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THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

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RENATO DULBECCO

celebrare una leggenda

July 2012
Inside Salk

Renato Dulbecco: A Giant of Cancer Biology

Next generation: Carol Marchetto

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ON THE COVER

Maureen Dulbecco took this photo of her husband Renato Dulbecco in their red '63 Jaguar XKE just as they were about to hike into the Borrego Palm Canyon in 1964.

Dear Friends,

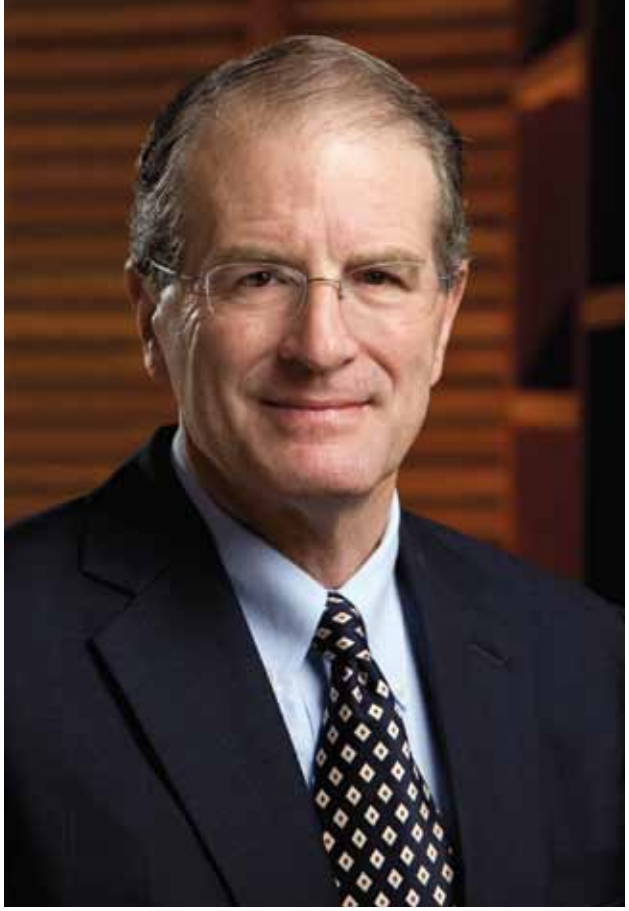
IN THIS ISSUE OF *INSIDE SALK*, WE CELEBRATE THE LIFE AND legacy of a visionary scientist, **Renato Dulbecco**, who died February 19. He was a pioneer, a Nobel laureate, a leader, a colleague and a friend. He was all of these things to the Salk community, and his passing at age 97, like his remarkable life, has had a profound impact on everyone at the Institute. A founding fellow, former president and groundbreaking researcher, Renato embodied everything that makes the Salk such an extraordinary place, and all of us will miss him deeply. As you'll read in our cover story, he was a supremely insightful and talented man who changed the direction of cancer research forever and whose legacy will continue to influence future generations of investigators.

Some of those researchers, not surprisingly, are making significant inroads against cancer right here at the Salk Institute. The following pages highlight a few recent examples—important discoveries by **Geoff Wahl**, **Jan Karlseder** and **Inder Verma** concerning breast cancer, cell division and lung cancer. We have also enjoyed several very productive months in neuroscience, metabolism, plant biology and aging research, with major papers published by **Sam Pfaff**, **Ron Evans**, **Marc Montminy**, **Joanne Chory**, **Joe Noel** and **Martin Hetzer**, to name just a few.

Our March of Dimes High School Science Day in March had a great turnout, as you'll see in our "Next Generation" section. This annual event, part of our education outreach effort, brings students and teachers to the Institute from around San Diego County for hands-on science experiences in Salk labs, a talk and lunch. Based on the feedback we get, it has a lasting impact on the participants.

And speaking of lasting impact, I particularly want to mention a heartfelt tribute the Institute paid to the late **Wylie Vale**, a longtime Salk faculty member and the subject of our previous issue's cover story. On the afternoon of March 22, we convened the Wylie Vale Memorial Symposium. Afterward, friends and colleagues shared their warm memories of Wylie. It was, in my opinion, the Salk Institute at its best.

I'm delighted to report that we've set a record for private giving during the past eight months, capped by a $10 million gift from Switzerland-based Ferring Pharmaceuticals. With the sharp decline in federal funding for basic research and more cuts threatened, philanthropic gifts are essential if we are to sustain our outstanding momentum—an impetus that will continue to benefit humankind as our scientists' work produces innovations and discoveries that lead to new therapies and diagnostics.



William R. Brody

> **"I'm delighted to report that we've set a record for private giving during the past eight months."**

Lastly, I hope you've marked August 25 on your calendars for the premier event of the summer: Symphony at Salk. Each year, members of the community flock to the Institute's courtyard for this sold-out evening of gourmet dining, camaraderie and splendid music (courtesy of the San Diego Symphony and a celebrated guest artist—this year, LeAnn Rimes), all in support of Salk's research and education outreach programs. It's always a memorable experience and one that audience members cherish for a long time afterward. If you've never attended Symphony at Salk, I urge you to join us and enjoy what all the excitement is about. I hope to see many of you there for this outstanding San Diego summer tradition.

Thank you for your continued support. You are so very important to the work being done at Salk.

William R. Brody

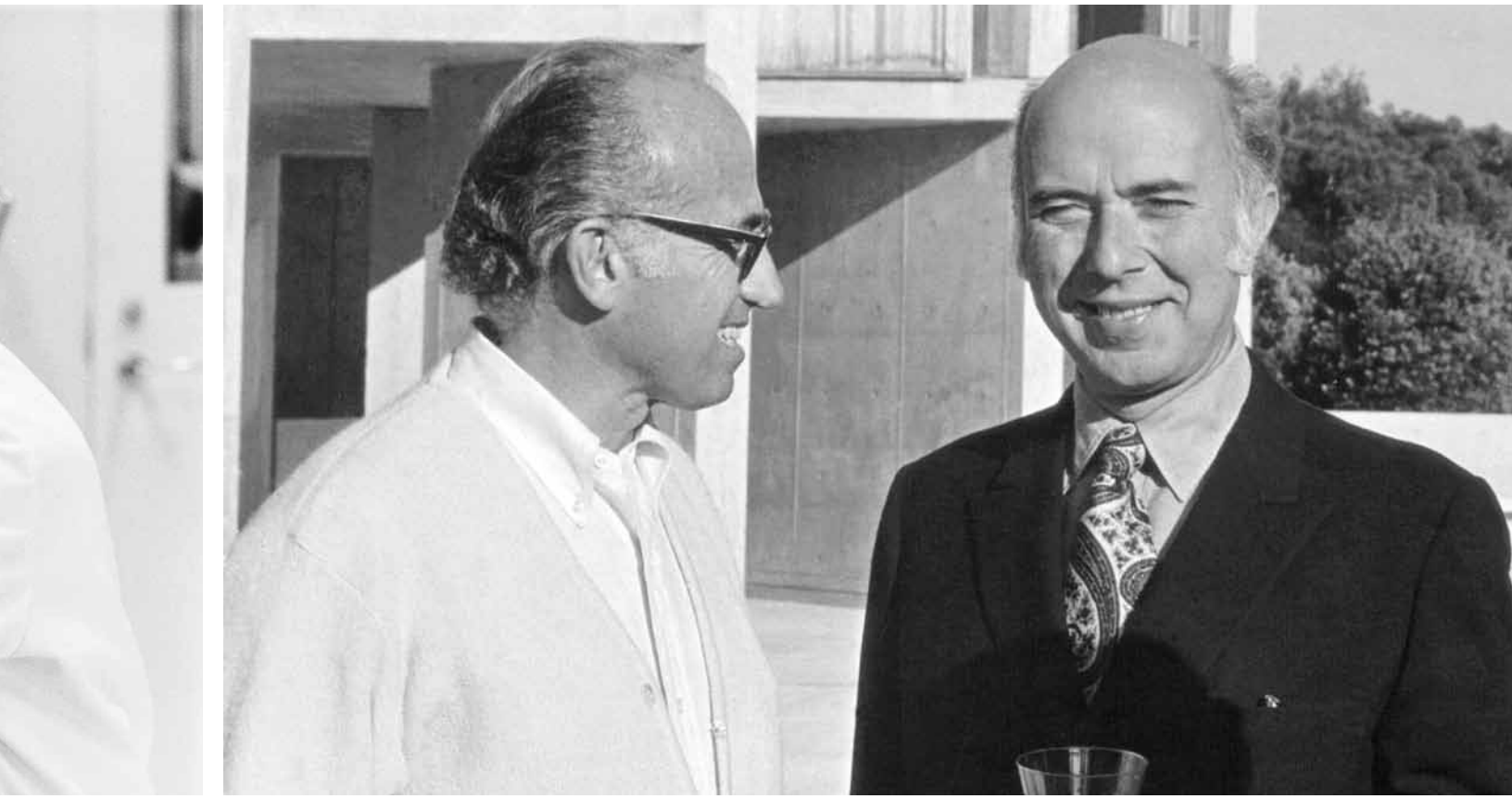
William R. Brody, M.D., Ph.D.
President, Salk Institute
Irwin M. Jacobs Presidential Chair

RENATO DULBECCO:
A Giant of Cancer Biology

Young Renato Dulbecco as a Boy Scout in Italy.

Dulbecco in the lab, 1978.

To understand how the Salk Institute became one of the preeminent cancer research institutions in the world, look no further than the life and work of Nobel laureate Renato Dulbecco. Dulbecco, who died February 19 at age 97, pioneered the field of tumor biology, and his interest and talent in mentoring young investigators greatly influenced the direction that cancer research has since taken at the Salk and in other world laboratories.



Jonas Salk and Renato Dulbecco in the courtyard, 1967

DULBECCO, A FOUNDING FELLOW OF SALK, was awarded the Nobel Prize in 1975, along with Howard Temin and David Baltimore, who worked with Dulbecco at different times, for their discoveries illuminating how tumor viruses interact with the genetic material within a cell. Dulbecco demonstrated how a virus could insert its own genes into the DNA of the cell it infects, sparking cancer growth. In essence, his work helped uncover some of the molecular pathways that define cancer growth however it occurs, providing the conceptual breakthrough that has guided the field ever since.

Dulbecco's story is one of a remarkable scientist, and it is also a story of an enduring scientific legacy that carries on to this day. Over the course of his career, Dulbecco trained and collaborated with some of the leading biologists in the world, and his life and work charted a course for many young cancer researchers.

"He had a broader vision of science than most and a keen instinct for important problems to solve," says **Tony Hunter**, holder of the Renato Dulbecco Chair and a professor in the Molecular and Cell Biology Laboratory and director of the Salk Institute Cancer Center. "His work drew outstanding young investigators to Salk and influenced a whole generation of biologists."

> “At the time, a lot of us didn’t quite appreciate the magnitude of what we were living. There was a lot to know and to discover. Dulbecco was a wonderful mentor.” – WALTER ECKHART

BRILLIANT MINDS

Dulbecco was born in Catanzaro, Italy, in 1914. When he was a student at the University of Torino in Italy—an institution he attended at age 16—he met scientists who would strongly influence his life. There, in the laboratory of Giuseppe Levi, a professor of anatomy, he met students Salvador Luria and Rita Levi-Montalcini, both of whom would also go on to win Nobel Prizes.

Before and during the Second World War, Dulbecco served forced stints as a medical officer in Italy’s military, both on the French front and the Russian front, where he was wounded. He later joined the resistance and served as a village physician near Torino. After the war, he and Levi-Montalcini left Italy for the United States. In 1947, Dulbecco joined Luria at Indiana University—the university awarded Dulbecco the President’s Medal for Excellence in 2011—and together they worked on viruses that infect bacteria. Luria and Dulbecco shared a small lab, and James Watson, another future Nobel Prize winner, soon joined them, as Luria was Watson’s doctoral advisor.

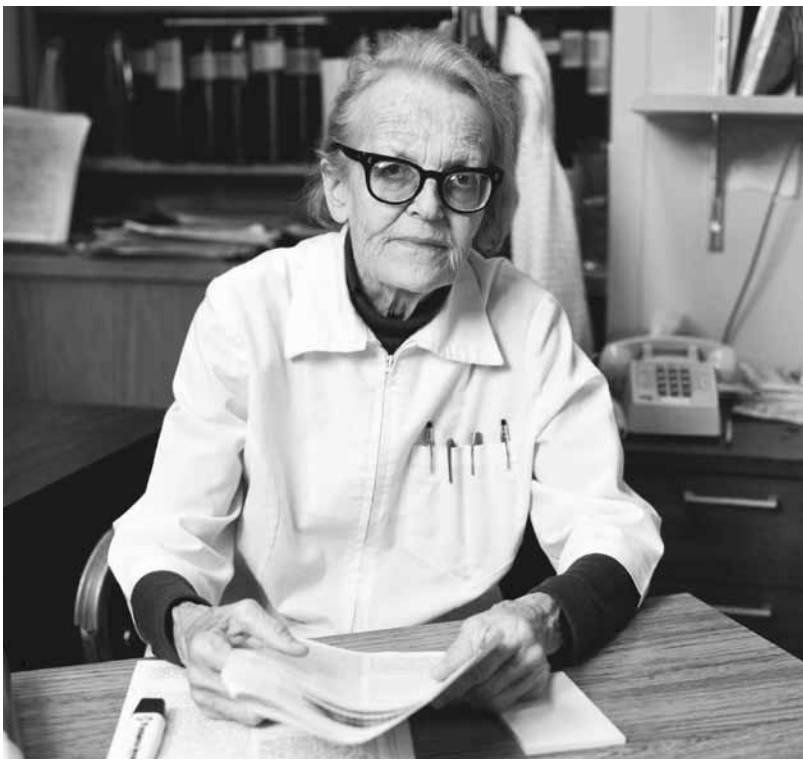
While at Indiana, Dulbecco attracted the interest of Max Delbrück, who in 1949 offered Dulbecco a job at Caltech as a research fellow. Delbrück later won a Nobel Prize for discovering that bacteria become resistant to viruses as a result of genetic mutations.

At Caltech, Dulbecco met Marguerite Vogt, another European immigrant, who would become his longtime scientific collaborator. Together they first described how the poliovirus forms plaques in cell cultures—work that transformed virology from a descriptive to a quantitative science.

In 1963, Dulbecco left Caltech to become one of the first Fellows of the Salk Institute, (a position equivalent to a full professor in a regular faculty) which had been founded three years earlier by polio vaccine pioneer Jonas Salk—a move that would establish Salk as a beacon for talented cancer scientists.

SHARED PURPOSE

Vogt joined Dulbecco at Salk, where they worked on tumor viruses. They studied Simian vacuolating virus 40 (SV40) and mouse polyomavirus, a related virus that can cause cancer in rodents. Their work showed that SV40 inserted its genes into the cells it infects, causing the cells to grow uncontrollably. This definitively proved the essential role of SV40 genes in transforming cells into cancers and, more fundamentally, provided the first clear evidence that genetic mutations cause cancer.



Marguerite Vogt, 1989

At Salk, Dulbecco had the opportunity to cultivate the next generation of scientists through his mentorship. He wrote that the daily interaction through the years with a continuously changing group of young investigators shaped his work. “For although I had general goals, the actual path followed by my research was pragmatically determined by what could be done at any given time, and my young collaborators were an essential part of this process,” he wrote.

Walter Eckhart, now professor emeritus in Salk’s Molecular and Cell Biology Laboratory, remembers the intellectual pull that Dulbecco had on him. He began working with Dulbecco in 1965 as a postdoctoral fellow and was later appointed to the Institute’s faculty. Eckhart and other young scientists at the Salk focused on the regulation of cell growth and what happens when cancer disrupts that regulation and forces cells to run amok.

“It was exciting to work around the clock and to be part of experiments that solidified the idea that genes could be instrumental in provoking cancer,” Eckhart says. “At the time, a lot of us didn’t quite appreciate the magnitude of what we were living. There was a lot to know and to discover.

Maureen and Renato Dulbecco at the 2007 Salk International Council meeting in Austria

Salk Cancer Research Milestones

1950s

Renato Dulbecco and **Marguerite Vogt** describe how a tumor virus can "turn on" the uncontrolled growth that is the hallmark of cancer, providing an important clue to the genetic nature of cancer.

1970

Salk Cancer Center is established under the direction of Nobel laureate **Robert Holley**. Salk professor **Leslie Orgel** discovers a straightforward way to synthesize cytosine arabinoside (Ara C), a compound that becomes one of today's most commonly used anti-cancer agents.

1972

The National Cancer Institute designates the Salk center as one of the first seven basic cancer centers in the United States.

1975

Dulbecco shares the Nobel Prize in Physiology and Medicine with Howard Temin and **David Baltimore**.

1979

Tony Hunter discovered a process called tyrosine phosphorylation turns out to be the underlying cause of many types of human cancer, a discovery that leads to the development of the leukemia drug Gleevec.

> "Renato was a giant of cancer biology, and he did not shy away from making bold, visionary statements."
>
> – INDER VERMA

Dulbecco was a wonderful mentor."

The Salk Cancer Center's focus on the genetics of cancer and cellular processes began with Dulbecco, Eckhart says. "He was always ahead of his time," he says. "He had the big picture in mind."

Four of the investigators who trained or worked with Dulbecco at Salk were later awarded Nobel Prizes. Susumu Tonegawa, a 1987 winner, was a postdoctoral fellow with Dulbecco working on transcription by SV40. Lee Hartwell, also a postdoctoral fellow in Dulbecco's lab, eventually switched from working on polyomavirus to yeast, which led to his work on the genetics of cell division and his 2001 Nobel Prize. Paul Berg, a 1980 Nobel laureate, spent a year in Dulbecco's lab, conducting research that led to developing SV40 as a vector for introducing new genes into mammalian cells using recombinant DNA techniques. **David Baltimore**, a Salk Non-Resident Fellow and president emeritus of the California Institute of Technology, who conducted research at Salk for three years, credits Dulbecco for his influence in setting the direction of Baltimore's later work on mammalian tumor viruses. Although the problem he worked on was separate from Dulbecco's investigation, Baltimore says he was clearly influenced by Dulbecco's clarity of thought.

LEGACY OF DISCOVERY

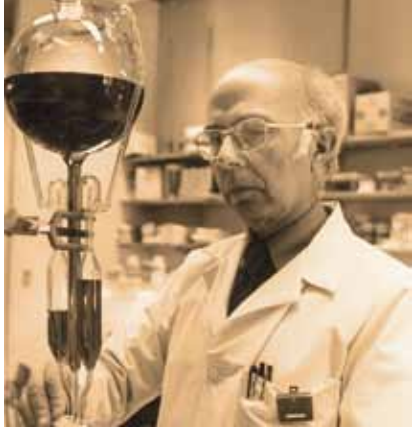
The Salk Institute Cancer Center was established in 1970 under the direction of **Robert Holley**, who had received the Nobel Prize two years earlier, and in 1973, the National Cancer Institute designated the Salk center as one of the first seven basic cancer centers in the United States.

Dulbecco left Salk in 1972, moving to London with his wife, Maureen, and their young daughter, Fiona, to serve as deputy director of research at the Imperial Cancer Research Fund Laboratories. At Salk, four of the original faculty appointed to the Tumor Virology Laboratory set up their labs in Dulbecco's previous research space—**Walter Eckhart**, **Gernot Walter**, **Bertold Francke** and **Tony Hunter**—and worked on polyomaviruses as a model for human cancer.

Their work spawned a number of key findings at Salk, including Hunter's discovery that tyrosine phosphorylation is a chemical "on-off" switch responsible for telling cells to become cancerous. Discovery of this important signaling mechanism, which proved to be the underlying cause of many types of human cancer, revolutionized cancer medicine and ultimately led to the development of several innovative cancer therapies, including the leukemia drug Gleevec.

Dulbecco returned to Salk in 1977 and launched a new research program focused on breast cancer. He used monoclonal antibody technology to identify proteins found on the surface of normal mammary cells. This provided important insights into the normal development of mammary glands and allowed him to study how mutagens might cause mammary cells to become cancerous.

Dulbecco closed his laboratory to serve as Salk's president from 1988–92. After winning the Nobel Prize in 1975, he used his influential voice to speak out for fundamental changes



1983

Inder Verma pioneers the use of stripped-down versions of viruses to insert genes into cells throughout the body, paving the way for gene therapy trials in cancer patients.

1985

Ronald Evans identifies the first of a large family of molecules, named "nuclear receptors," which are primary targets in the treatment of breast cancer, prostate cancer and leukemia.

1992

Geoffrey Wahl and his lab identify the central player that stands guard over the stability of the genome, a protein called p53, which is often disarmed in cancer cells.

2012

Salk scientists continue Dulbecco's legacy, explaining how a popular class of chemotherapy drugs works, discovering a new target for lung cancer drugs and showing that stem cells in developing organs may help us understand the genetic underpinnings of cancer.

Top left: Francis Crick, Jonas Salk and Renato Dulbecco at a party at the La Jolla Playhouse hosted by the Women's Association for the Salk Institute, October 1994.

Top right: Dulbecco in the lab, 1978.

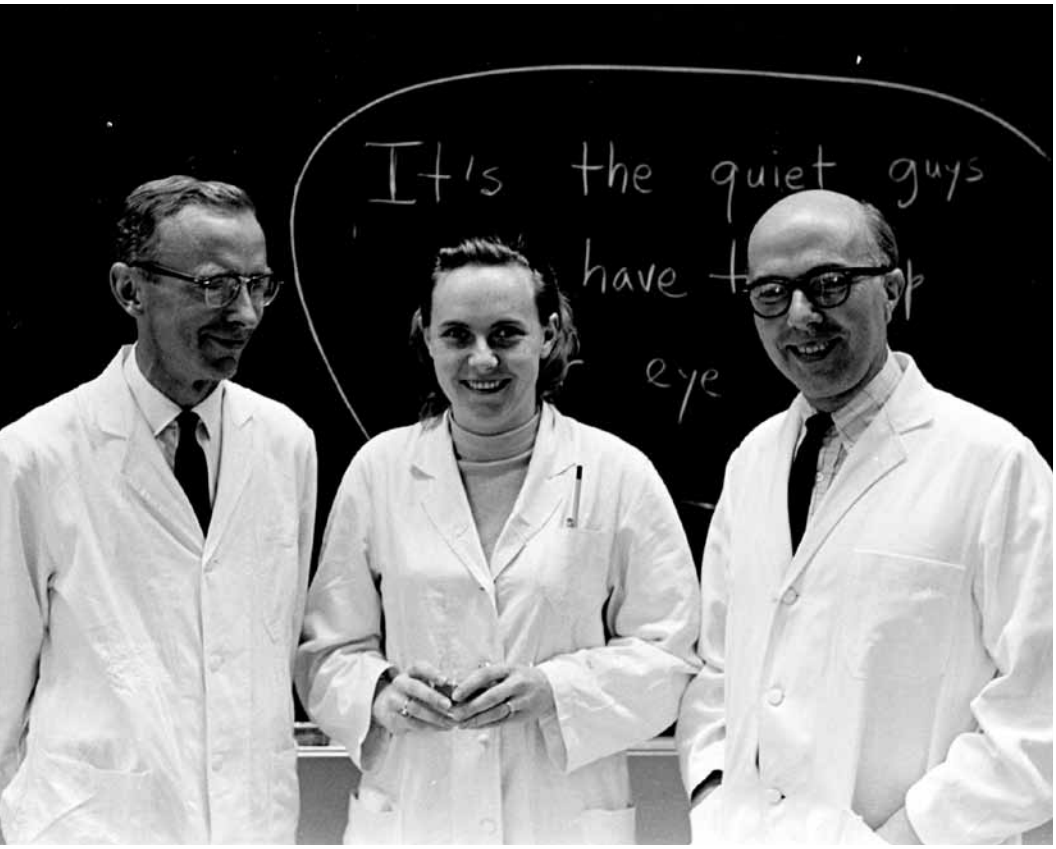
Second row: Dulbecco accepting the Nobel Prize in Physiology or Medicine in 1975 for his work on reverse transcriptase.

Third row left: Dulbecco with 1987 Nobel laureate Susumu Tonegawa.

Third row right: Dulbecoo and Queen Elizabeth II in 1974.

Bottom row, from left: William R. Brody, Roger Guillemin, and Renato Dulbecco, 2011.

> “He was one of the first prominent people to stand up and take a very public position about the cancer risks of smoking.”
>
> – TONY HUNTER



Robert W. Holley, Maureen Dulbecco and Renato Dulbecco at a party celebrating Holley's having won the Nobel Prize, 1968.

Maureen and Renato Dulbecco

in the way that cancer research is conducted.

“Renato was a giant of cancer biology, and he did not shy away from making bold, visionary statements,” says **Inder Verma**, a professor in Salk's Laboratory of Genetics.

One example was the two-page “Perspective” he wrote for *Science* magazine in 1986, in which he argued that the best way to understand cancer would be to sequence the entire human genome and that an international collaboration should be convened to tackle the project.

Geoffrey Wahl, a professor in Salk's Gene Expression Laboratory, says this assertion, which led to the Human Genome Project, completed in 2003, may have been Dulbecco's most transcendent contribution to science.

“Little could he have imagined that this suggestion would not only become a reality in his lifetime, but would transform all areas of biology,” says Wahl.

Eckhart adds that at the time, many people felt the genome project was premature and was going to be very expensive, siphoning off a lot of National Institutes of Health money that could otherwise be spent on research.

In his Nobel Prize lecture, Dulbecco took the opportunity to warn that substances in the environment, such as tobacco smoke, can cause genetic mutations that lead to cancer. “While we spend our life asking questions about the nature of cancer and ways to prevent or cure it, society merrily produces oncogenic substances and permeates the environment with them,” he told the audience.

He urged governments to discourage use of tobacco and also to test chemicals for their ability to produce cancer-causing mutations.

“He was one of the first prominent people to stand up and take a very public position about the cancer risks of smoking,” says Hunter. “It was daring—not what the committee expected to hear. We—all of us—owe a great deal to Renato Dulbecco. Many of us are in cancer biology because of the example he set for us.”

» Watch the video

www.salk.edu/isjuly12/video1

Salk scientists honored with endowed chairs

Geoffrey M. Wahl

Martyn Goulding

Joseph R. Ecker

AT A SPECIAL CEREMONY AT THE INSTITUTE ON MARCH 29, FACULTY members **Geoffrey M. Wahl**, **Martyn Goulding** and **Joseph R. Ecker** were each honored as recipients of endowed chairs, in recognition of their significant scientific accomplishments.

"Salk discoveries are transforming our understanding of human health, and we are deeply grateful to our generous donors," said **William R. Brody**, Salk Institute president, as he acknowledged each of the investigators at the ceremony. "Establishing the chairs is an outstanding way to support researchers who are at the forefront of their fields. It honors the excellence of these remarkable scientists who have made preeminent contributions to scientific discovery."

In 2008, **Irwin Jacobs**, chairman of the Salk board of trustees, and his wife, Joan, made a $10 million challenge grant to encourage donors to establish ten endowed chairs for senior scientists. For every $2 million that a donor contributes toward an endowed chair at the Institute, Joan and Irwin Jacobs add $1 million to achieve the $3 million funding level required to fully endow a chair for a Salk senior scientist. Thanks to the enthusiastic response to the chair challenge, the Jacobses added five more endowed chairs to the challenge, for a total of 15. To date, 14 have been established. The endowments provide essential funds to support the leading-edge science being done at the Institute.

Geoffrey M. Wahl, professor in the Gene Expression Laboratory, was named the inaugural holder of the Daniel and Martina Lewis Chair. The Lewises, Salk supporters since 2002 and International Council members, created the chair to help future generations benefit from the basic research conducted at the Institute.

Wahl seeks to determine how cancers originate and progress and why tumors become resistant to even the most powerful anti-cancer drugs. His goal is to translate the knowledge and understanding gained from basic research into the development of new treatment strategies to more effectively manage all types of cancer. His lab has uncovered key mechanisms that control the stability of the genetic material in cancer cells, and most recently has uncovered strong links between genetic pathways expressed in breast stem cells generated in the embryo and some of the most lethal human breast cancers. This work holds promise for developing new diagnostic and prognostic strategies and for developing new individualized treatment methods.

The Wahl lab has developed numerous technologies widely used in molecular and cellular biology, and Wahl was lead author of a "citation classic," concerning methods of DNA detection that were among the most widely cited in molecular biology. Wahl is an ardent advocate for increased funding of biomedical research as a mission that both saves lives and produces a substantial return on investment.

Martyn Goulding was appointed holder of the Frederick W. and Joanna J. Mitchell Chair, created through the Mitchell estate in memory of their daughter, Marian, to support research in connection with birth defects and children's diseases.

Goulding, professor in the Molecular Neurobiology Laboratory, studies the early development of the nervous system and how it functions, focusing on defining the genetic program that generates different interneuron cell types in the embryonic spinal cord. His lab has explored how these interneurons not only play a critical role in relaying sensory information from the surface of our body to the brain, but are also important for locomotion and posture. This research could eventually contribute to new therapies for spinal cord injuries and movement disorders associated with aging and diseases affecting children.

Goulding pioneered the use of mouse genetics in combination with classical electrophysiological studies to reveal the identity and assign specific functions to neural networks in the spinal cord. His work led to a paradigm shift in spinal cord physiology and changed the way scientists study neural circuits in the spinal cord.

Joseph Ecker, professor in the Plant Molecular and Cellular Biology Laboratory and director of the Genomic Analysis Laboratory, was awarded the Salk International Council Chair in Genetics, which was created in 1997 and has provided critical resources to further the understanding of genetic contributions to human health. Ecker is one of the world's leading authorities on the molecular biology and genetics of plants and is internationally recognized for his pioneering contributions to plant genomics. He was a principal investigator in the multinational project that sequenced the genome of *Arabidopsis thaliana*, a modest weed that has become a model organism for the study of plant genetics and the first plant whose genome was sequenced, an achievement expected to have widespread implications for agriculture and perhaps human medicine as well. Ecker also led the groundbreaking research that produced the first detailed map of the human epigenome using two human cell types.

Ecker is widely regarded as one of the foremost experts on how the gaseous hormone ethylene regulates a variety of basic plant processes. For agriculture, ethylene gas is a vital chemical messenger important for such processes as fruit ripening and how plants respond to pathogenic organisms. Ecker's research has yielded essential insights into the mechanisms of plant growth control and led to the development of new technologies that delay fruit ripening and disease processes.

Non-Resident Fellow Elizabeth Blackburn joins Salk professors Suzanne Bourgeois and Tony Hunter at the Board of Trustees Reception and Dinner.

Elizabeth Blackburn awarded 2012 American Institute of Chemists Gold Medal

NOBEL LAUREATE ELIZABETH H. BLACKBURN, A PROFESSOR AT the University of California, San Francisco and a Salk Non-Resident Fellow (NRF), was honored with the 2012 American Institute of Chemists (AIC) Gold Medal, its highest award. It is the first time in eight decades that a woman Nobel laureate was selected for the prize.

Blackburn, an NRF since 2001, is a leader in the area of telomere and telomerase research. She discovered the molecular nature of telomeres—the ends of eukaryotic chromosomes that serve as protective caps essential for preserving the genetic information—and the ribonucleoprotein enzyme telomerase. Blackburn and her research team at UCSF are working with various cells, including human cells, with the goal of understanding telomerase and telomere biology.

The AIC Gold Medal has been given annually in acknowledgment of service to the science of chemistry and to the profession of chemist or chemical engineer in the United States. In recognition of their achievements, gold medalists receive a life fellowship in the institute. Previous winners include Nobel laureates as well as other renowned researchers and engineers representing many facets of chemistry.

Blackburn was presented with the medal April 12 in Philadelphia, during Heritage Days, a yearly celebration of achievement in chemistry and related sciences hosted by the Chemical Heritage Foundation.

Caroline Dean

The Salk Institute welcomes new Non-Resident Fellow

THE SALK INSTITUTE IS PLEASED and honored to welcome **Caroline Dean** as the newest Non-Resident Fellow. Non-Resident Fellows are a group of distinguished scientists from world-renowned academic and research institutions that help advise the Institute's faculty on appointments, promotions and scientific programs.

Dean's research concentrates on the timing of the transition to reproductive development in plants. For the last 20 years, she has focused on understanding the molecular controls used by plants to judge when to flower. Her lab also contributed to the genetic and physical mapping of the *Arabidopsis* genome and established a transposon tagging system.

Dean completed her graduate education at the University of York in 1983. She then spent five years in California conducting postdoctoral research at the plant biotech company Advanced Genetic Sciences. In 1988, she returned to the UK to take a position as project leader at the John Innes Centre. Among her many notable achievements, Dean served as president of the International Society of Plant Molecular Biology (1999-2001), as a Royal Society Council Fellow (2005-2007), and as associate research director of the John Innes Centre (1999-2008). She was elected a Fellow of the Royal Society and Officer of the Order of the British Empire in 2004 and Foreign Member of the U.S. National Academy of Sciences in 2008.

A record-setting year for fundraising

THE SALK INSTITUTE'S DEVELOPMENT TEAM has set a historic milestone, raising nearly $50 million this fiscal year. That amount is the most money ever raised annually at the Institute.

Switzerland's Ferring Pharmaceuticals made a major commitment to the Institute with a gift of $10 million. Salk board member Frederik Paulsen, chairman of Ferring's board of directors, played a pivotal role in securing the gift on behalf of the Institute.

"There are few places like the Salk that exist in the world," he said. "It is our responsibility to humanity that the research is supported. It's the work of Salk scientists that leads to the development of improved therapies and treatments for diseases that plague us today."

$3.5 million from the Ferring Pharmaceuticals gift will fund the Frederik Paulsen Chair in Neurosciences and the Françoise Gilot-Salk Chair, of which scientist **Greg Lemke** has been named the inaugural holder.

Lemke's lab focuses on the role that TAM receptors play in immune regulation. These receptors, which were discovered by Lemke's team, are central inhibitors of the innate immune response to bacteria, viruses and other pathogens.

The remaining $6.5 million will be designated to support the highest scientific priorities at the Institute.

"The support from our donors worldwide is a testament to the highest quality of our science and the lasting impact our discoveries will have on future generations," said **Rebecca Newman**, vice president of development and communications.

"We are deeply grateful, as these gifts will insure our scientists the necessary resources to continue their seminal research."

There are 22 endowed chairs at the Salk, 14 of which have been completely or partially funded by Irwin and Joan Jacobs. As part of the historic fundraising surge this year, the Jacobses generously contributed an additional $10.5 million in support of Salk science.

Faculty members receive promotions

SALK SCIENTISTS REUBEN SHAW AND LEI WANG HAVE EACH BEEN promoted to associate professor after a rigorous evaluation process by Salk senior faculty, Non-Resident Fellows and scientific peers. The career milestone distinguishes these two investigators as leading authorities in their respective disciplines who have made original, innovative and notable contributions to biological research.

"Awarding promotions to scientists as talented as Reuben and Lei assures that Salk will continue to bring outstanding leadership, vision and excellence in science and discovery to the global community," said Salk president **William R. Brody**. "We are proud of all that these two scientists have accomplished as researchers at the Salk Institute and look forward to many more cutting-edge contributions impacting human health."

Reuben Shaw, a member of the Molecular and Cell Biology Laboratory, is a Howard Hughes Medical Institute early career scientist as well as holder of the Hearst Foundation Developmental Chair. He studies signal transduction pathways that underlie the development of cancer and metabolic disorders such as type 2 diabetes. While investigating one of the most commonly mutated genes in lung cancer, Shaw discovered an energy-sensing pathway that shuts down cell growth and reprograms metabolism when nutrients are scarce. His lab went on to molecularly decode a number of new components of this biochemical pathway, which connects nutrition to both cancer and diabetes. In addition, Shaw's lab uses genetic mouse models to further examine the connections between cancer and metabolic diseases and to tease out the precise role of each component of the signaling pathway. In the past five years at Salk, studies from his lab have led to the discovery of new therapies for both cancer and type 2 diabetes.

Lei Wang, of the Chemical Biology and Proteomics Laboratory and holder of the Frederick B. Rentschler Developmental Chair, studies the genetic code and signaling processes in vivo using genetically encoded novel amino acids. A Searle Scholar, a Beckman Young Investigator and a recipient of the NIH Director's New Innovator Award, Wang pioneered a method to accommodate additional amino acids, the molecular building blocks of all proteins, into proteins produced by bacteria. Since then, he has developed innovative strategies to expand the natural repertoire of amino acids for building proteins in mammalian cells, including neurons and stem cells. Using these new amino acids, his group has found new signaling mechanisms for ion channels and G-protein–coupled receptors, which may guide the development of therapeutics for depression and neurological diseases. The synthetic biomolecules being built by Wang's lab also hold promise for making proteins and drugs with biological functions far beyond what is possible with proteins that include only naturally occurring amino acids.

Associate professors Lei Wang (left) and Reuben Shaw

A License to Heal

SALK'S OFFICE OF TECHNOLOGY DEVELOPMENT HELPS TURN discoveries into marketable therapies. **Robert MacWright** sees his job as building bridges between Salk laboratories and patients' lives.

Guided by that philosophy, he has worked to establish a closer relationship between his office and Salk's researchers since joining the Institute in February 2011 as the executive director of the Office of Technology Development. He and his team are helping Salk scientists to identify discoveries that could be turned into marketable therapies and to navigate the process of patenting and licensing those breakthroughs.

"A lot of academic research is aimed at trying to understand and defeat human disease," says MacWright. "The reality, however, is that important discoveries will never make it to the market if they aren't patented."

Before coming to Salk, MacWright served for over a decade as executive director, CEO and chief patent counsel of the University of Virginia Patent Foundation and as executive director of the Rutgers University Office of Corporate Liaison and Technology Transfer. This experience taught him that legal protection of research discoveries helps support an academic institution's research mission, through returns on licensing agreements with private companies, and by paving the way for discoveries to be translated into therapies.

"If a technology isn't protected, it's too risky for a company to develop it into a product," MacWright says. "A pharmaceutical company isn't going to risk the hundreds of millions of dollars it costs to bring a new drug to market if they don't have patents that protect them from competition until they make enough profits to justify that early expense."

Members of the Office of Technology Development team, from left to right: Ha Nguyen, Lina Axanova, Robert S. MacWright, Kiren Rockenstein, Rachel Mullen, Paul Roben

To better acquaint Salk researchers with patents and their importance to academic institutions, MacWright's team has held a series of popular monthly seminars. He has also formed a faculty advisory committee to pinpoint the needs of Salk scientists and introduce the faculty to the philosophy of the office. A team of four licensing experts in the Office of Technology Development is meeting with Salk laboratories to become familiar with their research and scout for breakthroughs that might be patented and licensed.

MacWright offers the example asfotase alfa, a drug developed in the laboratory of the late Salk scientist **Leslie Orgel**, as a success story in commercializing a biomedical discovery. The drug has not yet been approved by the FDA but has shown promise in early trials for treating children with hypophosphatasia, a rare genetic disease that prevents normal bone development, and it could eventually be used for treating osteoporosis. First patented in 2002, asfotase alfa was licensed exclusively in 2006 to Enobia Pharma, which was later acquired for nearly $1 billion by Alexion Pharmaceuticals.

"Infants with this disease rarely survive, and this technology literally gives them life," MacWright says. "I've seen the most remarkable set of x-rays of an infant's hand, one taken before treatment, where there are almost no bones in the hand, and another taken after treatment, showing a completely normal bone structure."

More recently, **Reuben Shaw**, an associate professor in Salk's Molecular and Cell Biology Laboratory, worked with the technology development office to license a genetically engineered strain of mice to a major biotechnology company. The company plans to use the mice in preclinical trials of lung cancer therapies.

"This gives the company a valuable tool to develop better cancer therapies without having to spend an inordinate amount of time and money duplicating our work," Shaw says. "It's very gratifying, because drug development is where the rubber hits the road. I'm proud our research is being put to direct and immediate use to help people."

» WEBEXTRA

www.salk.edu/faculty/otd_presentations.html

Salk professor Fred Gage awarded Fyssen Foundation International Prize

Fred "Rusty" Gage

FRED "RUSTY" GAGE, A PROFESSOR IN THE Salk Institute Laboratory of Genetics and holder of the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases, was honored with the Fyssen Foundation's 2011 International Prize on the theme "The Epigenetics of Cognition."

"The award is for our discovery of adult neurogenesis in the hippocampus derived from stem cells in humans and that mobile elements in neural stems cells add to somatic diversity, which creates a repertoire of cells on which selection can act for epigenetic adaptation," said Gage. "This blurs the boundary between epigenetic and genetic mechanisms, both of which can contribute to unique differences in cognition."

Established in 1979, the Paris-based Fyssen Foundation seeks to encourage all forms of scientific inquiry into such cognitive mechanisms as thought and reasoning, which underlie animal and human behavior, their biological and cultural bases, and phylogenetic and ontogenetic development. The organization has given out the international prize annually since 1980 in recognition of an outstanding scientist who has conducted distinguished research in ethology, human paleontology, anthropology, psychology, epistemology, logic or the neurosciences.

Gage's selection as the recipient of the organization's International Prize is further acknowledgement of his reputation as one of the world's foremost experts in neurobiology. He is the first Salk scientist to receive the prestigious award, which was presented at a ceremony March 23 in Paris.

Salk scientist elected to American Academy of Arts and Sciences

WHAT DOES SALK RESEARCHER EDWARD M. CALLAWAY HAVE IN common with former Beatle Paul McCartney?

Callaway, a professor in the Systems Neurobiology Laboratories, has joined the legendary recording artist as a member of the American Academy of Arts and Sciences. It's a distinction Callaway shares with some of the world's most accomplished leaders from academia, business, public affairs, the humanities and the arts. Among this year's other new fellows are actor and filmmaker Clint Eastwood, U.S. Secretary of State Hillary Rodham Clinton, philanthropist Melinda F. Gates and Walt Disney president and CEO Robert A. Iger.

Callaway's research is aimed at understanding how neural circuits give rise to perception and behavior and focuses primarily on the organization and function of neural circuits in the visual cortex. Relating neural circuits to function in the visual system, where correlations between neural activity and perception can be directly tested, provides fundamental insight into the basic mechanisms by which cortical circuits mediate perception. In particular, Callaway pioneered a method that allows him to trace a single neuron's connections to its neighbors.

"Election to the academy is an honor," said Salk president **William R. Brody**. "We are proud of Ed's induction, as it underscores the impact of his research and scientific contributions."

In addition to being one of the nation's most prestigious honorary societies, the American Academy of Arts and Sciences is a leading center for independent policy research. Members contribute to academy publications and studies of science and technology policy, energy and global security, social policy and American institutions, the humanities and culture, and education. Current members include more than 250 Nobel laureates and more than 60 Pulitzer Prize winners. Callaway is the 11th person from the Salk Institute to be inducted.

The Salk Institute received an SDG&E Energy Efficiency Business Incentive in recognition of its environmental leadership and contribution to sustainable communities through its energy effciency efforts.

Salk Institute named SDG&E 2012 Energy Champion

Infrastructure improvements generate major energy performance and savings

AT AN AWARDS CEREMONY ON MAY 10, SAN DIEGO GAS & ELECTRIC (SDG&E) named the Salk Institute an Energy Champion for its outstanding efforts in energy efficiency and conservation. The Institute is one of 13 local businesses recognized for "going above and beyond to save energy and money by taking advantage of the many rebates and incentives that are available through SDG&E's energy-efficiency and demand response programs," said Hal Snyder, vice president of customer solutions for SDG&E.

With a set of energy demands that has evolved since the campus was originally built in 1962, the Institute completed an entire retrofit and expansion of its central plant mechanical and electrical infrastructure to improve overall energy efficiency, sustainability and cost savings.

"The ultimate challenge was trying to complete the full scope of the project within the confines of an historic and iconic structure," says **Tim Ball**, senior director of Facility Services. "In addition to maintaining design integrity, changing out the entire infrastructure without interruption to the science was an endeavor in and of itself."

The electrical infrastructure upgrade and new energy-efficiency measures have resulted in an annual savings of 3 million kWh for the Institute. And in recognition of its environmental leadership and contribution to sustainable communities through its energy efficiency efforts, the Salk also received $284,000 in incentives by working with SDG&E's Energy Efficiency Business Incentives (EEBI) program and $974,346 California Solar Initiative incentives for a photovoltaic system consisting of more than 2,350 photovoltaic solar panels that sit on top of all four major buildings on the campus, generating 465 kilowatts of electrical power; the natural power combined with the EEBI efficiency measures provides annual savings of nearly $340,000.

The environmental impact of the solar arrays and efficiency measures are significant; they keep approximately 846,000 pounds of carbon dioxide out of the atmosphere annually, along with nearly 800 pounds of sulfur dioxide and 1,240 pounds of nitric oxide, two of the major pollutants produced by power plants. Over the next 25 years, the solar system and efficiency measure installations will be equivalent to planting 128 acres of trees.

"Although challenging, the opportunity to enhance this infrastructure with energy efficiency improvements was monumental, as the Salk Institute is a haven for discovery with global impact on human health," adds Ball.

Michael Powers of Stellar Solar, San Diego County Supervisor Pam Slater-Price, San Diego Planning Commission member Peder Norby, and San Diego County Supervisor Dianne Jacob visited the Salk Institute on March 31 to examine the state-of-the-art rooftop solar electric system installed at the architecturally renowned campus.

Tickets will be available starting July 9 at $250 each and will include a pre-concert champagne reception; seating for the concert; a gourmet supper prepared by Jeffrey Strauss, executive chef and owner of Pamplemousse Grille; wine; refreshments and parking. For more information, visit **www.salk.edu/symphony**.

17TH ANNUAL

SYMPHONY at SALK

a concert under the stars

MULTI-AWARD–WINNING SINGER AND COUNTRY/POP music sensation LeAnn Rimes will perform with the San Diego Symphony and returning guest conductor Thomas Wilkins on August 25 for this year's Symphony at Salk—A Concert under the Stars. The al fresco fundraiser supports the leading-edge biological research at the Institute and its award-wining community education programs.

Famed for her rich vocals, Rimes has won many awards, including two Grammys, three Academy of Country Music Awards and 12 Billboard Music Awards. She is the youngest recipient of a Grammy Award, as well as the first country recording artist to win in the "Best New Artist" category. Her records have sold over 40 million worldwide, with 42 singles placed on the Billboard Hot Country Songs chart, 13 of which were top 10 hits. She has recorded numerous hit singles in her career, including "Can't Fight the Moonlight," which went #1 in 11 countries, and "How Do I Live," which is the second longest charting song ever on the Billboard Hot 100 chart.

Wilkins returns for his eighth successive year as guest conductor, giving the symphony and audience members another opportunity to enjoy the special energy he brings to every performance. Wilkins is the principal guest conductor of the Hollywood Bowl Orchestra, and he continues his role as the music director of the Omaha Symphony. His extraordinary skill and tireless dedication to promoting lifelong enthusiasm for music has made him a favorite guest conductor for orchestras throughout the country.

Symphony at Salk is one of approximately 100 annual performances by the San Diego Symphony, considered one of the leading orchestras in the United States. The event, which sells out every year, is a San Diego summer tradition, an unforgettable blend of music, camaraderie and fine dining, set amid the Institute's iconic buildings designed by Louis Kahn. Because of its unique nature, it attracts audiences from throughout the region and beyond, and is Salk's premier annual fundraising event.

FRANÇOIS GILOT-SALK CELEBRATED HER 90TH BIRTHDAY at a special evening hosted by **John** and **Stephanie Foster** and **John** and **Laing Rikkers** in conjunction with the Salk Institute. Friends gathered at the classic French restaurant La Grenouille in New York City to share a wonderful night of dining and music with the guest of honor.

Gilot-Salk, the internationally renowned artist and widow of Jonas Salk, has graciously served as Honorary Chair of Symphony at Salk each year since its inauguration in 1996.

Salkex**cell**erators cabinet member Laing Rikkers, François Gilot-Salk and John Foster enjoy her birthday festivities.

Discovery Roundup

The road to diabetes

IN TWO SEPARATE STUDIES FROM SALK LABS, both published in *Nature*, new information about metabolic switches in fat and the liver suggest new avenues for treating diabetes.

A team led by **Ronald M. Evans** has discovered that a simple and long-ignored protein known as fibroblast growth factor 1 (FGF1) may be the secret to surviving long bouts of famine. "Facts do not cease to be important just because they are ignored," Evans says. His team found that FGF1 activity is triggered when we eat sugar and fat, and it helps the body to save this energy for lean times. Mice lacking the protein cannot expand their fat and thus swiftly develop diabetes. Evans suggests that FGF1 is crucial for the ebb and flow of energy throughout our bodies and is needed to maintain normal levels of sugar in the blood.

"The discovery of FGF1 as a missing nutrient switch was unexpected—and intriguing—because it was believed to do nothing," says **Jae Myoung Suh**, a postdoctoral researcher in Evans's laboratory. "If you deplete FGF1 from the body, nothing happens, which is why it was considered uninteresting and ignored. Yet when given a high-fat, 'Western-style' diet, mice develop an uncontrollable form of diabetes and experience a system-wide breakdown of their metabolic health."

Michael Downes, a senior staff scientist working with Evans, says that "without FGF1 abdominal or stomach fat becomes inflamed—an important finding because inflamed visceral fat increases risk for diabetes and other obesity-related diseases, such as heart disease and stroke."

If FGF1 deficiency makes the metabolism worse, then perhaps increasing its levels could make things better. Evans and his colleagues next plan to explore whether FGF1 "therapy" might offer a new way to control diabetes that avoids the side effects of the drug Actos, which regulates FGF1, and thus provide an improved and safer means of increasing insulin sensitivity.

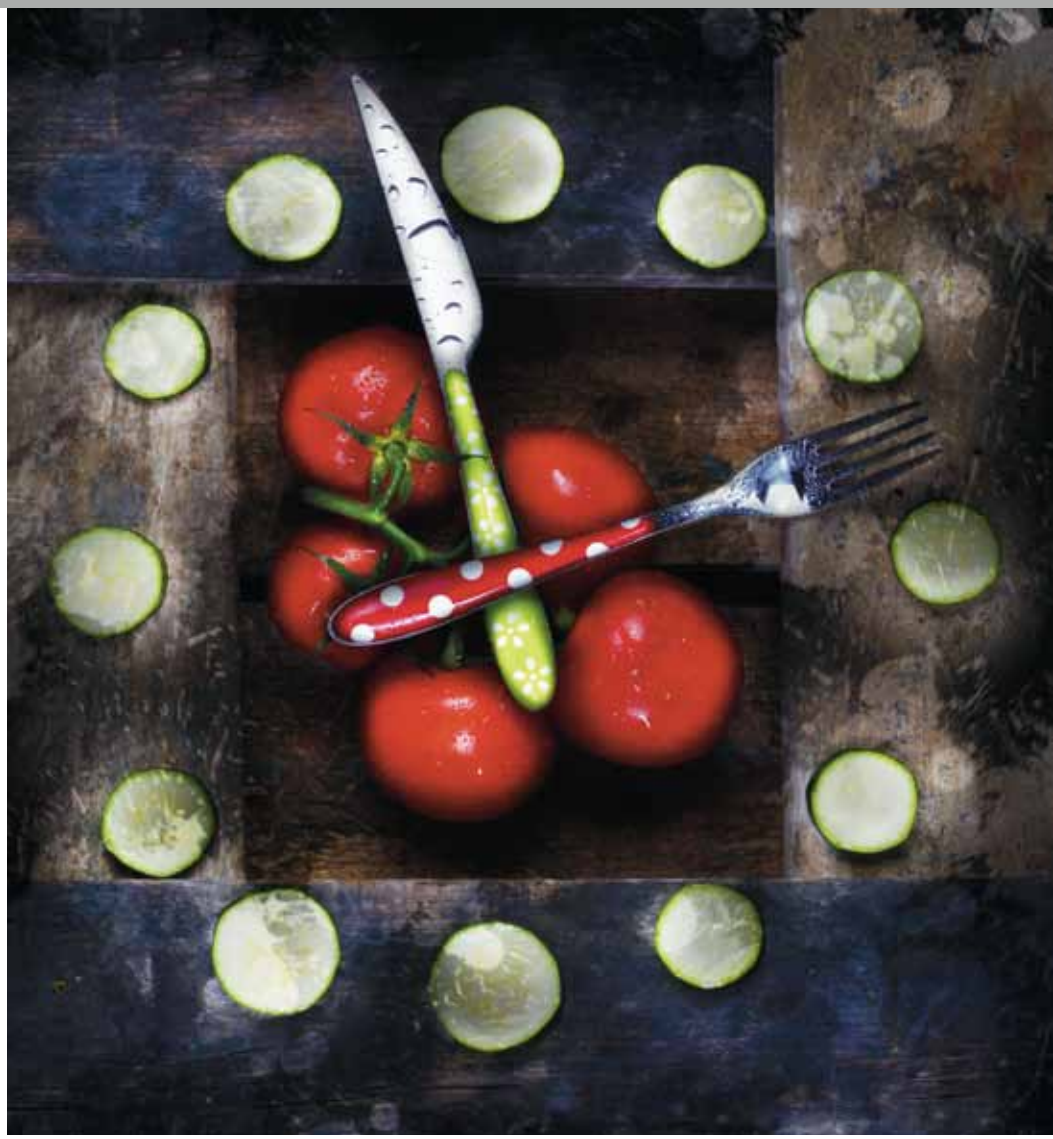
Researchers in **Marc Montminy**'s lab have discovered a pair of molecules that regulate the liver's production of glucose. His team found that controlling the activity of these two molecules, which work together to allow more or less glucose production, could potentially offer a new way to lower blood sugar in type 2 diabetes.

During the day, humans burn glucose, derived from food. At night, when we sleep, we revert to stored fat as a source of very dependable but slowly released energy. But certain parts of the body, most notably the brain, require glucose as a source of energy, even when we fast.

Pancreatic islet cells control both sides of this energy equation, producing glucagon, a hormone released during fasting, to tell the liver to make glucose for the brain. This process is reversed when we eat, when the islets release insulin, which tells the liver to stop making glucose.

Earlier, Montminy found that glucagon turns on a genetic switch (CRTC2) that ramps up production of glucose in the blood. Conversely, when insulin is increased in the blood, activity of CRTC2 is inhibited, and the liver produces less glucose. The new findings identify a relay system that explains how glucagon activates the CRTC2 switch during fasting, and how that system is compromised during diabetes. The scientists say this relay system involves a molecular receptor that they call a "molecular spigot." Glucagon opens the spigot during fasting, allowing an increase in calcium, a common cellular signaling molecule. This stimulates a molecular gas pedal, of sorts, which revs up CRTC2, activating genes that allow the liver to drive the metabolic engine by producing more glucose.

The findings suggest that agents that can selectively damp down activity of the spigot and the accelerator might help to shut down the CRTC2 switch and lower blood sugar in type 2 diabetic patients.



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» Watch the video
www.salk.edu/isjuly12/video6

Members of Noel's lab: postdoctoral researcher Ryan N. Philippe (center) with staff researcher Gordon V. Louie (left) and lab coordinator Marianne E. Bowman.

Discovery of plant proteins may boost agricultural yields and biofuel production

SCORING A RARE SCIENTIFIC HAT TRICK, researchers in the lab of **Joseph Noel**, in collaboration with colleagues at Iowa State University, have identified three related proteins in thale cress plants (*Arabidopsis thaliana*) that regulate the metabolism of fatty acids, chemical components of all cell membranes and vegetable oils.

Plant oils are composed primarily of triglycerides, formed by linking together three fatty acid molecules, and are stored mostly in seeds, where they are used for energy during germination. Seeds are crucial sources of oils for nutrition, flavoring and industrial applications, such as the manufacture of soap and cosmetics as well as for biofuels.

In their study, reported in *Nature*, Noel and his collaborators identified three promising genes by analyzing plant genomic data, then used a variety of techniques to functionally characterize the proteins these genes produce. They found that the proteins, dubbed FAP1, FAP2 and FAP3, bind fatty acids, including the major plant omega-3 fatty acid, an important nutritional component found in certain seeds. The proteins were found in the chloroplasts, the site of fatty acid production and photosynthesis. This suggested that these proteins play a role in the metabolism of fatty acids and thus in the production of fatty acids for plant membranes and oils.

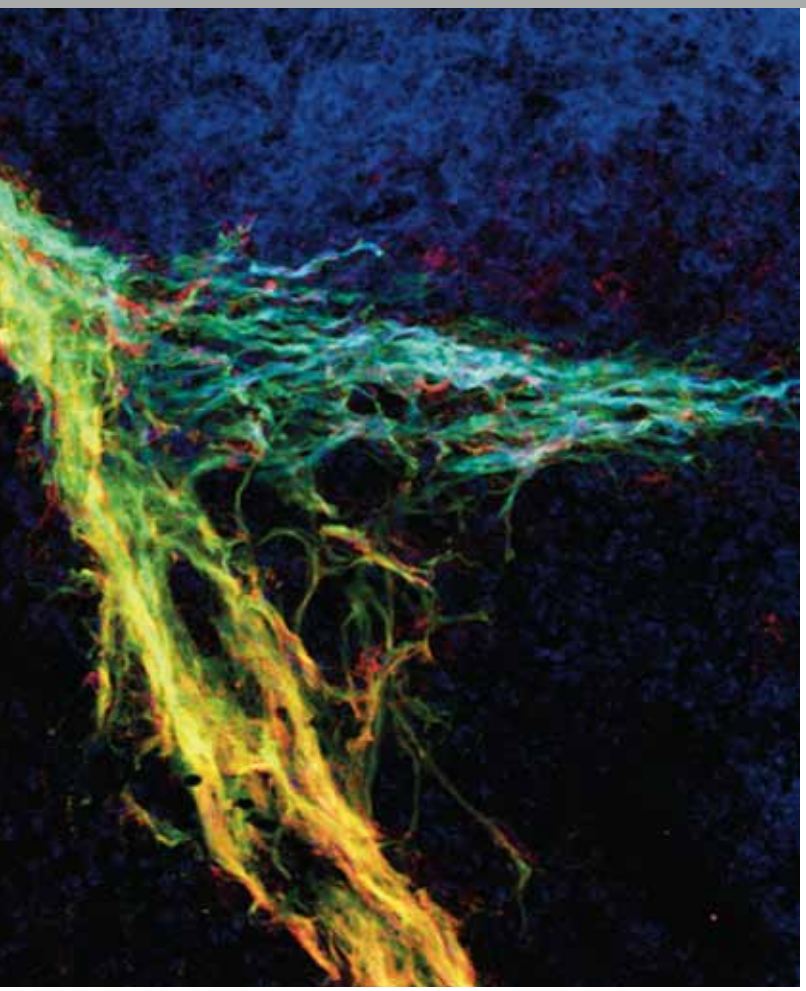
"The proteins appear to be crucial missing links in the metabolism of fatty acids in *Arabidopsis* and likely serve a similar function in other plant species since we find the same genes spread throughout the plant kingdom," says **Ryan Philippe**, a postdoctoral researcher in Noel's lab.

"This work has major implications for modulating the fatty acid profiles of plants, which is terribly important, not only to sustainable food production and nutrition but now to biorenewable chemicals and fuels," adds Noel.

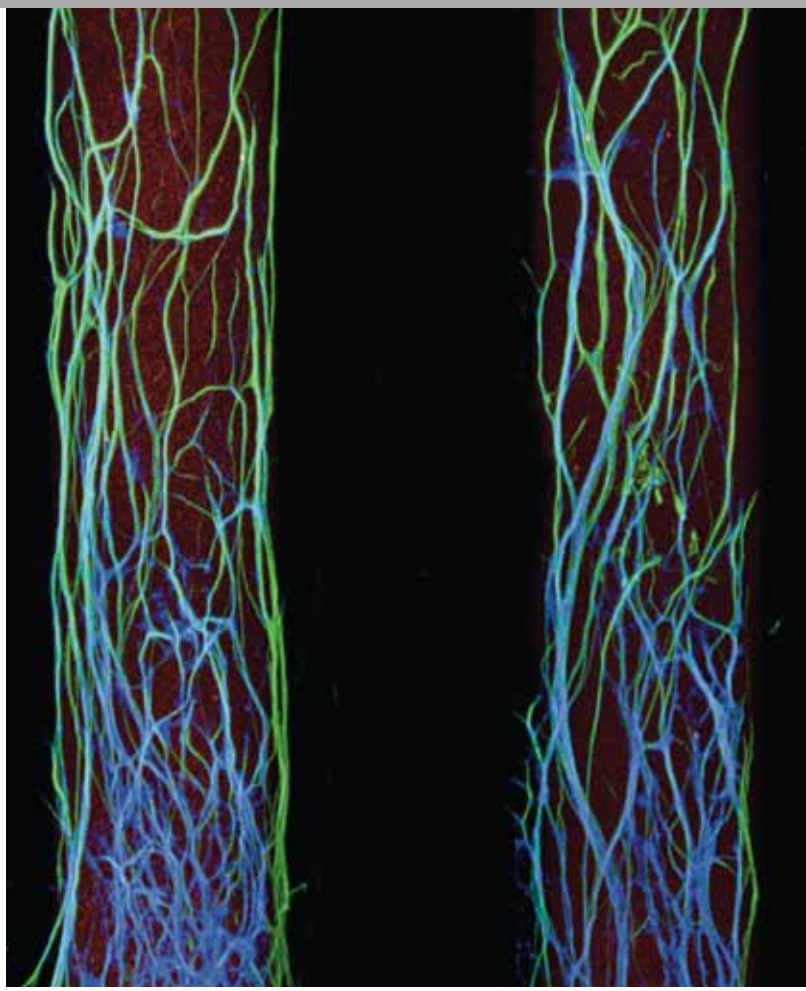
» WEBEXTRA

www.salk.edu/isjuly12/video7

Discovery Roundup



Above: Axons of motor neurons as they make a pathfinding decision to reach and innervate specific muscle compartments in the limb of a mouse embryo.



Above: Motor neuron axons extending preferentially on alternating stripes of recombinant EphA, a growth-promoting signal for these cells.

Images courtesy of Dario Bonanomi, Salk Institute

Complex wiring of the nervous system may rely on just a handful of genes and proteins

RESEARCHERS IN THE LAB OF SAM PFAFF HAVE DISCOVERED a startling feature of early brain development that helps explain how complex neuron wiring patterns are programmed using just a handful of critical genes. His team studied how motor neurons grow axons over the long distance from the spinal cord to muscles, a feature that is essential for creating the connections that allow the brain to control our movements. The growing motor neurons are tipped with a navigational device called the growth cone, which detects factors in the extracellular environment traversed by the neuron. The way that growth cones respond to their complex environment dictates where the neurons will grow and the connections the cells will form, but it has been a struggle to understand the molecular basis for growth cones' ability to detect minute differences in the concentration of factors in their environment. Pfaff's team discovered that motor neuron growth cones have "coincidence detectors" that cause a very strong growth response when two factors converge on the cell simultaneously, rather than sequentially.

"The budding neuron has to detect the local environment it is growing through and decide where it is and whether to grow straight, move to the left or right, or stop," says Pfaff. "It does this by mixing and matching just a handful of protein products to create complexes that tell a growing neuron which way to go."

The brain contains millions of times more neuron connections than the number of genes found in the DNA of brain cells. The Pfaff study is one of the first to try to understand how a growing neuron integrates many different pieces of information in order to navigate to its target and make a functional connection.

The findings might eventually shed new light on a number of clinical disorders related to faulty nerve cell functioning, such as ALS, also known as Lou Gehrig's disease, says **Dario Bonanomi**, a postdoctoral researcher in Pfaff's laboratory. They are also a jumping-off point for understanding defects that might arise during fetal development of the nervous system.

In addition, the researchers say the study, which was published in *Cell*, offers insights into cancer development, because a protein crucial to the "push and pull" signaling system, as well as other protein receptors described in the study, is also linked to cancer.

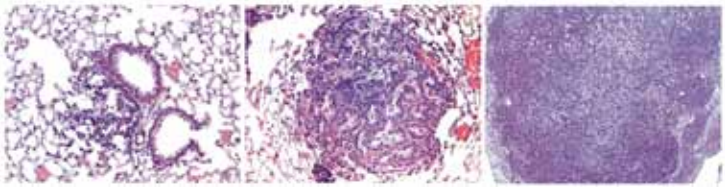
A new drug target for lung cancer

DRUGS TARGETING AN ENZYME INVOLVED IN INFLAMMATION might offer a new way to treat certain lung cancers, according to a new study from the lab of **Inder Verma**. His team discovered that blocking the activity of an enzyme that helps activate the body's inflammation response slowed the growth of tumors in mice with lung cancer and increased their lifespan.

"Lung cancer is one of the most lethal cancers, and the prognosis for patients is often poor, with only about 15 percent surviving more than five years," Verma says.

Scientists have long known that there is a link between cancer and inflammation, the body's first line of defense against infection. Some of the same biochemical players that protect the body by controlling cells' inflammation response can also be hijacked by genetic mutations involved in the development of cancer. To better understand how these normally helpful components of the immune system are put to nefarious tasks in cancer cells, Verma and his colleagues developed a new method of inducing non-small-cell lung cancer in mice. This type accounts for as much as 80 percent of all lung cancer cases.

They then turned their attention to a protein complex, NF-KB, that initiates the inflammation response to infection by orchestrating a cell's genetic activity. Malfunctioning regulation of NF-KB has been linked to various types of cancer, including lung cancer, but due to its many functions in the cell, drugs that directly target NF-KB would likely cause severe side effects.



These images show the development of cancer (dark purple) in the mouse lung, initiated by lentiviral vector. A few cancerous cells (left image) proliferate over time into a full-blown tumor (right image).

Image courtesy of Yifeng Xia, Salk Institute for Biological Studies

To get around this limitation, Verma's group focused on IKK2, an enzyme that spurs NF-KB's activity in response to stress. When they blocked IKK2 activity in the mice with lung cancer, the mice had smaller tumors and lived longer, suggesting that the enzyme is necessary for NF-KB to stimulate tumor growth. This was unexpected because the conventional wisdom is that loss of NF-NB activity will reduce inflammation.

The findings, reported in *Nature Cell Biology*, suggest that drugs that hinder IKK2's ability to command cellular activity might prove effective as lung cancer therapies.

"Systemically and chronically blocking IKK2 activity is too toxic to be used in chemotherapy," says **Yifeng Xia**, a postdoctoral researcher in Verma's lab, "but we might be able to target another molecule in the signaling pathway by which IKK2 regulates tumor growth."

Salk scientists use an old theory to discover new targets in the fight against breast cancer

REVIVING A THEORY FIRST PROPOSED IN the late 1800s, a team of researchers led by **Geoffrey Wahl** reported striking similarities between genetic signatures found in certain types of human breast cancer and those of stem cells in breast tissue in mouse embryos. These findings, published in *Cell Stem Cell*, suggest that cancer cells subvert key genetic programs that guide immature cells to build organs during normal growth.

"Stem cells in a healthy developing embryo have a GPS system to alert them about their position in the organ," says Wahl. "It stimulates the stem cells to grow and form more stem cells or to change into different cells that form complex organs, such as the breast. Our findings tell us that this GPS system is broken during cancer development, and that may explain why we detect stem-like cells in breast cancers."

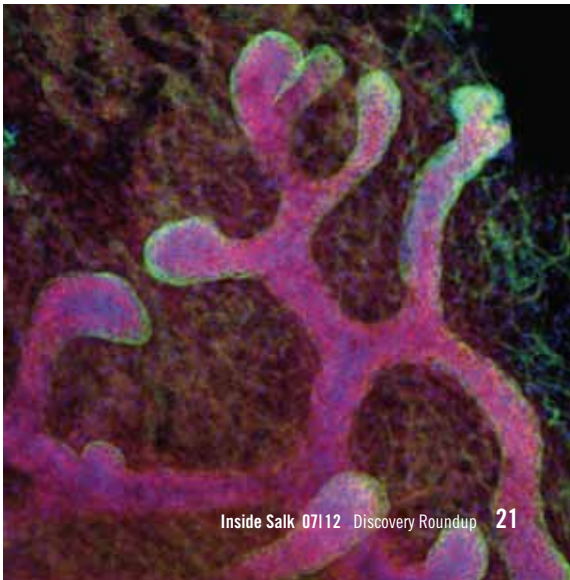
Studying the genetic activity of organ-specific stem cells is difficult because the cells are very rare, and it is hard to separate them from other cells in the organ. But by focusing on tissue obtained from mouse embryos, Wahl's group, which included **Benjamin Spike**, **Dannielle Engle**, **Jennifer Lin**, **Justin La** and **Samantha Cheung**, was able for the first time to identify and isolate a sufficiently large number of fetal breast stem cells to begin to understand how their GPS works.

The signatures of the breast stem cells in the fetus were stunningly similar to the stem-like cells found in aggressive breast cancers, including a significant fraction of a virulent cancer subtype known as "triple-negative," which until now lacked the molecular targets useful for designing personalized therapeutic strategies. The discovery of the shared genetic signatures provides a new avenue for scientists to explore the links between development and cancer. By uncovering new biological markers, Wahl and his team hope to develop tests that individualize treatment by showing how the GPS system of a tumor operates. This should help doctors determine which patients may benefit from treatment, and the correct types of treatment to administer.

» **Watch the video**
www.salk.edu/isjuly12/video3

Mammary stem cells found in developing mouse embryos (pictured here against a background of fat tissue).

Image courtesy of Dannielle D. Engle



Discovery Roundup

Salk scientists discover how plants grow to escape shade

MILD MANNERED THOUGH THEY SEEM, plants are extremely competitive, especially when it comes to getting their fair share of sunlight. A plant's primary weapon in this contest is the ability to grow toward light, getting the amount it needs and shadowing its competition.

Scientists knew that a pigment found in leaves of thale cress plants (*Arabidopsis thaliana*), phytochrome B (PHYB), is excited by both the red wavelengths of light that drive photosynthesis, as well as the near infrared light that is enriched in shady spots. But no one had found a direct link between this response to light and the hormone-driven growth response to shade.

A team in the lab of **Joanne Chory** recently determined precisely how leaves tell stems to grow when a plant is caught in a shady place. In a paper published in *Genes and Development*, the researchers reported that a protein known as phytochrome interacting factor 7 (PIF7) serves as the key messenger between a plant's cellular light sensors and the production of auxins, hormones that stimulate stem growth.

If a sun-loving plant finds itself in a shady place, sensors in its leaves will tell cells in the stem to elongate, causing the plant to grow upward toward sunlight. When a plant remains in the shade for a prolonged period, however, it may flower early and produce fewer seeds in a last-ditch effort to help its offspring spread to sunnier real estate. In agriculture, this response, known as shade avoidance syndrome, results in loss of crop yield due to closely planted rows of plants that block each other's light.

In their study, Chory and her colleagues used biochemical and genomic analyses to identify PIF7 as the key molecular link between a plant's light sensors and production of auxins.

"We already knew that auxin is made in the leaves and travels to the stem to stimulate growth," she says. "Now we know how shade stimulates the leaves to produce auxin, and it turns out that it's a remarkably simple pathway to control such an important function."

These findings may offer new avenues for developing crops with stem architectures better suited to tightly planted field rows, making them less prone to shade avoidance syndrome and capable of producing higher food and biofuel yields than existing strains.

Arabidopsis thaliana

Sending out an SOS: How telomeres incriminate cells that can't divide

THE WELL-BEING OF LIVING CELLS requires specialized squads of proteins that maintain order, chewing up worn-out proteins, wrapping up damaged organelles, and—most importantly—repairing anything that resembles a broken chromosome. If repair is impossible, the crew foreman calls in executioners to annihilate a cell. As unsavory as this last bunch sounds, failure to summon them is one aspect of what makes a cancer cell a cancer cell.

This microscope image shows chromosomes in human lung cells exhibiting telomere damage caused by colcemid, a drug that arrests cell division.

Image courtesy of Jan Karlseder, Makoto Hayashi, research associate, and James Fitzpatrick, Waitt Advanced Biophotonics Center

A recent study by scientists in the lab of **Jan Karlseder** showed exactly how cells sense the possibility that their DNA is damaged as a first step to responding to the failure to divide properly. The study, published in *Nature Structural and Molecular Biology*, found that if cells take too long to undergo cell division, protective structures at the tips of their chromosomes, known as telomeres, send out a molecular SOS. The findings have dual implications for cancer chemotherapy. First, they show how a class of anti-cancer drugs that slows cell division—known as mitotic inhibitors—kills cells. More significantly, the findings suggest ways to make therapy with those inhibitors more potent.

Initially, the group searched for specific proteins that might keep telomeres intact during cell division. What they found was unexpected—that any manipulation that crippled and prolonged cell division produced increased numbers of telomere blobs indicative of "unprotected" telomeres. Moreover, treating cells with mitotic inhibitors used in cancer chemotherapy did the very same thing. Those studies established a link between arrested mitosis, telomere perturbation and cell death. Karlseder's group then confirmed that as cells stalled in mitosis, telomeres started to disintegrate.

This work suggests novel strategies that could be used in combinatorial cancer chemotherapy regimes, which rely on the synergy between two or more drugs.

"To make therapy more effective and reduce side effects, we might be able to use more moderate levels of mitotic inhibitors, which at high doses can cause severe side effects, paired with a different drug that sensitizes cells to the DNA damage response," says Karlseder. "That could improve the chances of catching 100 percent of the tumor cells."

» Watch the video

www.salk.edu/isjuly12/video4

> “All cells combat functional deterioration of their protein components through the process of protein turnover.”
>
> – MARTIN HETZER

» **Watch the video**
www.salk.edu/isjuly12/video2

Discovery of extremely long-lived proteins may provide insight into cell aging and neurodegenerative diseases

ONE OF THE BIG MYSTERIES IN BIOLOGY is why cells age, but a team led by **Martin Hetzer** has recently provided some intriguing clues. He and his group have discovered a weakness in a component of nerve cells that may explain how the aging process occurs in the brain. They found that certain proteins, called extremely long-lived proteins (ELLPs), which are found on the surface of the nucleus of neurons, have a remarkably long lifespan. Whereas the lifespan of most proteins totals two days or less, the scientists identified ELLPs in the rat brain that were as old as the organism, a finding they reported in *Science*. Their results suggest the proteins last an entire lifetime.

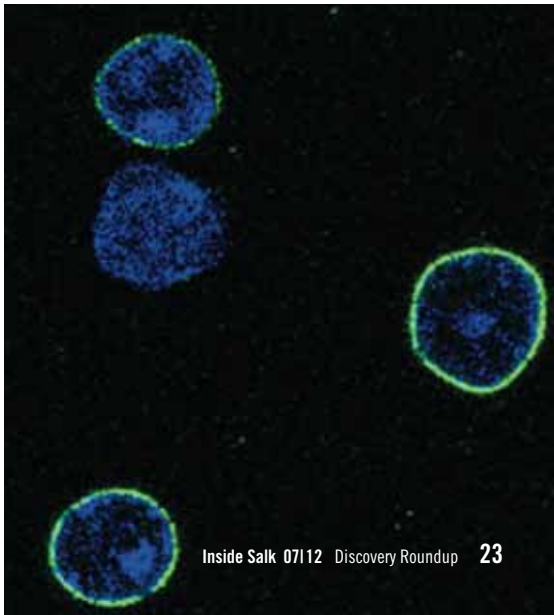
ELLPs make up the transport channels on the surface of the nucleus, called nuclear pore complexes, which function as gates controlling what materials enter and exit. Unlike other proteins in the body, ELLPs are not replaced when they sustain aberrant chemical modifications and other damage. Damage to the ELLPs weakens the ability of the nuclear pore complexes to safeguard the cell’s nucleus from toxins. The toxins may alter the cell’s DNA and the activity of genes, resulting in cellular aging.

“The fundamental defining feature of aging is an overall decline in the functional capacity of various organs such as the heart and the brain,” Hetzer says. “This decline results from deterioration of the homeostasis, or internal stability, within the constituent cells of those organs. Recent research in several laboratories has linked breakdown of protein homeostasis to declining cell function.”

The results that Hetzer and his team report suggest that declining neuron function may originate in ELLPs that deteriorate as a result of damage over time.

“All cells combat functional deterioration of their protein components through the process of protein turnover, in which the potentially impaired parts of the proteins are replaced with new functional copies,” he explains. “Our results also suggest that a class of proteins exists that cannot be replaced. Therefore, these proteins might be part of a general aging mechanism leading to age-related defects in nuclear function.”

The findings may prove relevant to understanding the molecular origins of aging and such neurodegenerative disorders as Alzheimer’s and Parkinson’s diseases.



This microscope image shows extremely long-lived proteins, or ELLPs, glowing green on the outside of the nucleus of a rat brain cell. DNA inside the nucleus is pictured in blue.

Image courtesy of Brandon Toyama, Salk Institute for Biological Studies

The **next** generation:

Carol Marchetto

A passion for the lab bench—and beyond

> “I’m not ashamed to say I love spending my days culturing cells. It’s who I am. It rejuvenates me.”
>
> – CAROL MARCHETTO

AT FIRST BLUSH, CAROL MARCHETTO’S PASSIONS—YOGA, DANCE and cell culture—seem an odd mix. But the more time one spends with her, the more it makes sense. All three activities require focus, energy and grace, traits that she exudes.

“I guess you’d say I’m a doer,” says Marchetto, a staff scientist in the laboratory of Salk professor **Fred Gage**. “I love to be in the action, whether I’m dancing, in yoga class or working at a laboratory bench.”

A highly experienced and successful laboratory scientist, Marchetto finds herself in a period of transition in her career, still committed to hands-on laboratory work but also exploring new and unfamiliar directions in her research and learning to communicate her work to the world outside her lab.

“I’m not ashamed to say I love spending my days culturing cells,” she says. “It’s who I am. It rejuvenates me. But I’m discovering that being a scientist is more than just bench work. There’s also coming up with new ideas, finding funding to support those experiments and explaining to the public why science is so important.”

Talking with Marchetto, a native of Brazil, one immediately notices her beaming smile, enviable posture and dancer’s penchant for expressing herself with her hands, which move constantly to illustrate ideas and events.

With those same hands, Marchetto coaxed skin cells taken from patients with Rett syndrome, a debilitating form of autism that occurs most often in girls, to develop into induced pluripotent stem cells (iPSCs) and then into neurons. This feat allowed neurons from autistic patients to be studied in the laboratory, opening the door to understanding the genetic causes of the disease.

“Carol has a remarkable ability to make experiments work,” Gage says. “She also really enjoys science—you can see it. She loves to talk about it, she reads deeply in the literature, she brings incredible energy to the lab. We are very fortunate to have Carol as a colleague.”

As a child, Marchetto was equal parts inquisitive and creative, fascinated with the strength of ants and possessed of a deep aversion to following recipes, preferring to mix ingredients according to her own whims. She once left a piece of raw meat out in the Brazilian sun to see the worms consume it, an experiment that was cut short by her mother’s reaction to the smell. “I’ve always been super-curious,” says Marchetto.

She received her doctorate in genetics in 2005 from Brazil’s University of São Paulo and that same year joined Gage’s lab as a postdoctoral fellow, where she’s focused on using iPSCs to study brain development and model human neurological diseases.

“It’s all so new and cool,” Marchetto says. “You’re not going to open a textbook and find instructions on what experiments to do. We have to figure it out as we go.”

Last summer, she was promoted to staff scientist at Salk and has since expanded her research to explore how the human brain evolved from those of our primate ancestors. Humans and apes share a large number of genes—around 96% in the case of chimps—but our brain sizes and cognitive abilities are vastly different.

Marchetto is studying how iPSC-derived neurons from chimps, monkeys and bonobos develop and make connections with one another in the laboratory and is comparing them to iPSC neurons from humans.

“It’s amazing that our DNA is so similar but our brains so different,” Marchetto says. “Many of these differences arise during development, probably due to varying patterns of gene expression. By comparing development of iPSC-derived neurons from humans and apes, we can study human evolution in a laboratory dish.”

Marchetto also has recently devoted more of her time to sharing her infectious passion for science with other people through mentoring postdocs; mentoring students on Salk’ s March of Dimes High School Science Day; and delivering Back to Basics talks, public lectures on Salk research organized by the Planned Giving office. With government funding for basic science in decline, she hopes her talks will help the public better understand the positive impact of science on people’s lives and the need to fund research.

“I love to go to my little cell culture room and work,” she says. “But you have to look at the big picture and get out of your comfort zone. It takes a while to learn how to explain science to non-scientists, but if you don’t take the time to explain to people what you are doing, they won’t respect and appreciate your work.”

Science and Salk bat 1000 at annual expo

USUALLY IT'S BASEBALL THAT TAKES OVER PETCO PARK EACH SPRING, BUT ON MARCH 24, it was scientists from the Salk Institute and 139 other San Diego institutions, along with thousands of curious minds learning about the world of science. More than 25,000 people visited **EXPO DAY**, the culminating event of the weeklong San Diego Festival of Science and Engineering. Salk had a special exhibit on genetics and DNA, where kids learned how to extract DNA from wheat germ. With opportunities to participate in hands-on activities, meet real scientists and engineers and learn how their discoveries and research affect our daily lives, the festival provided a unique opportunity to reach students of all ages and backgrounds, inspiring the next generation of innovators.

The future of science visits the Salk

THE SALK INSTITUTE WELCOMED MORE THAN 200 STUDENTS FROM 18 SAN DIEGO COUNTY schools to the 22nd annual March of Dimes High School Science Day on March 3. The students, accompanied by their teachers, had an opportunity to work side by side with Salk researchers, collectively visiting 20 different laboratories, where they conducted hands-on experiments. Several dozen Salk employees volunteered for the half-day event. Salk laboratories generally are not open to the public, making it a unique—and unforgettable—experience for the participants.

Up close with fruit flies.

THE WAITT ADVANCED BIOPHOTONICS CENTER AT THE SALK was a classroom for middle school students visiting from St. Anne's School in Laguna Niguel. The young students peered into microscopes, looking at fruit flies (*Drosophila melanogaster*).

» **Watch the video**
www.salk.edu/isjuly12/video8

Inaugural Alumni Fellowship awarded

COLLABORATIONS BETWEEN FACULTY, graduate students and postdocs are a mainstay and core value of research at the Salk. These collaborations recently took a new direction—outside the laboratory.

Recognizing the ongoing need for postdoc support, Salk faculty issued a challenge to alumni—those scientists who trained in the Institute's labs—to match their philanthropic contributions dollar for dollar to establish the Alumni Fellowship Fund. Many alumni responded with gifts, and the first Alumni Fellowship has now been awarded, to **Seung Choi** in **Katherine Jones**'s lab.

"I am extremely grateful for the support the Alumni Fellowship is providing for my work," Choi says. "This will allow me to expand my research into a key molecular pathway involved in the development of cancers."

Choi's research is focused on the Wnt signaling pathway, which controls cell proliferation, differentiation and embryonic stem cell growth. Although the Wnt pathway is normally active only during development, it can become inappropriately reactivated in adult cells, giving rise to colon cancer, melanomas, prostate cancer, breast cancer and several other aggressive malignancies, resulting in a poor prognosis. Therefore, the deregulation of this pathway is directly responsible for the vast majority of human cancers.

Choi is specifically studying the Wnt pathway in human colon and prostate cancers, and he made the surprising discovery that the APC tumor suppressor protein, which is mutated in 85% of human colon cancers, collaborates with a metastatic tumor suppressor, called alpha-catenin, to switch off the expression of genes that drive cell growth and proliferation. Consequently, colon cancer cells with mutant APC protein, or prostate cancers that lack the alpha-catenin tumor suppressor, fail to turn off these same sets of pro-growth genes.

Choi has created a new model for Wnt signaling that makes clear predictions that can be directly tested experimentally, and he is developing a stable human prostate cell line to explore the pathway further.

"The Salk faculty are very generous in their support of science research, and we are excited that Seung Choi was recently selected as the inaugural fellow for this award," says Jones. "The funding from the Salk Alumni Fellowship Fund will provide essential support for this early, promising research."

Please collaborate with Salk faculty in this critically important endeavor and make your contribution today. Your support of the Alumni Fellowship Fund will help especially talented postdocs get a jump on their careers. To learn more, call (858) 453-4100, ext. 1405 or email mshockro@salk.edu

> "I am extremely grateful for the support the Alumni Fellowship is providing for my work."
>
> – SEUNG CHOI

Qualcomm donates $1.5 million to Salk in honor of trucking pioneer

IN MEMORY OF DON SCHNEIDER, FORMER president, CEO and chairman of trucking company Schneider National, Qualcomm has made a $1.5 million gift to establish the Don Schneider Qualcomm Innovation Fellowship at the Salk Institute. The fellowship will endow a postdoctoral position in Schneider's name and enable the Institute to continue hiring the world's best scientists in perpetuity to conduct biological research that impacts humanity.

Schneider died January 13 after a long battle with Alzheimer's disease. He was 76 years old.

"Don was a trendsetter in the industry, and his belief in the merits of advancing the integration of technology into transportation and logistics continues to benefit drivers, customers and fleet operators today," said Paul E. Jacobs, chairman and CEO of Qualcomm Incorporated. "Qualcomm is proud to continue Don's legacy through the donation of $1.5 million in his name to the Salk Institute."

In 1988, San Diego–based Qualcomm Incorporated launched OmniTRACS, a satellite-based data communications system for the transportation industry that revolutionized how truck fleet operators tracked and monitored their vehicles in the field. Although Qualcomm was still a young company, Schneider made a bold move and became an early adopter of Qualcomm's new technology. Schneider was a visionary and his became the first trucking company to install a two-way satellite communication and tracking system in its trucks, ushering in a new era for the industry.

"I was fortunate to have met, worked with and learned from Don during the very early days of our company," said Irwin Jacobs, Salk Institute board chairman and founding chairman and CEO emeritus of Qualcomm. "It is a rare privilege to have had the opportunity to know an individual who modeled kindness, intelligence, integrity, philanthropy, compassion and outstanding business leadership."

The Don Schneider Qualcomm Innovation Fellowship at the Salk Institute will support scientific research in the areas of molecular biology, genetics and neurosciences.

salkexcellerators

San Diego **Salk**ex**cell**erators spring into science

MEMBERS OF THE SAN DIEGO SALKEXCELLERATORS TOOK PART IN TWO SPECIAL functions hosted at the Salk Institute, where they had the opportunity to witness the leading-edge science supported by their charitable donations.

On April 18, guests enjoyed an exclusive behind-the-scenes lab tour with **Sreekanth Chalasani**, an assistant professor in the Molecular Neurobiology Laboratory. Chalasani, whose research applies a combination of genetics, functional imaging and behavioral analysis to study how the tiny *C. elegans* worm's nervous system responds to changes in the environment, shared his latest findings in behavioral neuroscience.

Sreekanth Chalasani

From left: Melanie Casey, Holger Mueller, Heather Mueller, Kristin Gibson-Trikas and George Trikas.

The following month, on May 2, attendees gathered for a private reception catered by Pamplemousse Grille before adjourning to the Trustees Room to listen to a presentation titled "Going Nuclear on Aging," given by faculty members **Jan Karlseder** and **Martin Hetzer**, both professors in Salk's Molecular and Cell Biology Laboratory.

Karlseder, whose research focuses on understanding the functions of mammalian telomeres, spoke on "The Ends of Aging," explaining how telomeres—the protein-DNA complexes at the ends of linear chromosomes—are crucial in DNA replication, tumor suppression and aging. Every time a primary human cell divides, its telomeres get shorter, until critically short telomeres lead to terminal cell cycle arrest. Karlseder believes that a better understanding of this process will eventually allow scientists to influence the aging process and, as a result, restrict cancer cell growth.

Hetzer followed with a talk titled "You're Only as Old as Your Proteins," about his discovery that certain proteins, called extremely long-lived proteins (ELLPs), found in neurons and other non-dividing cells, have a remarkably long lifespan. His lab found that while most proteins turn over in two days or less, ELLPs discovered in the rat brain were as old as the organism, a finding that was recently published in *Science*. These discoveries may enhance understanding of the molecular origins of aging and such neurodegenerative disorders as Alzheimer's and Parkinson's disease.

***Salk**ex**cell**erators are the next generation of business professionals, entrepreneurs, and volunteers committed to supporting the groundbreaking research conducted at the Salk Institute. Join our community of philanthropists at special events year round that include opportunities to engage with Salk's renowned scientists.*

For additional information, please contact: ***Megan Shockro,*** *Associate Director, Development. Phone: 858 453-4100 ext. 1405. E-mail: mshockro@salk.edu*

Jeff Barany, Kurt and Maggie Cellar, and Charlie and Meghan Hannigan

New York **Salk**ex**cell**erators: Supporting scientific discovery

MORE THAN 50 GUESTS ATTENDED THE NY SALKEXCELLERATORS private reception and scientific presentation, which was held April 26 at the spectacular Norwood Club, a landmark townhouse in the city.

The evening began with **Salk**ex**cell**erators member **Kurt Cellar** speaking on his role in philanthropy and the importance of supporting scientific discovery. Cellar, a Chartered Financial Analyst, private investor and successful consultant and board member to companies in a variety of industries, first became involved with the Salk Institute in 2008 after a visit to the campus with his wife, Maggie, and their sons. Impressed by what they learned on their tour, the Cellars made the Salk Institute one of their significant charities since they felt "the Salk is the right group to back and will do amazing things over our lifetime." The Cellar family also generously underwrote the evening's event.

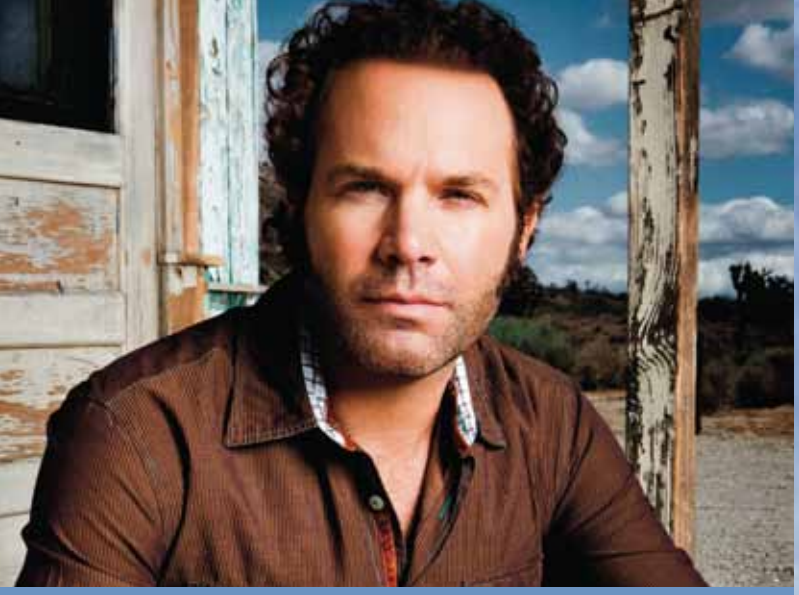
The discussion was followed by an engrossing lecture titled "Naming the Emperor: Linking Development, Stem Cells and Cancer," presented by **Geoffrey M. Wahl**, a professor in the Salk Gene Expression Lab. Wahl studies the cellular and genetic underpinnings of breast cancer, working with clinical oncologists to derive better diagnostic and prognostic tools based on the genes expressed in stem-like cells, which his lab has shown are present in some of the most aggressive forms of breast cancer.

Impacting human health through scientific discovery depends on the vision and generosity of philanthropists. For more information about future Salk events in New York City, please contact Betsy Reis at 858-452-8051 or breis@salk.edu.

Salk on the Road

THE SALK HOSTED A SPECIAL LUNCHEON IN PHOENIX TO SHARE THE message that "Tomorrow's Discoveries Rest in the Hands of Today's Young Scientists." **Kristen Brennand**, a research associate, and **Dinorah Morvinski**, a senior research associate, both in Salk's Laboratory of Genetics, gave talks about the cutting-edge science they conduct and the potential of their studies to lead to breakthrough discoveries that impact human health. **Jo Norris**, Salk International Council member, helped coordinate the event to welcome current supporters and to introduce new friends to Salk science and the importance of basic biological research.

From left: Dinorah Morvinski and Kristen Brennand



John Ondrasik

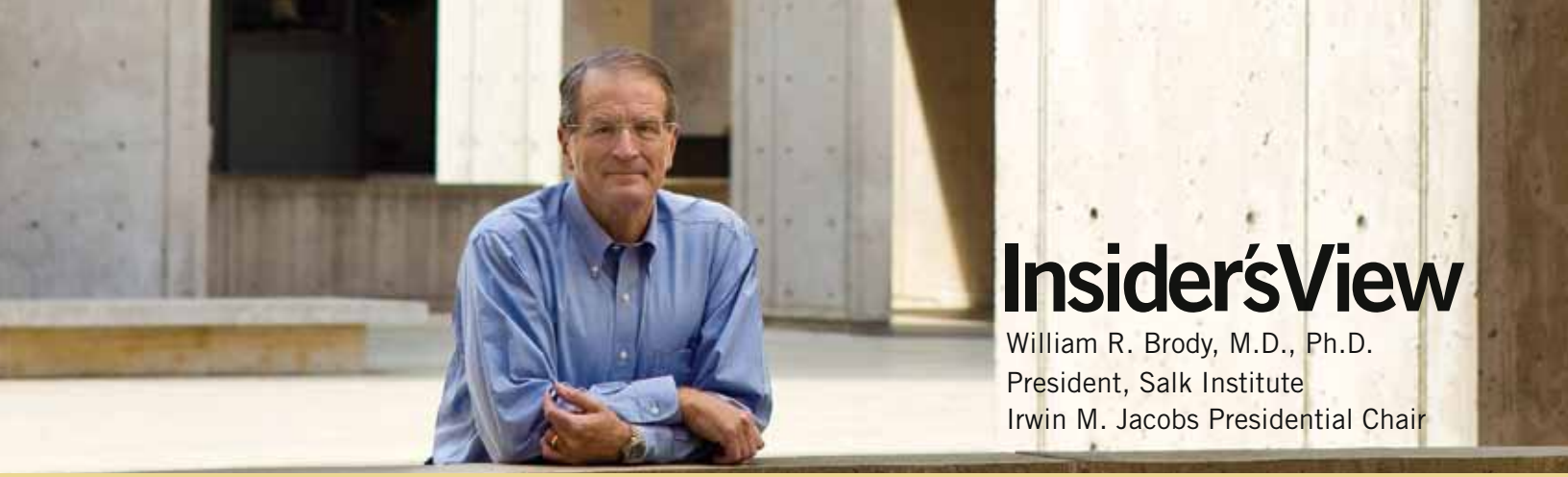
40th Annual Tax and Management Seminar for Private Foundations

> "I always talk about making a difference and changing the world. The Salk is where that is happening."
>
> – JOHN ONDRASIK

THE SALK INSTITUTE WELCOMED NEW AND LONGSTANDING foundation partners to the 40th Annual Tax and Management Seminar for Private Foundations on March 14. The three-day conference offered a unique program featuring expert speakers and topics of importance to foundation trustees, family and staff. The seminar is an ongoing tradition at the Institute that continues to flourish and grow every year.

John Ondrasik, singer and songwriter from the musical group Five for Fighting, delivered the keynote address and treated guests to a special musical performance. Ondrasik, an ardent philanthropist, shared personal stories throughout the intimate concert, explaining what motivates him to use his musical talents to make a positive impact on the world.

» **Watch the video**
www.salk.edu/isjuly12/video9



Insider's View

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

About thinking...fast and slow

IF YOU HAVEN'T HAD A CHANCE TO READ DANIEL KAHNEMAN'S NEW BOOK, *Thinking Fast and Slow*, I highly recommend it to you. Dr. Kahneman is one of only two people to win the Nobel Memorial Prize in Economics who is not an economist; rather, he is a behavioral psychologist. Many of his landmark studies have pointed out the irrationality in our decision making that violates the well-accepted "laws" of economics—like supply and demand.

In *Thinking Fast and Slow*, Kahneman outlines evidence for the existence of two separate "functions" within the brain—one that makes judgments and decisions quickly but often highly irrationally and the other that uses a slower, more methodical process of analytical thinking. The insight I gained from reading his book is how irrationally biased our decision-making process can be. Even when we are alerted before the fact that our brain is likely to be biased in determining some outcome, we are often unable to overcome that bias.

There are many interesting studies of human behavior presented in the book, but the one observation that Kahneman makes repeatedly is our inability to make accurate, or even semi-accurate predictions of the future. While we are great at analyzing the past and understanding the present, we don't do better than chance in trying to opine what will happen next. Embracing this uncertainty, as I see it, is crucial to fostering creative research that leads to surprising discoveries—just the sorts of breakthroughs you've read about in this issue of *Inside Salk*.

People often ask me, "Bill, what will be the next big breakthrough that Salk scientists are working on?" And my answer simply is, "I haven't a clue." While I would like to sound erudite and provide some predictions, scientific breakthroughs are by definition not predictable. Would we have known a decade ago that we could make stem cells from a small piece of skin? I am sure some people predicted this, but the experiment that led to this discovery wasn't even focused on this challenge; the result happened in a completely serendipitous way and has since changed the face of stem cell research—and for the better, I should say.

The key for the Salk is simply to encourage our young scientists to try bold experiments, pursue the unpredictable and keep their eyes open for unexpected results.

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Salk **Calendar**

AUGUST 2012

25 **Symphony at Salk with LeAnn Rimes**

OCTOBER 2012

17 **Salk Photography Contest Reception**

NOVEMBER 2012

7 **San Diego Salkexcellerators Reception & Scientific Presentation**

DECEMBER 2012

6 **President's Club Holiday Luncheon**

JANUARY 2013

23–25 **International Council Meeting at the Salk Institute**

From Yellow to Red
Oil on canvas, 39 x 32 inches
From the collection of Caparis & Meignen, Paris

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