WEEDS OF WISDOM

50 YEARS OF DNA

GUIDING FRAYED NERVES

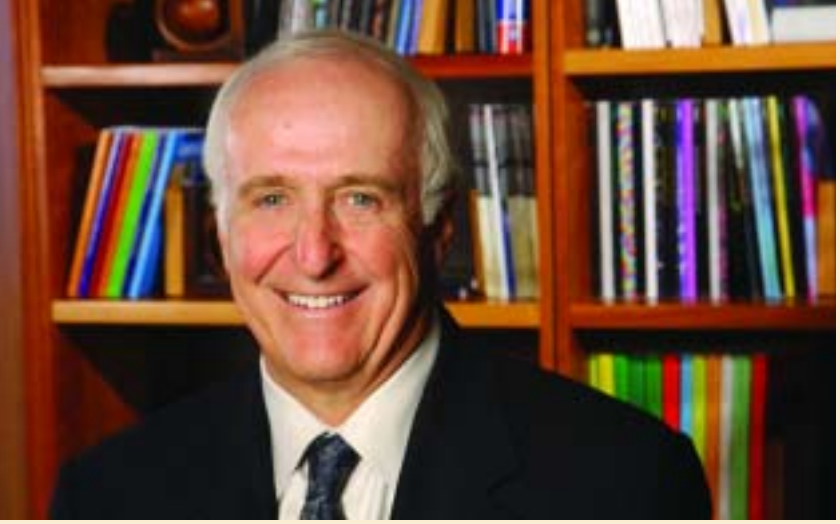
FALL 2003

SALK SIGNALS

A PUBLICATION OF THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

SALK SCIENCE'S GLOBAL ACCENT

THE INSTITUTE'S INTERNATIONAL FLAVOR ENHANCES RESEARCH



President's Message

The Institute benefits enormously from the scientific and cultural diversity that comes from internationalism.

THIS ISSUE OF *Signals* describes the global character of the Salk Institute, where today trustees, faculty, postdoctoral fellows, and graduate students come from more than 40 countries. The desire to be international began with Jonas Salk, whose ambitious vision was to bring the best minds in the world together to focus on the complex questions of biology.

The Institute benefits enormously from the scientific and cultural diversity that comes from internationalism. In addition, our faculty, staff, and trainees enjoy the opportunity to establish personal and scientific relationships with each other that are life-long. In our cover story, we give you a sense of how our international character ultimately bolsters our research efforts.

The tradition of thinking globally clearly has an influence on Salk science. In our feature story, Joanne Chory and Joseph Ecker describe the global implications of their work to understand the inner workings of plants. The knowledge they uncover will ultimately be used to address some of the world's most pressing problems: hunger, malnutrition, childhood blindness, and effective land use, issues that will have an impact on millions of people.

This issue of *Signals* also summarizes some of the major scientific advances that have been made recently at the Institute. Salk scientists and their trainees have provided new insights into how the AIDs virus thrives by inactivating key proteins within the immune system, how hormones regulate the deposition of body fat, how a newly discovered protein contributes to insulin resistance in diabetics, and how nerve cells release neurotransmitters, the chemical signals that regulate information exchange in the brain and which are central to the problems of addiction and mental illness.

Finally, we pay tribute to Francis Crick and his seminal discovery 50 years ago, with Jim Watson, of the helical structure of DNA. An icon in science, Francis Crick has been an integral part of the Salk Institute since its inception. He was one of the original fellows of the Salk who in the early 1960s worked with Jonas Salk and others to shape the Institute. In 1977, he became a permanent faculty member, and for the past 20 years his research has focused on understanding the biological basis of consciousness.

Francis Crick has helped engrain exceptionally high standards for hard work, scientific excellence, and collegiality at the Institute. Besides being among the most influential scientists of our time, he is a true gentleman with a generous spirit who is genuinely beloved by his colleagues. Privileged to have him among us, we marvel how his discovery continues to influence new generations of scientists, both here and around the world.

Richard A. Murphy
President and
Chief Executive Officer

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Salk scientists look for pathways that trigger new nerve cells to make vital connections to muscles and organs.

ON THE COVER An international contingent of soccer players at the Salk. Photograph by Marc L. Lieberman

FROM THE BENCH

Lean and Mean

It is possible to keep the body lean despite high-fat diets. But this leanness only appears under certain conditions, including a high-fat diet.

A cellular receptor, a component of the body's response to stress, appears to control the body's leanness. The findings suggest possible new avenues for finding treatments for obesity and associated diseases like heart disease, diabetes, and stroke.

Wylie Vale, professor, and Tracy Bale, a postdoctoral fellow in the Clayton Peptide Biology Laboratories, and colleagues found that despite high-fat diets, mice that lacked the receptor CRFR2 were leaner and more muscular and had lower levels of potentially harmful triglycerides and cholesterol than mice with CRFR2. The effect occurred even though mice lacking the receptor ate more than normal mice and gained about as much weight.

Wylie Vale

The mutant mice had smaller fat cells and could better handle large doses of glucose and tolerate the actions of insulin. Mutant mice also were more anxious than normal mice. The researchers attribute this to interactions between CRFR2 and its sibling receptor, CRFR1.

"The CRFR2-mutant mice were better able to burn and utilize fat stores, indicating that an increased sensitivity to outside stress enhanced their ability to stay lean," said Bale.

Are There 'Social Behavior' Genes?

A rare genetic disorder may lead to finding genes for social behavior.

Two Salk Institute researchers have zeroed in on the genes that may lead to the marked extroverted behavior seen in children with Williams syndrome. The study by **Teresa Doyle** and **Ursula Bellugi** and their colleagues demonstrates that "hyper-sociability" — especially the drive to interact with strangers — follows a unique path in Williams syndrome. The path is different from typical children and children with other developmental nervous system disorders.

"We not only have shown hyper-social behavior as a hallmark symptom that follows a characteristic developmental course in Williams syndrome, we may be closer to identifying the genes involved in regulating that behavior," said Doyle.

Williams syndrome occurs in only one in every 20,000 people, and is caused by a deletion of a series of genes. The researchers analyzed the genetic deletion of a two-year-old girl with Williams syndrome who did not exhibit outgoing behavior. The girl retained at least one gene that most people with the disorder are missing. The gene (or genes) she retained might be helping to check the hyper-sociability usually seen with Williams syndrome.

"We don't know whether these genes are involved in regulating social behavior in the general population, or whether their involvement is specific to Williams syndrome," said Bellugi.

'During the evolutionary war between the virus and the host, the virus developed an effective counter-measure.' **Ned Landau**

HIV Inactivates the Body's Smart Bomb

HIV eludes one of the body's key smart bomb defenses against infection, and this finding may lay the groundwork for new drugs to treat AIDS, according to a new Salk Institute study.

Professor **Nathaniel Landau** and his team have pinpointed how the body battles HIV, a tremendously complex and relentless virus. Their findings appeared in the July 11 issue of *Cell*. "We have been focusing on an antiviral system that we never knew about long ago — a single protein called APOBEC3G. The protein would be a powerful inhibitor of viruses such as HIV, except for one problem: the virus has outsmarted it. During the evolutionary war between the virus and the host cell, the virus developed an effective counter-measure."

That counter-measure is a gene in HIV called virion infectivity factor (Vif). Vif prevents APOBEC3G from getting into the new viruses, enabling them to replicate and spread throughout the body.

Having identified the interaction between Vif and APOBEC3G, Landau and his team then focused on the next question: would it be possible to beat the virus at its own game?

"We found that mice also have the antiviral protein," said Landau. "But interestingly, HIV can't recognize the mouse protein. As a result, mouse APOBEC3G is a powerful blocker of HIV replication. The mouse APOBEC3G protein goes into HIV, and Vif can't kick it out."

Mouse APOBEC3G functions like a smart bomb with a time-delayed fuse. When the virus is produced in an infected cell, APOBEC3G molecules get into the virus. At first, the protein does nothing; however, when the virus infects a new cell, APOBEC3G is activated. As HIV begins to copy its genes into DNA, APOBEC3G attacks the virus, creating massive mutations.

"Drug companies may be able to use this information to design a novel type of drug to treat HIV infection. They could develop drugs that attach to APOBEC3G, physically blocking Vif from attaching. If Vif can't bind to APOBEC3G, the process of HIV replication could be halted," said Landau.

Charles Stevens

'Kiss and Run'

Scientists long suspected that neurons had a quick way of using chemical signals to communicate, but never could see it — until now.

Professor **Charles Stevens**, postdoctoral fellow Sunil Gandhi, and colleagues caught neurons in the act of "kiss-and-run," where nerve cell membranes open for half a second, release their neurotransmitters and then close, poised to send another signal.

The researchers also discovered a new form of transmission in which a structure containing the neurotransmitter becomes trapped in the cell membrane. Electrical impulses then free it. The findings appeared in a recent issue of *Nature*.

"Our research pinpoints the important activities that take place at a junction between nerve cells," said Stevens.

When electrical impulses travel to the nerve cell's end, they trigger the release of neurotransmitters into the gap between the sending and receiving nerves.

Neurotransmitter release is now known to happen three ways: by slowly releasing chemical-containing structures and absorbing them into the cell membrane, by the "kiss-and-run" method, and by trapping the structures and waiting for future electric pulses.

The study advances our understanding of how nerve cells conduct messages and could eventually boost our ability to treat damaged or diseased nerve cells.

Ron Evans Receives Two Major Prizes

Professor **Ronald Evans**, March of Dimes Chair in Molecular and Developmental Biology, has received the 2003 March of Dimes Prize in Developmental Biology for pioneering work elucidating the molecular pathways that lead to the most common chronic diseases affecting humans. He has also been awarded the Alfred P. Sloan Prize, one of three awards given annually by the General Motors Cancer Research Foundation.

The March of Dimes Prize is given every year to scientists whose research has profoundly advanced understanding of birth defects. The Sloan Prize is given for the most outstanding recent contribution in basic science related to cancer research.

Evans shares both prizes with Pierre Chambon, MD, director of the Institute for Genetics and Cellular and Molecular Biology in Strasbourg, France, for their work in discovering nuclear hormone receptors, revealing their structure and function, and defining their central role in human physiology.

"These prizes will further advance the progress of our efforts to understand how obesity, heart disease, diabetes, and cancer begin, and I believe will one day provide us with a successful treatment for these deadly disorders," Evans said.

'These prizes will further advance the progress of our efforts to understand how obesity, heart disease, diabetes, and cancer begin, and I believe will one day provide us with a successful treatment for these deadly disorders.'

Ronald Evans

Evans joins a list of notable scientists who have been awarded the prize since the March of Dimes began the program in 1996 as a tribute to Dr. Jonas Salk. The Salk Institute's Sydney Brenner received the 2002 prize.

Evans has been cited for opening new areas of study in the machinery of hormones and cellular physiology. His work shows that these seemingly divergent aspects of physiology in the body employ a similar molecular logic to achieve their control. His research also suggests specific ways chemistry can be employed in the development of approved drugs such as Targretin and Panretin, used to fight certain cancers, and exploratory therapeutics for pediatric and adult onset diabetes as well as obesity, heart disease, and chronic inflammation. His research focuses on genetic switches, known as hormone receptors, that control sugar, salt and fat metabolism, metabolic rate, and reproduction.

Marc Montminy

On the Trail of Diabetes

The incidence of diabetes has increased to epidemic proportions worldwide.In the United States alone, about two million individuals have juvenile-onset or Type I diabetes, and 16 million people have adult-onset or Type II diabetes.

In a June 6 *Science* paper, Professor **Marc Montminy** and his colleagues detail how a protein called TRB3 contributes to insulin resistance in individuals with susceptibility to Type II diabetes. TRB3 interferes with an enzyme called Akt in the liver and promotes glucose production. Understanding the function of TRB3 may establish the protein as a drug target in the treatment of Type II diabetes.

The ultimate problem in both Type I and Type II diabetes is a failure of so called islet cells in the pancreas to make enough insulin. To address this problem, Montminy's laboratory is working on switch proteins that increase islet cell numbers in the pancreas by turning on specific genes. By producing these switch proteins in embryonic stem cells and other cell types, he hopes to develop a new method to make more islet cells in the laboratory. These studies may eventually pave the way for transplantation of islet cells into diabetic patients.

Gene Therapy Postpones Lou Gehrig's Disease Symptoms

Professor **Fred H. Gage** and his team have developed a unique gene therapy method that postpones the onset of symptoms of Lou Gehrig's disease in a mouse model and nearly doubles the life span of the mouse. The findings may lead eventually to a new, gene-based treatment for the disease, which affects more than 30,000 Americans. The study appeared in the August 8 issue of *Science.*

Gage, Salk research fellow Brian Kaspar, Jeffrey Rothstein, professor of neurology at Johns Hopkins University and their colleagues found that injecting a gene that produces the nerve cell growth-stimulating protein, insulin like growth factor-1 (IGF-1), into muscles resulted in longer life spans, preserved nerve cells, and reduced muscle wasting.

Lou Gehrig's disease, known as amyotrophic lateral sclerosis (ALS), is marked by the degradation of nerve cells that control muscle movement. It quickly attacks motor nerve cells in the brain and spinal cord, resulting eventually in total paralysis and death. Its cause is unknown. While the disease was first identified in the 19th century, it gained international attention in 1939 when baseball great Lou Gehrig announced he had ALS and retired from the New York Yankees. He died two years later.

Lou Gehrig

"IGF-1 protein has been used in clinical trials for awhile, with marginal results," said Gage. "The biggest challenge has been to deliver the protein across the blood-brain barrier into the central nervous system. Injecting our viral vector into muscles allows the gene to deliver the protein into nerve cells that control the muscle, preserving the nerve cells that would otherwise have succumbed more quickly to ALS."

While this research is still in the experimental animal stage, human trials for this gene therapy method are being contemplated.

SUPPORTING THE SCIENCE

Her Majesty The Queen of Sweden and Salk President Richard Murphy

Sweden's Queen Addresses International Council

Her Majesty **Queen Sylvia of Sweden** opened the Salk Institute's annual International Council meeting in Stockholm. This year's meeting, in June, focused on diseases of childhood and early infant development, a topic of particular interest to Her Majesty.

Members of the Salk's International Council, who act as informed ambassadors worldwide for the Institute, reviewed research directions and discussed recent projects with Salk President **Richard Murphy** and faculty members. They heard overviews from a range of Salk professors, from Nobel laureates **Sydney Brenner** and **Renato Dulbecco** to presentations from **Ursula Bellugi**, **Beverly Emerson**, **Marc Montminy**, and **Wylie Vale**. Topics included connecting the human genome to birth defects, reviewing strategies to cure diabetes in children, discovering how genes build young brains, identifying the roles genes play in behavior, and the effects of maternal and childhood stress on later life.

The International Council consists of approximately 90 members, who live in Europe, Asia, and North America. Council members include leaders in business and industry, medicine, law, finance, communications, the arts, and community affairs.

Major Gift Funds Mass Spectrometry Center

The Vincent J. Coates Foundation has contributed $550,000 to create a new mass spectrometry center at the Institute. Mass spectrometry is a powerful analytical technique that is used to identify unknown proteins and their chemical properties.

The Coates Center also received funding from the Donald and Darlene Shiley and the Marky K. Chapman Foundations. These private gifts matched a grant from the National Science Foundation to establish the center. The center will advance Salk research in a range of areas, including the Institute's focus on proteomics.

"Researchers at the Salk Institute have been at the forefront of discovering novel proteins," said Wolfgang Fischer, a Salk senior staff scientist who oversees the new Coates mass spectrometry center. "The Coates center will allow us to speed up the discovery of new proteins, and we will also learn how these molecules interact with other proteins to influence fundamental biological functions."

Vincent J. Coates and his wife, Stella, have been important philanthropists at the Institute, having also endowed a chair for Salk professor Charles Stevens in the Molecular Neurobiology Laboratory. Vincent Coates is the founder of Nanometrics, Inc., which is based in Milpitas, Calif. The company serves the global semiconductor industry as its primary market, and is a leading metrology supplier to the flat panel display and magnetic recording head industries.

The new Coates mass spectrometry center will allow Salk researchers, like Chris Park (above) to identify unknown proteins.

Board of Trustees Elects Three New Members

During its spring meeting, the Salk Institute Board of Trustees elected three new members: Corinne Mentzelopoulos, Alain Merieux, and Jerre L. Stead.

Corinne Mentzelopoulos is the owner and CEO of Chateau Margaux, an internationally known winery in Bordeaux, France. She also served as vice chairman of Exor, S.A., a holding company for food retail distribution and real estate. In the early 1980s, Mentzelopoulos was a financial controller for Primisteres, a diverse holding company in Paris, and also worked as a manager for a major French advertising firm.

Mentzelopoulos has served on the Salk International Council since 1988. She served on the board of directors of the Exor Group in Luxembourg, as well as the Société des Industries Chimques du Nord de la Grece in Athens, Greece. She has earned the titles of Chevalier of the Legion D'Honneur and Chevalier of the Ordre National Du Mérité for achieving excellence in her field. In 1999, she was appointed to the French Foreign Trade Council. She received her bachelor's degree from Paris University and her MBA from the Institut D'Etudes Politiques.

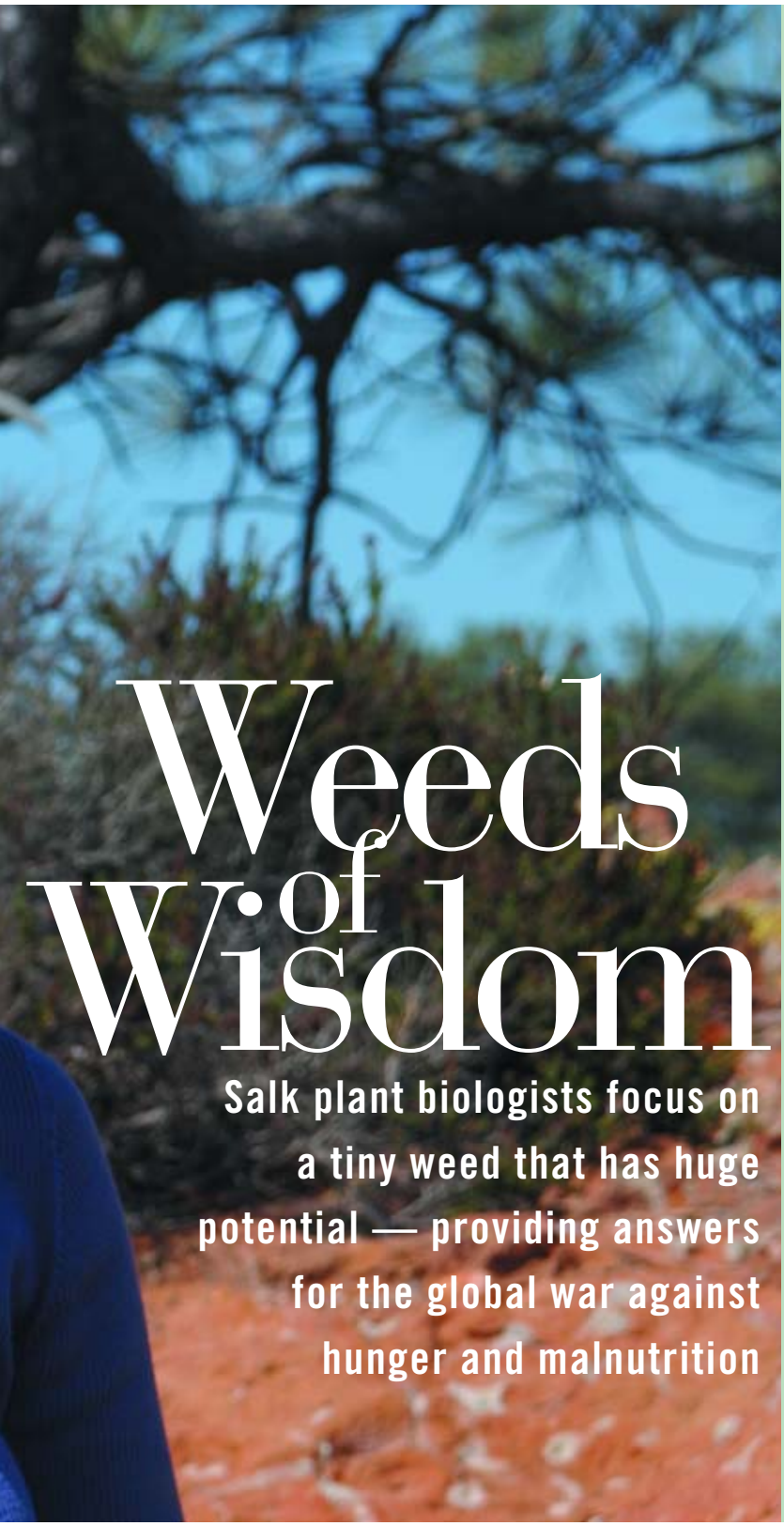
Alain Merieux serves as chairman and CEO of bioMerieux, which he founded in 1963. Based in France, bioMerieux specializes in infectious disease diagnostics, coagulation diagnostics, and industrial microbiology control. The company ranks among the top ten biological diagnostics company in the world and is an international leader in the field of microbiology.

Merieux served as chairman and CEO of Institut Merieux from 1968 to 1994. During his tenure the institute became the world leader in the field of human and animal vaccines. In 1991, he became chairman of Transgene, which specializes in gene therapy, and he held that position until 2002. Merieux has served as premier vice president of the Rhone-Alpes Regional Assembly and received numerous decorations, including commander of the national order of merit and officer of the Legion of Honour. A member of several international boards, including Wendel Investissement, Plastic Omnium, and Akzo Nobel, he received his medical degree from Faculté de Medicine de Lyon and attended the Program for Management Development at the Harvard Business School.

New trustees Corrine Mentzelopoulos, Alain Merieux, and Jerre Stead

Jerre Stead is the retired chairman and chief executive officer of Ingram Micro Inc. of Santa Ana, Calif. He now chairs two companies — HAIC/HIS and BMC. Stead began his distinguished business career at Honeywell Inc., where he spent 21 years in various management positions in the United States and Europe. In 1987 he was named president and chief operating officer of the Square D Company, a leading electrical distribution and factory automation manufacturer based in Palatine, Ill., becoming chairman and chief executive officer in 1989. In 1992, Stead was named chairman and chief executive officer of AT&T's Global Business Communications Systems.

In January of 1995, Stead became chairman and chief executive officer of the Legent Corporation. He headed up Ingram Micro, a distributor of high-tech products, from 1996 until he retired in 2000. Stead has served on the board of directors of Armstrong World Industries, Conexant Systems, SoftBank eCommerce, TBG Group, and Brightpoint, Inc. He received his bachelor's degree from the University of Iowa and attended the Harvard University Advanced Management Program.



Weeds of Wisdom

Salk plant biologists focus on a tiny weed that has huge potential — providing answers for the global war against hunger and malnutrition

Depending on which report you read, the numbers vary slightly. But any way you look at it, the evidence is staggering, almost incomprehensible:

- *About 3.8 billion people — nearly two-thirds of the world's population — live in food-deficit countries where millions experience hunger and starvation.*
- *Worldwide, more than 800 million people are chronically malnourished.*
- *Population pressures across the globe have degraded about two billion acres of arable land — an area the size of the United States and Canada.*
- *By 2025, when the world population approaches eight billion people, 48 countries containing three billion people will face severe shortages of fresh water, leading to profound problems with food production.*

Salk plant biologists Joanne Chory and Joe Ecker are keenly aware of these reports. There are times when they, too, are overwhelmed by the numbers. But in their labs, as they focus on a tiny mustard weed called *Arabidopsis*, they are confident that by understanding its genes they will be able to provide answers to some of the most fundamental problems that millions of people confront each day — how to get enough food to survive.

"Plant scientists, by the nature of their work, think about the global implications of their research," says Chory. "What we're doing as a program here is trying to understand some of the most basic growth properties of plants. We need to understand the basic biology of how growth is regulated by complex interactions with the environment.

"If you understand the basic biology of a plant like *Arabidopsis*, it will inevitably have an impact on the big picture of agriculture."

Only the Beginning During the 1990s, as a huge international cadre of scientists worked to sequence the human genome, a multinational group of plant biologists worked on a parallel track to sequence the *Arabidopsis* genome. In December 2000, six months after the initial sequencing of the human genome was announced to accolades

Salk plant biologists Joe Ecker and Joanne Chory

"A LOT OF PEOPLE EAT, BUT THEY'RE ACTUALLY MALNOURISHED BECAUSE WHAT THEY'RE EATING LACKS ALL OF THE ESSENTIAL VITAMINS. MALNUTRITION, AS OPPOSED TO NO NUTRITION, IS A MUCH BIGGER PROBLEM," SAYS CHORY.

from scientists, physicians, and politicians, the first comprehensive sequence of *Arabidopsis* was published in *Nature*.

The response to the news did not approach the excitement generated by the human genome project, but the *Arabidopsis* genome project will nonetheless have profound implications for world health issues.

"The information you get from *Arabidopsis* is very likely to be immediately applicable to all plants," says Ecker, one of the leaders of the sequencing project. "Genome information will be used by lots of people to improve plant growth, yield, and drought tolerance."

Ecker is quick to point out, however, that sequencing is only the start of the complex and intricate process to understand plant, or for that matter, human biology.

"Sequencing is just the beginning of understanding how any organism functions," he says. "Once the *Arabidopsis* genome was sequenced, we asked how many of the plant's approximately 25,000 genes have people actually worked on. Less than 10 percent have been touched by any scientist."

"IT'S ALL ABOUT YIELD" As Chory, Ecker, and their colleagues immerse themselves in understanding the function of genes in *Arabidopsis*, they have a clear endgame in sight — increasing yield.

Chory is looking at the yield question from the perspective of how seedlings establish themselves and when plants flower, focusing on what is known in plant biology as the "shade-avoidance syndrome." When plants grow in high density, they perceive a decrease in incoming light. This change of light prods the plants to flower and create seeds. The byproduct of this process is that plant stems grow longer and leaf volume declines, leading to decreases in the mass of the plants, and ultimately to decreases in plant yield.

To understand the biology behind this process, Chory and her team looked at a group of phytochromes, photoreceptors in plants that trigger the shade-avoidance response. By using *Arabidopsis*, Chory has identified the specific protein that triggers flowering in response to suboptimal light conditions.

"In agriculture, it's all about yield," says Chory. "Flowering-time pathways in *Arabidopsis* have a great degree of similarity to rice, and we hope that this research will ultimately have applications for improving the yield of rice and other crops."

"Rice has 85 to 90 percent of the genes in the *Arabidopsis* genome," says Ecker. "There are a few things that are highly specialized, but for the most part it's the same plant in terms of the gene content."

Ecker is looking at the yield question from a different perspective — how and when fruits ripen.

From apple orchards to corn fields, farmers struggle with the question of crops dropping to the ground too quickly; the result is a tremendous waste of crops and reduction in yield. "If you could just stop that process, in canola for example, you could increase yield by 20 percent," he says.

Ecker is regarded as one of the foremost experts on how the gaseous hormone ethylene regulates a variety of basic plant processes. For agriculture, ethylene gas is a vital chemical messenger important for such processes as fruit ripening and the plants response to pathogenic organisms.

In his laboratory, Ecker has been trying to unravel the precise molecular pathway that governs how ethylene gas works in plants. To accomplish this task, Ecker and his colleagues have been inducing changes, or mutations, in the genetic code of *Arabidopsis* to help identify a specific gene's function.

"We believe that these genes will function in all plants,



and you can use the *Arabidopsis* genes to engineer traits in other plants," he says.

A Wider Web While plant biologists are looking at fundamental questions about yield, they are also addressing myriad other issues that will affect human health and world ecology.

"A lot of people eat, but they're actually malnourished because what they're eating lacks all of the essential vitamins. Malnutrition, as opposed to no nutrition, is a much bigger problem," says Chory.

A striking example of this paradox exists throughout Africa and Asia, where hundreds of millions of children are vitamin A-deficient, putting them at risk for night blindness as well as infectious diseases. To address this pressing problem, biotech researcher Ingo Potrykus and his colleagues at the Swiss Federal Institute of Technology have developed a variety of rice that makes beta-carotene, the precursor to vitamin A. The strain of golden rice, created by inserting genes from daffodils and bacteria into rice, has the potential to remedy vitamin-A deficiency on a global scale. The technology is also being applied to other essential crops, from wheat to sweet potato to bananas.

"By engineering a few genes to make a pathway in the rice, you can now have rice that is more nutritious," says Ecker. "And the implications of this discovery will be profound because biotech companies have agreed to offer free licensing of golden rice to developing countries."

Tied to the push to increase the nutrition of foods for people in developing countries is developing crops that can be grown effectively and efficiently.

"In the developing world, you can now grow cotton in places you could never grow it before. That has been an extremely effective transgenic technology," says Chory. "And this has an impact on the economies of the developing countries and allows them to be more independent.

"In developing countries, it's too often all or nothing. They don't have the money to buy pesticides, and if they can't grow crops without spraying pesticides, they can't grow the crops at all."

Ecker is quick to point out that the connection between transgenic crops, ecology, and economics often eludes people. "I think that's something that people don't get. People who focus on the fact that some plants are genetically modified don't realize that with a crop like transgenic cotton, you only have to spray half the amount of pesticides," he says.

"Some people say that the only benefits from GM crops are for the farmer. It is for the farmer. But it's also for everyone downstream from the farmer."

Science and Social Justice When Dr. William Foege, a pioneer in eradicating smallpox in developing countries, came to the Institute in December 2002 to deliver the Jonas Salk Lecture, he emphasized that scientists must be more concerned about social justice issues as they pursue their research.

"We have a world of billions who are no better off because we have vaccines, drugs, computers, or even an alphabet," Foege said. The gap between those few who benefit from advances in science and technology, and the many who do not, "is perceptible and costly," he said.

As Chory and Ecker pursue their work, they come across a diverse group of people — farmers and biotechnology leaders, politicians, and environmentalists. From these groups, they hear often heated and emotional debate about genetically modified foods and biotechnology. As scientists, they listen and try to inject accurate data into the debate.

"There was a poll in New Jersey, where I'm from, that asked a basic question," says Ecker. "Do you believe that cross-breeding plants is a good thing? Most people checked no. They have no idea how their food has evolved.

"People are looking at these issues from different perspectives, including questioning whether a few companies should control all of the food distribution in the world. That's a much different issue than understanding how a plant functions."

For Chory, the economic and political ramifications of her work drive her to find solutions to problems that she knows will ultimately have an impact on millions of people.

"Certainly within the next decade we will see significant improvements in plants. Maybe not the holy grail, but improvements in flowering time or cold tolerance," she says.

"We know that the things we work on will ultimately be applied in the field."

50 Years of DNA

"Rather than believe that Watson and Crick made the DNA structure, I would rather stress that the structure made Watson and Crick." Salk professor Francis Crick wrote these words in 1974 in the midst of the revolution in biology that followed the discovery of DNA's structure and function. But the discovery went far beyond making Watson and Crick. It created entire new industries, one of which is making "gene chips" that identify activity in thousands of genes simultaneously. It produced new medicines and food derived from knowing which gene produces what proteins. It created unprecedented, if disturbing, possibilities for gene therapy and the cloning of entire organisms. DNA and the genome have become household words, moving from quiet laboratories to starring roles in hit movies. This photo essay highlights a sample of Salk Institute people whose important work was in no small way made possible by the 1953 discovery.

For more than 50 years, James Watson (left) and Francis Crick have been friends and colleagues. They often meet at the Salk Institute.

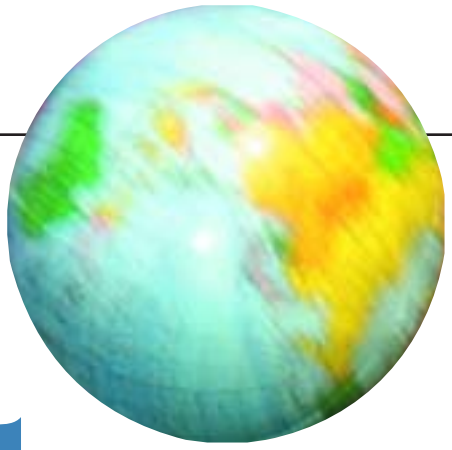
Renato Dulbecco (below right, with founder Jonas Salk), was one of the first scientists to suggest sequencing the entire human genome — a concept that came directly from the Watson and Crick's momentous discovery in 1953. Dulbecco, who received the Nobel Prize for his work on viral genes that cause cancer, came to the Salk Institute in the early 1960s as one of the original faculty members and worked closely with Francis Crick, Jonas Salk, and others, to define the scientific focus of the Institute.

Professor Tony Hunter has been studying protein kinases — enzymes produced by genes to orchestrate a wide range of cellular activities — since the late 1970s. His work on these proteins, he says, simply would not have been possible without the Watson and Crick discovery. Understanding these proteins may provide new ways to treat cancer, Alzheimer's disease, and other disorders.

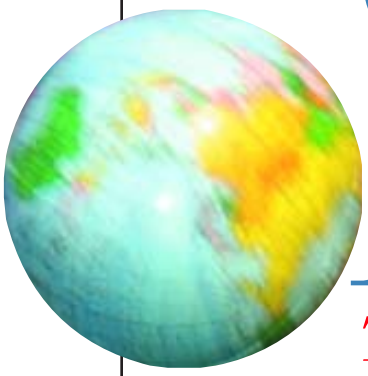
Using eggs and tadpoles of frogs native to Africa, Professor Chris Kintner searches for how genes influence the steps taken to develop a mature nervous system from simple stem cells.

DNA's train of information is now sequenced rapidly, determining the molecular arrangement of genes and the proteins they produce. Melissa Baker directs the DNA sequencing facility at the Institute, which handles 4,000 samples a month.

Professor Inder Verma (above) uses genetically engineered viruses to insert new genes into cells that can then be returned to the body. He is employing these gene therapy techniques to focus on diseases ranging from Alzheimer's to glaucoma to hepatitis.



Salk Science's Global Accent



The Institute's International Flavor Enhances the Research

THE MOROCCAN OFFICIAL'S request took Roger Guillemin by surprise. The Nobel laureate and Salk Institute professor was not a Muslim and observed neither the holy month of Ramadan or its fasting practices. But the Moroccan government was asking him to preside over a meeting in Casablanca dedicated to discussing the medical effects of 40 days of fasting.

Intrigued, Guillemin accepted. "We discussed the practice of fasting, its meaning and its relationship to the Quran. We met with Imams at first. Then we discussed the effects of fasting on healthy people, on people with diabetes, pregnant women, the elderly."

The surprise request was germinated by a visit to the Salk Institute years before. "The host had been impressed by what he had seen. It was very touching," Guillemin recalls.

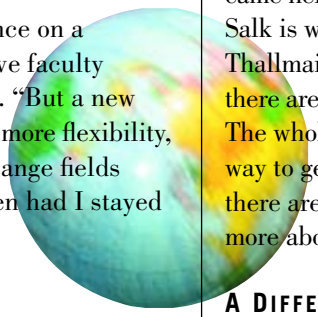
Such visits from international scientists are commonplace. It comes as no surprise, however, that the Salk Institute is one of several biological research institutions that enjoys a powerful global reputation. The Institute was set up that way.

Global Beginnings

Jonas Salk, fresh from his triumph of the world's first polio vaccine, intended to create an internationally known institute of science in La Jolla. And he attracted international leaders: Jacob Bronowski, Polish-born and living in London; Francis Crick and Leslie Orgel from England; Jacques Monod from France; Salvador Luria from Italy (via MIT) and Leo Szilard from Hungary and London (via Chicago). The Americans Edwin Lennox and Warren Weaver were internationally known scientists, as well. Guillemin, in fact, came to the Institute from France (via Houston), and has lectured in Israel, China and Europe as well as throughout the United States.

Orgel remembers that the international mix of faculty and advisors was a strong attraction for him. "I had been a successful organic chemist, but I wanted to do something different. I happened to know the people at the Salk, all of whom had outstanding reputations.

"I was taking a chance on a new institution with five faculty members," Orgel says. "But a new institution would have more flexibility, and it was easier to change fields than it would have been had I stayed in England."



Overseas Benefits

Jonas Salk's founding strategy paid off. Currently, about half of the Salk's 56 faculty members were born overseas. That number doesn't include Americans who've trained overseas. Of the Institute's 1,100 staff, 300 arrived here from about 40 countries. Every continent except Antarctica is represented: Argentina, Australia, Brazil, China, France, Germany and Britain, India, Iran, Israel, Japan, Ethiopia, and the Philippines are a sampling of just some of the nations Salk employees call home.

"The Salk had a great start with some of the world's top scientists," says Senyon Choe, professor of structural biology, a native South Korean who trained in the United States. "You take a slice of basic science people and there is an international mix at any level, especially if they're a strong organization."

The representation has other payoffs. "Since about half of our postdocs are foreign nationals, we're providing both a training ground and a way to promote the Institute," says Tony Hunter, a professor of molecular and cell biology from England whose laboratory has spawned talented researchers now working all over the globe. "This adds to the excellence of the place, with new science, new perspectives and new experiences."

Postdoctoral fellow Michaela Thallmair left her native Switzerland to work with Professor of Genetics Fred H. Gage. "I knew him before I came here, and I also knew that the Salk is well known in neuroscience," Thallmair says. "I liked the fact that there are lots of seminars and meetings. The whole environment was a better way to get started. Over the years, there are certain institutes you hear more about — Salk is one of them."

A Different Flavor of Science

The international influence has also rubbed off on the way the Salk conducts its work. Laboratories are smaller and focus on more specific projects, reflecting a European style of research.

"Salk's founders had a European background," says Choe. "Therefore, we've married European culture with an American capitalist culture."

Echoing that view is Matthew Weitzman, an associate professor who studies viruses as agents for gene therapy. Weitzman came from England to see how American science worked. "Europeans will deliberate; they want to find out how things won't work, how many actions are going on. Americans say, 'Just do it.'

"Here, we don't have isolated, American-style labs, but we don't have a European-style hierarchy. Ambition is rewarded, which isn't always true in other countries."

Cebus, Meet *Rhesus*

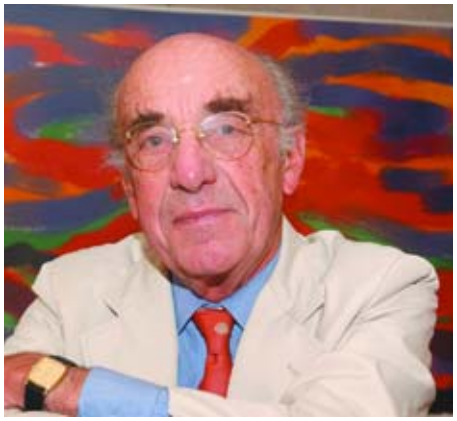
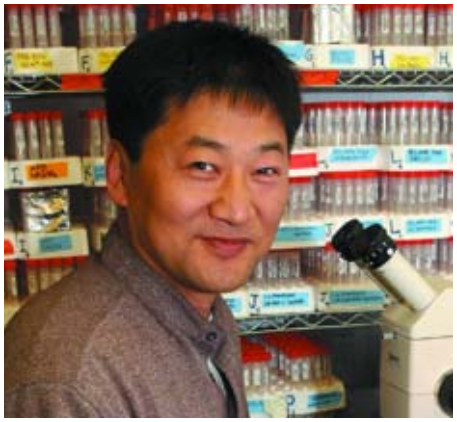
In Tom Albright's lab, international collaboration has boosted our understanding of the connections between the genetics of vision and the ways we adapt to new environments. When Albright was a graduate student at Princeton University, he met Brazilian researcher Ricardo Gattass. They've been collaborating ever since.

Albright and Gattass, working from nearly opposite sides of the planet, have compared the visual systems of New World Cebus and Old World Rhesus monkeys to see how they have evolved.

"The standards we use in this research are derived from Rhesus monkeys," Albright says. "But now, we can compare New World Cebus monkeys to look at how animals handle visual processing in essentially the same type of environment. We've found that although Cebus and Rhesus monkeys have been divergent for more than 35 million years, they handle visual stimuli in almost the same way."

New Indian Opportunities

Meanwhile, a chance encounter at a February meeting in India sparked a dramatic research opportunity for Lisa Stefanacci, a staff scientist in the Computational Neurobiology Laboratory.


From left, French Nobel laureate Roger Guillemin, South Korean professor Senyon Choe, and international collaborator Tom Albright, director of the Institute's vision laboratory, embody the Salk's global connections.

"About 40 years ago, Indian surgeons used to remove the amygdala to treat hyperactivity and other behavioral problems in children," says Stefanacci, who met an Indian researcher in New Delhi who knew one of those surgeons.

About 638 surgeries were performed on the amygdala, a brain structure that processes emotional memories. Its functions are still not known exhaustively. "There were anecdotal reports about the cases, but no scientific follow-up," says Stefanacci.

"The surgery patients are now in their 40s and 50s, and the surgeon wants to help us follow up. We are very lucky," Stefanacci says. "In the United States, studies are hampered by very small numbers of subjects with relatively selective amygdala damage. Now, studies with at least dozens of subjects are possible, which may bring us much closer to understanding the brain's basis of emotion."

An International Nature

Such tales underline the international nature of science. "Science is a way to connect with cultures around the world," says Albright.

"The business of science is a unique discipline," says Choe. "Truth wins the game eventually" — this was a note on the door of the late scientist Max Perutz. Science builds on previous accomplishments by adding and correcting, and passing them on," without regard for geography, nationality or politics.

"Science belongs to humanity," says Guillemin, who in the early 1940s postponed medical school to join the French resistance against Nazi Germany. "It itself is part of human evolution. Since knowledge belongs to everybody, there can never be barriers to sciences."

Global Warnings?

But recent concerns over terrorism, security, and war have raised more barriers today than anytime since World War II, if not to research, but to the logistics of traveling to conduct that research.

Visa requirements for foreign scientists have toughened, requiring personal interviews in most cases, and lengthening waits into the United States. U.S. officials are particularly concerned about issuing visas to specialists and students in neurochemistry, biochemistry, immunology, virology, recombinant DNA technology, and a number of specialties making up the backbone of modern biology.

A recent editorial in *Science* by David Galas and Henry Riggs of the Keck Graduate Institute of Applied Life Sciences warned that "having spawned a global community that depends on it, the United States is also fully dependent on that community...to drive the research in commercial, educational, and even military technical enterprises in our own country."

"I think the way we're responding is deeply disturbing," says Guillemin, referring to the visa crackdown. "What we're generating may be worse than what we're defending against."

Albright sees glimmers of hope through the latest tightening, however. "It's more complicated to get into the United States, but there's a lot of enthusiasm for foreigners to come here."

In an international mileau where a book about getting into Harvard ranks as a bestseller in China, this enthusiasm is hard to resist. And researchers' international connections, including those at the Salk, will no doubt continue to be irresistible.

Albright recalls that during his visit to India in February, "Some of the students had never seen a Westerner before. One woman came up and told me that 'I'll remember this the rest of my life.'"

Salk scientists look for pathways that trigger new nerve cells to travel and make vital connections to muscles and organs.

Guiding Frayed Nerves

TO THE ANCIENT EGYPTIANS, a spinal cord injury was "an ailment not to be treated." The father of neuroscience, Santiago Ramon y Cajal, a century ago concluded that nerves of the central nervous system could not regenerate, and as modern research eradicated a long list of diseases, the nervous system remained in stasis.

Can the ancient Egyptians and the father of neuroscience be wrong?

John Thomas, professor of molecular neurobiology at the Salk, thinks that understanding how nerves grow up might help us understand how to repair nerve cells that are damaged by injury or disease, although he would never presume his work could heal damaged nerves directly.

"We are a long way from spinal cord repair," he says. "We have very little idea what's keeping nerve cells from regenerating. There's been a lot of movement in this area in the last ten years, and we at least understand some receptors and


R470
C200
C181
HD74LS37P
SIA F925XJ
SN74S04N
J91582K
SN74LS221N
NEC JAPAN
C1458C
8840E
J8488

Sam Pfaff works to understand how nerves are created from the ground up, which could lead to new ways to repair injured nerves.

ligands (molecules that bind to receptors.) But there's still a lot to know."

To scientists like Thomas, the spinal cord is a very convenient window to view the central nervous system's machinery.

"My work focuses on how neurons develop normally, how they're attracted or repelled as they get to their target area. This may shed light on the ability of spinal cord neurons to regenerate. On the other hand, it may have nothing to do with regeneration," he warns.

Sam Pfaff, a Salk Institute associate professor who has worked with Thomas, says that an investment in understanding the basic ways that nerves grow may help break through these stalemates, but in ways that nobody can guess now.

"There isn't a treatment waiting to be translated out there," says, Pfaff who serves on the scientific advisory board for the Christopher Reeve Foundation (as does Salk Professor Fred H. Gage). "We don't have that understanding yet. But understanding how nerves are created from the ground up may help us find a way to restore nerves that have been injured."

Meanwhile, the hope for a cure for spinal cord injuries and degenerative diseases that kill nerve cells continues.

Recent work on restoring function, currently in animal studies has not been encouraging, despite some early successes. Reeve's 1995 horseback riding accident and his subsequent advocacy for research aimed at repairing the damaged nervous system brewed new optimism toward the possibility of regenerating spinal cord nerves, and in the late 1990s, scientists in labs throughout the world were making important discoveries related to nerve growth. This was great news, particularly to the 450,000 people who live with spinal cord injury in the United States. But five years later, the miracle hasn't materialized.

Scientists worldwide (including at the Salk Institute) have investigated the possibility of:

- using stem cells to grow new neurons
- grafting tiny nerves from the rib cage into the spinal cord
- using growth factors and hormones to goad severed nerves into reconnecting

While some of the results have been encouraging, scientists like Thomas

"We're trying to find out what happens at a molecular level," Thomas says. "We're trying to examine a process that involves many receptors and ligands and trying to answer the questions: how is this coordinated over time? How is the nervous system wired up? These are fascinating questions."

and Pfaff are returning to the drawing board to gather more clues on how neurons develop.

Thomas looks at how nerves develop normally, and how their long appendages known as axons are attracted and repelled as they make their way to their final connection site. "We're trying to find out what happens at a molecular level," he says. "We're trying to examine a process that involves many receptors and ligands and trying to answer the questions: how is this coordinated over time? How is the nervous system wired up? These are fascinating questions."

In his career, Thomas has been interested in finding out how axons are guided to their targeted connection sites. He focuses on the foremost tip of the growing axon, the growth cone.

"Growth cones of neurons have receptors, and these receptors respond to extra-cellular signals along the routes to the neurons targets. The target sites secrete signals, too," he said. While targets secrete attractive signals, other molecules along the way secrete chemical signals that turn away axons; the entire network, once figured out, could form a neural road map, complete with traffic signals and roadblocks, of the developing nervous system.

But mapmaking may take awhile. A recent *Nature* paper by Thomas and colleagues showed for the first time, that two seemingly separate groups of receptors and signals actually worked together to set growing axons on the right path. Specifically, Thomas studied how axons grow from one side of the nervous system to the other, providing vital communications between the left and right sides of the nervous system and the body in general. The work took five years.

Looking at fruit flies because they breed easily and have very fast growth cycles and relatively simple nervous systems, Thomas and his laboratory of six postdoctoral fellows and one technician discovered that one member of a well-known family of signaling molecules, called Wnt, helped guide the growing axons across the spinal cord's midpoint. Wnt's guidance came through binding with a receptor on the axon's growth cone called Derailed.

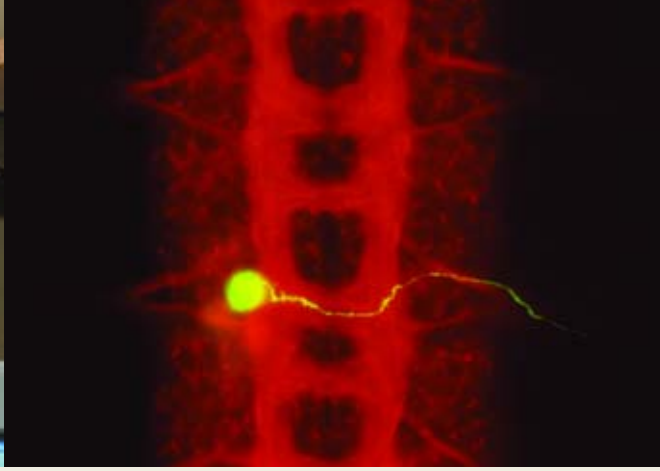
This guidance is important because axons cross from one side to the other through one of two bundles of nerves, called anterior and posterior commissures.

"Crossing through the right commissure is important," Thomas says. "Flies with mutated Derailed receptors were uncoordinated and had nerves that crossed the wrong commissure, which suggests some connection to locomotion. There also were learning and memory defects in the flies with the mutated Derailed receptor."

The study was one of the first to uncover a role for the large Wnt family in guiding axons. "The findings bring an important new player to the Wnt signaling system, and may represent the first of many connections between these two protein families," Paul Garrity, professor of biology at the Massachusetts Institute of Technology, wrote in the same issue of *Nature*.

Thomas' study has important implications for humans. "A huge number of these signaling factors are conserved in higher animals, including humans," says Thomas. Fruit flies have seven types of Wnt molecules and humans have more than 20, but each of the seven fly Wnt molecules corresponds directly with a human Wnt, he adds.

One of the challenges faced by basic science researchers is the smallness — and surprising complexity — of the world they explore. And that world is very different.



John Thomas, professor of molecular neurobiology, studies how developing nerve cells find their connection sites. At right, a young nerve cell (in green), winds its way across the spinal cord.

In this world, gravity does not weigh in as important; movement up, down, forward, and backward is not impeded by the earth's pull. But a molecule is impeded by a veritable forest of huge cell structures, such as membranes, cytoskeletal timbers, and vesicles, large and powerful proteins, fats, and carbohydrates, and signaling molecules, guiding and prodding young growth cones into the right — or sometimes wrong — direction. Even water in this world constitutes a formidable obstacle, requiring cells to spend most of their energy pushing through what to them is a thick, syrupy liquid.

A growing axon's job is to push through this chemical underbrush and connect to a site. The signaling molecules act as axonal guides through forest so thick, that, in 1906 Santiago Cajal remarked that it "by a refinement of complexity has no spaces in it, so that the trunks, branches, and leaves touch everywhere."

While every leaf, branch, and tree may never be catalogued, researchers like Thomas and Pfaff try to at least identify the types of foliage in this microscopic forest, at least to determine how to get in and out.

Pfaff, for his part, works on determining how nerve cells are manufactured and become a specific type of cell; either a motor neuron containing dopamine neurotransmitters, or a glial cell, whose job it is to provide support for active neurons.

Pfaff and postdoctoral fellow Soo-Kyung Lee in the June 5 issue of *Neuron* constructed a detailed model of how stem cells are prodded, regulated and otherwise encouraged to become motor neurons. The study provided an important blueprint for the cellular influences that produce motor neurons from embryonic stem cells.

"In the embryonic nervous system, many types of neurons are generated with distinct properties," says Pfaff. "We used nature as a model to understand how genes interact to develop motor nerves in the spinal cord. This study showed an unusually efficient yield of 60 percent motor nerves."

Working with chick embryo cells, the researchers achieved this efficiency by tracing how two important gene and protein-regulated pathways of nerve generation collaborate to create specialized nerve cells, including motor neurons. One pathway, called bHLH (short for basic-helix-loop-helix), creates a wide range of neurons from simple stem cells. The other pathway, called LIM Homeodomain (or LIM-D), determines what type of neuron is produced. The two pathways interact, comprising the cellular factory that makes motor neurons.

Pfaff is looking at how nerve cells take on their identity in the early stages of life. "There's a rich diversity of cell types in the nervous system," says Pfaff. But Pfaff and Thomas have used somewhat different methods to determine the next step.

"One thing John and I have in common is that we both want to know what happens once a nerve cell has taken on its identify," Pfaff says.

"The science we do isn't always linear," says Thomas. "Sometimes we muck around, see what happens, see where it leads us. There's a playful aspect to that."

Pfaff follows a similar approach, following where nature leads. "This can take us into problems we never meant to solve," he says. And this approach, which takes us to a more microscopic level than either Cajal or the ancient Egyptians ever imagined, may one day prove the ancients wrong and provide an effective treatment for spinal cord injury.

Financial Overview

The Salk Institute's financial position is strong, with revenues reaching a new high of nearly $90 million for fiscal year 2002. Our outstanding faculty continues to be highly successful in obtaining federal grant funding; these grants provide for nearly two-thirds of our annual operating funds. The second largest source of research funding is philanthropy, which represents more than 20 percent of revenues. Private gifts provide seed funding for a wide range of research programs that will enable us to better understand human disease. Other sources of support include voluntary health organizations, the March of Dimes, and income from our endowment.

Like many other institutions, we have experienced declines in our investment portfolio due to the poor performance of the capital markets during the year. Yet, I am happy to report that despite the downturn, the Institute's total cash and investments as of June 30, 2002, were nearly $127 million. Early indications are that investment results for fiscal year 2003 will be more favorable.

The Institute's advances would not be possible without the generous support of the Board of Trustees, foundations, and individual donors. From all of us at the Institute, I express our deepest appreciation for the contributions that fuel our research efforts.

Sincerely,

Delbert E. Glanz

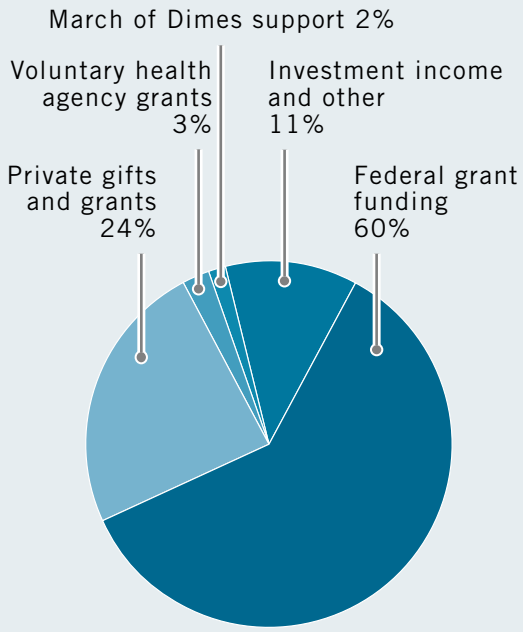
Delbert E. Glanz
Executive Vice President

FINANCIAL DATA

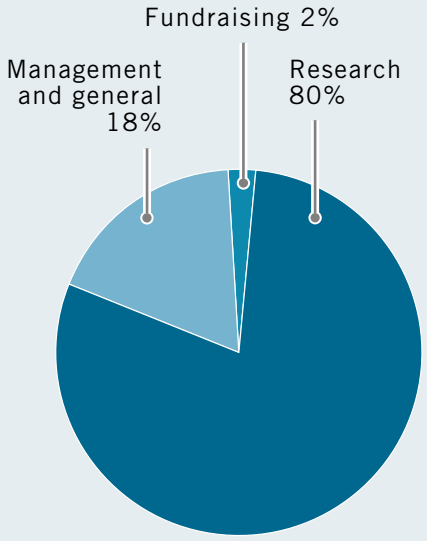
FISCAL YEAR ENDED JUNE 30, 2002

(IN THOUSANDS)

REVENUES



EXPENDITURES



REVENUES AND EXPENDITURES

REVENUES	
Federal grant funding	$ 53,794
Private gifts and grants	21,494
Voluntary health agency grants	2,153
March of Dimes support	1,354
Investment income and other	10,411
TOTAL REVENUES	**$ 89,206**
EXPENDITURES	
Research	$ 66,575
Management and general	15,027
Fundraising	2,030
TOTAL EXPENDITURES	**$ 83,632**
EXCESS REVENUES OVER EXPENDITURES	**$ 5,574**
Investment Shortfall	(16,925)
DECREASE IN NET ASSETS	**$ (11,351)**

BALANCE SHEET

Cash and investments	$ 126,910
Grants receivable, pledges receivable, and other	15,074
Property	82,906
TOTAL ASSETS	**$ 224,890**
Accounts payable and accrued expenses	$ 14,686
Advances and deferred obligations	13,809
Capital projects debt	44,735
TOTAL LIABILITIES	**$ 73,230**
Unrestricted	$ 84,855
Temporarily restricted	14,039
Permanently restricted	52,766
TOTAL NET ASSETS	**$ 151,660**
TOTAL LIABILITIES AND NET ASSETS	**$ 224,890**

Steve and Jean Hamerslag

Get Involved at the Salk

Helping Salk 'Reach the Stars'

What started with a phone call five years ago has blossomed into a family affair of support, ranging from sponsoring events and research to an art exhibition.

Steve Hamerslag, an entrepreneur from Rancho Santa Fe, remembers being contacted by now-Board of Trustees Chairman Jerome Kohlberg, asking for support of the Institute. "In the process, I learned something. I really liked what I heard about the Salk, and told my wife," Steve says.

Jean Hamerslag, who describes herself as "an artist who loves science," was curious about the Salk, too. "I fell in love with the Institute," she says. "The tour, meeting the scientists, I was very impressed."

When the family weathered Jean's bout with cancer, their daughter Carrie set up a fundraiser to support postdoctoral fellows conducting cancer research in Professor Inder Verma's lab. The fundraiser had an unusual twist, with 15 year-old Carrie selling Jean's artwork. She raised more than $60,000.

The Hamerslags have continued to participate. Jean was named to the International Council, she and Steve co-chaired this year's Gridiron Glamour benefit, and the family has supported the Symphony at Salk and the President's Club.

"The activity at the Salk resonates with me," says Steve. "We enjoy supporting the activities that are unique, and often difficult to justify for a government grant. We want to help Salk scientists reach for the stars and do extraordinary things over time."

Jean's focus includes building an awareness of science — especially Salk science — among younger people. "I appreciate the science and the level of world-wide talent and philosophy there. Younger generations don't hear much about Jonas Salk these days, so it's important to sell Salk to the world," she says.

To the Hamerslags, the breadth of innovative research is the heart of Salk's future. "It's the totality of the research, including neuroscience, cancer, AIDS, plant biology," says Jean. "Add to that the talent of individual scientists and how much they're willing to share and get laypeople to understand their work. That is truly a great benefit."

For information on how to participate in Salk Institute activities, please contact the Institute Relations office at (858) 453-4100, ext. 2062.

Become A Partner In Discovery

For more information on how you can get involved in:

- The President's Club
- Estate/Gift Planning
- Symphony at Salk
- Volunteer Opportunities

Please contact:

Institute Relations Office
Salk Institute for Biological Studies
P.O. Box 85800
San Diego, CA 92186-5800
(858) 453-4100, ext. 2062

The President's Club Giving Levels

Fellow	$100,000 & above
Benefactor	$50,000 to above
Patron	$25,000 to above
Advocate	$10,000 to above
Sponsor	$5,000 to above
Researcher	$2,500 to above
Associate	$1,000 to above

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