REMEMBERING Wylie
Dear Friends,

IT’S BEEN A REMARKABLE FEW MONTHS AT THE SALK INSTITUTE, but before I bring you up to date on all that is happening here, I must share with you the sad news that Salk lost a true leader, family member and dear friend, Wylie Vale, on January 3. Wylie was professor and head of the Clayton Foundation Laboratories for Peptide Biology and held the Helen McLoraine Chair in Molecular Neurobiology. He was widely regarded as the global authority on peptide hormones and growth factors that provide communication between the brain and endocrine system. He and his collaborators identified the central switchboard, a group of neuropeptides and their receptors that mediate the body’s responses to stress and stress-related disorders. Their research led to new methods for the diagnosis of pituitary disease and opened new possibilities for the development of drugs aimed at treating anxiety, depression, irritable bowel syndrome and even drug abuse. In addition to his wife, Betty, Wylie is survived by his two daughters and their husbands, a granddaughter and his brother and father.

But just as we bid Wylie farewell, we are saying hello to three extraordinary new members of the Salk faculty: Hu Cang, who joins us as an assistant professor in the Waitt Advanced Biophotonics Center, and Xin Jin and Nicola Allen, both assistant professors in the Molecular Neurobiology Laboratory and the Crick-Jacobs Center for Theoretical and Computational Biology. You can learn more about them in the following pages, but briefly, Hu has developed nanophotonic contrast enhancement agents that are now used in cancer imaging and also developed the first microscope to track single nanoparticles inside a cell; Xin is a rising star in the field of circuits and behavior; and Nicola works at the interface of molecular and systems neurobiology, investigating how astrocytes contribute to the formation, maturation and stabilization of synaptic contacts.

From a scientific standpoint, the past few months have been exceptionally productive, leading to a number of important discoveries. You can read more about them in this issue, but here is a sneak peek: scientists led by Inder M. Verma discovered that a protein that defends the body against cancer also plays a key role in the anti-inflammatory action of steroids; Leanne Jones found clues to slowing human aging and fighting disease by studying long-lived fruit flies; Juan Carlos Izpisua Belmonte led a team in finding a safe way to repair sickle cell disease genes; Dave Schubert has developed a new drug that improves memory and prevents brain damage in mice; Christopher R. Kintner and his team have identified a gene that tells cells to develop multiple cilia, a finding that may help scientists generate new therapies that use stem cells to replace damaged tissues in the lung and other organs; and scientists led by Ronald M. Evans have gained new insights into respiratory distress syndrome, which is the leading cause of death among premature babies, and have also discovered a missing link between the body’s biological clock and sugar metabolism system, a finding that may help prevent the side effects of drugs used for treating asthma, allergies and arthritis.

I hope it’s apparent from these and other breakthroughs that Salk discoveries are literally changing the world. But I want to emphasize that science of this caliber is only possible because of the continued support and commitment of our steadfast donors, friends and trustees. As I explain in my Insider’s View column this time, government funding for science is declining. This means that you, more than ever, ensure that Salk remains at the forefront in discoveries that address the growing need for new ways to prevent and treat human health problems. Over the past six months we have raised over $32.5 million, breaking all of our previous records for philanthropy at Salk. We thank you for your extraordinary support!

Your generosity and your appreciation of our faculty and their groundbreaking science are giving us the confidence to pursue a bold vision for the future. We are most grateful, and I look forward to sharing more dynamic plans in coming issues.

William R. Brody
Irwin M. Jacobs Presidential Chair
Salk scientists are teaming up to unravel the complex metabolism behind diabetes.

**THINK OF THE MOST FUTURISTIC, INTRICATE HYBRID CAR POSSIBLE,** one that effortlessly and efficiently balances battery and fuel use to whisk you to your destination. It won’t be one fraction as complicated as human metabolism—the production and use of energy that provides our motion, our life.

Now think of all the things under the hood that can go wrong in the fantastically involved electronics that match fuel use with need, and you get an idea of what could be happening when diabetes, a disease of energy utilization, develops.

Salk researchers are trying to understand the human “hybrid car” of metabolism and what happens when this biological system breaks down. The problem is attracting a growing number of scientists worldwide, given the increasing burden that diabetes and other metabolic dysfunctions have on human health and society.

According to the latest figures from the American Diabetes Foundation, nearly 25.8 million Americans have type 2 diabetes, and an estimated 79 million people are at risk of developing the condition. It is the sixth leading cause of death, and treatment of the disease costs the country...
$116 billion annually. If current trends continue, the U.S. Centers for Disease Control and Prevention estimate that one in three Americans will have diabetes by 2050, making it by far the most dominant and costly disease to manage.

Despite a growing focus on diabetes research in centers around the world, progress in understanding and treating the disease is hard won. But at the Salk Institute, a unique collaboration among three molecular biologists—Ronald Evans, Marc Montminy and Reuben Shaw—is decoding the labyrinth of genetic switches that control human metabolism. With a generous grant from the Leona M. and Harry B. Helmsley Charitable Trust, these investigators established the Salk Center for Nutritional Genomics in 2009, helping to meld their strengths into a powerful and cohesive unit.

The research in the three labs in the Center for Nutritional Genomics employs a molecular approach to nutrition and its impact on the role of metabolism in diabetes, obesity, cancer, exercise physiology and lifespan, thereby increasing the understanding of how nutrients affect health. It includes a metabolic core facility and an interdisciplinary fellows program. Their work has already uncovered key discoveries regarding genetic switches that potentially point to new ways of controlling the body’s production of glucose, the simple sugar that is the source of energy in human cells and the central player in diabetes.

“If you control those switches, you can control the production of glucose, which is really at the heart of the problem of type 2 diabetes,” says Marc Montminy, professor and head of the Clayton Foundation Laboratories for Peptide Biology.

Ronald Evans, professor in the Gene Expression Laboratory and a Howard Hughes Medical Institute investigator, adds that understanding diabetes requires more than just looking at what a person eats.

“The use of food to power our bodies is an old story,” he says. “The new story is that the foods we eat interact with genes that control nutrient metabolism. To tackle the enormous problem of diabetes and metabolic disease, we have to understand how the genome controls the flow of energy in the body.”
Food fuel in the day, fat batteries at night

To understand the exquisite metabolic machine that is a human, it helps to think of that hybrid car.

During the day, humans burn “gas,” the high-octane glucose derived from the food we eat. This is the fuel that supplies the muscles, the brain and all other parts of the body expending energy. At night, when we sleep, we revert to our “batteries”—our stored fat—as a source of very dependable but slowly released energy.

This shift from burning one kind of fuel to burning the other is controlled by pancreatic islet cells, which can be viewed as the “central transmission.” Islet cells control the release of insulin from the pancreas during the day. The role of insulin is to allow high-octane glucose, produced from the food we eat, to be taken up into muscle. Insulin also tells the liver to stop making glucose, with the net effect of lowering glucose levels in the blood.

At night, the body shifts to glucagon, hormones that are also produced in the pancreatic islets, which can be viewed as the “central transmission.” Islet cells control the release of insulin from the pancreas during the day. The role of insulin is to allow high-octane glucose, produced from the food we eat, to be taken up into muscle. Insulin also tells the liver to stop making glucose, with the net effect of lowering glucose levels in the blood.

At night, the body shifts to glucagons, hormones that are also produced in the pancreatic islets. That changes the nutrient mix from one based on glucose to one based on fat. (There is an exception: during the night, the liver needs to provide enough glucose to keep the brain and red blood cells going.)

Glucagon, which is also released during a fasting state, is thus the opposite of insulin; it tells the liver to convert stored fat into glucose, which is released into the blood. Glucagon and insulin are part of a feedback system designed to keep blood glucose at a stable level.

“We are really looking at how the whole body constantly reprograms its metabolism in response to changes in nutrition, hormones, environment or day and night cycles,” says Reuben Shaw, an assistant professor in the Molecular and Cell Biology Laboratory and a Howard Hughes Medical Institute early career scientist.

Multiple organs constantly talk to each other during this metabolic dance, but in diabetes, communication within this complex system breaks down in two different ways. One is the inability of muscle and fat tissues to recognize the insulin signal that is coming primarily during the day. The other is the inability of the islet cells in the pancreas to produce enough insulin to meet the demands. As a result, the liver increases its glucose production, resulting in high levels of “sugar” in the blood.

“It’s kind of remarkable that we don’t all develop diabetes, given that these very sensitive systems are naturally affected by age, as well as genetics, not to mention body weight,” Montminy says. “The Salk provides an ideal environment in which to study this problem. Because we have no barriers between different laboratories, we are in an excellent position to piece together the very complex puzzle of human metabolism.”

Looking under the hood at the metabolism’s wiring system

In their quest to decode metabolism, the Salk researchers focus on different tissues: the liver (Shaw and Montminy), muscle and gut (Evans and Shaw) and pancreas (Montminy and Evans). Much of their work has centered on the genetic “switches” that regulate metabolic control.

Montminy’s lab has for years focused on the central switches that control glucose production in the liver and others that control glucose sensing and insulin production in the pancreas.

Among his key findings are how a protein (CREB) controls glucose metabolism; that two genetic “fasting” switches (CRTC2 and FOXO1), are needed to turn on glucose-making genes during fasting; and how a glucagon hormone (GLP-1) turns on a series of switches inside the pancreas that increases production of insulin.

Evans’s lab studies many different aspects of metabolism, including the way muscles use glucose and how that process can be reprogrammed. One of his seminal discoveries was a “superfamily” of at least 50 different cell receptors that regulates the absorption, storage and burning of fat.
Some of these receptors also control metabolism of sugar, salt and the amount of calcium stored in bones. He has also found a new hormone that appears to trigger the formation and expansion of fat cells.

It was Shaw's arrival at Salk in 2006 that sparked a focused collaboration between the three different labs, resulting in a transformative discovery in 2011—the precise sequences of switches that turn on the liver's production of glucose when blood sugar levels drop. The hope is that this finding may result in an exquisitely sensitive drug that lowers glucose in diabetes, which would reduce the need for replacement insulin in patients.

**The glue linking the labs**

Shaw came to Salk from Harvard Medical School, where, as a postdoctoral researcher, he found how a pathway involved in cellular hunger links diabetes and cancer. This circuit tells cells to slow down and stop dividing when food, in the form of glucose, is scarce. The finding helped explain why people with type 2 diabetes have an elevated risk of certain forms of cancer and also provided insights into how popular diabetes drugs work.

The day he realized that an enzyme (LKB1), which was important in cancer, acted on a key metabolism protein (AMPK), Shaw says he knew the discovery was going to set the course of his career.

“AMPK was well studied, and it was known to be a central regulator of glucose metabolism,” he says. “But no one knew it had any role in cancer.”

Montminy and Evans, too, were well aware of AMPK. The protein acts as a hunger sensor.
Confocal microscope image of a pancreatic islet. Cell nuclei are labeled in blue, insulin-producing beta cells in red and glucagon-producing alpha cells in green.

Image courtesy of Sam Van de Velde, Montminy lab and taken in the Waitt Advanced Biophotonics Center Core Facility.
Stem cell–based therapies and thus is an important regulator of glucose in muscle, liver and the pancreas. When food (glucose) gets scarce, AMPK pushes the cell into a low-energy state, and Shaw found that LKB1 was the molecule that flipped on the AMPK switch. Shaw showed that LKB1 is often mutated in cancer, meaning that cancer cells can continue to grow even in a low-energy state. He then found that the most popular diabetes drug in the world, metformin, works by controlling blood glucose levels via LKB1.

But it was unknown exactly how AMPK regulates metabolism—or, in other words, no one knew the precise sequences of switches that controlled the system. Shaw became familiar with Evans’s work in the metabolism of muscle and how the tissue that stores glucose is reprogrammed during exercise. He also studied Montminy’s research into central switches that control glucose production in the liver.

“And it turns out that the thing in common between their different kinds of switches, the thing that controls Marc’s switches and separately but directly controls Ron’s switches, is actually the LKB/AMPK pathway that I had been studying,” Shaw says. “That was not known, and it was unexpected. It totally makes sense now that we have worked out much of the details over the past five years.”

Shaw says the pathway’s role is to normalize the production and use of glucose and lipids in the cell, which impacts both cell growth and hormones like insulin that are released from the pancreas based on the level of glucose present in the blood. “If you eat too much sugar, it’s basically trying to deal with that problem,” he says. “It’s saying, ‘No, no, no, you took in too much sugar, so we have to deal with it—get rid of it this way, store this part of it over there, and then shut off the liver. You don’t need to make your own glucose, because you just ate five hamburgers, so stop making glucose and tell your muscles to take up more glucose because you have too much in your blood.’”

AMPK was the glue that linked the three laboratories, and in 2011, the researchers discovered that a group of enzymes (histone deacetylases, or HDACs) are the molecules that activate the production of glucose in the liver when glucose levels run low or after prolonged periods of fasting or during the night.

The study, published May 13, 2011, in Cell, put all the pieces together. Spearheaded by a Ph.D. student in Shaw’s lab named Maria Mihaylova, but with critical assistance from researchers in both the Montminy and Evans labs, they showed that in liver cells, these HDACs normally stay outside the cell’s nucleus. Strikingly, in response to fasting signals (from glucagon), they move into the nucleus, where they activate glucose synthesis from scratch inside the liver.

They further discovered that AMPK turns off the HDAC enzymes, by transferring them outside the cell nucleus, where they can no longer function.

Evans, who studies the circadian basis of metabolism (use of glucose during the day and fat at night), notes that AMPK controls that clock mechanism. It revs up production of glucose as you wake up, as a Science paper from his lab showed in 2009, with assistance from Shaw’s lab. Evans’s lab also found that a small molecule that activates AMPK can promote endurance in inactive mice by reprogramming metabolism genes in their skeletal muscle—the so-called “exercise pill.”

The new HDAC findings offer another connection with cancer research. Oncologists are currently testing HDAC inhibitors as anticancer therapies. The exact mechanism by which these agents block cancer is unknown, but two different HDAC inhibitors have already been approved for treating a form of lymphoma.

Shaw is excited about testing how effective an inhibitor targeting the specific subclass of HDAC they found might be in shutting off glucose production in the liver. “These drugs all go to the liver first, so that is a big advantage because that is where we want them to function,” he says. “And if an HDAC inhibitor with the correct specificity could cut off glucose production at the source in the liver, diabetic patients would not need as much insulin as they do now because there would already be much less sugar in the blood.”

The researchers recently talked about their research with hundreds of interested listeners—including many from San Diego and the surrounding region—at a Salk Exchange event on diabetes, held at Salk last September (see page 10). “We were able to air these new findings and have a discussion with the audience,” Shaw says. “It was fantastic because the level of interest in the community is so high. Everyone knows what is at stake, and they want to know what can be done, both personally and for society.”

"It totally makes sense now that we have worked out much of the details over the past five years."

- REUBEN SHAW
THE SUBJECT WAS DIABETES AT THE INSTITUTE’S FIRST-EVER SALK EXCHANGE, a panel discussion and forum for the general public held on September 13. More than 200 neighbors and friends of Salk were on hand as faculty members Marc Montminy, Ron Evans, Satchidananda Panda and Reuben Shaw joined Salk president William Brody and UC San Diego professor Daniel Einhorn for the program titled, “Dissecting Diabetes: What New Findings from the Lab Can Mean for You.” Event underwriting was generously provided by the L. and M. Rosenthal/Leo S. Guthman Fund and the Greenway family.

WEBEXTRA

www.salk.edu/diabetes/
Tamara Kinsella (a family friend), wife Betty and Wylie at his beloved vacation home in Hana.

Remembering
Wylie Vale

Scientist, Pioneer, Leader, Friend

WYLIE VALE, A SALK INSTITUTE PROFESSOR AND WORLD-RENOVED expert on brain hormones, died January 3 while on vacation in Hana, Hawaii. He was 70 years old.

Vale, head of the Clayton Foundation Laboratories for Peptide Biology and holder of the Helen McLoraine Chair in Molecular Neurobiology at the Salk, was highly regarded as the global authority on peptide hormones and growth factors that provide communication between the brain and endocrine system. During his distinguished scientific career, Vale discovered a number of hormones and growth factors that provide a molecular link between the brain, endocrine and immune systems. These hormones are now recognized as key regulators of the stress response and as modulators of appetite, metabolism, growth, reproduction and cardiac function. Vale's research helped identify new avenues for the diagnosis and treatment of endocrine as well as behavioral disorders, including anxiety, depression and anorexia. Building on his seminal research, Vale cofounded two biotech companies, Neurocrine Biosciences and Acceleron Pharma. He was a member of the boards of directors for both companies.

“We have lost one of our distinguished leaders and brightest minds,” said William R. Brody, Salk president. “Wylie was a pioneer in science and was loved and revered worldwide. He was a friend and a leader, and he helped make the Salk what it is today. He will be deeply missed by all.”

Vale was born in Houston, Texas, on July 3, 1941. He earned his B.A. in biology from Rice University and his Ph.D. in physiology and biochemistry from Baylor College of Medicine. He would later work with Roger Guillemin, Nobel laureate and Salk scientist, before joining the Salk in 1970, where he spent 41 years conducting groundbreaking research.

“First I was the teacher, and later we were colleagues,” said Guillemin. “I have much respect for what Wylie accomplished in his life. He was a brilliant man, a wonderful exchanger of ideas. His legacy impacts us all, and I will deeply miss him.”

Vale received his appointment as professor at the Institute in 1980. Since then, he discovered more than a dozen novel peptide hormones and receptors, coauthored more than 600 peer-reviewed papers and was among the most-cited scientific authors of the past several decades. He was also an adjunct professor of medicine at the University of California, San Diego.
“Wylie was a pioneer in science and was loved and revered worldwide.”

— WILLIAM R. BRODY

“I learned a lot about life from Wylie,” said Ron Evans, professor in Salk’s Gene Expression Lab. “He had great insight and great humanity; he was a great scientist. He brought a lot to the field of endocrinology and was one of the giants of the field.”

In 1981, Vale and his colleagues became the first to characterize the peptide known as corticotropin releasing factor (CRF). They demonstrated that the production of CRF by certain cells in the brain triggered many of the body’s hormonal, immune and behavioral responses to stressful situations. Vale’s work revealed that an unusually high production of CRF is associated with several disorders, including anxiety, drug abuse, depression and anorexia.

In 2004, Vale and his colleagues at UC San Diego established the firmest link between a family of hormones that helps the body adapt to stress and possible new treatments for congestive heart failure. Vale discovered that the hormone urocortin-2 has a positive impact on heart function, and the hormone was shown to significantly enhance heart muscle contractions.

“Wylie was a brilliant scientist, witty, always optimistic, full of life and one of the wisest faculty colleagues,” said Inder Verma, a professor in Salk’s Laboratory of Genetics. “I will miss his constant bantering and self-deprecating humor more than I can imagine.”

Vale’s accomplishments have been widely recognized by the scientific community. He was elected to membership in several prestigious organizations, including the National Academy of Sciences, the American Academy of Arts and Sciences and the Institute of Medicine. He served as a past president of the Endocrine Society and the International Society of Endocrinology.

Vale also received a number of awards, including the Edwin B. Astwood Lectureship Award, the Frederick J. Koch Award from the Endocrine Society, the Clinical Lectureship Award (British Royal Society of Medicine), the Fourth Yrjo Reenpaa Lecture Award from the Finnish Cultural Foundation, the H.B. van Dyke Award, Fondation IPSEN Prize in Endocrine Communication, the Henry Dale Medal presented by the British Society for Endocrinology and the Rolf Luft Award from the Karolinska Institute.

“I think Wylie represented something that we all strive for, but probably didn’t know we should be striving for it until we saw Wylie exhibit it,” said Fred Gage, professor in Salk’s Laboratory of Genetics. “Wylie was able to balance his brilliant scientific career with a wonderful family.”

“I always felt like I could be who I was naturally around Wylie,” said Marc Montminy, professor in Salk’s Clayton Foundation Laboratories for Peptide Biology. “Perhaps that was the biggest part of who Wylie was, and I’ll miss him for that.”

Vale passed away in his sleep. He is survived by his wife, Betty, their daughters, Elizabeth and Susannah, and his granddaughter, Celeste.
We will miss you Wylie.
Martin Hetzer doesn’t look like a scientist. The professor in the Salk Institute’s Molecular and Cell Biology Laboratory and holder of the Jesse and Caryl Philips Foundation Chair is 6’ 5” tall and more closely resembles a power forward for Austria’s national basketball team. Fortunately for the Salk, he hung up his high-tops and contributed his talents to science. He finds purpose in research, his family and mentoring future scientists.

As the new director of the Salk’s Waitt Advanced Biophotonics Center, Hetzer brings a unique eye into unraveling the mysteries of aging and diseases such as Alzheimer’s and Parkinson’s. A thoughtful leader, who had many influential people in his life steering him into a science career, he is now paving the way for others, including his son.

How will your research lead to a better understanding of aging?

Proteins are essential building blocks of our cells. As proteins age, they are more likely to encounter molecular damage. To combat the functional decline of proteins, cells use the process of protein turnover, by which potentially impaired polypeptides are constantly replaced with new functional copies. Consequently, a protein with a slow or no rate of turnover is at great risk of accumulating damage over extended periods of time. We have recently discovered that the components of essential multiprotein channels do not turn over and are extremely long-lived in the brain. The lack of a replacement mechanism of this class of proteins leads to a deterioration of their function over time that is ultimately associated with a loss of cell function. Strikingly, similar defects have been linked to various neurological disorders, including Parkinson’s and Alzheimer’s diseases, raising the possibility that our findings might form the basis for the development of therapeutic interventions.

Nearly 6 million Americans are afflicted with Alzheimer’s, and aging is the greatest risk factor. How important is it that we understand how the brain ages?

The projected cost for treating Alzheimer’s disease over the next 20 years in the U.S. is $1.6 trillion. It is completely unsustainable, and we will not be able to care for those affected by Alzheimer’s. As our aging population continues to grow, it is critical that we discover solutions for treating this disease.

We are trying to understand the causes of neuronal aging and hope that our results ultimately will help us to delay the onset of Alzheimer’s. When it comes to health care costs, the most expensive period in one’s life span is typically the last three years. If we can delay the onset and progression by just a few percentage points, we will have made a significant impact by improving the lives of many people and lowering the costs of health care.

How will technology from the Waitt Advanced Biophotonics Center help scientists with their research?

Advanced imaging is probably one of the central technologies that will be influential and continue to be at the forefront of science in the next several decades. The center has had a major impact on the vast majority of the faculty at the Salk. In addition to the technology, we have been fortunate to assemble a strong team with great leadership. The team has pushed the envelope and has transformed the way we look at science.
The challenge today is that technology is changing at a rapid pace. Twenty years ago when you were an assistant professor, you could buy a microscope for $50,000 and use it for your entire career. Now when you buy a microscope, it’s probably good for five years and will cost anywhere from $500,000 to $700,000. We need to work on an endowment in the center that will allow us to acquire new technology as it comes along, and continue to train staff to perform sophisticated analysis with microscopy.

What do you hope your lasting contribution will be in the field of science?

When I look back on my career, it is my hope that I will have made significant scientific contributions in the field of molecular and cell biology. As a scientist, a son, a husband and father, it is a personal mission that I strive for. I also take great pride and cherish the opportunity to train the next generation of scientists. It is extremely gratifying to help young scientists grow in their profession and watch them move on to start their own labs and make important discoveries.
“It is extremely gratifying to help young scientists grow in their profession...”

—MARTIN HETZER
I consider mentoring a way of life. I am building a rich network of colleagues who will hopefully go on to make major contributions to science and pass the torch of mentorship to future scientists.

My postdoc advisor opened my eyes to science and taught me early in my career to enjoy science and be generous with your knowledge.

You have an eight-year-old son, Moritz. What are some life lessons you want him to learn from you and your wife?
Some life lessons I hope Moritz will embrace are the ability to remain curious about the world and deeply enjoy whatever he chooses to do in life. I hope that he will find purpose in his work, as I have. I want him to ask a lot of questions and not take answers for granted.

What kind of world do you hope to leave for him?
My wife, Claudia, and I would like to create a world that is both nurturing and intellectually stimulating for Moritz. I’d like my son to see a world that is not only focused on the bottom line and materialism. I want him to see the joy and passion in life and spend as much time as possible with people he cares about.

What lessons have you learned from your son?
The biggest lesson I have learned from Moritz is to enjoy the moment and to spend as much time as possible with family and friends. He also taught me to be more patient, and I am still learning. When he’s caught up in his magical world, it reminds me that the same life lessons I am trying to instill in him. Moritz is actually showing me that I need to pause and rediscover the passion in everything that I do.

What would people be most surprised to know about you?
Most people don’t know about my passion for hunting....Just kidding. I think that many people see me as this rather organized and serious Austrian with little or no sense of humor. Although it is true that I am quite focused, I really enjoy laughing my head off, and one of the great perks that come with being a father is that you get a license to be silly. At home we have a bedtime routine that involves me performing some slapstick, like running into doors and falling down stairs. Oh, and then there is our Friday evening family tradition of listening to loud music and dancing till the neighbors come and tell us to turn it down.

How did you first become interested in science?
As a teenager I wanted to become a journalist or a philosopher or a rock star (our band for very good reason only had a handful of gigs). I also read a lot about explorers and scientists. My grandmother would tell me that I should go into science, and that stuck with me. I had many interests, though. I was curious about philosophy, journalism and even went to medical school and was enrolled in an MD/Ph.D. program. I soon realized that I had a strong passion for research.

What would you do if you weren’t a scientist?
I would have been a filmmaker. I like the technical aspect of making a movie. It’s more than the story. I imagine that there are some parallels to running a lab. As a movie director, you have to recruit a strong cast, secure financing, convince people to support the project and develop a marketing plan. It is a very creative process.
Three top scientists join Salk faculty

THE SALK INSTITUTE WELCOMES THREE NEW ASSISTANT professors who epitomize the next generation of outstanding scientists. “The hiring of these exceptionally talented scientists will strengthen the Salk’s efforts in conducting the most innovative research possible,” says Salk president William R. Brody. “The Institute’s ability to recruit them is a testament to the quality of the science conducted here. The new investigators recognize the benefits of our uniquely interactive environment for discovery.”

Hu Cang joins the Salk as assistant professor in the Waitt Advanced Biophotonics Center. Cang received his B.S. in chemical physics and obtained his Ph.D. from Stanford University, working with Michael D. Fayer developing novel ultrafast optical spectroscopy. Currently he is a postdoctoral scientist working with Xiang Zhang on biophotonics at the Lawrence Berkeley National Laboratory. He has developed nanophotonic contrast enhancement agents for optical coherence tomography; this work is now exploited for cancer imaging. Cang also developed the first microscope to track single nanoparticles inside a cell.

Cang’s future research plans include the development of new photonics tools to manipulate light at the nanoscale for bioimaging. His goal is to build miniature devices to measure protein conformational dynamics. He also plans to detect single fluorescent molecules in live mammalian cells.

His appointment offers an outstanding opportunity to build new bridges to the bioengineering department at UC San Diego and to attract students and postdocs with backgrounds in physics, engineering and mathematics.

“The hiring of these exceptionally talented scientists will strengthen the Salk’s efforts in conducting the most innovative research possible.” – WILLIAM R. BRODY
Xin Jin was hired as assistant professor in the Molecular Neurobiology Laboratory and the Crick-Jacobs Center for Theoretical and Computational Biology. Jin received his undergraduate and graduate education in China, first training in physics as an undergraduate and then in systems neuroscience for his Ph.D. Since 2007, he has served as a postdoctoral fellow at the National Institutes of Health, where he worked with Rui Costa on circuits in the basal ganglia that are involved in planning and executing motor movements. In this relatively short postdoctoral training period, he has emerged as a rising star, not only in this field, but generally in the field of circuits and behavior.

Jin will help to strengthen the interface between molecular and systems neuroscience. He is the first author on a Nature article and more recently has had a second first author paper under revision for publication in Nature. He was awarded the 2011 Gruber Prize for the best young neuroscientist by the Society for Neuroscience.

Nicola Allen will join Jin as an assistant professor in the Molecular Neurobiology Laboratory and the Crick-Jacobs Center for Computational and Theoretical Biology. Currently a postdoctoral fellow at Stanford University in the Department of Neurobiology, Allen received her undergraduate degree from the University of Manchester and her Ph.D. from University College London in England. During her thesis work, she trained with David Attwell, examining various aspects of central nervous system dysfunction during ischemia. For her postdoctoral work, she moved to the laboratory of Ben Barres at Stanford, where she initiated studies of astrocyte-derived factors that modulate synapse formation.

Allen is an expert biochemist adept in proteomic analysis to isolate and identify factors produced by astrocytes that could potentially modulate synaptic formation and efficacy. This work, along with collaborations with other members of the Barres laboratory, has generated a number of high-profile papers in both Nature and Cell. Her own research lies at the interface of molecular and systems neurobiology, addressing an important but poorly understood aspect of brain development and function: how astrocytes contribute to the formation, maturation and stabilization of synaptic contacts. Combining strengths in physiology and biochemistry, she has a unique tool set for investigating how glia impact synaptic function. Her goal—to understand the mechanisms by which neural networks are formed during development and regulated during health and disease—complements existing neurobiological research taking place at the Salk.
Salk scientists receive significant philanthropic support with four distinguished chair appointments

PATRONS, FRIENDS AND COLLEAGUES GATHERED TO CELEBRATE at the Salk Institute for the Board of Trustees Dinner and Endowed Chair Recognition Ceremony held on November 17. Salk scientists Tom Albright, Sam Pfaff and Martin Hetzer were selected as inaugural holders of the new chairs created through the Joan Klein Jacobs and Irwin Mark Jacobs Senior Scientist Endowed Chair Challenge, and Dennis O’Leary was named the holder of the Vincent J. Coates Chair in Molecular Neurobiology.

The four faculty members were named the recipients of endowed chairs that these philanthropic leaders established in support of scientific research. The creation of three new chairs and the rededication of the one existing chair is a testament to the strong commitment that private donors have to the mission and vision of the Salk Institute. These endowments will provide crucial resources to support the work of some of the Institute’s leading investigators—research that impacts humanity.

“These chairs, established by our generous donors, provide vital support that sustains the scientists and their laboratories, and they are instrumental in encouraging more seminal research,” said William R. Brody, president of the Salk Institute, in announcing the appointments. “We look forward to continued success from these outstanding individuals as they push the frontiers of basic research.”

In 2008, Irwin Jacobs, chairman of the Salk Board of Trustees, and his wife, Joan, created a $10 million challenge grant to encourage donors to establish ten endowed chairs for senior scientists. For every $2 million that a donor contributes toward an endowed chair at the Institute, Joan and Irwin Jacobs will add $1 million to achieve the $3 million funding level required to fully endow a chair for a Salk senior scientist. Because of the enthusiastic response to the Chair Challenge, the Jacobses committed to add five more chairs to the challenge, for a total of 15. To date, 12 chairs have been established.

Tom Albright, professor and director of the Vision Center Laboratory, was named to the Conrad T. Prebys Chair in Vision Research. Albright is an authority on the neural basis of perception, probing the relationship between the activity of brain cells and the experience of perceiving motion. He found that single neurons in a brain area specialized for processing motion exhibited robust form-cue invariance, a discovery that came as a surprise at the time. Albright also uncovered a specific neuronal process by which visual pictorial recall serves to augment sensory data with “likely” interpretations in order to overcome the ever-present noise, ambiguity and incompleteness of the retinal image.

Sam Pfaff, professor in the Gene Expression Laboratory, was selected as the inaugural holder of the Benjamin H. Lewis Chair. Pfaff’s lab explores how nerve cells are formed and wire up correctly, focusing on the fetal development of the spinal cord. Pfaff is especially interested in determining how motor neurons develop and make connections between the spinal cord and muscles in the body, since these connections are necessary for all body movements. Spinal cord injuries lead to paralysis because motor
neuron function is disrupted, and degenerative diseases such as ALS (Lou Gehrig’s disease), spinal muscle atrophy and post-polio syndrome result from the loss of motor neurons.

Martin Hetzer was named the inaugural holder of the Jesse and Caryl Philips Foundation Chair. A professor in the Molecular and Cell Biology Laboratory, Hetzer uses live cell imaging and biochemistry as well as genetic and computational approaches to study the molecular basis of nuclear assembly and its regulation during cell division. The endowment will support his research to shed light on the nucleus and how the breakdown of its structure is implicated in disease; it will also enable the development of new technologies to investigate aging and neurodegenerative diseases.

Dennis O’Leary, professor in the Molecular Neurobiology Laboratory, was named the holder of the Vincent J. Coates Chair in Molecular Neurobiology, which was established in 2001 to support research in molecular neurobiology aimed at the chemistry of the brain. Coates and his wife, Stella, have been important philanthropists for Salk and provided significant funding to create a mass spectrometry center at the Institute in 2003. O’Leary studies the development and plasticity of the vertebrate nervous system. His research seeks to understand fundamental developmental events and to use this knowledge to make the most efficient therapeutic use of stem cell biology and to design effective strategies to overcome birth defects, neural injury and neurological diseases and disorders.

“These chairs, established by our generous donors, provide vital support that sustains the scientists and their laboratories, and they are instrumental in encouraging more seminal research.”

— WILLIAM R. BRODY

Salk Institute board of trustees elects leader in venture capital

BENJAMIN S. SCHAPIRO, FOUNDER, CHAIRMAN and CEO of QuestMark Partners, a late-stage venture capital fund in Baltimore, Maryland, was named to the Salk board of trustees in November.

Schapiro, who graduated from Randolph-Macon College in 1964 with a degree in economics, began his career in investment banking in 1966 at Robert Garrett & Sons, which merged into Alex Brown and Sons in 1974. During his 32-year tenure, his efforts encompassed institutional, international, and private client accounts, real estate finance, corporate finance, merger and acquisition transactions, as well as public and private investing in emerging growth companies.

Schapiro currently serves as chairman of the board of Lifebridge Health, a regional health care organization based in Baltimore, and on the board of the Deer Valley Music Festival; he has also served as chairman, vice chairman and trustee or board member of a number of endowment funds, charitable organizations and professionally managed portfolios.

www.salk.edu
Salk investigator receives developmental chair

JEFF LONG, ASSISTANT PROFESSOR IN THE Plant Molecular and Cellular Biology Laboratory, was awarded a Hearst Foundation Developmental Chair that will contribute annually to his lab over a period of three years. Long studies embryogenesis in Arabidopsis thaliana, the “lab rat” for plant biologists. His lab focuses on the TOPOLESS gene, so named because of its power to regulate the development of a shoot or a root structure from a seedling. His team has learned how to control the function of this gene, which ultimately can serve to manipulate plant structure and agricultural output.

Ronald M. Evans receives prestigious Wolf Prize

RONALD EVANS, PROFESSOR AND HEAD OF THE Salk Institute’s Gene Expression Laboratory, has been named the recipient of the prestigious 2012 Wolf Prize in Medicine, Israel’s highest award for achievements benefiting mankind. According to the Wolf Prize jury, Evans was selected for his discovery of the gene super-family encoding nuclear receptors and elucidating the mechanism of action of this class of receptors.

Evans, holder of the March of Dimes Chair in Molecular and Developmental Biology, is world renowned for his seminal research into nuclear hormone receptors, which has since led to more than a half-dozen drugs for cancer, diabetes and heart disease. Israel President Shimon Peres will present Evans with the award at a special ceremony at the Knesset, the House of Representatives for the state of Israel, in Jerusalem on May 13.

Evans is only the second Salk scientist to be chosen for the Wolf Prize; Tony Hunter received it in 2005. Wolf Prizes have been awarded since 1978 to outstanding scientists and artists for achievements in the interest of mankind and friendly relations among peoples, irrespective of nationality, race, color, religion, sex or political view." Prizes of $100,000 in each area are given every year in agriculture, chemistry, mathematics, medicine and physics, as well as one prize in the arts. Over a third of the 272 Wolf Prize winners in medicine, physics and chemistry have gone on to receive the Nobel Prize.

The Wolf award honor comes on the heels of another distinguished benchmark in Evans’s list of achievements. In 2010, on behalf of the Aventis Foundation and an elite selection committee, he was named a Rolf Sammet Guest Professor at Goethe University. As a Sammet professor, he spent a week in Frankfurt in 2011, teaching internationally outstanding scientists who make important research contributions in life and natural sciences.

Joanne Chory awarded 2012 Genetics Society of America medal

THE GENETICS SOCIETY OF AMERICA (GSA) HAS honored Joanne Chory, director of the Plant Molecular and Cellular Biology Laboratory and holder of the Howard H. and Maryam R. Newman Chair in Plant Biology, as the recipient of the prestigious 2012 Genetics Society of America Medal.

GSA established the Genetics Society of America Medal in 1981 to recognize mid-career researchers for outstanding contributions to the field of genetics during the previous 15 years of their careers; it is one of five awards given out annually by the organization for “distinguished service in the field of genetics.”

Chory, an expert on how plants regulate their growth, pioneered the analysis of plant responses using genetic approaches in Arabidopsis thaliana to reveal the molecular mechanisms underlying plant development. Her laboratory has led the plant field for 20 years and made major discoveries in how plants detect and respond to changes in their environment, particularly light, which has implications for the growth and development of agricultural crops in challenging environments. She elucidated how plants perceive light; identified how chloroplasts signal to the nucleus; and defined a new pathway for the biosynthesis of the plant hormone auxin. She also discovered a novel steroid hormone in plants, identified the steroid receptor and elegantly dissected the signaling network.

“The Genetics Society of America Medal is a tremendous honor and underscores Joanne’s extraordinary impact and leadership in the field of plant biology,” said Salk president William R. Brody.
Plugged in

THE SALK INSTITUTE IS GETTING CHARGED UP. FOUR ELECTRIC VEHICLE CHARGING STATIONS HAVE been installed in the east parking lot as part of a nationwide U.S. Department of Energy initiative to install 14,000 chargers in 18 major cities. The initiative, known as the EV Project, is funded by a $230 million government grant and is the largest deployment of electric vehicles and charge infrastructure in the nation’s history. What it means at Salk is that owners of either the Chevrolet Volt or the Nissan LEAF will now be able to charge their cars in one of the four stations while they’re at work.
Salk researcher named Damon Runyon Fellow

LORA B. SWEENEY, A POSTDOCTORAL RESEARCHER IN
the laboratory of Christopher Kintner, has been named a
Damon Runyon Fellow.

The Damon Runyon Cancer Research Foundation, a nonprofit
organization focused on supporting innovative early career
researchers, selected Sweeney as one of only 18 recipients last
fall. The prestigious $156,000 award is intended to encourage
the nation’s most promising young investigators to pursue careers
in cancer research by providing them with independent funding to
work on innovative projects.

Sweeney was cosponsored by Kintner, a professor in the
Molecular Neurobiology Laboratory, and Thomas M. Jessell, a Salk
Non-Resident Fellow (NRF) and professor in Columbia University’s
Department of Biochemistry and Molecular Biophysics.

As a NRF, Jessell is part of an elite group of scientists nominated
by the President and faculty who serve as Salk faculty members for
renewable six-year terms, advising the institute on appointments,
promotions and scientific programs. These individuals come from
world-renowned academic organizations where they have achieved
high levels of success in the scientific disciplines investigated
at the Salk Institute. Their expertise helps identify new research
trends, and ensures that the Institute maintains the highest
standards accomplishing world-class science.

Sweeney is using the frog as a model to study how neurons
diversify in the spinal cord as limbs develop and a swimming tad-
pole becomes a hopping frog. Many different types of nerve cells,
each with their own unique characteristics, make up the healthy
nervous system. Understanding how a cell’s fate is specified will
provide the basis for understanding how cancer reprograms a cell.

“I hope that by tracking the same course as evolution—from
swimming to limb-based movement—in a single organism, we
will reveal new principles of neuron identity, organization and
ultimately, function,” says Sweeney. “As one of the first scientists
to work on the metamorphic frog, we are developing a new system.
It is wonderful to have the support of the Damon Runyon Founda-
tion on this pioneering journey.”

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A new era of stem cell research on November 29, with the opening of the Sanford Consortium for Regenerative Medicine in La Jolla. The $127 million, 150,000-square-foot campus will allow researchers from the Salk Institute, Sanford-Burnham Medical Research Institute, the La Jolla Institute for Allergy and Immunology and the University of California, San Diego to collaborate as they learn more about the nature of stem cells and how to use them to treat disease. Resources from the Salk that are now at the consortium building include some researchers from the labs of Fred “Rusty” Gage, Juan Carlos Izpisua Belmonte and the Gene Transfer Targeting Therapeutics Core (formerly known as the Viral Vector Core).

Former trustee passes
TED CRANSTON, A FORMER MEMBER OF THE Salk Institute board of trustees, passed away January 31, at age 72. A vibrant and tireless trustee, Cranston served on the Salk board from 2001-2009 and was a chair of the President’s Club.

As a partner in the law firm DLA Piper, specializing in trusts, Cranston initially got involved with the Salk in the early 1990s, when he was asked to advise the Institute about estate planning. He and his wife, Warrine, worked diligently to secure a strong financial future for Salk.

“We want the Salk and its world-class researchers to have the flexibility to use annual gifts to address the greatest areas of need,” Cranston said in a 2003 interview. “Once you get involved with the Salk and get to know the people and mission, you want others to get involved, to produce closer ties to the community, and generate additional support.”

Beyond his work with the Institute, Cranston was active in the community, serving on the boards of the La Jolla Playhouse, Stanford Law School, San Diego Symphony, Girl Scouts of San Diego, United Cerebral Palsy Foundation of San Diego, and San Diego Center for Children, among others.

Cranston is survived by his wife, Warrine, daughters Julie and Jodi Cranston, four grandchildren, and brother, Hal Cranston.
International Council members meet in City of Light

Patrons gather in Paris to learn about latest Salk research

THE 2011 SALK INTERNATIONAL COUNCIL (IC) ANNUAL MEETING was held October 27–29 in Paris, France. Eighty guests attended, including board and council members and their spouses, faculty and Salk leadership, and special guests.

Ten of the Salk’s most renowned scientists presented on topics related to “The Grand Challenges of Biology.” Attendees also enjoyed a dinner cruise on the Seine aboard a 170-foot yacht, the Excellence. In addition, board member Madame Corinne Mentzelopoulos generously hosted an elegant dinner at the Louvre, with a tour of the exhibition “In the Kingdom of Alexander the Great—Ancient Macedonia,” as well as a memorable dinner and tasting at her winery, Chateau Margaux.

Board liaison to the council, Mary Jane Salk, led the business meeting, during which IC members were asked to contribute to a giving opportunity specifically for the council—a $1 million endowment to establish the Jonas Salk Endowed Fellowship, which will support a postdoctoral fellowship in perpetuity and will be the first fund at the Institute named for Jonas Salk.


“...We are indebted to Corinne Mentzelopoulos for providing this unique opportunity and extraordinary venue for our International Council, Trustees and Faculty to come together and celebrate Salk science.” – MARSHA CHANDLER

Salk Board Chair, Irwin Jacobs, presenting Trustee Corrine Mentzelopoulos, host of the International Council gala dinner at the Louvre, with a thank you gift.
Third Breathing and Sleep meeting held at the Salk

MORE THAN 125 GUESTS, SOME FROM as far away as New York, attended the third annual Breathing and Sleep Symposium, held at the Salk Institute on October 29. The free symposium seeks to define neuromuscular breathing basics and empower people with post-polio syndrome (PPS) or similar motor neuron and neuromuscular disease issues to better participate in their own care.

The half-day event featured guest speakers, medical experts, nurses, therapists and vendors, who shared information and insights with the post-polio and professional care communities about breathing compromise caused by past polio. The meeting also highlighted the continued popularity of Salk’s PolioToday.org website. Launched in August 2009 and featuring a steadily growing list of over 750 members from around the world, the site offers a forum for distributing important polio and post-polio-related information, while creating a crucial link for polio survivors worldwide to connect with one another using modern social networking capabilities. It also features video testimonials from polio survivors who share recollections about their personal battles with polio when they were young, their more recent diagnosis and management of PPS and how they are coping with their condition.

To become a member, join the site on PolioToday.org or on facebook.com/poliotoday.

To share a story, go to PolioToday.org and click on the Tell Your Story link for instructions and guidelines. You can also write your polio story and send it via e-mail to: poliotoday@salk.edu

BLOOMINGDALE’S AND THE SALK INSTITUTE TEAMED UP OCTOBER 20, to raise awareness for breast cancer. At the store’s first annual Ready, Set, Pink! event at the Fashion Valley Mall in San Diego, Salk scientists Geoffrey Wahl and Dannielle Engle presented their latest findings in breast cancer research. Staff from the Salk interacted with shoppers and guests, sharing the Institute’s story and ways the community could help support breast cancer research. Bloomingdale’s selected Salk as the only research institution in San Diego to benefit from the proceeds raised from Ready, Set, Pink!'
The next generation:

Luciano DiTacchio

A young scientist combines doggedness with teamwork
The scientists at Salk are some of the best in the world, and the work is demanding. I was intimidated at first, and I still never feel like I know enough. There were times I wanted to quit—but I hung in there.” — Luciano DiTacchio

Luciano DiTacchio is scouring the Internet for images of the room where he will soon interview for a position as a junior professor at a top university in the Midwest.

“I want to see the layout of the interview room so I can plan my presentation—there’s bound to be a photo or video posted somewhere,” says DiTacchio, seated in a meeting room at the Salk Institute, where, now at the end of a postdoctoral fellowship, he’s holed up to plan for his coming interview.

If luck indeed favors the prepared, DiTacchio will have no problem finding a faculty position—the next career move for many junior researchers. Among his colleagues and family, he is known as much for his intense curiosity and diligence as for his congenial nature.

DiTacchio’s colleagues tell of finding him in the laboratory late at night, testing ideas that came to him at home in the evening and that he continued to work on at the laboratory bench despite chronic back pain from a serious car accident in 2006.

Already he has coauthored over a dozen papers with his colleagues in the laboratory of Satchidananda Panda, an associate professor in Salk’s Regulatory Biology Laboratory, where DiTacchio has worked for the past six years. Most recently, he was the lead author on a paper reporting the discovery of the gene that wakes us every morning by revving up our metabolism, published in the influential journal Science.

“I think he’s the hardest working man I know,” says Kacee DiTacchio, his wife and fellow scientist, whom he met at Salk while she was working on her doctorate at the University of California, San Diego. “He does not give up. If something goes wrong with an experiment, he’s not going to start it again the next day or the next week, he starts it the next minute.”

When he was young, DiTacchio’s mother and father sold timeshares in the Mexican resort city of Puerto Vallarta for a living. But DiTacchio had no interest in going into sales. In high school he played guitar and sang in a band that played music ranging from the Beatles to Metallica and later considered studying music in college. But he also had an interest in and aptitude for science and decided instead to study microbiology at the University of Texas at El Paso. He went on to earn his doctorate in molecular biology in 2003 from Mayo Graduate School.

DiTacchio attributes his hard-driving nature in part to growing up in a developing country where limited opportunity and family difficulties, including his father’s death when DiTacchio was 19, required him to work hard to accomplish his goals.

“I learned early on that you’ve got to fight for what you want and stick with it like a pitbull,” he says.

That intensity, combined with his solid linebacker’s build and shaved head, can lend DiTacchio an intimidating air. In conversation, however, he smiles easily and talks freely about a broad range of topics, from agricultural sustainability, an interest he shares with his wife, to beer...
brewing, a recent hobby that he finds well suited to the scientific mind because “lots of measuring is involved.”

He is also an adoring father to his stepdaughter, Kayla, and 16-month-old son, Sydney, who, according to Kacee DiTacchio, matches his father’s intensity. “I think he passed that gene on,” she said.

Panda, DiTacchio’s mentor at Salk, was often surprised by how broadly DiTacchio read the scientific literature and the depth of his knowledge about different laboratory techniques. “He is a walking search engine,” Panda says. “If something goes wrong in the lab or somebody is having difficulty with a certain concept or technique, the first impulse is usually to find Luciano because he’ll know how to fix it.”

Panda also attributes DiTacchio’s success to his willingness to help other researchers and his curiosity about nearly any scientific problem. For a recent study led by one of his colleagues, DiTacchio made over 20,000 measurements over Veteran’s Day weekend, making it possible to submit the manuscript for publication in an influential scientific journal.

“There are two types of scientists,” says Panda. “Some try to solve all the problems by themselves, but they don’t get very far. Others work with their colleagues to solve problems, sometimes leading, sometimes supporting. Luciano is the second kind, and that’s why he’s been successful in making discoveries and prodding others in the right direction.”

As for DiTacchio, he attributes much of his own success to working with researchers at the Salk Institute, who, he says, made him a much better scientist. “The scientists at Salk are some of the best in the world, and the work is demanding,” he says. “I was intimidated at first, and I still never feel like I know enough. There were times I wanted to quit—but I hung in there.”

“"He is a walking search engine. If something goes wrong in the lab or somebody is having difficulty with a certain concept or technique, the first impulse is usually to find Luciano because he’ll know how to fix it."”

– SATCHIDANANDA PANDA
Salk Movember

MOVEMBER ENCOURAGES MEN TO GROW MUSTACHES AND BECOME WALKING, talking billboards for the 30 days of November. Through their actions and words they raise awareness by prompting private and public conversation around the often ignored issue of men’s health. The movement, which started in Australia, has raised $174-million since 2004. Salk’s own Team Telomere, led by Daniel Lackner raised over $3000.00 for the cause.

Back row standing, from left to right: Shigeki Miyake-stoner, Christopher Kohler, Dan Egan, Tony Cesare, Roddy O’Sullivan, Arkaitz Ibarra, Rafael Demarco, Laure Crabbe, Makoto Hayashi, Liana Oganesian, Pau Francesc Pascual-Garcia, Sebastian Gomez, Pedro Resende, Sofia Aligianni, Horng Ou, Dan Gibbs

Front row, from left to right: Govind Shah, Michal Krawczyk, Teresa Rivera Garcia, Mariano Loza-Coll, Daniel Lackner, Jonathan Goodwin, Filipe Jacinto
RESPIRATORY DISTRESS SYNDROME (RDS) AFFECTS ABOUT 1 percent of infants born in the United States and is the leading cause of death among premature babies. It occurs because the infants' lungs are not yet fully developed at birth and lack a slippery substance called surfactant, which is crucial for the newborn lung to inflate with air. To encourage the lungs to develop faster, doctors treat many expecting mothers and premature infants with anti-inflammatory glucocorticoids, steroid drugs that speed maturation of surfactant-producing cells, known as type 2 pneumocytes.

In some cases, however, infants fail to respond to the steroid treatment and die from the respiratory syndrome, which suggests that some other biological mechanism might be at work. To explain this, researchers in the lab of Ronald Evans turned their attention to another type of cell lining the lungs, type 1 pneumocytes, ultra-thin flat cells that allow air exchange between the bloodstream and the lung's interior. They developed a strain of mice in which they disrupted the ability of type 1 pneumocytes to respond normally to thyroid hormone, which prevented the cells from maturing.

Unlike type 2 pneumocytes, which mature rapidly in infants given steroid hormones, the type 1 cells failed to respond to steroid treatment, and the mice died due to their lungs' inability to function. However, mice treated with the medications propylthiouracil or methimazole, normally given to people with thyroid disease, recovered from the disorder, and their type 1 cells matured normally.

“This might explain why some infants don’t respond to steroid treatment, which only targets the type 2 pneumocytes,” Evans says. “There may be an entirely different underlying problem than what the doctor is treating.”

The genetic makeup of mice and humans is very similar, so the researchers are optimistic that their findings, which were published in *Nature Medicine*, will eventually lead to new treatments for infants with RDS. “These mechanisms could also play a role in healing lung tissues,” says Liming Pei, a postdoctoral research associate who led the project. “They might help older children and adults who have suffered lung damage from flu, asthma, emphysema or other types of respiratory disorders.”
Sickle cell disease is one of the most prevalent devastating genetic disorders in the world. It is caused by genetic mutations in the HBB gene, whose normal function is to make hemoglobin, the iron-containing protein that allows red blood cells to carry oxygen. The sickle cell mutation in hemoglobin causes red blood cells to become rigid and sticky and deform to a sickle-like shape. The disorders can be cured by stem cell or bone marrow transplantation, but the scarcity of compatible donors and the high risk of immunorejection prevent most patients from benefiting from these therapies.

Researchers in the lab of Juan Carlos Izpisua Belmonte set out to devise a safe method using induced pluripotent stem cells (iPSCs) to correct the HBB gene in patients who have defective copies of it. Traditional iPSC generation and gene therapy techniques have proven to be potentially unsafe, according to the researchers. Many have used viruses that insert themselves into the human genome to convert adult cells to stem cells and to deliver a normal HBB gene to repair hematopoietic stem cells—stem cells that give rise to all blood cells. But when these repaired stem cells are returned to patients, they may include unwanted mutations introduced by the viruses that are inserted in the genome. In the most severe cases, these mutations may lead to cancer formation.

To fix the mutation so that it did not leave any unwanted traces in a patient’s genome, the researchers used a two-step approach, first creating iPSCs using a technique that avoids the use of viruses, then using a modified adenovirus (common cold virus) that, unlike viruses used in other methods, neither replicates itself in the body, nor expresses viral genes. The engineered adenovirus contains a normal HBB gene. Once inside the iPSCs, the modified adenovirus performs a precise swap between the normal HBB gene it carries and the broken gene that was in the patient’s cells.

The correction of the mutant HBB gene, reported in Cell Research, was highly efficient, and the research team conducted multiple tests to ensure that no errant genes were integrated into the genome. By replacing a relatively large region of DNA, the technique allows the scientists to fix many gene mutations at once, which suggests it might provide a way to treat hundreds of HBB-related diseases.
Salk discovery may lead to safer treatments for asthma, allergies and arthritis

GLUCOCORTICOIDS ARE STEROIDS THAT OCCUR naturally in the body and help control the amount of sugar in a person’s blood. They also play a role in regulating inflammation and are used as anti-inflammatory drugs for diseases caused by an overactive immune system, such as allergies, asthma and rheumatoid arthritis. And they are used to treat inflammation in cancer patients. Because of their role in sugar metabolism, however, they can disrupt a person’s normal metabolism, resulting in dangerous side effects, including excessive blood sugar levels, insulin resistance and diabetic complications.

Now researchers in the lab of Ronald Evans may have found a way around these side effects. In a study published in Nature, the team reported that proteins controlling the body’s biological clock, known as cryptochromes, also interact with metabolic switches that are targeted by certain anti-inflammatory drugs.

“We knew that our sleep and wake cycle are tied to when our bodies process nutrients, but how this happened at the genetic and molecular level was a complete mystery,” says Evans. “The link we’ve found between our biological clock and metabolism serves as a model for how other cellular processes communicate with each other and could hold promise for better therapies.”

Cryptochromes were previously known for their function in the biological clock, serving to slow its activity and signal our biological systems to wind down each evening. With the morning sun, they stop inhibiting the clock’s activity, helping our physiology ramp up for daytime activities. In their study, Evans and his colleagues made the surprising discovery that beyond the “clock,” cryptochromes also interact with glucocorticoid receptors that help to mobilize sugar production in the body. The finding suggests that side effects of current drugs might be avoided by considering patients’ biological rhythms when administering drugs, or by developing new drugs that target the cryptochromes.

It could have important implications for treatment of autoimmune diseases and cancer, enabling doctors to better time administration of glucocorticoid drugs. It also raises the possibility of developing new anti-inflammatory drugs that avoid some side effects altogether by targeting cryptochromes instead of the glucocorticoid switches. More broadly, Evans says, the study may help explain the connection between sleep and nutrient metabolism in our bodies, including why people with jobs requiring night work or erratic hours are at higher risk for obesity and diabetes.
Scientists identify gene crucial to normal development of lungs and brain

MOST CELLS IN OUR BODY PROJECT A single, nonmoving cilium—a tiny hairlike structure—used as a minute antenna for detecting chemical and physical stimuli. But certain specialized tissues require cells with 100 to 200 moving cilia that beat in concert to move fluids through the body. These cells aid in pushing cerebrospinal fluid through the brain and spinal cord, helping to circulate and replenish this fluid. In the respiratory system, the cilia push mucus that traps dust, pathogens and other foreign matter from the lung up into the trachea, helping to prevent infections.

In research reported in Nature Cell Biology, a team in the lab of Christopher R. Kintner has identified a gene that tells cells to develop multiple cilia. In a previous study, Kintner and his group identified a protein, FoxJ1, that promoted the formation of a single moving cilium. What remained unclear was how certain cells activate FoxJ1 in a way that leads to the formation of hundreds of motile cilia per cell. In their new study, Kintner and his collaborators worked with mice and African clawed frogs to identify a gene that produces a second protein, which they dubbed “multicilin,” that tells cells to develop multiple cilia. When cells are exposed to multicilin, their genetic mechanisms for developing multiple cilia are activated. In a developing embryo, the protein instructs certain stem cells that will line the lungs, kidney and skin to develop into multiciliate cells.

Kintner notes that patients with respiratory diseases such as chronic asthma, emphysema and cystic fibrosis often suffer from lung infections, which may result from damage to the ciliated cells that move protective mucus out of the airways. In the future, stem cell therapies might replace those damaged cells with new ciliated cells, but first scientists need to know how to guide stem cells along a pathway into multiciliate cells.

“Our findings suggest that multicilin could be central to differentiating stem cells into replacement cells,” Kintner says. “It’s a necessary step in developing therapies.”
Salk scientists map the frontiers of vision

TO UNDERSTAND THE EXTRAORDINARILY COMPLEX COMPUTATIONS of the human brain, scientists have mostly relied on studies of primates, our closest relatives in the animal kingdom. Powerful new scientific tools are now emerging, that could allow scientists to complement primate studies by studying the relatively simpler brains of mice.

In a study published in *Neuron*, a team led by Edward Callaway produced for the first time neuron-by-neuron maps of the regions of the mouse brain that process different kinds of visual information, laying the groundwork for decoding the circuitry of the brain using cutting-edge genetic research techniques only possible in mice.

Although such genetic engineering techniques in mice offer huge potential, little was known about what areas of the mouse visual cortex were responsible for processing different elements of the visual information. To remedy this, Callaway and his colleagues set out to chart a map of the mouse’s visual processing system. They first mapped the representations of the mouse’s visual field, the area of three-dimensional space visible through its eyes, to identify distinct cortical areas each containing full neuronal “maps” of the visible outside world. They then injected seven of these areas with a calcium-sensitive fluorescent dye that glows when exposed to a certain color of light. The amount of calcium in nerve cells varies depending on the activity level of the neurons, so the scientists could measure the activity of brain cells based on how brightly they glowed. Callaway’s team then displayed different visual stimuli on a television monitor and recorded what stimuli were preferred by neurons in each area. They found that each area has a specialized role in processing visual information, such as the direction objects move in space or distinguishing fine detail.

Ultimately, Callaway says, understanding in detail how the mouse brain works will illuminate the workings of the human mind.

“This gives us new ways to explore the neural underpinnings of consciousness and to identify what goes wrong in neural circuits in the case of diseases such as schizophrenia and autism,” he says.
SCIENTISTS HAVE LONG KNOWN THAT calorie restriction can extend the healthy lifespan of a range of animals. In some studies, animals on restricted diets lived more than twice as long on average as those on unrestricted diets. While little is known about the biological mechanisms underlying this phenomenon, studies have shown that the cells of calorie-restricted animals have greater numbers of energy-generating structures known as mitochondria. In mammals and flies, the PGC-1 gene regulates the number of these cellular power plants, which convert sugars and fats from food into the energy for cellular functions.

The connections between mitochondria and longevity inspired Leanne Jones and her colleagues to investigate what happens when the PGC-1 gene is forced into overdrive. To do this, they used genetic engineering techniques to boost the activity of the fruit fly equivalent of the PGC-1 gene, called dPGC-1. They found that increasing its activity resulted in greater numbers of mitochondria and more energy production in flies—the same phenomenon seen in organisms on calorie-restricted diets. When the activity of the gene was accelerated in stem and progenitor cells of the intestine, which serve to replenish intestinal tissues, these cellular changes produced better health and longer lifespans. The flies lived between 20 and 50 percent longer, depending on the method and extent to which the activity of the gene was altered, and the flies with the modified gene activity were much more active and robust than the control flies.

Part of the reason might be that boosting the fruit fly version of PGC-1 delays the aging of stem cells that replenish the intestinal tissues, keeping the flies’ intestines healthier for longer. The findings, reported in Cell Metabolism, suggest that the fruit fly version of PGC-1 can act as a biological dial for slowing the aging process and might serve as a target for drugs or other therapies to put the brakes on aging and age-related diseases.

In young fruit flies (top), the intestinal tissues are highly organized, as shown by the even distribution of different cell types, each represented by a different color. As flies age, this order breaks down (bottom), caused by unregulated stem cell activity and inability to form cells with specialized functions. The Salk scientists and their collaborators discovered that activating the fruit fly version of the PGC-1 gene delayed this aging process, while simultaneously extending lifespan.

Image courtesy of Salk Institute for Biological Studies

Fruit fly intestine may hold secret to the fountain of youth

Studies have shown that the cells of calorie-restricted animals have greater numbers of energy-generating structures known as mitochondria.
“Alarm clock” gene explains wake-up function of biological clock

Ever wondered why you wake up in the morning, even without an alarm clock? Wonder no more. Researchers in the lab of Satchidananda Panda have identified a new component of the biological clock, a gene responsible for starting the clock from its restful state every morning.

The biological clock ramps up our metabolism early each day, initiating important physiological functions that tell our bodies that it’s time to rise and shine. Discovery of this new gene and the mechanism by which it starts the clock every day may help explain the genetic underpinnings of sleeplessness, aging and chronic illnesses, such as cancer and diabetes, and could eventually lead to new therapies for these illnesses.

In their research, Panda and his colleagues identified JARID1a, a type of enzyme, as the molecular bugle call for cells and organs to get back to work each morning. By studying the genetic mechanisms underlying circadian rhythms in human and mouse cells and in fruit flies, the researchers discovered that JARID1a was required for normal cycling, both at the cellular level and in terms of an organism’s daily behavior.

Now that scientists understand why we wake each day, they can explore the role of JARID1a in sleep disorders and chronic diseases, possibly using it as a target for new drugs.

“So much of what it means to be healthy and youthful comes down to a good night’s sleep,” Panda says. “Now that we have identified JARID1a in activating our daytime cycle, we have a whole new avenue to explore why some people’s circadian rhythms are off and to perhaps find new ways to help them.”

WEBEXTRA
www.salk.edu/insideSalk/panda1/
www.salk.edu/insideSalk/panda2/
Back to Basics

TWICE A YEAR, SALK PRESENTS BACK TO BASICS, A PROGRAM introducing the Institute's science to the general public. Nearly 80 people attended the most recent event, on November 9, where Salk researchers Carol Marchetto and Kristen Brennand gave presentations about their research on autism and schizophrenia using induced pluripotent stem cells. If you have any questions about our Back to Basics programs or would like to attend future events, please contact Cheryl H. Dean, senior director of planned giving, at 858.453.4100 x1228 or cdean@salk.edu. The next Back to Basics talk will take place May 23, at 2 pm, with plant biology as the topic.

» WEBEXTRA
www.salk.edu/insidesalk/backtobasics/
Loyal Donor Luncheon

MORE THAN 60 SUPPORTERS GATHERED AT THE SALK INSTITUTE ON December 1 for the annual Loyal Donor Appreciation Luncheon. The program featured Salk professor John Young, who spoke on “Infectious Disease: Cellular Control of Viral Infections,” as well as Salk president William R. Brody, who talked about rising health care costs and the role of basic research in addressing chronic disease care, one of the primary drivers behind the health care crisis.
Brain Trust: The Gatsby Charitable Foundation

WHAT HAPPENS WHEN THREE FAMOUS names—Salk, Sainsbury and Gatsby—come together? The answer: a significant boost to cutting-edge neuroscience research.

David Sainsbury is the great-grandson of the couple who founded the well-known British supermarket chain that bears his surname. A successful business magnate, Labor peer, former UK Minister of Science and Innovation recently elected Cambridge University Chancellor, Lord Sainsbury of Turville, as he is also known, is equally renowned for his dedication to the arts, science and social causes. In 1967, just four years after graduating from King’s College, Cambridge, he founded the Gatsby Charitable Foundation (named as a wry reference to F. Scott Fitzgerald’s hedonistic hero), whose first grant was a modest £50 to the Liverpool School of Tropical Medicine.

Since then, the foundation has generously supported exciting projects around the world, principally in plant science research, neuroscience research, science and engineering education, economic development in Africa, public policy research and advice and the arts.

In 2010, Dr. Sarah Caddick, a former scientist who serves as Sainsbury’s Senior Advisor in neuroscience, identified one of those projects in California. As part of its goal to invest in research programs around the world in the field of neural circuits and behavior, the Foundation made a $4 million grant to establish the California Circuits Consortium. The consortium, including Salk’s Edward Callaway and John Reynolds, along with research teams from the University of California, San Diego, and Stanford University, was created to study neuronal circuits underlying higher brain function. As with other projects in its portfolio, it will complement the Sainsbury Wellcome Centre for Neural Circuits and Behavior which is currently being built at University College London and will open in 2014.

The grant reflects Sainsbury’s lifelong interest in cognitive neuroscience, which is stronger than ever, he has said, “now that we have the opportunity to bring together the behavioral side of brain science with advances in physiology and molecular biology to start asking how neural circuits really work.”

An enduring interest in neuroscience is something Sainsbury has in common with the Salk Institute, which sponsored the first neuroscience meeting on the Torrey Pines mesa in 1964 and is now one of the world’s most influential centers for neuroscience research.

The Gatsby Foundation grant is extending the Salk Institute’s long tradition of leadership in the field, as well as its scientists’ penchant for collaboration.

“The grant from the Gatsby Charitable Foundation creates a tremendous opportunity to work more closely together than ever before,” says Callaway. “It allows us to capitalize on the unique strengths we have as a team.”

“ "The grant from the Gatsby Charitable Foundation creates a tremendous opportunity to work more closely together than ever before." ”

– EDWARD CALLAWAY
A LEGACY OF GIVING: The H.N. and Frances C. Berger Foundation

VENTURE OUTSIDE THE SALK INSTITUTE’S EAST BUILDING, TO THE EAST END OF THE BRICK COURTYARD, AND YOU’LL FIND THREE WALLS inscribed with the names of especially generous and steadfast donors. Listed among them is the H.N. and Frances C. Berger Foundation, which has landed a place of honor for contributing more than $10 million over the last twenty years.

What the inscription doesn’t reveal, however, is the story behind the foundation’s extraordinary support, for it would be hard to find a donor with farther-reaching impact on the Institute. Through a longstanding relationship that began in 1990 at the Salk’s Annual Tax Seminar for Private Foundations, the Berger Foundation has funded everything from state-of-the-art imaging, infectious disease research and laboratory construction to the work of multiple faculty members and even a meeting center. Most notably, early support from the foundation enabled Inder Verma to establish the Laboratory of Genetics and make huge strides in gene therapy; its contributions for lab renovations were also crucial in attracting Fred Gage, one of the world’s top neuroscientists, to the Institute.

This expansive approach to grantmaking characterizes the foundation, which typically gives to an array of causes, benefiting everything from educational, healthcare and religious organizations to youth, arts, social service and community programs.

The Berger Foundation is the legacy of its namesakes, H.N. and Frances C. Berger, a self-made couple who built a successful Southern California real estate and banking empire. They created the private family foundation in 1961, with a mission to support “established organizations, particularly ones promoting healthcare, social services and education, in a valiant effort to help people help themselves.” Since 1988, when H.N. “Nor” Berger passed away, the foundation has contributed more than $350 million to a wide range of charitable organizations.

Because the Berger Foundation preselects its grant recipients, it is a testament to the caliber of Salk science that it identified the Institute as a potential grantee and has provided support in so many ways for more than two decades.

“Our commitment is to help others attain their goals and demonstrate that success can be achieved by mutual cooperation, clear objectives and steadfast determination,” says president and chief executive officer Ronald Auen. “The H.N. and Frances C. Berger Foundation and the Salk Institute have a valued and productive relationship that exemplifies this philosophy and has ultimately advanced many key areas of science and discovery.”

“It is hard to imagine any other foundation whose support of the Salk Institute has had such a wide-reaching impact on the scientific endeavors of our world-class faculty,” adds William R. Brody, Salk Institute president. “Sustained support from the Berger Foundation continues to make a significant difference in both the quality of science and the Institute’s ability to undertake research in new and cutting-edge areas of biomedical science.”

H. N. and Frances C. Berger Foundation president and CEO Ron Auen with wife, Sherrie-Auen.
THE BOB DYLAN SONG “THE TIMES THEY ARE A-CHANGIN’” COULDN’T BE MORE apropos of our situation at the Salk Institute. In the United States the federal government has historically committed to fund basic science, and certainly the Salk Institute wouldn’t have reached the heights of excellence over the past 50 years without this magnificent support.

Yet it is important to recognize that funding for basic science peaked in the United States in the 1960s, not long after the Salk was founded, at about 1.9 percent of the gross domestic product. In recent years it has declined to approximately 0.7%, less than half that of the peak, and there is no sign of that trend reversing. The decline in funding is a result of pressures on the federal budget from defense spending and entitlements, which winnow down any room left for “discretionary” funding like research and education support.

The success of our nation’s biomedical research organizations has, to some extent, been buffered from the overall decline in basic science funding because patient advocacy groups have been effectively lobbying to increase the National Institutes of Health (NIH) budget. In addition, philanthropic support has become a growing source of crucial support for basic biomedical research.

The days of increasing NIH budgets are probably behind us—in fact, since 2003, the NIH budget has been declining in constant dollars, with the exception of the two-year American Recovery and Reinvestment Act (ARRA) stimulus bill, which pumped extra money into the NIH along with most other sectors of the federal government.

Just before the December holiday break, we learned that Congress has reduced the amount of salary support that faculty can be provided via NIH grants. While we have yet to understand the full impact of this change, it appears that it adds another $1 million per year to the expense budget of the Salk Institute. And I believe that this is just one of many administrative “adjustments” that will be put in place in the near future.

In these “changing times,” the support of our loyal benefactors becomes more and more important to offset the loss of support from the government. NIH support has declined from roughly 75 percent of our research budget to less than 60 percent, with the difference being compensated for by private foundations and donors.

As we begin 2012 with exciting discoveries being uncovered almost daily at the Salk, I want to thank our generous donors for their magnificent support. You have been and will continue to be important partners in discovery.
Salk Calendar

APRIL 2012
18 San Diego Salkexcellerators Lab Tour
26 NY Salkexcellerators

MAY 2012
2 San Diego Salkexcellerators
9 Scientific Update for Professionals
21 3rd Annual Golf Tournament
23 Back to Basics

AUGUST 2012
25 17th Annual Symphony at Salk

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

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©Françoise Gilot
From Yellow to Red, 1978
Oil on canvas, 39 x 32