INSIDE » Waitt Advanced Biophotonics Center Grand Opening » One on One with...Thomas Albright

InsideSalk

Where cures begin.

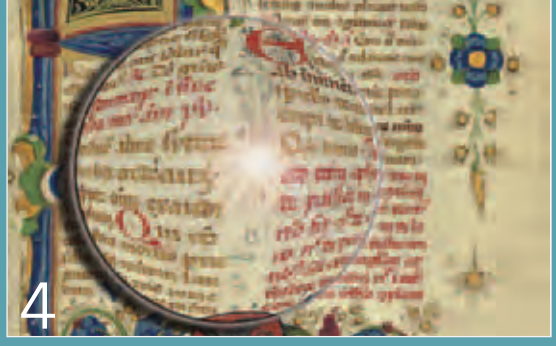
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

05 | 11

Mirror mirror on the wall, who is the fittest of us all? iPSC and ESC epigenomes reveal subtle differences.

ALSO IN THIS ISSUE

May 2011
Inside Salk



Science at the speed of light

One on one with…Thomas Albright

William R. Brody, M.D., Ph.D.
President

Marsha A. Chandler, Ph.D.
Executive Vice President

Rebecca Newman
Vice President,
Development and Communications

Stacie Spector
Chief Communications Officer

Gina Kirchweger, Ph.D.
Director, Scientific Communications

Sarah Lifton
Science Writer

Sarah Loffler
Design and Production Coordinator

Liz Hincks
Web Editor

Joe Belcovson and Kent Schnoeker
Photographers

Mike Sullivan
Web Extra Videography

Kat Kearney
Media Specialist

studio L.
Graphic Design

Visit the Salk Institute at www.salk.edu

InsideSalk is printed on recycled paper

InsideSalk is published by the Salk Institute for Biological Studies. We welcome your input. Please send comments to communications@salk.edu or contact the communications department at 858.453.4100 x1226.

Dear Friends,

ACROSS THE GLOBE, QUALITY OF LEADERSHIP IS AT THE center of our consciousness and the public dialogue—about the U.S. government, health care policy, the strength of our economy and the political arena—and in connection with international leaders in many sensitive areas of the world.

In much the same way, leadership is also on our minds here at the Salk Institute, mainly because the extraordinary leadership of our faculty, staff and board is enabling us to remain at the forefront of scientific innovation and discovery, despite the challenges posed by the outside world. I witness it on a daily basis, and it is publicly noted again and again in the many appointments, honors, awards and accolades that organizations from around the globe bestow on our science and our faculty.

You are part of an institution that attracts and supports many high-caliber individuals who contribute to the Institute's success, and as you read through this issue of Inside Salk, I'm sure you will be proud to learn about some recent examples of this kind of recognition. You will read about **Terry Sejnowski**, who was elected to the National Academy of Engineering; **Robert MacWright**, newly appointed as executive director of the Salk Institute's Office of Technology Management and Development; **Edward M. Callaway**, who was named a 2010 AAAS fellow; **Conrad T. Prebys**, who created an endowed chair in vision research; **John Young,** whose article was noted by *Science Watch* as the most cited paper in his field; as well as **Fred "Rusty" Gage**'s landmark stem cell grant for Parkinson's research, and the trailblazing opening of the Waitt Advanced Biophotonics Center, which inspired our lead story. What is more, in April we welcomed two new extraordinary leaders to our board of trustees, Dr. **Benjamin H. Lewis** and Ms. **Faye H. Russell**. That is leadership.

During my career, I have had the pleasure of leading large, groundbreaking institutions. I have come to appreciate, intuitively, that successful leadership engenders programmatic, scientific and environmental diversity. At Salk the diversity of our work is part of our basic infrastructure, and it is unmatched. So many of you play a critical role in our ability to implement and grow our scientific environment, which is rich in collaboration and creativity, and we are most grateful for your continued commitment and support. Salk's success and the many acknowledgements it has received are a direct result of your leadership.

William R. Brody

> **"At Salk the diversity of our work is part of our basic infrastructure, and it is unmatched."**

In all of our communications, we continue to grow and enhance the areas that you have indicated are of the greatest interest, which is why I hope you will enjoy a couple of new features that are debuting in this issue of *Inside Salk*. I invite you to visit a new feature showcasing one of our postdoctoral researchers. In addition, I have written a new column, *The Insider's View: Sutton's law and chronic illness*. As we continue to bring new ideas and perspectives, we look forward to your feedback.

William R. Brody

William R. Brody, M.D., Ph.D.
Irwin M. Jacobs Presidential Chair

ON THE COVER

Stem cells created from mature cells and rewound to an embryonic-like state retain a distinct "memory" of their former purpose that might limit their potential for therapeutic use. In a side-by-side comparison of these induced pluripotent stem cells and embryonic stem cells, **Joseph Ecker** and his collaborators found a consistent pattern of reprogramming errors — places where the iPS cells did not revert completely to an embryonic state.

Science
at the Speed of Light

The Salk Institutes's brand-new

WAITT ADVANCED BIOPHOTONICS CENTER

is opening up new vistas as cutting-edge imaging technologies promise to transform scientific inquiry.

WAITT FOUNDATION

Jared Sewell, a graduate student, prepares samples in the biophotonics core facility.

EVASIVE AND DEADLY, GLIOBLASTOMAS RESIST THE harshest of treatments**.** They might lie low for a while, encouraging the faintest glimmer of hope in patients who have endured withering therapies, only to strike back with a vengeance.

Salk scientist **Inder Verma**'s recent work on glioblastoma found entirely new evidence that 30 to 40 percent of blood vessels in tumors were originating from tumor cells themselves, explaining why drug therapy to inhibit blood vessel formation, while successfully used to treat many other types of tumors, might not be effective to stop glioblastomas in their tracks. "They are the ultimate shape shifters," says Verma, an American Cancer Society professor in the Laboratory of Genetics and holder of the Irwin and Joan Jacobs Chair in Exemplary Life Science, but he had a difficult time convincing other scientists.

"We showed this data in a paper, but the reviewers came back and said we needed much better resolution to show that these blood vessels really originated from tumors themselves," he explains.

Fortunately, Verma would soon have access to a brand-new, cutting-edge imaging resource that would provide the imaging resolution the panel demanded: the Waitt Advanced Biophotonics Center.

"We couldn't do that until the biophotonics laboratory was set up," he recalls, "but then we were able to do the high-resolution imaging that bore out our results. The paper is now published and hopefully will have an impact."

Postdoc Dino Morvinski and Inder Verma

More than 200 people attended the grand opening of the Waitt Advanced Biophotonics Center.

Ted Waitt and Salk professor Ron Evans

Perhaps the most important aspect of the biophotonics core facility, however, is that it encourages creativity by freeing researchers from the responsibility of costly investment in technology for individual experiments.

Beaming science forward

WHILE BIOPHOTONICS CAPABILITIES HAVE BEEN EXPANDING AT THE Salk Institute for several years, the science of manipulating light to investigate biological functions took a giant leap forward when the Institute launched the Waitt Advanced Biophotonics Center, made possible thanks to a landmark $20 million gift from the Waitt Foundation. Officially dedicated in February, the Waitt Center serves as a state-of-the-art research hub within Salk, enabling investigators from across many disciplines to gain unprecedented insight into the inner workings of cells and tissues, probing molecular mechanisms of life at microscopic resolutions that not long ago were unimaginable. It also ensures that the Institute remains at the forefront of this rapidly evolving technology.

The center is made up of two complementary parts that together provide Salk investigators with state-of-the-art biophotonic and analysis technology required to answer today's key biological questions: a core facility and faculty laboratories. The core facility provides state-of-the-art visualization and analysis tools to Salk investigators from across many biological disciplines. The faculty research labs housed within the Waitt Center are engaged in both next-generation technology development and answering fundamental life science problems through imaging-rich investigations.

"By putting these incredible tools in the hands of Salk investigators in an interdisciplinary teamwork environment, breakthroughs are bound to happen," says **Ted Waitt**, vice-chair of the Salk Institute board of trustees and chairman of the Waitt Foundation.

Advanced biophotonics will allow Salk investigators to observe how single molecules and cells function in real time, for instance, and provide visualizations of how living systems function at the molecular level. Researchers will be able to watch the changes when a living cell malfunctions; how it turns cancerous and responds to drug therapy; or how neurons in a living brain respond to stress, exercise, learning and diet, to name just a few examples. The aging process could be viewed as it happens at the cellular level.

"In the past, scientists were limited to snapshots of cells frozen in time," explains **James Fitzpatrick**, who joined Salk from Carnegie Mellon University in December 2009 to direct the center's core facility. "Now it is possible to watch highly dynamic cellular processes, such as viruses invading their host cell, in real time and at high spatial resolution."

James Fitzpatrick

» WEB EXTRA

Watch a video about biophotonics at:
www.salk.edu/insidesalk/biophotonics2011

From image to discovery

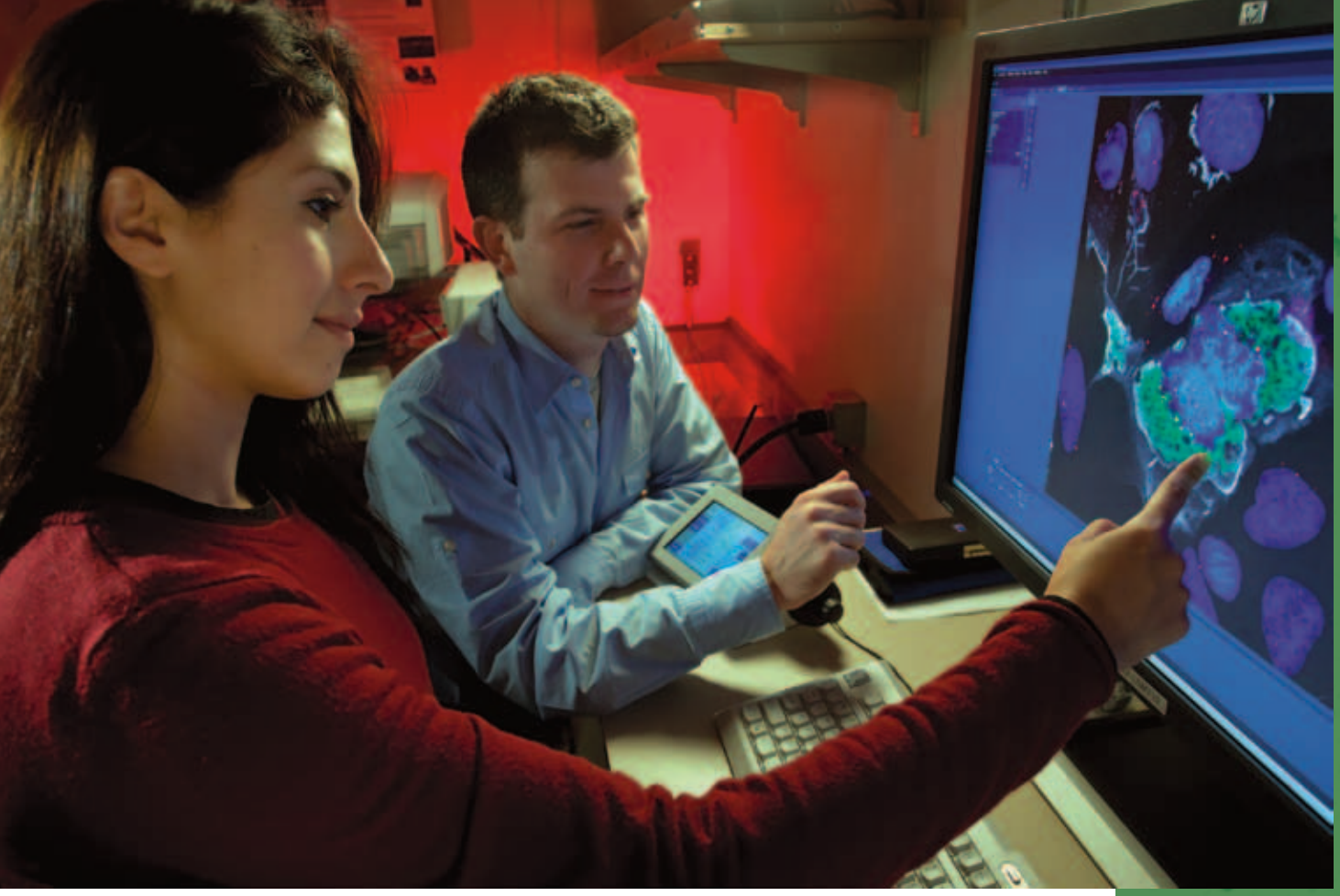
WHILE THE BUZZ ABOUT BIOPHOTONICS may revolve around advanced microscopy and the remarkable images it produces, the ability to peer into the complex workings of a living cell generates an avalanche of new data. A single experiment can require hundreds of gigabytes, so data management and image analysis are crucial parts of the Waitt Center's function.

The center also provides training in the different technologies so investigators understand the possibilities and learn how to use the options available to them. "The core trains us and empowers us to use these tools whenever we need them," says **Satchidananda Panda**, an assistant professor in Salk's Regulatory Biology Laboratory. "We feel like this is part of our lab."

Perhaps the most important aspect of the biophotonics core facility, however, is that it encourages creativity by freeing researchers from the responsibility of costly investment in technology for individual experiments. Traditionally, at many other institutions, researchers decide they need a particular instrument and then pay for it out of their own funding, or the institution provides it for them. In contrast, the biophotonics core facility provides all Salk faculty with access to a much vaster array of advanced imaging technologies than they could acquire independently. This is a transformative approach to research because it allows investigators to formulate new experiments they may not have considered before and gives them the freedom to explore without the burden of developing, funding and learning to use costly technology on their own.

"The core facility is not just a service; it's a collaborative environment, like the Salk Institute itself, where people can do imaging-based cellular research," Fitzpatrick says. "We've worked hard to create a facility where investigators come and say, 'Here is the type of experiment that I want to do,' and we direct them to the right techniques and technology, and work with them on training for the imaging and also on data analysis."

Light microscopy has come a long way since Jonas Salk observed poliovirus-infected cells through his simple microscope (shown farthest left). Today, Salk scientists work with fully automated million-dollar microscopes controlled by computers.



Graduate student Kristen Espantman and postdoctoral researcher Anthony Cesare study a high-resolution image of a virus-infected cell.

Axel Nimmerjahn: Microscopy in miniature

AT THE CENTER'S OPENING IN FEBRUARY, physicist-turned-neuroscientist **Axel Nimmerjahn** demonstrated an advanced microscopic tool that exemplifies the kind of transformative technology the faculty labs will bring to the new Waitt Center: a miniature epifluorescence microscope, no bigger than a penny, and weighing the equivalent of a paperclip. Mounted on a mouse's head, it enabled and produced the first-ever optical recordings of brain cells functioning in freely behaving mammals.

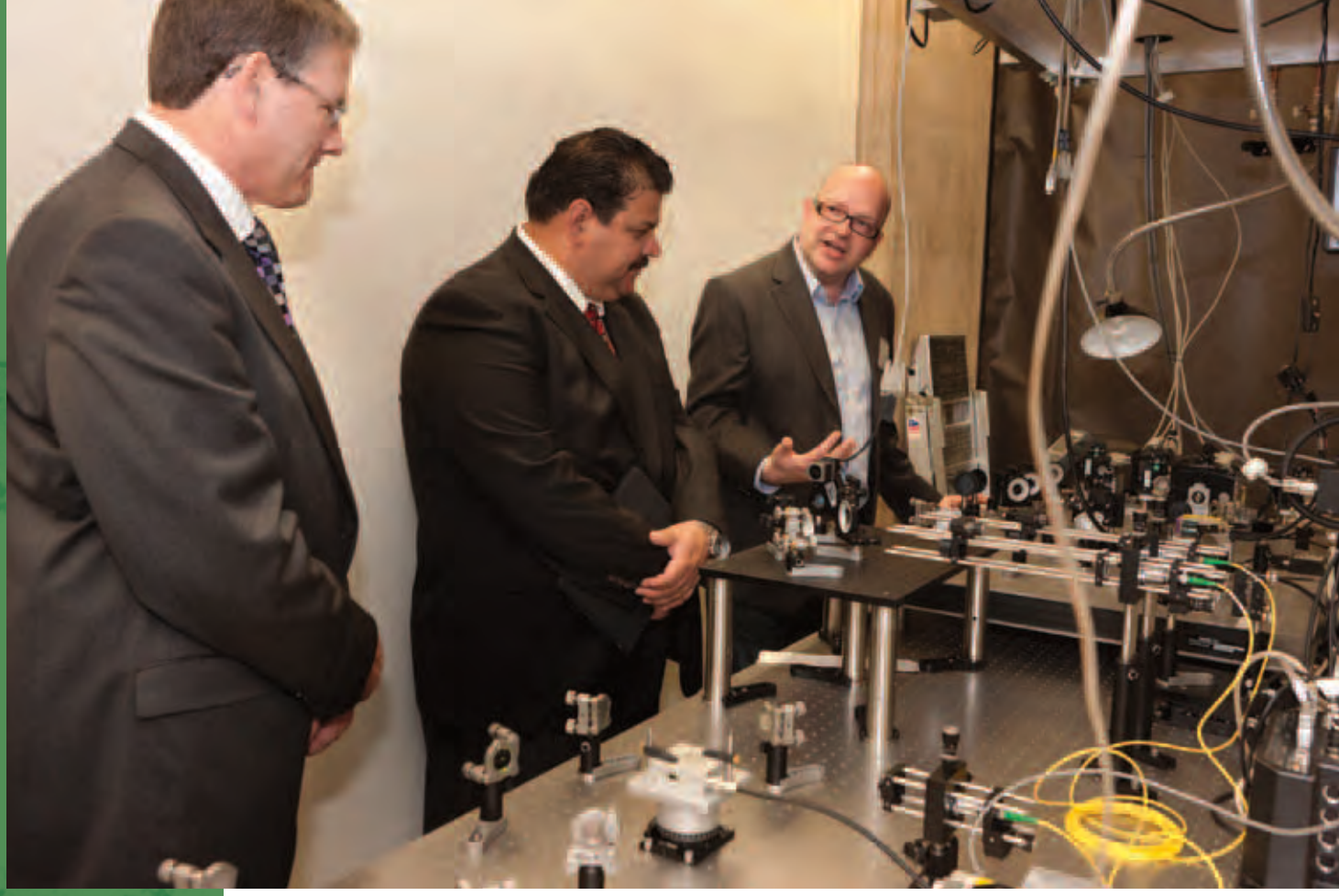
"This type of technology represents the ideal of the Waitt Advanced Biophotonics Center," says Nimmerjahn, assistant professor in the Waitt Center and holder of the Richard Allan Barry Developmental Chair. "By putting new tools into the hands of researchers, it allows them to directly address longstanding questions they have been unable to answer before."

Nimmerjahn, who joined the Salk Institute last November, began creating miniature microscopes in graduate school at the Max Planck Institute for Medical Research in Heidelberg, Germany, and since then has used this and other technology for his research into how glial cells, which constitute the majority of human brain cells, interact with neurons and other cells. Once thought to play only a passive, supportive role, glia are now known to be critically involved in the healthy brain's function. Additionally, they play major roles in disease onset, progression and regeneration.

In the Waitt Center, he will continue pursuing his research into the function of glial cells while also developing new technologies such as miniature microscopy that can be applied to other areas of biological research. "The Advanced Biophotonics Center, along with the remarkable environment of the Salk, is the main reason I decided to come here," he says. "The opportunities are extraordinary."

> **"By putting new tools into the hands of researchers, it allows them to directly address longstanding questions they have been unable to answer before."**

Axel Nimmerjahn



From left: Rudolf & Sletten's Martin Sisemore (president) and Rene Olivo (vice president of operations) get an insider's look at Björn Lillemeier's super-resolution microscope.

Björn Lillemeier

Björn Lillemeier: Decoding cellular signals

BJÖRN LILLEMEIER, ASSISTANT PROFESSOR IN BOTH THE WAITT ADVANCED Biophotonics Center and the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis, uses advanced biophotonics to study the complex structure of plasma membranes—the outer shell of cells—and how they contribute to relaying molecular signals in T-cells.

Studies of plasma membrane–associated signaling had been hampered by the limited resolution of light microscopy. Lillemeier's laboratory is overcoming that problem through the development of high-resolution imaging techniques that allow researchers to observe directly the spatial distribution of membrane-associated molecules on a nanometer scale.

Using advanced biophotonics, for example, Lillemeier discovered that membrane-associated proteins are clustered into what he calls "protein islands," which led to a new concept about the architecture of plasma membranes. In the past, he explains, it was possible to see that signaling molecules would come together in clusters, but where the molecules ended up within a cluster was thought to be random. Now, with the ability to look at them in much more detail, it is clear that these clusters have sub-organizations to them, which affect the molecular mechanisms of signaling.

"We are now developing super-resolution microscopy that basically can measure molecule distributions down to ten nanometers," Lillemeier says. "The great thing about these new technologies is that we can now close the gap in our understanding of how these mechanisms become altered in diseased cells, which will provide routes to potentially new therapies for autoimmune diseases and cancer."

Martin Hetzer: Training a spotlight on the nucleus

NUCLEAR PORE COMPLEXES, THE communication channels that regulate passage of molecules to and from a cell's nucleus, are made up of proteins known as nucleoporins. In studying nucleoporins, **Martin Hetzer**, Hearst Endowment associate professor in Salk's Molecular and Cell Biology Lab, discovered that the organization and architecture of the cell nucleus influences gene activity, playing a role in the organization of the genome and a very direct role in gene expression. This finding is significant because one of the hallmarks of cancer is abnormal organization of the cell nucleus.

"Over the past 50 years, scientists were limited to studying molecular mechanisms either in the test tube or on fixed cells," he says, "but this has major limitations. The Waitt Center core facility is vital to our research because of its live cell imaging capacity."

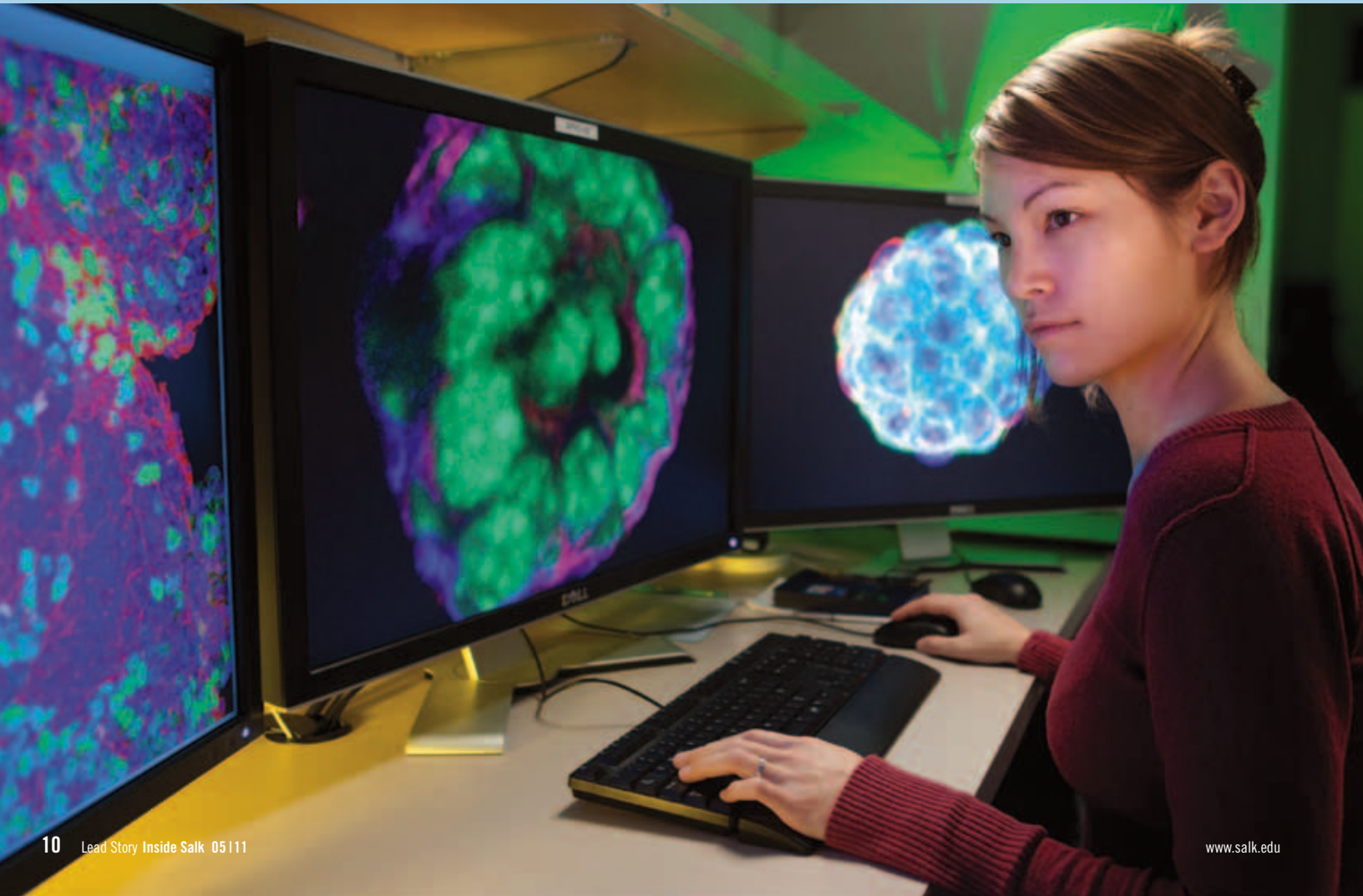
Using conventional light microscopes, nuclear pore complexes appear simply as fuzzy dots of light. Even electron microscopes, which have a superior resolution, cannot be used to study these protein complexes in living cells. Advanced microscopy in the biophotonics core facility, however, has allowed Hetzer to visualize the nuclear pore complexes at the structural level as they are assembled and inserted into the nuclear membrane. Looking ahead, super-resolution microscopy will allow him to drill still deeper into the individual components of nuclear pore complexes in living cells.

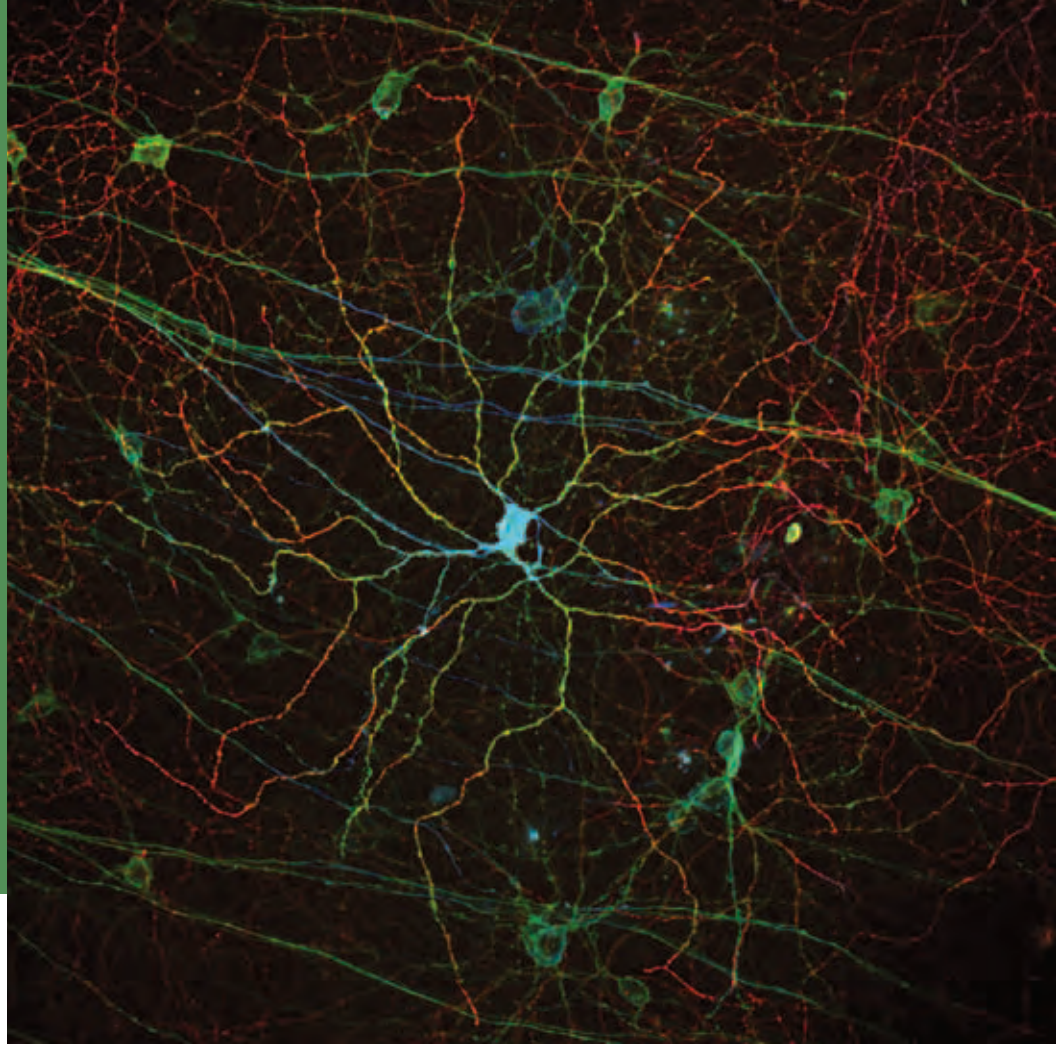
"Our goal is to visualize transcription and expression of a gene inside a nucleus in real time as tissue undergoes developmental processes," he says. "What makes this so exciting for us is that nucleoporins are key regulators for developmental genes and also potential markers for causes of cancer."

Martin Hetzer

> **"The Waitt Center core facility is vital to our research because of its live cell imaging capacity."**
>
> **— Martin Hetzer**

Dannielle Engle, a graduate student, works in the laboratory of Geoff Wahl, professor in the Gene Expression Laboratory.





Rare, spider-like cells embedded in the retina measure the brightness of incoming light.

Satchidananda Panda

Satchidananda Panda: Illuminating visual processing

FOR NEARLY A CENTURY, SCIENTISTS BELIEVED THAT ONLY THE PHOTORECEPTORS rods and cones in the retina converted light into electrical signals to the brain. That changed with **Satchidananda Panda**'s discovery of melanopsin, a photoreceptor in the retina that sends signals to the body's biological clock and that is only present in a few thousand cells embedded in the retina.

Before the advent of advanced biophotonics at Salk, Panda's work required lengthy imaging processes that ultimately didn't produce the kind of visualization he and his colleagues wanted. But his research into melanopsin has evolved along with the expanding capacity of advanced biophotonics at the Institute. With the installation of new microscopy technology, Panda changed his research strategy to work with imaging that became significantly more precise. "Suddenly," he says, "we could go to the biophotonics core and get a beautiful three-dimensional view of the retina—and a nice view of the brain to see where mRGCs connect."

Panda and his collaborators used advanced biophotonics to discover that melanopsin-expressing retinal ganglion cells, or mRGCs, reach out to visual processing centers in the brain, where they relay information about the brightness of incoming light. The findings reveal a new role for melanopsin during image-forming vision that could make a significant contribution to support vision in people with advanced retinal degeneration.

Clearly, biophotonics has broad application across multiple areas of investigation. But what does the dawn of the biophotonics age mean to biomedical research?

"Biophotonics is one of those transforming technologies that will impact nearly all the science being done at the Salk Institute," says Inder Verma, who was one of the driving forces behind the establishment of the Waitt Center. "By opening new vistas at the level of individual cells or molecules, it will revolutionize our understanding of the brain, the aging process and the development of cancer and lead to new diagnostic tools and treatments for hitherto intractable diseases."

One on One with... Tom Albright

SINCE HIGH SCHOOL, TOM ALBRIGHT HAS BEEN FASCINATED BY HOW WE SEE. THAT FASCINATION led to his undergraduate studies in experimental psychology because at the time that's where most efforts to find out how the visual system functioned were being done. But by the time he entered graduate school, new techniques to study vision through neurobiology had begun to emerge, so he switched his focus to neuroscience. Today Albright directs the Vision Center Laboratory at the Salk Institute, and his research into the mechanics of visual information processing is at the forefront of the field. He has received numerous honors for his work, including membership in the National Academy of Sciences; he is also a fellow of the American Association for the Advancement of Science. Last month, a $2 million gift from Conrad Prebys, a Salk trustee, along with a matching $1 million gift from Joan and Irwin Jacobs, established the Conrad T. Prebys Endowed Chair in Vision Research. Albright is the first holder of the chair.

In his spare time, Tom Albright enjoys working with his hands. He built the dining table on the opposite page himself.

Your research is at the nexus of vision, perception and consciousness. How does what we see become part of our consciousness?

Broadly speaking, the visual system works in three stages that take place from the retina through the visual cortex. The first stage breaks down the visual input into a number of qualitatively different attributes—brightness, color, texture, movement, distance. The second stage takes that information and puts it back together with a structure to it, a picture of the scene before you. The third stage is to assign meaning and emotional content, which enables recognition. This latter stage taps into your prior experiences with the world. And this is where vision becomes really interesting because the things you sense are no longer simply dependent on signals coming up from the retina, but they're heavily dependent upon what you have seen in the past, on your memories. This final stage comprises your conscious experience of the world.

How does our brain process all that visual information?

You open your eyes in the morning and close them at night, and during that time you acquire an enormous amount of information. A lot of that information is irrelevant to your needs and goals, and you ignore it, focusing instead on those things that are critical for your understanding of the world around you. In this sense, vision acts like an adjustable filter that continually fine-tunes the flow of information ascending from the retina and descending from the memory store, the part of our brain where memories are preserved. This tuning or adaptive plasticity of visual sensitivity optimizes performance of the system for the environment we happen to be in—much like one might differently tune a car's engine to drive on city streets versus highways. It's something our laboratory has been looking at for the last few years.

What is the frontier of your field today?

The frontier today involves efforts to figure out how vision actually works. Based on our experiments, I can tell you a lot about the behavior of different classes of cells in the visual cortex, and I can draw compelling correlations between neuronal behavior and perception. I might even be able to convince you that the neuronal signals we record are the cause of specific perceptual states. But until recently, we've known very little about how all of this actually works. This lack of mechanistic knowledge largely reflects limitations of traditional techniques. But there is a revolution afoot today; the fields of molecular biology and genetics have provided us with fabulous new ways to probe the neuronal components of vision with unprecedented precision. For example, we can now manipulate the activity or precisely trace the connections of specific populations of brain cells. From these data we can begin to develop detailed pictures of the cellular mechanisms that enable us to see—to hit a baseball, to find our car in the parking lot or to recognize the face of our lover.

You spend a lot of time thinking about how vision works. Does it influence how you look at the world?

I'm a very visual person. I think a lot about the things I see and why they look the way they do. Although most of what we study in the lab are very simple visual experiences, I have an irrepressible tendency to try to explain more complex perceptions in terms of what we've learned from sensory biology. Why are certain architectural spaces capable of eliciting strong responses? What is so special about the October light? Why do some works of art elicit all-consuming illusions of reality? Richard Dawkins called this "unweaving the rainbow" in reference to John Keats's complaint that Isaac Newton had destroyed the beauty of the rainbow by explaining the science behind it. For me, scientific understanding enhances rather than diminishes beauty.

continued on next page...

Watercolor (untitled) by Thomas Albright

"Visual artists have always had, at the very least, an implicit understanding of why things look the way they do. Conversely, as a vision scientist, I find that experimenting with the way things look just comes with the territory."

What question would you like to see answered in your lifetime?

I'd like to know enough about the brain to be able to fix it when it breaks and to optimize its use for learning, communication and action. To those ends, one of the most important things to understand would be object recognition. How is it that I'm able to recognize something I've seen before? Failure of object recognition effectively strips perceptual experience of meaning and is a devastating hallmark of many psychiatric and age-related brain disorders. There are many elements to the recognition process, but some of the most important questions include: Where and how are memories stored, how are they accessed, and how do they influence the processing of visual information? And there's a related element to the process of object recognition—something we've been studying recently—which is visual imagery. We readily produce pictures in our heads without visual stimulation. Among other things, I have in my head a very detailed image of Hogwarts Castle, which of course I have never seen. We hypothesize that this imagery is a form of recall—a fabricated construct derived from bits and pieces of things I've seen before and consistent with the properties of the world I know, such as gravity, volume and opacity. We believe that these internal experiences in the "mind's eye" result from memory-driven use of the same brain systems that underlie normal vision. Moreover, we argue that the only way to fully understand perception is to get a sense of how these memory-driven signals interact with signals arising from the retina. This is one of the major goals of research in our lab today, and our findings are beginning to illuminate how features of this imagery system account for dreaming and hallucinations.

How will the Conrad T. Prebys Endowed Chair help?

Generous sources of funding like this that are given without restrictions on their use provide greater freedom to do inventive science. You can stretch the boundaries of current thinking. Unrestricted sources of funding for research enable creative approaches to solving scientific problems, and that's how I plan to use it. Also, in this economy—and I hope it changes before too long—this private funding is a life preserver for basic research, given the difficulty of obtaining funding from traditional public sources.

Robert MacWright appointed executive director of the Salk Office of Technology Development

THE SALK INSTITUTE HAS WELCOMED Robert MacWright, Ph.D., Esq. as the new executive director of the Office of Technology Development. Widely recognized for his skill, innovation and leadership in the field of academic technology transfer, MacWright brings extensive experience and expertise to the department.

For over a decade he served as executive director, CEO and chief patent counsel of the University of Virginia Patent Foundation, where he successfully spearheaded a broad expansion and modernization of its patent and licensing activities. A strong advocate of faculty startup companies, he helped establish a subsidiary of the foundation to encourage and support young businesses based on University of Virginia inventions and also launched The Jefferson Corner Group, an angel fund designed to invest in emerging technologies and support in-house technological breakthroughs.

Previously, he led the creation and development of technology transfer programs at Rutgers University and served as executive director of the Rutgers Office of Corporate Liaison and Technology Transfer.

MacWright also brings expertise as a biotechnology patent attorney, having practiced law at Kenyon & Kenyon; Skadden, Arps, Slate Meagher & Flom; and most recently, at Frommer Lawrence & Haug. He received his Ph.D. in biochemistry jointly from Rutgers University and the University of Medicine and Dentistry of New Jersey and has academic and industry research experience in protein chemistry and molecular genetics. He holds a law degree from the Rutgers School of Law—Newark.

"Robert's strategic and academic experience will be a huge asset to the Salk," says Salk president William R. Brody. "His deep understanding of basic research, academia and industry is unique, and he is poised to take our technology transfer to new heights."

Salk Institute receives $2.3 million grant to develop stem cell–based treatments for Parkinson's disease

THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE (CIRM) has awarded the Salk Institute a $2.3 million grant for translational research focusing on developing a novel stem cell–based therapy for Parkinson's disease. Led by **Fred H. Gage**, a professor in the Laboratory of Genetics and holder of the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases, the research will be a joint effort among Salk researchers; Christopher Glass, a professor of medicine and cellular and molecular medicine at the University of California, San Diego; and collaborators in Germany. The project will seek to replicate Parkinson's disease in the lab using human induced pluripotent stem (iPS) cells derived from patients suffering from the disorder, in order to investigate the role of inflammation in the condition.

Parkinson's is a chronic, progressive neurological disease that usually occurs later in life and is linked to decreased dopamine production, the chemical messenger involved in communication between the brain and the muscles. The most common neurodegenerative movement disorder, it is characterized by motor impairment such as slowness of movements, shaking and gait disturbances.

"Given that age is the most consistent risk factor for Parkinson's, and we have an aging population, it is of the utmost importance that we unravel the cellular, molecular and genetic causes of the highly specific cell death characteristic of the disease and find new therapies to limit the social, economic and emotional impact," says Gage.

In the past, scientists had been limited to studying the brains of those with Parkinson's via imaging technologies or postmortem brain tissues, and most studies to find better drugs for the condition were done with mice and often failed when tested in patients. Now the ability to obtain iPS cells from patients' skin cells, which can be reprogrammed into neurons, provides researchers with a model for studying the pathological development of Parkinson's in a human system and, the group hopes, to identify key molecular events involved in the early stages of the disease, which can be exploited as potential points of therapeutic intervention.

Edward M. Callaway named 2010 AAAS Fellow

SALK RESEARCHER EDWARD M. CALLAWAY, a professor in the Systems Neurobiology Laboratories, has been named a Fellow of the American Association for the Advancement of Science for his "distinguished research on the organization and function of neocortical circuits." Election as a Fellow of the AAAS is an honor that members bestow upon their peers for scientifically or socially distinguished efforts to advance science—a tradition that began in 1874.

Callaway's research is aimed at understanding how neural circuits give rise to perception and behavior and focuses primarily on the organization and function of neural circuits in the visual cortex. Relating neural circuits to function in the visual system, where correlations between neural activity and perception can be directly tested, provides fundamental insight into the basic mechanisms by which cortical circuits mediate perception.

A native of Southern California, Callaway received his bachelor's degree from Stanford University and his doctorate from the California Institute of Technology. After traveling east to conduct postdoctoral studies at The Rockefeller University and Duke University, Callaway returned to California to join the Salk Institute, where he has been a faculty member since 1995.

With Callaway's election, the total number of Salk faculty currently designated as AAAS Fellows now stands at 13.

The Making of a Scientist

SALK PROFESSOR TERRY J. SEJNOWSKI has been elected to the National Academy of Engineering, making him one of only ten living individuals who are members of all three branches of the National Academies. For him, it is all about asking the right kinds of questions.

"So, Terry. What would it look like if there were a really big black hole in the middle of our galaxy?"

This first big question was posed by theoretical physicist John Wheeler, best known for coining the terms *worm hole*, *quantum foam* and *black hole*. Propelled by his interest in astrophysics, Sejnowski had joined lab Wheeler's at Princeton University as a physics graduate student just weeks earlier. At the time, black holes were nothing more than a mathematical curiosity based on the theory of general relativity, which predicted their existence. Undeterred, Sejnowski went off and found the answer by simulating the orbits of stars as they fell into a big black hole.

(All his predictions were later confirmed. He only missed the so-called accretion discs, Saturn-like rings formed by the stellar debris.)

"Nobody had ever asked that question before, and it was a transformative experience for me," he remembers. "It taught me that you need to ask a good question if you are going into a new area where there aren't lot of facts on the ground yet. When I became interested in the brain, in a sense it was like a black hole since back then not much was known about how things like memory work."

During his first hot and muggy summer in Princeton, as Sejnowski was cramming for his physics qualifying exams, he often went to the library to cool off body and mind. His recreational reading included picking up books on the brain, and soon the question that would change the course of his career arose: "Are the signals in the brain regular, like signals in a computer, or random?"

Sejnowski quickly found the answer. (They are random.) But the uncharted depths of the human brain had gripped his imagination. "I thought to myself, 'My god, here we are trying to understand the mysteries of the universe, when the mysteries of the brain are just as exciting,'" he says and adds with a laugh that "the advantage of biology is that you can actually do experiments, but you can't do experiments on the universe."

After completing his master's degree with Wheeler and his doctoral degree with John Hopfield at Princeton, he quickly immersed himself in neurobiology, learned how to record from neurons and before long was invited to join the Harvard lab of Steve Kuffler, who is often referred to as the "father of modern neurobiology." Remembers Sejnowski, "It was like jumping from a swimming pool into the ocean, but it was a fantastic experience."

As a young assistant professor at Johns Hopkins University, he continued to work on synapses, the specialized connections between neurons, but he also picked up some of the theoretical work on computational models of neuronal networks that he had done during his thesis.

Together with his lifelong friend Geoffrey Hinton, he developed the first neural network capable of learning to solve difficult computational problems. By overcoming a logjam that had hindered meaningful progress on neural networks for decades, the so-called Boltzmann machine helped spark the neural networks revolution in computing in the 1980s. "It was a beautiful model and actually one of my most influential projects from the perspective of the impact it had," he says.

Throughout his quest to understand behavior through the lens of neuronal circuits, Sejnowski has combined experimental and computational tools. "When I started, there were only a few people who were thinking about the brain in a theoretical way, and there was no real connection with biology," he says. "But I realized that to make progress you really have to connect it to the biology, and that's why I took the neurobiology summer course in Woods Hole after I got my Ph.D. From there it snowballed."

Today Sejnowski is regarded as one of the world's foremost theoretical brain scientists and celebrated as the founding father of the field of computational neurobiology.

His advice to the next generation of scientists?

"Find a really good question, and follow it through as far as you can push it. If it is a really good question, you are bound to come up with something truly interesting."

> **“Margaret had a heart as big as the sky, a spark of wit that could light up a room and a larger-than-life presence that filled our days.” — Thomas Albright**

Remembering Margaret Mitchell

FRIENDS AND COLLEAGUES CONVENED IN THE Trustees Room on January 10, 2011 for an emotional memorial to a woman who was nothing short of a Salk institution: **Margaret Mitchell**. Mitchell played a vital role at the Institute for over 30 years, beginning her Salk career in the president’s office as an administrative manager and then working in several other departments before joining the Vision Center Laboratory—perhaps the position closest to her heart—in 1994.

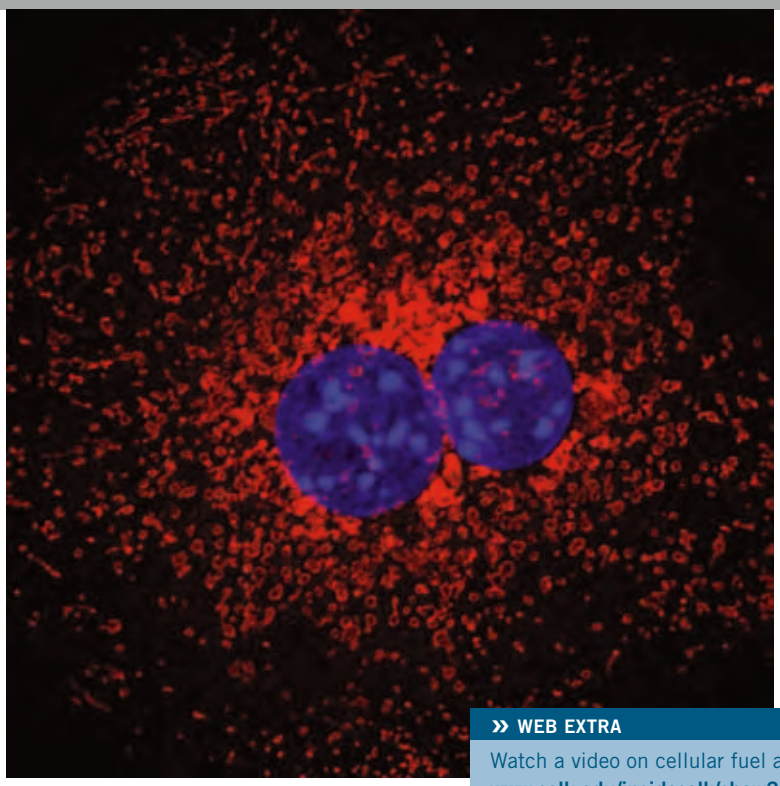
“She absolutely loved this place,” said Mitchell’s son, Robert. “She would say, ‘I love my children and job in that order.’ You spent as much time with her as we did. She worked here because this is what she wanted to do, and she wanted to be with all of you.”

The tribute featured a slide show documenting her life and career, and coworkers, friends and family members filled a book of remembrances to overflowing with stories, poems and photographs.

“It was a great privilege to work with her for 17 years on a daily basis,” said **Thomas Albright**, professor and director of the Vision Center Laboratory. “Margaret had a heart as big as the sky, a spark of wit that could light up a room and a larger-than-life presence that filled our days.

“When we remember and celebrate Margaret’s life, the thought of her will always bring smiles to our faces,” he added. “We will laugh at the things she taught us to laugh at and find joy where she found it and know our lives are richer and greater for having shared them with her.”

Discovery Roundup



When the process of autophagy is defective, cells are unable to recycle cellular organelles such as mitochondria (shown in red) to generate molecular building blocks when needed. Cell nuclei shown in blue. *Image: Courtesy of Daniel Egan*

» WEB EXTRA

Watch a video on cellular fuel at:
www.salk.edu/insidesalk/shaw2011

Recycling cellular fuel

IF YOU EXERCISE REGULARLY, FEEL GOOD ABOUT DRINKING RED WINE, TAKE diabetes meds and/or starve yourself in hope of a long life, then you have a personal stake in AMPK signaling.

AMPK is a metabolic master switch that springs into gear when cells run low on energy. Now researchers in the lab of **Reuben Shaw** have uncovered one of its principal secrets: how it revs up a cellular recycling program to free up essential molecular building blocks in times of need.

In a study published in *Science*, Shaw and his team report that AMPK triggers a cellular recycling function known as autophagy by activating an enzyme known as ATG1, which jumpstarts the process. The newly uncovered direct molecular connection between AMPK and ATG1 is significant because dysfunctions in both AMPK signaling and autophagy are implicated in a plethora of aging-related diseases, including type 2 diabetes, cancer and neurodegerative diseases such Parkinson's and Alzheimer's.

Add to that the possibility that AMPK itself may have anti-tumor activity, and it is no wonder that pharmaceutical companies are keenly interested in what proteins AMPK "talks to" and how drugs that stimulate that conversation work.

Despite its ominous name—derived from "self" (auto) and "eating" (phagy)—cells use autophagy to dispose of debris before it becomes toxic enough to kill a cell. "Autophagy is an ancient process that evolved to break down components cells don't need to create things they do need," explains Dan Egan, a graduate student in Shaw's lab.

Previously, Shaw's lab had not only demonstrated that AMPK is deregulated in certain forms of cancer but also that the enzyme is a critical target of the type 2 diabetes drug metformin. "Taking a drug that activates this pathway, like metformin, is the equivalent of taking several different drugs," says Shaw, reeling off a list of anti-tumor and anti-diabetes pathways activated by AMPK. "Now we can add regulation of autophagy to that list."

Hungering for longevity

SUBSTANTIAL EVIDENCE SUGGESTS THAT lifespan is increased if an organism restricts its daily calorie intake, a spartan regime that some say works by just making life seem longer. A team of scientists from the lab of **Andrew Dillin**, however, has discovered a molecular switch flipped by hunger that could not only make longevity more appetizing but identify drug targets for patients with aging-related diseases such as type 2 diabetes or cancer.

Researchers already knew that hunger promoted longevity by activating an enzyme called AMPK, which senses that food is scarce and pushes cells into a low energy state (see "Recycling cellular fuel," left). But they but didn't know what it was talking to. To define the circuitry, Dillin joined forces with **Reuben Shaw**, who has a long-term interest in AMPK's role in mammalian metabolism. "It was clear that one pathway that regulated cell growth was AMPK signaling," says Shaw. "Studies had also suggested that AMPK might regulate lifespan in worms. What was not known was what factors downstream of AMPK mediated those effects."

Together they searched the genome of the roundworm *Caenorhabditis elegans* for likely AMPK targets and identified one suspect encoding a protein called CRTC1, which was expressed at the same time and place as AMPK. When they fed roundworms an inhibitory RNA engineered to deplete them of CRTC1 protein, the worms' lifespan—normally about three weeks—was a whopping 40 percent longer, suggesting that AMPK retards aging by antagonizing CRTC1 activity. The group also discovered how AMPK silences CRTC1.

The good news for the burger and fries crowd is that the entire pathway and a host of interacting factors may operate similarly in worms and humans. "Whether you are talking about yeast, worms, Labradors or rhesus monkeys, dietary restriction is the best intervention we have so far against age-related conditions like neurodegeneration, cancer and diabetes," says postdoctoral researcher **William Mair**. "Our goal now is to use information we have derived from worm studies to find a way to treat many of these diseases with one magic bullet."

With any luck, that magic bullet will be maximally effective when taken on a full stomach.

» WEB EXTRA

Watch a video on longevity at:
www.salk.edu/insidesalk/dillin2011

A kinder, gentler presenilin

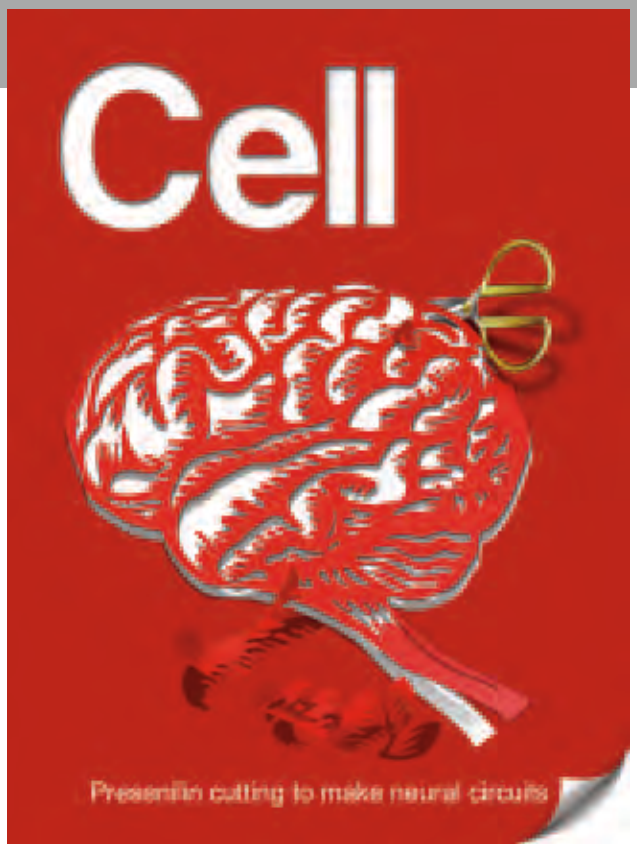
MUTANT PRESENILIN IS INFAMOUS FOR ITS ROLE IN THE MOST aggressive form of Alzheimer's disease—early onset familial Alzheimer's—which can strike people as early as their 30s. A new study by researchers in the lab of **Samuel Pfaff**, however, has revealed presenilin's beneficial side: it helps embryonic motor neurons navigate the maze of chemical cues that pull, push and hem them in on their way to their proper targets. Without it, budding motor neurons misread their guidance signals and get stuck in the spinal cord.

Presenilin is a component of the enzyme gamma secretase, which cleaves the amyloid precursor protein, resulting in accumulation of beta amyloid fragments. In Alzheimer's, these fragments form hard, insoluble plaques, one of the hallmarks of the disease.

The study's findings, however, published in the journal *Cell*, put genes associated with Alzheimer's disease in a new light, revealing an important link between the formation of neural circuits and neurodegenerative disorders. "It was a bit of a surprise since we always thought about presenilin in the context of severing neuronal connections rather than wiring the nervous system during embryonic development," says Pfaff.

Many embryonic guidance molecules persist in the adult central nervous system, where they participate in maintenance, repair and plasticity of neural circuits. During normal development, trillions of neurons reach out for others with long, slender extensions to touch, connect and wire the budding nervous system. As the hair-like protrusions, called axons, grope around in the developing embryo, trying to find their proper targets, molecular ushers stationed along their path steer them in the right direction.

"[Presenilin] provides a way of creating some of these intermediate temporal steps," explains postdoctoral researcher **Ge Bai**. "It allows the use of a small number of genes to regulate axonal growth by regulating the signals' effects in very precise temporal and spatial ways."



Presenilin, better known for its role in Alzheimer's disease, aids with the correct wiring of the embryonic nervous system. *Image courtesy of Samuel Pfaff*

"This could explain how a deregulation of guidance signaling by abnormal presenilin may play a role in the pathogenesis of Alzheimer's disease," adds Pfaff.

Understanding how axons find their destinations may also help restore movement in people following spinal cord injury, or in those with motor neuron diseases such as Lou Gehrig's disease, spinal muscle atrophy and post-polio syndrome.

Cell reprogramming leaves a "footprint" behind

REPROGRAMMING ADULT CELLS TO recapture their youthful "can-do-it-all" attitude appears to leave an indelible mark, a team of Salk researchers including **Joseph Ecker** and **Ronald Evans** has found. When the scientists scoured the epigenomes of so-called induced pluripotent stem (iPS) cells base by base, they discovered a consistent pattern of reprogramming errors. What's more, these incompletely or inadequately reprogrammed hotspots are maintained when iPS cells are differentiated into a more specialized cell type, providing what the researchers dubbed an iPS cell–specific signature.

"We can tell by looking at these hotspots whether a cell is an iPS cell or an embryonic stem cell," says Ecker. "But we don't know yet what it means for their self-renewal or differentiation potential."

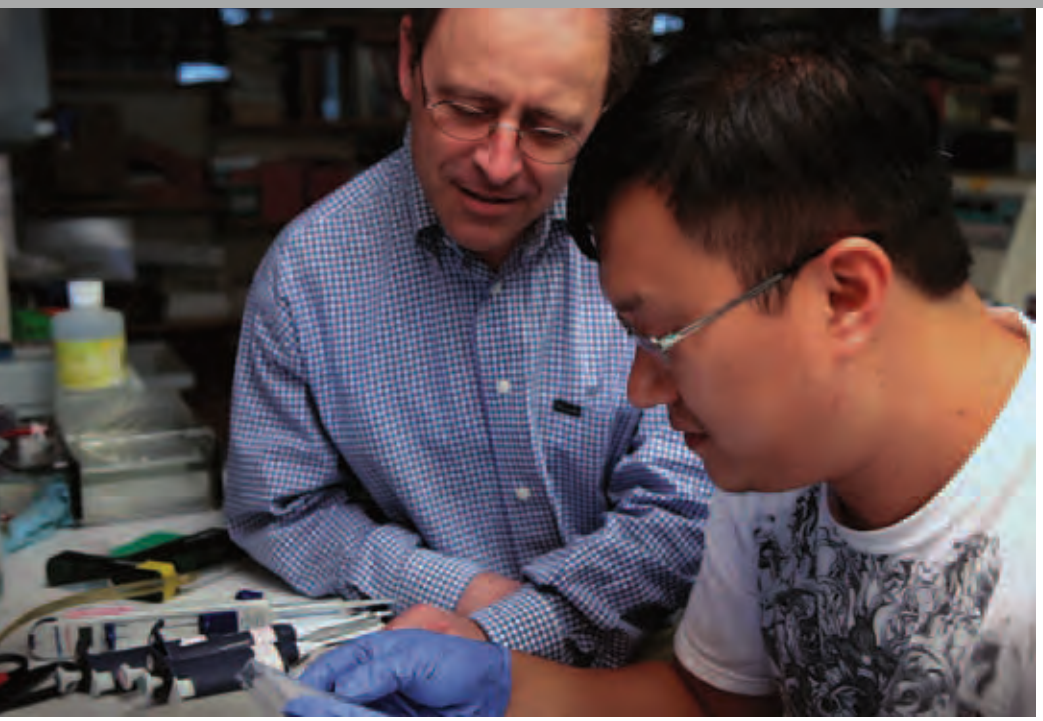
These findings, published in *Nature*, confirm that iPS cells, which by all appearances look and act like embryonic stem (ES) cells, differ in certain aspects from their embryonic cousins, emphasizing that further research will be necessary before they can rightfully take embryonic stem cells' place.

The fact that reprogramming of somatic (body) cells does not pose the same ethical quandaries as working with stem cells isolated from eggs or embryos prompted Japanese and U.S. scientists to develop human iPS cells that are just as potent as human embryonic stem cells, with the hope that one day, iPS cell technology can be applied to regenerative medicine. But Ecker's study makes it clear that before cells derived from iPS cells can be used to repair tissue damaged through disease or injury, some remaining questions have to be solved. "Embryonic stem cells are considered the gold standard for pluripotency," says Ecker. "So we need to know whether—and if so, how—iPS cells differ from ES cells."

» WEB EXTRA

Watch a video on cell reprogramming at:
www.salk.edu/insidesalk/ecker2011

Discovery Roundup



Marc Montminy (left) and postdoctoral fellow Youngsup Song

Feast, famine and the genetics of obesity

IN ADDITION TO FAST FOOD, DESK JOBS and inertia, there is one more thing to blame for unwanted pounds—our genome, which has apparently not caught up with the fact that we no longer live in the Stone Age. That is one conclusion drawn by researchers in the lab of **Marc Montminy**, who recently showed that mice lacking a gene regulating energy balance are protected from weight gain, even on a high-fat diet.

In a study published in *Nature*, Montminy and his team report that a gene known as CRTC3 decreases energy expenditure by fat cells. "Ideas about obesity are based on concepts of feast or famine," he says. "As humans, we developed ways of coping with famine by expressing genes like CRTC3 to slow the rate of fat burning. Individuals with these active "thrifty genes" had an advantage—they could survive long periods without food." In the 21st century, however, those genes have become a liability.

To analyze its role in fat metabolism, the researchers engineered mice lacking the CRTC3 gene and put them on diets of varying fat composition. Normal and CRTC3 gene "knockout" mice appeared similar when fed a moderate fat diet. But when fed the mouse version of the Philly cheese steak diet, only the normal mice became obese. "The CRTC3 knockout mice were leaner and protected from obesity," reports Montminy. "They also had about twice as many brown fat cells as normal mice."

Brown fat tissue actually burns white fat tissue to generate heat as a way to maintain body temperature. In fact, some evidence suggests that humans with a genetic propensity to leanness have more brown fat cells than "ample" individuals do. As desirable as that trait may seem in a "super-size me" world, those folks likely had a pretty tough time in the Paleolithic era.

Although the researchers found that CRTC3 loss also perturbs how all fat cells respond to brain signals controlling energy expenditure, they remain particularly intrigued by the brown fat connection. "CRTC3 could be a switch controlling the number of brown fat cells," says Montminy. "That is key because if you could make more brown adipocytes, you could potentially control obesity."

» WEB EXTRA

Watch a video on genetics of obesity at:
www.salk.edu/insidesalk/montminy2011

Seeking answers to a hairy question

IT'S LONG BEEN KNOWN THAT SOME OF the most influential discoveries in science are the product of serendipity. But, as the 1st century Roman philosopher Seneca observed, "Luck is what happens when preparation meets opportunity."

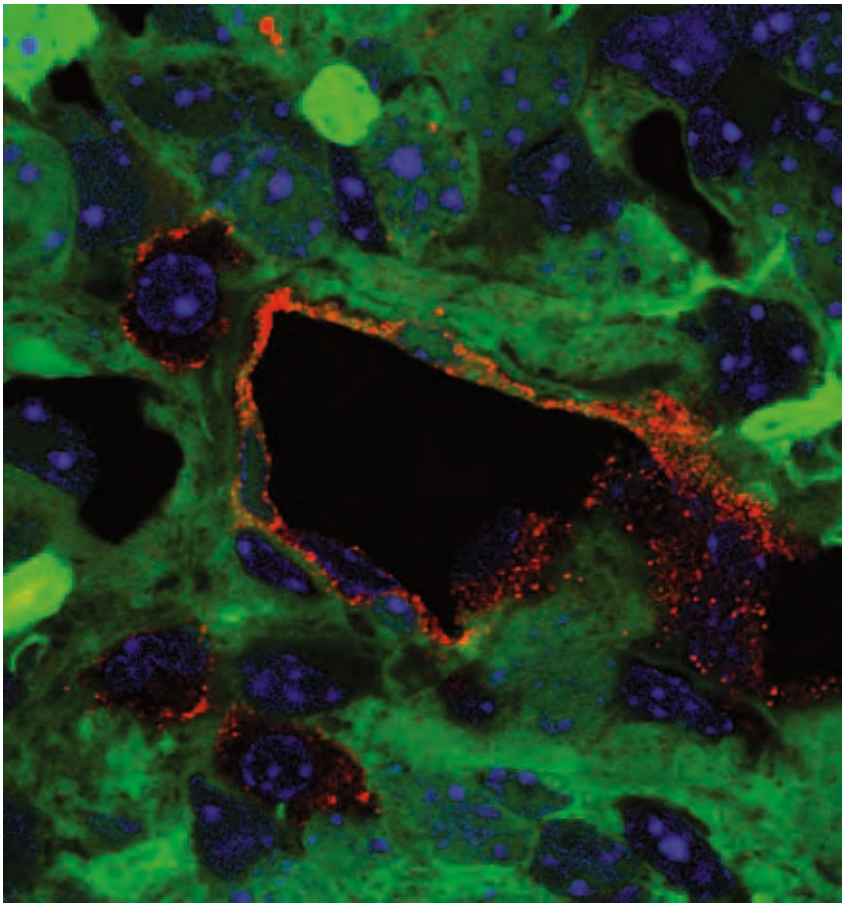
Recently, a team of researchers from the University of California, Los Angeles, and the Veterans Administration made an unexpected discovery that was grounded in earlier work by Salk researchers **Jean** and **Catherine Rivier**. The investigators, who were originally studying brain-gut interactions in stress, stumbled on unanticipated effects of a chemical compound the Riviers had developed called astressin-B, which blocks a stress hormone called corticotrophin-releasing factor, or CRF. In mice, as in humans, stress can cause hair loss, and as mice engineered to overexpress CRF age, they lose hair and eventually become bald on their backs, making them visually distinct from their unaltered counterparts.

The UCLA and VA researchers injected astressin-B into the bald mice to observe how its CRF-blocking ability affected gastrointestinal tract function. The initial single injection had no effect, so the investigators continued the injections over five days to give the peptide a better chance of blocking the CRF receptors. They measured the inhibitory effects of this regimen on the stress-induced response in the colons of the mice and placed the animals back in their cages with their hairy counterparts.

About three months later, the investigators returned to these mice to conduct further gastrointestinal studies and found they couldn't distinguish them from their unaltered brethren. They had regrown hair on their previously bald backs.

The serendipitous discovery, which so far has been observed only in mice, is described in an article published in *PLoS ONE*. Whether it also happens in humans remains to be seen, say the researchers, who also treated the bald mice with minoxidil alone, which resulted in mild hair growth, as it does in humans. This suggests that astressin-B could also translate for use in human hair growth.

UCLA and the Salk Institute have applied for a patent on the use of the astressin-B peptide for hair growth.



Glioblastoma tumor cells (shown in green) can transform into endothelial cells (shown in red), which line the interior surface of a tumor vessel. *Image courtesy of Yasushi Soda*

> **"We have to prevent the conversion of tumor cells into blood vessel cells."**
>
> **— Inder Verma**

Shape-shifting brain tumor cells thwart treatment

TO GROW BEYOND ONE TO TWO millimeters in diameter—roughly the size of a pinhead—tumors need their own independent blood supply. To recruit new vasculature from existing blood vessels, many overexpress growth factors, predominantly vascular endothelial growth factor (VEGF). This led to the development of Avastin, a monoclonal antibody that intercepts VEGF.

Glioblastoma, however, the most common and lethal form of brain cancer, resists nearly all treatment efforts, even when attacked simultaneously on several fronts. In fact, studies have shown that tumor cells often become more aggressive after anti-angiogenic therapy, but the reason had been unclear.

One explanation can be found in the tumor cells' unexpected flexibility, discovered researchers the lab of **Inder Verma**. When faced with a life-threatening oxygen shortage, glioblastoma cells can shift gears and morph into blood vessels to ensure the continued supply of nutrients. The study, published in the *Proceedings of the National Academy of Sciences*, not only explains why cancer treatments that target angiogenesis—the growth of a network of blood vessels that supplies nutrients and oxygen to cancerous tissues—routinely fail in glioblastoma, but may also spur the development of drugs aimed at novel targets.

Postdoctoral researcher **Yasushi Soda** studied a mouse model of glioblastoma that recapitulates the development and progression of human brain tumors that arise naturally. The glioblastoma mice grow brain tumors within a few months of being injected with viruses that carry activated oncogenes. When Soda peered at the tumor cells, he found—much to his surprise—that about 30 percent of vascular endothelial cells—specialized cells that line the interior surface of blood vessels—appeared to have originated from tumor cells. Further experiments revealed that these tumor-derived endothelial cells are not specific to mouse tumors but can also be found in clinical samples taken from human glioblastoma patients.

"This surprising effect of anti-angiogenic therapy with drugs such as Avastin tells us that we have to rethink glioblastoma combination therapy," says Verma. "Disrupting the formation of tumor blood vessels is not enough; we also have to prevent the conversion of tumor cells into blood vessel cells. But as we learn more about tumors' molecular flexibility, we will be able to design novel, tailor-made combination therapies to combat deadly brain tumors."

The next generation: Will Mair

Postdoctoral fellows are the lifeblood of Salk's research laboratories, bringing talent, fresh perspective and creative thinking to the bench. But they are also laboring apprentices acquiring the experience and credentials they need to launch independent research careers and establish cutting-edge laboratories of their own.

WILL MAIR JOINED THEIR RANKS FIVE YEARS ago when he became a member of **Andrew Dillin**'s team after earning his doctoral degree at University College, London. He has just capped his successful postdoctoral career with a landmark paper (for more details see "Hungering for Longevity," page 24), making him a sought-after candidate for assistant professorships at universities and research institutes worldwide.

"This project was a great example of being in the right place at the right time," he says. "I was lucky in that there were so many labs close by that were experts in related areas. I could draw upon their knowledge for my own work, which would have never happened if I hadn't come to the Salk Institute. Here the science just seeps into you; you can't help it."

Mair may credit Salk's unique environment for his success, but his own collaborative approach to

> **"I was lucky in that there were so many labs close by that were experts in related areas. I could draw upon their knowledge for my own work, which would have never happened if I hadn't come to the Salk Institute."**
>
> **— Will Mair**

science (he is listed as a co-author on papers from three other Salk laboratories), a very clear idea of the question he was trying to answer and the persistence of a long-distance runner made him a perfect fit.

"During my doctoral thesis, I worked on dietary restriction in fruit flies and found that restricting amino acids was enough to get the full life-prolonging effect. But I really had no idea what was going on," he explains. "I specifically came to the Salk trying to get at the mechanics of the process."

He chose the lab of Howard Hughes Medical Institute investigator Dillin, an associate professor in the Molecular and Cell Biology Laboratory (MCBL), who studies aging using the roundworm *Caenorhabditis elegans* as a model system and who had discovered the first gene that is essential for the increased longevity seen in mice and other animals kept on low-calorie diets.

But the project was off to a rocky start. "In the beginning we just didn't have the proper tools," he remembers. What he did have, though, were many opportunities to discuss the project with **Reuben Shaw**, an assistant professor in MCBL and an expert on AMPK, a protein that serves as a metabolic master switch.

"Reuben had just joined the Salk Institute and was still in the process of getting his lab up and running, so he had the time to have lengthy scientific discussions with me," he says. "It quickly became clear to me that AMPK was the way to go."

Yet progress was still slow. CRTC1, the protein that he had picked as his reporter for AMPK activity, just didn't do what he expected it to do. With the determination of a scientist who knows that he is on the right track, Mair kept going back to it. Eventually, he decided to change gears and use worms' lifespan as the readout. All of a sudden everything started to make sense. "I realized that CRTC1 itself was important for longevity. What was supposed to be merely a marker became the linchpin of the whole paper," he says.

At the moment, Mair is in the process of applying to research institutions worldwide so he can continue his research in his own laboratory. "I am not interested in how long a worm lives. I want to know how we can take this pathway and use it to treat a whole range of aging-associated pathologies to get new therapies for human patients," he says.

A student loads a protein mixture into a gel to separate the proteins based on size, as **Charisse Crenshaw** (right), a postdoctoral fellow in the laboratory of **Joseph Noel**, and another student look on.

High School Science Day **Marks 21 Years**

NOT EVEN A POWERFUL WINTER STORM WAS STRONG enough to keep 200 high school students from the Salk Institute's 21st annual High School Science Day. The February 26 event, which attracted budding scientists and their teachers from 18 area schools, opened labs throughout the Institute to the young people, who collectively were guided through 28 different hands-on lab activities and presentations by nearly 50 Salk scientists. Each group visited two labs before rejoining the full contingent of attendees for lunch. Following the meal, assistant professor **Satchin Panda** presented his latest research on circadian clocks, and participants received a special commemorative High School Science Day T-shirt before heading home.

Salk president William R. Brody welcomes the day's guests in the Frederic de Hoffman Auditorium.

Sharing SALK SCIENCE

The opportunity to introduce Salk research to new friends across the country is a very important component of Salk's outreach program, and we are very grateful to our hosts for helping to organize and support these talks.

Salk researchers **Fred "Rusty" Gage** and **Andy Dillin** brought Salk science to our friends in the communities of Charlevoix, Michigan, and Palm Beach, Florida.

(Left) **Andy Dillin** met with co-host Dorothy Lappin and guests to present his research: **Tapping the Brakes on Aging and Steering Clear of Alzheimer's Disease.**

(Right) Salk president **William R. Brody** with Arlene and Harvey Cherner

Rusty joined co-hosts Del and Adriane DeWindt, Mason and Lynne Rosenthal, and Bob and Wally Klein in Charlevoix to share with friends and neighbors: **The Dynamic Brain: Stem Cells to Brain Cells to Behavior.**

SALK in the city...

NEW YORK

Professor Vicki Lundblad, Diana Kalman and Kristina Kalman Fares during the luncheon at The Modern.

Dr. Irwin M. Jacobs, Chairman of the Salk Institute Board of Trustees

AT TWO SPECIAL EVENTS LAST NOVEMBER, NEW YORK friends of the Salk Institute had a chance to learn first-hand how their philanthropic investments are impacting groundbreaking research.The events, which took place in New York City for members of the Salk President's Club and NY salkexcellerators, both featured **Vicki Lundblad**, a professor in the Molecular and Cellular Biology Laboratory, who is renowned for her work in a fast-moving area of basic research called telomere biology.

To both audiences, Lundblad explained how telomeres, the very ends of chromosomes, play a crucial role in both cancer and aging. Each time our cells divide, a little bit of DNA is lost from the telomeres. Whether cells have a finite or infinite ability to proliferate is determined by the telomeres, which are tended to by an enzyme called telomerase. The limited number of divisions that telomerase-defective cells undergo eventually contributes to the aging process. Conversely, cancer cells have learned how to keep telomerase turned on all the time, and this fuels the unlimited cell division that is a hallmark of tumor growth.

More than 60 guests attended the NY salkexcellerators dinner, which was held November 9 at the law offices of Covington and Burling. In addition to Lundblad, the program featured remarks by John Codey, trustee of the Leona M. and Harry B. Helmsley Charitable Trust, and a member of the Salk Institute International Council, who has facilitated several generous grants to the Salk Institute. A special

Guests attending the luncheon at The Modern.

Alex Elman with Hanley, her seeing eye dog, speaking to the NY **salk**ex**cell**erators.

salkexcellerators NY

OF BREAD AND WINE: The Influence of Science and Biology on MODERN Life

feature of the evening was a wine tasting hosted by Alexandra Elman of Alex Elman Wines LLC. Elman, who recently became involved with the New York salkexcellerators, has a personal interest in advancing basic biological research: in her late 20s, due to complications from diabetes, Elman lost her vision. Underwriters for the evening were Kurt and Margaret Cellar and Sylvester and Gillian Miniter.

The following day, some 70 friends of the Institute attended the "Salk in the City…New York" luncheon which was held at The Modern restaurant, located in the Museum of Modern Art. Salk trustee Linda Chester and her husband, Kenneth Rind, underwrote the event. In addition to Lundblad's presentation, the occasion paid tribute to longtime Salk International Council member C. A. "Joe" Kalman, who passed away in 2010.

Impacting human health through scientific discovery depends on the vision and generosity of philanthropists. For more information about future Salk events in New York City, please contact **Betsy Rei**s at 858-452-8051 or breis@salk.edu.

Elizabeth Bennett, Carrie Hamerslag, Greg Rogers and Salk graduate student presenter Bari Braunstein-Ballew were among the many who attended the NY salkexcellerators event.

salkexcellerators

San Diego salkexcellerators go "green"at February event

SAN DIEGO SALKEXCELLERATORS ENJOYED a private reception and a lecture by associate professor **Jeff Long** at the Institute on February 16. The lecture, titled "Respect your Greens! Food, Fuels & Fundamental Findings," spoke to the current challenges we face in the food and biofuel supply and important recent Salk discoveries that may impact our ability to influence the quality and quantity of plants better suited to our agricultural needs. He was joined in his presentation by research associate Rhiannon Macrae and UCSD graduate student Jared Sewell.

Securing the world's food supply in a changing climate may be one of the biggest challenges we face in this century. Understanding the molecular underpinnings of how plants adapt to inhospitable environments and defend themselves against insects and fungal infections will be crucial to ensuring the world's food supply into the future, making basic plant research more important than ever.

Since its founding 25 years ago, the Salk's Plant Biology Laboratory, home to some of the world's leading plant biologists, has made several seminal discoveries related to genetic adaptation, flowering time and the mechanisms that control how plants perceive and respond to changes in their environment.

San Diego **salk**ex**cell**erators receive a variety of invitations to visit the campus throughout the year for lectures, laboratory tours and special events. The next event, set for May 4, will feature **Geoff Wahl**, a professor in the Salk's Gene Expression Laboratory and former president of the American Cancer Society, who will discuss his findings in cancer research.

You can help accelerate scientific innovation at the Salk Institute, where scientists like these are making groundbreaking discoveries and mentoring future leaders in research. For more information, please contact **Megan Shockro** at (858) 453-4100, ext. 1405, or mshockro@salk.edu.

Salkexcellerator Tammy Moore (left) and guest Karen Fredrich with Dr. Jeff Long

An enduring friendship

Lucy Miller is living proof that Salk science can touch a life in multiple ways.

Lucy Miller and her Labradoodle, Muffin.

THE SALK INSTITUTE WAS LITTLE MORE THAN AN ABSTRACTION to Lucy Miller when Salk researcher **Ursula Bellugi** contacted her in the early 1970s, seeking students who could help with her investigations into American Sign Language (ASL). Miller, a psychotherapist and expert in special education, was working as the student advisor in the Center on Deafness at California State University, Northridge (CSUN), and recommended several of the ablest students. Hearing-impaired herself, she became very interested in Bellugi's seminal work, which was exploring the neurological bases of ASL.

Coincidentally, and unbeknownst to Miller, around the same time, the Salk Institute also appeared on her parents' radar, and they became donors. Her father died in 1981, and in time, her mother developed Alzheimer's disease, passing away in 1993 after a long, slow decline. "By this time, I knew that Salk researchers were making groundbreaking discoveries about Alzheimer's," she says.

The following year, Miller, as trustee of her parents' trust, donated a significant property in their names to the Salk Institute. "When my parents died, I didn't know of their contribution history with Salk, but it was the one organization I felt was a worthy beneficiary of my inheritance," she says. The Institute celebrated the gift—and her parents—at a memorial luncheon that was attended by both **Jonas Salk** and Sir **Francis Crick**. Then, in 1996, Miller began to follow in her parents' footsteps, making annual President's Club contributions to Salk.

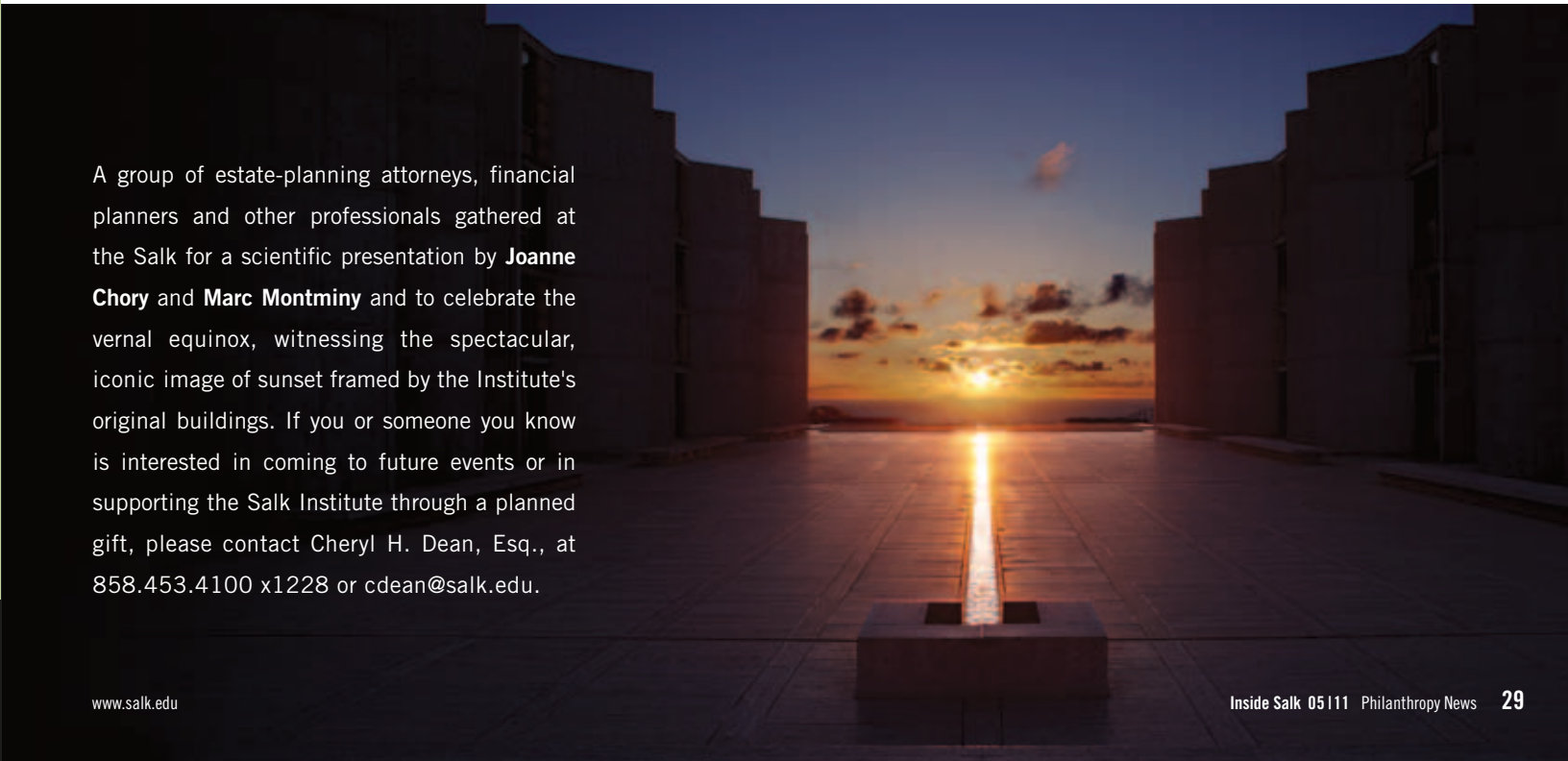
Today Miller, whose career has included positions as a rehabilitation counselor at the California State Department of Rehabilitation, assistant professor in the CSUN Department of Special Education and associate professor of special education at Pasadena City College, among others, is semi-retired and living in Hawaii, but the term *semi-retirement* is relative.

"I get to do what I love doing, although sometimes I overdo it when perhaps I should be slowing down," she admits. She serves in leadership positions on many boards, including the Disability and Communication Access Board for the State of Hawaii Department of Health and locally on the Mayor's Advisory Committee for Equal Access. She recently stepped down as the Kauai representative to the Hawaii Association of Marriage and Family Therapy, though remains active in a mentorship capacity. And as a frequent speaker in her various career fields, she gained confidence in public speaking through the Toastmasters organization and is still active with her local group.

She has also branched out in new directions. Two and a half years ago, after being involved in a serious pedestrian accident because she couldn't hear a car running a stop light, Miller acquired a Labradoodle puppy and with the aid of books and online discussion groups, trained her to be a hearing dog so she could alert her to environmental sounds for her own safety.

Somehow, despite her busy "semi-retirement," Miller finds the time to read all the Salk publications and stay abreast of the research taking place in its labs.

"What impresses me the most is its independence and the level of integrity it brings to biomedical research," she says, "and, as a result, the high level of people the Institute attracts who remain passionate about their creative pursuits."



A group of estate-planning attorneys, financial planners and other professionals gathered at the Salk for a scientific presentation by **Joanne Chory** and **Marc Montminy** and to celebrate the vernal equinox, witnessing the spectacular, iconic image of sunset framed by the Institute's original buildings. If you or someone you know is interested in coming to future events or in supporting the Salk Institute through a planned gift, please contact Cheryl H. Dean, Esq., at 858.453.4100 x1228 or cdean@salk.edu.

Visionary donor endows chair in vision research

THE SALK INSTITUTE'S RENOWNED program in vision research has received a significant boost, thanks to a generous $2 million gift from Salk trustee Conrad Prebys. The gift, which is being matched with an additional $1 million from the Joan Klein Jacobs and Irwin Mark Jacobs Senior Scientist Endowed Chair Challenge, will endow a new chair in vision research. **Thomas Albright**, professor and director of the Institute's Vision Center Laboratory and a leader in vision research worldwide, will be the first holder of the chair (see article, page 12).

"I couldn't be more pleased to support this extraordinary research," Prebys says. "To work with the Salk on discoveries that can potentially impact millions of people is what draws me to the Institute. Supporting this caliber of groundbreaking science under the leadership of Dr. Albright is inspiring."

Owner of Progress Construction Company and a developer of real estate enterprises in California and Texas, Prebys is a prominent philanthropist in San Diego who has shared his good fortune with the local community and is actively building a legacy of generosity throughout the region. A native of South Bend, Indiana, he was raised in a neighborhood where most of the residents worked in local factories. Through the encouragement of an inspirational teacher, he became the first of five brothers to graduate from college.

Albright, whose research focuses on the neural structures and events underlying the perception of motion, form and color, provided the first systematic evidence that humans' perception of motion does not depend on the physical characteristics, such as brightness, color or texture, of the object that is moving—a feature known as "form-cue invariance." 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. He 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.

Conrad Prebys

As Albright continues to seek new avenues to understand the neuronal structures and events that underlie visual perceptual experience and their contributions to knowledge, behavior and consciousness, the Prebys Chair will add significant momentum to his already distinguished research career.

"This unique gift will help change the way we view the world," says Salk president **William R. Brody**. "The discoveries from Tom's lab will illuminate the mechanics of information processing in these high-level visual areas and define their unique contributions to visual perception and visually guided behavior."

Chapman Foundations keep pace with Salk science

AS ONE OF TWO TRUSTEES OF THE H.A. AND MARY K. CHAPMAN Charitable Foundations, Donne Pitman is dedicated to facilitating the vision, hope and optimism that spur scientific discovery. His responsibility, which he shares with co-trustee Jerry Dickman, is to extend the legacy of the foundations' benefactors, H.A. and Mary K. Chapman, by pursuing grantmaking to benefit humankind, particularly in the areas that were most important to the Chapmans themselves. With medical research prominent on that list, the foundations have supported top institutions around the world. But Pitman and Dickman are particularly impressed with the Salk Institute because of its world-renowned faculty's leadership in basic biological research. The Chapman Foundations' resulting support, partnership and friendship with the Institute over close to two decades exemplifies their determination to advance human health by investing in stellar scientific research.

Pitman's unique perspective about the Salk stems from a keen understanding of the need for long-term relationships with investigators whose work is having a positive impact on scientific discovery. Pitman and Dickman visit the Salk campus annually to stay abreast of the latest findings in the Institute's labs and learn more about its needs. Most recently, under their direction, the Chapman Foundations made a generous $500,000 gift toward a multiphoton confocal microscope to enhance instrumentation in the biophotonics core.

In addition to supporting technology, Pitman also strongly believes that investing in young scientists at critical points in their careers will help propel them to become leaders in their fields. As a consequence, he and Dickman established the Chapman Scholars program to provide critically needed financial support for the gifted graduate students who play an essential role in Salk laboratories and to help accelerate especially promising scientific careers.

Sandie and Donne Pitman

Pitman's unique perspective about the Salk stems from a keen understanding of the need for long-term relationships with investigators whose work is having a positive impact on scientific discovery.

Over the years, the Chapman Foundations' contributions to the Salk Institute have totaled more than $6 million. This visionary investment in basic research is making a fundamental difference, laying the groundwork for improved human health worldwide, now and for generations to come.

Insider's View

President William R. Brody, M.D., Ph.D.

Sutton's law and chronic illness

Remember Willie Sutton, the infamous bank robber of the early 20th century? When he was finally apprehended, a reporter asked him, "Willie, why do you rob banks?" His alleged response was quite simple: "Because that's where the money is."

Willy's retort (which he later denied saying) is often referred to as Sutton's law.

Today with all the concern about rapidly rising healthcare costs, there has been little public attention drawn to the fact that the majority of costs—some studies say up to 75%—are incurred by patients with one of a handful of so-called chronic illnesses: cancer, stroke, Alzheimer's, diabetes, arthritis, heart failure.

Sutton's law of healthcare says if you want to reduce healthcare costs, you have to find ways of reducing the economic impact of chronic illness, ideally by preventing or significantly delaying when affliction occurs, or finding better and more cost-effective ways of treating the illness.

At the Salk Institute, our scientists are engaged in understanding the processes by which important chronic diseases such as cancer, diseases of aging, autoimmune disease, diabetes, etc. damage the body. Often genetic mutations are associated with these diseases, so understanding the genome and how it functions is an underlying theme of many of the Salk investigators. A thorough understanding of the mechanisms by which diseases occur is the first step toward better therapy.

Perhaps you have heard the term *disease markers*. These are biological handles by which physicians and scientists can track the onset and progression of various diseases. An early biologic marker for diabetes, for example, was sugar in the urine; later, elevation of the fasting level of glucose in the blood was used. Today there are more sophisticated markers for diabetes—for example, a blood test called Hemoglobin A1c that allows an accurate assessment of how well insulin and dietary therapy are working.

Another test, the PSA, helps identify early the possibility of having prostate cancer. In the past decade, many genetic markers have been developed to indicate one's risk for a particular form of cancer, especially the risk for breast cancer.

It is axiomatic that unless one has good markers for susceptibility or to track the early onset and progress of a disease, one cannot readily find and evaluate new drugs or other treatment modalities. Alzheimer's disease is particularly challenging because the onset of the disease most likely occurs years and perhaps decades before clinical signs of dementia appear in the patient, at which point the brain damage may likely be too extensive to treat successfully.

Our desire for fast cures must be tempered by the understanding that much work needs to be done for many diseases at a very basic level before we have the knowledge to know what treatments have a good likelihood of success and which do not.

We need a good marker for the early detection of Alzheimer's disease, but right now one doesn't exist that could be used routinely. Part of the important work of scientists here at the Salk is to try to identify markers of diseases such as Alzheimer's and place them within the context of biological and genetic alterations that might characterize disease.

> "At the Salk Institute, our scientists are engaged in understanding the processes by which important chronic diseases such as cancer, diseases of aging, autoimmune disease, diabetes, etc. damage the body."
>
> — William R. Brody

SALK INSTITUTE
FOR BIOLOGICAL STUDIES

STREET ADDRESS
10010 North Torrey Pines Road
La Jolla, California 92037-1002

Telephone: 858.453.4100
Fax: 858.552.8285
www.salk.edu

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

Salk **Calendar**

MAY 2011

4 **San Diego salkexcellerators**

10 **2nd Annual Salk Institute Golf Tournament**

11–13 **39th Annual Tax and Management Seminar for Private Foundations**

JUNE 2011

17–21 **Cell Cycle Symposium**

AUGUST 2011

10–14 **Mechanisms & Models of Cancer Symposium**

27 **Symphony at Salk with special guest Idina Menzel**

Summer Pleasure, 2010
Oil on canvas, 20" x 16"
Collection of the artist
© Françoise Gilot-Salk

Follow us on:

facebook.com/salkinstitute **twitter.com/salkinstitute**