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InsideSalk

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

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Plant Biology Lab Celebrates 25 Years of Discoveries

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Inside Salk is published by the Salk Institute for Biological Studies. We welcome your input. Please send comments to communications@salk.edu or contact the Communications department at 858-453-4100 x1226.

ON THE COVER

Arabidopsis thaliana is an ideal model for plant biologists to study because it has a small genome (about 25,500 genes) and a generation time of just six to eight weeks. The cover features a small Arabidopsis specimen that has begun to flower. It is one of hundreds that are grown in Salk's greenhouses and studied by scientists in the Plant Biology Laboratory.

Photo by Joe Belcovson, Multimedia Services manager.

Salk Receives Worldwide Media Attention

SALK RECEIVED SIGNIFICANT MEDIA attention in August, beginning with worldwide coverage of a very recent discovery in **Ronald Evans**' lab. The study offers strong evidence for the potential health benefits of exercise through a pill that can be taken orally.

His lab's research demonstrated the power of two experimental drugs: One tricked the body's muscles into thinking they had been exercised, while a second dramatically boosted endurance by more than 70 percent when combined with exercise.

While this research focused on a particular gene in mice, which is also conserved in humans, this amazing breakthrough may one day provide much-needed relief to those who cannot physically exercise as a result of trauma or disease. The *British Broadcasting Company* (BBC), the *New York Times,* ABC's "World News Tonight" and NBC's "Nightly News" and others covered the study.

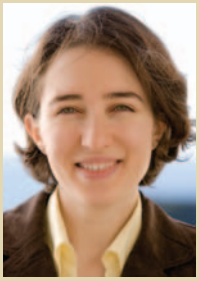
Inder Verma's lab also received strong coverage when NBC aired a story featuring a study that uncovered the molecular mechanisms behind allergies. This finding raises renewed hope for the development of therapies to treat hypersensitive allergic diseases, including hay fever.


Ronald Evans


Inder Verma

Tatyana Sharpee Honored Three Times in 2008

TATYANA SHARPEE, AN ASSISTANT professor in the Salk Institute's Laboratory for Computational Biology, has been named a 2008 Searle Scholar. The honor comes with a $300,000 award paid over three years in support of her research titled "Computational Principles of Natural Sensory Processing."


Tatayana Sharpee

The Searle Scholars Program supports scientists who have demonstrated innovative research with the potential for making significant contributions to biological research over an extended period of time.

In August, Sharpee received a Career Developmental Award from the Ray Thomas Edwards Foundation, which honors early career scientists with $150,000 paid over three years. She was also named an Alfred P. Sloan Research Fellow earlier this year. The fellowship includes a $50,000 grant paid over two years. The Sloan Research Fellowships support the work of exceptional young researchers often at pivotal stages in their work.

Sharpee, who is interested in how the brain processes information, is an authority on applying information theory to parse the code used by neurobiological systems to handle widely varying inputs. Neurobiologists' perennial quest centers on deciphering how the brain codes and processes information.

Sam Pfaff, Gage Lab Partner with Reeve Foundation

SALK'S SAMUEL L. PFAFF, A PROFESSOR in the Gene Expression Laboratory with expertise in motor neuron development and stem cell biology, has partnered with the Christopher and Dana Reeve Foundation to be a lead member of its International Consortium on Spinal Cord Injury.

Fred H. Gage's lab at Salk will also work with the Consortium as it expands its focus to the study of human embryonic stem cells in injury and repair. Gage will also oversee a stem cell core laboratory that will serve as infrastructure for the research network.

At Salk, Pfaff concentrates on the embryonic development of motor neurons – cells that transmit signals from the brain or spinal cord to muscles throughout the body to generate movement. Recently named a Howard Hughes Medical Institute investigator, Pfaff has a long history with the Reeve Foundation as a member of its Science Advisory Council, which oversees the Individual Grants Program.

Pfaff and his colleagues have been seeking answers to their questions via mouse and human embryonic stem cell research. Further, they have been using mouse genetics to study the underpinnings of the neural network known as the central pattern generator (CPG), which generates the coordinated and rhythmic firing of motor neurons needed for walking.

"Dr. Pfaff's expertise in the embryonic development of the spinal cord will add significant value to our research enterprise," says Susan Howley, executive vice president for research at the Reeve Foundation. "The spinal cord is so complex that the role of stem cells in repair and regeneration has to be considered within the context of what we know about the uninjured and injured spinal cord."


Samuel L. Pfaff (top) and Fred H. Gage

Salk Receives Grant from Foundation for Prader-Willi Research

THE SALK INSTITUTE AND THE FOUNDATION FOR PRADER-WILLI RESEARCH (FPWR) have created a partnership that will foster new research to study a rare genetic disorder that thwarts appetite regulation and leads to extreme obesity.

FPWR's initial $50,000 grant will fund a collaborative effort between three Salk Institute laboratories to study Prader-Willi syndrome (PWS), a disorder that occurs in approximately one out of every 15,000 births regardless of gender or race. Individuals with PWS lack the normal hunger and satiety cues, and constantly crave food.

Without continual supervision, those with Prader-Willi eat excessively and risk becoming extremely obese. Scientists believe it is caused by the loss of genetic material on chromosome 15. The research performed by the Salk investigators, **Wylie Vale, Paul Sawchenko** and **Marc Montminy,** will focus on understanding why appetite is not properly regulated in PWS.

Arabidopsis Takes Root

Plant Biology Laboratory celebrates 25 years of discoveries centered on a small, unassuming weed

THERE REALLY WASN'T ANY REASON FOR Detlef Weigel to believe the experiment would work. By the summer of 1994, studies of Arabidopsis thaliana, the lab rat of plant biology, were still in their infancy. Although his lab at the Salk Institute had identified a gene that was involved in causing the plant to flower, no one up until that point had ever attempted what his postdoc was suggesting.

The research team hypothesized that if they transferred the LFY gene into poplar, they would genetically alter the tree and cause it to flower much faster.

"I thought this was just too outlandish," Weigel says. "Trees are so different from Arabidopsis and I thought it simply wouldn't work."

They tried it anyway, and what they discovered not only boggled Weigel's skeptical mind, but also captured the attention of the media and the entire plant biology world.

After the team's first experiment, and several others that followed, the tiny poplar stems began to sprout flowers well ahead of their normal time, some while still in the Petri dish.

Poplar trees normally take 10 years to flower. Weigel's stems flowered in just a few months.

"At that point we all realized that this was a completely amazing finding," Weigel says. "It was almost too much to hope for, but it was the ultimate dream come true."

Published the following year in *Nature,* the study was recognized as a major breakthrough among plant biologists because it was the first demonstration of how scientists could take developmental control genes from Arabidopsis and put them to work in completely difference plants. If the experiment worked in poplar, why not apply it to agriculture?

The breakthrough led to collaborations with **Joanne Chory,** now professor and director of Salk's Plant Molecular and Cell Biology Laboratory. Together, their labs developed a technique called activation tagging, which today is widely used to identify new plant genes. Their work also eventually led to the discovery of FT, a second gene that works in conjunction with LFY to induce flowering.

Joanne Chory

> "... molecular biology and plant transformation revolutionized plant biology ... the first Arabidopsis transgenic plants were made, which allowed scientists to think about a whole different kind of experiment..."

These are just some of the major discoveries by Salk's Plant Biology Laboratory, which will celebrate its 25th anniversary during a two-day symposium in October. The event is expected to reunite more than 100 scientists, postdocs and donors who contributed to landmark findings over the years.

Chief among the lab's earliest contributors is The Samuel Roberts Noble Foundation, which provided the start-up funds for Salk's Plant Biology program in 1983 and continued to support it for 15 years. Former Salk President Frederic de Hoffmann spearheaded the search for funding and hired the program's first scientist, **Chris Lamb.**

The timing couldn't have been better. Salk got in on the ground floor when Arabidopsis was just being studied as a reliable model organism for plant biology research.

The little mustard weed, which grows in wide-ranging environments all over the world, was shown to have a small genome and a fast generation time of about 6 to 8 weeks. This was perfect for research purposes, especially since many of its genes are conserved in agricultural plants such as wheat and corn.

"Chris had the vision for the program, and he was willing to take the risk on Arabidopsis really taking off," says Chory. "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 from before because we could now manipulate genes."

Detlef Weigel

Chris Lamb

Genetic Variation Studies

Chory joined the Institute in 1988 and brought a complementary perspective to plant research at Salk. While Lamb worked on plant pathogen interactions, Chory was interested in how plants perceive and respond to changes in their environment, particularly to light.

Stronger collaborations followed after Weigel joined the Institute in 1993.

Although they studied two different traits – Chory the emergence of seedlings from the soil and Weigel flowering time – both of these traits are influenced by light and are important for plants' fitness in the wild.

Following their work on the FT gene, they formed a joint program at Salk in 1998 to study genetic variation and adaptation using a collection of Arabidopsis strains from

around the world. Taking advantage of differences among these strains, they identified additional genes that are involved in enabling Arabidopsis to adapt to various environments.

More surprising, however, was their discovery of the roles played by the plants' light-sensitive photoreceptors themselves.

"Variation in a number of different photoreceptors caused changes in flowering time or the sensitivity of a seedling to light," Chory explains. "This was unexpected because most people thought proteins that influenced gene expression would be the cause of variation observed in wild strains. It turns out that it's subtle differences in the photoreceptors themselves that nature selects for.

"We were able to show that plants from northern latitudes, such as Sweden, were much more sensitive to light than plants from latitudes close to the equator," she says. "An Arabidopsis plant from the Mediterranean has desensitized these pathways."

The finding was important because it provided the first clues to how crops could be developed to adapt to challenging environments, while also boosting yield.

Similar studies were being done elsewhere, says Weigel, who is now at the Max Planck Institute for Developmental Biology. But at the time, he and Chory formed one of three leading groups around the world that was studying genetic variation at the molecular level—10 years before the subject became a hot topic in human biology research.

Among Chory's widely reported contributions is her lab's discovery that steroid hormones, called brassinosteroids, play an important role in plant growth and development. Genetic studies in Arabidopsis led to a new paradigm for how steroid hormones are perceived.

Her lab also found that brassinosteroids are a key element in a plant's response to light, allowing plants to adjust their growth to reach its light source or strengthen stems to support leaves. The potent hormone has applications in increasing yield in grain and fruit crops, and makes plants more resistant to drought and cold weather.

In contrast, reducing the naturally occurring steroid causes dwarfism. The idea that you can possibly control the height of grass, for example, drew strong attention from the media. *The New York Times Magazine* placed the finding at No. 2 in a June 11, 2000 story that ranked the Top 100 New Technologies. The headline read: "The Lawn That Never Needs Mowing."

Hunting for Missing Genes

All of these findings would not have been possible without studying plant genetics, Chory says. But they were conducted by studying one gene at a time to determine its function. That all changed beginning in late 2000 when a team of scientists around the world completed the Arabidopsis genome-sequencing project.

Joe Ecker, a leading plant geneticist and professor in Salk's Plant Biology Laboratory, was part of a team of multi-national scientists that helped sequence the plant's approximate 25,500 genes. Knowing the gene sequence now enables plant biologists worldwide to study the genome as a whole, he says.

Having the genome sequenced doesn't necessarily tell scientists each gene's function, however. But a major project in Ecker's lab recently funded with a $4 million grant is chipping away at this mystery. The long-term goal is to develop a database that describes the role and cross-function of all 25,500 genes through a network of researchers who will test mutant forms of Arabidopsis genes, a

Hundreds of Arabidopsis plants are grown in Salk's greenhouses for research by scientists in the Plant Biology Laboratory.

standard trick to determine their function.

"What we'll be able to start to see is an interconnection of the biology that you might not ever test if your particular lab only works on [response to] light," Ecker explains. "But if you can see that someone else found that the mutation affects another process, then you can say, 'I found a new connection.' The idea is to integrate the biology through the gene networks."

can then apply that knowledge to other plants like soybean or wheat."

Of course, being able to develop a genetic reference book for Arabidopsis assumes that the structures and functions of all the genes in the genome are known. But this isn't the case, Ecker says. Although plant biologists now have the genome, Ecker estimates that the exact structures for many of the genes are still waiting to be discovered.

Marc Montminy, professor of the Clayton Foundation Laboratories for Peptide Biology, who is interested in deeper research of protein-DNA interaction.

Also, the same technique Ecker's lab developed to pinpoint bacterial T-DNA insertions in Arabidopsis has been applied in a collaborative study to look at integration of the HIV/AIDS virus into the human genome.

> "Using Arabidopsis as the reference plant, the functions of its genes can be determined by studying their mutations. By having a complete genetic guide to Arabidopsis, we can then apply that knowledge to other plants like soybean or wheat."
>
> – JOE ECKER

The Genomic Analysis Laboratory's massive collection of Arabidopsis seeds.

A valuable and highly used resource for gene testing is readily available through the Salk Institute's Genomic Analysis Laboratory, which preserves a massive collection of Arabidopsis gene mutations, copies of which are used for research worldwide.

Just steps away from Ecker's office is the temperature-controlled room that houses what is perhaps the world's largest bank of Arabidopsis seeds that represent 400,000 insertions, or points on the genome where bacterial "transfer-DNA," or T-DNA, entered and caused a unique gene mutation.

Ecker developed the sophisticated technique that enables his lab to identify the exact location of each insertion point. In 2003, *Science* published the revolutionary study, which has since been cited more than 1,100 times and is ranked No. 14 among ISI's highly cited, "Super Hot" papers.

"The plant biology world knows Salk because the Institute is linked to these seeds," Ecker says. "But again, by using Arabidopsis as the reference plant, the functions of its genes can be determined by studying their mutations. By having a complete genetic guide to Arabidopsis, we

How is this possible? Some genes are expressed at very low levels and their signals can't always be detected. To hunt them down, Ecker's lab developed powerful high-throughput DNA sequencing technology. The new-generation sequencing machine maps the precise location of the missing genes by isolating their byproduct: RNA.

"By performing a deep sequencing of the transcriptome, we're asking the genome to tell us, 'Where are your genes?' " Ecker says.

This is an ongoing project in his lab, but others in the scientific community have taken notice of this new tool.

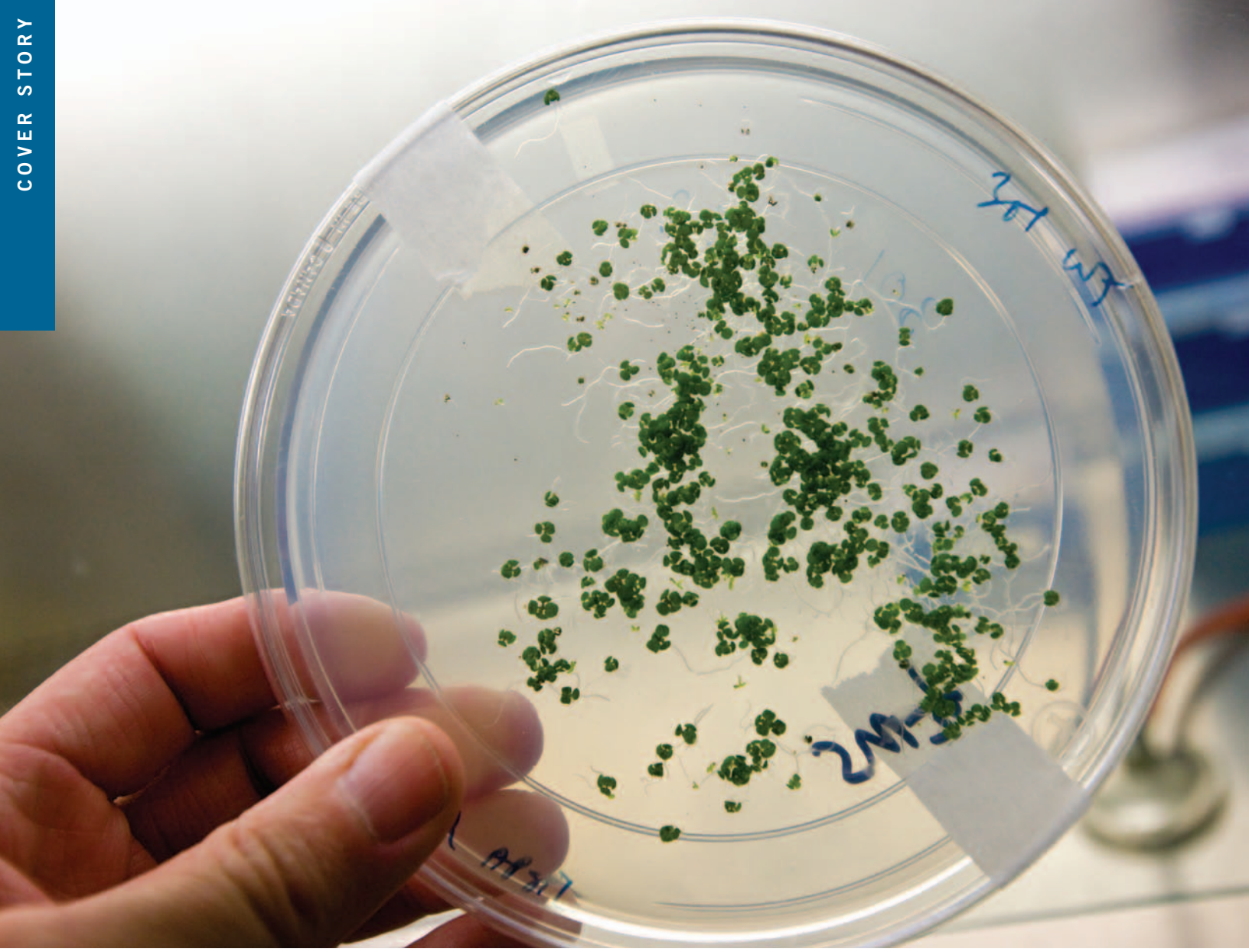
Applications to Human Biology

Ecker's sequencing technology, for example, 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 other sub-DNA molecules contribute to the development of tumors and disease.

This has led to additional interdisciplinary collaborations at Salk between Ecker's lab and **Fred H. Gage,** professor of the Laboratory of Genetics, and

"The biology that's carried out by plants can have a direct impact on understanding human biology because genes are genes, proteins are proteins," Ecker says. "If I can understand the function of a particular molecular transporter in plants, for example, it probably does the same thing in humans."

Jim Umen



Brassinosteroid mutant seedlings of Arabidopsis in a Petri dish.

Connections to human biology are also being made in Salk studies of even lower plant life. Assistant professor **Jim Umen's** research of the microscopic alga Chlamydomonas reinhardtii revealed that the retinoblastoma protein (RB), which works as a tumor suppressor in mammalian cells, also regulates cell size and division. Further research in his lab found that two more proteins (DP and E2F), found in both his alga model and in humans, work in concert with the RB protein to perform this size-regulation function, the loss of which is one property that is shared by cancer cells.

More in-depth research of the alga's flagella, or tiny appendages that enable the organism to swim, could answer additional questions related to human disease. Remarkably, most human cells have similar appendages called cilia whose malfunction is linked to a growing number of genetic disorders such as polycystic kidney disease, retinitis pigmentosa and male infertility.

"When Chris Lamb came back for a visit, he was so pleased and amazed to see how plant biology at Salk had gone through a generation of biologists studying individual genes to now high-throughput plant biology," Ecker says. "It's evolved into a totally different form of research from when he started it."

Noble Foundation Plays Key Role

In 1982, Lamb's laboratory in Oxford was beginning to gain international attention for its research on how plants defend themselves against pests and pathogens when Salk approached him with the offer to start the Plant Biology program. His lab had made progress at the physiological and biochemical levels and Lamb was now looking to apply the emerging plant molecular biology technology to his work.

"This seemed a fantastic, if somewhat risky, opportunity," said Lamb of his decision to come to Salk. "Fantastic because of Salk's great prestige and reputation in biomedicine and neurobiology. Risky, but exciting, because I would be starting something from ground zero."

Despite offers from other institutions, he decided to take the risk. At first, Salk's Plant Biology Laboratory was split between two locations: One group worked in a downtown La Jolla building on plant disease resistance, and a second worked on a new project on monoclonal antibody approaches to characterize functions at the plant cell surface.

The split was short-lived as the program grew from an initial team of six researchers to 12 by 1985, then again to about 20 researchers by 1988. As space became available at Salk's main campus, the entire

> "This is definitely the most collaborative place I've been, for sure. Juan Carlos [Izpisúa Belmonte]'s research in limb regeneration and his questions about how to keep stem cells in an undifferentiated state, for example, is similar to what we're asking in plants."
>
> – JEFF LONG

laboratory was combined under one roof in 1988.

There's no question that The Noble Foundation played a crucial role in establishing plant biology at Salk, Lamb says. It contributed significantly to start-up costs and an initial five-year grant for Lamb. The agreement also called for the creation of a small plant cell biology program in Ardmore, Oklahoma, the foundation's headquarters and where Lamb served as an advisor.

By 1987, that program eventually morphed into the foundation's new Plant Biology Division, which was directed by Lamb's Oxford colleague and recruit Richard Dixon. The strong synergy between both groups led to a second (in 1988) and third (in 1993) five-year funding cycle that allowed the Salk Institute to expand the program and hire Chory and Weigel.

"Salk's proven reputation, along with joint postdoctoral fellowships, yearly retreats and mentorship for some of the young scientists, helped provide fertile ground for the Noble Foundation's Plant Biology Division to grow," said Noble Foundation President and CEO Michael A. Cawley.

"Both organizations and the scientific community have benefited greatly from this collaboration, which has spanned more than 30 years and will continue for as long as man poses questions about the world around him."

The Samuel Roberts Noble Foundation initially focused on funding agriculture in an attempt to rejuvenate the state's industry following the Dust Bowl of the 1930s and World War II. It is named after the family's patriarch, a farm merchant who acquired land as farmers left the area. The land was later found to be rich in oil and natural gas.

Former Salk President Frederic de Hoffmann played a key role in securing funding from the foundation when he identified the potential for great collaboration between the two organizations. He had a strong relationship with a foundation board member and believed Salk's Plant Biology program could provide a modern scientific approach to the foundation's historic interest in agriculture.

He was right. The synergy led to the growth, success and many discoveries that are still proving to be vital.

"In hindsight this was kind of the vision, but I don't think anyone imagined it would be on this scale or with this impact," says Lamb, who left Salk in 1998 and is now director of the John Innes Centre in Norwich, England.

Chory agrees.

"They made a big difference by contributing

to Salk. The program exists today because of funding from the Noble Foundation," says Chory, a Howard Hughes Medical Institute investigator since 1997. "Noble Foundation funding allowed the Salk to recruit plant scientists to an environment populated by some of the world's most innovative biomedical scientists. The high standards of our colleagues influenced our program tremendously."

Several organizations and individuals throughout the years have also made significant financial contributions to plant biology at Salk, including the Rockefeller Foundation, the Seaver Institute, the Mary K. Chapman Foundation, the Henry L. Guenther Foundation, among many others.

Most recently, Salk's donor-funded Innovation Grants Program has provided a fresh injection of funding for the development of new investigative techniques and novel discoveries that otherwise would not be funded by traditional government sources.

Collaborative Environment

Assistant professor **Jeff Long** is among Salk's plant biologists who has benefited from the Innovation Grants Program since arriving to the Institute in 2003. A developmental biologist who studies embryogenesis of Arabidopsis, Long studies the TOPLESS gene, so named because of its power to regulate the development of a shoot or a root structure from a seedling.

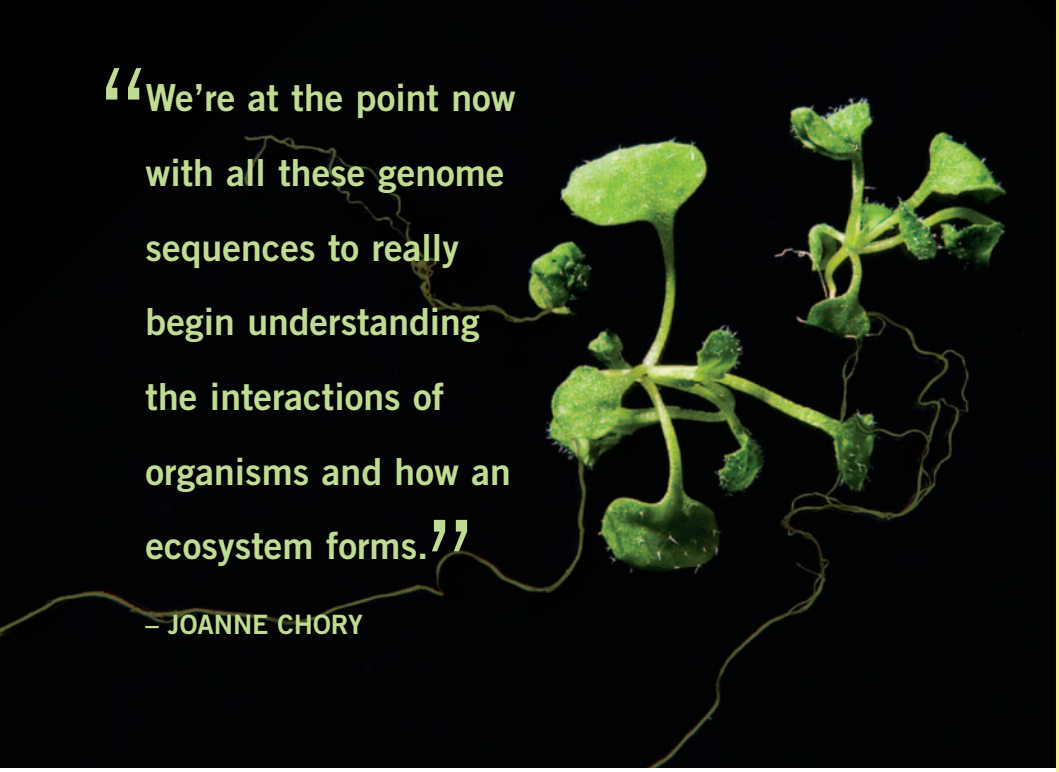
His lab has learned how to control the function of this gene, which ultimately can serve to manipulate plant structure and agricultural output, he says. But having access to Salk scientists from various disciplines is a major benefit that helps him look at plant biology from a new perspective.

"This is definitely the most collaborative place I've been, for sure," Long says. "**Juan Carlos [Izpisúa Belmonte]'s** research in limb regeneration and his questions about how to keep stem cells in an undifferentiated state, for example, is similar to what we're asking in plants.

"Those types of conversations, along with stem cell meetings at Salk, are great because they make me think outside of plants and look into new experiments by using similar ideas other stem cell scientists are using," he says.

Further collaborations have developed between the Plant Biology Laboratory and **Joseph Noel,** director of the Jack H. Skirball Center for

Salk scientists identified the Arabidopsis genes involved in flowering time in the mid 1990s.



Chemical Biology and Proteomics at Salk. His lab has applied its study of the chemical factories that give rise to vital molecules such as phytoalexins – natural forms of anti-fungal and antimicrobial compounds found in many plants, including tobacco and henbane.

Using structure analyses, Noel and his colleagues discovered that changing only nine of its 550 amino acids shifts the production from tobacco-specific phytoalexins to the henbane versions and vice versa. Studies like these are helping the Noel lab better understand how plants adjust their chemical cocktail to adapt to their changing environment and may provide the necessary tools to fine tune the production of natural and environmentally friendly fungicides and pesticides.

Within the Plant Biology lab itself, the lack of dividing walls has historically been a major contributor to the collaborative environment. In the early 1990s, they functioned on the "balloon principle," Weigel says. If Chory and Lamb hired more people, then his space would shrink and vice versa.

Today, it's not much different. The labs have an open design, allowing scientists to tap into the expertise of others around them – a major advantage when you're starting a new lab, Umen says.

In the end, it comes down to the basic principle of freely sharing knowledge with the intent to propel science forward. If the last 25 years of discoveries in plant biology has taught scientists anything, it's that the humble Arabidopsis plant has provided its fair share to that knowledge base.

And it will continue to do so, say Salk plant biologists, since what's been discovered so far equates to approximately 10 percent of what they may ultimately learn from Arabidopsis.

"Understanding how plants grow and alter their growth is important and I think Salk has made a number of contributions in this area," Chory says. "We're at the point now with all these genome sequences to really begin understanding the interactions of organisms and how an ecosystem forms.

"To me, the future is going to be studying organisms in the context of their environment – environmental genetics, and plants will play a key role in that."

Joseph Noel

Fast Facts

Joanne Chory

professor and director, Plant Molecular and Cell Biology Laboratory

- Investigator, Howard Hughes Medical Institute
- Member of the National Academy of Sciences
- Fellow of the American Academy of Arts and Sciences
- Fellow of the American Association for the Advancement of Science

Joseph Ecker

professor

- Member of the National Academy of Sciences
- Recipient of the John J. Carty Award for the Advancement of Science
- Recipient of the American Society for Plant Biology Martin Gibbs Medal
- Scientific American 50 Research Leader of the Year

Jeff Long

assistant professor

- Ray Thomas Edwards Foundation Career Development Award
- Helen Hay Whitney Postdoctoral Fellowship

Jim Umen

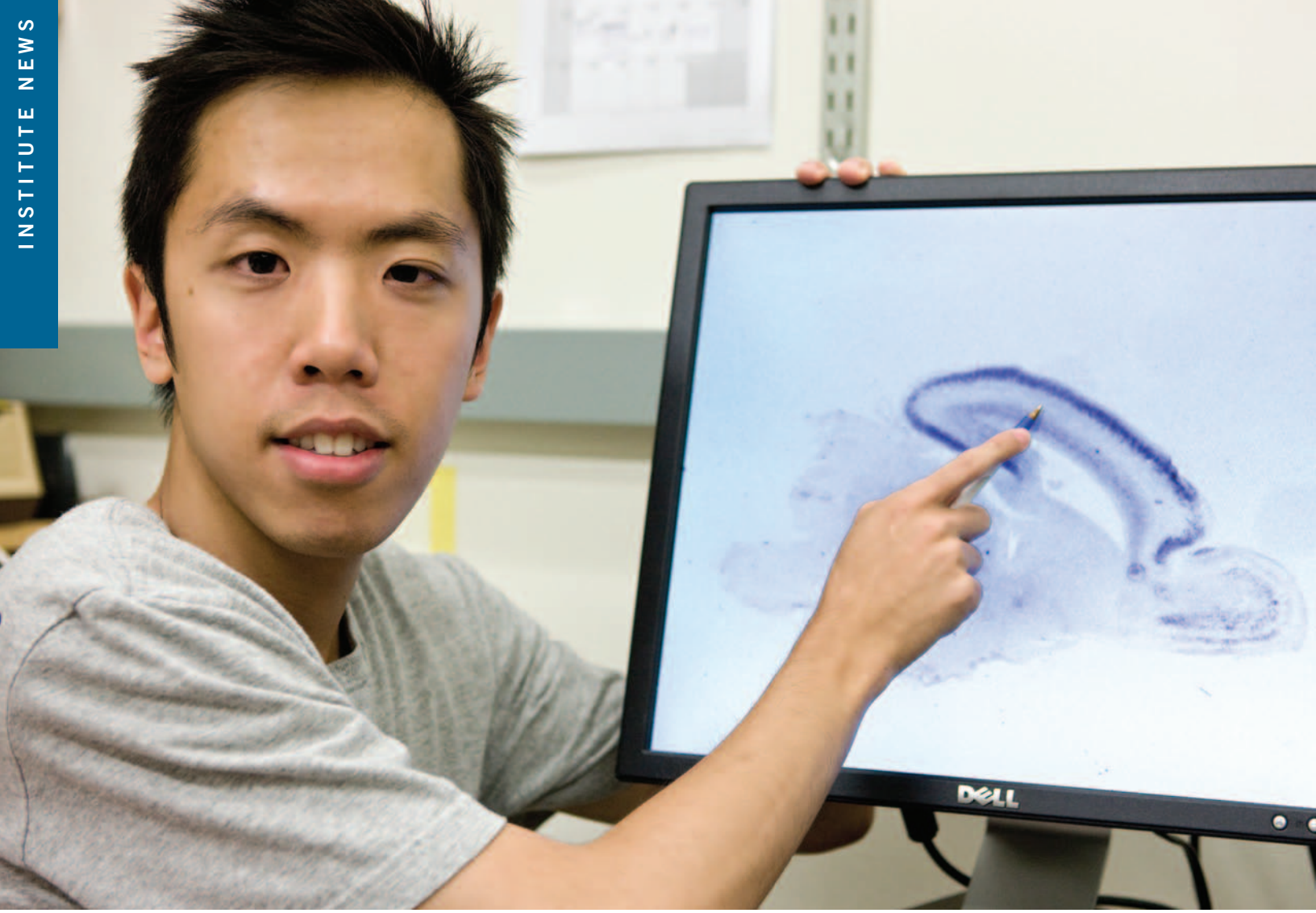
assistant professor

- NIH Postdoctoral Research Fellow
- NSF Predoctoral Training Fellowship

Joseph Noel

professor, Jack H. Skirball Center for Chemical Biology and Proteomics

- Investigator, Howard Hughes Medical Institute
- NIH Postdoctoral Fellow
- National Science Foundation Chemistry Postdoctoral Fellow



William "Will" Mak

Scholars Give Up Summer in New York for Lab Training in La Jolla

IN THE NEW YORK CITY BOROUGH OF BROOKLYN, SUMMER was hot and muggy, as usual. Riding the crowded subway or bus to work during the week, commuters worried about the impending transit fee hike. On Sundays, some of them perused the outdoor flea market to shop for vintage wares and munch on pupusas or pizza by the slice.

These could have been the recollections of **William ("Will") Mak** and **Diana Kachan,** two Brooklyn residents who recently graduated from the City University of New York (CUNY) with plans to attend medical schools in the fall.

But they weren't.

Instead, Will and Diana came to work at the Salk Institute for the summer, after receiving the coveted Jonas E. Salk Scholarships. The scholarships were created in 1955 at the request of the late Dr. Jonas Salk, an alumnus of CUNY, when the city of New York wanted to celebrate his discovery of the Polio vaccine with a ticker-tape parade. He suggested that the money might have a better use.

The Salk Institute's participation with the scholarship program began in 2005. In addition to helping with medical school tuition, the students receive a salary and an allowance for living expenses while they perform research for eight weeks during the summer.

Diana and Will came to Salk from mid-June through the first week of August to work on projects that, for each of them, held personal importance.

A native of Belarus, the landlocked Eastern European country where her parents still live, Diana, 28, moved to New York City in her early 20s through a work-exchange program and began taking courses at CUNY, where her interests turned first to chemistry, then physics, and ultimately biology.

"I just loved it," says Diana, who remembers considering a career in medicine many years earlier after volunteering at an orphanage for children who were handicapped from radiation exposure after the Chernobyl explosion. "[Biology] wasn't just about memorization and facts, but about real life. It wasn't until after I came to the U.S. that I realized this was something I want to do."

Diana is now enrolled in the M.D./Ph.D. program at the University of Miami School of Medicine. She plans to pursue both epidemiology and neurology. At Salk, she learned a theoretical approach to neurology, guided by **Tatiana Sharpee,** assistant professor in the Computational Neurobiology Laboratory.

Imagine that neurons are like rubber bands. If one end is anchored and the other stretched, then released, the "snap" that occurs is similar to the way a neuron receives input and fires its own signal down the chain. The snap looks like a spike when it is plotted on a

Diana Kachan

graph, and so they are called spikes.

Scientists understand the physiology of neurons and how they create a spike, but what actually determines a spike, and what different patterns of spikes mean, is still unclear.

This is the focus of Sharpee's work. Using data collected by collaborators at the University of California, San Francisco from retinal cells and the relay cells in subcortical regions, she used a computer code to analyze how input spikes are transformed into sequences of output spikes.

Diana came to the lab with no experience in theoretical neuroscience, and only a little bit with computer programming. But after two weeks of reading computer programming textbooks at her desk, she managed to make some sense of things.

"See this portion of the code here?" she asked, scrolling down more than 500 lines on her computer screen. To the untrained eye, it looked like an e.e. cummings poem. "This is the section that I'm really interested in."

Sharpee had hoped for an acute response such as this.

"I think it is important to expose students to computational and theoretical techniques, even if these techniques are not going to be the main focus of the their future research," she said. "Besides, Diana brought a fresh approach to our research.

"There's a practical side to this arrangement," Sharpee admits. "I had projects that I needed to get done. But also, in the field of neuroscience we are working toward the goal of merging theoretical and experimental techniques. We need a common language to do this, and by giving Diana theoretical exposure, this may help in the future."

Analyzing Gene Sequences

Working in Professor of Molecular Neurobiology **Dennis O'Leary**'s laboratory alongside postdoctoral fellow **Todd Kroll,** Will's project focused on understanding whether a section of genetic code is responsible for development of the brain region that controls movement, including vision and balance, in mice.

"My research in New York was more behavioral than this," Will explained. "The project focused on measuring eye movement in patients to understand how stimuli could grab their attention. But my work in Dr. O'Leary's lab is much more 'wet' than what I'm used to."

He began at the computer, analyzing gene expression patterns that are published online, finding one that is complimentary to another gene that specifically identifies the visual cortex. He then cloned the new gene into a plasmid vector so that it could be used to make a probe that will identify where this gene is turned on. Finally, he used the probe he generated to analyze thin brain sections with a staining technique that allowed him to see where the gene "appeared" in the overall developing brainscape.

"I wish that I could have done something like this for the summer when I was his age," admitted Kroll, who has worked in the O'Leary lab as a postdoctoral fellow for six years.

At the lab bench pouring careful measurements from bottles of buffer solution, or at the cryostat tissue preparation machine, Will, a preppy young man, appeared slightly slouched, as though about to give himself a hug. This is because he was born with scoliosis, an S-shaped curvature of his spine that restricts some of his movement and causes him daily pain.

"When I was in high school, I had my lower lumbar spine fused," he explained. "At the time, it dashed my hopes of joining the NBA or becoming a football player, but I dealt with it."

He can joke about it now, but it was his traumatic experiences working with doctors as a child and young adult that led him to study at the New York College of Osteopathic Medicine. One day he hopes to work as an orthopedic surgeon, focusing on pediatrics.

His experiences as a scoliosis patient are also what led him to choose this project in O'Leary's lab.

"Perhaps one day the discoveries in this lab will lead to cures for spinal deformities, or ways to prevent them from happening in the first place," he ventured. "It's really exciting for me to think that I could say, 'I helped with that research.' "

Institute Friends Take 'Journey' Through Françoise Gilot's Exhibit and Life

IT'S SAFE TO SAY THAT JONAS SALK WAS LUCKY **Françoise Gilot** had a fascination for stylish architecture. That's what hooked her into agreeing to a personal tour of the Salk Institute by its founder in 1969.

The way she described their initial encounter in an interview with journalist Charlie Rose, Gilot wanted nothing to do with scientists. What could an artist possibly have in common with a researcher? A lot, she would find out – and lucky for Gilot, Salk's natural curiosity fed his desire to get to know the quiet French woman he had met days earlier over lunch. His persistence would lead to a cross-Atlantic courtship and their eventual marriage of 25 years.

This is just one of many stories shared during the opening reception for "The Floating Paintings 1980-1986, Works by Françoise Gilot," an exhibit of the artist's work currently on display at the Institute. Through slides of her artwork and video clips, Dr. **Mel Yoakum,** curator and director of the F. Gilot Archives, told the fascinating story of Gilot's life as a young artist who, against her father's wishes, dropped out of law school to pursue painting.

Along the way, she engaged in a much-publicized and combative 11-year relationship with Pablo Picasso, before striking out on her own to become an internationally renowned artist and best-selling author. A group of more than 160 members of the Salk's President's Club, distinguished faculty and friends of the Institute filled the Frederic de Hoffmann Auditorium in June to hear Yoakum's presentation, entitled "Francoise Gilot: An Artist's Journey," which was followed by a reception and viewing of the exhibit.

Each of the nine pieces on display is part of a series Gilot painted in the early to mid 1980s using thin layers of acrylic paint on unstretched canvas. They were intended to "float" on the wall and demonstrate powerful color palettes reminiscent of theater backdrops.

To create the pieces, each of which measures about 100 inches by 100 inches, Gilot laid the large canvases on the floor of her New York studio and used brooms and rollers to apply the paints – creating geometric motifs with her signature dramatic use of color.

Detail of *A Day's Journey* (1981), and *Bliss* (1984) in the background – both acrylic on canvas, 105" x 91" and 97 5/8" x 71 3/4", respectively.

The Hawk (1943) oil on canvas, 51 1/4" x 35", private collection.

However, gauging her progress wasn't as easy as simply taking a few steps back from an easel, especially for the 5-foot, 4-inch artist. Instead, Gilot used a stepladder placed next to the painting to get a bird's eye view, Yoakum said.

"It's like the Stairmaster for artists because all day long she would go up and down the stairs to get a view of her paintings," he said.

By 1986, Gilot became allergic to the acrylic paint and was forced to abandon the series. As a result, the pieces on display at the Institute represent the last of her works created in that particular medium.

Life With Picasso

That period in her career coincided with a sense of freedom Gilot experienced after having resolved the legal acknowledgment of the two children she had with Picasso – Claude and Paloma. Since Picasso died in 1973 without ever having written a will, the estate, including the inheritance rights for Gilot's children, was not officially settled until 1985, Yoakum said.

It was reminiscent of another period in the mid 1960s when Gilot painted birds and open windows to reflect the freedom she felt after publishing "Life With Picasso," a book that described her observations of the complex Spanish artist during their time together. Picasso responded with three lawsuits, each of which

resulted in victory for Gilot and her publisher.

"Pablo called Francoise and told her, 'I don't approve of what you did, but you know how much I admire a winner,' " Yoakum said.

The phone call in the autumn of 1965 was the last conversation the two ever shared.

Birds are a reoccurring motif in Gilot's paintings, Yoakum explained. However, the environment in which they are depicted serve as strong metaphors for the message she conveys.

A Gilot painting Yoakum shared from the early 1940s during the German occupation of Paris, for example, displays a hawk with its wing tip stretching high over its head, but just short of reaching the tip of the Eiffel Tower that can be seen outside the latched window in the background.

"The hawk represents the German forces, but the Eiffel Tower, which is the symbol of Paris, is higher than the hawk's wing, which is saying: 'We will prevail even though our current situation is locked,' " Yoakum explained.

His presentation also included slides of other paintings and photographs from the early 1950s that evoked the growing strain in Gilot's relationship with Picasso. The pair met in 1943, the same year of Gilot's first exhibit in Paris when she was 21 and he was 61.

Yoakum described Gilot's life with Picasso as a "whirlpool" that included an undercurrent of competitiveness between the two. Yoakum best described this with another story of when a young Claude was trying to get into the studio where his mother was busy painting behind the closed door.

Twice he knocked relaying sweet messages to Gilot who acknowledged him, but wouldn't let him in. Playing to her competitive spirit, Claude succeeded on his third attempt when he knocked again and said:

" 'Momma, I think your paintings have fantasy in them … I think they're better than Poppa's.' "

During that period in her life, though, she was surrounded by the legendary artists of the day and developed strong friendships with Henri Matisse, Georges Braque and Jean Cocteau. The art-focused conversations she witnessed between Picasso and Matisse would eventually serve as the inspiration for her second book, "Matisse and Picasso: A Friendship in Art," published in 1990.

In 1953, Gilot abruptly ended her relationship with Picasso and two years later, she married Luc Simon, a French artist with whom she had a third child, Aurelia. They shared love and passion, Yoakum said, but lacked the dialogue Gilot experienced with Picasso. The marriage was short-lived and by the early 1960s, Gilot was working on the manuscript for "Life With Picasso," as well as a group of paintings that became known as her Labyrinth series.

During one of her visits to the West Coast in 1969 to make lithographs, she met Salk and ultimately agreed to his invitation to a personal tour of the Institute. They married the following year while Gilot split her time between her studios in Paris and La Jolla.

Gilot and Salk traveled extensively throughout their marriage and together created a vital international presence in art circles and the scientific community, Yoakum said. Although Gilot returned to New York after Salk's death in 1995, she remains close to the Institute as an active member of the International Council and by serving as the honorary chair of Symphony of Salk for the last 13 years.

Her paintings have also been featured as the signature artwork for each of the concerts since the event's inception in 1996.

Gilot's journey as an artist continues to this day, Yoakum said. She remains active in the art scene through her exhibits in galleries throughout Europe and the United States. She also recently began a new series of paintings, which Gilot describes as some of her best work to date because she's now painting with more ease and spontaneity – something that Yoakum believes she also found in her marriage with Salk.

"I think what Françoise found was the dialogue that she had earlier (with Picasso), but without the combativeness. Jonas and Françoise experienced fame early in their careers and one might think that having that would be a really solid platform to continue the rest of your work," Yoakum said.

"However, creativity is an experiment, it's trial and error – and with the loss of anonymity, there is also the added scrutiny. This creates an additional burden that they had to carry," he said. "I think they both understood that very well, and one of the many characteristics that they each brought to their relationship was their ability to understand that in each other."

From left: *A Night's Journey* (1981), *Sun Emblem* (1980), and a partial view of *A Day's Journey* (1981) – all acrylic on canvas, 105" x 91"

Want to be notified of similar Salk events in advance? E-mail us at: info@salk.edu

Institute Launches

Scientists' Presentations and Twist of Fate Endear Dan Lewis to Salk

DAN LEWIS IS THE FIRST TO ADMIT that it didn't take much to convince him to get involved with the Salk Institute six years ago.

It started with some encouragement by Joe Kalman, his business partner at consulting firm Booz Allen Hamilton and longtime Salk supporter, followed by a few meetings at the Institute where Lewis heard Salk scientists explain their groundbreaking research. That's really all it took to ensure his connection to the Institute took root, he says.

"There's simply no substitute for having these remarkable people talk about their work and why they are doing it," says Lewis, who made his first contribution to the annual fund in 2002 and has since become a member of Salk's International Council – a group of distinguished community and corporate leaders who serve as Salk ambassadors around the world.

So when the Institute launched the Chairman's Circle earlier this year (a new leadership giving level of the President's Club starting at $25,000), Lewis was among the first to increase his commitment.

Unrestricted gifts of this level are crucial for Salk because they provide scientists with the financial flexibility to expand their research into promising new areas of discovery – studies that aren't typically funded by traditional government resources. They also help equip Salk laboratories with today's latest research technology and train young scientists.

"It was my belief in what you guys do, first and foremost," says Lewis of his decision to become a charter member of the Chairman's Circle. "But it's also a continuing desire to have a connection with Salk."

That connection took a new turn last year when doctors diagnosed Lewis with chronic myelogenous leukemia (CML), a common, slow-growing cancer of the white blood cells. His appreciation for Salk deepened even further when he learned that Gleevec, the drug he now takes to treat the condition, was developed from basic research conducted at the Institute.

More than 20 years ago, **Tony Hunter,** professor in the Molecular and Cell Biology Laboratory, discovered a new group of enzymes called tyrosine kinases, which regulate vital cell functions such as growth and development. Today, 90 human tyrosine kinases are known – half of which are involved in cancer.

CML is caused by a change in the genetic code in bone marrow cells, which leaves a key tyrosine kinase stuck in the "on" position. This triggers a chain reaction that ultimately causes the body to make too many white blood cells. Gleevec directly binds the enzyme and shuts it off. There are more than 20,000 CML cases in the United States and about 4,600 new cases are diagnosed each year.

"This is an amazing drug," Lewis says. "When you can actually speak to Tony Hunter, the researcher whose work led to the number one cancer drug in the world … that endeared me to the Institute."

Lewis's interest goes beyond cancer research at Salk. He's also a firm believer of basic research that's linked to age-related diseases and says continued efforts and support of science need to be made to ensure treatments and cures. His belief is echoed by the Salk Institute, which has included the Center of Aging and Mechanistic Analysis Research (CARMA) as part of its scientific strategic initiatives.

"I think research in brain diseases is a must, which was Francis Crick's passion. Parkinson's and Alzheimer's are tremendously debilitating diseases, and obviously everybody knows someone who has one or the other of these diseases," Lewis says. "[Research] is needed to improve the quality of life because people are living longer, and like CML, these diseases have an increase of incidence rate with age."

Dan Lewis

> "When you can actually speak to Tony Hunter, the Salk researcher whose work led to the number one cancer drug in the world … that endeared me to the Institute."
>
> – DAN LEWIS

Chairman's Circle

Life-Changing Research Seals Marna Whittington's Commitment

FOR ANYONE CONSIDERING A contribution to the Salk Institute but hasn't fully made up their mind, Marna Whittington offers this piece of advice: "Go visit the laboratories and talk to the scientists. Their passion, the technology and the environment in which they have the ability to improve our quality of life will make all the difference."

Whittington speaks from experience. She was first introduced to the Salk Institute three years ago when she was invited to meet some of its senior scientists and hear about their research. The experience and learning about some of the groundbreaking discoveries at Salk was enough to convince Whittington that becoming closely involved with the Institute was the right thing for her to do.

Today, she is a member of the Salk Institute's Board of Trustees and, most recently, joined a group of supporters who are charter members of the Chairman's Circle, a new Annual Fund giving level launched earlier this year for gifts starting at $25,000.

"I believe in the work that's being done [at Salk]. The environment is right for significant breakthroughs. With the increasing difficulty in funding high-quality research, the private sector needs to step up," she says.

Whittington had a few peripheral connections and interests in scientific research before deciding to commit her time to the Institute.

She received her doctorate degree in Quantitative Methods from the University of Pittsburgh, the same educational institution where Jonas Salk led the Virus Research Laboratory beginning in 1947. She was also the Chief Operating Officer for the University of Pennsylvania, where she was in charge of the medical and research facilities from 1984 to 1992.

And although her husband leads a healthy life today, he was diagnosed as a child with polio, the disease eradicated in 1955 by Salk's vaccine. The Salk Institute's research in post-polio syndrome was a natural interest for Whittington, but so was its work in cancer and diabetes, she says.

"We are all touched by people who are important in our lives and the Institute is working to find scientific solutions for their problems," says Whittington, who is managing director and CEO of the investment firm Nicholas-Applegate Capital Management.

"But you can't turn this research on and off. The research takes many years to develop. If we don't keep funding it, you can't necessarily come back in a year or two when the National Institute's of Health has more money and pick up where you left off," she says. "It's a long-term commitment."

Marna Whittington

Chairman's Circle Members

Mr. and Mrs. John Adler

Mr. Louis Borick

Mr. Arthur Brody and Ms. Phyllis Cohn

Ms. Linda Chester and Dr. Kenneth Rind

Mrs. Kathryn Colachis

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Dr. Marna C. Whittington and
Mr. Thomas Whittington

> "Go visit the laboratories and talk to the scientists. Their passion, the technology and the environment in which they have the ability to improve our quality of life will make all the difference."
>
> – MARNA WHITTINGTON

Clockwise from top: Guests at the 13th annual Symphony at Salk included Martha Dominguez (from left), sponsors Jean and Steve Hamerslag, Reza Jarrahy with his wife, actress Geena Davis, Mimi Guarneri, Rauni King and David Dominguez. Night falls as the San Diego Symphony plays. Jazz guitarist John Pizzarelli takes the stage. Standing: Rafael and Marina Pastor, Jahja Ling and Jessie Chang, Nancy Marlboro and Bob Coates; Seated: Linda Chester, Kenneth Rind, Jeri and Richard Rovsek. Guests enjoy supper alfresco.

Symphony at Salk Raises Record $690K for Research

MORE THAN 580 GUESTS AND MUSIC aficionados gathered at the Institute on Aug. 23 to attend the 13th annual Symphony at Salk where more than $690,000 was raised in support of scientific research and community outreach programs such as the Salk Mobile Science Lab and the High School Science Day.

Jazz vocalist and guitarist John Pizzarelli gave a memorable performance that demonstrated why has come to be known as a consummate entertainer when he crooned to the delight of the audience.

Playing several classic jazz standards, including selections made famous by Frank Sinatra, The John Pizzarelli Trio brought a whole new vibe to the Institute's annual fundraiser this year. Rounding out Pizzarelli's group was pianist Larry Fuller, bassist Martin Pizzarelli, and Tony Tedesco on drums.

The San Diego Symphony, led by returning guest conductor Thomas Wilkins, joined Pizzarelli on stage, starting off each set with moving pieces by Tchaikovsky, Rossini, Delibes and Bizet. This year's fundraiser also included a delicious supper specially prepared by guest chef Jeffrey Strauss, whose flair for presentation and taste has been enjoyed by U.S. Presidents and Hollywood stars alike.

'CEO' Group Gets Personalized Tour of Salk

A GROUP OF FORMER YOUNG Presidents Organization (YPO) members and their spouses recently received a private tour of the Salk Institute during their annual retreat that brought them to Del Mar.

During their half-day visit, the group was led through a program that included an architectural tour, a stop at the "The Floating Paintings" exhibit by **Françoise Gilot** and a view of the Institute's new Stem Cell Core facility.

"We all thought the core facility was just amazing and the architecture, of course, is very different and attractive," said William King, a 20-year member of the group, whose affiliates refer to themselves as the CEOs – short for Chief Executive Organization.

Salk professors **Inder Verma** and **Joe Noel** also presented before the group to explain their respective areas of research and to provide them with a better understanding of the Institute's mission.

Our annual retreat is meant to have an educational focus," King explains, "so it was especially interesting to hear Dr. Noel's perspective on the likelihood of personalized medicine in the future. The tour of Salk was certainly a welcomed addition to our weekend of activities."

If you are interested in a private tour of Salk for your executive group, please contact Betsy Reis, director of Donor Relations at (858) 452-8051, or via e-mail: breis@salk.edu.

Members of the CEOs and their wives visited Salk during the group's recent annual retreat.

From Plants to Stem Cells, Salk Research Generates Wide-Reaching Impact

Marsha A. Chandler

SINCE THE SALK INSTITUTE'S FOUNDING IN 1960, ITS scientists have asked daring questions to probe the fundamental principles of life in an effort to conquer disease and improve human health. Their world-renowned basic research has led and continues to lead to many significant applications that have a very direct impact on human health. Let me give you a few examples drawn from the past year.

John Young developed a highly effective, single-injection agent against anthrax that works faster and better than any current vaccine when administered to rat models. The new anti-anthrax agent is an important and potentially critical development for anyone who works with the bacterium or for those who might be exposed to it in a bioterrorism attack.

The potential for a groundbreaking pill drew headlines worldwide in August when **Ronald Evans** published his "Exercise in a Pill" study. His lab's research demonstrated the power of two experimental drugs: One tricked the body's muscles into thinking they had been exercised, while a second dramatically boosted endurance by more than 70 percent when combined with exercise. While this may appeal to so-called "couch potatoes," the possibility of being able to achieve the benefits of exercise through a compound that's taken orally may provide much-needed relief to those who cannot physically exercise as a result of trauma or disease.

Satchidananda Panda has found that a sensitive light meter in the retina called melanopsin is involved in setting our biological clocks. Further studies in this area may one day allow scientists to reset the body's clock with a pill to alleviate symptoms associated with jet lag, shifts in work schedules and disorders such as insomnia and depression.

Inder Verma published a study in August that uncovered the molecular mechanisms behind allergies. This discovery raises renewed hope for the development of therapies to treat hypersensitive allergic diseases, including hay fever.

Scientists at Salk are strongly committed to stem cell research and the promise it holds for treating neurodegenerative diseases such as Alzheimer's and Parkinson's. In a study this summer that's a first, **Fred H. Gage** successfully changed the fate of adult neural stem cells that were still in place within the brains of mice. Previously, scientists had only been able to accomplish this feat with cells that were cultured in the lab. The discovery not only attests to the versatility of neural stem cells but also opens new possibilities for the treatment of other conditions such as multiple sclerosis, stroke and epilepsy.

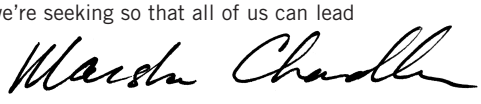
In this issue, we celebrate the leading discoveries made by Salk's Plant Biology Laboratory over the last 25 years. During that time, several of its scientists have established new paradigms for the field that has led to a better understanding of plant genetics and climate resistance. The results of their studies have applications that may allow growers to produce higher-yielding crops to keep up with the world's increasing demand for food.

Early studies in genetic variation by **Joanne Chory** and former lab member **Detlef Weigel,** for example, revealed several genes that enable plants to thrive in varying climates, as well as the previously unknown similar role played by the plants' photoreceptors. Their findings provided the first clues to how crops could be developed to adapt to challenging environments while also boosting yield.

> "Salk investigators are pushing forward the boundaries of scientific knowledge, and it's this ever-increasing knowledge that will continue to provide the answers we're seeking so that all of us can lead healthier lives."

Joseph Noel has discovered how to radically change the production of a plant's natural anti-fungal chemical by working with a key enzyme. The study not only gives Salk scientists a glimpse of the model plant's evolutionary past, but will help them fine-tune the production of natural and environmentally friendly fungicides and pesticides.

In a wide variety of areas of groundbreaking basic research, Salk investigators are pushing forward the boundaries of scientific knowledge, and it's this ever-increasing knowledge that will continue to provide the answers we're seeking so that all of us can lead healthier lives.



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

Salk **Calendar**

OCTOBER 2008

14-15 **DNA Replication Meeting**

Plant Biology Symposium – Celebrating 25 Years

20 **Jacobs Symposium: "The Crossroads of Biology & Bioengineering"**

21-23 **La Jolla Immunology Conference**

NOVEMBER 2008

19 **The Marguerite Vogt Lecture with speaker Mina Bissell**

DECEMBER 2008

11 **Roger Guillemin Nobel Lecture with speaker Barbara Kahn**

JANUARY 2009

8 **Brenner Nobel Lecture with speaker Cynthia Kenyon**

8-10 **Salk/Nature/Ipsen Symposium on Biological Complexity: Processes of Aging**

29 **Umesono Lecture with speaker Pierre Chambon**

FEBRUARY 2008

5 **Leslie Orgel Lecture with speaker Tom Czech**

23 **Renato Dulbecco Nobel lecture with speaker Mario Capeechi**

Shaker Loops Ecstasy 2 (6' x 7' oil on canvas) is among the selected works of the Shaker Loops series by artist Ellen Salk to be exhibited at the Institute in the fall.

For additional information about these and other Salk events, please contact the Development Office at 858.453.4100 x1658

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