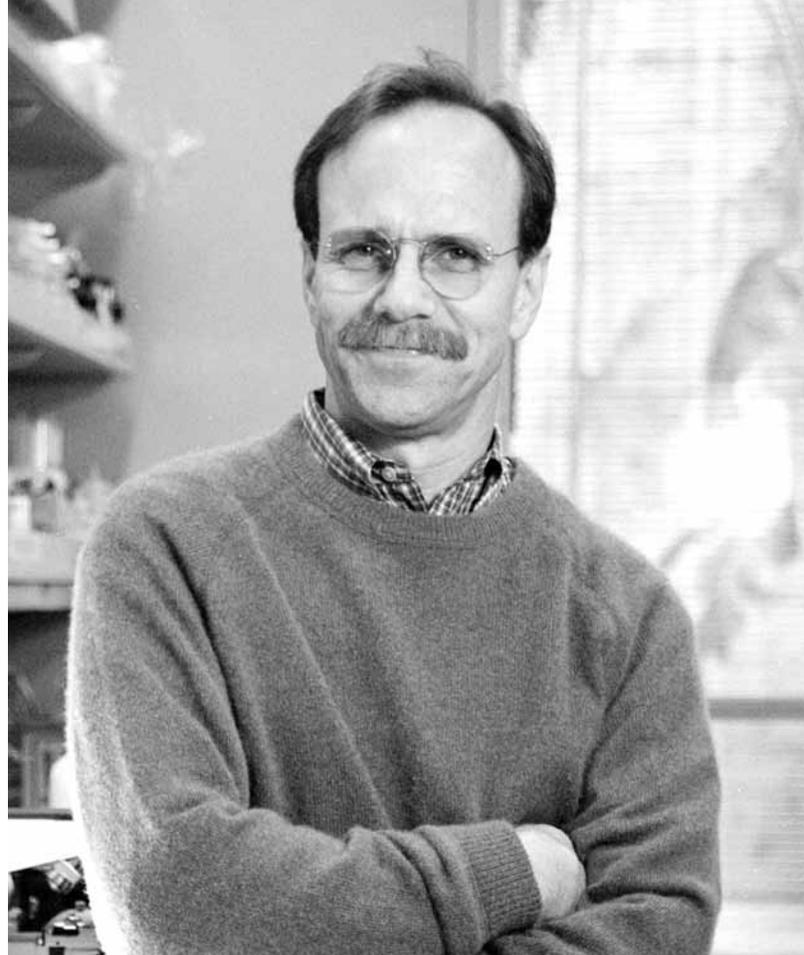
"After Renato left, [Nobel Laureate and Resident Fellow] **Robert Holley** submitted our first grant application to the National Cancer Institute (NCI), which provide core funding for us," Eckhart says. "That was essentially the start of the Cancer Research Center at the Salk."

Eckhart directed the Center for 32 years before handing over the reins to **Tony Hunter**, whom Eckhart recruited to the Institute in 1975. Today, 29 principal investigators, supported by more than 160 post-docs and 70 graduate students, are part of the Salk's NCI-designated Cancer Center.

Key recruitments by Eckhart followed throughout the 1970s, most notably **Ron Evans** (Gene Expression Lab), **Geoff Wahl** (Gene Expression Lab), and **Inder Verma** (Laboratory of Genetics). Each of them made seminal discoveries in cancer research and have since gone on



Ron Evans



Fred H. Gage

“The atmosphere was complete freedom to do whatever you wanted.”

—INDER VERMA

to contribute major findings related to diabetes and metabolism, stem cell research and gene therapy.

This core group of scientists primarily conducted their work in what was then called the Tumor Virology Laboratory. As the Cancer Center grew, the programs broadened to include various areas of molecular, cell and developmental biology.

Hunter and Eckhart discovered tyrosine phosphorylation, a biological process that can trigger the uncontrolled cell growth that leads to cancer. Hunter and **Bart Sefton**, another early member of the Center, carried the observation further. The discovery later served as the foundation for the development of drugs that today are used to treat leukemia and lung cancer.

Evans began his research on nuclear hormone receptors, which led to his discovery of a large family of receptors that respond to steroids, making them primary targets for treating diseases ranging from cancer to asthma. Wahl demonstrated the role of the p53 gene as a key mechanism in the genetic instability that is a precursor to cancer.

In later years, Heinemann isolated and cloned the gene for a glutamate receptor that plays a key role in memory and learning, brain damage, and a range of neurodegenerative diseases. Bellugi discovered that the left hemisphere of the brain is specialized for processing language, including the visual modality of sign language. And **Fred H. Gage** (Laboratory of Genetics), who joined the Salk in 1995, showed that, contrary to scientific dogma, human beings are capable of growing new nerve cells in the brain throughout life.

Verma, who identified several cancer-causing genes, remembers there were about 20 faculty members in total when he arrived to the Salk in 1974. The South Building was still practically empty except for a couple of labs on the bottom floor, some administrative offices in the middle floor, and a ping-pong and billiards table on the top floor, where they also had a pottery-making area with a kiln. But the environment on campus was the same as Jonas Salk had first envisioned.

“The atmosphere was complete freedom to do whatever you wanted,” explains Verma, whose revolutionary gene therapy technology was recently used to successfully arrest a fatal genetic brain disorder in two Spanish boys. “We had no teaching responsibilities or committees to run. My sole job was to park the car and come in. All we did was explore and just do science.”

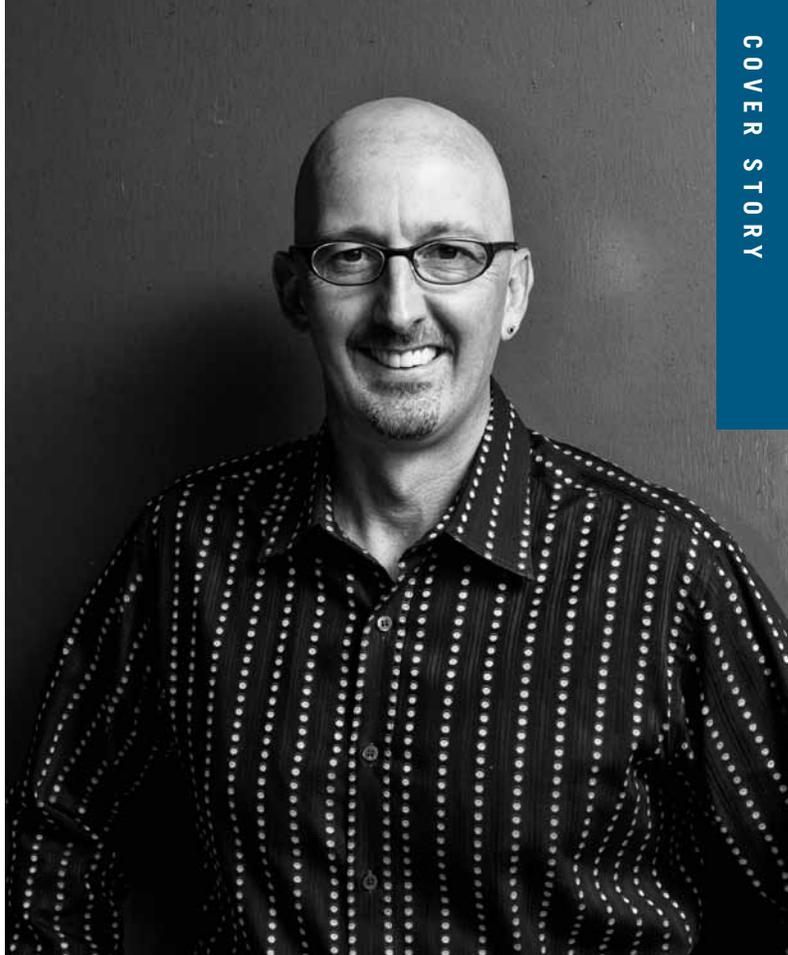
STUDYING DNA SHARED BY PLANTS, HUMANS

The 1990s also saw the growth of an infectious disease program, which evolved into the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis, headed by Professor **John A. T. Young**. The Center also includes Salk’s newest recruits **Ye Zheng** and **Bjorn Lillemeier**, both assistant professors.

Structural Biology also grew in prominence with the addition of Professors **Senyon Choe** and **Joseph Noel**, as did Developmental Biology with the arrivals of Professors **Juan Carlos Izpisua Belmonte**, **Kuo-Fen Lee** and **Samuel Pfaff**.



Joanne Chory



John A. T. Young



Juan Carlos Izpisua Belmonte



Samuel Pfaff



Joe Ecker



Senyon Choe



Charles Stevens



Joseph Noel



Kuo-Fen Lee

De Hoffmann was mainly responsible for establishing the Plant Molecular and Cellular Biology Laboratory at the Institute when he hired the program's first scientist in 1983, **Chris Lamb**.

"Chris had the vision for the program, and he was willing to take the risk on [plant lab model] Arabidopsis really taking off," says **Joanne Chory**, professor and director of the Plant Biology Lab, who joined the Institute in 1988. "But what changed in the mid-'80s was that molecular biology and plant transformation revolutionized plant biology. By then, the first Arabidopsis transgenic plants were made, which allowed scientists to think about a whole different kind of experiment because we could now manipulate genes."

Since its founding, that lab has made several seminal discoveries related to genetic adaptation, flowering time and the mechanisms that control how plants perceive and respond to changes in their environment. Today, the Salk Institute is widely recognized as having one of the world's leading plant biology laboratories.

And collaborations aren't confined to the green house. In what is perhaps the best example of Jonas Salk's vision for unconventional interaction, plant biologists are actively working with scientists conducting research with mammalian cells.

"The biology that's carried out by plants can have a direct impact on understanding human biology because many genes and proteins in plants and people are very similar," says **Joe Ecker**, a professor in Salk's Plant Biology Lab whose lab developed methods that use powerful high-throughput DNA sequencing technology for studying how the genomes of



Andy Dillin



Satchidananda Panda



Vicki Lundblad



Jan Karlseder



Martin Hetzer



Reuben Shaw

Aside from the sophisticated microscopes and sequencing machines, scientists at Salk will continue to depend on their imagination and curiosity as the basis for a new era of scientific breakthroughs.

plants and people are regulated. “If I can understand the function of a particular molecular protein in plants, for example, it probably does the same thing in people.”

Ecker’s sequencing technology is now being applied to understand the dynamics of the human genome, and is providing greater insight into human stem cells’ capacity to self-renew and how the epigenome, the mechanisms that control our DNA, contribute to the development of tumors and disease.

The technology has led to additional collaborations with Evans’ lab, which is studying protein-DNA interactions and the epigenome in fat stem cells, and Satchin Panda’s lab, which is researching how the circadian clock affects the epigenome and gene expression.

Over the last 10 years, Institute leaders made the strategic decision to strengthen the cell biology program and recruited a strong group of young scientists with varied, but complementary, research backgrounds.

Vicki Lundblad and **Jan Karlseder** each study telomeres and cellular replication. **Martin Hetzer** focuses on nuclear assembly, while **Reuben Shaw** studies tumor suppression and gene function. **Andy Dillin**, director of Salk’s Glenn Center for Aging Research, and his team are providing new clues about the aging process and neurodegenerative diseases such as Alzheimer’s and Parkinson’s.

Other young recruits in the last decade include **Leanne Jones** (stem cell research); **Clodagh O’Shea** (adenovirus transformation mechanisms); **Satchidananda “Satchin” Panda** (circadian rhythms); and **Lei Wang** (chemical biology).



Clodagh O'Shea

Salk by the Numbers

3 Nobel Laureates (Resident Faculty)

- Sydney Brenner, Renato Dulbecco, Roger Guillemin

15 National Academy of Sciences Members

- Thomas Albright, Ursula Bellugi, Sydney Brenner, Joanne Chory, Renato Dulbecco, Joseph Ecker, Ronald M. Evans, Fred H. Gage, Roger Guillemin, Stephen F. Heinemann, Tony Hunter, Marc R. Montminy, Charles F. Stevens, Wylie Vale, Inder M. Verma

8 Howard Hughes Medical Institute Investigators

- Joanne Chory, Andrew Dillin, Sascha du Lac, Ronald M. Evans, Joseph P. Noel, Samuel L. Pfaff, Terrence J. Sejnowski, Reuben Shaw

'GENOME-ENABLED SCIENCE'

After returning to the Institute, Renato Dulbecco made a wise proposal when he suggested in a 1986 Science article that in order to fully understand human disease, it would be necessary to sequence the human genome so that it could be compared to its diseased counterpart.

This set off the Human Genome Project four years later by an international group of scientists who completed the mammoth work in 2003. Ecker likens that discovery to Francis Crick and James Watson's elucidation of DNA's structure in 1953.

"The Genome Project was a sea change discovery. Salk's been around for 50 years, so for 43 years we've been doing non-genome-enabled science – meaning molecular biologists have studied just one gene at a time," Ecker says. "And that's been very profound and lots of great science has come out of the Salk.

"But now we've got all the genes in front of us and you have to ask, 'How are we going to use all that information?' We're at a point that if you don't consider all of the genes, you're probably not going to come up with the right answer," he says.

Finding those answers in today's era of scientific research will rely heavily on emerging technology, in which the Salk Institute is investing through several new initiatives – most notably the Waitt Advanced Biophotonics Center, launched in 2008 with a \$20 million grant from the Waitt Family Foundation.

Setting aside the sophisticated microscopes and sequencing machines, scientists at Salk will continue to depend on their imagination and curiosity as the basis for a new era of scientific breakthroughs. It's what investigators at the Institute collectively regard as "The Salk Way."



Leanne Jones



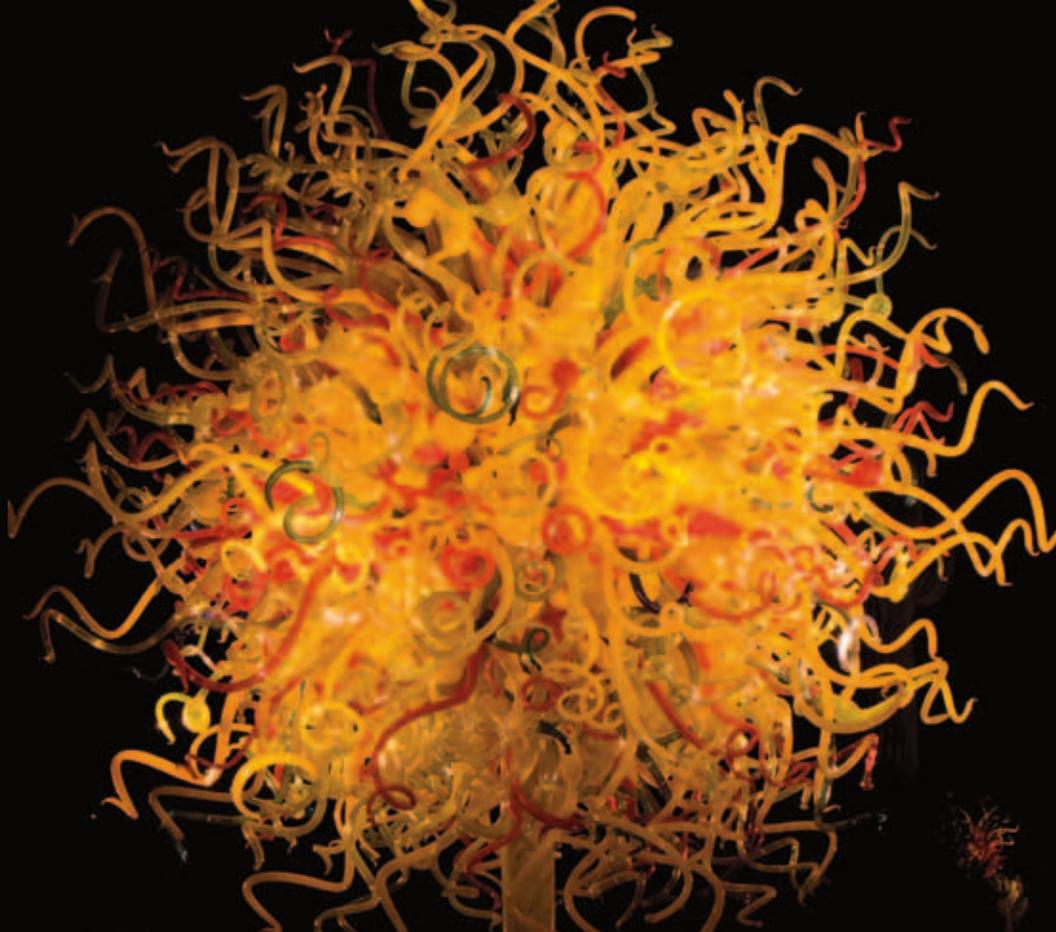
Lei Wang

"The Salk Way is not definable by a known criterion. It is not a recipe or potion that can be bottled and sold," Verma explains. "It is an atmosphere that is felt. It's a community of scholars who interact, thrive on each other's knowledge and good will, and are inspired to do cutting-edge research because of their curiosity to do something which others haven't done." ■■■

Breaking Ground for Ground-Breaking Facility

Salk Board Chair **Irwin Jacobs** and President **William R. Brody** don hard hats March 26th to herald construction of the Sanford Consortium for Regenerative Medicine's stem cell research facility – a state and privately-funded collaboration of scientists from UCSD, the Salk, the Sanford-Burnham Medical Research Institute and the Scripps Research Institute – set to open in 18 months. 





Institute Kicks off 50th Anniversary Celebration with *Chihuly at the Salk*

THE BOLD ICONIC LABORATORY BUILDINGS OF THE SALK INSTITUTE will receive an equally dramatic jolt of colorful artwork April 22-27 when the Institute kicks off its 50th anniversary celebration with *Chihuly at the Salk* – an outdoor installation of sculpture by artist Dale Chihuly.

The celebratory event is open to the public for day and some evening guided tours (\$15/ticket), in the course of which visitors can experience Chihuly's fantastically colorful and expressive glass pieces. The artwork will be positioned throughout the grounds of the Salk Institute, marking the first time a Chihuly installation has ever been displayed at a working research institution.

"This fusion of extraordinary scientific, architectural and artistic creativity is indicative of the true spirit of our founder, Jonas Salk," said Salk Institute President William R. Brody. "We are absolutely delighted that we can open our doors to the public to share this unique experience. And we are deeply appreciative of the generous sponsorship of Joan and Irwin M. Jacobs that made this exhibit possible."

Chihuly's *The Sun* and *White Tower*, each standing about 15 feet tall, are among the largest sculptures that will be set against the Salk's austere, angular buildings and courtyard overlooking the Pacific Ocean, and in the adjacent eucalyptus grove.

Other signature pieces on display will include *Niijima Floats*, large spheres—up to 40 inches in diameter and approximately 60 pounds—with surfaces richly colored in gold and silver leaf and foil; *Chandeliers*, large hanging sculptures assembled from hundreds of colorful, tentacle-like glass components; *Reeds*, translucent spears that appear to jut out from the ground.

A lecture and book signing (\$50/ticket) with the artist is scheduled on April 25 from noon-2 p.m. in the Salk Institute's Frederic de Hoffmann Auditorium. Chihuly will discuss some of his most significant exhibits

from around the world and touch on the installation at the Salk and the landmark architecture that inspired it. A 15-minute Q&A session will follow.

Chihuly has led the avant-garde in the development of glass as a fine art. His work is included in more than 200 museum collections worldwide. He has created many well-known series of works, among them the *Baskets*, *Persians*, and *Seaforms*, but he is also celebrated for large architectural installations. 



Chihuly at the Salk

(All tours: \$15)

April 22-23: Public Tours, 9 a.m.-noon; 2-5 p.m.

April 24: Public Tours, 9 a.m.-2 p.m.

April 25: Chihuly Lecture/Book Signing, noon-2 p.m.; \$50
(Gates open at 11:00 am for self-guided tours)

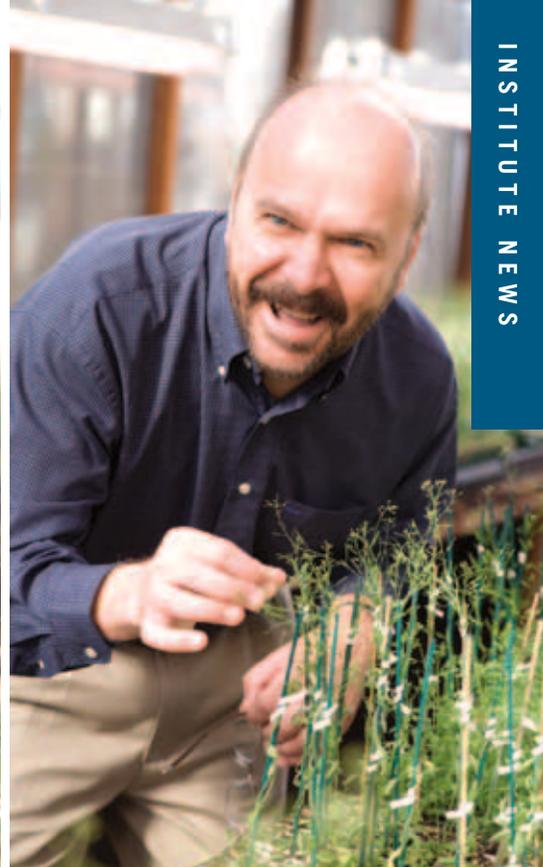
April 26-27: Public Tours, 9 a.m.-noon; 2-6 p.m.; 7-9 p.m.

For tickets, visit: www.salk.edu/chihuly or call 858-597-0657.

One on One with... Joe Ecker

SALK PROFESSOR JOE ECKER MADE NATIONAL HEADLINES IN DECEMBER WHEN TIME MAGAZINE RANKED his most recent study, in which his lab mapped the epigenome of two human cell types for the first time, the No. 2 most important scientific finding of 2009. Interestingly, the techniques Ecker's lab used to map the human epigenome – the mechanism that controls our DNA – were the same he previously developed to decipher the “epigenetic” code in plants. A renowned plant geneticist and member of the National Academy of Sciences, Ecker was part of the team that sequenced the entire genome of *Arabidopsis thaliana*, a modest weed that has become the model organism for plant biologists. Discoveries first made in plants are now being applied toward better understanding human biology.





Were you at all surprised that the mainstream media picked up on the epigenome story?

No. We knew it was a big deal. We spent the last two years racing against many other groups. There is a group of scientists in China that got \$1.5 billion to work on epigenetics and other projects. And there were others in Singapore and Scripps. So there were some very good people out there working on this, yet here we are, this relatively small group at the Salk Institute that was able to complete the first two examples of the human epigenome and publish first in *Nature*. The good news for us is that we already had a lot of experience from working with *Arabidopsis*. So we had already worked out the methods. In fact our competitors were using our sequencing methods.

Can you explain epigenetics in basic terms?

The mechanism that controls the expression of DNA is the so-called epigenome. It sits on top of your DNA, hence the term “epi” (on top of). You can think of it as being the software in a computer. A computer running Windows looks very different from a Macintosh, it just depends on the software you are running. So in similar fashion, the epigenome is controlling the genome, making different cell types using the same “hardware” (genome).

So what controls the epigenome?

What we eat or the environment can cause changes in your epigenome. For example, there’s a study that just came out about plastic containers containing bisphenol. It looked at changes in methylation profiles, not using whole genome sequencing, but using an array-based method. And sure enough it looks like bisphenol is having an effect on the epigenome. So that is a clear environmental effect of diet and toxins in the environment that are affecting your DNA methylation profile.

There are drugs on the market that target the epigenome. Which diseases do they treat? And what other applications are possible as science learns more about the human epigenome?

There are many places in your genome where the epigenome is in control. If you take a drug that affects the epigenome, you’d want to know specifically which area of the epigenome is being changed. But that’s not entirely understood yet. The drugs on the market that affect the epigenome are primarily used to treat cancer. One of the characteristics in cancer is the silencing of tumor suppressor genes. So if these genes are turned off by the epigenome, which is a bad thing, you could potentially turn them back on by removing the DNA methylation. But of course these drugs also cause other changes in the epigenome. So trying to understand exactly what the drugs are doing depends on being able to look across the entire genome. I think physicians will soon begin to treat patients with a drug, isolate the cells from that person after treatment and look at the changes in their epigenome to understand their effect, good and bad. And then maybe in the future drugs can be designed to target the enzymes involved to control specific areas of the epigenome.

In your lab’s recent study, your team mapped the epigenomes of two human cell types: embryonic stem cells and fibroblasts. But this is just the tip of the iceberg in terms of what still needs to be discovered.

Absolutely. The textbooks tell us that there are 250 or so cell types. Well, we know there is more than that. Our colleagues at Salk who study the retina tell us it alone has 20 cell types, and probably many more. Cell types are designated by their shape and size, but that’s probably a very naive view of what cells are because as an embryo forms, for example, those cells are changing and moving. So cells that are in motion may look like the ones that aren’t, but yet something is telling them to move. So they are genetically programmed differently. So you can imagine that there are millions of epigenetic states at one extreme, and minimally 250. Somewhere in between is the real number, which we don’t know, but we’ve done two so far. So we’re definitely at the tip of the iceberg.

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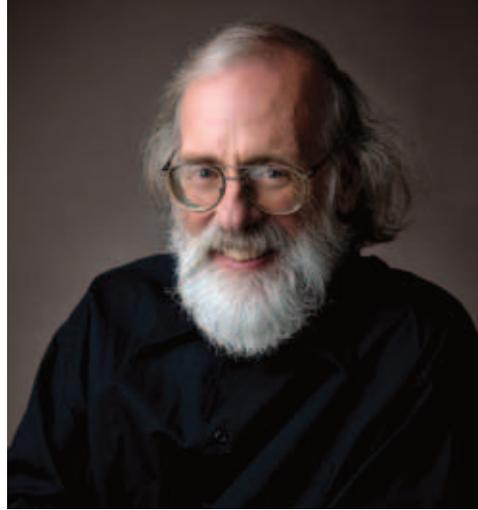
What fascinates you most about plant genetics?

Not only what we eat but a lot of what we wear comes from plant material. And so I think its an area where you can have a lot of impact. So one of the goals of our research is to understand plants well enough to be able to manipulate them for various purposes: energy, biofuels, creating new crops that can withstand the changing environments. There are a lot of things about plants that have an impact on humans. Not necessarily disease, but impact human biology, hunger being at the top of the list.

What's the one scientific question in your field you'd like to answer in your lifetime?

I'd like to know how much of what we see affecting the epigenome is transmitted into the next generation. That has very profound implications for human biology because some of the things that we don't understand about disease may be due to epigenetics. This is where plants actually help because the information gathered from animal and plant model systems can easily transfer from one another. And one of the things we know very well about plants is that they can have stable epigenetic events that last hundreds of years. So that means that if such an event can be stable and inherited over many generations maybe it's true in people as well.

So trying to understand the impact of the environment on plants and people is one of the goals that we have. What happens to the epigenome when you change your diet or in disease states such as if you have diabetes? Does either have implications for your kids or grandkids? Just like we try to understand how genetic mutations have effects on diseases, this is a whole other area I think that's ripe for trying to understand how people interact with their environment and how it affects them. 



Cancer Researcher Tony Hunter Named to Frederick W. and Joanna J. Mitchell Chair

RESEARCHER AND AMERICAN CANCER SOCIETY PROFESSOR

Tony Hunter has been named the inaugural holder of the Frederick W. and Joanna J. Mitchell Chair, created in memory of their daughter Marian Mitchell through a \$2 million gift by the estate of Frederick W. Mitchell.

The endowed chair was established in February under the Joan Klein Jacobs and Irwin Mark Jacobs Senior Scientist Endowed Chair Challenge, which augments the Mitchell estate's gift with an additional \$1 million.

As the director of the Institute's NCI-designated Cancer Center, Hunter studies how cells regulate their growth and division, and how mutations in genes that regulate growth lead to cancer. His lab has made significant research contributions in the area of signal transduction – how signals that stimulate or rein in cell growth are routed.

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

Hunter is a member of the National Academy of Sciences and a fellow of the Royal Society of London. He holds the 2006 Robert J. and Claire Pasarow Award for Cancer Research; the 2005 Wolf Prize in Medicine, Israel's top recognition for achievements in the interest of humanity; the 2004 Louisa Gross Horwitz Prize, a leading national award for scientific achievement; and Japan's 2001 Keio Medical Science Prize.

"We are deeply grateful to the Mitchell estate for this most generous gift that enables us to honor and recognize one of our most distinguished senior scientists," said Salk Executive Vice President **Marsha A. Chandler**. "The contribution, along with the Jacobs' matching gift, allows us to provide Dr. Hunter and subsequent holders of this chair with financial support that will encourage continued breakthroughs in childhood disease research at the Salk Institute."

Launched in 2008 with a \$10 million matching fund, the Jacobs Chair Challenge encourages and enables donors to create prestigious, permanent chairs in support of senior faculty members at Salk.

The \$2 million endowed chair is part of a more than \$3.2 million bequest to the Salk Institute from the Frederick W. Mitchell estate. 



Research scientist Tom Bartol gives a brief talk for journalists before launching a three-dimensional computer simulation using M-Cell, a modeling program he developed.

International Journalists Tour Neuroscience Labs

ABOUT 45 STAFF AND FREELANCE SCIENCE journalists from around the world visited the Salk Institute in February to tour four laboratories working in various aspects of neuroscience.

The two-hour stop at Salk was part of a joint effort between the Institute and UCSD designed to bring science writers to both campuses and familiarize them with the research while they were in San Diego for the American Association for the Advancement of Science's conference.

"It was a great opportunity to learn about research I don't ordinarily cover (and therefore know precious little about)," said Janet Raloff, senior editor for *ScienceNews*, who wrote about the tour's stop at the Salk Institute's Stem Cell Core Facility in the Feb. 18 issue. "And it was so interesting—and potentially worthy of covering—that I only wish we had been given a lot more time with the teams in each lab."

A visit in the lab of **Samuel Pfaff**, a professor in the Gene Expression Laboratory and HHMI investigator, included a short video that showed spinal cord motor neurons induced to fire signals that mimicked walking motions. A second video taken during a separate experiment depicted axons, or nerve fibers, reaching out for their intended muscle targets.

Sophisticated visual illustrations continued in the Computational Neurobiology Laboratory of Professor **Terry Sejnowski**, who gave a brief

presentation on synapses, the structure that allows a neuron to pass electrical or chemical signals to another cell, before research scientist **Tom Bartol** launched a three-dimensional, computer simulation of a synapse and its surrounding structure created with M-Cell, a program he developed and widely used for scientific research.

The group also received a brief overview of the Salk Institute's Vision Center when they visited **E. J. Chichilnisky**, an associate professor of the Systems Neurobiology Laboratory, who studies ganglion cells – the output cells of the retina that send messages related to vision to the brain.

Chichilnisky explained the process his team follows to take hundreds of simultaneous electrode readings of retinal tissue using highly advanced equipment developed in collaboration with physicists at UC Santa Cruz. The lab's long-term goal is to contribute to the development of visual prosthetic devices – a possibility that is about five to 10 years away, Chichilnisky said.

The journalists also received a quick lesson on stem cells and their potential use to treat neurodegenerative diseases such as Lou Gehrig's disease by postdoctoral fellows **Carol Marchetto** and **Kristen Brennand**, who conduct their research in Professor **Fred H. Gage**'s Laboratory of Genetics.

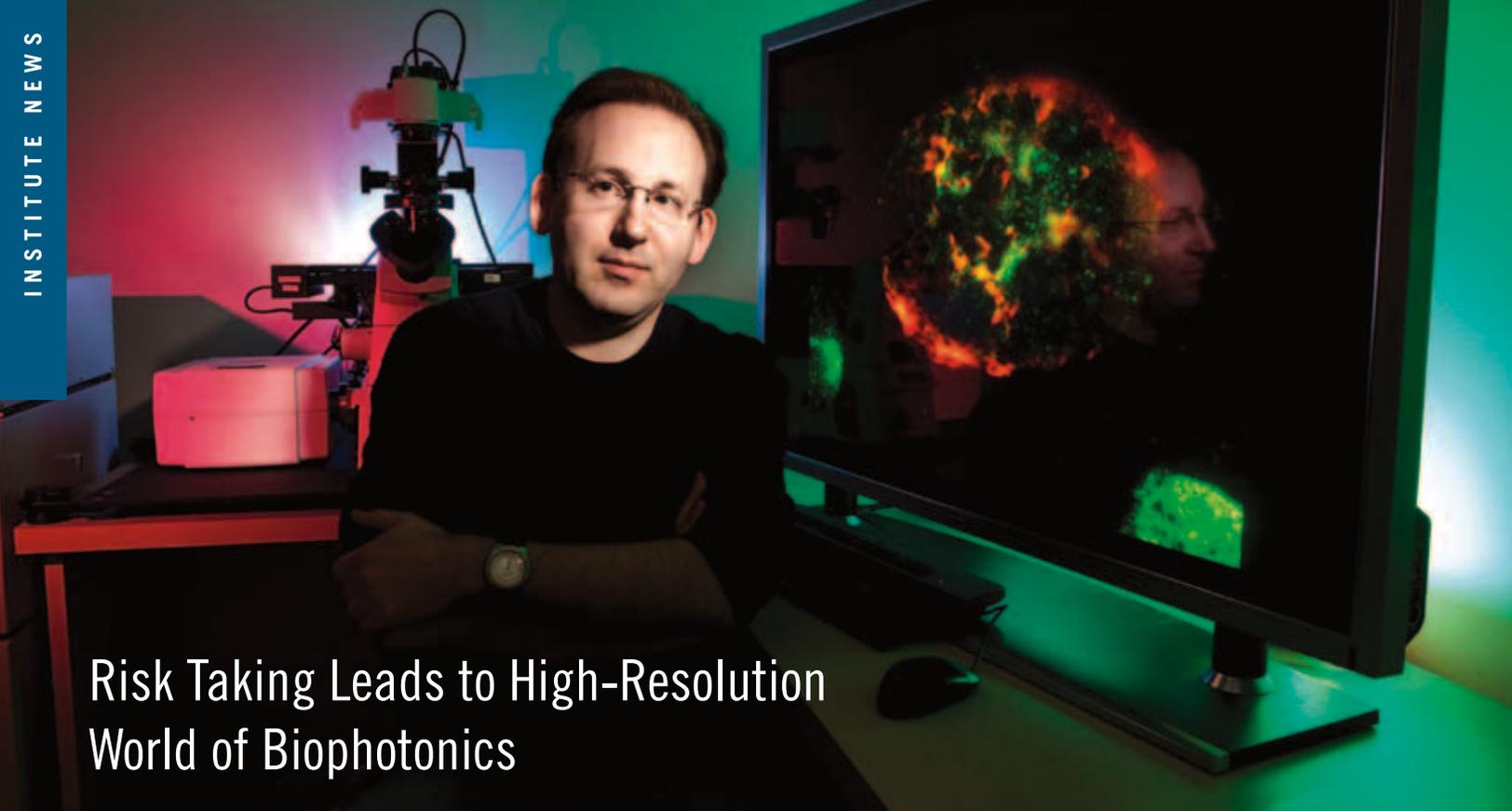
Both Marchetto and Brennand explained how they study the differences between healthy brain cells and their diseased counterparts. To do so, they take differentiated cells from patients and reprogram them into stem cells, from which they generate live human brain cells afflicted with the disease of interest.

More than 10 years ago, work from the Gage lab debunked the long-held belief in the scientific community that neurogenesis (the birth of new neurons in the brain) does not occur in adults. His lab has gone on to show that voluntary exercise is positively correlated with an increase in neurogenesis in the adult brain and with an improvement in learning and memory abilities. 📊

“It was a great opportunity to learn about research I don't ordinarily cover.”

– JANET RALOFF

senior editor of *ScienceNews*, who wrote about the tour's stop at the Stem Cell Core Facility in the Feb. 18 issue.



Risk Taking Leads to High-Resolution World of Biophotonics

James Fitzpatrick considers himself a risk-taker. An optical engineer with a background in chemical physics, he has a tendency to gravitate toward all things “death-defying.”

ON A PERSONAL LEVEL, HE IS NOT DRAWN TO SAFE PURSUITS.

He nearly drowned after falling overboard while rafting on a class IV river in Pennsylvania. He does not shy away from treacherous cliff-top hikes like those in Bryce Canyon, Utah. And now that he’s moved to San Diego to direct the Salk’s Biophotonics Core Facility, Fitzpatrick can be found zipping around town, the pedal to the metal in his turbo-charged Subaru Impreza WRX, just like the World Rally Championship heroes he admits to obsessively follow on television.

“I spend a lot of my time devoted to science so when I do get the chance to relax I like to tear it up a little bit,” he jokes.

For this adrenaline junkie, who grew up outside of London and earned his Ph.D. at age 23, his penchant for doing the boldly non-traditional is what eventually led Fitzpatrick to a career in biophotonics, the science of applying photon-based microscopy to biology. And for that, he credits Harry Potter -- the fictional boy wizard made famous in the popular children’s book series.

“At first I didn’t want to read the books, I thought it was complete rubbish, but there’s something about the writing. There’s something there for children and for adults,” explains Fitzpatrick, who read the first Harry Potter book when he was in graduate school developing optical techniques to probe diatomic molecules at ultra-high resolution.

“It taught me that sometimes you shouldn’t judge a book by its intended audience, and that I should think about pushing myself to do things outside of my comfort zone.”

That was about the time Fitzpatrick started white-water rafting. But it was also when he started thinking about applying his own laser optics wizardry to biological systems. “There’s only so much you can look at in two or three atom molecules. It tends to get a bit boring after a while,” he says.

He applied his laser-based techniques to probe proteins and their interactions at Carnegie Mellon University, where he was invited in 2006 to develop fluorescence correlation microscopy technology in the new NIH Technology Center for Networks and Pathways. He was eventually promoted to direct the Microscopy and Imaging Facility at the Center.

“I found myself energized by all these biological problems and there were so many opportunities for technological approaches to solve those questions,” Fitzpatrick says. “Most biologists really didn’t know about imaging methods or how we could integrate the technology and the biology in order to get a more robust answer in a quicker timeframe.”

Salk’s biophotonics initiative was funded in 2008 with a \$20 million challenge grant by the Waitt Family Foundation, an organization led by its president and founder Ted Waitt, who is also Vice-Chair of Salk’s Board of Trustees. The grant not only launched the Waitt Advanced Biophotonics Center, but it is also helping to usher in what Fitzpatrick says will ensure the next generation of biological breakthroughs at the Institute.

Using laser-based imaging technology that facilitates deep probes within living cells and tissues at unprecedented resolutions, scientists are now able to view the interactions of single molecules. To put the power

“Problems that people wouldn’t necessarily think about tackling because they may not have had the technology to do so, we can now help to make happen. And that’s really what makes the biophotonics initiative transformative.”

– JAMES FITZPATRICK



of biophotonics in perspective, an average, off-the-shelf light microscope can zoom in on the surface of a cell (about half the diameter of single strand of human hair), but microscopes in the Biophotonics Core Facility can dive deep within single components of that cell to study how they interact with one another in their healthy and diseased states.

Ultimately, the goal is to make and study movies of these interactions so scientists can better understand the inner workings of cells, and how they relate to the functionality of the entire body.

“Starting from the ground up and building working models of how living organisms function and how they are impaired during human disease is key,” Fitzpatrick says. “Cutting-edge, technological approaches in imaging will really help to facilitate all areas of research at Salk, including cancer, aging, obesity and neurodegenerative disease.

“Problems that people wouldn’t necessarily think about tackling because they may not have had the technology to do so, we can now help to make happen,” he says. “And that’s really what makes the biophotonics initiative transformative.”



Former Institute Lab Tech Julia Miller Returns as Salk’s General Counsel

JULIA MILLER HAD TO THINK A LITTLE TOO LONG AND HARD when someone once asked her what she envisioned as her dream job at the biotech company where she was working.

A UCSD graduate with a degree in Cell Biology and Biochemistry who also spent two years as a undergraduate student in Wylie Vale’s lab at Salk, Miller was enjoying her work in both the basic science and product development divisions, but the answer to the “dream job” question just didn’t come very easily, she says.

“I realized I didn’t really want any job in the company. I didn’t want my boss’s job, or to work in a department other than R&D such as marketing or sales. So I needed to figure out what I really wanted to do,” Miller says.

The answer became abundantly clear when she started working for the biotech company’s patent lawyer after returning from an extended trip to South East Asia. She had toyed with idea of going to law school before, but the experience at the firm solidified her decision. Within a year she enrolled at Boston University School of Law.

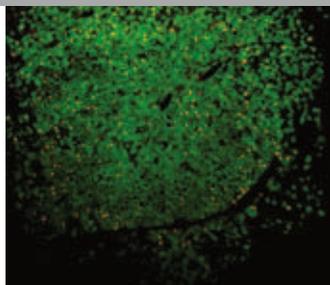
“I saw that I could be involved in the legal world, while applying some of the same skills that one uses in science,” Miller says. “In the scientific discovery process, you put forth a hypothesis, then test it with experiments and analyze the results before giving a fair and objective interpretation of the data. And similarly in law, you gather and analyze facts and apply the law to those facts to reach conclusions and make judgments about what to do next.”

Now after 10 years as a litigator and corporate patent attorney in the biotech field, Miller has returned to the Salk Institute to serve as its General Counsel. In her role, she is primarily charged with overseeing the Institute’s commercial contracts, facilitating the technology transfer and licensing process, assisting with regulatory affairs and compliance, managing litigation matters, and providing legal counsel to the Institute’s senior management team.

She spent the later half of her career at Paul, Hastings, Janofsky & Walker LLP in San Diego in the corporate department focused on contracts, so in addition to having the essential experience, Miller says she’s pleased to be back in a scientific environment – Salk’s in particular.

“I always had a special place in my heart for the Institute, for the quality of the people and the science,” she says. “I always kept it in the back of my mind that if I were to leave the law firm, it would be a dream to come back and work at the Salk Institute.”

Discovery Roundup



Mouse liver containing 95 percent human hepatocytes.

Chimeric Mouse Developed to Test Human Liver Disease

A TEAM LED BY SALK INSTITUTE RESEARCHERS

has developed a mouse model with 95 percent of its liver containing cells of human origin, making it an ideal system to test novel therapies for debilitating human diseases, including cancer.

The team, led by senior author **Inder Verma**, a professor in the Laboratory of Genetics, had previously generated a mouse with a partially “humanized” liver, but wanted to improve their method to achieve almost complete transformation. They use a special mouse that has liver problems of its own, but whose problems can be kept in check with a drug called NBTC. Taking away NBTC allows human hepatocytes to take hold and populate the mouse liver with human cells.

The new model is susceptible to human liver infections and responds to human drug treatments. To test this, the researchers exposed the mice to Hepatitis B and Hepatitis C and found that, unlike normal mice, that are resistant to these viruses, the chimeric animals developed the disease.

More importantly, using pegylated interferon alpha 2a – the standard treatment for Hepatitis C – the researchers showed that the “humanized” liver inside the mouse responds just like a normal human liver. The team tested additional experimental drugs and found that they too behaved as they did in humans.

“This shows that our chimeric mouse model is medically relevant and can be used to validate novel drugs in a pre-clinical setting,” says first author **Karl-Dimiter Bissig**, an internist and post-doctoral researcher in the Laboratory of Genetics. “This is great news as it provides us with a tool with which we can examine many human hepatotropic pathogens, including malaria. In the future, it also has potential applications for regenerative medicine; allowing confirmation of the true hepatocyte nature of cells prior to human transplantation.”

The study was published in the online edition of the *Journal of Clinical Investigation* in February.

Dual Role for Immune Cells in the Brain

SYMPTOMS ASSOCIATED WITH INFECTION ARE ORCHESTRATED BY

the brain in response to circulating cytokines, the signaling molecules of the immune system. But just how cytokines cross the almost impenetrable blood-brain barrier has been the topic of much dispute.

Now, Salk scientists have described how resident macrophages lined up along the blood-brain barrier play opposing roles in the transmission of immune signals into the brain. Their findings may pave the way for novel therapies for sufferers of chronic neurodegenerative diseases, such as Amyotrophic Lateral Sclerosis (ALS), Parkinson’s, Alzheimer’s and prion diseases, in which central inflammatory mechanisms play an important role.

Earlier research by **Paul E. Sawchenko**, a professor in the Neuronal Structure and Function Laboratory and the study’s senior author, and others suggested a vascular route whereby cytokines interact with vessel walls to generate secondary messengers, which then engage the relevant circuitry in the brain. Tightly packed endothelial cells, which line almost 400 miles of narrow capillaries throughout the brain, are perfectly positioned to record circulating immune signals but they require a very strong signal to become activated. Perivascular macrophages, on the other hand, are more sensitive but don’t have direct access to the bloodstream.

To disentangle the exact role of these two cell types, the researchers took advantage of the macrophages’ ability to engulf and ingest solid particles. They injected liposomes containing clodronate, a drug that can cause cell death, into the lateral cerebral ventricle. The liposomes were taken up by the macrophages, which were selectively killed off.

Without perivascular macrophages, the animals were unable to respond to blood-borne interleukin-1, an inflammatory cytokine, and initiate the brain’s so-called acute phase responses, which help the body deal with the challenge at hand but also cause the familiar feeling of “being sick.” But to their surprise, the Salk researchers found that the same cells put a damper on the pro-inflammatory activities of endothelial cells, which form the lining of blood vessels and are only stirred to action when they encounter lipopolysaccharide, a key component of the cell wall of certain bacteria.

“Many neurodegenerative diseases are worsened by systemic inflammation or infections,” says Sawchenko. “Once we identify the molecules that mediate the two-way communication between perivascular macrophages and endothelial cells, we can develop strategies for managing the adverse health consequences of central inflammatory responses.”

Salk scientists have described how resident macrophages lined up along the blood-brain barrier play opposing roles in the transmission of immune signals into the brain.

Nuclear Pore Complexes Offer Clues to Gene Expression and Cancer

NOT ONLY DO NUCLEAR PORE COMPLEXES serve as communication channels between molecules and a cell's nucleus, but researchers at the Salk Institute have now shown that some of the pores' constituent proteins, called nucleoporins, also pull double duty to regulate gene activity.

This marks the first time nucleoporins' gene regulatory function has been demonstrated in multicellular organisms. These findings not only reveal a new class of transcription factors but they may offer new insights into the mechanisms behind cancer.

It was previously unknown whether similar regulatory properties were present in multicellular organisms. For more than a decade, however, scientists had known that when the protein called Nup98, a nucleoporin, abnormally fuses with certain proteins that regulate gene expression, causing leukemia. What is more, nucleoporins Nup214 and Nup88 are highly over-expressed in other cancers, including colon cancer and very aggressive forms of lung cancer.

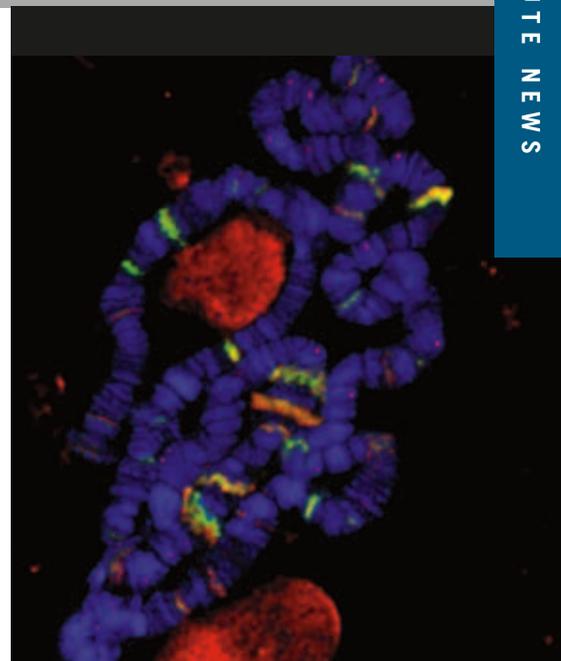
Scientists had long questioned why these components of the cell's transport channel are implicated in cancer and had theorized that

the connection might stem from a problem related to the conveyance of molecules in and out of the nucleus.

To probe the role of these proteins, **Martin Hetzer**, Hearst Endowment associate professor in Salk's Molecular and Cell Biology Laboratory, and his group studied the development of salivary glands in fruit flies. Using antibodies, the scientists were able to detect the binding of Nup98, SEC13, and FG-containing nucleoporins to specific genes on the polytene chromosomes. When they did a three-dimensional reconstruction of the nuclei, they found the nucleoporins inside the nucleus.

"Very few studies have looked at nuclear pore components for their potential role in gene regulation in animal cells," says Hetzer. "The fact that NPC components can interact with genes inside the nucleus makes a lot more sense in how they can regulate gene activity. The gene doesn't go to the pore; the pore protein goes to the gene."

The nucleoporins don't regulate all genes, but are required for a subset of genes, including developmentally regulated genes, which are turned on and off in a controlled



Polytene chromosomes revealed that nucleoporins pull double duty as transcription factors regulating the activity of genes active during early development.

manner during cell differentiation and tissue development.

"What is exciting to us is that they are key regulators for developmental genes and also potential markers for causes of cancer," Hetzer explains. 

Stress Peptide and Receptor May Have Role in Diabetes

SALK SCIENTISTS HAVE DISCOVERED THAT THE NEUROPEPTIDE corticotropin-releasing factor (CRF), which initiates the stress response in the brain, also plays a role in the pancreas, where it increases insulin secretion and promotes the division of the insulin-producing beta cells. The findings may provide new insights into diabetes, particularly type 1, as well as suggest novel targets for drug intervention.

CRF, in concert with its receptor, CRFR1, has long been known as key to the body's response to various forms of stress, but the pair is also involved in many more processes. As early as the 1980s, studies had suggested that pancreas cells can respond to CRF, but the few limited observations did not demonstrate the nature of the response.

Working with cell lines, pancreatic islets from mice and human donors, as well as mouse models, **Wylie Vale's** lab, which discovered CRF in the early 1980s, conducted a series of experiments that collectively demonstrated the presence and actions of CRFR1 in the islets.

What the team discovered was that beta cells exposed to CRF, one of the peptides that activate the CRFR1 receptor, can respond in at least

two ways. First, they increase their secretion of insulin if they simultaneously encounter high levels of glucose. The higher the levels of glucose, the more insulin they release in response to CRF and the more rapidly blood levels of glucose are reduced.

Working in collaboration with a group at the Panum Institute in Copenhagen, the researchers went on to establish that beta cells exposed to CRF also activate the MAPK pathway, which is a key pathway implicated in beta cell division. Mature, differentiated beta cells can divide, albeit slowly, but if they are exposed to a molecule that will activate the CRFR1 receptor, they will start to divide somewhat more rapidly, which is especially relevant in the context of type 1 diabetes.

"Being able to stimulate beta cells to divide a little faster may be part of a solution that may ultimately, hopefully, allow management of type 1 diabetes," Vale says. "But because it is an autoimmune condition, making the cells divide won't be enough. That is why researchers are working hard to solve the problem of destruction of beta cells." 

Discovery Roundup



When cells with DNA damage are infected with HSV-1 virus (top image, virus shown in red) the viral ICPO protein prevents the DNA repair proteins (bottom image, DNA repair proteins shown in green) from accumulating at sites of DNA damage. Matthew Weitzman (center) pictured with Mira Chaurushiya (left) and Caroline Lilley.

Scientists Identify Key Protein in Herpes Simplex Virus

RESEARCHERS AT THE SALK INSTITUTE HAVE IDENTIFIED A KEY protein that allows herpes simplex virus (HSV) DNA to fly under the radar of their hosts' involuntary hospitality. Their findings may suggest a common mechanism by which viruses can successfully infect host cells.

To the host cell, invading viral DNA looks just like the product of DNA damage, which must be repaired or removed in order for the cell to stay healthy. As a result, DNA "security guards" continuously patrol our cells.

Matthew Weitzman, associate professor in the Laboratory of Genetics and the study's leader, and his team looked at what happens in a virus-infected cell when its DNA is damaged. In a normal cell, DNA damage sensor proteins rush to the site of damage. In cells infected with HSV, however, the cells' emergency repair teams don't respond correctly.

The team went on to identify a single viral protein that is to blame for knocking out the cell's security system, a protein called ICPO. They discovered that it flags for destruction two important DNA "security guards," the proteins called RNF8 and RNF168, thereby taking out the DNA damage response in human cells. ICPO attaches so-called ubiquitin marks, which instruct the cell to get rid of the very proteins that protect it.

Delving deeper, the team looked at the role of these DNA "security guards" that are singled out by ICPO. Surprisingly, RNF8 and RNF168 also leave ubiquitin tags, but in this case, they mark regions of damage. They tag a protein called histone H2A, which directs DNA damage response proteins to accumulate at the sites of damage. The Salk team discovered that by removing RNF8 and RNF168, the viral ICPO protein results in a decrease to the tag on the cellular H2A protein.

"We found that HSV targets the mark that is required to keep DNA damage sensors at damage sites," says postdoctoral researcher and first author Caroline Lilley. "We now think that HSV deliberately removes this mark so that the virus can infect cells without any trouble from its new host."

The findings highlight the importance of these histone marks in DNA damage. "By identifying how HSV dismantles the host's defense systems, we are shown the key steps, not only in viral infections, but also in the human DNA damage response," Weitzman explains. [▶▶▶](#)

Ballroom Dancer Gives Back to Basic Research

IT WASN'T VERY LONG INTO A WALTZ AT

his local ballroom dancing club before Merlin Woesner got a strong indication that he had found his new partner. A widower and retired radiologist, Woesner says the feeling was mutual the night he met Helen Kerger.

"I don't think it was more than four measures of music before I realized this lady knew how to dance," Woesner says. "It turns out she had been dancing for several years in the North County San Diego area, so she knew the dancing scene pretty well. But on that first dance, we immediately knew we were suited for each other."

These days, the dancing partners also attend science presentations at the Salk Institute, which Woesner has generously contributed to over the last 10 years and has included in his estate plans. Woesner says he was quickly taken by the Institute's leading scientific research after first learning about it with his wife, Velma, more than a decade ago.

"What impressed us about Salk was its size, it's not too big," he says. "And we got the impression right away that there is cross-fertilization between professors there, and that's a good thing. I don't think that exists at a lot of similar institutions."

Woesner says he developed his belief in "giving back" after growing up throughout South East Asia where his father worked as a businessman for missionary groups. The family returned to the United States so Woesner could start his formal education. He eventually graduated from medical school at Loma Linda University in Los Angeles.



Helen Kerger and Merlin Woesner

It was during one of the many cruises he took with Velma that they discovered ballroom dancing, he says.

"We would stop at the lounge before going to dinner and see people dancing," Woesner says. "It looked like they were having a lot of fun and it seemed like a nice social activity and a chance to get a little extra exercise. So we decided that when I retired, we were going to learn how to dance."

True to his word, they started taking classes in their community and joined a local chapter of the National Smooth Dancers Club after retiring to Oceanside, Calif. Within a few years they were proficient at the cha-cha, the rumba, the foxtrot and the tango. They danced together for 22 years before Velma died in 2008 after 62 years of marriage.

"I became very, very depressed, but being a physician I knew I had to get back reasonably quick to the things that I liked to do," he says. "And dancing was one of them."

Today, his medical training also continues to give Woesner a strong appreciation and value for basic research and the need to fund such work at Salk.

"Unfortunately a lot of people don't realize how important basic biological research is to the future of medicine," he says. "Basic science is required before you're going to get clinical research to come through." 🏢

If you are interested in including the Salk Institute in your estate plans, please contact Cheryl H. Dean, Esq, Senior Director of Planned Giving 858.453.4100 x1228 or cdean@salk.edu.

Broadway, Film Star Liza Minnelli to Perform on Symphony at Salk Stage

LIZA MINNELLI, THE MULTI-AWARD-WINNING star renowned for her performances on Broadway and in Hollywood films, will be the guest artist for the 15th annual Symphony at Salk – A Concert Under the Stars Aug. 28.

A four-time Tony Award winner, Minnelli will share the stage with the San Diego Symphony under the direction of Maestro Thomas Wilkins, who returns to the Salk Institute's alfresco fundraiser for the sixth consecutive year.

An unforgettable singer and dancer with a career spanning more than 50 years, Minnelli most recently won critical acclaim – and her latest Tony Award – with her 2008 comeback Broadway performance in Liza's at the Palace.

Minnelli has been performing on stage since the age of 10. By the time Minnelli was 19, she

landed the lead role in *Flora, The Red Menace*—the Broadway musical that garnered her first Tony. Her film career includes memorable roles in such movies as *Charlie Bubbles*, *Tell Me That You Love Me*, *Junie Moon* and *Cabaret*, the last earning her the Academy Award for Best Actress, the Golden Globe and the British Film Academy Award.

She went on to star opposite Robert DeNiro in the musical *New York, New York*, directed by Martin Scorsese, and co-starred with Dudley Moore in the comedy *Arthur* and its sequel, *Arthur 2*.

In 1997 Minnelli returned to the Broadway stage in *Victor/Victoria* before starring in *Minnelli on Minnelli*, a show that paid tribute to her father, the late film director Vicente Minnelli.

After a bout with encephalitis in 2000, she made a triumphant comeback two years later with the CD *Liza's Back!* and on television's *Arrested Development*. Today, Minnelli continues her music career with concert tours in the United States and Europe. 🏢



If you are interested in sponsorship opportunities for Symphony at Salk, please contact Judy Hodges, director of Annual Fund, at 858.453.4100 x1882 or hodges@salk.edu.

MIT and Stanford Scientists join Salk Institute's Non-Resident Fellows

TWO HIGHLY ACCOMPLISHED RESEARCHERS from the stem cell and genomics fields are the newest members of Salk's Non-Resident Fellows, a distinguished group of scientists that help benchmark and guide Salk faculty and scientific programs.

Eric S. Lander, founding director of The Eli and Edythe L. Broad Institute of MIT and Harvard, and **Irving L. Weissman**, M.D., director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, joined the Salk faculty in November.

Recently named by President Barack Obama to co-chair the President's Council of Advisors on Science and Technology, Dr. Lander and his

team have developed many of the key tools and information resources of modern mammalian genomics, and have applied these tools and data to pioneer novel approaches to understand the molecular basis of disease.

Dr. Weissman directs Stanford's National Cancer Institute-designated Cancer Center, and is the Virginia & D.K. Ludwig Professor for Clinical Investigation in Cancer Research. In 1988, he became the first to isolate stem cells of any kind when he isolated hematopoietic or blood-forming stem cells from mice. He subsequently isolated human hematopoietic stem cells, human neuronal stem cells, and human leukemia stem cells. His work has opened up



Dr. Irving L. Weissman



Dr. Eric S. Lander

an entirely new area of scientific research with enormous potential for life-saving therapies.

"The Salk faculty and I are pleased and honored to welcome Drs. Weissman and Lander as our newest Non-Resident Fellows," said Institute President William R. Brody. "The Salk Institute's faculty relies on outstanding research leaders like these to help keep our research on the leading edge of science." 

Institute Receives \$4.4M NIH Recovery Act Grant for New Data Center

THE SALK INSTITUTE RECEIVED A \$4.4 million grant in December from the National Institutes of Health to build a state-of-the-art data center that will dramatically increase its research computing power for the next decade.

Only one of two such construction grants awarded in California and 14 nationwide, Salk's latest grant is part of the American Recovery and Reinvestment Act of 2009, which was designed to immediately create jobs and lay

a foundation for a robust and sustainable economy through infrastructure modernization projects.

"This NIH grant comes at just the right time considering Salk's growing strength in computational neurobiology and studies in epigenetics, fields of research that require intense computing power," said Salk's President **William R. Brody**. "Having a modernized data center with the ability to compute and store hundreds of terabytes of information opens the

door to a new level of scientific exploration and discovery at the Salk."

While the Salk Institute's traditional strength has been in "wet-bench" molecular and genetic research, its influence in computational biology has grown in recent years. Salk investigators now apply increasingly powerful computational approaches, such as neurobiological modeling, to answer an array of research questions. 

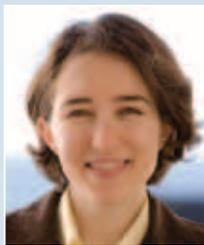


New Faces

The Salk Institute made several important hires in the last few months. Pictured during a welcoming reception at the Salk are: (from left) Assistant Professors **Sreekanth Chalasani** (Molecular Neurobiology Lab), **Bjorn F. Lillemeier** and **Ye Zheng** (Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis); **James Fitzpatrick** (Director of the Waitt Biophotonics Core); and **Julia Miller** (General Counsel).



Sreekanth Chalasani



Tatyana Sharpee



Leanne Jones



Ye Zheng



Björn Lillemeier

Early-Career Scientists Receive Developmental Chairs

FIVE SALK INSTITUTE ASSISTANT PROFESSORS are the recipients of new developmental chairs created in support of their careers and their very promising scientific research. Each will receive \$50,000 annually over the next three years.

The new chair-holders and the donors that funded them are **Sreekanth Chalasani**, an assistant professor in the Molecular Neurobiology

Laboratory, and **Tatyana Sharpee**, an assistant professor in the Computational Neurobiology Laboratory. They will each receive the Helen McLoraine Developmental Chair in Neurobiology; **Leanne Jones**, an assistant professor in the Laboratory of Genetics, and **Ye Zheng**, an assistant professor in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis,

will each receive an Emerald Foundation Developmental Chair; **Björn Lillemeier**, an assistant professor in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis and the Waitt Advanced Biophotonics Center, will receive the Rudolph and Sletten Developmental Chair in Immunobiology and Microbial Pathogenesis. 🏢

Inder Verma to Receive Pasarow Award for Cancer Research

INDER VERMA WILL RECEIVE THE 22ND annual Robert J. and Claire Pasarow Award in Cancer Research for fundamental basic research throughout his career. The award is designed to recognize distinguished accomplishments in basic and/or clinical research while increasing public awareness of vital areas of investigation.

Verma will share the award with Brian Druker, M.D., director of the Knight Cancer Institute, for his role in developing Gleevec, a powerful drug used to treat chronic myeloid leukemia.

Verma, holder of Irwin and Joan Jacobs Chair in Exemplary Science and a professor in Salk's

Laboratory of Genetics, has made outstanding advances in research ranging from cancer biology to development of gene transfer technologies. He is one of the world's leading authorities in gene therapy, having developed a vector, based on a stripped-down version of HIV, that successfully delivers genes for therapeutic purposes. His innovations revolutionized gene therapy, stem cell and cancer research, among other areas of molecular biology.

An American Cancer Society Professor, Verma is a member of the National Academy of Sciences, Institute of Medicine, American

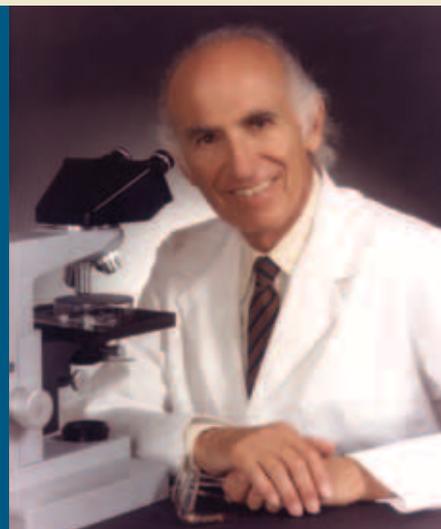
Academy of Arts & Sciences, American Philosophical Society and Third World Academy of Sciences. He is the recipient of numerous awards, including: the 2009 Outstanding Achievement Award from the American Society of Gene Therapy; the 2008 Vilcek Prize; the 2010 Spector Prize; and the 2007 Cozzarelli Prize. Verma will receive the Pasarow award, which includes a \$50,000 prize that he will share with Druker, at a dinner in Los Angeles later this year. 🏢

Jonas Salk the Focus of Israel's Owl Competition

THE OWL CENTER, AN EDUCATIONAL FACILITY dedicated to the development of scientific and creative thinking in Israel, has chosen Dr. Jonas Salk as this year's inspiration for its annual Owl Competition.

Teams of students in 7th through 9th grade representing 27 schools are participating in this year's competition, which consists of various assignments requiring students to develop strategies for distributing scientific knowledge in their respective schools. Medicine was the theme for the competition.

Administered through the Center's Web site, the Owl Competition is now in its sixth year and was established in memory of Ran Baron, a graduate of the School for Nature, Science and Society in Tel-Aviv, who was murdered in a terror attack in 2003. The competition began in November 2009 and will conclude with a ceremony on May 4. 🏢



Jonas Salk

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Salk Calendar

APRIL 2010: 50th Anniversary Celebration Begins

13 A Taste of Discovery New York

22–27 *Chihuly at the Salk*

MAY 2010

11 First Annual Salk Golf Tournament

12–14 38th Annual Tax and Management
Seminar on Private Foundations

AUGUST 2010

25–28 Salk Institute International Council Meeting
at the Salk

28 Symphony at Salk Fundraiser

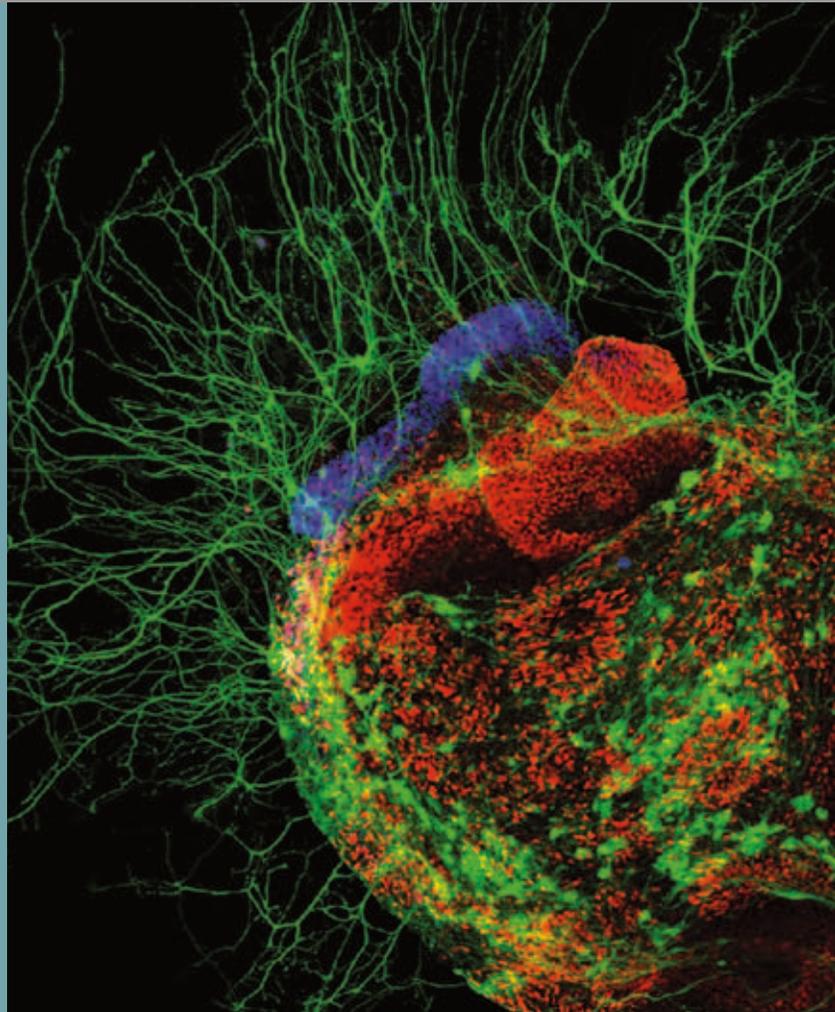
SEPTEMBER 2010

29 A Taste of Discovery San Diego

OCTOBER 2010

27–29 Faculty Symposium and Salk Medal Awards Ceremony
Salk Institute Medal for Health & Humanity
Salk Institute Medal for Research Excellence

50



Spinal cord motor neurons (in green) have differentiated from the cluster of embryonic stem cells (large globular structure) in this picture taken with a confocal microscope at 10x magnification.

Photo courtesy of Shane Andrews of the Pfaff Laboratory.

