INSIDE SALK

California Embraces Stem Cell Research with Proposition 71

On November 2nd, California voters approved the adoption of Proposition 71, the California Stem Cell Research & Cures Initiative, by an 18-point margin. Proposition 71 provides stable, long-term support for human stem cell research so that California researchers may pursue a fuller spectrum of stem cell biology. Restrictive Federal policies had limited researchers to a small number of established cell lines, narrowing scientific exploration of this field to a fraction of the Federal research budget ($25 million in 2003, or less than 0.1% of the total National Institutes of Health budget).

Proponents of Proposition 71 believe that stem cell research will impact the understanding and treatment of ills as diverse as diabetes, cancer, heart disease, Parkinson's, HIV/AIDS, lupus, arthritis and spinal cord injury. All told, these conditions affect millions of children and adults around the world, including an estimated 130 million Americans. At the same time, scientists emphasize that the stem cell field is in its infancy and a great deal of basic research will be necessary before these cells become useful in treating clinical diseases.

Proposition 71 issues bonds to support $3 billion of stem cell research over

PROPOSITION 71 LEADERSHIP GROUP

establishes standards and practices of the *California Institute for Regenerative Medicine*

- Chairperson & vice chairperson
- Eight academic or non-profit research institution representatives
- Ten patient advocacy representatives
- Four representatives of commercial life science entities
- Five executive officers of UC campuses with medical schools

Proposition 71 establishes the California Institute for Regenerative Medicine to oversee the disbursal of funds to scientists at Californian universities and research institutions. It taps statewide elected officials and UC chancellors to appoint the Institute's leadership, a group comprised of: five representatives of University of California campuses with medical schools, eight representatives of other non-profit or academic research institutions in California (including Salk), four representatives of California's commercial life-sciences sector and 10 Californian patient advocates. These 27 individuals, in turn, elect a chairperson and vice-chairperson.

10 years, or an average of $295 million a year, with bond repayment deferred until 2010 to protect the state budget during its recovery. A granting agency called the California Institute for Regenerative Medicine will oversee the disbursal of funds to scientists at Californian universities and research institutions. At least 94% of its funds will go toward research support, with up to 10% earmarked for facilities construction or remodeling so that scientists may pursue Proposition 71-funded research in addition to Federally supported projects. The size and structure of grant awards have yet to be determined. However, strict legal and ethical safeguards will be adopted to ensure protection of patient rights, safety and privacy, as well as a firm prohibition of human reproductive cloning.

Proposition 71 entrusts the stewardship of this program to 29 representatives of California's patient and medical research communities (see illustration on pg 1), including Salk President & CEO Richard Murphy. This group met to elect its leadership in December of last year. They met again in mid-January to establish funding and ethics guidelines, first steps in a process geared towards making initial grant awards by summer 2005.

Stem cells are unspecialized cells that can give rise to the various tissues and organs of the body. Adult stem cells reside within specific tissues and work to replace the cells of that tissue following injury. Adult stem cells are limited in the number of specialized cell types that they can become, and thus far have been difficult to grow in the laboratory. In contrast, embryonic stem cells—stem cells found very early in embryonic development—may transform into nearly all specialized cell types, and can be grown experimentally for long periods of time.

Medical researchers hypothesize that stem cells may one day be used to replace cells damaged by disease. More immediately, these cells could facilitate novel investigations of the fundamental processes underlying tissue development. This new knowledge base would open doorways to understanding some of our most puzzling diseases, like Alzheimer's and autism, and even provide a platform technology for the design of more effective drugs (see illustration above).

Proponents hope that Proposition 71 will accelerate stem cell research so that scientists can more rapidly develop this therapeutic potential.

Embryonic Stem Cell Derivation and Drug Design.
Research with human embryonic stem cells may accelerate the development of cancer drugs. Embryonic stem cells, derived from the inner cell mass of late-stage fertilized eggs (blastocyst), may be directed to become cancer cells harboring a specific cancer-causing trait (like a genetic mutation). These cells may then be used to investigate a drug's activity in the presence or absence of the trait, point to possible side effects or indicate which patients will respond to a particular drug. Illustration by Jamie Simon.

The Telomeres of Dorian Gray

Aging and death—once the preserve of religion, poets, and expensive face-cream—is now being subjected to the rigors of science. Salk Institute geneticists have begun to provide startling insights into why our clocks run down and what can be done to slow the hands of time.

PhD student Laure Crabbe and Jan Karlseder have discovered that a small piece missing from a single chromosome may be sufficient to trigger the aging process. Crabbe and Karlseder made their discovery, published in *Science* in December, while working on the genetics of Werner's syndrome. In this rare genetic disorder people age rapidly from their mid-teens and frequently die of cancer in their 40s. Geneticists naturally ask the question, why does the Werner's clock tick faster than normal?

Laure Crabbe and Jan Karlseder

The generally accepted theory of aging is that the 'caps' (telomeres) at the ends of all 46 chromosomes get shorter and shorter with each cell division throughout life, thus exposing the chromosome to genetic damage and triggering age-related changes in the cell.

Crabbe and Karlseder expected to find that the telomeres wore down faster in Werner's syndrome. To their surprise, the telomere shortening rate was no different to anyone else's. They found instead that one or more telomeres were missing completely and a single missing telomere was enough to accelerate the aging process.

Further investigation revealed that people with Werner's are unable to create normal chromosomes during cell division because they lack a crucial protein called WRN. This protein acts as a 'detangler' that unravels knots in the DNA during the complicated process of chromosome replication.

This discovery has wide-ranging applications in cancer research, said Laure Crabbe. Missing telomeres likely lead to a condition called genomic instability. "We know that genomic instability is involved in almost all cancers, likely caused by chromosome breakage and loss of gene function," Crabbe said. She is currently trying to prove the link between telomere loss and genomic instability.

The discovery also has potential implications for those of us reaching for the wrinkle cream because Crabbe and Karlseder were able to recreate the missing telomeres in cultured cells in the laboratory. "The wider implication of this work," said Karlseder, "is that in normal people this discovery might lead to new approaches for therapies for cancer and even aging."

SALK IN THE NEWS

Ron Evans

Fred H. Gage

Ned Landau

Dennis O'Leary

■ **Ron Evans**' marathon mice have attracted significant media attention. *Scientific American* featured his team's research on mice that were genetically engineered to burn more fat by activating PPAR-delta, a receptor that regulates metabolism and the breakdown of fat. Evans' work was hailed as a breakthrough in understanding the link between muscles and metabolism, with clear applications to humans fighting obesity or athletes looking for that extra edge. His research was also cited in a *Science News* story about gene therapy and mouse muscles.

■ *The Washington Post* and the *New Scientist* have cited an investigation led by **Fred Gage** that has uncovered flaws in current stem cell research methods. Both articles reported that Gage, along with Ajit Varki of UC San Diego, has discovered that human stem cells cultivated with mouse 'feeder' cells are attacked by the human immune system and killed – results that affect all Federally approved stem cell colonies.

■ *San Diego Magazine* has published a feature on the Salk Institute and "San Diego's most celebrated hero of medicine," **Jonas Salk**. The article chronicled Salk's polio vaccine discovery and highlighted some of the exciting advances in biology that have taken place at the Salk Institute since its first labs were set up in 1963. Several Salk Institute researchers were mentioned, including **Francis Crick, Joe Ecker**, and **Ned Landau**.

■ **Dennis O'Leary**'s innovative research on binocular vision was showcased in the November 25th issue of the respected science journal *Nature*. O'Leary and his colleagues found that Islet-2, a regulatory protein, is responsible for determining the degree of binocular vision in mammals. Their work appeared in Research Highlights, a section in *Nature* devoted to outlining notable articles appearing in other journals, designed to connect its readers with current and cutting-edge scientific investigations. Research Highlights reviewed an article by O'Leary and his team published in the journal *Cell* in November, 2004.

Awards & Honors

Terry Sejnowski brings it all together

Terry Sejnowski, professor and head of the Computational Neurobiology Laboratory has been awarded the Francis Crick Chair, funded by the J.W. Kieckhefer Foundation, taking on the mantle of the late Francis Crick. "It's a great honor," said Sejnowski.

Terry Sejnowski

"The intent is to reaffirm the important role of theory in biology that Francis represented."

One of the most important tasks currently engaging Sejnowski and his colleagues is the creation of the Cricks-Jacobs Center for Theoretical and Computational Biology. Endowed by Joan and Irwin Jacobs in honor of Francis Crick, this cutting-edge research initiative is now becoming a reality, following its inception at the Crick Lecture in 2003. A roster of three new faculty members and at least three junior fellows is planned that will bridge Francis Crick's two areas of interest, molecular genetics and neuroscience. "The intention is to recruit faculty who are bringing genetic techniques into neuroscience," Sejnowski said, "to use them as tools for understanding the higher functions of the brain."

Computational neurobiology is a hugely promising area of research, offering the ultimate prize to neurobiologists: an understanding of how the brain works. Sejnowski's team uses a suite of sophisticated electrical, chemical and computer-based techniques to measure and define communications within the hippocampus, involved in learning and memory, and the cortex, which holds all our knowledge of the world and governs how we interact with it.

Traditional neuroscience involves scooping out regions of the brain and observing what happens at a macro level. By contrast, molecular genetics allows scientists to manipulate individual genes to understand function at the cellular level. "It's like a molecular scalpel," said Sejnowski. "For the first time in history we have the tools and techniques to understand how neurons work and the challenge is to integrate all of that information."

Integration is the power of the Crick-Jacobs Center and potentially offers the greatest rewards, says Sejnowski. The nature of consciousness—what makes someone a person—is now within the grasp of science. "Areas such as these have been off-limits to science up until now," he said. "Francis Crick did more than anyone to open up the study of consciousness to scientific scrutiny. We are now developing tools that will allow biologists over the next 10 years to integrate all the information from all the molecular techniques and synthesize them, and come up with a much better picture of how synapses work, and ultimately, how the brain works."

Awards & Honors

Joe Ecker Scientific American Leader

Joe Ecker of the Plant Molecular and Cellular Biology Laboratory has been named to the 'top 50 leaders' by the journal *Scientific American*. Ecker was lauded for three ground-breaking publications in plant genomics during the year, two in *Science* and one in *Cell*. In 2000, Ecker's group was part of an international team that published a paper in *Nature* describing the first complete plant genome sequence, using the reference plant *Arabidopsis*, revealing its 25,000 protein-coding genes. In 2003, his group created insertion mutations in 21,700 of these genes. A database of the mutations is now accessible to researchers worldwide (http://signal.salk.edu), who can instantly order from a 'seed bank' to investigate mutations of interest. The site now receives over one million hits a year. *Arabidopsis* mutations have already yielded many genes that confer important traits for crop plants, including resistance to disease, drought, and cold. The award also went to the Salk plant biology team in 2003, when Joanne Chory took the prize.

Joe Ecker

J.W. Kieckhefer Professorship for Marc Montminy

The newly endowed J.W. Kieckhefer Professorship has been awarded to **Marc Montminy**, professor in the Clayton Foundation Laboratories for Peptide Biology. Montminy has spent the last two decades unravelling diabetes and the complex chemical relay-race in the liver and pancreas that controls glucose metabolism. The significance of Montminy's work has increased exponentially in recent years as type 2 diabetes rises to epidemic proportions worldwide.

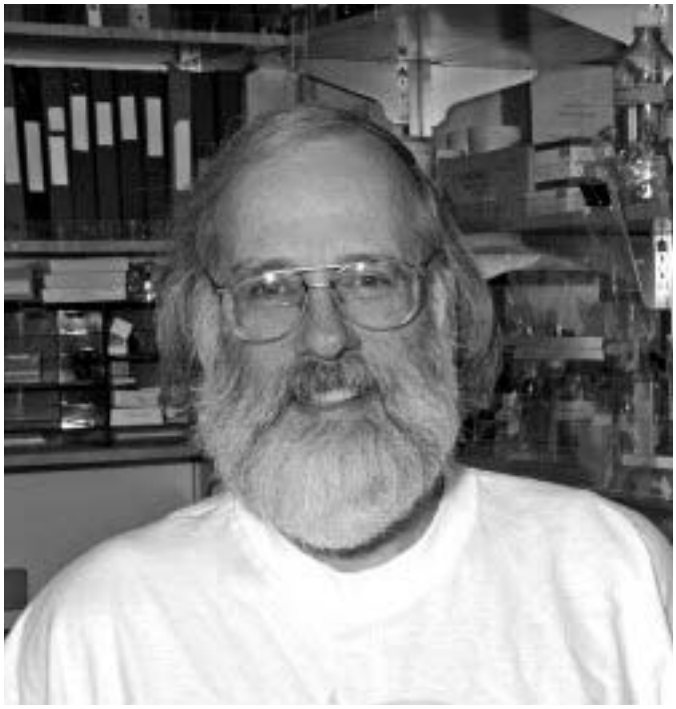
Montminy's research has revealed many of the key signalling pathways within cells that go awry to produce the cornerstones of type 2 diabetes: insulin resistance (in the liver and muscles) and insulin deficiency (in the islet cells of the pancreas). Montminy's early work revealed the existence of a pivotal transcription factor called CREB that regulates the body's response to changes in blood glucose. His current research focuses on the identification of CREB target genes. Recent work on mature-onset diabetes of the young (MODY) genes, and their corresponding proteins, offers the potential to find a unifying explanation for what goes wrong in type 2 diabetes. "The reason this is so exciting is that type 2 diabetes is a problem of insulin resistance and insulin secretion," said Montminy. "Because these proteins do very similar tasks in both the islets and the liver, from a reductionist point of view, it allows us to explain the two phenomena with one molecule."

Marc Montminy

Double honors for Tony Hunter

At the close of last year, **Tony Hunter** received the 2004 Louisa Gross Horwitz Prize, a leading national scientific achievement award, for a lifetime of ground-breaking research. Hunter is best known for his discovery of a process called tyrosine phosphorylation, the chemical 'switch' that can turn healthy cells cancerous. His work has led to three new cancer drugs and many significant advances in gene research.

Hunter was also recently named a member of the Institute of Medicine of the National Academies of Sciences. The National Academy elects new members each year, who serve as advisors on national health and health policy. Hunter is the sixth Salk Institute scientist to hold this honor.



Tony Hunter

Catherine Rivier

Catherine Rivier receives Geschwind award

Catherine Rivier has been awarded one of the most prestigious academic prizes in endocrinology, the Geschwind Award. Rivier, a professor in The Clayton Foundation Laboratories for Peptide Biology, received the award for her life-long contributions to the endocrinology of stress responses. Rivier gave the Geschwind Memorial Lecture in 2004, speaking on nitric oxide as a mediator of the stress response in the brain. The award commemorates Irving Geschwind, the 'father of endocrinology' and chief editor of the journal *Endocrinology* from 1973 to 1977. It is endowed annually by the Department of Animal Science, University of California at Davis.

The colorful parade of science

■ A lively and fascinating Jonas Salk Lecture was delivered on December 2, 2004 by Donald Kennedy, Editor-in-Chief of *Science*. Kennedy shared his "unique and revealing perspective on the scientific community" gained from his "interesting perch" at one of the world's pre-eminent journals. Through real letters to the editor, Kennedy covered balance in scientific publishing; hostile reviewers and disputes between co-authors; the peer-review process itself; and the dangers of a "tournament model" for science, where few win and many lose. He said researchers at all levels should foster quality, not just citation tallies. He also urged scientists to take seriously their responsibility to speak out on science policy.

Honoring Françoise Gilot-Salk

■ On December 3, 2004, Françoise Gilot-Salk became the inaugural honoree in a new donor holiday party tradition of paying tribute to individuals who have made significant contributions to the Salk Institute. Ms. Gilot-Salk is an artist, honorary chair of *Symphony at Salk*, and wife of the late Jonas Salk.

Françoise Gilot-Salk

Razavi-Newman Center for Bioinformatics takes shape

■ The bioinformatics initiative at Salk has now taken formal shape as the Razavi-Newman Center for Bioinformatics. Following a generous donation from Salk Board of Trustees member Howard Newman and his wife Maryam Razavi, the Center recently welcomed director Gerard Manning, who will work on applying modern genomics and bioinformatics techniques to research topics throughout Salk, as well as exploring fundamental questions in genomics and evolution.

"For over one billion years, every organism that has been born has been part of a cumulative experiment in mixing their parents' DNA, making new mutations, and testing the mix for survival advantage," explains Manning. "This decade, for the first time ever, we are starting to read out the result of that experiment in genome sequences. This treasure trove will help unlock the secrets of DNA sequence and function and allow us to apply our findings to almost every aspect of science carried out at the Salk."

Gerard Manning

Left Top: Donald Kennedy and Renato Dulbecco. Left Bottom: Françoise Gilot-Salk, Dianne Day, Mel Yoakum and Donald Kennedy

Leanne Jones

Vicki Lundblad

Satchidananda Panda

DEVELOPMENT NEWS

Celebrating Salk supporters at the Annual Donor Holiday Party

■ On December 3, 2004, 200 of the Salk Institute's donors, special friends, *Symphony at Salk* sponsors, and community leaders gathered to enjoy champagne and hors d'oeuvres at the annual donor holiday party. Guests were treated to the Caprice Strings, a musical quartet that performed throughout the night, and a projected photo montage of past Salk Institute events.

Salk president and CEO Richard Murphy thanked attendees for making time during the busy holiday season to recognize the essential role that donor contributions have played in 2004's exciting and successful research advances at the Salk Institute. He acknowledged Salk board and faculty members, and highlighted the approaching 50th anniversary of the Salk polio vaccine, 40th anniversary of a fully realized Salk Institute facility, and 10th anniversary of *Symphony at Salk*.

Leanne Jones, who recently joined the Salk as an assistant professor in the Laboratory of Genetics, also addressed the guests. She praised her Salk colleagues and the donors for their support, and discussed the anticipation of laying the groundwork for future scientific discoveries through Proposition 71, California's stem cell research legislation.

Finally, the Institute honored artist Françoise Gilot-Salk, wife of the late Jonas Salk and honorary chair of *Symphony at Salk*. Ms. Gilot-Salk shared personal memories and expressed her delight in celebrating with so many Salk Institute supporters, several of whom had been present during Salk's early research endeavors. The Institute presented her with a framed, inscribed photograph of *Symphony at Salk 2004* in appreciation of her continued efforts and enthusiasm.

Right: The Honorable Charles and Chin-Yeh Hostler
Below: Steve Milz, Gad Shannon and Martha Dennis
Below right: Natasha Josefowitz and Herman Gadon

Academic Appointments

■ **Leanne Jones** has joined the Institute as an assistant professor in the Laboratory of Genetics. Jones joins the Salk from Stanford University and brings with her a research background in the mechanisms that control stem cell differentiation. "I knew I had to come to the Salk," Jones said, "People are so excited about their work here, so turned on to science all the time."

■ **Vicki Lundblad** has been appointed to the position of professor in the Molecular and Cell Biology Laboratory. Lundblad's research interest is the role of telomeres in cell proliferation, a topic of central interest in both cancer and aging biology. Lundblad's appointment at the Salk follows 12 years on the faculty of Baylor College of Medicine in Houston, Texas.

■ **Satchidananda Panda** joins the Regulatory Biology Laboratory to focus on the genetic and molecular basis of circadian rhythms, or the biological clock. Panda's immediate goal is to determine how this mysterious structure located in the suprachiasmatic nucleus of the brain allows us to readjust to changes in the light cycle. The answer could have wide-ranging implications for treating depression, jet lag, sleep disorders, infertility and even heart disease.

Jonas Salk inoculates a boy in Pittsburgh, Pa. during the field trials. Courtesy of the Smithsonian Archives.

Smithsonian commemorates the polio vaccine

■ This year is the 50th anniversary of Jonas Salk's introduction of the first successful vaccine for polio. The Smithsonian's National Museum of American History will commemorate this medical triumph with a display called *Whatever Happened to Polio?* that will open for one year starting April 12, 2005, the exact day 50 years ago when the vaccine was declared safe and effective. The exhibit will recount the course of the polio epidemic in the United States, the development of the vaccine, the current status of worldwide polio transmission control, and the stories and influence of polio survivors. The presenting sponsor of the exhibit is the March of Dimes, with additional funding from Rotary International and the Salk Institute.

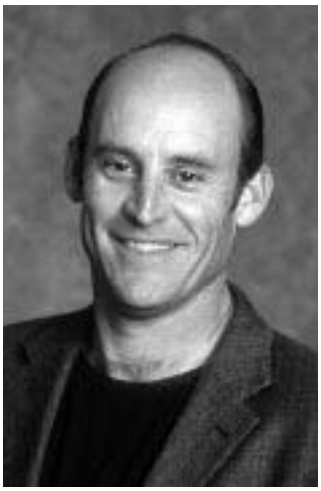
Ron Evans gives students the skinny on fat

■ Ron Evans was a featured speaker in the latest Howard Hughes Medical Institute's 2004 Holiday Lecture Series. By following the fate of a fat molecule as it journeys from a meal to the arteries, Evans presented the "soup to nuts" story of the worldwide obesity epidemic and scientific approaches to solving the problem. The interactive lecture, called *Understanding Fat: Syndrome X and Beyond*, is scheduled for broadcast by PBS and can also be found on the Salk Institute website (www.salk.edu). The audience were science students selected by their high schools. "The best part was learning how talented and enthusiastic the next generation of scientists is," said Evans. "It was amazing seeing 100 hands go up when I asked a question."

Ron Evans

Board of Trustees welcomes Theodore W. Waitt

■ The Salk Institute welcomes Theodore W. Waitt as our newest Board of Trustees member. Until recently, Waitt was the founder and chairman of Gateway, Inc., the third largest manufacturer of computer products in the United States. Now an entrepreneur and philanthropist, Waitt is the chairman and CEO of the Avalon Capital Group, a private equity company, and chairman of the Waitt Family Foundation, which brings technology to underserved communities. Waitt also sits on the board of directors for several charitable organizations and corporations, and has garnered numerous leadership and entrepreneur awards, as well as an honorary doctorate from the University of South Dakota.



Theodore Waitt

From the President

Proposition 71: Next Steps

Californians have voted to commit $3 billion in state funds and to establish the California Institute for Regenerative Medicine (CIRM) to support human stem cell research over the next ten years. This funding will kick-start research aimed at understanding the early stages of organ and tissue development, for creating engineered cells that can help explain human diseases, and perhaps eventually for transplanting healthy cells into patients suffering from degenerative diseases.

The funds are ready to flow, and the time has come to face the thorny challenges of ensuring the program's success.

The first challenge will be to establish a funding agency that can run a large research grants program. CIRM's governing board, the Independent Citizen's Oversight Committee (ICOC), made a good start by electing as its chair Robert Klein, the originator of the ballot referendum. Klein, a businessman whose son suffers from type 1 diabetes, showed impressive leadership and administrative skills in establishing a coalition of groups to support Proposition 71. His efforts earned him Governor Schwarzenegger's endorsement for the chairmanship and that of the state's other constitutional officers. Ed Penhoet, who was elected ICOC's Vice Chair, has complementary skills, including experience in academic research, biotechnology, and grants management. Rounding out the team will be CIRM's president, yet to be selected.

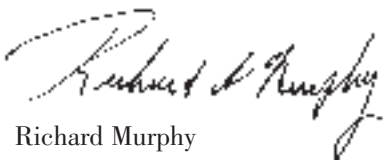
Their first priority must be to develop funding mechanisms and conflict-of-interest guidelines that are above reproach. Structures need to be devised to protect ICOC members from making decisions that could benefit their own academic organizations or businesses in which they have interests. Furthermore, to ensure that research quality is the only metric by which funding is decided, peer-review of grant applications should be carried out by researchers based outside California.

CIRM's ethical review board, which is mandated by the legislation, will need to sort out the myriad complicated dilemmas that will arise as stem cell technology develops. The country's best bioethicists should be asked to guide the Institute on questions related to patient's rights, tissue procurement, and the nature of scientific experimentation, to name just a few.

Finally, CIRM needs to launch an effective public information effort to keep Californians informed about the Institute's research. No one can predict how long it will take for stem cell research to go from the laboratory to the bedside, but exciting results will undoubtedly emerge as soon as California's scientists begin their work. Frequent updates on scientific progress will increase the public's understanding of stem cell science—and help correct unrealistic expectations that cures are just around the corner.

The Salk Institute is ideally positioned to compete successfully for CIRM funding. Presently on our faculty are outstanding stem cell researchers who are studying the basic principles of stem cell biology. Moreover, other Salk scientists who are not identified as stem cell biologists are nonetheless answering fundamental questions of cell function that are central to the field, including how gene expression is regulated and how genetic programs lead to the formation of different tissues and organs. The interests and quality of these scientists will also help us attract new stem cell biologists to the Institute, should we decide to do so. The Institute could also benefit from interactions with stem cell scientists at other California institutions and from capital funds for new laboratories made available through the program.

California may be just the first of many states to approve embryonic stem cell research. The stakes are high, and the challenges large, but the return on investment may be huge. If well implemented, California's stem cell research program will earn the confidence of voters—and be the start of a historic scientific effort with extraordinary potential for advancing scientific progress and improving human health.



Richard Murphy

CELEBRATING 40 YEARS

INSIDE SALK

The year 2005 is the 40th anniversary of the Salk Institute for Biological Studies and the 50th anniversary of the Salk polio vaccine.

The Salk Institute was founded in 1965 by Jonas Salk M.D., whose 1955 polio vaccine all but eradicated the crippling disease poliomyelitis. Salk's vision of an independent research organization dedicated to the improvement of human health has been more than realized in the last 40 years. The Salk Institute is now renowned worldwide for its fundamental discoveries in the life sciences and its mentorship of the next generation of researchers.

1964. Construction at the Salk Institute

Calendar

JANUARY 27
3rd Annual Umesono Lecture
Salk Institute

FEBRUARY 8–9
Adler Symposium
on Alzheimer's disease
Salk Institute

FEBRUARY 25
Renato Dulbecco Nobel Lecture
Speaker: David Livingston
Salk Institute

MARCH 11–12
La Jolla Origins of Humans
Annual Symposium
Salk Institute

MARCH 17–19
Molecular Medicine Symposium
Salk Institute

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

SALK INSTITUTE
FOR BIOLOGICAL STUDIES

STREET ADDRESS
10010 North Torrey Pines Road
La Jolla, California 92037-1099

MAILING ADDRESS
Post Office Box 85800
San Diego, California 92186-5800

Telephone: 858.453.4100
Fax: 858.552.8285
www.salk.edu

ADDRESS SERVICE REQUESTED

NONPROFIT ORG.
U.S. POSTAGE
PAID
PERMIT NO. 611
SAN DIEGO, CA

Inside Salk is printed on recycled paper.