

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

INSIDE SALK

Brain cells “talk” with each other outside the synapse

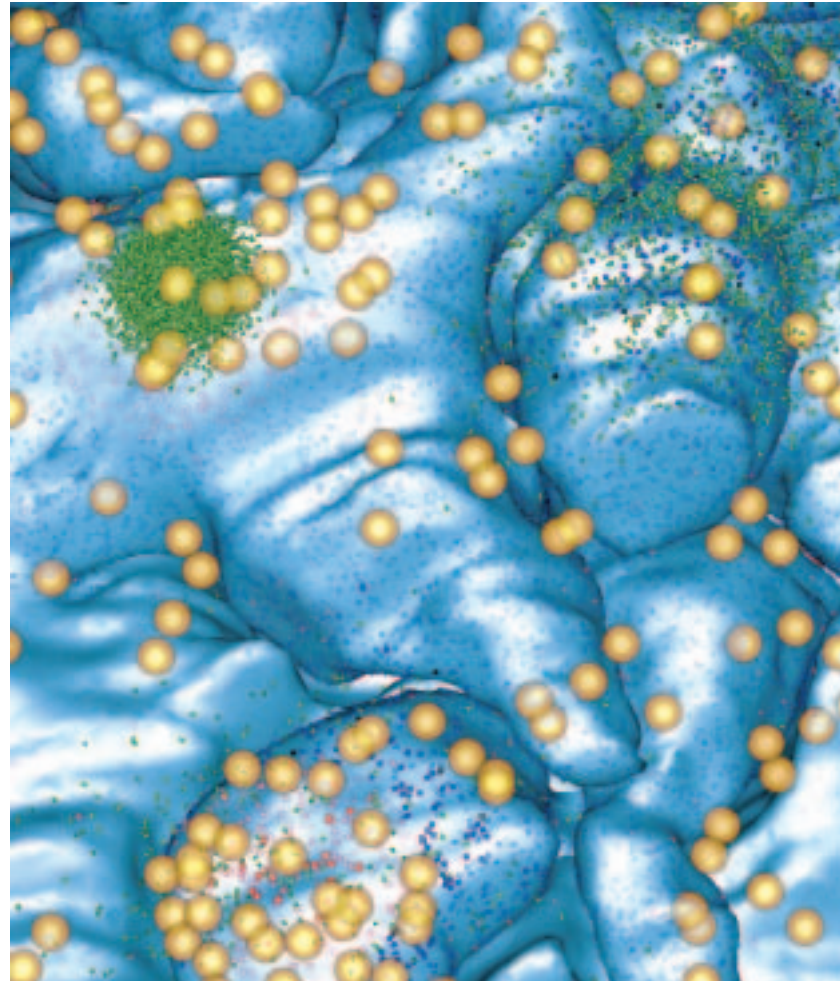
The popular anti-depression drug Prozac has introduced many members of the public to “neurotransmitters” and related scientific terms, such as “synapse.” By reading newspaper and magazine articles about the drug, many of us know that Prozac works because it boosts the brain’s supply of a neurotransmitter called serotonin. Serotonin and other chemical messengers enable the brain to function — enabling you to read this text.

Many newspaper and magazine articles and, more

continued on page 2

Brain cells dispatch chemical messengers to communicate with each other.

The yellow colored sacs in the foreground of this computer-simulation image release the messenger molecules into the gap between the “sending” and “receiving” cells. Once they are set free from the sacs, the green-colored chemical messengers bind to special receiving molecules on the surface of neighboring cells. In this image, the blue represents the surface of the receiving cell. The receptors, or receiving molecules, are the very small, square shaped structures on the cell’s surface.



“Our results opened up the possibility that neurons can communicate many other ways, not just at the traditional places that are defined by their anatomy.”

importantly, neurobiology textbooks explain that neurotransmitters flow from one brain cell to another through synapses, the specialized cell-cell contacts found at the end of the cells’ threadlike extensions. For decades, synaptic communication has been accepted dogma.

But it soon may be out of date, as a result of research at the Salk Institute and the University of California, San Diego. Salk and UCSD scientists have discovered that nerve cells, or neurons, may not have to rely on traditionally defined synapses

to “talk” to each other.

“Our results opened up the possibility that neurons can communicate many other ways, not just at the traditional places that are defined by their anatomy,” said Terrence J. Sejnowski, head of the Institute’s Crick-Jacobs Center for Computational and Theoretical Biology and lead author of the study that was published in *Science* in July.

It took a unique collaboration between anatomists and physiologists at the University of California, San Diego and theoretical neurobiologists at the Salk

Institute to challenge the standard model of neurotransmission.

“Combining mathematical modeling with physiological, anatomical and behavioral data is the future of neurobiology. It allows us to draw conclusions that we could not have reached in any other way,” said Sejnowski.

This new research no doubt will influence how scientists view and study the brain in drug development studies, as well as basic research.

By bringing together all these elements from different disciplines for the first

time, Sejnowski’s research epitomizes the mission of the Crick-Jacobs Center: mining the enormous amount of data about brain function and structure with the help of computational methods, to understand how the brain works.

In addition, it also demonstrates the crucial role of private donors, who not only funded the Crick-Jacobs Center but also helped this particular project get off the ground.

“Private philanthropy was critically important in the early stages of this project and helped us obtain funding from government sources,” explained Sejnowski.

Irwin and Joan Jacobs generously contributed the funding. The Center was named in honor of the Jacobses as well as the late Nobel laureate Francis Crick.



Terrence J. Sejnowski

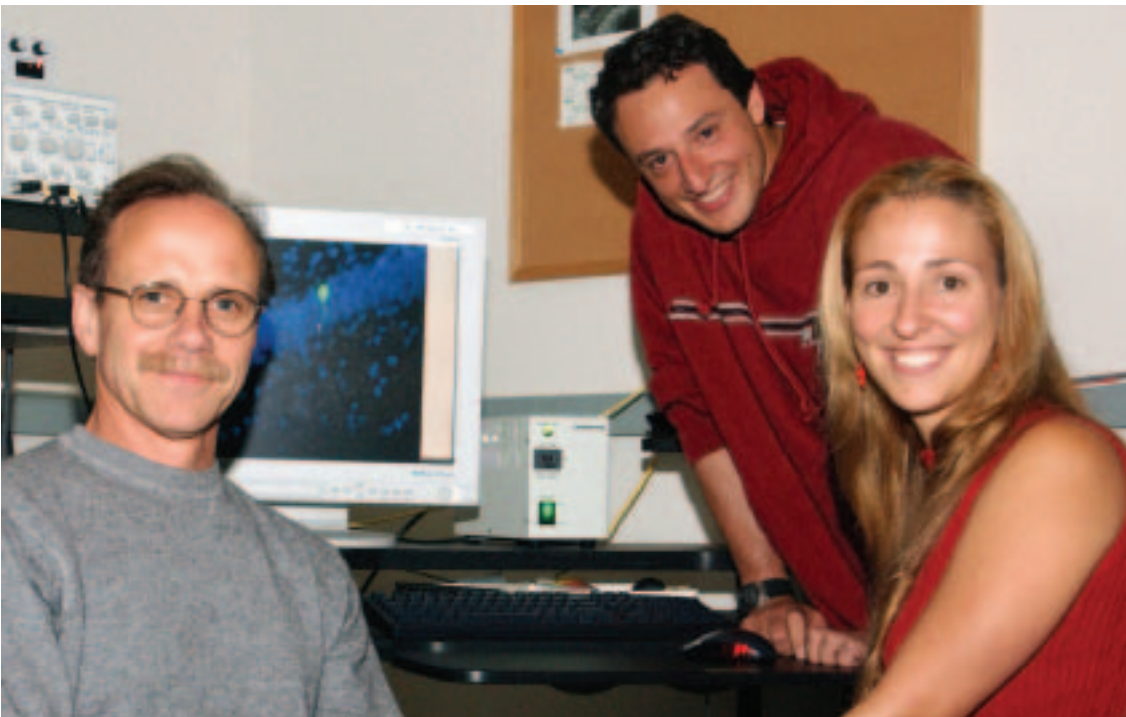
“Jumping genes” make each brain unique

BBrains are marvels of diversity: no two look or behave the same, not even those of identical twins. Now Salk researchers have found one possible explanation for this puzzling variety in brain organization and function: mobile pieces of DNA that jump from one place in the genome to another, randomly reshuffling the genetic blueprint in individual brain cells.

Scientists have long been puzzled how basic brain precursor cells go on to develop into the enormously diverse array of nerve cells (neurons) that together form the brain. Mobile elements, sometimes known as “jumping genes,” are one possible explanation.

“This mobility adds an element of variety and flexibility to neurons in a real Darwinian sense of randomness and selection,” said Fred H. Gage, co-head of the Salk’s Laboratory of Genetics and lead author of the study published in *Nature* in June.

Jumping genes make up one-fifth of our DNA but very little is known about them and they have frequently been dismissed as “junk DNA” left over from our distant evolutionary past. Most of them have lost their jumping ability, but in humans about one hundred are still free to move by a “copy and paste” mechanism. Until now, mobile genes had only been seen moving in the testes and ovaries, where they give evolution a helping hand by adding tiny but important variations to cells destined to become the next generation. *continued on page 4*



Salk scientists Fred H. Gage,
Alysson Muotri and Carol Marchetto.

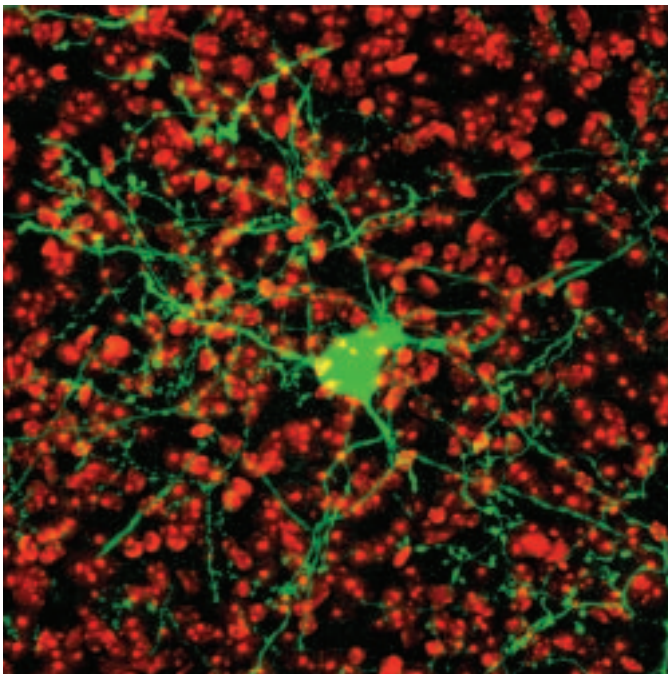
“We were very excited when we saw green cells all over the brain in our mice, because then we knew it happened *in vivo* and couldn’t be dismissed as a tissue culture artifact.”

In the *Nature* study, Gage and co-authors Alysson Muotri, Vi Chu, Carol Marchetto, Wei Deng and John Moran introduced a human-derived mobile gene into a tissue culture of rat neuronal precursor cells — cells fated to develop into the brain.

The researchers found that the jumping elements were only active in cells destined to become nerve cells. Other cell types found in the brain, such as supportive tissue cells, were unaffected.

To see whether this happened in real life, the Salk scientists engineered a mouse with a specially designed mobile element. If the element jumped within a cell’s genome, it caused the cell to glow green. “We were very excited when we saw green cells all over the brain in our mice,” said Marchetto, “because then we knew it happened *in vivo* and couldn’t be dismissed as a tissue culture artifact.”

It still remains to be seen whether mobile elements are active in human brains, and what effect they might have. The Salk researchers are encouraged by the possibility that jumping genes may turn out to be an important mechanism for controlling how human brains develop. “We examined only one, artificially introduced element,” said Gage. “Mobility is likely to be significantly greater for naturally occurring elements.”



The green colored structure in the middle of this image is a brain cell whose genetic information has been altered by “jumping genes,” mobile elements that are small pieces of DNA that can jump from one place to another in the genetic code. Salk scientists genetically engineered a mobile element so that every time it jumped into a cell’s genetic code, the cell glowed. This allows researchers to reveal how often mobile elements are on the move and the particular cell types that are affected.



John Young

New window of opportunity against HIV

Some viruses, such as HIV, invade body cells by first merging, or fusing, with the cell's outer membrane before their genetic material enters and reprograms the host cell. Scientists had assumed that once a virus began fusing with a cell's membrane, infection of the host cell was inevitable. However, Salk scientist **John Young** and biophysicist Gregory Melikyan of Rush University Medical Center in Chicago captured on video an intermediate stage between the virus' merger with the cell membrane and the entry of deadly genetic material, when the fate of the host cell still hangs in the balance. This intermediate stage, which can last several minutes, may represent a window of opportunity for drug development. The observations were published in the *Proceedings of the National Academy of Sciences*.

Mixing and matching enzyme may help create possible new drugs

Joseph Noel, Stéphane Richard and Tomohisa Kuzuyama isolated and examined a totally new enzyme that can mix and match biological chemicals to create a wide range of different molecules that could be used as the basis for new drugs. The Salk researchers tested whether their new enzyme could modify small aromatic molecules, a group of compounds that includes potent cancer-fighting anti-oxidants as well as substances with antibiotic and antifungal properties. Unlike other previously known enzymes that add chemical modifications known as prenyl groups only to a small number of different molecules, this new enzyme, named Orf2, was able to attach prenyl groups to most of the different compounds tested. Their findings were published in the journal *Nature*.

Painting, by artist Jacques Deshaies, depicting a novel enzyme structure discovered by Salk Institute scientists. As described in *Nature* by Joseph Noel and colleagues, the structure can build a wide range of hybrid chemical molecules, creating a "library" of compounds that could possibly form the basis for new drugs.



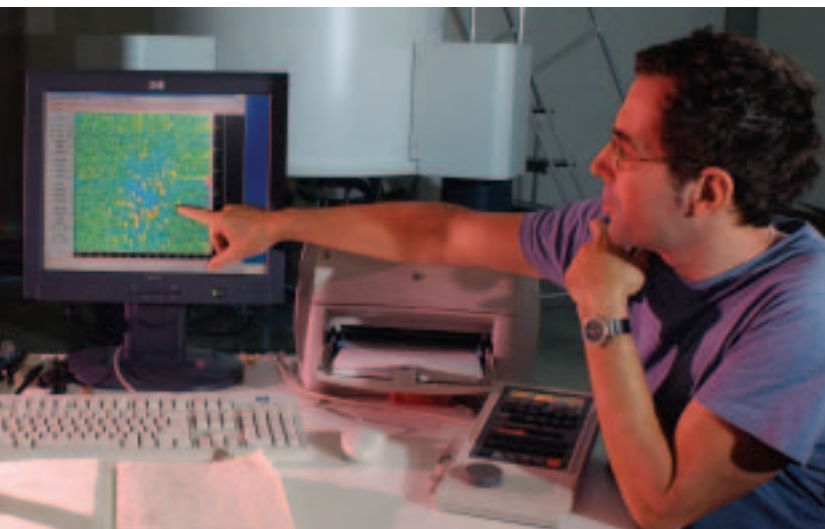
Joseph Noel

“Mad cow disease” infectious agent: Dr. Jekyll/Mr. Hyde versions

Roland Riek described in *Nature* how mysterious, highly infectious prions, which cause the severe destruction of the brain that characterizes “mad cow disease,” can be rendered

harmless in the laboratory. Prion proteins switch from their normal into their infectious state by changing their three-dimensional shape. Riek and colleagues discovered that the region critical for the ability to flip from “normal” to “infectious” is arranged in a flat structure called a beta-sheet. Meddling with the shape of the beta-sheet destroys the prion’s ability to transform into its disease-causing incarnation. This research opens up new directions for researchers studying prion diseases in humans and other animals, since targeting the beta-sheet shape might turn out to be a strategy for controlling feared brain-wasting prion diseases.

Roland Riek



Signaling the brain at speed of moving car

E.J. Chichilnisky and Eric S. Frechette, in collaboration with an international group of physicists, developed a microscopic electrode array that, for the very first time, records the activity of hundreds of nerve cells simultaneously. It allows the scientists to study precisely how the retina, a thin tissue lining the back of our eyes, conveys information about movement and speed. The research, reported in the July issue of the *Journal of Neurophysiology*, helps lay the technological and biological groundwork needed to develop visual prosthetic devices that, one day, could restore some degree of vision to people whose retinas have been damaged by disease or trauma.

Spain to send postdoctoral researchers to the Salk for training in stem cell biology

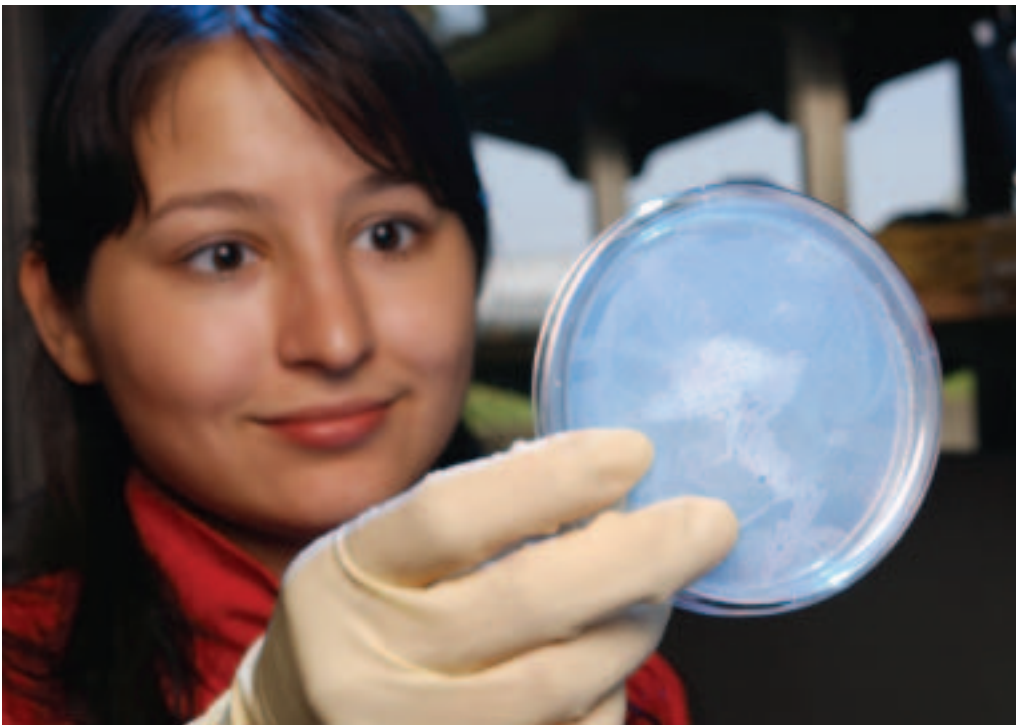
Over the next five years, the Salk will be a training ground for a total of 30 selected post-doctoral researchers from Spain, in the science of stem cell biology. After completing their two-year research rotations in Salk laboratories, the researchers are expected to return to Spain to continue studies there.

Salk professor Juan Carlos Belmonte, an international leader

in research on how genes and molecules orchestrate embryonic development, organized the new program between the Salk and Spain.

“Spain, as one of the leading countries worldwide in the field of tissue and organ transplantation, is firmly committed to support efforts in the field of regenerative medicine,” said Belmonte. “This agreement

is designed to develop and enhance research opportunities for Spanish postdoctoral fellows training for careers in the field of human stem cell biology, while at the same time establishing close scientific relationships between the Salk Institute and overseas institutions that are going to play a leading role in the next decade in the field of regenerative medicine.”



Salk Scholars Fiona Smith (top) and Irina Chaikhoutdinov in the laboratories of Martin Hetzer and Geoff Wahl, respectively.

Salk scholars at the Salk this summer

■ In 1955, the New York City officials wanted to honor Dr. Jonas Salk with a ticker tape parade. Dr. Salk, who that year had developed the first effective and safe polio vaccine, suggested that the city instead fund the medical school tuition of several promising students at his 1934 alma mater, the City University of New York (CUNY).

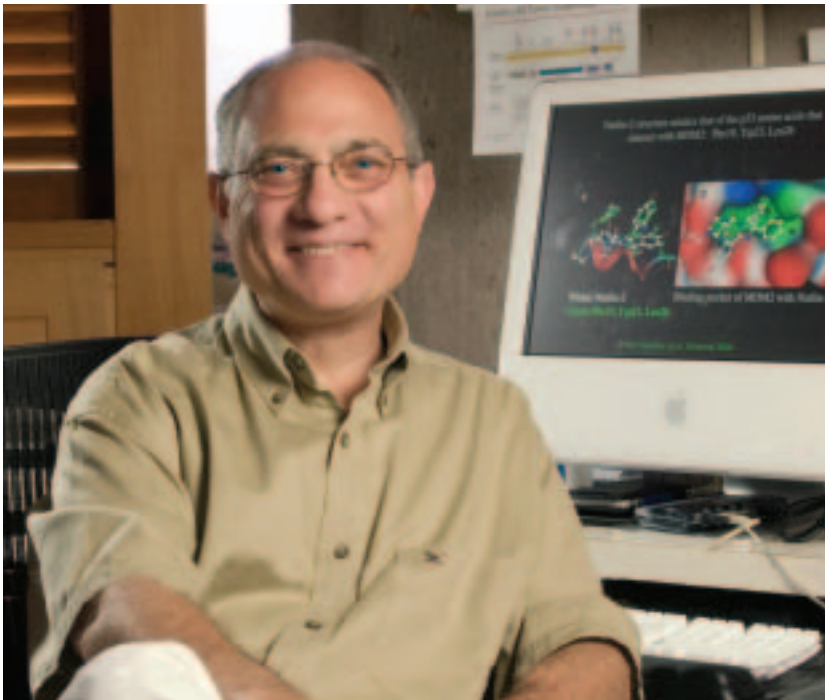
This summer, for the first time in the 50 years of the Salk Medical Scholarship, the recipients worked in Salk labs, where they learned science by doing science under the tutelage of Salk faculty.

Their summer internships were funded by International Council member Richard Phelps and the Institute in honor of the 50th anniversary of the Salk polio vaccine and the 40th anniversary of the opening of the main research buildings of the Institute, which was founded by Dr. Salk in 1960.

The interns were Irina Chaikhoutdinov and Fiona Smith.

Chaikhoutdinov, an award winning biology major at CUNY's Hunter College, was born in Russia and is interested in research on beta-thalassemia, a poorly understood inherited form of anemia that causes changes in the bones and characteristic facial and limb deformities. She has been accepted at Cornell's Weil College of Medicine.

Born in Guyana, Smith majored in biology at CUNY's York College, where she studied in the genetics lab for the past three years, investigating genes important to the development of eggs and embryos in the fruit fly. She will attend Pennsylvania State College of Medicine.



Geoff Wahl

Salk Institute scientist Geoff Wahl named President-elect of AACR

Salk Institute professor **Geoff Wahl** has been elected the 2006-07 President of the American Association for Cancer Research (AACR), placing him at the helm of the world's oldest and largest professional organization dedicated to accelerating scientific progress in cancer prevention and treatment.

Recognized worldwide for his work on duplication errors and genetic instability in cancer cells, Wahl carries out research into how cancer

originates and progresses, and why tumors become resistant to even the most powerful anti-cancer drugs. He has authored over 120 research papers including one deemed a "citation classic" because it is cited so frequently by other researchers.

"I see significant opportunities for advances in cancer prevention, diagnosis and treatment as our knowledge of the molecular biology of cancer increases," he said.

Martin Hetzer named Pew Scholar

Martin Hetzer, assistant professor in Salk's Molecular and Cell Biology Laboratory, has been designated one of 15 Pew Scholars in the Biomedical Sciences for 2005.

This prestigious fellowship recognizes highly

regarded scientists with exceptional potential in the biomedical sciences.

Hetzer's research focuses on the molecules that guide the assembly of the membranous envelope that surrounds the cell nucleus, where the genetic code is located.



Martin Hetzer



Ron Evans

France's highest scientific honor to be awarded to Ronald M. Evans

Ronald M. Evans, professor and head of the Gene Expression Laboratory, will receive the 2005 Grande Médaille D'Or (Grand Gold Medal), France's highest scientific honor, for his research discovering how hormones and drugs control the body's metabolism, development and reproduction.

Evans, the 2004 recipient of the prestigious Lasker Award for Basic Medical

Research, will receive the Grand Gold Medal on Nov. 15, at the French Academy of Sciences in Paris.

Previous award recipients include Louis Pasteur, Pierre and Marie Curie, Gustave Eiffel and Henri Poincaré. Nobel laureate and theoretical physicist David Gross of the University of California, Santa Barbara was awarded the prize last year.

Fred H. Gage elected to American Academy of Arts and Sciences

Salk scientist **Fred H. Gage** has been elected a Fellow of the American Academy of Arts and Sciences, a distinction awarded annually to top individuals in business, government, public affairs, the arts, popular culture and biomedicine.

Gage's research has advanced scientific understanding about the potential of the adult brain and

nervous system to self-repair.

This year's 213 awardees also include Supreme Court Chief Justice William Rehnquist, sculptor and painter Jeff Koons, actor and director Sidney Poitier, choreographer Judith Jamison, TV journalist Tom Brokaw, Google co-founders Sergey Brin and Larry Page, and architect Maya Lin.



Rusty Gage

Salk Nobel laureate honored at dedication

The dedication of the Renato Dulbecco Laboratories for Cancer Research celebrated a beloved faculty member and a true giant of 20th century biology.

Renato Dulbecco, one of the first scientists to join the Salk Institute, conducted the pioneering studies with tumor viruses that revealed that these viruses can cause cancer when they insert their genes into cells. This first solid evidence that cancer originates when a cell's genes become mutated helped to spark a seismic shift in the way that the biomedical research community viewed and investigated cancer.

In 1976, Dulbecco was

honored with the Nobel Prize in Physiology or Medicine.

At the dedication ceremony at the Salk Institute, Dulbecco was heralded not just for his research, but also for his mentoring of many of today's scientific leaders. Five of his former trainees went on to receive the Nobel Prize.

At the dedication ceremony, speakers also highlighted Dulbecco's taking the steps that helped to launch the massive scientific undertaking that became the Human Genome Project. As Dulbecco predicted in 1986, deciphering the human DNA code has expedited scientists' search for the genes



important to health and disease.

Dulbecco, who served as president of the Institute from 1988 to 1992, says the Salk laboratories that today bear his name are an intellectual continuation of his former Institute lab.

Above: opening the Dulbecco Laboratories for Cancer Research were (l-r) Renato Dulbecco, Lynn Streim, Maureen Dulbecco and Ed Streim. The Streims, long-time friends and donors, generously supported the renovation of the Dulbecco Laboratories.

Left: As Edith Piaf's recording of "La Vie en Rose" played, Dulbecco danced with Ellen Potter, coordinator for the Salk's educational outreach programs.



Faculty Promotions



■ **E.J. Chichilnisky**, promoted to associate professor in the Institute's Systems Neuroscience Laboratory, records and analyzes the simultaneous patterns of activity of the many specialized cells in the retina that transmit visual signals from the eye to the brain so that we are able to see and perceive our world. His highly innovative research may one day contribute to the development of visual prosthetics, devices that could be implanted in the eye and substitute for retinal tissue damaged by disease or accidents.



■ **Samuel Pfaff**, promoted to professor has been a key contributor to the Institute's Gene Expression Laboratory for almost a decade. The medical treatment of spinal cord injuries and degenerative disorders such as Lou Gehrig's disease and post-polio syndrome one day may benefit from Pfaff's basic research on how the muscles of the body are "wired up" to the spinal cord through motor neurons, which are the specialized nerve cells that transmit signals from the brain to the body's muscles that enable movement to occur.



■ Promoted to associate professor in the Clayton Foundation Laboratories for Peptide Biology, **Paul Slesinger** investigates the structure and function of the "molecular gates" through which potassium and other ions enter and exit body cells. The flow of these molecules creates the nerve signals that enable body cells to communicate with each other, so that we are able to think, move, and generally function. Slesinger's outstanding basic research may advance the treatment of disorders based on faulty flow of ions through the molecular gates.

New Board of Trustee Members

■ **Steven R. Altman** is president of QUALCOMM Incorporated. Altman has a BA in criminal justice from Northern Arizona University and a Juris Doctor from the University of San Diego. Altman is a former board member of the Juvenile Diabetes Research Foundation and remains a supporter of the JDRF and other charities.



■ **Richard C. Helmstetter** is vice-chairman and senior executive vice-president of Callaway Golf. Fluent in Japanese, Helmstetter was for many years the only American to own and operate a manufacturing business in Japan. Today Helmstetter is a well-known technical innovator and principal holder of more than 400 international patents.



■ **Marna C. Whittington** is chief operating officer of Allianz Global Investors and CEO of Nicholas-Applegate Capital Management. Formerly secretary of finance for the State of Delaware and chief financial officer of the University of Pennsylvania, Dr. Whittington serves on the boards of Rohm & Haas and Federated Department Stores, Inc.



INSIDE SALK

Salk in the Community

Why can Sammy Sosa hit home runs while Salk scientist Chuck Stevens cannot?



The question “why is Sammy Sosa better at hitting home runs than I am?” was answered by Salk scientist Charles F. Stevens (above left) at an informal gathering at the new Solana Beach, California home of San Diego’s famous restaurant owner and chef Jeffrey Strauss. Stevens, professor in the Molecular Neurobiology Laboratory at the Salk, described the differences in people’s brains that help explain why one person can hit home runs while most individuals cannot.

Salk scientists thank donors



John and Jean Hardy were among the over 100 attendees at the Salk Institute’s annual dinner to thank our donors. Also attending were many Salk scientists, including Fred H. (Rusty) Gage, the event’s featured speaker.

Over 100 International Council members meet in France for research briefings



Over 100 members of the International Council and Board of Trustees as well as special guests learned about Salk science from seven of the Institute's faculty members. Salk scientist Joseph Ecker (above) talked about his research in plant biology. At right is Corinne Mentzelopoulos, member of the Salk Board of Trustees and owner of Chateau Margaux, the site of this year's International Council meeting in France.



New York City leaders updated about stem cell research



Olivia Tournay Flatto (left) and Caryl Philips at a luncheon in New York City that was hosted for the Salk Institute by Jerome Kohlberg, chairman of the Salk's Board of Trustees. Over 70 people attended the event, at which Richard Murphy, President and CEO of the Salk, spoke about the stem cell research initiative that California voted to approve in last year's election. The Institute's next luncheon in New York City will be held this fall.

Tax seminar attendees take a break from taxing talks



Foundation officials take a break from the Salk Institute's 33rd annual Tax Seminar on Private Foundations, to visit the greenhouses for the Institute's plant biology studies.

Skirball Center applies Human Genome Project data to target proteins with roles in health and disease

The Institute's new Center for Chemical Biology and Proteomics has been named in honor of Jack H. Skirball.

The Skirball Foundation donated \$3 million to the Center and pledged an additional \$2 million if the Institute raised \$2.6 million from other donors.

Matching donations were generously provided by Salk board members Frederick Paulsen and Darlene Shiley, as well as long-time friends of the Institute, the Mary K. Chapman Foundation and the H.A. and Mary K. Chapman Charitable Trust.

"The Salk Institute is grateful to the trustees of the Skirball

Foundation for their foresight in not only providing generous funding critical to the success of the Center, but also providing the Institute with the incentive to raise additional funding to meet this challenge," said Salk scientist Joseph Noel, who heads the new Jack H. Skirball Center for Chemical Biology and Proteomics.

The Skirball Center harnesses the vast amount of information derived from the Human Genome Project (HGP), which deciphered the DNA code of humans, and from similar genome projects in such laboratory models as mice, plants and bacteria.

The HGP produced a "gold mine" of information, including the genetic recipes for the body's proteins: the molecules, such as insulin, that carry out essential activities within our cells.

Because many diseases are thought to begin when our genes produce malfunctioning proteins, Salk scientists want to better understand the structure and

function of proteins and to create chemical molecules that will alter or mimic the proteins that play roles in health and disease.

At the Skirball Center, scientists will synthesize small molecules and test their ability to modify or replace a specific protein's function.

The natural chemicals made in plants, animals and bacteria also will be tested and modified in unique ways developed at the Salk Institute. In addition, the Skirball Center will provide the resources for genetically altering cells so that they can produce their own special protein-modifying agents at the most appropriate time and place to halt disease and repair cells and tissues.

Other research programs at the Salk will benefit from the Center's focus on atomic-level three-dimensional structure, protein function and cellular chemistry. Its novel technology will be shared with other Salk laboratories.



Salk scientist Stéphane Richard freezes protein crystals in liquid nitrogen in a laboratory of the Jack H. Skirball Center for Chemical Biology and Proteomics.

MAKING THE GRADE AT SALK

On page 11 of this newsletter, we report that three faculty members have advanced up the academic ladder. E.J. Chichilnisky and Paul Slesinger, promoted to associate professors, and Sam Pfaff, now a full professor, deserve our congratulations because the academic ladder at the Salk is especially steep and arduous. Only the best and brightest in the biological sciences make it.

Being recruited initially as a Salk faculty member is an achievement of its own. Commonly, for each new faculty position, 100 to 300 candidates are screened on the quality of their training, research productivity, and the importance and relevance of their science. The best are invited to the Institute to give research seminars and meet with current faculty — their potential colleagues. Candidates who are offered positions generally join the Institute as assistant professors, although occasionally Salk will recruit a senior scientist. For example, Vicki Lundblad and John Young, international leaders in chromosome-related research, and HIV and anthrax biology respectively, were recently recruited as full professors.

The scientists who come to Salk as assistant professors have five to six years to establish research programs that are innovative, unique and important. And they must gain essential but hard-to-get research support from funding agencies such as the National Institutes of Health.

To be promoted to associate professor, an assistant professor must conduct groundbreaking research and report it in top-tier scientific journals, i.e., those that publish only the most outstanding research findings.

Faculty members promoted to associate professor have another five to six years to conduct the research that will make them eligible for a tenured full professorship. To reach this senior level, faculty members must be regarded in the scientific community as one of a handful of the world's experts in their field of discovery. A common measure of those making this cut is to have achieved scientific accomplishments significant enough to warrant inclusion in the latest textbooks.

Salk professors play an important role in judging the research programs of their junior colleagues, but the promotional process is based also on the evaluations of two groups of outside scientists who themselves are leaders in biomedical research. The first group consists of 10 to 20 outside experts who evaluate the substance, quality, impact and significance of the Salk scientist's research contributions.

The second group includes the Institute's eight non-resident faculty members, themselves renowned senior scientists from across the world (three are Nobel laureates). Along with the resident faculty, they vote up or down on each candidate up for promotion. Then, after consideration by the Institute's president, the faculty's vote goes to the Board of Trustees for final approval.

The promotion process can be harrowing for scientists, since the quality and significance of their life's career is evaluated by numerous Salk and non-Salk scientific peers voting anonymously. Only the best make the grade, and when they do, the satisfaction is enormous; moreover, those not promoted at Salk generally go on to excellent positions elsewhere, either at first-rate universities or in industry.

For the Institute, a tough but fair promotion process is the best way to ensure that the Salk's faculty members are making major discoveries that change the direction of science. Sam, Paul and E.J. have done that, and to them we say well done and congratulations!



A handwritten signature in dark ink, which appears to read "Richard Murphy". The signature is fluid and cursive, written over a light-colored background.

Richard Murphy
President and CEO



CELEBRATING 40 YEARS

INSIDE SALK

In 1960, just five years after developing the first safe, effective vaccine against polio, Jonas Salk, M.D., founded the institute that today bears his name. Home to 11 Nobel laureates since its founding, the Salk Institute for Biological Studies is a world leader in basic research on the biological principles governing life at all levels, from the individual cell to an entire population. For more information: www.salk.edu.

This year marks the 40th anniversary of the opening of the Salk's main research campus, which was designed by the renowned architect Louis Kahn as envisioned by Jonas Salk.



Calendar

SEPTEMBER 21

LEADership Trend Series, hosted by LEAD San Diego, sponsored by KPBS. Keynote speaker: PBS Television Host of *Now*, David Brancaccio

NOVEMBER 12

"Sensational Salk" featuring presentation of inaugural Salk Institute Medal for Health and Humanity to Dr. Paul Farmer and the Medal of Research Excellence to Dr. Donald Metcalf

Please note: the above represents a selected list of events. For additional information about these and other Salk events, please contact Institute Relations at 858.453.4100 ext. 1200.



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