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Where cures begin.

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

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Symphony at Salk

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ON THE COVER Scientist Marguerite Vogt, M.D., Salk's longest-working researcher, passed away on July 6, 2007 at age 94. Her 80-year career is marked by seminal collaborations, most notably with Nobel Laureate and fellow Salk scientist Renato Dulbecco. Their research changed how both viruses and cancer are studied and provided some of the first clues to the genetic nature of cancer. Vogt is credited with training scores of young scientists, four of whom went on to receive the Nobel Prize. Read her story on page 6.

Newborn Neurons Like to Hang With the 'In' Crowd

IT IS NOW WIDELY ACCEPTED THAT new neurons are in fact generated in adult brain. What is not understood is how those newborn brain cells, once they emerge from neural stem cells, muscle their way into networks already established by more mature nerve cells.

In a study published in *Nature Neuroscience,* **Fred H. Gage,** professor in the Laboratory of Genetics, showed that the newcomers jump right into the fray and aren't shy about reaching out to the mature nerve cells, or neurons, that have already established complex brain circuits.

Knowing how young neurons integrate into mature circuits is critical if neural stem cells are ever to be used to replace damaged neurons in neurodegenerative conditions such as Alzheimer's or Parkinson's disease.

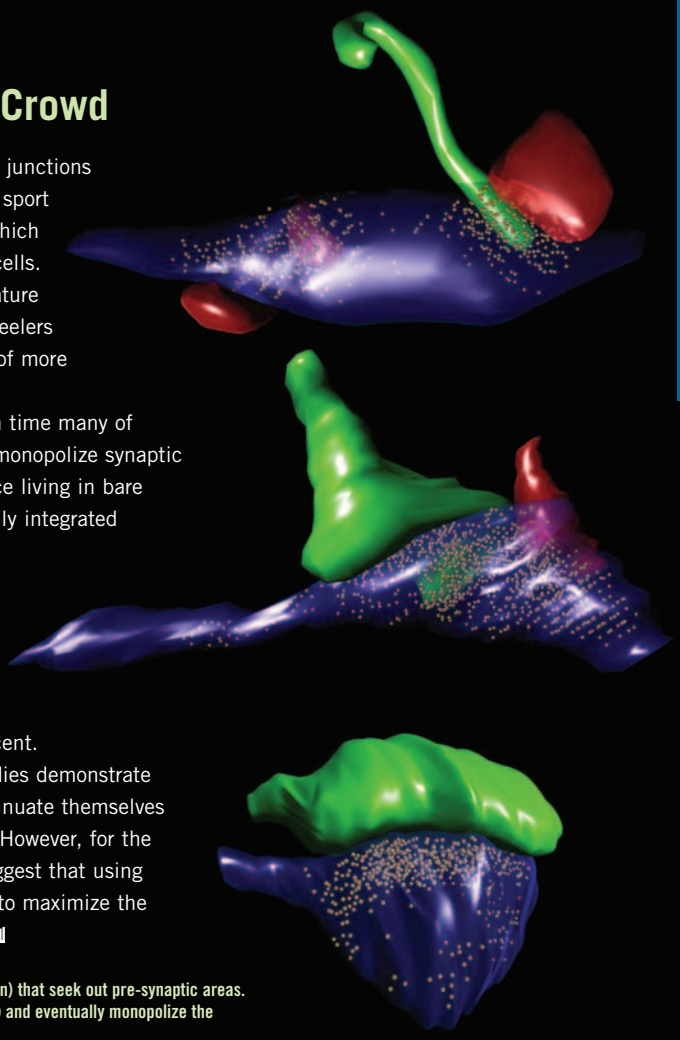
To follow the social dynamics of young neurons, Gage and postdoctoral fellow **Nicolas Toni** labeled neural stem cells in adult mouse brain with a fluorescent dye so they could literally watch how they behaved on the brain playground as they developed into full-fledged neurons.

Neurons contact each other at junctions called synapses. Typical neurons sport about 7,000 synapses through which they touch roughly 1,000 other cells. The researchers found that immature neurons assertively put out tiny feelers at synaptic "cliques" consisting of more mature cells.

The investigators found that in time many of those feelers actually started to monopolize synaptic connections. Interestingly, in mice living in bare cages, only about half successfully integrated into those networks.

But in mice living in enriched environments filled with running wheels or colored tunnels, the number of young neurons successfully hooking up with existing networks rose to 80 percent.

For neuroscientists, these studies demonstrate how newborn mouse neurons insinuate themselves into pre-existing brain networks. However, for the rest of us, these observations suggest that using one's brain cells is the best way to maximize the brain's regenerative capacity.



Newborn neurons send out feelers (top, green) that seek out pre-synaptic areas. These protrusions thicken over time (middle) and eventually monopolize the synaptic connection (bottom) site.

A Possible Mechanistic Link Between Stress and Development of Alzheimer's Tangles

AGING IS THE GREATEST RISK FACTOR FOR ALZHEIMER'S disease, but evidence suggests that emotional stress may also contribute to accumulation of neurofibrillary tangles, a hallmark of that condition.

Paul Sawchenko, professor in the Neuronal Structure and Function Laboratory, showed in the *Journal of Neuroscience* that damage triggered by negative emotions is relayed through two receptors expressed by certain brain cells, CRFR1 and CRFR2, to modulate a key process in the development of Alzheimer's neuropathology.

In Alzheimer's disease, a protein called tau becomes overly decorated with small chemical modifiers called phosphate groups. Hyper-phosphorylated tau then becomes insoluble within nerve cells, contributing to cell death.

In their study, Sawchenko and senior research associate **Robert Rissman** stressed mice by physically restraining them just once for 30 minutes and observed marked, but short-lived, increases in tau phosphorylation in the brain's hippocampus, a critical structure in learning and memory. When restraint was administered daily for two weeks, phosphorylated tau accumulated in the hippocampus, some of it in an insoluble form, which may represent an initial step in tangle formation.

Paul Sawchenko (left) and Robert Rissman

To understand what factors were responsible for these changes, the investigators did similar experiments in mice engineered to lack either CRFR1 or CRFR2 in collaboration with Salk professors **Kuo-Fen Lee** and **Wylie W. Vale** in the Clayton Foundation Laboratories for Peptide Biology.

They found that mice lacking CRFR1 failed to show stress-induced tau modification, while in mice missing CRFR2, tau phosphorylation was increased. This work indicates that crosstalk between CFR1 and CFR2 in some way modulates tau phosphorylation and suggests a biochemical mechanism for how chronic stress induces deleterious changes that may promote neurodegeneration and cognitive impairment characteristic of Alzheimer's disease.

Significantly, drugs that target CRF receptors are already in phase II clinical trials for depression and other mood disorders. This work indicates that these drugs could also potentially delay the progression of Alzheimer's disease.

Cancer Stem Cells Can Go It Alone


Renato Dulbecco

AT THE HEART OF MOST CANCERS lies a very small number of abnormal cells known as cancer stem cells. Unlike normal stem cells, cancer stem cell growth cannot be controlled. A goal of cancer researchers is to first identify molecular markers of these rare cells in order to find them and then devise strategies to kill them.

Nobel Laureate **Renato Dulbecco,** distinguished research professor and president emeritus of the Salk Institute, recently re-examined a cultured cell line he made in 1979 from a rat mammary adenocarcinoma. Three decades later, he finds that these cells exhibit many qualities of breast cancer stem cells.

This work, reported in *Proceedings of the National Academy of Sciences,* means that Dulbecco's breast cancer line, known as LA7, will likely provide researchers with a ready and abundant source of cancer stem cells for analysis through every step of tumor formation. It also supports the current hypothesis that an entire tumor can emerge from one aberrant stem cell.

Together with **Ileana Zucchi,** a molecular biologist at the Institute for Biological Technology in Milan, Italy, Dulbecco observed that cells from the LA7 line formed tumors after they were injected into normal breast tissue of female mice.

Injection of even one single cell from the cultured line gave rise to breast tumors in those mice. Interestingly, like normal stem cells, LA7 cells prodded with appropriate cues can form cell types usually seen in the mammary gland, such as milk-producing alveoli and duct tissues. And, also like normal stem cells, these cells can divide or "self-renew."

However, cancer stem cells do not respond to environmental signals that would regulate the process of self-renewal in normal stem cells.

Confirmation that a tumor can arise from one unregulated cell is sobering: It means that successful and permanent removal of a tumor will require eradication of every potential cancer stem cell.

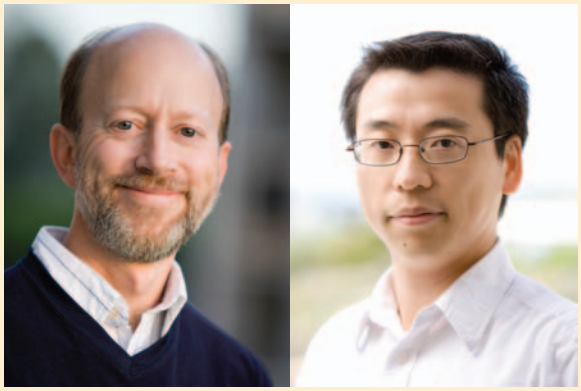
The good news is that Dulbecco and Zucchi's work should speed identification of early markers of these cells as well as suggest therapies to target these cells for destruction before they have time to give rise to a breast tumor.

Expanding the Genetic Code in Mammalian Cells

SALK RESEARCHERS HAVE DEVELOPED A METHOD TO MAKE mammalian cells crank out designer proteins by incorporating synthetic amino acids, a feat that suggests cells could make their own therapeutic proteins.

Lei Wang, assistant professor in the Chemical Biology and Proteomics Laboratory, and **Paul Slesinger,** associate professor in the Peptide Biology Laboratory, reported the method in *Nature Neuroscience* and tested it in a proof-of-principle experiment.

Plants and animals construct protein chains from 20 naturally occurring links, or amino acids. Although the amino acid order differs depending on the protein, the 20 amino acids are invariant.


Paul Slesinger

Lei Wang

Using bits and pieces of the protein synthesis machinery borrowed from bacteria and yeast, Wang and Slesinger devised a way to make nerve cells insert an unusually large "ringer" amino acid into a test protein that forms a channel through the cell membrane.

Normally, that channel, which is a conduit for potassium ions, comes equipped with its own tethered "plug" to regulate ion flow. To test their strategy, the researchers manipulated nerve cells to place the bulky, artificial amino acid in the region where the protein plug should fit into the channel pore.

They observed that once in the membrane, the synthetic channel regulated the flow of ions very inefficiently, indicating that inclusion of the bulky amino acid had made the plug too big to fit through the pore.

Chemists can already make proteins containing synthetic amino acids in a test tube. Although bacterial cells have been coerced into manufacturing similarly engineered proteins, this is the first report of nerve cells being tricked into doing the chemistry themselves.

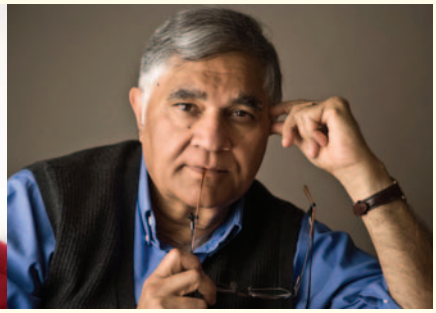
Coaxing mammalian cells — even high-maintenance cells like nerve cells — into manufacturing proteins with novel properties will be extraordinarily useful for both basic and medical research, potentially leading to new ways of delivering proteins with unimagined activities to cells.

Researchers Successfully Deliver Protein Across the Blood-Brain Barrier

A DILEMMA IN TREATING DISEASES of the central nervous system is that many drugs infused into the bloodstream cannot pass through a network of specialized capillaries that allows passage of only sanctioned molecules to the brain.

This protective brain fence, otherwise known as the blood-brain barrier, keeps toxins and pathogens out of the brain circulation. Having a means to circumvent it when necessary would give clinicians a major leg up in treating brain disorders.

Brian Spencer



Inder Verma

In a study published in *Proceedings of the National Academy of Sciences,* postdoctoral fellow **Brian Spencer** and **Inder Verma,** professor in the Laboratory of Genetics, have developed a technique that allows the transport of proteins like glucocerebrosidase, an enzyme whose deficiency causes Gaucher's disease, as a model to create a means to get around this problem.

Gaucher's disease, an inherited and often fatal disorder, is caused by the build-up of substances called glucocerebrosides due to deficiency in the enzyme that metabolizes them, a protein known as glucocerebrosidase.

Researchers have been unable to deliver glucocerebrosidase across the blood-brain barrier to prevent glucocerebroside accumulation in the brain, which results in neuronal degeneration.

Working in the Verma laboratory, Spencer was successful in shepherding glucocerebrosidase into mouse brains by first fusing the gene encoding it to portions of another gene encoding the protein apolipoprotein B, which readily crosses the barrier.

Next, they used a gene therapy approach to express the hybrid gene in the liver. This manipulation provided a continuous supply of the glucocerebroside/apolipoprotein B fusion protein in the bloodstream.

Two weeks later, glucocerebrosidase was detectable in the brain, indicating that the apolipoprotein B part of the hybrid protein acted as a guide and dragged the unsanctioned glucocerebrosidase across the barrier and into brain cells.

Verma and Spencer's approach is a major breakthrough in the field which could potentially be developed into a method to deliver other therapeutic proteins through the capillary barrier and into the central nervous system.

Paying Attention to Attention

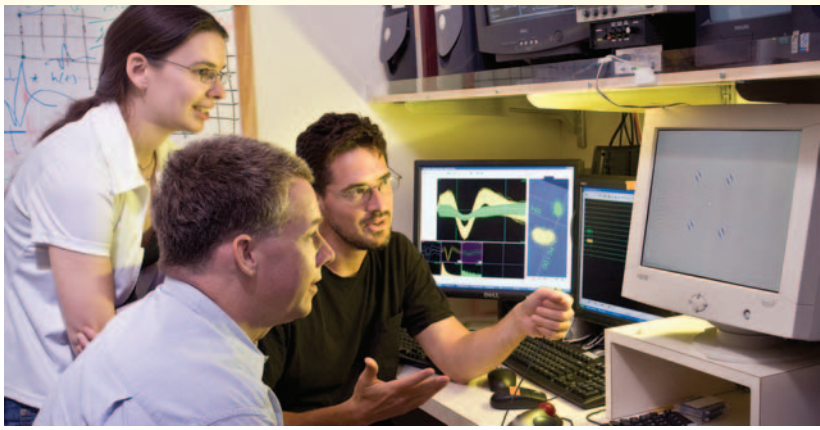
ALL KIDS KNOW THAT PARENTS HAVE "EYES IN THE BACK of their heads." **John Reynolds,** associate professor in the Systems Neurobiology Laboratory, post-doctoral researcher **Jude Mitchell,** and graduate student **Kristy Sundberg** are starting to understand how people and other higher animals manage to pay attention to certain objects while keeping an eye on others.

In their study, published in the journal *Neuron,* the researchers report two classes of brain cells with distinct roles in visual attention, and highlight at least two mechanisms by which these cells mediate attention.

In the experiments, animals learned how to play a sophisticated attention-demanding video game. Throughout the game, Reynolds and Mitchell measured electrical activity from individual neurons involved in mediating visual attention.

During the video game, moving objects appeared on a computer monitor, occasionally falling at a location that elicited a response from the neuron, in the form of a volley of electrical spikes known as action potentials. The researchers examined this neuronal response to see if it changed when the animal either ignored or attended to the stimulus. They found that neurons typically produced stronger electrical signals when the animal attended to the stimulus.

But they also noticed that different neurons produced different shaped action potentials: "broad spikes" or "narrow spikes." Other researchers had previously identified two different types of brain cells that produce these two waveforms. The most common neuron type, called pyramidal cells, produce broad spikes. These neurons carry signals between distant areas of the brain. The other type, called fast-spike interneurons, produce narrow spikes. These neurons only connect to nearby neurons.



Kristy Sundberg (from left), John Reynolds and Jude Mitchell

By sorting the neurons according to the waveform they produced, the researchers discovered that attention had different effects on the two different types of brain cells. The narrow-spiking cells usually fired more rapidly when attention was directed to the object than when it was ignored. What's more, attention caused the stream of spikes produced by these neurons to be much more even-paced. Broad-spiking neurons, on the other hand, were less influenced by attention. Some fired faster, while others fired more slowly when attention was directed to the moving object.

This is the first study of attention to distinguish between different classes of neurons. By making these distinctions, Reynolds and Mitchell are beginning to piece together the biological underpinnings of attention. This will improve scientists' understanding of neurological diseases in which attention is impaired, such as schizophrenia and autism.

Marguerite Vogt
1913-2007

Colleagues and friends share their fondest memories of Salk's longest-working scientist

NEARLY 100 THREE-RING BINDERS LINE THE SHELVES IN Marguerite Vogt's office at the Salk Institute. They are filled with her notes on experiments during the 42 years she worked there — some from even before. The first page of each includes the date, the stated problem, and her results. Nearby is a four-drawer filing cabinet that archives her correspondence with fellow scientists.

"I've seen the names of a lot of people who are famous in those letters," says Candy Haggblom, who was Marguerite's laboratory assistant for the last three decades of the professor's career. "In a way, going through them is like reading a history of science."

Marguerite, along with her sister, Marthe, was raised by her parents, Oskar and Cecile Vogt, to be an impeccable biologist. She was wholly dedicated to this endeavor. She worked long hours and always at the bench, even until she was well into her 80s. And when she stopped doing research in the late 1990s, Marguerite continued to show up daily at the laboratory to read and discuss the latest publications with her colleagues.

She died on July 6 at age 94, following an 80-year career marked by numerous important scientific discoveries and collaborations. She helped train scores of young scientists during that time, four of whom went on to receive the Nobel Prize. Collaborations with Nobel Laureate Renato Dulbecco, also a long-time Salk investigator, changed how both viruses and cancer are studied.

The team first described how the polio virus forms plaques in cell cultures — work that transformed virology from a descriptive to a quantitative science — and then how a virus can turn a cell cancerous. Their studies provided some of the first clues to the genetic nature of cancer. They continued working together for 18 years and developed a strong friendship during that time, Dulbecco says.

Marguerite never received major awards or invitations to honor societies for her scientific contributions. But she didn't seem to mind, once telling a reporter from *The New York Times* in 2001: "I'm happy not to have been bothered. When you get too famous, you stop being able to work."

"She was a wonderful scientist," says Inder Verma, who met Marguerite during a summer in the tumor virology laboratory at Salk, and who later joined her on the Salk faculty. "She was the person who everybody went to for guidance on tissue culture and tumor viruses, and she was absolutely passionate about science and helping others to do excellent science. She was engaged completely. This is a unique characteristic."

Marguerite is said to have had a green thumb with tissue culture, the secret to which may have been her ability to maintain a sterile environment. Teaching the related procedures, she insisted that others follow her example precisely, down to which hand held a pipette and which finger pushed the plunger.

Marguerite Vogt

Roger Greig

She was also particular about how the numbers were to be written on test tubes, and how to annotate the work. Though it may have seemed a nuisance at the time they were learning her process, many of her students continue to use it today.

"She was so patient," recalls Duke University professor Dona Chikaraishi, who first met Marguerite when she joined Dulbecco's lab as graduate student in 1969. Chikaraishi remembers how her first attempt at tissue culture ended with bacterial contamination.

"It happens to everybody," she says Marguerite told her, "but it doesn't pay to try and figure out why it happened. The best thing is to just throw out your cells and start again."

This philosophy was also a precept for Marguerite's life. She didn't like to talk about the past, but preferred to focus on the future. And she subjugated whatever tinges of personal ambition she may have felt because she believed contributing to the broader knowledge base through discovery — whether her own or that of a fellow scientist — was far more important, say those who knew her best.

"Marguerite had unwavering integrity," says University of California, San Diego, research scientist Katherine Koch, who met her as a graduate student at Salk in 1972. "Working at the bench with a few people at a time allowed her more control of the quality of research, to which her ground-breaking publications attest."

Marguerite particularly enjoyed helping scientists who were just getting started in their careers. Jakob Bogenberger was one such researcher who worked at Stanford University and in private industry before retiring.

He trained at Salk as a visiting post-doc from Germany in the mid-1980s and got first-hand experience of Marguerite's generosity after wrecking his car in a traffic accident. To make sure he could continue coming to work, she bought him another vehicle.

"She was extremely good at defining her interests in life and making sure she could live her life as she wanted to," Bogenberger remembers of Marguerite. "Anything she didn't need, she gave away."

Susan Swift, who worked as Marguerite's lab technician for 11 years, says she learned what it was like to be an old-fashioned scientist, one who's slow, methodical and pays strict attention to detail. But she's also appreciative of the German lessons Marguerite gave her, an attempt to help Swift with basic conversation when visiting Bogenberger in Germany later on. The couple eventually married.

Memories such as these, filled with respect and gratitude, are pervasive among the colleagues who Marguerite adopted as a surrogate family, regardless of their rank in the lab. They are what Haggblom was thinking of as she was helping to clean out Marguerite's office at the Salk.

"Marguerite came from an era in which science was different," she concludes, packing the notebooks away. "She was not the kind of person who was out there ringing her own bell, but people who interacted with her knew how bright she was and how many good ideas she had.

"I'm still excited about science after all of these years and I don't know if that rubbed off on me from her, or if it was already there," Haggblom says. "But to this day, I perform tissue culture operations in a little plexiglass box the way Marguerite taught me."

Remembering Marguerite: *'The Sort of Lady She Was'*

ROGER GREIG RECALLS NOTICING something peculiar during his morning drive soon after joining the Salk as the security supervisor in 1993: an elderly women jogging on the side of the road wearing a backpack. It was Marguerite Vogt, professor in the Molecular and Cell Biology Laboratory, also on her way to work. She was 80 years old at the time.

A few years later, a faculty member who was concerned for her safety approached Greig about arranging transportation for Marguerite. Greig agreed wholeheartedly. He drove her to work for the next eight years, including Saturdays for two of those years. Sometimes his wife would drive, other times colleagues from Salk would pitch in.

"You just couldn't say no to her," Greig admits. "She was such a sweet-natured lady. She would have gone in seven days a week if she could."

Around 6:20 a.m., he would pull up in front of Marguerite's house and see her sitting inside, checking her wristwatch. She usually wore trousers, tennis shoes, a sweater, and a scarf around her neck. She carried her lunch box and a bag of science magazines with her to the front passenger seat.

Greig remembers how she would tease him if he was a minute late for pickup, or if he was cautious at a yellow light. On one morning, Marguerite had something stuck in her throat during the drive in and she asked him to strike her on the back to dislodge it.

"I said, 'Marguerite, there are people watching! It's not going to look good!' " But at the next traffic light, he obliged.

She urged him to whack her back even harder, he says, and then she chuckled, "I'm going to tell them you hit an old lady."

Over the years, Marguerite's hearing and memory began to falter. Eventually she moved to a retirement home in Del Mar Heights. "She loved to watch the sun rise over the Torrey Pines Mesa," Greig recalls.

When the two of them arrived at work, he would offer her his arm as they walked from the car to her office, and then he would help her put on her lab coat. After that, he says Marguerite would spend the day reading the magazines she had brought along. And sometimes, she would fall asleep.

"She would leave things out to share with the post-docs, like the sandwiches she brought with her, with a little note saying, 'Please help yourself'," Greig says fondly. "That's the sort of lady she was."

To read the April 10, 2001 *New York Times* feature story on Marguerite Vogt, visit: http://query.nytimes.com/gst/fullpage.html?sec=health&res=9F01EEDC1E3EF933A25757C0A9679C8B63. Former Salk scientist Susan Forsberg has launched a website in honor of Marguerite Vogt at: http://www-rcf.usc.edu/~forsburg/vogt.html

Tony Hunter Receives Pasarow Award for Cancer Research

SALK SCIENTIST TONY HUNTER IS the recipient of the 2006 Pasarow Award in Cancer Research for his key discoveries of the chemical "switch" that turns healthy cells into cancer cells.

In 1979, Hunter, an American Cancer Society professor in the Salk's Molecular and Cell Biology Laboratory, discovered that a biological process called tyrosine phosphorylation is a chemical "on-off" switch that can trigger the uncontrolled division of cells — the hallmark of many cancers. Discovery of this important signaling mechanism, which proved to be the underlying cause of many types of human cancer, revolutionized cancer research and, ultimately, led to the development of several innovative cancer therapies.

Phosphorylation — the addition of a tiny phosphate ion to a large protein molecule — is a common way in which the body turns on or off proteins such as enzymes. Thus, phosphorylation of proteins in cells, which is often triggered by external stimuli, acts as a signaling mechanism for cells to respond to their environment, and in particular to respond to factors that promote cell proliferation. Hunter discovered that phosphorylation of tyrosine, one of the 20 amino acids found in proteins, governed how cells multiply.

Tony Hunter

American Philosophical Society Inducts Ronald Evans and Baldomero Olivera

THE AMERICAN PHILOSOPHICAL SOCIETY (APS) HAS elected to its ranks two leading scientists affiliated with the Salk Institute: **Ronald M. Evans,** a professor in the Gene Expression Laboratory, and adjunct professor **Baldomero Olivera** of the University of Utah.

Evans' work elucidated the unexpected common mechanism by which a diverse group of hormones and vitamins control the body's metabolism, development and reproduction. Because nuclear receptors wield such physiological power, his discovery provided a multitude of targets for clinical scientists to develop new, more effective and safer drugs. Evans' technology has been used to discover more than a half dozen drugs for cancer, diabetes and heart disease with many more on they way.

Olivera identified and characterized the effects of a family of biomolecules found in the venom of tropical cone snails. He and members of his lab have pinpointed several drug candidates to treat disorders, including pain, epilepsy, cardiovascular disease, and various neurological disorders.

Modeled after the Royal Society of London, the APS was founded by Benjamin Franklin in 1734 and is the first organization in America to promote science.

Ronald M. Evans

Baldomero Olivera

Baldomero Olivera *photo courtesy of Kerry Matz, University of Utah.*

Reuben Shaw

'Scientist to Watch'

REUBEN SHAW RECENTLY made the "Scientist to Watch" list in a feature article published by The Scientist. Shaw, assistant professor in the Molecular and Cell Biology Laboratory, studies signal transduction pathways that underlie the development of cancer as well as type 2 diabetes.

Damon Runyon Fellow

MAYA CAPELSON, a postdoctoral researcher in Martin Hetzer's lab, has been named a Damon Runyon Fellow. The prestigious, three-year award is intended to encourage the nation's most-promising, young investigators to pursue careers in cancer research by providing them with independent funding to work on innovative projects. Capelson will investigate the role of "gene gates," or nuclear pores, in tumor formation and cancer progression.

Maya Capelson

Salk Appoints Nobel Laureate Roger Guillemin as Interim President

THE SALK BOARD OF TRUSTEES VOTED TO APPOINT Nobel Laureate and distinguished professor **Roger Guillemin** as Interim President. Guillemin officially took office Oct. 1 and will remain in this capacity during the Institute's ongoing search for a president.

"Roger's distinguished reputation as a Nobel Prize-winning scientist and his 37 year history with the Salk makes him ideal to lead the Institute's scientific community at this time," said Irwin Jacobs, chair of the Salk's Board of Trustees. "His pioneering contributions to science are a reflection of the Institute's excellence in research and discovery."

Guillemin received the Nobel Prize for Medicine and Physiology in 1977 for discoveries that laid the foundation for brain hormone research. His work and that of his group brought to light an entire new class of substances shown to be important for the regulation of growth, development, reproduction and responses to stress.

Research laboratories and pharmaceutical industry have produced many synthetic analogs of these brain hormones. Analogs of somatostatin are used to treat several types of tumors and are the primary medical treatment of the pituitary adenomas leading to acromegaly. Analogs of another hormone (GnRH) are used in problems of infertility and tumors of the prostate.

Guillemin also was among the first to isolate endorphins, brain molecules known to act as natural opiates. Following the isolation of endorphins, his work with cellular growth factors (FGFs), in addition to inhibins and activins, led to the recognition of multiple physiological functions and developmental mechanisms.

Roger Guillemin

Born in France, Guillemin graduated from Lyon's medical school in 1949 before studying endocrinology at the Institute of Experimental Medicine and Surgery at the University of Montreal, where he received his doctorate degree in 1953. Guillemin continued his work at Baylor College School of Medicine for 17 years before joining the Salk Institute in 1970.

His many honors include: Election in 1974 to membership in the National Academy of Sciences; 1974 Gairdner International Award; 1975 Lasker Award in Basic Sciences; election in 1976 into the American Academy of Arts and Sciences; 1976 Dickson Prize in Medicine; 1976 Passano Award in Medical Sciences; 1976 National Medal of Science (USA).

Salk Receives $2.3 Million Stem Cell Research Facility Grant

THE SALK INSTITUTE RECEIVED A $2.3 million share of the stem cell research facilities grants approved by the governing board of the California Institute for Regenerative Medicine (CIRM).

The grant will support the development of shared laboratory space to be used by multiple investigators, and provide an environment for scientific research on human embryonic stem cells (hESCs) under CIRM's medical and ethical standards. The grant will also provide funds for equipment and operating expenses over three years.

"The availability of this shared research laboratory will allow Salk researchers to initiate research on human embryonic stem cells and to contribute to this very exciting field of biology," says Program Project Director **Inder Verma,** professor in the Laboratory of Genetics, who spearheads the stem cell facility project at the Salk Institute.

To date, the Salk Institute has received more than $7.5 million in stem cell research grants from CIRM.

Michael J. Fox Foundation Awards Two-Year Grant

PAMELA MAHER, A RESEARCHER IN the Cellular Neurobiology Laboratory, has received a two-year, $330,000 grant from the Michael J. Fox Foundation to further study fisetin, a promising lead for the treatment of Parkinson's disease. Fisetin is a naturally occurring flavonoid commonly found in strawberries and other fruits and vegetables.

Maher hit upon fisetin's neuroprotective abilities when she screened a collection of flavonoids, substances with anti-oxidant activities found in many plants. In these experiments, fisetin promoted the survival of cultured nerve cells in response to a variety of toxic insults and boosted memory in healthy mice — making it a promising candidate for further studies.

Upon completion of the studies, Maher hopes to have a fisetin derivative that is more effective at a lower dose than fisetin, while also maintaining all of its other beneficial properties, including boosting intracellular levels of GSH, an antioxidant produced naturally by cells.

Pamela Maher

Friends Remember Odile Crick's Love of Adventure and Art

ODILE CRICK MAY BE REMEMBERED AS AN ARTIST AND the wife of the late Salk Nobel Laureate Francis Crick, but her closest friends and family recall an attribute that was less apparent: Odile's love of adventure.

On a whim, she once went hiking in the Pyrenees with a friend after reading about the European mountain range in a book. With little preparation, she set off to retrace the steps outlined in that story, family members say.

Odile later became widely known for the iconic drawing of the double-helical structure of DNA, which her husband co-discovered with James Watson in 1953. Her sketch became a reference for other scientists and is still considered a symbol of biochemical discovery.

Odile's typical art subjects, however, were not biochemical structures, but rather portraits and curvaceous nudes in the style of Matisse. And though she enjoyed discussing science with her husband and their friends, she seemed most interested in the culture of science, its people and relationships, say those who knew her well.

"She was a counterpoint to Francis," says Terry Sejnowski, a friend of the couple and professor and head of the Computational Neurobiology Laboratory at the Salk Institute. "Without her, he would have had a drier life."

Born in England to Alfred and Marie-Therese Speed, Odile attended art school in Vienna until the Nazi occupation of 1938. After this, she returned to England and joined the Women's Royal Naval Service as a code breaker and German translator. She married Crick in 1949 and had two daughters in addition to his son from a previous marriage.

Odile enjoyed fine food and entertaining as well as art, opera, and music. She was naturally athletic, walking and swimming regularly even into her later years. She died on July 5 at age 86, but her daughters, who spoke at Odile's memorial service at Salk, say she lived a life of someone much younger than her true age.

Beatrice Golomb, a University of California, San Diego (UCSD), physician who is married to Sejnowski, can attest to Odile's youthful spirit. Golomb first met Odile as a graduate student at UCSD and remembers being impressed by her bravery, a characteristic she didn't expect from Odile's petite frame and soft-spoken demeanor.

A former competitor in vaulting, a gymnastic sport performed on horseback, Golomb invited Odile for a lesson and was surprised by how quickly she took to the sport.

"This was in the 1980s, so Odile would have been in her 60s at the time," Golomb says. "But she had no trouble at all. She kneeled at the canter and had perfect form. She was always willing to try something new."

Odile and Francis Crick punting in England.

Resident Artist Jamie Simon's Witty Illustrations Display the Lighter Side of Salk

Jamie Simon

JAMIE SIMON HAS A KEEN MEMORY. As he illustrates how neurons compete with one another to form a synapse, he remembers how biochemical pathways can determine a cell's behavior.

"Not to sound Darwinian, but it's probably a matter of whose signal is louder," he guesses, referring to three, knob-like protrusions reaching for an axon in the picture on his computer screen. "Of course," he muses, pointing to the most distant bouton, "this one may have a subtle, but much more important, message."

At 57, Jamie is rangy and tanned, with boyish ears and a receptive face. He usually wears shorts, a T-shirt, and hiking sandals to Salk, where he has worked for 33 years, 31 of which as a graphic artist designing scientific models to support researchers' papers and presentations, as well as cartoon illustrations to publicize lectures, meetings, and various events.

The items around his workspace are a reflection of Jamie's humor and the lighthearted spirit he brings to the Multimedia Resources department and to Salk. On the shelf over his head, for example, you'll find a bottle of Polygamy Porter (from a brewery in Utah) and a plastic action figure of Tao Berman, the world-renowned waterfall kayaker. (Jamie is a kayak enthusiast.)

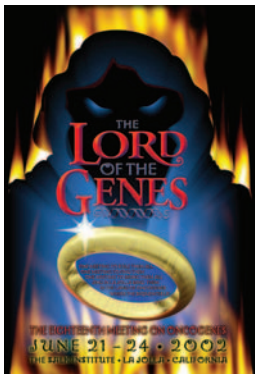
Also on this shelf is a small reference library of college texts and orphaned books. The most important component is a first edition with a faded tan cover and "General Zoology" in flaking gold on the spine. It was his father's in college and Jamie says he's read it hundreds of thousands of times, cover to cover, since he was about 10.

"This is where I first learned about organ systems and genetics," he remembers, thumbing through it to show stippled illustrations. "I used to draw with dots as a consequence. It's a great technique, but it leaves calluses on the hands."

Beyond appreciating its pictures, the book fueled his passion for biology. Growing up in Alhambra, CA, "I would savage the tide pools at the beach," he remembers, bringing specimens home to tanks in the family garage and keeping the water cold with bags of ice. He eventually earned his undergraduate degree in Biology at the University of California, San Diego, and was hired at Salk in 1974 as a cell culture technician in the Molecular and Cell Biology Laboratory (MCBL) — then called the Tumor Virology Laboratory (TVL).

His lab technique was not good, Jamie admits, and to make matters worse, "I realized I was never going to see a live animal in the lab except to extract some portion of its body," he says. But, on the bright side, the MCBL is where his talent for creating scientific graphs and illustration was first noticed. It's also where he met his wife, Suzanne, and many of his longtime friends.

Today, his in-depth knowledge of science, pop culture, and world events imbues Jamie's work with tremendous wit, as does recalling personal trivia around Salk. The cartoon posters for the annual Oncogene meeting, which he designed for 20 years, for example, capture the discoveries and changing emphasis in cancer research with creativity that resembles the current events pages from high school yearbooks. The journal *Oncogene* featured a history of the meeting in February 2007 and highlighted several of Jamie's illustrations as part of the article.



Most of the jokes in Jamie's artwork stir widespread chuckles. But on very rare occasions, they don't. Such was the case with the *Oncogene* meeting poster in 1990. Titled "Showdown at the Onco-Corral," Onc and Anti-Onc square off during a game of cards with the bad guy dressed in black sitting across from the good guy in white, while a wide-eyed, buxom-blonde bar maid leans provocatively between them.

"This one got me into trouble with a few of the women at the meeting. My wife's attitude was 'dream on'," he recalls.

Looking around Salk, you can see Jamie in more than just his art. You'll likely catch him emceeing at the Institute's picnic, working his core at the lunch-hour Pilates class, or hanging a poster in the East building with a device he built in his garage from fishing line, a broken rod, and a reel. And if you ever visit the MCBL and notice a jeweled sword hanging over Tony Hunter's office, ask him about it — there's a story about Jamie behind that, too.

"Jamie is essential to the way the Institute as we know it is run," says Hunter. "I think it's important in any serious business to have a lighter view at times. Jamie has helped to make it that way."

Dianne Day Retires and Leaves Behind a 33-Year Legacy of Leadership

ANYBODY WHO EVER WITNESSED DIANNE DAY REVVING IT up in a room full of people knew she loved her job. One minute she could be discussing some of Salk's latest scientific discoveries with one donor, then quickly switch gears with another to share details on the next tax seminar she was organizing.

To say she was good at her job is an understatement. After 33 years as the chief development officer at Salk, and millions raised through her efforts to show for it, it's safe to say she perfected the art of fundraising.

"Raising money for the Salk Institute was never just a job for her, it was a passion," said Jim Handelman, executive director of the G. Harold & Leila Y. Mathers Charitable Foundation.

After a long and fruitful career, Dianne retired from Salk on July 1 to pursue her other two passions, golf and traveling. However, the impact of her leadership and the legacy she leaves behind at Salk is remembered most by her closest colleagues and friends.

"The most important thing I learned from Dianne is that when you truly love what you do and believe in your mission, success will follow," says director of Foundation Relations Lisa Marvin, who worked with Dianne for 11 years.

Dianne started her career at Salk in 1974 as an assistant in the development office, but it wasn't long before others at the Institute recognized her talent.

Dianne Day and Del Glanz

"Within a few months it became evident that Dianne was a lot smarter than her boss," says former Salk Executive Vice President Delbert Glanz, who worked closely with Dianne for three decades. "We let him go and she took over as chief development officer. The rest is history."

Dianne's knack for building relationships with foundation managers, donors and scientists was most evident in the success of the Salk's annual Tax Seminar on Private Foundations. The three-day meeting gathers managers, directors and trustees of private foundations from all over the country to update them with current tax regulations. Presentations by Salk scientists are also folded into the schedule.

Over the next 33 years, the seminar developed into more than just a well-respected informational briefing. It also became a family reunion of sorts. Eventually, many of these relationships stretched over several decades and often turned into genuine friendships.

"It was always like a visit from a friend when Dianne came into town," Handelman says.

Tom Brorby, a trustee on the Board of the Clayton Research Foundation, agreed: "Next to the legendary Fred de Hoffmann, Dianne Day is the best fundraiser I've ever seen. Her annual Tax Seminar on Private Foundations has been one of Salk's biggest sources of private gifts thanks to her efforts and unique skills."

Looking back at it, the last 33 years wasn't necessarily all about the work she enjoyed so much, Dianne says.

> "Raising money for the Salk Institute was never just a job for her, it was a passion."

"The people are really the best part. People who support the Institute are very special and forward thinking and the scientists who work at the Salk are simply brilliant," she says. "They are all dedicated to bettering the future of humankind."

During her career, Dianne worked under seven Salk presidents and prevailed through numerous organizational changes. Her strong staying power, which is virtually unheard of for a development officer, is credited for maintaining relationship continuity between Salk and its donors.

"She is one of the unsung heroes we depend on and who is crucial for our scientific success," says Inder Verma, a professor in the Laboratory of Genetics.

Brorby took it a step further, saying: "C. W. Wellen, the president of the Clayton Research Foundation, which has spent $36 million on research over the years, has been heard to say on several occasions: 'To me, Dianne IS the Institute.' And that says it all."

Friends of the Institute Gather for Annual Symphony at Salk

A TOTAL OF 800 GUESTS ATTENDED this year's Symphony at Salk, which featured an evening of music and entertainment by the San Diego Symphony and guest artist Hershey Felder. The annual fundraiser directly benefits research at the Institute by providing resources that are crucial to Salk's mission of scientific discovery. For more photos from the event, please visit our website at www.salk.edu.

Guests enjoy the evening concert in the Theodore Gildred Court.

Fred Applegate (from left), Laura Bradly with Charles and Tanya Brandes.

Hershey Felder

International Council Members Learn About Salk's Latest Studies in Vienna

WELCOMED BY VIENNA'S OLD WORLD CHARM AND A CADRE of eminent Salk scientists, members of the Salk International Council and Board of Trustees as well as special guests congregated at the banks of the Danube river to hear firsthand about the latest research findings made at the Salk Institute.

The topics of the scientific presentations at the Grand Hotel ranged from stem cells and the mechanisms underlying aging and age-related diseases, to the nuts and bolts of metabolic syndrome and the inner workings of a cell's nucleus. A palpable sense of excitement accompanied the talks as faculty members explained their research and reinforced what it means to be part of an institution whose investigators publish more seminal papers per scientist than any other biomedical research facility worldwide.

Nobel Laureates **Renato Dulbecco** and **Roger Guillemin** discussed the impact of basic science on everyday life and Salk's unique environment for moving science forward. "I came [to Salk] because I would be totally independent and there wouldn't be any departmental partitions. That's the basis for doing really great science," said Dulbecco.

Former Salk President **Frederic de Hoffman** founded the International Council in the 1970s to help broaden awareness of the Institute's cutting-edge research being conducted by some of the world's most noted scientists.

Vienna's Grand Hotel, the site of the International Council meeting.

Today, the Council consists of more than 80 distinguished men and women who are worldwide leaders in business, medicine, law, the arts and community affairs. They meet bi-annually to learn about the fast pace of basic biological research at the Salk. In return, members give of their time and treasure and serve as ambassadors of the Institute by sharing their understanding and enthusiasm about the Salk's groundbreaking research with new audiences worldwide.

Donor Gail Hoffman 'Remembers Polio'

IT WAS 1947, JUST TWO YEARS AFTER World War II, when polio became personal for Gail Hoffman. She was 10 years old and remembers not being able to go to the movies, or go swimming in the lake.

The outbreak was especially bad that summer growing up in Rochester, New York, which caused her parents to be concerned when she developed a 105-degree fever that lasted for days.

"My mother panicked because she was sure that I had come down with polio," Hoffman says. "Although doctors initially suspected I had pneumonia, they admitted me into the hospital for further tests that would reassure her."

Many children had already died from the disease, and those who didn't would be left crippled from it. No public place seemed safe from polio and it was a frightening time for everyone, Hoffman says.

"When I arrived at the hospital, I thought that the nurses were being mean at first, but they were just so focused on caring for the war veterans who were there," she says. "It made such a huge impact on me because I was so young and there was so much going on."

After enduring a painful earache and undergoing extensive penicillin treatment, the doctors confirmed their original diagnosis. She and her parents were relieved that she didn't have polio, but the experience — which she described as "outstanding" — is one reason Hoffman makes a yearly donation to the Salk Institute.

She took the opportunity to encourage new gifts to the Institute when her friends asked her what she wanted for her birthday recently. "I didn't need another purse, so my birthday wish was that they make a donation to the Salk Institute," she says.

Her other source of motivation for giving comes from her father, who made it a Monday night ritual to visit the hospital and show movies to children who were in iron lungs.

Some of her friends who were diagnosed with polio when they were young are still feeling the effects today — yet another reason to give, she says. By 1960, she became a mother, which got her interested in the Salk Institute because she was grateful that she wouldn't have to worry about polio outbreaks like her mother did thanks to Dr. Jonas Salk.

Gail Hoffman

As a result, her first donation, and many others after that, was mailed along with a note that reads: "Thank you, Dr. Salk, from a mother of four who remembers polio."

"It's important for me to continue to donate because I believed in Jonas Salk," Hoffman says. "The Institute is doing such wonderful research and I believe there's another answer in Salk."

Innovation Grants Program Infuses Cutting-Edge Projects with Start-up Funds

CUTS IN FEDERAL FUNDING HAVE LEFT MANY SCIENTISTS struggling with the reality that some of their groundbreaking experiments may just have to be shelved. But a recent program at the Salk Institute circumvents this hurdle. The Innovation Grants Program (IGP) is a donor-funded mechanism for supporting riskier, but potentially very rewarding, projects that would otherwise be orphaned.

"Salk's mission has always been one of unobstructed discovery," says **Joseph Ecker,** who chairs the program and is a professor in the Plant Biology Laboratory at Salk. "This program provides researchers with the financial flexibility to ask bold scientific questions, which they can attempt to answer by exploring their most creative ideas."

Though, historically, donors have supported new scientific research at Salk, the IGP is the first mechanism to ensure that the most promising projects receive immediate funding. Scientific proposals are reviewed by a committee of seven Salk faculty members who rank the prospects and recommend funding for those that meet program criteria.

Since it was established in 2006, the IGP has attracted $1.5 million in donations. More than half of that has been distributed in two rounds of funding, with grants ranging from $25,000 to $100,000 for one year. A third round of grants is scheduled to be distributed in the coming weeks.

Among those who received an IGP grant in the first round is **Gerard Manning,** a senior staff scientist in the Razavi-Newman Center for Bioinformatics. Manning is a computational biologist who studies genomes to understand the function of all kinds of life forms.

Manning is testing a radical strategy for piecing together DNA fragments scooped from the environment to assemble genomes of new bacterial species. This genetic information can then be used to determine the organisms' function in the environment. If it works, it could revolutionize the ability to understand the functions of the 99 percent of bacteria that cannot be cultivated or studied in the lab.

"Many of the projects that have received funding from the IGP involve the development of a new technique such as this," says **Christopher Kintner,** who co-chairs the program and who is a professor in the Molecular Neurobiology Laboratory. "New technical breakthroughs are one of the primary engines driving scientific discovery."

Executive Vice President's Message

Partnerships and Strategic Plans Ensure Salk's Forward Momentum Into the Future

Marsha A. Chandler

> "Taking the appropriate steps to ensure [the Salk's] place as a world-class facility today and into the future is our responsibility."

SINCE ARRIVING AT SALK IN JULY, I have been enormously impressed by so many facets of the Institute, but nothing (except perhaps the architecture) is more striking than the exceptional quality of the scientific research. As I have been meeting with each member of the faculty, I have been able to see first-hand one of the attributes that makes Salk so unique – the benefits that the research draws from the many collaborations among the scientists. It is these interactions that have truly made Salk greater than the sum of its parts. The strategic plan and the various collaborative programs on the horizon will, no doubt, further the path-breaking research at Salk that ensures new scientific discoveries ultimately benefiting humanity.

California has led the nation by putting together a $3 billion fund for stem cell research. Having already begun to draw on these funds, Salk's team of established stem cell experts, as well as scientists who work in gene expression and related fields, are poised to substantially increase our understanding of how stem cells can be developed for therapeutic purposes. Construction is already underway at Salk for a new stem cell core facility funded in part with a $2.3 million grant awarded in June by the California Institute for Regenerative Medicine (CIRM). The new facility will serve as a training center for the next generation of scientists who work in this very promising field of research.

Further securing our commitment to this emerging field is Salk's participation in the San Diego Consortium for Regenerative Medicine (SDCRM). The consortium, consisting of the Salk Institute, the Burnham Institute for Medical Research, the Scripps Research Institute, and the University of California, San Diego, will catalyze and bring together the intellectual resources from each of these institutes to further expedite discoveries in stem cell research.

Over the past year, our Salk Innovative Grants Program has flourished. Thus far, 12 Salk scientists (with five more awards to be announced shortly) have received immediate support for cutting-edge studies in their beginning stages. Although such projects often offer promising and significant scientific breakthroughs, they are normally not funded by traditional agencies which tend to focus on more established proposals. The Innovative Grants Program, funded totally by private philanthropy, provides Salk scientists with the financial feasibility to ask bold scientific questions which they can seek to answer by exploring their most creative ideas. It is also our intention to establish a Technology Innovation Fund, which will enable our scientists to more nimbly adopt new technologies and equipment. This fund will help our technologies to keep pace with the dynamism of our ideas.

All of these steps, intended to accelerate the Salk Institute's forward momentum and to maintain its preeminence as a world leader in basic biological research, are rounded out by the Institute's update to its Master Plan. The plan will support Salk's anticipated growth and development for the next 50 years. It proposes a number of new facilities that will expand scientific research space, accommodate emerging technologies, and provide new and improved support facilities for the Institute. The plan will soon be submitted to the City of San Diego for approval, which we are hopeful to receive early in 2008.

The entire Salk community: scientists, researchers, Trustees, staff, students, and supporters, can rightly be proud of Salk's outstanding record of achievement. With the potential of this community, the future promises to be even more illustrious.

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

Salk **Calendar**

NOVEMBER 2007

2-3 **Motor Systems Symposium**

JANUARY 2008

10-13 **Genes, Circuits and Behavior: A Symposium on Biological Complexity**

15 **Consortium for Systems Biology Meeting**

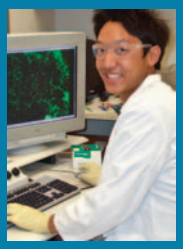
FEBRUARY 2008

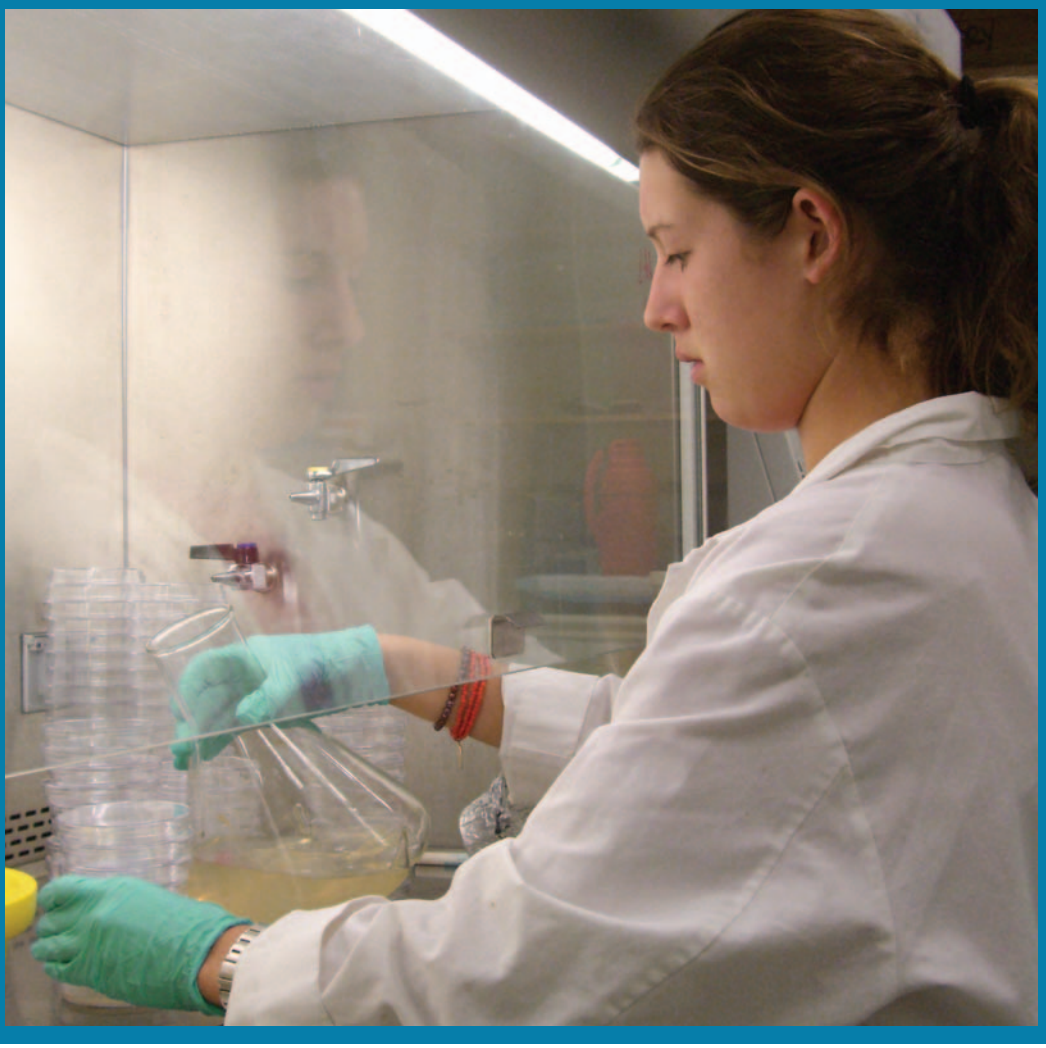
4-6 **The Adler Symposium**

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









High school students from the San Diego area work in various laboratories as part of the Salk Institute's annual Summer Enrichment Program. Over an eight-week period, they participate in hands-on experiments under the mentorship of Salk scientists.

SALK INSTITUTE
FOR BIOLOGICAL STUDIES

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