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THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

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What Really Triggers This Plant to Grow?

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ON THE COVER *Arabidopsis thaliana,* a small plant related to cabbage and mustard, has long been widely used among plant biologists. It became the gold standard for plant research in the 1980s because it's easy to grow in the laboratory and reproduces quickly. A group of Salk researchers participated in an international effort to successfully decode the plant's approximate 25,000 genes in 2000. Photo by Joe Belcovson.

What Really Triggers This Plant to Grow?

Plant Size Morphs Dramatically as Scientists Tinker with Outer Layer

Jack's magical beans may have produced beanstalks that grew into the sky, but something about run-of-the-mill plants limits their upward reach. For more than a century, scientists have tried to find out which part of the plant both drives and curbs growth.

IS IT A SHOOT'S OUTER WAXY LAYER? Its inner layer studded with chloroplasts? Or the vascular system that moves nutrients and water? The answer could have great implications for modern agriculture, which desires a modern magical bean or two.

Researchers in the Plant Biology Laboratory at the Salk Institute have unlocked the mystery after successfully making tiny plants big and big plants tiny by controlling growth signals emanating from the plants' outer layer, their epidermis.

The findings, reported in *Nature*, could eventually be used by agronomists to manipulate plant growth pathways to maximize crop yield, says the study's lead author **JOANNE CHORY**, professor and director of the Plant Biology Laboratory and investigator with the Howard Hughes Medical Institute.

Chory and her team have spent years helping to define how a plant "knows" when to grow and when to stop — which is a "big question in developmental biology," she says. For their experiments, they rely on the model system *Arabidopsis thaliana*, a small plant related to cabbage and mustard, whose genome has been decoded.

The researchers have built up a whole tool kit over the years, learning how to add and subtract genes in order to determine form and function. Among their discoveries is a class of dwarf plants whose size is about one-tenth the size of a single leaf of the full-sized plant.

Over the past decade, Chory's laboratory and others have shown that these dwarf plants are defective in making or responding to a steroid hormone called brassinolide. Among the genes identified was the plant steroid receptor BRI1 ("bry-one"). The dwarfed *Arabidopsis* doesn't express BRI1 at all, unlike normal *Arabidopsis*, which expresses BRI1 on both the outer waxy epidermis, and the inner sub-epidermal layer, which contains the chloroplasts that conduct photosynthesis.

In the current study, first author **SIGAL SAVALDI-GOLDSTEIN**, a postdoctoral researcher in the Plant Biology Laboratory, and **CHARLES PETO**, an electron microscopy specialist in the Laboratory of Neuronal Structure and Function, conducted a series of experiments that address an old question: Which leaf tissue controls growth?

They found that when they drive the expression of the BRI1 receptor in the epidermis of a dwarf *Arabidopsis* while leaving the sub-epidermal layer alone (without BRI1 receptors), the tiny plant morphed into a full-sized plant. In the second set of experiments, they used an enzyme to break down the steroid hormones in the epidermis, and found that a normal sized plant shrunk into a dwarf.

"These are simple experiments, but it took 10 years of work in order for us to be able to ask this question," Chory says.

The findings could eventually be used by agronomists to manipulate plant growth pathways to maximize crop yield.

CHARLES PETO, SIGAL SAVALDI-GOLDSTEIN AND JOANNE CHORY

Insulin: In Need of Some Restraint?

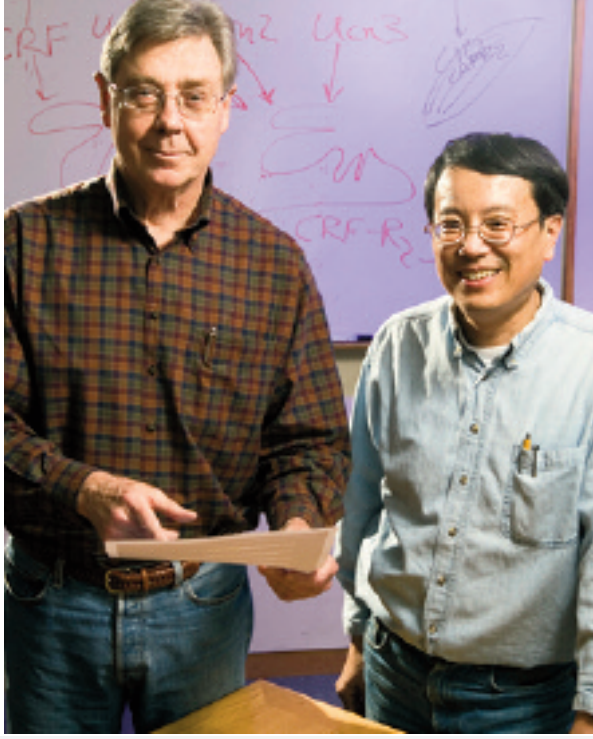
The Vale and Lee labs hypothesize that closely related peptides urocortin-2 and urocortin-3 act in concert to modulate insulin secretion.

WYLIE VALE AND KUO-FEN LEE, professors in the Clayton Foundation Laboratories for Peptide Biology, have reported in *Proceedings of the National Academy of Sciences* that loss of a gene encoding a peptide promoting insulin secretion protects mice against harmful effects of a high-fat diet.

Vale and postdoctoral fellow **CHIEN LI** had shown that the peptide, urocortin-3, which is expressed in pancreatic islet cells, promotes increased insulin secretion following high caloric intake.

So the researchers deleted, or "knocked out," urocortin-3 in genes of a mouse and analyzed the metabolism of knock-out mice. When fed a high-calorie diet, urocortin-3 knock-out and normal mice gained equivalent weight and showed lower insulin levels. But knock-out mice showed lower blood sugar and improved glucose tolerance curves, and didn't develop fatty livers seen in normal mice under that diet.

The Vale and Lee labs with postdoctoral fellow **ALON CHEN** had shown that the closely related gene, urocortin-2, acts within muscle to regulate insulin sensitivity of that tissue.



WYLIE VALE AND KUO-FEN LEE

They hypothesize that the two urocortins act in concert to modulate insulin secretion and sensitivity.

They will now determine whether urocortins have additive effects by examining mice in which both urocortin genes are knocked out. These studies may provide a rationale for developing therapeutic means of suppressing or blocking the actions of both peptides for the management of type 2 diabetes.

Study of Heritable Disease Links Cancer to Aging

TO UNDERSTAND HOW CANCER might be related to aging, **JAN KARLSEDER**, associate professor in the Molecular and Cell Biology Laboratory, analyzed genetic damage in chromosomes of patients with a heritable disease known as Werner Syndrome (WS). These patients show signs of premature aging, such as wrinkling or balding, early in life and die in midlife often due to a predisposition to cancer.

LABELING TECHNIQUES USED BY SCIENTISTS TO "PAINT" EACH PAIR OF THE 46 CHROMOSOMES, ENABLES THEM TO SEE BREAKAGE OR FUSION AS SEEN BELOW IN CHROMOSOMES SIX AND 10. IMAGE COURTESY OF ANNA JAUCH.

Karlseder and postdoctoral fellow **LAURE CRABBE** reported in *Proceedings of the National Academy of Sciences* that protective structures at the tips of every chromosome — called telomeres — were missing on WS patient chromosomes. When telomeres are lost or damaged, chromosomes can randomly break, leading to a condition described as genomic instability, which often precedes cancer development.

The investigators grew cells taken from WS patients in culture and artificially supplied those cells with a gene encoding an enzyme that reconstructs damaged or missing telomeres. After the cells divided several times, their DNA was re-examined for evidence of damage.

The cultured cells supplied with the telomere-building enzyme showed evidence of chromosomal repair: their telomeres had been elongated, and no chromosomal aberrations accumulate. These findings indicate a direct relationship between aging, telomere loss and cancer. Karlseder predicts that cancer seen in older adults could have a similar basis as that seen in WS patients.

The cultured cells supplied with the telomere-building enzyme showed evidence of chromosomal repair: their telomeres had been elongated.

Deconstructing Brain Wiring, One Neuron at a Time

IMAGINE YOU WERE GIVEN a bowl of spaghetti then asked to draw a diagram of the contacts a single strand made with neighboring noodles. Sound challenging? Neuroscientists are faced with an even more gargantuan task in their effort to construct a wiring diagram of the connections made by billions of tangled neurons in the brain.

EDWARD CALLAWAY, professor in the Systems Neurobiology Laboratories, and postdoctoral researcher **IAN WICKERSHAM** reported in *Neuron* a method to make construction of that brain map feasible.

For decades researchers have attempted to devise a method, suggested by the late Francis Crick, in which a single neuron is injected with a substance that would stain all the neurons connected to it. The Salk group succeeded by infecting a single neuron — analogous to one noodle in the bowl — with a rabies virus carrying a gene for green fluorescing protein. The virus then spread to neurons directly connected to the first cell via their synapses — the gaps between neurons and their immediate neighbors — turning those cells green.

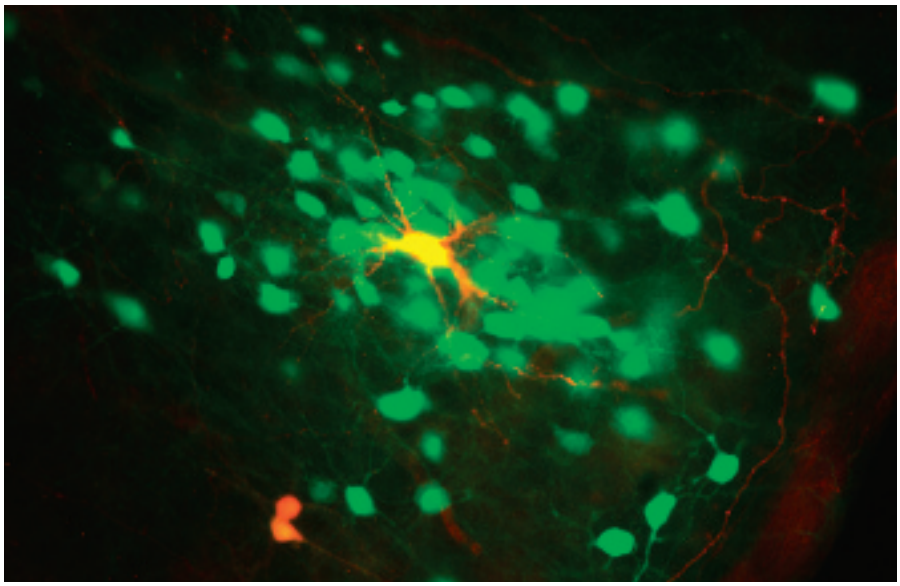
Developing this method required two different modifications of the rabies virus. The first trick was to devise a way to infect only a single cell. This was accomplished with a strategy developed by **JOHN YOUNG**, professor in the Infectious Disease Laboratory, and co-author on the study. The virus was coated with a protein from an avian virus so that it would only be able to infect cells expressing the avian viral receptor.

The second trick was to make a virus that could spread to directly connected cells, then stop so it could not continue to downstream cells. To accomplish this, researchers engineered the virus so that it was missing a gene required to cross a synapse. They then supplied both the avian virus receptor and the missing viral gene to neurons in rat brain tissues.

When they infected those tissues with the altered virus, the result was spectacular: selectively infected cells indeed transferred the virus to only their immediate neighbors, which could be identified by their brilliant green fluorescence. It was as if you could choose your target noodle and then magically light up only the noodles touching it.

This innovation will not only enable investigators to undertake functional studies of the way neurons affect their neighbors but it will also be invaluable in the effort to understand brain cell connectivity.

SCIENTISTS USE A GENETICALLY MODIFIED RABIES VIRUS TO LABEL THE NEURONS (GREEN) THAT MAKE CONNECTIONS TO A SINGLE NEURON (YELLOW). PHOTO COURTESY OF DAVID LYON IN THE CALLAWAY LABORATORY.



FRED H. GAGE

Experience Affects New Neuron Survival and Function in Adult Brain

FRED H. GAGE, professor in the Laboratory of Genetics, reported in the *Journal of Neuroscience* that new neurons in brain regions associated with learning and memory are more likely to survive when mice are exposed to the same experience more than once.

Researchers labeled dividing cells in mouse brain and then exposed mice to an "enriched" environment with tunnels and a running wheel. After they re-exposed mice to a second similar experience, they found increases in new neuron survival.

But not just any repetition would do — when the second exposure was to a different environment, like a water maze, neuron survival was enhanced but not as robustly as in mice that had the identical experience repeated.

Young neurons were most affected, and once they survived a critical developmental period, their activity became stable. The study shows that within a critical time window experience determines the survival of newborn neurons and could have a long-term affect on their function in learning and memory.

WATERCOLOR ILLUSTRATION BY KATHERINE NAGEL.

Neurons That Detect Motion Know What Meets the Eye

VISUALLY RESPONSIVE NEURONS in the brain only respond to a limited portion of the visual scene known as their "receptive field." How can these neurons interpret what they see given their restricted view of the world? Salk researchers **GENE STONER**, senior staff scientist, **THOMAS ALBRIGHT**, director of the Vision Center Laboratory, and **XIN HUANG,** the study's first author, have discovered that motion-selective neurons in the visual cortex know much more about what is outside their receptive field than was previously realized.

For a study published in *Neuron*, the researchers recorded the responses of neurons in monkeys while stimuli passed through each neuron's receptive field. They found that when moving features outside the receptive field were part of the same object as the feature within the receptive field, these neurons responded as if all the object's features were inside the receptive field — allowing them to correctly interpret the motion of the whole object.

However, when the features inside and outside the receptive field were part of *different* objects, the same neurons correctly distinguished the motions within the receptive field from those outside.

Human perception relies on the activity of billions of neurons. This new research suggests that visual perception owes much to the sophisticated properties of individual neurons, each of which dynamically adjusts its receptive field around the objects that populate a given visual scene.

The Time It Takes to Comprehend What You See

WHEN YOU VIEW AN OBJECT, information about its color, shape and motion travels to the brain through separate neurons. This segregation of visual information raises the question: How do these signals become integrated to give rise to coherent perception? **JOHN REYNOLDS**, associate professor in the Systems Neurobiology Laboratory, and **CLARA BODELÓN**, a mathematician in the laboratory, have taken a step toward understanding the mechanisms of perceptual integration by precisely timing them. They report in the *Journal of Neuroscience* that an object's properties are re-integrated in the cortex in 1/100th of a second.

To make that measurement, Bodelón designed pairs of simple images — for example a red vertical grating pattern and a green horizontal grating, or a rightward yellow grating and a leftward blue grating — which, when repeatedly presented very rapidly to human observers, cancelled one another and become invisible.

Bodelón found that when she slowed the presentation, the subjects could report the orientations of the gratings. When presentation rate was further lowered, the subjects perceived the colors and orientations but couldn't say which image — the vertical or horizontal one — was red or green. Their brains could "see" form and color but could not combine them.

Only after slowing the presentation by another 1/100th of a second could observers perceive the conjunctions of color and orientation of individual objects, indicating that the underlying computation is very fast, but measurably time-consuming.

Knowing the time required to integrate different sources of visual input has implications for ultimately treating disorders of perception, such as visual agnosia, a condition in which the patient has difficulty understanding complex visual stimuli.

When you view an object, information about its color, shape and motion travels to the brain through separate neurons.

CLARA BODELÓN AND JOHN REYNOLDS

ANDREW DILLIN

Researchers Discover First Gene Linking Calorie Restriction to Longevity

IN STUDIES GOING BACK TO THE 1930'S, mice and many other species subsisting on a severely calorie-restricted diet have consistently outlived their well-fed peers by as much as 40 percent. But just how a diet verging on the brink of starvation extends lifespan has remained elusive.

Now, **ANDREW DILLIN** and his team have cracked open the black box of how persistent hunger promotes long life and identified a critical gene, called *pha-4*, that specifically links calorie restriction (CR) to longevity in studies performed in the roundworm Caenorhabditis elegans.

"After 72 years of not knowing how calorie restriction works, we finally have genetic evidence to unravel the underlying molecular program required for increased longevity in response to calorie restriction," says Dillin, an associate professor in the Molecular and Cell Biology Laboratory, who led the study published online in *Nature*.

Having identified a key link between calorie restriction and aging also opens the door to development of drugs that mimic the effects of calorie restriction and might allow people to reap health benefits without adhering to an austere regimen that only ascetics can endure.

The potential payoff for cutting to 60 percent of normal while maintaining a healthy diet rich in vitamins, minerals, and other nutrients, is huge. Currently it is the only strategy, apart from direct genetic manipulation, that consistently prolongs life and reduces the risk of cancer, diabetes, and cardiovascular disease, while staving off age-related neurodegeneration in laboratory animals from mice to dogs. Although some people are already imposing this strict regimen upon themselves, it is too early to tell whether calorie restriction will have the same effect in humans.

Scientists Hammer Out Pathway That Promotes Muscle Cell Survival in Mice

MARC MONTMINY, professor in the Clayton Foundation Laboratories for Peptide Biology, and his colleagues have identified an enzyme that pumps up a cell's ability to maintain healthy muscle and restores normal muscle function in genetically engineered mice with weak muscles. The study, published in *Nature Medicine*, is the first to explore the part this enzyme, known as salt-inducible kinase-1, or SIK1, plays in a cascade of events triggered by exercise-induced hormones and other signals.

"In addition to muscle, this regulatory circuit is present in brain and heart tissue, where it also seems to control cell survival," said Montminy, senior author of the study. "Potentially, understanding the role of this enzyme in muscle cells may shed light on the underlying mechanisms of many diseases that affect cell survival, such as muscular dystrophy, neurodegenerative diseases, and congestive heart failure."

Montminy's team, led by postdoctoral researcher **REBECCA BERDEAUX**, first became interested in the enzyme when they observed that mice engineered to have a defect in a molecular switch, called cAMP responsive element binding protein (CREB), had hunched backs, muscle wasting, and other signs of unhealthy muscles.

Then, the researchers noticed that mice lacking CREB activity in their muscle cells also had a genetic brake, called histone deacetylase 5 (HDAC5), stuck in place. "SIK1 provides an unexpected link between two important mechanisms of gene regulation, CREB and HDAC5, and this pathway plays a major role in maintaining normal muscle function," said Berdeaux.

REBECCA BERDEAUX AND MARC MONTMINY

Ronald Evans Receives America's Top Prize in Medicine

RONALD EVANS, professor in the Salk Institute's Gene Expression Laboratory and a Howard Hughes Medical Investigator, has been named a recipient of the 2007 Albany Medical Center Prize in Medicine and Biomedical Research — America's top prize in medicine.

Evans was honored for his pioneering discovery of nuclear hormone receptors. He shares this year's award and the $500,000 prize with co-recipients Robert J. Lefkowitz, professor of Medicine at Duke University Medical Center, and Solomon H. Snyder of the Johns Hopkins School of Medicine. Each of their groundbreaking discoveries of how receptors transmit signals from hormones, drugs and other stimuli to trigger action within the cell helped give rise to a new and rapid phase of drug development, including many of today's most commonly used prescription drugs.

Evans' seminal discovery occurred in 1985 when he successfully cloned the first nuclear hormone receptor, the human glucocorticoid receptor. This action would soon lead to the finding of a superfamily of nuclear hormone receptors, all with similar molecular and genetic structures.

Interestingly, his superfamily of nearly 50 nuclear receptors can function like a car with forward, neutral and even reverse activities — allowing the development of unique classes of drugs. The impact on pharmaceutical research was dramatic as the industry could now target a whole new generation of therapies.

RON EVANS

Today, Evans' nuclear hormone receptors are among the most widely investigated group of pharmaceutical targets in the world. More recently, Evans has identified receptors that are targeted by drugs to treat type 2 diabetes and that play a pivotal role in helping to lower sugar levels and remove cholesterol from the body.

Earlier this decade, Evans identified the receptor to create the first genetically engineered mice with increased endurance for long-distance running. These marathon mice hold out promise for treating children with degenerative muscle disease as well as helping the growing numbers of overweight people burn more calories faster.

URSULA BELLUGI

Ursula Bellugi Elected to National Academy of Sciences

URSULA BELLUGI, professor and director of the Salk Institute's Laboratory of Cognitive Neuroscience, has been elected a member of the National Academy of Sciences, an organization that recognizes distinguished achievements in original research. It is considered one of the highest honors accorded a U.S. scientist.

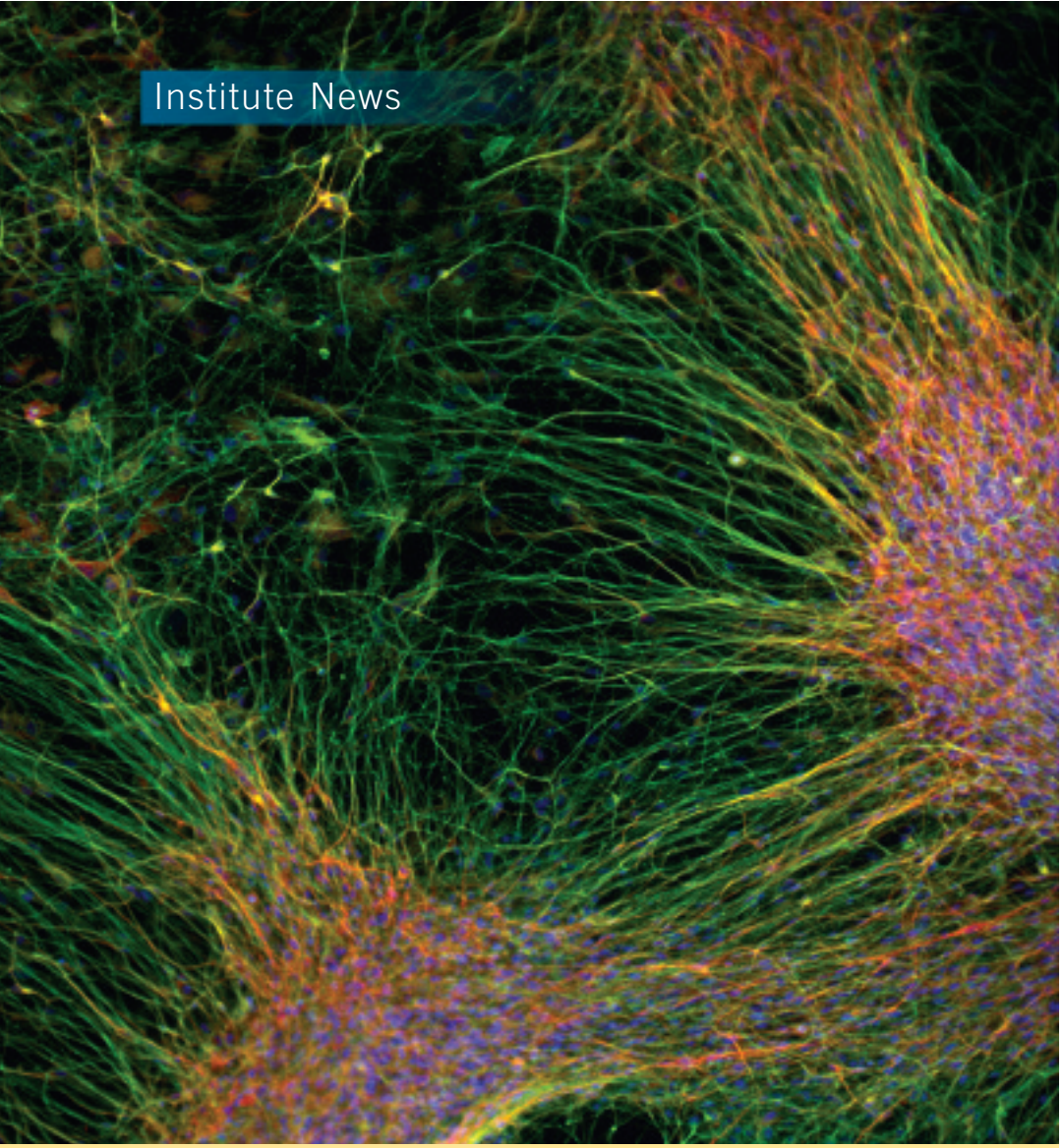
Bellugi is regarded as the founder of the neurobiology of American Sign Language since her research revealed that there are primary linguistic systems in the hands and for the eyes, which have become forged into complexly structured languages with complex grammatical properties based on the use of the hands in spatial patterning, not derived from spoken languages.

Before, it had been assumed that the organizational properties of language are connected with the sounds of speech. Her work has found that the left hemisphere of the human brain has an innate predisposition for language, even for a language in which spatial and visual processing plays a central role. This predisposition of certain brain systems to process language is a striking demonstration of neuronal plasticity.

During her career, Bellugi has been seeking new avenues for understanding the ties between molecular genetics, the brain and cognition. So she reached out across disciplines and assembled a team of experts from her work in cognitive neuroscience to brain systems and molecular under the umbrella of a Program Project from the National Institutes of Child Health and Human Development. A first of its kind, the program is helping her trace the influence of individual genes on the development and function of the brain and higher cognitive functions. Led by Bellugi, the researchers are looking to Williams syndrome to provide clues to some of the mysteries of the genetic and neural bases of behavior.

This puzzling genetically based disorder leaves language, facial recognition and social skills remarkably strong in contrast to severe inadequacy in other cognitive aptitudes. Williams syndrome arises from a faulty recombination event during the development of sperm or egg cells.

As a result, almost invariably the same set of about 20 genes is deleted from one copy of chromosome seven, making Williams syndrome a unique model system to study how a genetic predisposition interacts with ITS environment to sculpt the brain in unique ways.



NEURONS (GREEN AND RED) DIFFERENTIATE FROM HUMAN EMBRYONIC STEM CELLS. THE BLUE STAIN MARKS DNA, THUS ILLUSTRATING THE CELLS' NUCLEI. PHOTO COURTESY OF CHRISTIAN CARSON OF THE GAGE LABORATORY

State Awards Salk $5.18 Million in Stem Cell Research Grants

THE STATE OF CALIFORNIA awarded **FRED H. GAGE**, professor in the Laboratory of Genetics, $2.9 million for research to develop methods of turning human embryonic stem cells into neural stem cells.

The award, California's largest to date, was part of nearly 30 grants totaling $74.5 million allocated in March by the state's stem cell program for research intended to produce new treatments for incurable diseases.

Turning human embryonic stem cells into neural stem cells is a requirement for producing fully developed human brain cells. These would be useful in testing drugs for Parkinson's and other neurodegenerative diseases.

The state also awarded three additional Scientific Excellence through Exploration and Development (SEED) grants totaling $2.28 million to Salk. The funds will be used for human embryonic stem cell research and distributed over two years among laboratories headed by **SENYON CHOE**, professor in the Structural Biology Laboratory, **BEVERLY EMERSON**, professor in the Regulatory Biology Laboratory, and **SAM PFAFF**, professor in the Gene Expression Laboratory.

SEED grants are intended to bring new ideas and new investigators into the field of human embryonic stem cell research, and offer an opportunity for investigators to carry out studies that may yield preliminary data or proof-of-principle results that could then be extended to full-scale investigations.

All grants were approved by the 29-member Independent Citizens Oversight Committee (ICOC), which governs the board of the California Institute for Regenerative Medicine (CIRM).

SAM PFAFF

REEVE FOUNDATION AWARDS TWO-YEAR GRANT

SAM PFAFF, professor in the Gene Expression Laboratory, has received a two-year grant from the Christopher and Dana Reeve Foundation to conduct research that will focus on neurons within the lower spinal cord that comprise the central pattern generator (CPG).

This complex network of cells can generate locomotor activity — even if connections between the brain and the spinal cord have been lost. The CPG was discovered nearly a century ago, but the identity of the cells remains fragmentary.

Pfaff will receive $125,000 over two years to study how motor neurons, the nerve cells that activate muscles, and interneurons, the cells that link one neuron to another, organize themselves into the CPG and establish locomotor activity in the spinal cord.

His team of researchers will use several types of genetically engineered mouse lines to try to pinpoint the master genes that control the position and role of neurons in the CPG. Pfaff also will use electrophysiological recordings and sophisticated cell-labeling techniques to examine spinal circuitry in the mouse models. These experiments could help scientists understand how motor neurons form new connections following a spinal cord injury.

CHANGING OF THE GUARD

JOHN YOUNG (LEFT) OFFICIALLY BECAME CHAIR OF THE SALK'S ACADEMIC COUNCIL MARCH 31. HE IS PICTURED WITH OUTGOING CHAIR INDER VERMA.

Faculty Promotions

» Andrew Dillin Promoted to Associate Professor

ANDREW DILLIN, associate professor in the Molecular and Cell Biology Laboratory, studies the tiny roundworm *Ceanorhabditis elegans* to understand the process of aging by looking at the hormone most widely recognized for its role in diabetes: insulin. The insulin signaling pathway in worms is not only almost identical to that found in humans, but Dillin discovered how the insulin pathway controls aging without disrupting other physiological processes, such as reproduction and development.

In his most recent study, Dillin unraveled a mystery that had dodged scientists for the last 72 years. He identified a gene that specifically links calorie restriction with prolonged life span. A natural extension of his work on aging is to understand the link between the aging process and age-related diseases, such as Alzheimer's, Parkinson's and cancer. Recently, his lab discovered that the harmful beta amyloid aggregates found in Alzheimer's patients accumulate when aging impedes two molecular clean-up crews from getting rid of these toxic species.

» Martyn Goulding Promoted to Full Professor

MARTYN GOULDING, professor in the Molecular Neurobiology Laboratory, studies how the nervous system develops and functions. Efforts in his laboratory have focused on defining the genetic program that generates different interneuron cell types in the embryonic spinal cord. In addition to playing critical roles in relaying sensory information from the surface of our body to the brain, these neurons are also important for locomotion.

Knowing more about how these cells form and are "wired up" will further our understanding of how to regenerate and reconnect the nerve cells in the spinal cord that allow us to move. Goulding has discovered and characterized a number of genes that control the development of the spinal cord, including Pax3. He also demonstrated that mutations in Pax3 cause a human disorder called Waardenburg Syndrome.

Andrew Dillin

Martyn Goulding

Jan Karlseder

John Reynolds

» Jan Karlseder Promoted to Associate Professor

JAN KARLSEDER, associate professor in the Molecular and Cell Biology Laboratory, focuses on understanding the functions of mammalian telomeres. Telomeres, the protein-DNA complexes at the ends of linear chromosomes, are crucial in DNA replication, tumor suppression, and aging.

Current research centers on different aspects of telomere dynamics, namely the involvement of telomeres in premature aging diseases, interactions between the DNA damage machinery and telomeres, and telomere processing during the cell cycle.

» John Reynolds Promoted to Associate Professor

JOHN REYNOLDS, associate professor in the Systems Neurobiology Laboratory, focuses on understanding the neural mechanisms of vision and visual attention. This understanding is essential in order to develop treatments for disorders in which attention and vision are impaired, such as visual agnosia, Balint's Syndrome, visual neglect, and attentional aspects of autism.

One of the main goals of research in the Reynolds laboratory is to understand the different roles played by distinct classes of visual cortical neurons in transforming attentional feedback signals into improved visual processing. Reynolds and his colleagues are pursuing this goal using a combination of visual psychophysics, neurophysiology, and computational neural modeling.

New Online Donation Feature Makes Philanthropy Fast, Easy and Secure

SALK HAS MADE IT EASIER FOR SUPPORTERS to make a contribution to the Institute with the unveiling of its Web site's "Make Your Gift Online" feature. With just a few clicks of the mouse, donors can help move groundbreaking research forward from their home or office.

Giving to the Institute's Annual Fund online is fast and easy, and the gift is immediately made available to support promising research initiatives in infectious diseases, cancer and stem cell research — as well as ongoing efforts in the key areas of neurosciences, molecular and plant biology and genetics. Gifts provide operating flexibility that helps the Institute respond quickly to the greatest needs of the faculty.

Online giving is also safe since the process is hosted by a private company that specializes in state-of-the-art monitoring, full data encryption and advanced virus protection to ensure maximum security.

To make a gift online with a major credit card, visit www.salk.edu/support and click on the "Make Your Gift Online" button, where you'll be linked to a brief form. Unrestricted gifts can be made in any amount to the Annual Fund.

Gifts at $1,000 or more qualify for the President's Club — the leadership giving level for the Salk's Annual Fund. Tax-deductible gifts can also be made in honor of a friend, a special occasion, or in memory of a loved one. Upon completion of the process, donors will immediately receive a receipt for tax records.

Online contributions have the potential for increasing the resources that are crucial to maintaining Salk's tradition of discovery and scientific excellence.

FOR MORE INFORMATION ABOUT ONLINE GIVING or supporting the Salk's Annual Fund, contact Judy Hodges at 858.453.4100 x1882; e-mail: hodges@salk.edu, or visit

Master Plan Update Inches Closer to City Approval

THE SALK INSTITUTE MOVED a step closer in finalizing approval of its Master Plan Update when the city of San Diego released the plan's Environmental Impact Report (EIR) for public review in the spring.

The plan, which will guide the Institute's growth and development for the next 50 years, was carefully designed with environmental, historic and architectural preservation in mind. The recently completed EIR concludes that the project has minimal environmental impact.

As the first update to the original master plan developed by Dr. Jonas Salk and Louis Kahn in 1962, this plan stays true to the original vision for the campus while allowing the Institute to keep pace with the rapidly evolving world of scientific research.

The Master Plan Update will enable the Institute to better fulfill its mission of improving the human condition through basic biological research. It addresses several important needs such as additional laboratory space, facilities for equipment shared by scientists, a childcare facility for employees and the ability to return all staff members to the Salk campus.

"The Salk Institute needs the ability to grow and adapt to scientific changes to remain a world leader in scientific research," said Richard Murphy, president and CEO of the Salk Institute. "The environmental analysis shows that this can be done in a way that is sensitive to our neighbors, beneficial to the surrounding environment and respectful of the historical significance of the site."

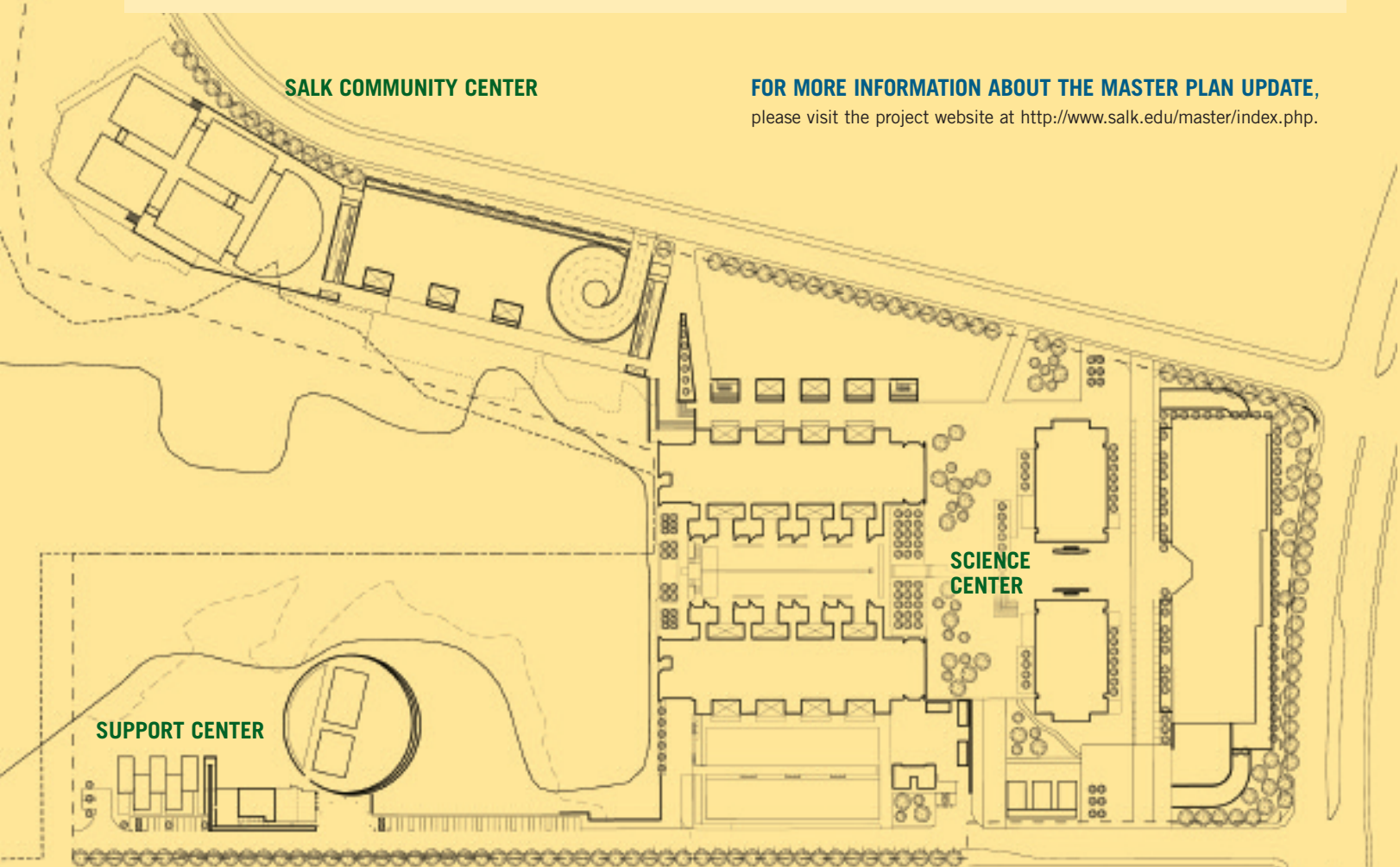
The Institute has sought input on the Master Plan from a number of stakeholders throughout the review process. Nearly 100 meetings have been held with neighbors and community groups, environmental interests, design professionals, business organizations and others. Several modifications have been made to the plan in response to the input that was received.

"The changes that we've made as a result of community input have made for a better plan," said Jack MacAllister, one of the principal designers of the master plan. MacAllister was also a protégé of Louis Kahn and has worked extensively on the original Salk Institute development since the early 1960's.

The approval of the Master Plan Update will provide the Institute with the necessary entitlements needed to fund and construct facilities that are needed in the future. This comprehensive planning effort will avoid piecemeal planning and save the Institute time and money when new facilities need to be built.

"The investment in a thorough planning effort today will ensure a smoother road for development of needed facilities in the future," Murphy said.

The plan is currently being reviewed by the City of San Diego, and is expected to be heard by the San Diego City Council in the fall.



FOR MORE INFORMATION ABOUT THE MASTER PLAN UPDATE, please visit the project website at http://www.salk.edu/master/index.php.

Board of Trustees Appoints EVP/COO

THE BOARD OF TRUSTEES FOR THE SALK INSTITUTE has appointed **MARSHA A. CHANDLER** to the new position of Executive Vice President/Chief Operating Officer. The group unanimously approved the appointment at its meeting in New York City on April 26. She will join Salk on July 1.

In her role, Chandler will oversee the fiscal and administrative functions of the Institute, providing support to approximately 870 research staff and 230 administrative personnel, and overseeing fund-raising activities. The facility operates on an annual budget of more than $100 million.

"The Board of Trustees, members of the Salk community, and of course myself are very excited about Marsha joining Salk," said Irwin Jacobs, chairman of the Board of the Salk Institute. "Marsha has an ideal background for this new position, having worked closely as senior vice chancellor with two chancellors at UCSD, helping guide major expansions of the student body, faculty, and campus, and maintaining excellent relations with the community.

"At Salk, she will work closely supporting our president/CEO and the faculty in further enhancing the quality of science at Salk and helping educate and excite the general public about the rapid advances in biological sciences."

"...[Marsha Chandler] will work closely supporting our president/CEO and the faculty in further enhancing the quality of science at Salk..."

A native New Yorker, Chandler graduated from the Bronx High School of Science and received her doctorate from The University of North Carolina at Chapel Hill. She brings more than 20 years of successful academic leadership and management experience to Salk.

Since 1997, she has served as Senior Vice Chancellor for Academic Affairs at the University of California, San Diego, where she is the chief academic officer responsible for the policies and decisions relating to all academic programs and faculty appointments and performance.

The Senior Vice Chancellor manages the full range of fiscal and human resources within Academic Affairs. As the second-ranking executive officer on campus, she acts in overseeing the university in the Chancellor's absence and served as Acting Chancellor from 2003-'04.

Chandler holds an appointment as Professor of Political Science in the Graduate School of International Relations and Pacific Studies at UCSD. In 2004-'05, she completed the Advanced Management Program (AMP) in the Business School at Harvard University and also served as visiting professor at the Kennedy School's Center for Public Leadership.

Prior to arriving at UCSD, she held the position of Dean of Arts and Science from 1990 to 1997 at the University of Toronto. In that role, she was responsible for 30 academic departments on two campuses.

A renowned scholar of political economy and comparative public policy, Chandler is a Fellow of the Royal Society of Canada. She is the author of five books and numerous journal articles and book chapters. The University of Toronto awarded Chandler an honorary Doctor of Laws degree in 2003.

Currently, she chairs the Board of Directors of the Canada-U.S. Fulbright Program and is a member of the Board of the San Diego Opera. She has previously served on the Board of Directors of the San Diego Economic Development Corporation and the La Jolla Playhouse.

While in Toronto, she was a Trustee of the Art Gallery of Ontario and Mount Sinai Hospital. She was also a member of the Advisory Committee on Federal Judicial Appointments and the Board of the Canadian Institute for Advanced Research.

Personal Connection to Science Drives Director's Work

In Profile

"Our number one priority is to make sure the Salk Institute remains a leader in scientific research."

DANIEL ANDRADE KNOWS THE IMPORTANCE OF SCIENCE. His daughter was born with an immature brain stem and a deficient immune system, which has led to chronic problems with the toddler. Without a reliable treatment, he looks to basic research to help his little girl.

Andrade never thought, however, that he would have the opportunity to indirectly contribute to the science that could help Kayla. As the director of the Salk's International Office, Andrade is in charge of recruiting and retaining the world's best and brightest scientists, 65 percent of whom are foreign nationals representing 43 different countries.

"My passion for the science stems from my personal experiences with my daughter, so once our faculty identify researchers to recruit, the International Office works to get them here as quickly as possible," Andrade says. "Our number one priority is to make sure the Salk Institute remains a leader in scientific research."

The department also ensures Salk complies with immigration and government policies. Keeping up with the ever-changing immigration laws and regulations is a challenge, Andrade admits, but his background as an adjudications officer for the Department of Homeland Security (DHS) provides him with a perspective that most people in his field don't have.

Since joining Salk, Andrade has also worked toward helping to shape the outlook of the U.S. Immigration Reform Bill through his contacts in the government and his affiliations with organizations such as the American Council on International Personnel, the National Association of Foreign Student Advisors, and the National Postdoctoral Association.

"Immigration reform only takes place every 15 years, so this is extremely important to Salk and the scientific community," Andrade says. "Changing the laws would make it easier for the world's best scientists to come to the United States to do their research and become permanent residents, which then makes them eligible to qualify for many government grants.

"The appeal to a researcher who is considering the Salk Institute is the quality of our faculty and the papers they publish," he continues. "At Salk, research is based on quality, not quantity, and that's an important draw for these researchers. Plus, you can't beat the location."

Thank you and good-bye

AS JULY 1 APPROACHES and I near the end of my nearly seven-year run as Salk's president and CEO, I am struck by what a stimulating time it has been, both for me and my wife, Elaine. We look back on these years with satisfaction and pride, recognizing that the high points came when the entire Salk community pulled together.

Salk scientists, whose research is truly remarkable, anchor that community. The scientific output here is even better than I imagined upon arriving in 2000, not only because of the quality of individual researchers, but also as a result of their interactions with each other and with their students. We all owe a debt of gratitude to the Institute's founding scientists for laying the groundwork for this collaborative environment by setting extremely high standards of scientific excellence and sharing, and to Jonas Salk and Louis Kahn for having the foresight to create an architectural masterpiece without internal walls, so that interactions would occur easily.

Back in 2001, when we crafted our first strategic plan for the Institute, it was Salk researchers who accurately predicted the future directions of science. That planning led to the hiring of 16 new-generation scientists to ensure the Institute's future, and it launched entirely new research efforts, including the Skirball Center for Genomics and Chemical Genetics, the Crick-Jacobs Center for Computational and Theoretical Biology, the Dulbecco Center for Cancer Research, the Razavi-Newman Center for Bioinformatics, the Coates Center for Mass Spectrometry, a stem cell facility established by the Lookout Fund, and a new facility for nuclear magnetic resonance spectroscopy gifted by the Kohlberg Foundation.

I have no doubt that our just-completed 2007 Salk Institute Strategic Plan, with scientific direction again provided by our researchers, will similarly shape the next five years of transformative research. Salk faculty members justly deserve their top ratings in neuroscience and molecular biology, as measured by international citations of their research achievements.

A large portion of the Institute's scientific output is generated by the Salk's 300 postdoctoral trainees and graduate students. They drive the research enterprise with their creativity, dedication, and long hours in our laboratories, and my sincere thanks go to all of them. Dealing with talented vibrant young people has been one of the true pleasures of my academic life.

It takes a village to support the Institute's science, and the unsung heroes working behind the scenes — and seldom sharing in the kudos — are the staff in our operating departments. I want members of our Accounting, Administrative Services, Animal Resources, Computer Services, Glassware, Grants Administration, Human Resources, Purchasing, Facilities, Lab Safety, Office of Technology Management, Development, Institute Relations, Communications, and Multimedia departments as well as those who work in our research labs to know how vital their talents, commitment, and high-quality efforts have been to our output, and how much they are appreciated. Special thanks to my assistant Patti Tzannos for keeping my life organized and for her limitless patience, energy and support.

Special thanks go to the splendid senior administrative team that served the Institute's researchers and me so well these seven years. All of them have worked tirelessly and selflessly to support the Institute's scientific mission, and it was a privilege and pleasure to be their colleague.

Bruce Stevenson, vice president of Academic Affairs and an accomplished cell biologist, provided numerous support functions for our

scientists and upgraded the departments responsible for animal services and laboratory safety. He recruited Virginia McFerran to head Computer Services, and she, in turn, transformed the department's capability to support the Institute's science and business systems.

Beth Alton, vice president of Human Resources, carried out the Institute's first benchmarking compensation analysis to ensure that all employees are being paid appropriately. She linked the business systems of HR with accounting, and she spearheaded with energy, determination, and intelligence the Institute's Master Plan, which is essential to the Institute's future growth and success.

Dianne Day, vice president of Development, has been especially generous in including me in friendships she's created over the past 34 years with individuals and foundations who support the Institute. Both Dianne and Kristin Bertell, vice president of Institute Relations, professionalized our development operations by creating a state-of-the-art donor data base. Through their efforts, the International Council was reinvigorated and enrollment and fundraising from our President's Club doubled. Donations to the Institute, which exceeded $170 million, increased by 32 percent in a five-year period acknowledged to be a ifficult time for fundraising.

Among the new initiatives Dianne and Kristin created were Sensational Salk, the San Diego Community Advisory Council, and the Taste of Discovery dinner series for donors. They transformed Symphony at Salk from a friend-raiser to an important fundraising event by involving generous underwriters. And under Kristin's direction, a formalized Planned Giving Office was established and the Institute's communications, including our website, became ever more effective and professional.

> I am struck by what a stimulating time it has been, both for me and my wife, Elaine. We look back on these years with satisfaction and pride, recognizing that the high points came when the entire Salk community pulled together.

Our Office of Technology Management, headed by Anne-Marie Mueller, has done a superb job of managing the Institute's inventions and licensing arrangements, educating our scientists and trainees on intellectual property matters, and acting quickly to protect the inventions of our scientists. And Kim Witmer, vice president of Finance, has been steadfast in ensuring that the Institute's finances are managed according to the highest professional standards.

Bruce, Dianne, Virginia, Beth, and Kristin have now moved on to new career challenges, and we wish them well.

The dedication of Salk Institute trustees has been constant and outstanding. Each brings unique and important strengths to the Institute, and no president could have received more support from such a distinguished board of advisors. Special thanks go to the Board chairs under whom I've served, Fred Rentschler and Jerry Kohlberg. Both are acclaimed business leaders, and both brought intelligence, honesty, dedication, impeccably high standards, and generous financial support to the Institute.

They helped us attract 24 new trustees to the Board, introduce term limits and emeritus trusteeships, and revamp the Board's committee structures, including establishing a superb investment committee that increased the Institute's endowment from $107 million in 2003 to over $170 million today.

Their spouses, Pam Rentschler and Nancy Kohlberg, were fully supportive of their husbands' efforts and accepted with grace my many phone calls and demands on their husbands' time, and I thank them.

I am confident the Institute will continue to thrive under the determined leadership of new Board Chair Irwin Jacobs and with the support of his wife, Joan. We are grateful to both of them for taking on the challenge.

Elaine and I have thoroughly enjoyed becoming acquainted with the Institute's many friends and donors, from those local to San Diego to those on the national and international scene. These include members of the Salk Institute Association, the new San Diego Community Advisory Council, the President's Club, and the Salk International Council, with whom we will meet one last time in June in Vienna. We thank them all for their interest in and support of the Institute and for enriching our lives with their friendship, and we look forward to continuing our relationships with many of them.

I could not have served the Salk Institute without the involvement of Elaine, who contributed in so many ways, including working alongside me to raise the Salk Institute's profile in San Diego. She generously attended and hosted Institute events, where she made and enjoyed many friends; she opened our home to the Institute for social events with enthusiasm; and she used her considerable skills as a writer/editor to make my prose sound intelligent. Her unflagging enthusiasm for the Institute made my job easy.

In sum, it has been a privilege for me to participate over the past seven years in furthering the legacy of one of the most unique collaborations in the history of science, that of the March of Dimes (MOD) and Jonas Salk, a partnership that all but eradicated polio and then went on to establish the Salk Institute. It has been a pleasure to meet and know Charlie Massey, who was there at the beginning of the MOD and the Institute, MOD president Jennifer Howse, and MOD's representatives on the Board of Trustees, Dick Freeman and Nancy Lukitsch.

Elaine and I treasure our friendship with several individuals in particular who have linked us to the legacies of Jonas Salk and Louis Kahn: Françoise Gilot, Jonas's widow and a remarkable and gifted woman; Jonas's sons, Peter and Jonathan; Jack MacAllister and David Rinehart, outstanding thinkers and architects who have remained devoted to the Institute since their collaboration with Kahn; and Nathaniel Kahn, whose filmmaking talents demonstrate his inheritance of his father's creative genes. Indeed, we are fortunate to have served Salk at a time when Nathanial's and Susan Behr's award-winning film "My Architect" brought ever-wider attention to this remarkable institution.

To my successor go my very best wishes for success, along with this advice: Build upon our achievements, correct our mistakes, and work to realize the full potential of this wonderful organization, whose noble goals are so important to bettering the human condition. I hope you will enjoy furthering the Salk Institute's scientific mission as much as I have.

Richard Murphy, President and CEO

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

JUNE 2007

7 **Structural Studies of Amyloids and Prions**

JULY 2007

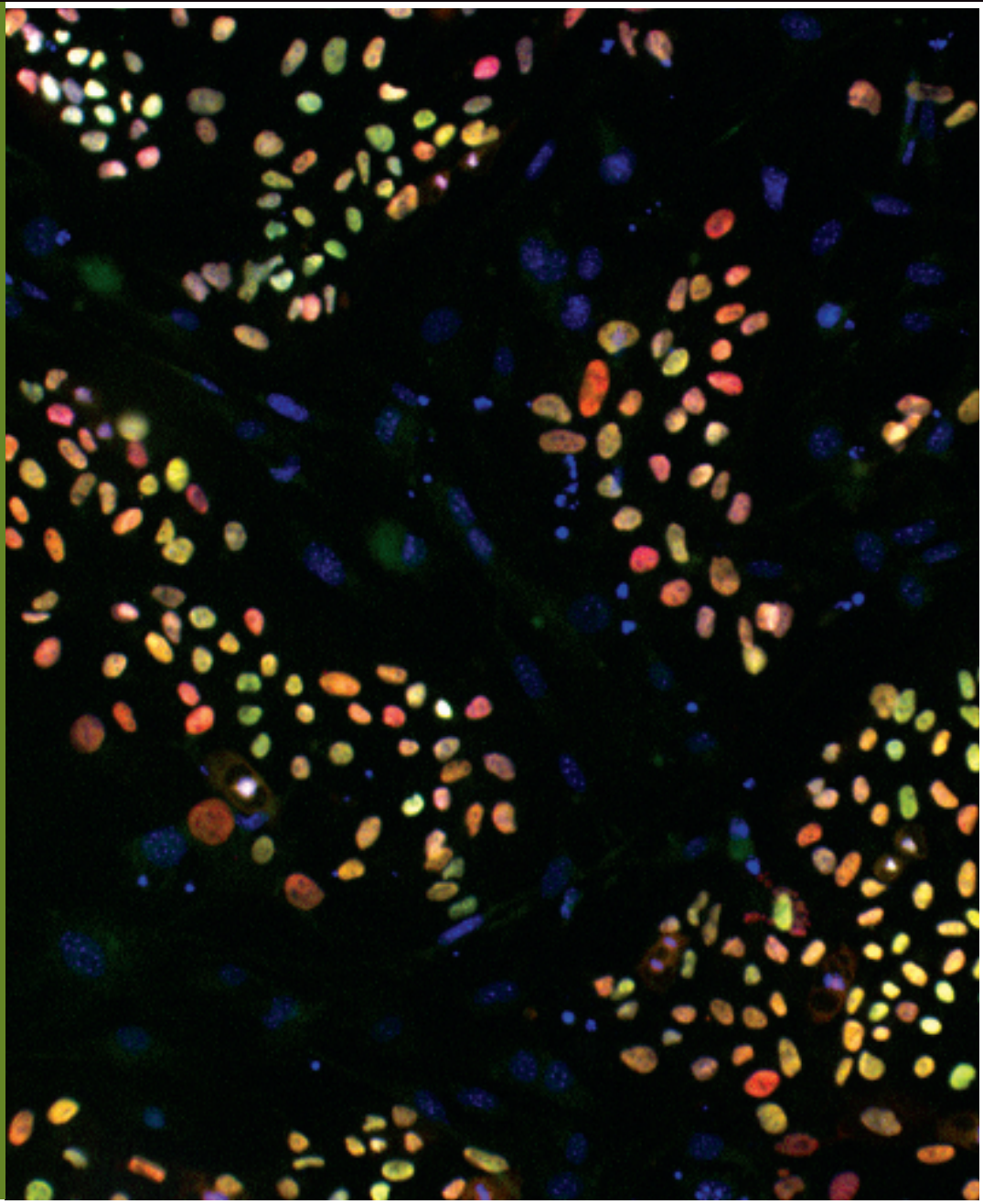
13-17 **The Cell Cycle Meeting**

AUGUST 2007

8-12 **Mechanisms and Models of Cancer Meeting**

25 **Symphony at Salk**

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



UNDIFFERENTIATED HUMAN EMBRYONIC STEM CELLS (RED AND GREEN) ARE DISTINGUISHED WITH STAINING TECHNIQUES USED BY SCIENTISTS. THE SALK INSTITUTE RECEIVED $5.18 MILLION IN STEM CELL GRANTS FROM THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE (CIRM). SEE PAGE 9.
PHOTO COURTESY OF CHRISTIAN CARSON OF THE GAGE LABORATORY

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