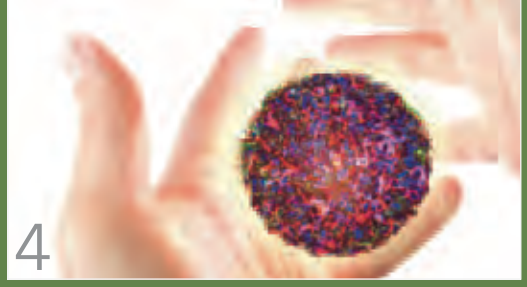
InsideSalk

Where cures begin
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES
12 | 11

Stem Cell Revolution

Salk scientists lead the way to new discoveries and therapies

December 2011
Inside Salk



Salk's 21st century revolution

One on one with…Joanne Chory

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

Andy Hoang
Director, Media Relations

Chris Emery
Director, Scientific Communications

Sarah Lifton
Science Writer

Jim Schnabel, Renee Twombly, Elise Lamar
Contributing Writers

Liz Hincks
Web Editor

Joe Belcovson and Kent Schnoeker
Photographers

Mike Sullivan
Web Extra Videography

Kat Kearney
Media Specialist

Sarah Loffler
Design and Production

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.

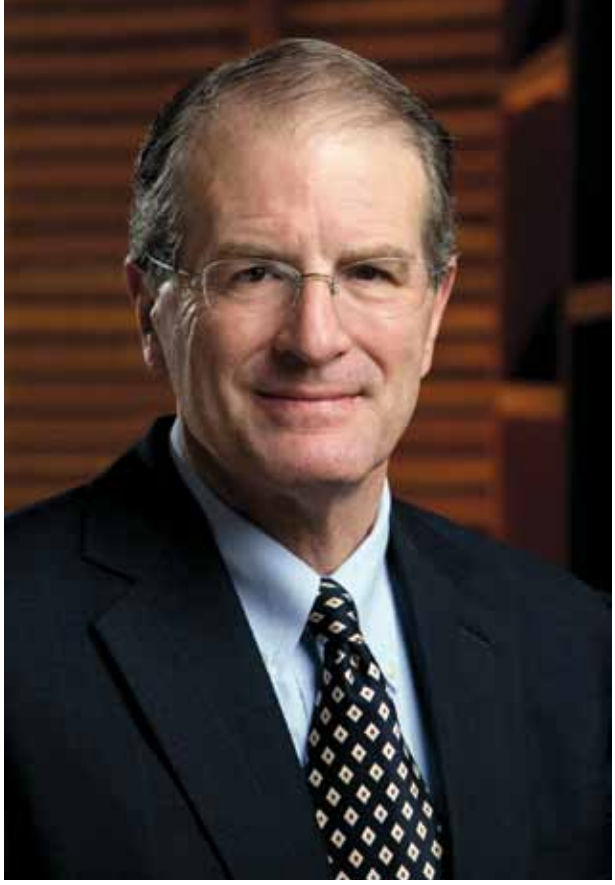
Dear Friends,

WITH THE HOLIDAYS ALMOST UPON US, IT IS A TIME OF WONDERFUL celebrations and opportunities to reflect. With all the life-changing work and growth at the Salk, I am happy to share with you exciting updates that have occurred over the last several months. One of the leading pieces of good news is that the SCImago Institutions Rankings World Report has identified the Salk Institute as one of the top five research organizations in the world, based on excellence and the high quality of our scientific findings.

Reading through *Inside Salk*, you will get a great feel for this year's Symphony at Salk: A Concert under the Stars. This was our 16th year of the event, and it was as spectacular as ever, with the extraordinary talent of Tony Award winner Idina Menzel, returning guest conductor Thomas Wilkins, and the San Diego Symphony. Over 700 people attended the event, and if you were not able to join us, I encourage you to plan on it for next year.

The Salk Institute has many things to be proud of, but we all agree that when it comes to our faculty, we are second to none. It gives me great pleasure to let you know about six promotions this year: **Leanne Jones** and **Satchidananda Panda** have been promoted to associate professor, and **E.J. Chichilnisky**, **Andrew Dillin**, **Martin Hetzer** and **Jan Karlseder** to full professor. Each of these stellar scientists underwent an extensive review process led by Salk senior faculty, non-resident fellows and scientific leaders in their respective fields.

A few other exciting highlights since our last issue include a $5.5 million grant from the NIH to study Williams syndrome, headed by **Ursula Bellugi**; two new endowed chairs paying tribute to **Renato Dulbecco** and **Roger Guillemin**, both former Salk presidents and Nobel Prize winners; and **Joanne Chory**'s election to the Royal Society (read the "One on One" article about Joanne inside). In addition, the San Diego Unified School District honored Salk's Education and Outreach Program with a 20-year Partner in Education Award; **Joseph Ecker** has been appointed an investigator with the Howard Hughes Medical Institute and Gordon and Betty Moore Foundation; and **Fred "Rusty" Gage** was recognized with several honors on two continents: Spain's Cátedra Santiago Grisolía Award 2011, an honorary doctorate in medicine from Lund University in Sweden and appointment as president of the International Society for Stem Cell Research (ISSCR). He is also the 2011 recipient of the prestigious National Institutes of Health Director's Transformative Research Project Program. **Axel Nimmerjahn**, assistant professor in the Waitt Advanced Biophotonics Center and holder of the Richard Allan Barry Developmental Chair, has been named a 2011 Rita Allen Scholar and is a recent recipient of a highly selective grant from the Whitehall Foundation; the National Institutes of Health announced that the Salk Institute will receive $4.5 million to establish a Neuroscience Core Center, and **Dennis O'Leary**, the Vincent J. Coates Professor of Molecular Neurobiology at Salk, will serve as director of the new center. The Ipsen Life Sciences Program has been renewed as part of an agreement between Ipsen and the Salk, and **Inder M. Verma** has recently been appointed editor-in-chief of the *Proceedings of the National Academy of Sciences (PNAS)*, the official NAS journal.



William R. Brody

> **"...when it comes to our faculty, we are second to none."**

In addition to the many accolades, awards and grants you will read about in the following pages, nearly a dozen papers have been published in leading journals and publications worldwide, based on the work and collaborations of Salk scientists.

While you are enjoying your holidays and spending time with family, remember that your Salk family is pursuing some of the most challenging scientific questions and needed discoveries that will enhance and impact the human condition. That is our gift to you.

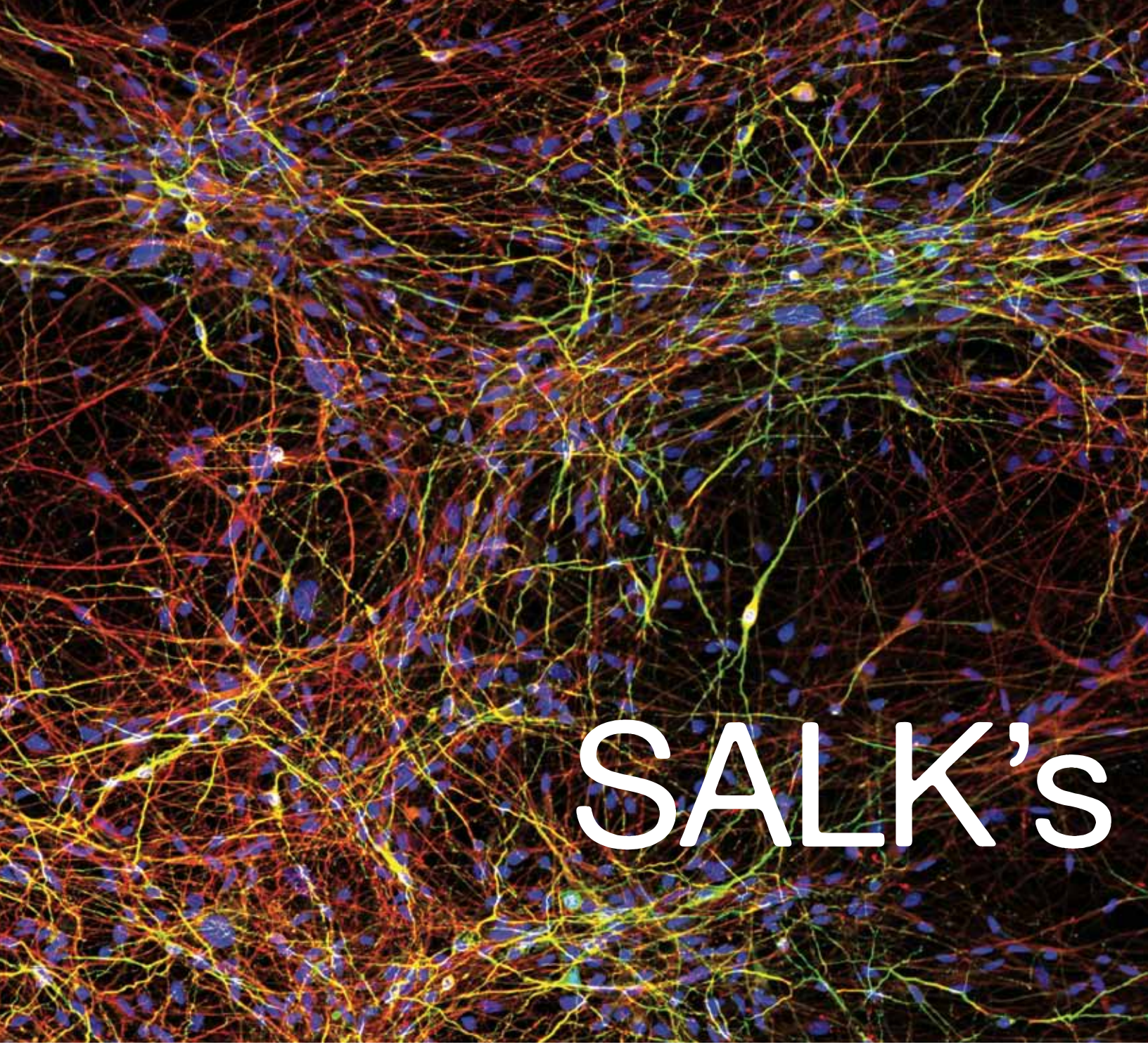
Thank you for your continued support and commitment.

William R. Brody

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

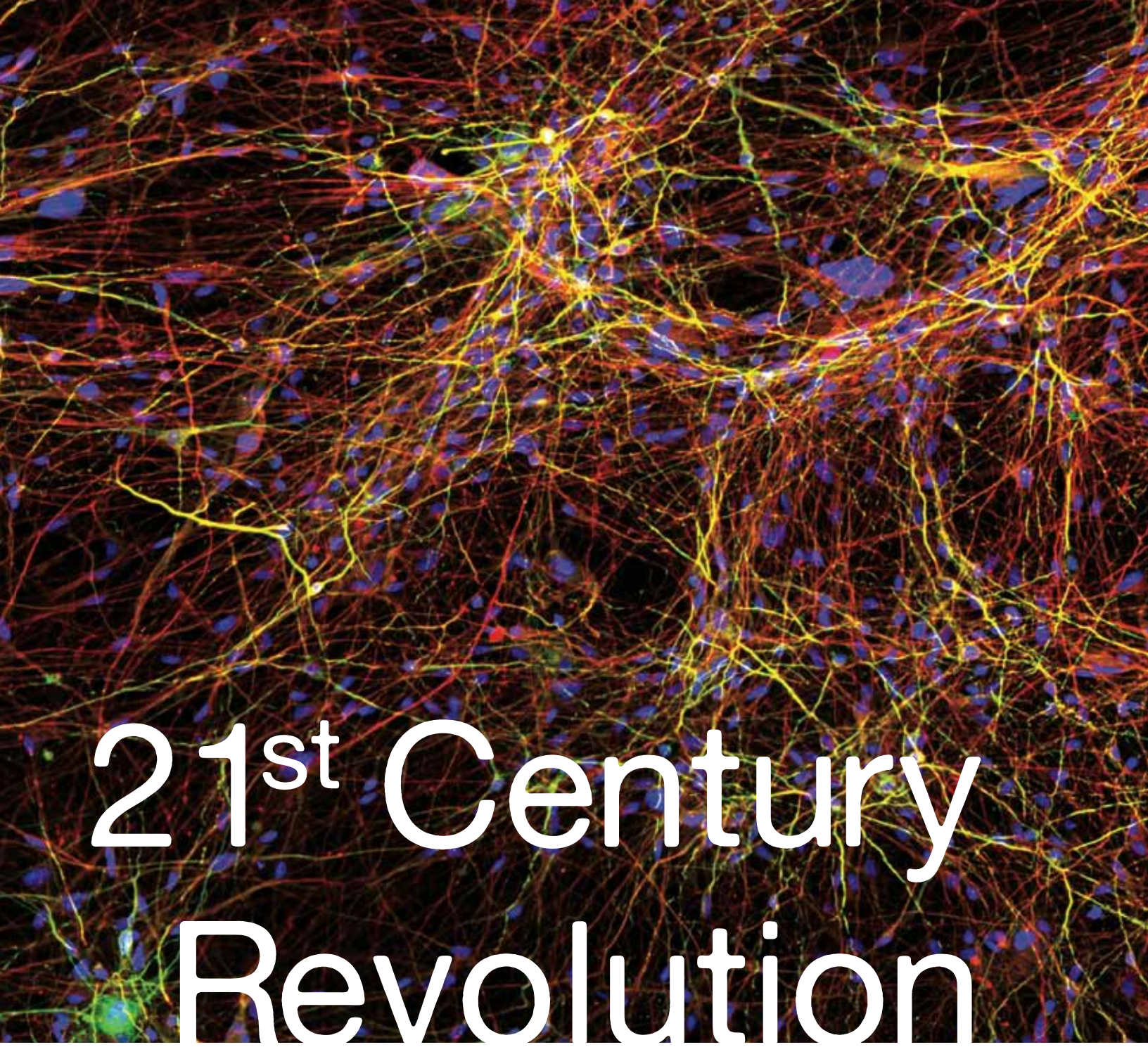
ON THE COVER

An environmental scanning electrograph of a *phabulosa-3D* mutant shoot. This mutant has a larger shoot stem cell population (center) and produces leaves that consist entirely of dorsal (top side) tissues. *Image courtesy of Matt Joens and Jeff Long.*



SALK's

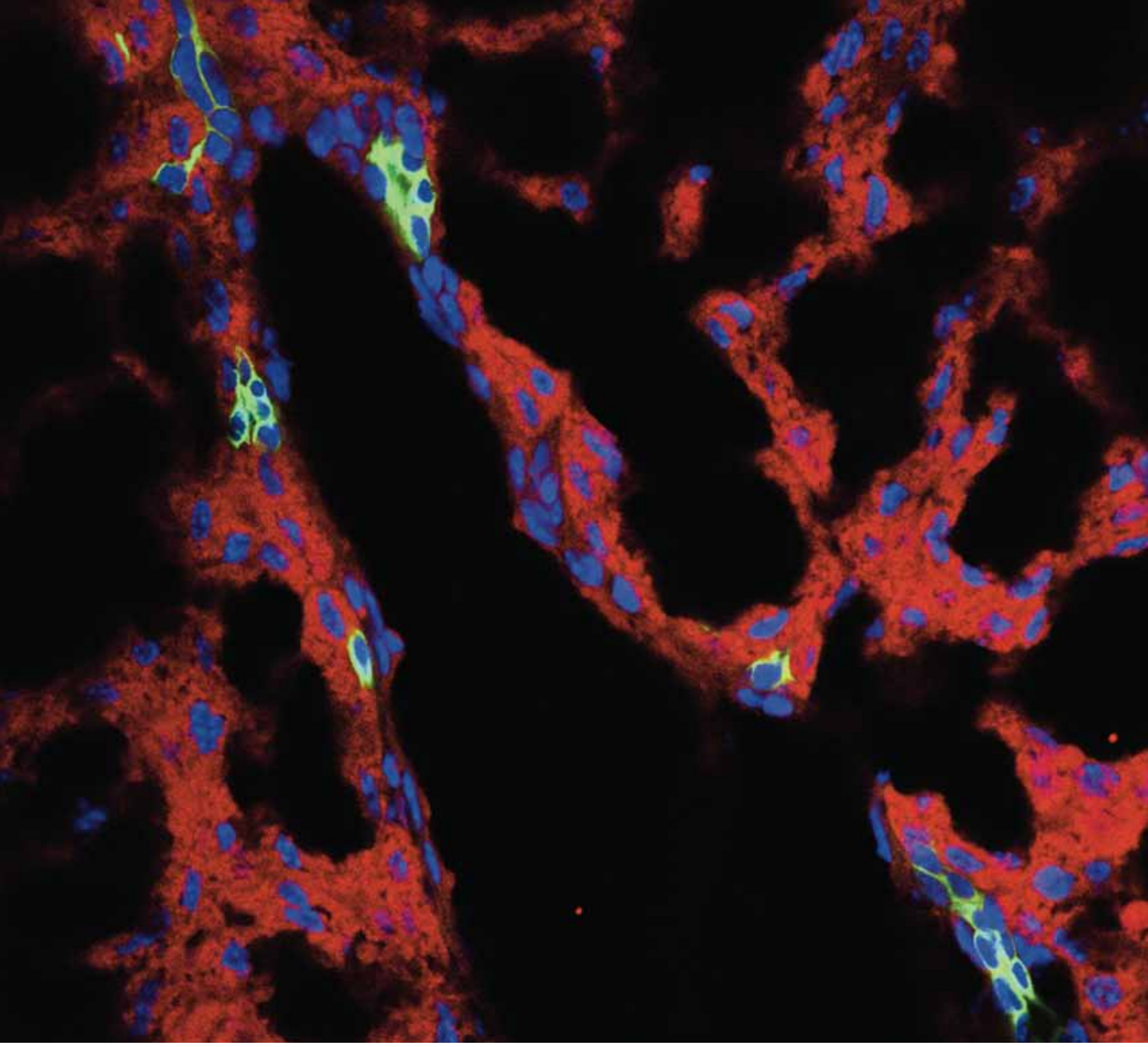
This is a large example mosaic image of hESC (human embryonic stem cell)-derived neurons labeled in three colors taken on one of the laser-based microscopes in the biophotonics facility. Blue represents cell nuclei, green is a dendritic marker and red is a neuronal cell marker. *Sample provided by T.J. Eames (grad student, Gage Lab) and imaged by James Fitzpatrick, director of the Biophotonics Core.*



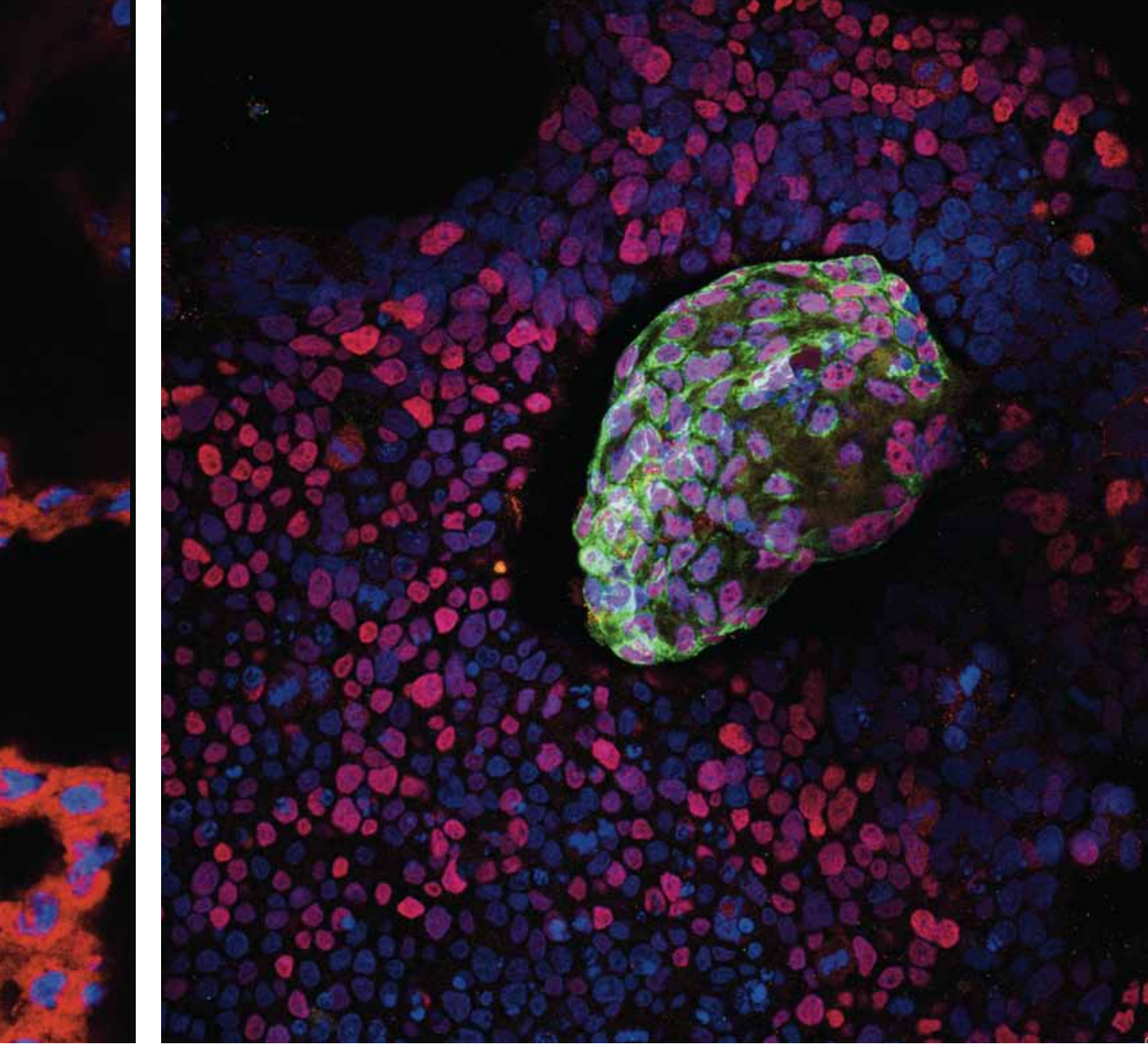
21st Century Revolution

Born from a medical revolution half a century ago, the Salk Institute has spent the past couple of decades on the front lines of an even more ambitious one: the stem cell revolution.

So far, it has been a simmering revolution. Researchers are still busy analyzing and perfecting the tricky dynamics of safely reprogramming the body's ordinary cells into stem cells and clearing the many obstacles that stand between hopeful science and useful therapies. But such therapies, when perfected, won't merely improve medicine. They'll also simplify and expand it. And the pace of recent progress suggests that the culmination of these efforts may be only years, not decades, away.



The Salk Institute is one of the principal drivers propelling basic stem cell research toward discovery and drug therapies. Virtually since the origins of modern stem cell research in the 1980s, Salk scientists have been producing influential science in the field, whether they are conducting basic studies of stem cell biology or developing stem cell–based disease models and even prospective therapies. In the early 2000s, Salk officials and researchers helped push for passage of California's Proposition 71, which provided for $3 billion in stem cell research funding and facility construction over ten years. Now more than a dozen Salk laboratories, collaborating with other leading labs in the U.S. and abroad, are taking part in this critical biomedical endeavor. "Our involvement in stem cell research has been escalating dramatically, across all the main areas of investigation, from basic science to potential therapeutics," says Salk professor and stem cell pioneer **Fred H. Gage**.



The human impact

Stem cells are the cells from which all animals and plants begin. Their power lies in their versatility. The "pluripotent" stem cells of a developing embryo have the potential to develop into all the cell types in the body, from red blood cells to heart muscle cells to dopamine neurons in the brain. Even in a full-grown organism, certain organs and tissues contain "multipotent" stem cells that stand ready to generate new local cells to replace those cells lost to injury and aging.

The basic idea of stem cell medicine is to use the youthful, replenishing, self-renewing properties of stem cells to treat disease. Neural stem cells, for example—stem cells that make new nerve cells—might help repair spinal cord ruptures and free paralysis patients from their wheelchairs, or boost the brain's defenses against Alzheimer's and Parkinson's diseases. Cardiac stem cells, injected into a failing heart, could rebuild it in place, making a heart transplant unnecessary. Scientists also hope to use stem cells to grow—in the laboratory—youthful, healthy organs, such as livers and windpipes, that later can be transplanted into patients.

Dozens of institutions around the world are now working to turn these stem cell dreams into medical realities, and among them, the Salk Institute stands out for its high-impact work. "We have great core facilities, a highly collaborative environment, broad expertise and a good mix of basic and clinically oriented science," says Gage.

Adds Salk professor **Juan Carlos Izpisúa Belmonte**: "We still need to know many things at a fundamental level, to advance stem cell science to the clinic. To that end, it helps greatly to be surrounded by Salk colleagues who are among the world's best in basic areas of cell biology."

Seeing how they grow

One area of research focuses on the adult stem cells that help maintain and repair the organs and tissues where they reside. The activity of these stem cells tends to decline with age, so a major goal is to find drugs or other techniques that can boost this activity to treat or even prevent disease.

Neural stem cells have always been an inviting target because of their potential to help the brain ward off Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (Lou Gehrig's disease), Huntington's disease, multiple sclerosis and possibly even the ordinary cognitive decline of aging. Gage was the first scientist to identify adult neural stem cells in humans in the mid-1990s, and his lab at Salk is still heavily involved in studying how the ability of these stem cells to generate new brain cells—a process called neurogenesis—can be boosted. "One of the more encouraging things we've found is that even in very elderly mice, factors such as exercise and social enrichment can cause neural stem cells to proliferate and generate fully functional neurons," Gage says.

Stem cells are at work elsewhere in the body too, and again, they have limitations that stem cell science could one day overcome. Some amphibians and fish can regenerate their organs even in adulthood, but humans and other mammals lose this capacity in the womb or early infancy. Izpisúa Belmonte and his lab have shown that zebrafish regenerate heart muscle by activating a certain signaling pathway in heart muscle cells. "The signals make the heart muscle cells go a little bit backward in their development, in the direction of the stem cell state, so that they can proliferate again," Izpisúa Belmonte says. "We have found recently that in mammals, this process is switched off shortly after birth, which explains why they no longer have this regenerative capability."

Salk researcher **Leanne Jones** has used the fruit fly *Drosophila* as a model for studying the age-related decline in stem cells' ability to repair organs and tissues. Her work has shown that aging affects not only stem cells but also the stem cells' "niche"—the other cells and proteins that make up stem cells' environment and that help regulate their normal functions. "To optimize the transplantation of stem cells in regenerative medicine, we may also need to consider rejuvenating the niche, especially in older patients," she says.

Reprogramming cells to the stem cell state

A decade ago, researchers thought that the only reliable way to get human stem cells that could be grown and studied in the lab was to take them from human embryos—typically the discarded pre-implantation embryos produced at fertility clinics. "We knew that human embryonic stem cells were potentially quite powerful, but there were ethical and technical issues that discouraged a lot of researchers from getting involved in that work," says Gage.

Even identifying adult stem cells in patient tissue samples was extremely difficult. Then in 2006 came a major breakthrough. Researchers reported that they had found a technique that would allow ordinary adult cells, such as skin cells, to be "reprogrammed" to a stem cell state by inserting four special genes into their DNA. The first demonstration was in mouse cells; then in 2007, researchers showed that the technique works in human cells too. "It meant that in principle anybody could have their own individualized stem cell therapy; it opened the floodgates of research," Gage says.

> “We have great core facilities, a highly collaborative environment, broad expertise and a good mix of basic and clinically oriented science.” – FRED GAGE

These “induced pluripotent stem cells,” or iPS cells, are now the focus of most therapy-oriented stem cell research. One of the big challenges facing researchers is to understand how iPS cells differ from embryonic stem cells, and a major contribution to the understanding of those differences was reported by Salk scientists **Joseph Ecker**, **Ronald Evans** and colleagues in *Nature* last March. Their team found that the pattern of gene activity within iPS cells differs extensively from that in embryonic cells. “We need to understand what these differences would mean if you were to inject such iPS cells into people for therapies,” says Ecker.

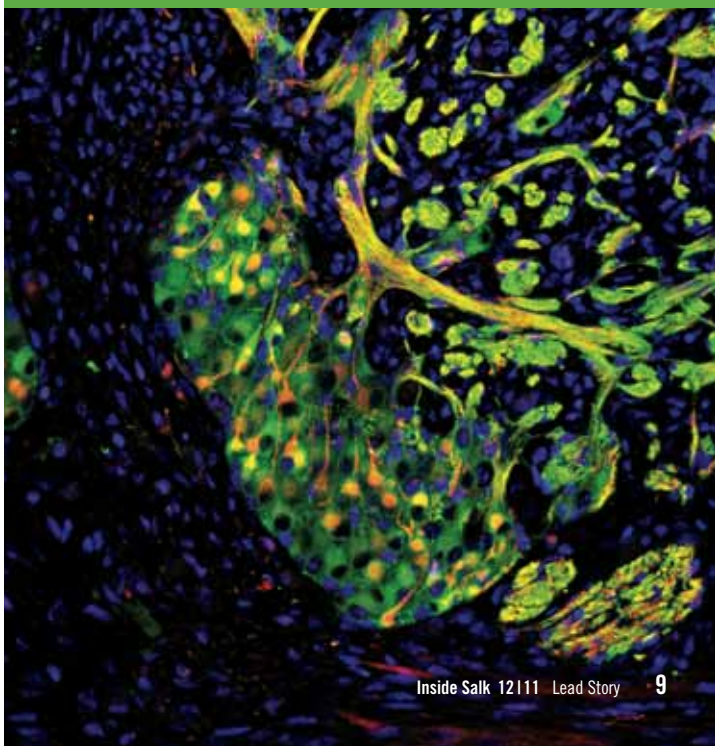
“Knowing these differences also gives us an opportunity to find drugs that can erase the changes and create a more effective cell,” adds Evans. The researchers now are collaborating with other labs to see how these differences change depending on the techniques used to reprogram cells to the iPS state.

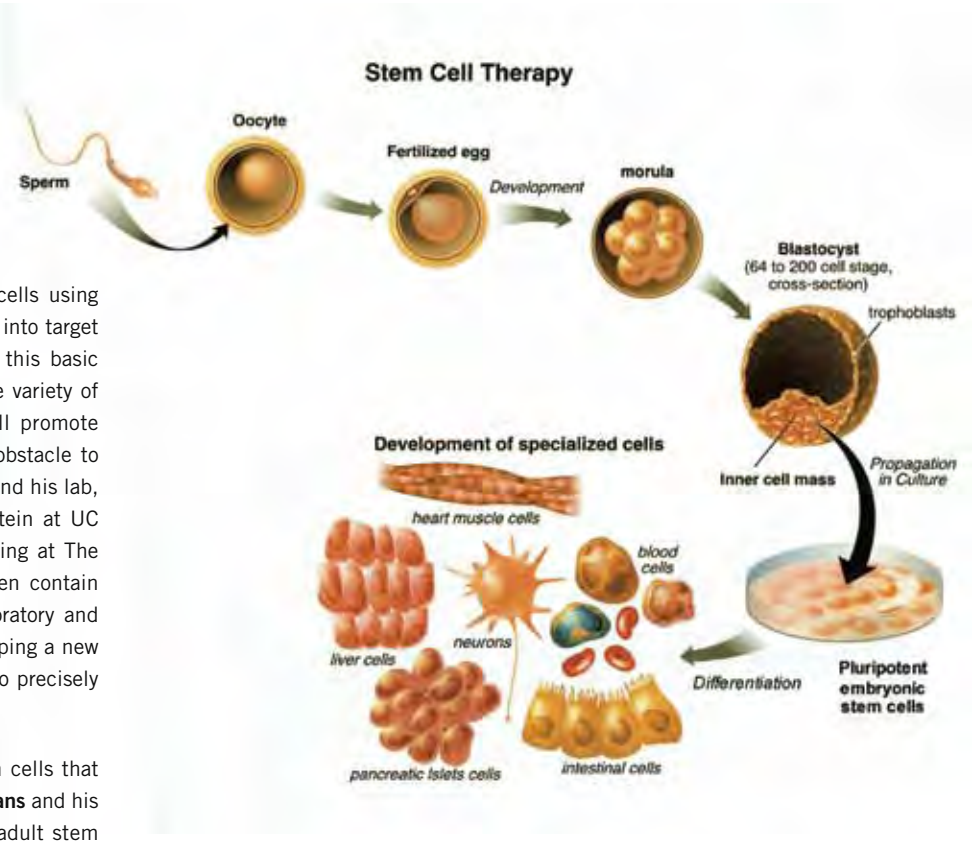
Stem cell–based therapies

Of the very few stem cell therapies now on the drawing boards, two are being developed at Salk.

Inder Verma’s lab is experimenting with a potential hemophilia cure, which involves generating liver cells from patient-derived iPS cells, conducting gene therapy to correct the hemophilia-causing DNA mutation and implantating the therapeutic, long-lived cells back into patients. His group has already succeeded in generating mice with human livers, in preparation for preclinical testing.

Another Salk project aims to slow or stop ALS, the motor neuron–killing disease that felled the baseball star Lou Gehrig in 1941 and that is inexorably fatal in most patients. Since 2009, Salk professor **Sam Pfaff** has received about $3 million in annual funding from the California Institute of Regenerative Medicine to do early development work on this strategy, along with collaborators Larry Goldstein and Don Cleveland of UCSD. Their idea is to use embryonic stem cells to generate cells known as neural precursor cells, which go on to generate astrocytes—support cells that normally provide neurons with nutrients and energy and that help them get rid of harmful cellular waste. “Our team’s goal is to demonstrate that we can safely implant these astrocyte precursor cells into the spinal cord in order to protect neurons from the damaging affects of ALS,” says Pfaff. “We hope to provide the data to the Food and Drug Administration for an investigational new drug study in patients within the next few years.”





Scientists normally reprogram adult tissue cells into iPS cells using an artificial virus that carries the four reprogramming genes into target cells and inserts the genes into the cells' DNA. But with this basic technique, the reprogramming genes may end up in a wide variety of places—and in some of these places, their insertion will promote cancer or otherwise harm the cell, which is a significant obstacle to the therapeutic use of iPS cells. Indeed, Izpisúa Belmonte and his lab, collaborating with the labs of Kun Zhang and Larry Goldstein at UC San Diego and the labs of Louise Laurent and Jeanne Loring at The Scripps Research Institute, have shown that iPS cells often contain unpredictable DNA abnormalities. Izpisúa Belmonte's laboratory and the laboratory of Salk professor Inder Verma are now developing a new technique that allows them to insert genes more safely, into precisely targeted locations in cellular DNA.

Another approach to making iPS cells safer is to start with cells that are already in the stem cell state. Salk researcher **Ronald Evans** and his team have developed a technique to make iPS cells from adult stem cells in people's fat deposits—the kind of deposits removed during liposuction, for example. Adult fat stem cells on their own can make only new fat cells, but when reprogrammed to the pluripotent iPS state, they can be directed to make virtually any other cell type. "Fat is a rich source of stem cells; we can efficiently turn them into iPS cells, and they also have a unique safety advantage," Evans says. Normally, cells that are reprogrammed to the iPS state have to be grown in the presence of special "feeder cells" that provide essential nutrients, but feeder cells typically come from other people or from mice and contain viruses and foreign proteins. "Exposure to this foreign material can create serious contamination problems, but fat cells don't require these foreign feeder cells, so they represent a real breakthrough," Evans says.

Therapies on the horizon

Salk researcher **Inder Verma** was known as an expert on gene therapy research when he decided to begin studying stem cells a few years ago. The first successful gene therapy trials, for children born with severe immunodeficiencies, were carried out using viral vectors he designed. "With gene therapy, ideally you want to introduce a therapeutic gene that keeps working for the rest of the life of the patient. If you put a gene in a cell that lasts for only a few months, it doesn't really help. But in a stem cell it could work for the rest of the patient's life," he says.

A stem cell that comes from the patient, rather than from a donor, would be particularly useful, so when the first iPS techniques were reported, Verma decided to extend his work to stem cells. His main goal now is to use iPS cells to create therapeutic quantities of the adult bone marrow stem cells that replenish our blood and immune cells. This past May, in the journal *Stem Cells*, Verma and his lab reported reaching a significant milestone on the way to this goal: the highly efficient

W. Travis Berggren, director of the Salk Stem Cell Core.

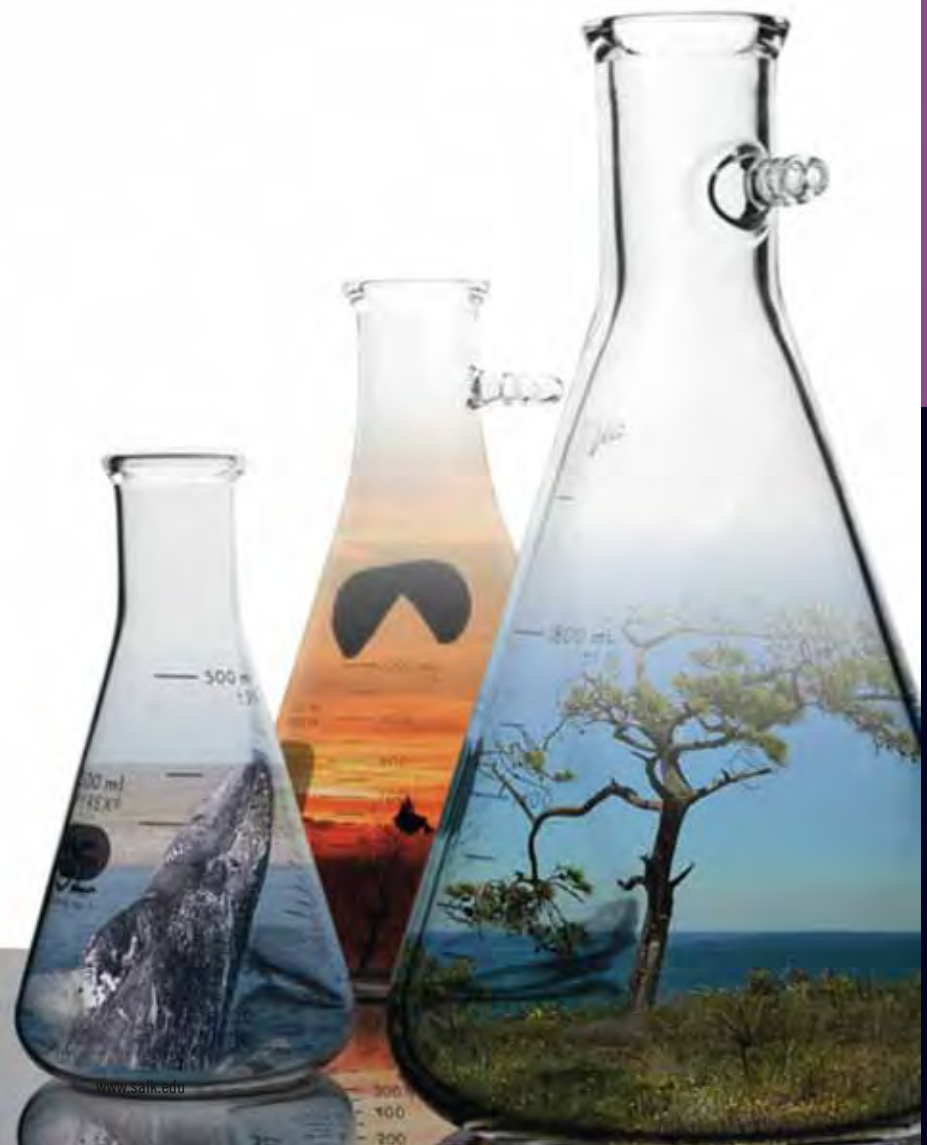
generation of human blood cells from iPS cells. The lessons learned from that study are now enabling them to zero in on the "recipe" for turning iPS cells into plentiful marrow stem cells. "We are quite close to being able to take ordinary cells from a patient, convert them to these marrow stem cells and give these marrow stem cells back to the patient, without worrying about immune rejection," says Verma.

That on its own would be therapeutic in many conditions—for example, in patients who need a bone marrow transplant. "Our ultimate goal is to use the marrow cells as vehicles for therapeutic genes, and then there is almost no limit to the medical applications," he adds.

Early gene therapy methods were risky because they used viruses to deliver new genes to unpredictable locations within the DNA of target cells. Researchers have needed new techniques that can deliver genes to precise locations and that can even cleanly replace bad genes with good ones. Izpisúa Belmonte's lab has made major progress in this area. Their technique (noted above) for inserting genes in a precisely targeted way can be used to repair the DNA of any cell, so that mutant, disease-causing genes are replaced with healthy versions of those genes. This past June, Izpisúa Belmonte's team reported a successful demonstration of their "gene-editing" technique in iPS cells derived from patients with Hutchinson-Gilford progeria syndrome, in which gene defects cause premature aging. "In principle, this technique could be applied to correct a wide variety of gene defects," Izpisúa Belmonte says.

Making stem cell-based models of disease

Even though stem cell therapies have not yet reached the clinic, stem cell science is having an impact on medicine. Researchers are using iPS techniques to take skin or other easily available cells from a patient, turn them



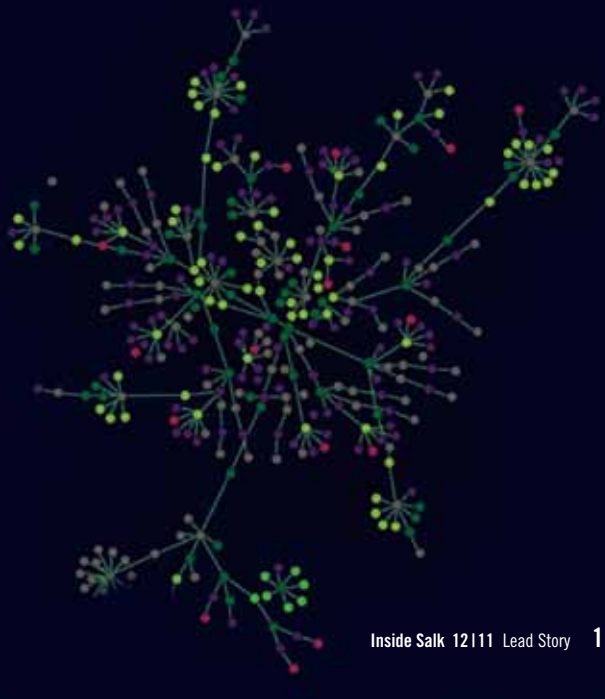
Critical mass: collaborations at Salk

Salk researchers have partnered with several leading stem cell labs at other institutions, including those of Larry Goldstein, Don Cleveland and Gage lab alumnus **Alysson Muotri** at UCSD; Rudolf Jaenisch at MIT; and James Thomson at the University of Wisconsin at Madison. In autumn 2011, Salk scientists will begin working side by side with partners from several other institutions in a new facility near the Salk campus, funded by the Sanford Consortium for Regenerative Medicine.

But Salk stem cell research is also powered by collaborations within the Institute. "This is one of the real strengths of the Salk—its highly collaborative environment," says Salk's **Joe Ecker**.

While working recently to map the epigenetics of iPS cells, Ecker was approached by fellow Salk researcher **Ron Evans**. "Ron is an expert on fat metabolism and has shown that you can harvest fat stem cells from the kind of fat deposits removed during liposuction procedures," Ecker says. "He asked if we could work together to look at the epigenetics of iPS cells that are derived from these fat stem cells."

Evans and his crew provided the fat stem cells as well as protocols to turn them into iPS cells. Ecker and his lab provided expertise in epigenetic analysis. The result was a groundbreaking paper in *Nature* last March on the epigenetics of different kinds of iPS cells. "It was a great collaboration," Ecker says.



Old cells, young cells, stem cells

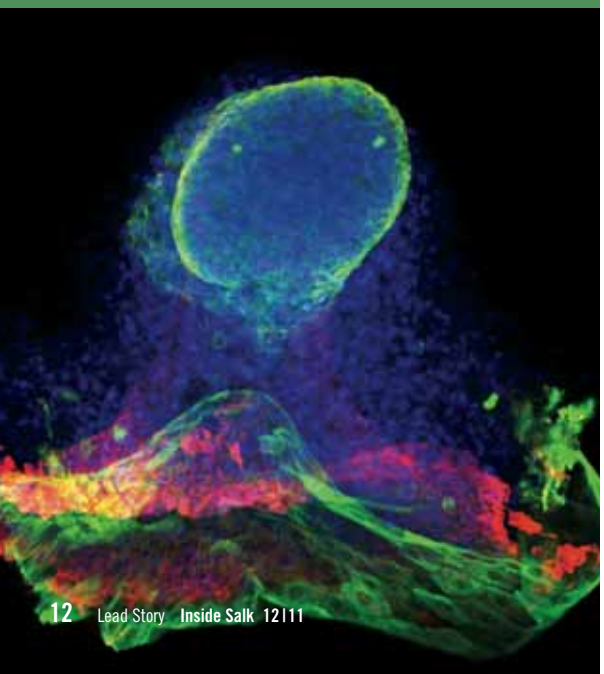
How does the biology of stem cells relate to the biology of ordinary cells as they age? It's a question that Salk professor **Jan Karlseder** is keen to answer.

Karlseder is an expert on telomeres, the lengths of DNA at the ends of chromosomes that serve as markers of cellular aging. In most ordinary cells, each process of cell division shortens telomeres, which in turn reduces the cells' ability to keep dividing. Eventually a threshold is reached, and cells stop dividing altogether, becoming "senescent" and, in time, dying.

Last year, Karlseder and colleagues published research showing that artificially re-lengthening telomeres in old cells brought about basic changes in the packaging of cellular DNA—"epigenetic" changes that make it easier for a wider range of genes to be expressed. "We ended up switching the epigenetic profile of old cells to the profiles of young cells," Karlseder says.

The young cell profile is also like that of a stem cell. "We hypothesized that we could increase the efficiency of reprogramming patients' cells into stem cells simply by elongating their telomeres," says Karlseder. "We're investigating that now."

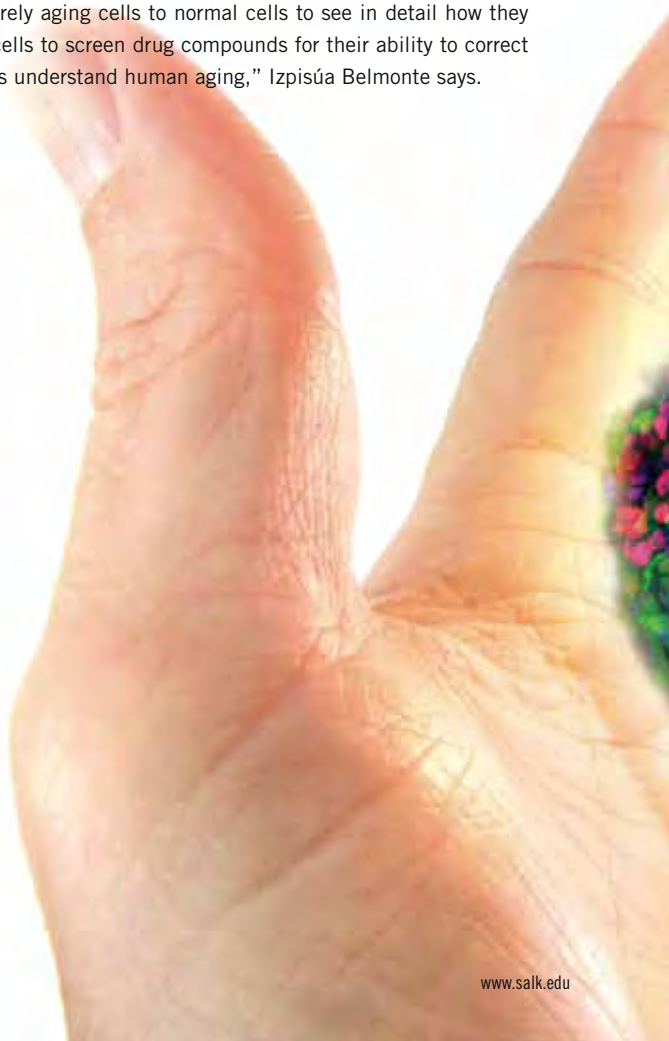
A mammary bud in a mouse at about 15 days of embryogenesis. *Image from Dannielle Engle in Geoff Wahl's lab.*



into iPS cells, and then direct those iPS cells to mature into brain cells, heart cells or cells from whatever tissue is diseased in that patient. Researchers can then study these cells to gain insights into the disease process and even to test possible disease-modifying drugs far more easily and quickly than they can in traditional animal models. They call these patient-derived cells "disease in a dish" models, and the number of papers describing them has been rising rapidly in the past few years.

One of the landmark achievements in stem cell–based disease modeling was reported by Gage and his lab last May in *Nature*. Taking cells from several schizophrenia patients, they converted the cells to iPS cells, then made them mature into neurons that grew so well that they formed spontaneous, brain-like networks in the lab dish. Using the iPS cell–derived neurons as a model of schizophrenia, Gage's team found that they had a host of abnormalities in gene expression as well as a reduced number of connections to each other. A standard antipsychotic drug, loxapine, reversed many of these abnormalities, thus demonstrating the potential of this iPS cell–based disease-modeling technique to help scientists test prospective drugs cheaply and easily. Gage and his lab now are improving their schizophrenia models and are working on autism-related and even Parkinson's disease models. "We're currently trying to get iPS cells to differentiate not just into basic neurons but into highly specific subtypes of neurons—for example, the midbrain dopamine neurons that are heavily affected in Parkinson's, to see if that gives us greater insight into the disease," Gage says.

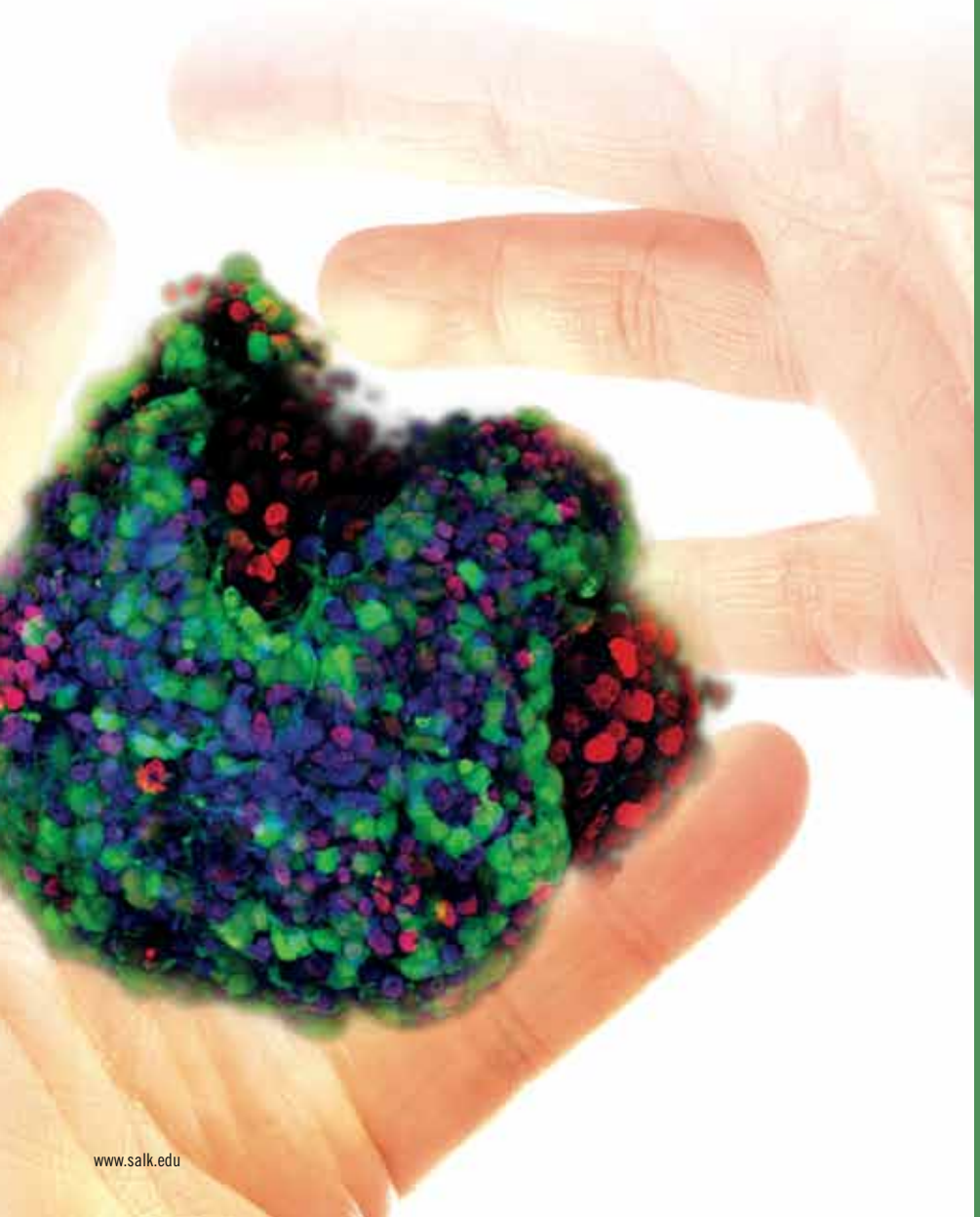
Izpisúa Belmonte and his lab are active in this area too. They are using their new gene-editing technique to repair the DNA in their iPS cell–based models of progeria. "In this way we can compare prematurely aging cells to normal cells to see in detail how they differ, and we can use these cells to screen drug compounds for their ability to correct these differences, and perhaps understand human aging," Izpisúa Belmonte says.



Looking forward

What stem cell medicine applications can we reasonably hope for in the next five years? "Certainly there will be drugs in clinical trials that have been discovered through the use of iPS-based cell models," says Gage.

Stem cell–based therapies are also likely to be in clinical testing, and Gage sees marrow stem cells as one of the first potential blockbuster applications. "There's already so much medical infrastructure in place for doing bone marrow transplants that this would be easy once we overcome the technical obstacles to making marrow stem cells safely," he says. "We're still in the early stages of developing these therapies. But it's all going to happen."



Cancer's stem cells

Studies of stem cells have been making a major impact on the scientific understanding of cancer. Researchers recently have learned, for example, that tumors typically contain their own stem cell-like cells that may survive chemo or radiation therapy and later seed the growth of new, more aggressive tumors. Several labs at Salk are now working in this area. **Inder Verma** recently reported that in the virtually incurable brain cancer known as glioma, some mature glial cells undergo an iPS-like transformation into a stem cell state. "That's why gliomas are so terrible," says Verma. "Even after a surgeon has operated, and 99.9 percent of cells are removed, tumor stem cells that have been left behind can make a whole new tumor."

Incipient cancer cells are often kept from proliferating by the activity of a protein called p53, known as a tumor suppressor and sometimes called the "Guardian of the Genome." Salk professor **Geoffrey Wahl** and his lab, in collaboration with Izpisúa Belmonte's lab, have shown that p53 also can obstruct the reprogramming events that produce iPS cells from ordinary mature cells. "When p53 is disabled, the reprogramming process happens much more efficiently," Wahl says.

Wahl's lab next asked whether cancer cells that contain inactivated p53—as many do—show signs of having reverted to a primitive, embryonic stem cell-like state. In collaboration with Arnold Levine's lab at Princeton, they studied p53-disabled breast cancer cells and found that they do indeed strongly resemble embryonic stem cells. More recently, the two groups extended this work by finding resemblances between these breast cancer cells and the normal stem cells that arise in the embryo and are destined to build the adult mammary gland. "These cancer cells become caricatures of normal developing cells by resurrecting gene activity patterns from their original developmental phase," Wahl says. "It's a phenomenon that could be very relevant to cancer treatment, drug resistance and metastasis."

»1997

Gage lab reports that a socially "enriched" environment increases the generation of new neurons ("neurogenesis") in aged mice.

»1998

Gage lab reports first evidence of neurogenesis in the brains of human subjects.

»1999

Gage lab reports that physical exercise boosts neurogenesis in mice and improves their cognitive abilities.

Verma lab reports the introduction of genes in human hematopoietic stem cells by lentiviral vectors that can reconstitute the repertoire of blood cells in the mouse.

»2003

Pfaff's lab describes details of how neural stem cells become motor neurons; the work suggests that stem cell therapies might help against neurodegenerative diseases such as ALS.

Izpisúa Belmonte lab describes a signaling pathway involved in heart regeneration.

Stem Cell Research at Salk

Salk scientists have long been at the cutting edge of stem cell research. Supported in large part by Proposition 71, which provided $3 billion in funding for stem cell research through 2014 and set up the California Institute for Regenerative Medicine (CIRM), Salk researchers have made many pioneering discoveries.

»2008

Gage lab finds that switching off neurogenesis in adult mice impairs learning and memory.

Gage lab reports controlling neural stem cell fate within mouse brains.

Izpisúa Belmonte lab reports that iPS cells can be efficiently obtained from a single human hair.

»2009

Ecker lab maps the "epigenome" in human embryonic stem cells and skin cells by determining the patterns of gene-silencing methylation marks on their DNA.

Izpisúa Belmonte lab reports that human umbilical cord blood cells could be an ideal source of iPS cells.

Izpisúa Belmonte and Verma labs report the generation of disease-free hematopoietic progenitor cells from iPS cells derived from Fanconi anemia patients.

Wahl and Izpisúa Belmonte labs find that p53 tumor suppressor pathway inhibits iPS reprogramming.

»2010

Gage lab and lab of Salk alumnus Alysson Muotri at UCSD report iPS-derived cell model of Rett syndrome.

Gage lab finds hormonal signal that regulates neural stem cells and that may link exercise to neurogenesis.

Izpisúa Belmonte lab reports the mechanism by which zebrafish can regenerate lost heart tissue.

»2004

Gage and Evans labs find key receptor that regulates neural stem cells.

»2005

Gage lab finds key signaling molecule that regulates neural stem cells.

»2006

Izpisúa Belmonte and Gage labs find factors that nudge embryonic cells toward muscle cell fate, or back to stem cell state.

Izpisúa Belmonte lab uses stem cell signaling factor to induce wing regeneration in fetal chicks, which normally cannot regenerate lost limbs.

»2007

Jones lab finds that stem cells' supportive environmental "niche" declines with age.

Salk's Stem Cell Core Facility

At the core of Salk's stem cell research effort is, well, "The Core," a central facility for stem cell culturing and cold-storing and experimenting. It was set up in 2007 after Salk professor Verma led a team of Salk scientists to secure funding from the California Institute of Regenerative Medicine (CIRM). Initially it was justified as a dedicated space for research on human embryonic stem cells, which was at that time hampered by stiff federal funding restrictions even though they were the only stem cells that could be cultured in the lab. Techniques to make iPS cells were developed at about that time, and the facility's director, **Travis Berggren**, soon turned it into a broader center of excellence. "It's really a central resource to allow people here at Salk to get quickly up to speed in working with both embryonic and iPS cells," he says. "Growing these cells involves some significant technical challenges, and we're here so that no one at Salk has to start from scratch."

The core houses live and frozen stored cultures of both embryonic and iPS human cell lines, validates the chemical "reagents" that make up culture media, maintains the physical space and equipment where Salk researchers come to study the stem cells, trains the steady stream of new researchers who conduct stem cell experiments, and keeps abreast of the latest culturing techniques—which owe much to work done by Berggren at the University of Wisconsin, his last post before Salk. The success of the Salk stem cell core has led CIRM to renew Verma's original grant for the facility for another three years.

Leanne Jones, whose lab recently began studying human stem cells, is one of more than a dozen principal investigators at Salk whose work has been made easier by the core facility's equipment and training. "I'm first and foremost a fruit fly geneticist, and there's no way my lab could have made such a quick transition to working with human stem cells if we didn't have this facility," she says.

»2011

Izpisúa Belmonte lab reports successful gene-editing corrections of laminin mutations in patient-derived iPS cells.

Verma lab reports highly efficient production of hematopoetic progenitor cells from patient-derived iPS cells.

Ecker lab contributes to mapping of hydroxymethylation epigenetic marks in mouse embryonic stem cells.

Gage lab reports iPS-derived disease-in-a-dish model of schizophrenia and demonstrates its potential utility for drug testing.

Ecker and Evans labs report on major study of epigenetic differences between iPS and embryonic stem (ES) cells.

Evans lab reports that human fat stem cells can be used to generate iPS cells without need for a contaminating feeder layer.

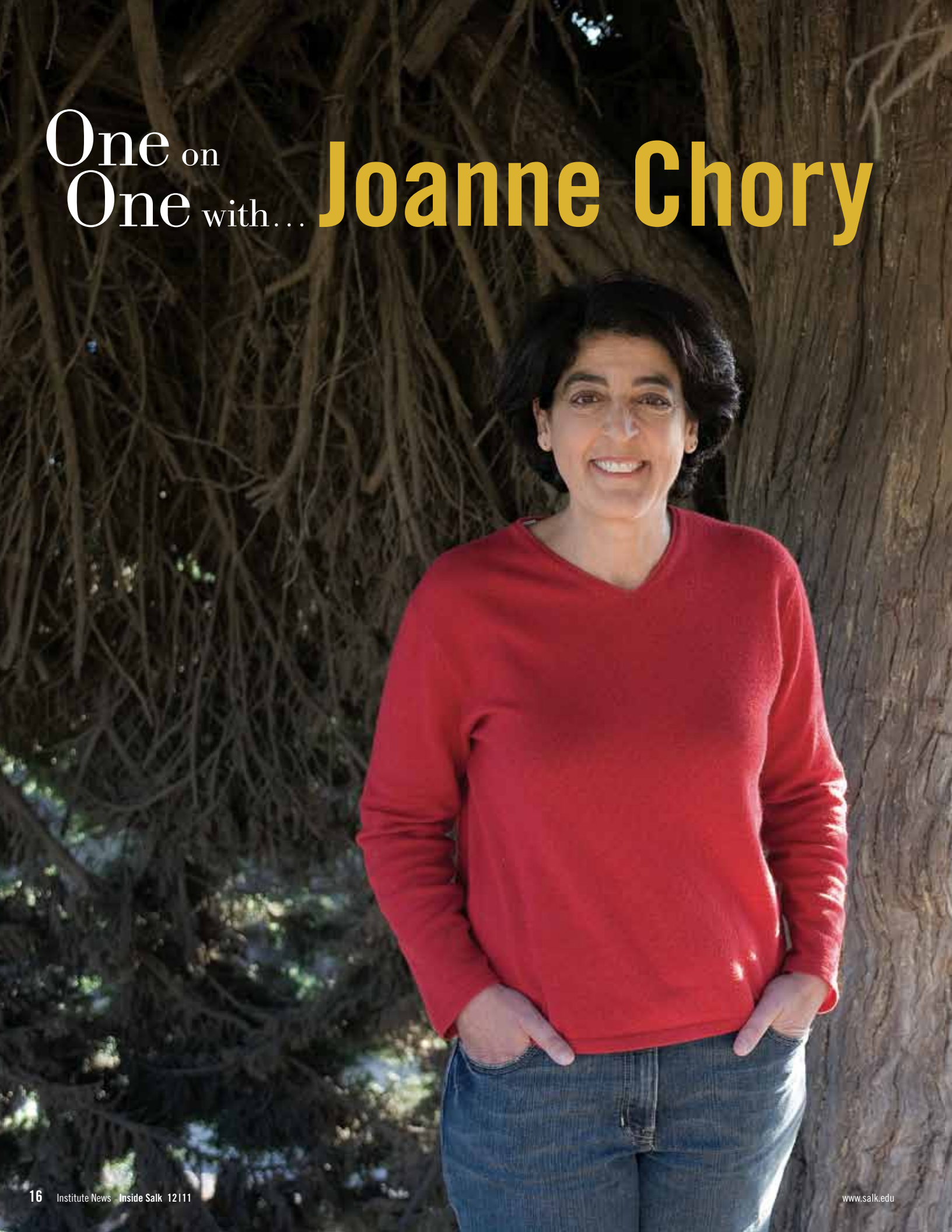
Izpisúa Belmonte lab reports iPS-derived model of Hutchinson-Gilford progeria.

Izpisúa Belmonte lab demonstrates that the initiation of pluripotency in humans starts during preimplantation development, earlier than previously thought.

Izpisúa Belmonte lab successfully achieves complete meiosis from human iPS cells.

Izpisúa Belmonte lab, in collaboration with Kun Zhang and Larry Goldstein at UCSD and Louise Laurent and Jeanne Loring at Scripps, uncovers genomic and epigenomic alterations in human iPS cells.

One on One with... Joanne Chory



A **SELF-DESCRIBED "LATE BLOOMER," JOANNE CHORY HAS BECOME ONE** of the world's leading plant biologists, driven by the prospect of creating a better world for her family and children around the globe. Chory, professor and director of the Plant Molecular and Cellular Biology Laboratory at the Salk Institute and a Howard Hughes Medical Institute investigator, has led the field of plant biology for more than 20 years, making major discoveries in how plants grow and develop. This past summer, she added more hardware to her collection of awards after being elected a foreign member of the Royal Society in London—the world's oldest scientific academy in continuous existence.

Joanne Chory enjoying some family time at her home with husband, Dr. Stephen Worland and children, Katie and Joe.

Why should the world care about plant biology?

Plants are the foundation for all human life on earth, providing food, fiber, drugs, building materials and even the oxygen we breathe. Yet remarkably little is known about the mechanisms of how plants grow and develop and adapt to diverse environments.

How did you first become interested in plant biology?

I was attracted to the field of plant biology in 1984. Very little was known about plants, but three papers had just been published about how to generate stably transformed plants. Also, Barbara McClintock had just won the Nobel Prize in Physiology or Medicine for her groundbreaking work on maize transposons (jumping genes). As such, it was a field ready for young people like me to apply some of the new tools of molecular biology.

I also feel it's very important to better understand how plants grow. This has the potential to better feed the human population. It is currently estimated that over 800 million people suffer from chronic malnutrition. About 7 million children a year under the age of five die from not getting enough calories. It is the single largest reason that children die.

Did you always know that being a plant biology scientist was the direction you wanted to take?

The short answer is no. While I was always good at math and science, I did not decide to major in biology until after my first year in college. I was inspired by my microbiology professor my junior year in college and got my Ph.D. in bacteriology. It wasn't until I looked for a postdoc that I decided to work on plants. I guess you'd call me a late bloomer (pun intended).

Were your parents or family members into science?

Neither of my parents were scientists. Of their five children, we are one mechanical engineer, one electrical engineer, one computer software specialist and one mathematician turned aerospace engineer, and then there's me—the molecular biologist. My siblings think my science should be more quantitative, and they can't understand why I have forgotten calculus.

Aside from plant biology and your research, what are you most passionate about in life?

Having two children and juggling two demanding jobs leaves us little time for other passions. But if I had to pick one thing, I have passion for providing a loving environment to my family, both my own family and our extended families.

> **“I feel it’s very important to better understand how plants grow. This has the potential to better feed the human population.”**

What would people be most surprised to know about you?

I like to embarrass my children by dancing wildly to 1970s music. The Who’s album *Who’s Next* is especially good for this.

If you had a month off, where everything stops…no worrying about not getting stuff done or losing time, what would you do with your time?

I’m inclined to say that I would read James Joyce’s, *Ulysses*, as well as some of the other great works of fiction that I missed. But it is possible that I would just watch every episode of *Mad Men* or *Desperate Housewives* with my daughter. A month of just goofing off at home and bonding with my family would be really special.

***Thomson Reuters* recently ranked the Salk Institute’s plant biology program number one in the world. What does this distinction say about the scientists and the work being done here?**

We were thrilled to see this statistic. I think what it says is self-evident: that we have uncovered basic pathways and fundamental knowledge about plants that is useful to the plant community and to the larger life science community as well. It is remarkable to think we’ve done this with just a handful of faculty over the years, including the current four “J’s”: **Joe Ecker**, **Joe Noel**, **Jeff Long** and myself (Joanne).

This year, you were elected a foreign member of the Royal Society in London. It is one of many honors you have earned in your career. Is there one particular award that has special meaning to you?

The best I could do was narrow this down to three, each for a different reason:

One, I was elected to the National Academy of Sciences within a few months of being promoted to full professor. This was a vote of confidence from my own peers at a young age. It meant a lot to me.

Two, in 2009, I became the first recipient of the Howard H. and Maryam R. Newman Chair in Plant Biology. This was special for two reasons: First, I was the first woman at Salk recognized by being given a chair. Second, I was thrilled that the Newmans and the Jacobses recognized the positive impact that plant research has had on the quality of human life.

And the third “honor” was bestowed upon me by my then ten-year-old daughter, Katie. It was in response to something that a former president of Harvard said when he was trying to be provocative about why there were so few women in science. One idea he threw out there was that there were innate differences in aptitude between men and women. When I told my daughter this anecdote over breakfast, she innocently looked up at me and said, “Well, he must have never met you, Mom.”

What inspires you to continue your research?

I remain interested in the following two questions: How does the chemical machinery of plants respond to light in order to make the plant grow, flower and produce seeds and fruit? And can we use this knowledge to increase crop yields? I am inspired by the simplicity of these questions and our relative ignorance of the answers. Plant biology/agriculture is an area where a single researcher can make a difference!

How will plant biology help feed the world over the next several decades?

Basic studies of plants will explain the most fundamental processes of plants: how they grow and develop, how they regulate and optimize the photosynthetic process and how they respond to stress. We will be able to correlate phenotype with genotype, and sequencing will explain many aspects of adaptation to different environments. Breeders will use this knowledge to manipulate crops, and this will increase yield, stress tolerance and sustainability.

What will be some of the biggest challenges we will face as we try to feed the world?

We need to do all the things I just mentioned now and with almost no funding (less than 2 percent of total research dollars in life and biomedical sciences). We are expecting 9 billion people by 2050, but we haven’t been thinking about what kind of world we are leaving for our children and grandchildren.

Salk Institute promotes latest generation of

extraordinary scientists


E. J. Chichilnisky


Andrew Dillin

E. J. Chichilnisky

Promoted to professor
Systems Neurobiology Laboratories

Chichilnisky is working on deciphering how the retina, the tissue lining the back of the eye, encodes visual information so the brain can use it to produce visual experience. Employing a microscopic electrode array to record the activity of retinal ganglion cells—each of which views the world only through a small, jagged window called a receptive field—he was able to show that receptive fields fit together like pieces of a puzzle, preventing blind spots and excessive overlap that could blur our perception of the world. Most recently, he was able to trace for the first time the neuronal circuitry that connects individual photoreceptors with retinal ganglion cells, shedding light on the neural code used by the retina to relay color information to the brain.

Andrew Dillin

Promoted to professor
Molecular and Cell Biology Laboratory

A Howard Hughes Medical Institute investigator and director of the Glenn Center for Aging, Dillin uses the tiny roundworm *Caenorhabditis elegans* to study the genetic and molecular pathways that regulate aging and aging-related diseases. His lab discovered the mechanisms that clear away toxic proteins in young, healthy brains—mechanisms that, he found, break down with age and lead to protein aggregate build-up, the hallmark of age-related neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's. Most recently, he identified a molecular switch flipped by hunger, which links caloric restriction and longevity and that could identify drug targets for patients with age-related diseases such as type 2 diabetes or cancer.

Martin W. Hetzer

Promoted to Hearst Endowment professor
Molecular and Cell Biology Laboratory

Hetzer explores how the organization of the nucleus influences gene activity and how disruption of its three-dimensional architecture can cause developmental defects, cancer and aging. Work from the Hetzer lab has established nuclear pore proteins as a new class of gene regulators and shown that nuclear membrane integrity declines with age and during the formation or production of tumors. Nuclear membrane irregularities are a hallmark of many diseases, including cancer and neurodegenerative disorders, and thus his work is relevant for many diverse aspects of human health.


Martin W. Hetzer


Leanne Jones


Jan Karlseder


Satchidananda Panda

Leanne Jones

Promoted to associate professor
Laboratory of Genetics

Jones uses the fruit fly *Drosophila melanogaster* to establish paradigms for how stem cell behavior is controlled and how the relationship between stem cells and their environment changes during development, aging and tumorigenesis. Using the fly intestine and testis as model systems, Jones discovered that during the aging process, the level of support from a stem cell's specialized environment, also known as the stem cell niche, drops off, diminishing stem cells' ability to self-renew and adequately maintain tissues. In a separate study, she also found that stem cells adjust their numbers depending on the availability of nutrients to coordinate tissue maintenance with environmental conditions.

Jan Karlseder

Promoted to professor
Molecular and Cell Biology Laboratory

Karlseder studies how cells keep tabs on their telomeres—the protective ends of chromosomes—and prevent catastrophic meltdowns to gain a better understanding of the interrelationship of aging and cancer. For example, he found that the telomere dysfunction observed in cells from patients with the premature aging disease known as Werner syndrome is a major cause of genomic instability and could explain the high incidence of cancer seen in this disease. In a finding with direct implications for the treatment of cancer, he discovered that telomeres, which commonly end in a string of DNA rich in the base guanine (G), can also terminate with a different motif, a strand abundant in the base cytosine (C).

Satchidananda Panda

Promoted to associate professor
Regulatory Biology Laboratory

Panda seeks to understand how our brain clock keeps track of time in all seasons and time zones and tells our body when to sleep, when to wake up and when to eat. His work focuses mostly on melanopsin, a photopigment he discovered before he joined the Salk Institute. His research in the Laboratory of Regulatory Biology has revealed that melanopsin not only reports the intensity of incoming light to the circadian clock but also to regular visual centers in the brain. In a different set of experiments, he discovered that the daily waxing and waning of thousands of genes in the liver—the body's metabolic clearinghouse—is mostly controlled by food intake and not, as conventional wisdom had it, by the body's circadian clock.

"Faculty are the intellectual capital of the Salk Institute, and these young scientists have proven their extraordinary talent and creativity," says Salk president **William R. Brody.** "They are the heavy hitters among their peers, and their research efforts and dedication will have a profound impact on human health through scientific discovery and creative research. That's what really matters."

Science, art, and history converge at Salk

DONORS, COLLEAGUES, FRIENDS AND SCIENTISTS GATHERED at the Salk in April to experience art, history and science at a series of memorable celebrations. The festivities commenced on April 14 with the dramatic unveiling of the Donor Honor Wall, a series of stainless steel plaques adorning the concrete at the entrance to the Institute. Each panel is engraved with the names of benefactors whose extraordinary generosity has provided critical funding to further the groundbreaking scientific research at the Institute.

The evening's celebration continued with the spectacular unveiling of *The Sun*, a soaring 9-foot glass sculpture by world-renowned artist Dale Chihuly that was given to the Institute by **Irwin Jacobs**, chairman of the Salk board of trustees, and his wife, **Joan Klein Jacobs**. The Jacobses commissioned the art installation after experiencing the dramatic response the internal and external communities had to the 2010 *Chihuly at the Salk* exhibit.

From left: Chris Fletcher, Sarah Thomas and Irwin Jacobs

The grand finale, which took place April 17, was a rare opportunity for more than 600 Salk staff, faculty, supporters, neighbors and friends to examine an original 1217 engrossment of the Magna Carta, considered one of the most significant legal documents in the history of democracy, which was on display in the Frederic de Hoffman Auditorium. Arranged for viewing at the Salk by **Irwin Jacobs**, it was one of four original engrossments belonging to the Bodleian Library from the University of Oxford and marked the first West Coast visit of the celebrated Great Charter. A panel of experts presented a fascinating lecture and offered a wealth of insights about the landmark manuscript, which remains an important symbol of freedom and the rule of law.

A group of staff honorees who achieved 25, 30 and 40 years of employment at the Institute celebrate with Geoff Wahl and President Bill Brody at the 2nd Annual Salk Service Awards.
Geoff Wahl, Karen Suter, Candy Haggblom, Beth Coyne, Amy Blount, Maureen Macias-Ballas, Bill Brody *(left to right, front)*, Cynthia Kosty, Bob Lizarraga, Kim Witmer *(left to right, back)*

Candy Haggblom

2nd annual Salk Service Awards ceremony honors staff

THIRTY-NINE STAFF MEMBERS WHO HAD attained between ten and 45 years of employment at Salk were acknowledged in May at the 2nd annual Salk Service Awards. At a special luncheon and ceremony, Salk president **William R. Brody**, Academic Council chair **Geoff Wahl**, faculty and colleagues paid tribute to the employees' long-term contributions to the Institute.

Brody noted that the group represented more than 640 combined years of service, which was a testament to their commitment to the Institute. "The success of the Salk is due to the longevity and dedication of the workforce," he said. "It's what keeps us at the forefront of scientific excellence. The people at Salk are simply terrific."

Wahl noted that although faculty gatherings usually produce many different opinions, there is one exception. "The one opinion we all share is that the staff here is the best in the world, and teamwork makes all that possible," he said. "I want to congratulate you for being an immensely proud and productive team that works to create synergy so we can all work together to produce the best science in the world."

After the recipients were called to the podium to accept certificates of appreciation and pose for photos with Brody and Wahl, two special rocking chairs were placed on the stage as "seats of honor" for the employees who had reached the milestone of 40 years of service with the Institute: **Candy Haggblom** and **Bob Lizarraga**.

Haggblom started her career in the tumor virology laboratory of Marguerite Vogt, where she spent the next three decades assisting Salk's "longest-working scientist" and continued to provide support when it morphed into the Molecular Biology and Virology Lab. She currently works with **Jan Karlseder**, a professor in the Molecular and Cell Biology Laboratory, where, Karlseder said, her contributions have facilitated the lab's high-level science and helped him advance to full professor.

Lizzaraga, who started out as a drafter in Facilities Services and retired in 2010 as project manager, said working at the Institute had been the best experience of his life. (To read more about his time at the Salk, see http://salk.edu/insidesalk/articlenin.php?id=142#apm1_2).

Brody capped the event with a musical performance, playing the piano and singing "The Elements," a comical recitation of the periodic table.

Salk goes solar

With the simple flick of a switch, solar power is now running through the veins of the Salk Institute.

More than 2,300 photovoltaic solar panels sit atop the Institute's four main buildings, generating 465 kilowatts of electrical power. The natural power provides a savings of nearly $10,000 per month.

The solar energy system went live in August and is part of a comprehensive overhaul of the mechanical and electrical systems at the Salk Institute.

Salk scientist receives a host of honors, including funding

IN RECOGNITION OF HIS SIGNIFICANT contributions to the field of neurobiology, Salk Institute professor **Fred "Rusty" Gage** has been honored with four awards on two continents: Spain's Cátedra Santiago Grisolía Award 2011, an honorary doctorate in medicine from Lund University in Sweden, appointment as president of the International Society for Stem Cell Research and recipient of a grant from the National Institutes of Health (NIH) Director's Transformative Research Projects (T-R01) program.

Gage, a professor in the Salk Institute Laboratory of Genetics and holder of the John Adler Chair for Research on Age-Related Neurodegenerative Diseases, has played a pivotal role in advancing knowledge of neurobiology. Through a groundbreaking experiment in 1998, Gage's lab showed that contrary to decades of common wisdom, human brains grow new neurons throughout life, a discovery that forced scientists to rethink some of their most basic ideas about how the brain works. He and his team also showed that physical exercise can enhance the growth of new nerve cells in the brain, a process called neurogenesis.

Spain's Cátedra Santiago Grisolía Prize is conferred annually on two internationally distinguished researchers in recognition of work that is of both high scientific and social interest. Gage, along with fellow recipient Mario Capecchi, a molecular geneticist, was honored in a public ceremony on May 3 in Valencia, Spain and presented with a medal.

On May 27, Gage also received an honorary doctorate in medicine from Lund University in Sweden, where he served as an associate professor from 1981 to 1985.

In June, Gage began his yearlong term as president of the International Society for Stem Cell Research at the society's annual meeting in Toronto, Canada—an extremely fitting appointment due to his worldwide reputation as one of the leading experts on stem cell research.

Fred "Rusty" Gage

THE 7th SALK INSTITUTE CELL CYCLE MEETING

APPROXIMATELY 175 PEOPLE ATTENDED THE 2011 Cell Cycle Meeting at Salk from June 17 to 20, representing leading scientific institutions from near and far, including The Scripps Research Institute; London Research Institute; New York University School of Medicine; Stowers Institute; Stanford University; Dana-Farber Cancer Institute; University of California, Berkeley; Ludwig Institute at UC San Diego; Edinburgh University; Ohio State University; Harvard University, Sanford Burnham Institute and University of Toronto.

"This symposium has become a labor of love and public service," said **Tony Hunter**, a professor in the Molecular and Cell Biology Laboratory, American Cancer Society professor and director of the Salk Institute Cancer Center. "Examining and sharing information about the crucial process of the cell cycle may lend new insights into the identification of biological markers that predict patients' responsiveness to chemotherapy drugs and ultimately could lead to the development of new cancer drugs with fewer side effects."

The Newport Lecture, honoring the late John Newport, a leading figure in the field, was given by Marc Kirschner of Harvard, himself a pioneer in cell cycle research. His talk, "New Insights into the G2/M Transition in Somatic Cells and Embryonic Stem Cells," was notably attended by Dr. Douglass Forbes, John Newport's widow.

NIH awards Salk Institute $5.5 million grant to study Williams syndrome

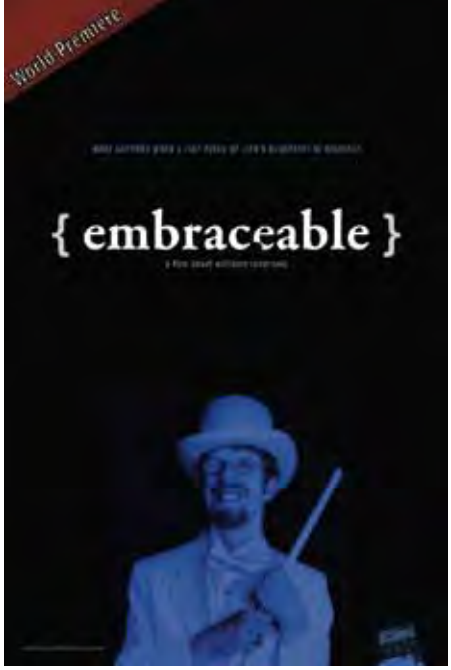
URSULA BELLUGI, PROFESSOR AND director of the Salk Laboratory for Cognitive Neuroscience, is heading a multi-institutional team that has been awarded a $5.5 million program project grant by the National Institute of Child Health and Human Development (NICHD) to link social behavior to its underlying neurobiological and molecular genetic basis, using Williams syndrome as a model.

"How the brain processes social information and integrates it with other forms of perception and learning is one of the major frontiers in neuroscience," says Bellugi. "Using Williams syndrome as the basis for a new approach to social neuroscience is exciting and promising, in part because its genetic basis is clearly understood, and it is associated with a very specific pattern of cognitive strengths and weaknesses and some puzzling paradoxes."

The current grant is the latest chapter in a unique and exceptionally successful scientific alliance. Led by Bellugi, a team of researchers that includes Salk scientists **Fred Gage** and **Terry Sejnowski** and collaborators at UC San Diego and the University of Utah, working in such disparate fields as social cognition, stem cell biology, neuronal architecture and neuroimaging, are looking to Williams syndrome to provide clues to some of the mysteries of the genetic basis of social behavior.

Williams syndrome arises from a faulty recombination event during the development of sperm or egg cells. To children with Williams syndrome, people are much more comprehensible than inanimate objects. Despite myriad health problems and generally low IQs, they are extremely gregarious, irresistibly drawn to strangers and insist on making eye contact. They are confounded by the visual world around them, however: when asked to draw a bicycle, they will show all the parts but strew them randomly across the page. It is this strange mix of mental peaks and valleys that Bellugi and her collaborators hope will allow them to untangle the connections between genes and social behavior.

"Understanding the mechanisms and pathways underlying the organization of human social behavior is important in a wide variety of mental disorders," Bellugi says. "By dissecting Williams syndrome, we hope to gain new insight into other neurodevelopmental disorders such as autism."



Embraceable is a feature documentary film about Williams syndrome. The film explores the lives of people living with this rare genetic abnormality, displaying their inherent beauty, charm and talents. Ursula Bellugi, professor and director of the Salk Institute's Laboratory for Cognitive Neuroscience is interviewed in the film and serves as the scientific director.

> "Understanding the mechanisms and pathways underlying the organization of human social behavior is important in a wide variety of mental disorders."
>
> – URSULA BELLUGI

Salk to accelerate brain research with $4.5 million NIH grant for new Neuroscience Core Center

THE NATIONAL INSTITUTES OF HEALTH HAVE ANNOUNCED THAT THE SALK Institute will receive $4.5 million to establish a Neuroscience Core Center, a new research center intended to accelerate brain research that lays the foundation for developing new ways to treat congenital brain defects and neurological diseases.

The new center is one of three established nationally this year by the National Institute of Neurological Disorders and Stroke to focus on basic brain research. More than half of Salk's faculty is engaged in neuroscience research, and the five-year grant will support their work by providing access to new technology and expertise.

"We are very excited about this center because it will provide unique services of great use to many of the institute's investigators, and will help expand our understanding of a range of neurological disorders," says **Dennis O'Leary**, the Vincent J. Coates Professor of Molecular Neurobiology at Salk, who will serve as director of the new center. "Salk is already a leader in brain research, and this center will be an exponential boost to our ability to do cutting-edge research in neuroscience."

The new NIH-funded center will provide research support in three areas that are particularly important for neuroscience: genome manipulation, imaging and behavioral studies.

Tour guides Cynthia Burke, Conrado Gallardo, Kendall Mower, Lily Robinson, Ellen Zimmerman *(not pictured- Don McKahan)*

Tours de force

IN 1959, JONAS SALK CHALLENGED Louis Kahn to "create a facility worthy of a visit by Pablo Picasso," and the architect did exactly that. Today, in recognition of the architectural masterpiece Kahn designed, people from around the world flock to the Salk Institute to experience and pay homage to his vision and achievement. And guiding these visitors for nearly 40 years have been scores of volunteers, who have shared their passion for the Salk's architecture on thousands of walking tours.

Year round, Monday through Friday at noon, a group of dedicated men and women lead the curious, the enthusiastic, the inspired and the reverent in and around the iconic structures, sharing their own unique perspectives about the famous buildings. Drawing on a wealth of knowledge, they take visitors on a journey through the Institute's past, present and future, often sharing anecdotes about memorable experiences and people from past tours.

There was the famous Japanese architect, for example, who came with an interpreter but surprised the guide when he declared in English, "I am renewed!" There was the German engineer who was moved to tears. And the awestruck third grader who found himself contemplating a new career path after visiting the Institute, unable to decide whether to become an architect or a professional athlete, to mention just a few.

The Salk architectural tour is about more than concrete, glass and steel. It's about energy and people. It's about imagination and ingenuity. And it's about the enthusiasm and knowledge the guides pass on to their tour groups, leaving them with indelible memories and unique insights that just may change the way they view the world.

The Salk Institute offers free guided architectural tours Monday through Friday at noon. Reservations are required a minimum of two business days in advance of the date requested and can be made online at www.salk.edu/about/architecture_tours.html. For additional information, call 858-453-4100, ext 1287.

Salk Institute earns top global ranking for scientific research

THE SCIMAGO INSTITUTIONS RANKINGS (SIR) WORLD REPORT has identified the Salk Institute as one of the top five research organizations in the world, based on excellence and high quality of its scientific findings.

The independent survey is the most comprehensive ranking of 3,042 worldwide research institutions, analyzing work from 2005 to 2009. The report scores each institute based on six indicators: output, international collaboration, normalized impact, high-quality publications, specialization index and excellence rate.

The Salk Institute ranked fifth globally in the category of high-quality publications and excellence rate. The indicators are based on the ratio of publications published in the most influential scholarly journals in the world, and the percentage of publications of an institution that are among the top 10 percent of publications in a field.

The SIR World Report compiled its data by identifying and comparing all the institutions through a large number of scientific articles, reviews and conference papers contained in Scopus, the world's largest abstract and citation database of peer-reviewed literature and web sources with tools to track, analyze and visualize research.

"This top global ranking is a testament to the exemplary science performed by some of the leading researchers in the world at the Salk," said **William R. Brody**, Salk Institute President. "Salk scientists are extraordinary leaders in their field, and the impact their work has on human health is the Salk legacy."

> **"This top global ranking is a testament to the exemplary science performed by some of the leading researchers in the world at the Salk."** – WILLIAM R. BRODY

Image courtesy of Indiana University.

Nobel Laureate Renato Dulbecco honored with Indiana University President's Medal

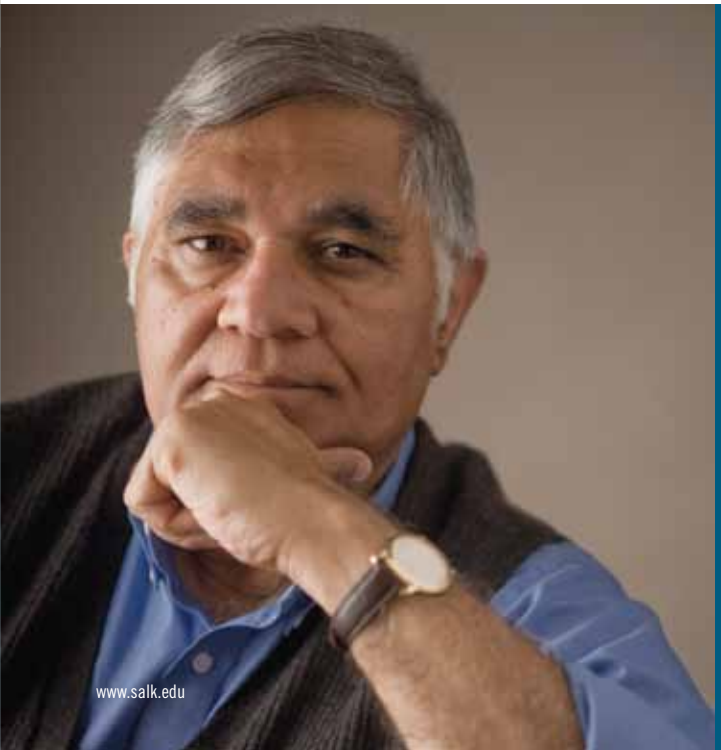
INDIANA UNIVERSITY (IU) HAS HAS AWARDED NOBEL Laureate and distinguished Salk Institute research professor **Renato Dulbecco** the President's Medal for Excellence, one of the highest honors an IU president can bestow. Criteria for recipients include distinction in public service, service to IU, achievement in a profession and extraordinary merit and achievement in the arts, humanities, science, education and industry.

"Indiana University's world-class reputation in the life sciences can in part be directly traced back to path-breaking researchers like Dr. Dulbecco," says IU president Michael A. McRobbie. "His seminal work involving tumor viruses and the genetic material of the cell dramatically increased our understanding of the cause of human cancer, and he has been an inspiration to scientists worldwide through his work on the origin of breast cancer and leadership of the Human Genome Project. IU shares great pride in his historic achievements, pioneering spirit and lifetime dedication to science."

A Founding Fellow of the Salk Institute and president emeritus, Dulbecco was one of four Nobel Laureates who worked together at IU in the life sciences during the late 1940s. He is credited with playing a pivotal role in the development of modern molecular biology and revealing the biochemical basis of our genetic codes. In 1986, he suggested studying all human genes, helping to launch the worldwide Human Genome Project.

Dulbecco's pioneering research provided the first clue to the genetic nature of cancer, and he was jointly awarded the 1975 Nobel Prize in Physiology or Medicine for discoveries concerning the interaction between tumor viruses and the genetic material of the cell. He is also the recipient of the Lasker Award and awards given by the National Academy of Sciences, the Royal Society of London and the Academia Del Lincei of Italy, among many others. To highlight his achievements, the Salk Institute established the Dulbecco Laboratories for Cancer Research in 2005 and created the Renato Dulbecco Chair in 2010.

"Renato Dulbecco is a brilliant investigator and scientific visionary," says Salk president **William R. Brody**. "His extraordinary contributions to science epitomize everything the President's Medal stands for, and we are delighted that Indiana University has recognized his remarkable achievements with this award."



Salk Institute molecular biologist Inder M. Verma named PNAS editor-in-chief

THE NATIONAL ACADEMY OF SCIENCES (NAS) ANNOUNCED THE APPOINTMENT of **Inder M. Verma**, Ph.D., as editor-in-chief of the *Proceedings of the National Academy of Sciences (PNAS)*, the official NAS journal. He formally assumed the editorship on November 1.

An American Cancer Society Professor of molecular biology in the Laboratory of Genetics at the Salk Institute, Verma was elected to the NAS in 1997 and has served on the editorial board of PNAS since 2001.

"Dr. Inder Verma is known worldwide for his scientific creativity and for his conscientiousness and fair-mindedness," said Ralph Cicerone, president of the National Academy of Sciences. "He is the ideal person to lead PNAS, an already-premier science journal that continues to improve."

Ipsen and the Salk Institute renew partnership to support cutting-edge research

THE IPSEN LIFE SCIENCES PROGRAM, LED BY INDER VERMA, holder of the Irwin and Joan Jacobs Chair in Exemplary Science, will for a period of three years, sponsor four research programs through targeted and innovation grants. Ipsen will provide funding for targeted research programs on novel therapeutic concepts for the treatment of pituitary adenomas, cancer and neurodegenerative diseases. Innovation grants will fund the exploration of advanced scientific concepts. Verma is one of the world's leading authorities in cancer biology.

Over the last three years, the partnership between the Salk Institute and Ipsen has delivered significant scientific advances in the cancer field, such as the development of biological models mimicking human cancerous processes, as well as identification of specific cells driving tumor growth. In addition, the development of stem cell technology has opened up promising new vistas of research in neurodegenerative diseases.

Marc de Garidel, chairman and chief executive officer of Ipsen, stated, "At a time when the magnitude and scope of the life sciences revolution challenge the imagination, it is critical for a biopharmaceutical company to secure close links with the leading academic institutions worldwide. The collaboration between Ipsen and the Salk Institute perfectly fits in our new strategy of increased focus on our key assets, investment in growth levers and leverage of our footprint. By capitalizing on partnerships with first-class research organizations, Ipsen will strengthen its links with the medical and scientific community so as to develop innovative therapies tailoring the needs and expectations of patients and physicians."

Salk scientist wins dual awards

AXEL NIMMERJAHN, ASSISTANT PROFESSOR IN THE WAITT ADVANCED BIOPHOTONICS Center and holder of the Richard Allan Barry Developmental Chair, was recently distinguished with two significant honors. He was named a 2011 Rita Allen Scholar and earned a highly selective grant from the Whitehall Foundation.

The Rita Allen Foundation awarded Nimmerjahn $500,000 over five years to pursue research into the role of glial cells in neurovascular coupling, the temporal and spatial coupling between increased neural activity and cerebral blood flow. Glial cells constitute the majority of human brain cells and dynamically interact with neurons and other cells. Once thought to play only a passive, supportive role, glia are now emerging as active players in healthy brain function. Glia are also critically involved in many injuries and diseases, including spinal cord injury, glioma and amyotrophic lateral sclerosis (ALS).

Nimmerjahn is one of just seven scientists out of 28 candidates that the Rita Allen Foundation selected for the honor this year and only the third Salk faculty member to receive the award.

"Our mission is to invest in transformative ideas and projects that result in significant breakthroughs and solutions to serious health challenges," explains Elizabeth G. Christopherson, the foundation's president and chief executive officer, Rita Allen Foundation. "We have traditionally embraced research with above-average risk and groundbreaking possibilities and are proud of the over 100 scholars, including a Nobel Laureate and members of the National Academy of Sciences, who have received our financial support."

The Whitehall Foundation grant will provide Nimmerjahn with $223,000 over three years to support research to better understand the contribution of astrocytes to normal brain function. Resolving this question will increase comprehension of the complex cellular processes underlying normal brain function and behavior, and could lead to the development of new treatments for neurological disorders.

"To be chosen for both these awards, which involve a rigorous, highly selective process, is an acknowledgement of Axel's outstanding scientific accomplishments," says Salk president William R. Brody. "I'm delighted these prestigious foundations have presented him with the recognition and support to facilitate his remarkable research."

Joseph Ecker appointed Howard Hughes Medical Institute and Gordon and Betty Moore Foundation investigator

PLANT BIOLOGIST JOSEPH R. ECKER, professor in the Plant Molecular and Cellular Biology Laboratory and director of the Genomic Analysis Laboratory, has been selected as an investigator of the Howard Hughes Medical Institute (HHMI) and the Gordon and Betty Moore Foundation (GBMF), a collaboration focusing on plant biology.

Only 15 investigators were selected from the 239 plant scientists who applied for the competition, chosen on the basis of individual scientific excellence. With Ecker's appointment, three plant biologists at the Salk hold HHMI appointments.

Ecker is internationally recognized for his pioneering contributions to plant genomics. Early on, he advocated for the mapping and sequencing of the genome of the tiny mustard weed *Arabidopsis thaliana* and directed much of the sequencing project. Commonly known as thale cress, *Arabidopsis* was the first flowering plant to have its entire genome unlocked and is now widely considered one of the most important model organisms for the study of plant genetics and genomes.

"Without Joe's groundbreaking contributions, *Arabidopsis* would be just another weed," says Howard Hughes Medical Institute investigator **Joanne Chory**, professor and director of the Plant Molecular and Cellular Biology Laboratory and holder of the Howard H. and Maryam R. Newman Chair in Plant Biology. As Chory has stated, "The study of plant genomes might contribute more to human health and well-being than the study of any animal genome. I am delighted for Joe because he has almost singlehandedly made *Arabidopsis* the model of choice for plant functional genomics studies, owing to his vision, his generosity to the community, and his great enthusiasm for solving problems of scale."

In the last few years, Ecker's laboratory has started to zero in on genomic methylation patterns, which are essential for normal development and associated with a number of key cellular processes, including carcinogenesis. After perfecting his high-throughput method of mapping the precise position of these individual DNA modifications throughout the genome in *Arabidopsis*, Ecker is now applying the technological innovations and analytical tools he developed in plants to work on disease-related problems in humans.

"Joe Ecker is highly deserving of this recognition, which is reserved for a select group of extraordinary scientists," said Salk president **William R. Brody**. "HHMI and GBMF have made a bold move into plant biology. This enhanced focus and appreciation for plant biology has the potential to help us understand and find solutions to critical issues of world hunger, human health, and environmental sustainability."

> **"Without Joe's groundbreaking contributions, *Arabidopsis* would be just another weed."**
>
> **– Joanne Chory**

Nobel Laureate Paul Nurse (president of the Royal Society) congratulates Joanne Chory on her election.

Salk professor Joanne Chory elected to Royal Society

SALK SCIENTIST JOANNE CHORY HAS BEEN named a Foreign Member of the Royal Society (UK), the world's oldest scientific academy in continuous existence. An expert on how plants regulate their growth, she is being recognized as a "beacon of scientific excellence and relentless ambassador for plant research in the international community."

Chory, a professor in the Institute's Plant Molecular and Cellular Biology Laboratory and a Howard Hughes Medical Institute investigator, pioneered the analysis of plant responses to their environment using a molecular genetic approach in the reference plant *Arabidopsis thaliana*, a member of the mustard family that is easy to grow, prolific and has the smallest genome of any flowering plant. Her laboratory has led the plant field for 20 years, making major discoveries in how plants grow and develop.

"Nobody is more deserving of this honor than Joanne," says Salk president **William R. Brody**. "Her research may eventually enable researchers to develop plants that are particularly well-adapted to challenging environments, boosting the yields of agricultural crops, a critical issue considering the millions of people worldwide suffering from hunger and malnutrition."

The Royal Society, founded in 1660, is a fellowship of the world's most eminent scientists, who are elected for life on the basis of scientific excellence and who have included Isaac Newton, Charles Darwin, Albert Einstein, **Francis Crick**, James Watson and Stephen Hawking. With the election of Joanne Chory and Salk non-resident fellow **Carla Shatz** (see sidebar), the Salk Institute's roster of Royal Society members includes Crick, **Leslie Orgel**, **Renato Dulbecco**, **Sydney Brenner**, **Tony Hunter**, and non-resident fellows **Elizabeth H. Blackburn**, **Thomas M. Jessell** and **David Baltimore**.

"...a beacon of scientific excellence and relentless ambassador for plant research in the international community."

Royal Society recognizes Salk non-resident fellow

Salk non-resident fellow **Carla J. Shatz**, a professor of biology and neurobiology and director of BioX at the James Clark Center at Stanford University, was elected to the Royal Society. Shatz is one of the pioneers who determined some of the basic principles of early brain development. She found that the spontaneous activity of neurons in utero is critical for the formation of precise and orderly neural connections in the central nervous system. Her recent work shows that waves of spontaneous activity in the retina can alter gene expression and the strength of synaptic connections.

Salk Scientists named to Dulbecco and Guillemin chairs

IN RECOGNITION OF THEIR TIRELESS research and groundbreaking contributions to science, **Tony Hunter** has been appointed the inaugural holder of the **Renato Dulbecco** Chair, and **Juan Carlos Izpisúa Belmonte** has been named the inaugural holder of the **Roger Guillemin** Chair.

Irwin and **Joan Jacobs** endowed the two chairs to pay permanent tribute to Dulbecco and Guillemin, both former Salk presidents and two of the Institute's Nobel Prize winners, for their remarkable achievements in science and for the legions of scientists they have mentored and inspired. The Jacobses generously funded each chair in full at $3 million as part of the Jacobs Chair Challenge. Launched in 2008 with a $10 million matching fund, the Jacobs Chair Challenge encourages and enables donors to create prestigious, permanent chairs in support of senior faculty members at Salk.

"Irwin and Joan's leadership is extraordinary," says Salk president **William R. Brody**. "Their honoring Renato and Roger and having these two distinguished scientific leaders as inaugural holders of the endowed chairs is a wonderful example of why the Salk Institute remains at the forefront of life-changing discovery."

Hunter, an American Cancer Society professor in the Molecular and Cell Biology Laboratory and director of the Salk Institute Cancer Center, explores how mutations in genes that control growth lead to cancer and has made crucial contributions in understanding how signals that stimulate or regulate cell development are routed. In 1979, his lab made a groundbreaking discovery that a biological process called tyrosine phosphorylation is a chemical "on-off" switch that can trigger the uncontrolled division of cells—the hallmark of many cancers. This important signaling mechanism, which proved to underlie many types of human cancer, revolutionized cancer research and ultimately resulted in a new approach to treatment and the development of several innovative therapies as researchers found ways to inhibit the proteins called tyrosine kinases that are responsible for tyrosine phosphorylation.

A professor in the Gene Expression Laboratory at Salk, Izpisúa Belmonte has been at the forefront of developmental biology research and studies how genes and molecules orchestrate the development of an embryo. Through the years he has produced cutting-edge results, such as uncovering the genetic network involved in organ embryogenesis, as well as identifying how molecular guideposts direct organs to their rightful place along the body axes in the developing embryo. His work has provided insights into the molecular basis implicated during organ regeneration in higher vertebrates, the differentiation of human stem cells into various tissues, and the molecular basis underlying somatic cell reprogramming. In addition to expanding knowledge of early human development, the research activities of Izpisúa Belmonte's laboratory are relevant to understanding the causes of human birth defects, as well as to the future development of regenerative medicine.

Back row from left: Juan Carlos Izpisúa Belmonte, Irwin Jacobs, William R. Brody, Tony Hunter. Front row from left: Roger Guillemin, Renato Dulbecco

The **next** generation:

Eirini Kaiserli

Scientist Soars to New Heights in the Lab

It was perhaps inevitable that Eirini Kaiserli would follow an audacious path in life. Born and raised on the Greek island Kos—which reportedly had been a stop for the mythical hero Heracles—she too sought adventure at an early age. Initially, that pluck manifested itself in activities such as horseback riding, but at age 17, it took her away from Greece altogether and eventually led her to the world's leading plant biology program at the Salk Institute.

> **“I’ve always been determined, and I knew at a young age I would have to take the road less traveled to achieve my goals.”**

Captivated by biology in high school, Kaiserli was determined to pursue a career in research. Although Kos is renowned as the birthplace of Hippocrates, the ancient Greek physician credited as the first person to believe that diseases had natural causes rather than stemming from acts of the gods or other superstitions, it boasts a population of only 30,000, and opportunities for a research career were limited, to say the least. But her intrepid spirit prevailed, and she left home to attend the University of Glasgow.

“I’ve always been determined, and I knew at a young age I would have to take the road less traveled to achieve my goals,” she says.

While an undergraduate in Glasgow, she was accepted into a one-year study-abroad program at Stanford University’s Carnegie Institution for Science in the plant biology department. It was there that she developed an affinity for plant photobiology and learned about J**oanne Chory**’s work at the Salk Institute.

“I admired her work as a person and a scientist from a distance,” she explains. “As a woman in science, it is empowering to see someone like Joanne pave the way for me.”

Returning to Scotland and the University of Glasgow for her doctorate, Kaiserli focused on the characterization of UVR8, a novel signaling component that regulates UV protection in the model plant *Arabidopsis thaliana*. She discovered that UVR8 translocates into the nucleus in response to UV-B light in order to orchestrate the expression of a range of growth promoting and photo-protective genes. Thanks to her discovery, scientists now have a better understanding of how plants sense and protect themselves against UV-B irradiation by producing their own sunscreen and it has recently been shown that UVR8 is actually the long sought-after UV-B receptor in plants.

After earning her Ph.D., Kaiserli accepted a postdoctoral position in Chory’s laboratory, which seeks to discover the molecular triggers that determine whether a plant matures into a spindly or robust specimen, ultimately improving the way we grow food. Kaiserli’s work there currently involves the study of molecular and cell biology approaches in order to understand how plants perceive and respond to light.

“The aim of my research is to better understand the function of a novel growth-promoting protein known as TZP, in response to light,” she explains. “We want to understand how this protein converges blue light, hormone signaling and circadian rhythms.”

Kaiserli is acutely aware of the fact that her research at Salk has the potential to make a positive impact on human life globally, particularly in terms of alleviating hunger, and she credits her success to her adventurous spirit.

“With research, you have to take risks, and my life mirrors my approach in the lab,” she says. “I believe in doing things that are out of your comfort zone. You learn, grow and sometimes reach significant discoveries.”

Education Outreach program honored for 20-year partnership with San Diego schools

THE SAN DIEGO UNIFIED SCHOOL DISTRICT HONORED THE SALK Education Outreach program May 25 as a 20-year Partner in Education at a special end-of-year partner/volunteer awards ceremony.

"Our scientists are passionate about their field of study and enjoy sharing it with young people, and this enthusiasm is often a key factor in changing students' perceptions about science," explains **Ellen Potter,** director of the Education Outreach program, which provides an array of educational activities aimed at bringing the excitement of scientific discovery to middle and high school students, educators and community members throughout San Diego.

The program's efforts include its flagship program, Salk High School Scholars, an eight-week curriculum that offers high school students the opportunity to be involved with a full-time research project under the mentorship of a Salk scientist. The popular Salk Mobile Science Lab is a free three-day biotechnology program serving middle schools throughout San Diego County. Launched in 1996 by Potter in conjunction with the San Diego County Office of Education, the Mobile Science Lab provides a unique hands-on opportunity for students to learn about genetics and DNA from real Salk Institute scientists. In the past ten years, the lab has reached more than 20,000 local students and this year visited a record 21 area schools and educational institutions.

"This type of inquiry-based, exploratory learning is fundamental to increasing student interest in the biological sciences," explains Salk education specialist **Dona Mapston**. "The hands-on lab experience helps students really connect to what they are learning—and it's fun."

Salk also hosts an annual High School Science Day at the Institute, and this February marked the 21st anniversary of the event. The half-day event includes one-of-a-kind presentations from scientists who share stories of their professional experience, laboratory tours and hands-on participation in ongoing research experiments. More than 200 students attended, and 47 scientists from 25 labs were on hand to help with the activities.

"The Salk's Education Outreach Program is a leader in connecting young students with the importance and impact of science on our health and our world," notes Salk president **William R. Brody**. "Ellen and Dona help students explore their interest and intrigue early in their academic careers, which will hopefully lead to our next generation of scientists. This recognition from the SDUSD is a well-deserved honor for the amazing work they do on behalf of Salk."

> "The Salk's Education Outreach Program is a leader in connecting young students with the importance and impact of science on our health and our world."
>
> —WILLIAM R. BRODY

HIGH SCHOOL STUDENTS FROM AROUND San Diego County successfully completed the Salk High School Scholars program this past summer.

The ten students were each involved with a full-time research project, learning how to formulate and test hypotheses, prepare experiments and draw conclusions.

Jonas Salk created the Salk High School Scholars program more than 40 years ago to give students the opportunity to experience life in a scientific laboratory and explore the possibility of a career in science.

Salk Institute inspires the next generation of scientists at **2011 San Diego Science Festival Expo Day**

HUNDREDS OF YOUNG PEOPLE BECAME scientists for the day when they visited the Salk Institute booth on March 26 during the 2011 San Diego Science Festival at Petco Park.

Over 30,000 participants joined the largest single-day science and engineering event in Southern California at EXPO DAY, the Festival's grand finale event held the final Saturday of Festival week at Petco Park. With opportunities to participate in hands-on activities, meet real scientists and engineers and learn how their discoveries and research affect our daily lives, the festival provides a unique opportunity to reach students of all ages and backgrounds, inspiring the next generation of innovators.

"The Salk booth was packed from start to finish," said **Dona Mapston,** Salk Institute education specialist. Based on the theme of genetics and DNA technology, Mapston and a team of volunteers assisted curious kids and parents alike in extracting actual DNA from wheat germ. "The kids must have performed over 500 extractions by the time we closed up. That's over one DNA extraction per minute!" she exclaimed.

Salk Institute president **Bill Brody** was also on hand as one of the volunteer experts in the "Ask Me, I'm a Scientist" booth, deftly answering questions from the eager crowd.

The San Diego Science Festival is the largest celebration of science on the West Coast and offers a weeklong roster of eclectic events and science-inspired adventures at venues throughout San Diego. Look for the Salk Institute booth at next year's San Diego Science Festival Expo Day at Petco Park on March 24, 2012.

Discovery Roundup

“The metabolic system is like a hybrid car. In the daytime we use glucose as high-octane fuel, but at night we switch to the battery, which in this case is stored fat.”
– Marc Montminy

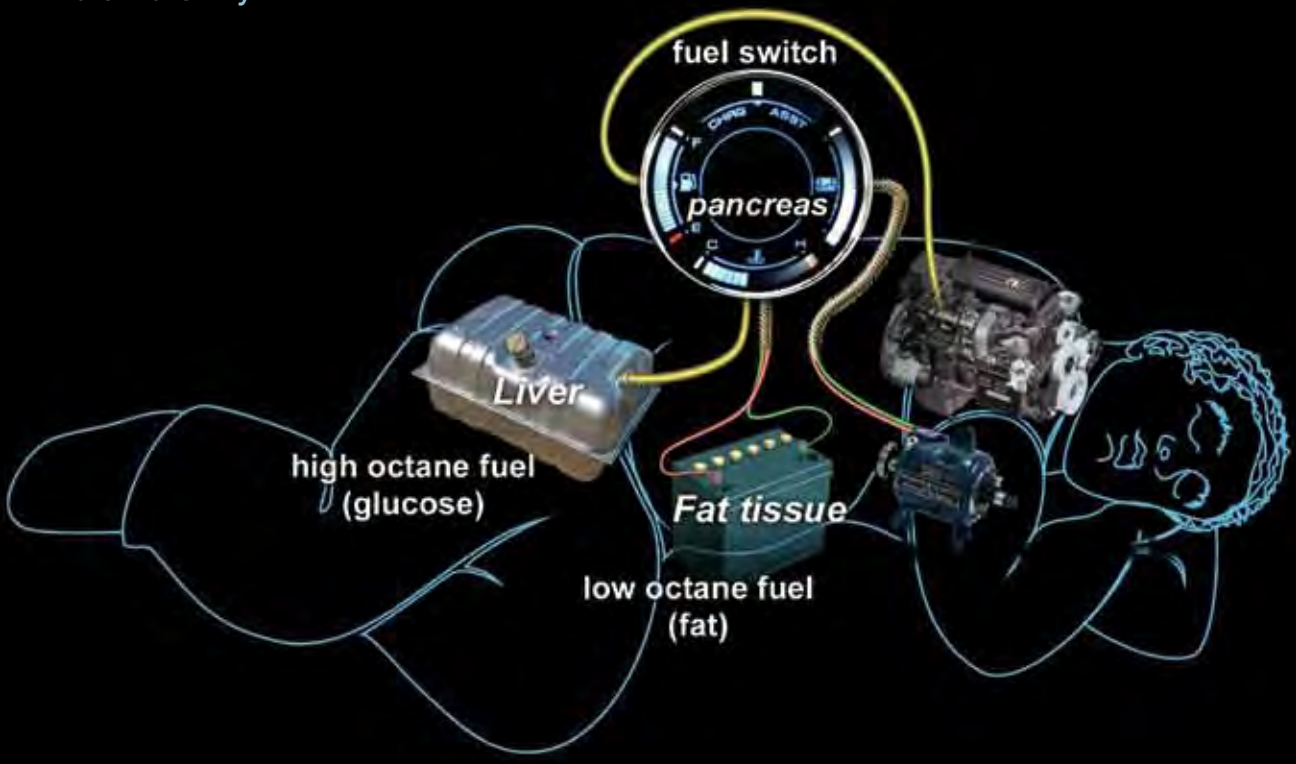


Image courtesy of Dr. Marc Montminy and Jamie Simon, Salk Institute for Biological Studies.

Findings may suggest novel ways to treat metabolic conditions

BY VIRTUE OF HAVING SURVIVED, ALL ANIMALS—FROM FLIES TO man—share a common capability. All can distinguish times of plenty from famine and adjust their metabolism or behavior accordingly. Failure to do so signals either extinction or disease.

A collaborative effort by investigators in the labs of **Marc Montminy** and **John Thomas** recently revealed just how similarly mammals and insects make critical metabolic adjustments when food availability changes, either due to environmental catastrophe or everyday changes in sleep/wake cycles. Those findings, published in *Cell*, may suggest novel ways to treat metabolic conditions such as obesity and type 2 diabetes.

In their study, Montminy and Thomas used the fruit fly *Drosophila melanogaster* to show that activation of a factor called SIK3 by insulin dampens a well-characterized pathway promoting fat breakdown, providing a molecular link between glucose metabolism and lipid storage.

“The metabolic system is like a hybrid car. In the daytime we use glucose as high-octane fuel, but at night we switch to the battery, which in this case is stored fat,” says Montminy.

During fasting, a group of fat-busting enzymes, called lipases, trigger the flow of energy from the fly’s low-power “battery” fat pack to different organs in the body. These lipases are turned on by a genetic switch, called FOXO, which is part of the central transmission for fasting metabolism. When the flies eat, SIK3 shuts off the FOXO switch, which both cuts off the battery’s energy stream by silencing the fat-busting enzymes and allows the fat pack to recharge its batteries.

Unexpectedly, SIK3 does not control the FOXO switch directly. Rather, much like a runner in a relay race, the SIK3 enzyme has to pass the baton to another enzyme, called HDAC4, which in turn regulates FOXO. The investigators found that the SIK3/HDAC4/FOXO machine they characterized in the fruit fly also controls the metabolic hybrid engine in mice.

“Currently, we have over 20 million people with type 2 diabetes and close to 60 million with insulin resistance,” says Montminy. “This is a huge problem tied to obesity. Finding a way to curb obesity will essentially require consideration of both environmental and genetic factors. The human counterparts of HDAC4 and SIK3 may be mutated in ways that make them work less effectively and enhance our proclivity to become obese.”

Fred "Rusty" Gage and Kristen Brennand in the lab

Patients' own cells yield new insights into the biology of schizophrenia

EVEN AFTER A CENTURY OF STUDYING THE causes of schizophrenia—the most persistent disabling condition among adults—scientists still don't know the cause of the disorder. Induced pluripotent stem cells (iPSCs) generated from schizophrenic patients, however, have brought researchers from the lab of **Fred H. Gage** a step closer to a fundamental understanding of the biological underpinnings of the disease.

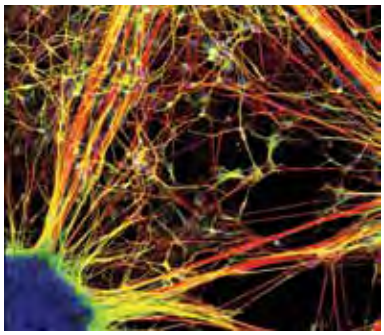
In their study, published in *Nature*, Gage's team reported both that neurons generated from these patient-derived iPSCs made fewer connections with each other and that Loxapine, an antipsychotic drug commonly used to treat schizophrenia, restored neuronal connectivity in iPSC neurons from all patients.

"This is the first time that a complex mental disease has been modeled in live human cells," says Gage. "This model not only affords us the opportunity to look at live neurons from schizophrenia patients and healthy individuals to understand more about the disease mechanism, but also to screen for drugs that may be effective in reversing it."

Schizophrenia, which is defined by a combination of paranoid delusions, auditory hallucinations and diminished cognitive function, afflicts 1 percent of the population worldwide, corresponding to nearly 3 million people in the United States alone. Accumulating genomic evidence indicates that many different combinations of genetic lesions—some of them affecting the susceptibility to environmental influences—may lead to a variety of signs and symptoms collectively labeled schizophrenia.

Trying to overcome the limitations of the past, such as limited accessibility of human neurons and the difficulty of separating genetic and environmental influences, postdoctoral researcher **Kristen Brennand** reprogrammed into iPSCs skin fibroblasts from four schizophrenia patients with a hereditary history of the disease. She then differentiated these cells into neurons, which allowed her to study how they differed from those in non-schizophrenics.

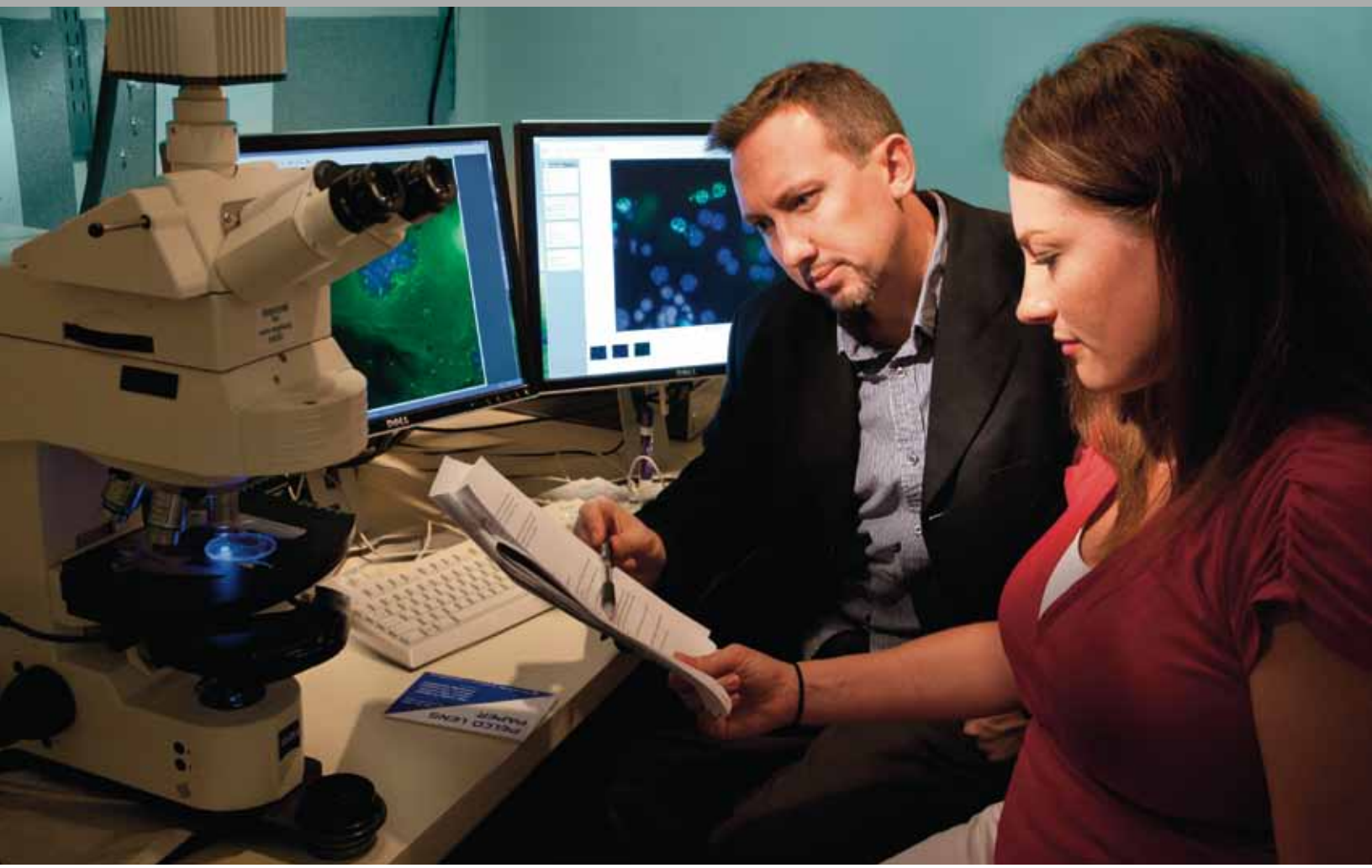
"Nobody knows how much the environment contributes to the disease," she explains. "By growing neurons in a dish, we can take the environment out of the equation and start focusing on the underlying biological problems."



Neurons generated from schizophrenia patient-derived iPSCs form fewer connections than neurons generated from healthy people. Image: Kristen Brennand.

"For many years, mental illness has been thought of as a social or environmental disease, and many thought that if affected people just worked through their problems, they could overcome them," adds Gage. "What we are showing are real biological dysfunctions in neurons that are independent of the environment."

Discovery Roundup



Reuben Shaw and Maria Mihaylova

"Fasting pathway" points the way to new class of diabetes drugs

AFTER A MEAL, INSULIN INSTRUCTS MUSCLE CELLS TO SQUIRREL away glucose for later use and turns off sugar production in the liver, ensuring that blood sugar levels don't rise too high. Conversely, the fasting hormone glucagon signals liver cells to flip on glucose production when supplies run low.

In many patients with type 2 diabetes, however, the body turns a deaf ear to insulin's urgent message, and as a result, the liver acts like a sugar factory on overtime, churning out glucose throughout the day, even when blood sugar levels are high. The most widely used drug to control blood glucose levels in type 2 diabetics is currently metformin.

A uniquely collaborative study led by researchers in the lab of **Reuben J. Shaw** recently uncovered a novel mechanism that turns up glucose production in the liver when blood sugar levels drop, pointing toward a new class of drugs for the treatment of metabolic disease. The findings, published in *Cell*, have revealed a crucial role for a group of enzymes called histone deacetylases (HDACs).

A few years ago, Shaw had discovered how metformin helps insulin control glucose levels: it binds to a "metabolic master switch" known as AMPK that blocks glucose production in the liver. Trying to identify novel targets of AMPK that might be relevant to diabetes, **Maria Mihaylova**, a graduate student in Shaw's laboratory, focused her efforts on a family of enzymes known as class II HDACs. Working closely with **Ronald M. Evans**, Mihaylova found that inhibiting class II HDACs shut down genes encoding enzymes needed to synthesize glucose in the liver. In collaboration with colleagues in **Marc Montminy**'s lab, she also discovered that HDACs themselves associated with the DNA regulatory elements controlling the expression of the glucose-synthesizing enzymes, but only after she had treated cells with the fasting hormone glucagon. In response, chemical modifications on class II HDACs are removed, and they can translocate into the nucleus, where they bind to a key metabolic regulator that is shut down by insulin.

Recently, many drug companies have been developing HDAC inhibitors as anti-cancer drugs, so Shaw speculates that some of these compounds, which may or may not be useful for cancer, could have therapeutic potential for the treatment of insulin resistance and diabetes.

A giant leap for plant biology

AN INTERNATIONAL TEAM OF SCIENTISTS, whose senior investigators included **Joseph Ecker**, recently reported a giant leap forward in plant biology, describing in the journal *Science* their mapping and early analyses of thousands of protein-to-protein interactions within the cells of the model plant *Arabidopsis thaliana*.

"With this one study we managed to double the plant protein interaction data that are available to scientists," says Ecker, noting that these data, along with data from future mapping studies, should enable biologists to make agricultural plants more resistant to drought and diseases, more nutritious and generally more useful to mankind.

The four-year project was headed by Ecker and colleagues at Boston's Dana-Farber Cancer Institute. In its initial stages, members of Ecker's lab converted most of their accumulated library of *Arabidopsis* protein coding gene clones into a form useful for protein interaction tests. The Dana-Farber scientists systematically ran these through a high-quality protein interaction screening process. Out of more than 40 million possible pair combinations, they found a total of 6,205 *Arabidopsis* protein-protein interactions, involving 2,774 individual proteins, which represents only about 2 percent of the full protein-protein "interactome" for *Arabidopsis*. "There will be larger maps after this one," says Ecker.

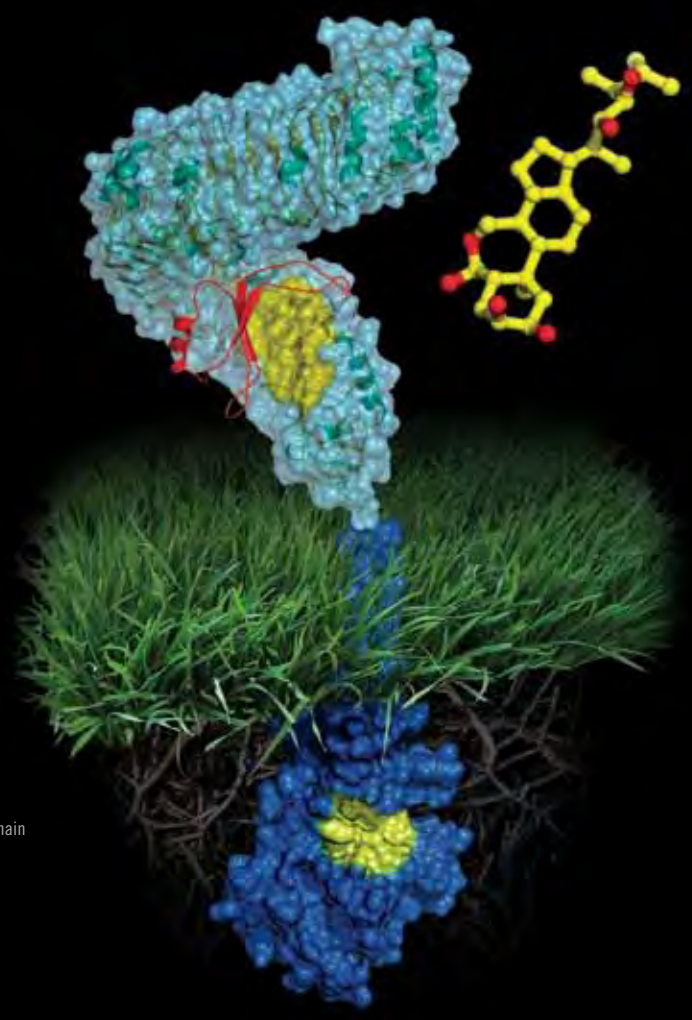
Even as a preliminary step, though, the new map is clearly useful. The researchers were able to sort the protein interaction pairs they found into functional groups, revealing networks and "communities" of proteins that work together. Further analysis provided new insight into plant evolution. Ecker and colleagues' *Arabidopsis* genome data, reported a decade ago, had revealed that plants randomly duplicate their genes to a much greater extent than animals do. These gene duplication events apparently give plants some of the genetic versatility they need to stay adapted to shifting environments. In this study, the researchers found 1,900 pairs of the mapped proteins that appeared to be the products of ancient gene duplication events.

Ecker and his colleagues hope that these studies mark the start of a period of rapid advancement in understanding plant biology. "This starts to give us a big, systems-level picture of how *Arabidopsis* works, and much of that systems-level picture is going to be relevant to—and guide further research on—other plant species, including those used in human agriculture and even pharmaceuticals," Ecker says.

The image shows an *Arabidopsis* plant overlaid on a network map of protein-protein interactions. The clusters of colors represent "communities" of interacting proteins that are enriched in specific plant processes. *Image: Joseph R. Ecker, Salk Institute for Biological Studies. Plant photo: Joe Belcovson, Salk Institute for Biological Studies. Network map: Mary Galli, Salk Institute for Biological Studies and Matija Dreze, Center for Cancer Systems Biology at the Dana-Farber Cancer Institute.*

Discovery Roundup

> **"Understanding how plants coordinate gene expression will ultimately increase crop yields in the field..."**
>
> **– Joanne Chory**



Atomic model of the plant steroid receptor BRI1

A molecule of brassinolide (yellow wire model) binds to the extracellular domain of the receptor (in light-blue). Binding ultimately causes phosphorylation of the receptor's cytoplasmic kinase domain (in dark blue), thereby transducing the signal across the membrane.

Image: Michael Hothorn and Jamie Simon, Salk Institute for Biological Studies

It's not easy being green

AS SEEDS SPROUT, THEY CONSUME A FINITE ENERGY PACK contained within them. Once those resources are depleted, the plant cell nucleus must be ready to switch on a photosynthetic program. A team of researchers led by postdoctoral fellow **Jesse Woodson**, in the lab of **Joanne Chory**, recently showed a new way that those signals are relayed. In a study published in *Current Biology*, Chory and her group identified a signaling factor that turns on photosynthesis-related genes—a finding that may help achieve greater crop yields and better plant health.

Although in plants and animals most genes reside in the nucleus, small DNA rings of genes are found in other cellular venues such as energy-producing mitochondria. Plant chloroplasts, whose primary function is to turn light and carbon dioxide into energy and carbohydrates required for growth, also contain genes that regulate photosynthesis-related factors encoded in the plant cell nucleus.

The Chory lab previously identified mutations in five genes in *Arabidopsis thaliana* plants that were unable to synthesize molecules such as chlorophyll or respond to signals generated by intermediates of the chlorophyll biosynthetic pathway. Those studies suggested that when plants undergo stress, an intermediate accumulates that tells the nucleus to stop "turning green."

These mutants—called GUN (for genomes uncoupled) 1 to 5—lack proteins necessary to generate signals or to relay information from these signals from stressed chloroplasts to the nucleus. Chloroplasts in normal plants might deploy those signals when plants encounter stress, such as too much heat or too little water. Inhibitory signals could also be sent when germinating sprouts are not yet mature enough to make the leap from relying on the seed energy pack to generating their own energy using sunlight.

Suspecting that healthy chloroplasts also generate signals, the team screened *Arabidopsis* for factors that switched photosynthetic proteins on, rather than off. What they found was a gene designated *gun 6*, the first gun mutant indicating that signals are sent from functioning chloroplasts, as well as chloroplasts that are not functioning well.

"Overall, this work answers basic questions regarding how a plant grows, builds chloroplasts and harvests light energy in order to turn into a photosynthetic organism," says Chory. "Understanding how plants coordinate gene expression between the chloroplast and nucleus will ultimately increase crop yields in the field, where plants often encounter multiple stresses during the growing season."

The genome guardian's dimmer switch: regulating p53 is a matter of life or death

A TEAM OF SCIENTISTS LED BY GEOFFREY M. Wahl has found clues to the functioning of an important damage response protein in cells. Although the protein, p53, is known as an important tumor suppressor, it is also critical for determining whether a cell survives stress and continues to function in a variety of situations. Wahl's study, which appeared in the journal *Genes & Development*, shows that a short segment on p53 acts as a dimmer switch that helps control the level of p53 activity in a critical stem cell population and the offspring they generate.

One vexing problem with p53 is that it apparently evolved to protect the integrity of the genome for future generations rather than to prolong the lives of individual cells or animals, so from the point of view of an animal, p53 sometimes goes too far in killing cells or suppressing growth. Experiments in mice have suggested that even modest reductions in p53's activity greatly increases survival after exposure to radiation without raising the long-term cancer risk to unacceptable levels.

Scientists therefore are eager to find out how cells regulate p53, so they can target these mechanisms with drugs. Wahl and colleagues, including postdoc **Vivian Wang** and Kenneth Kaushansky, M.D., a past president of the American Society for Hematology and former faculty member at UC San Diego, set out to illuminate the function of a stretch of regulatory amino acids at one end of the protein by creating "designer" mice with other amino acids in this region, thereby rendering it inoperative. What they found was that irradiation and the ensuing p53 response significantly damaged the blood-forming cells of the mice's bone marrow, but other parts of their bodies seemed normal. The results led the team to conclude that the loss of function of p53's normal "dimmer-switch" segment had allowed the protein to become too active, arresting the hematopoietic stem cells' proliferation and preventing them from replacing blood cells lost to irradiation.

One implication of the research is that drugs to lower p53 levels, or to reduce its transcription of other growth-stopping genes, might be used temporarily to reduce unwanted tissue damage from DNA-altering drugs or radiation. Another implication is that p53-boosting drugs, which are currently being tested in cancer patients, could have dangerous side effects if used in combination with other drugs that cause DNA damage.

Geoffrey M. Wahl

"Unnatural" chemical allows researchers to watch protein action in brain cells

RESEARCHERS IN THE LAB OF LEI WANG have genetically incorporated "unnatural" amino acids, such as those emitting green fluorescence, into neural stem cells, which then differentiate into brain neurons with the luminescent "tag" intact. This work, which appeared in *Stem Cells*, may help scientists probe the mysteries of many different kinds of stem cells in humans, as well as the cells they produce, and could be a boon to basic and clinical research, helping to speed development of stem cell–based therapies.

Stem cells hold great potential for the treatment of various diseases, yet it has been hard to study how they self-renew and produce all of the body's cells. Incorporating unnatural amino acids will allow researchers to study in real time a particular protein in a living cell or organism, compared to the traditional biochemical methods, which are conducted through such means as a test tube.

Wang and his colleagues pioneered the use of unnatural amino acids (Uaas), which were first incorporated into bacteria in 2001 and mammalian cells in 2007. This latest study, which was conducted in two stages, represented the first use of Uaas in stem cells. In the initial set of experiments, the researchers found that Uaas were successfully incorporated into neural stem cells, the incorporation lasted through the differentiation, and these cells then produced neurons carrying the fluorescent amino acid. The second set of experiments demonstrated how these Uaas can be used to help solve a biological question—specifically how voltage-sensitive ion channels, which are pore-forming proteins, work in neurons.

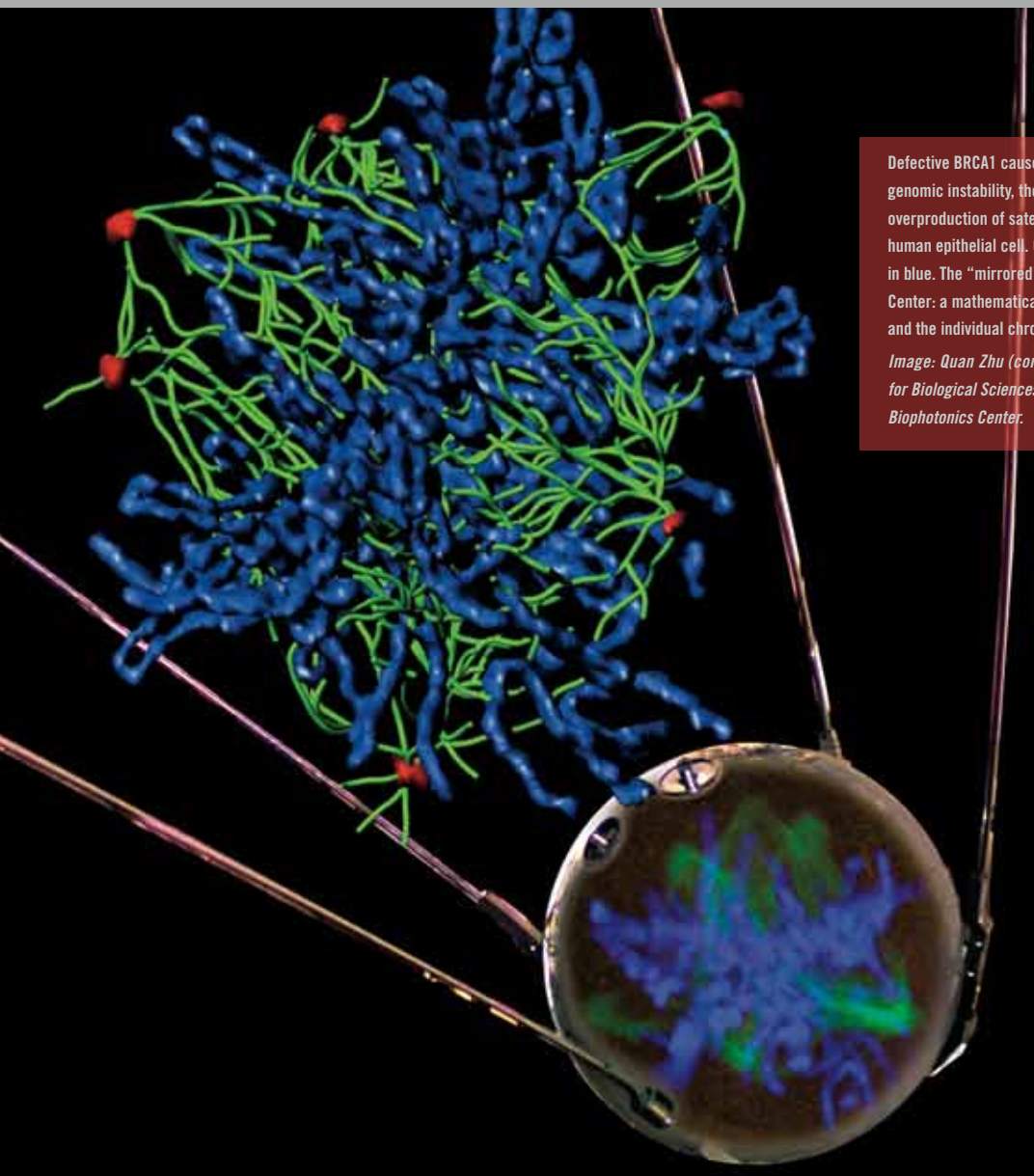
"We detected changes in fluorescence intensity of the Uaa when the neurons were stimulated," explains Wang, "and these changes are dependent on where the Uaa was incorporated, which hint that different positions of the protein are moving into or outside of the membrane in response to the electric field."

Wang says this experiment can also be adapted to study other membrane proteins in other cells, no matter where they exist in the body.

In related work, reported in *Angewandte Chemie*, researchers in Wang's lab reported a method for demonstrating how Uaas can be used to map the structure of a corticotropin-releasing hormone receptor (CRF-R1), which regulates human stress. They also show how this new tool helped locate three areas on the receptor to which peptide hormones can dock to activate or inhibit the receptor.

Photo of neurons differentiated from neural stem cells HCN-A94 with an unnatural amino acid incorporated.
Photo: Bin Shen.

Discovery Roundup



Defective BRCA1 causes aberrant expression of non-coding satellite RNA that leads to genomic instability, thereby promoting cancer development. The image shows that overproduction of satellite RNA leads to an abnormal number of centrosomes in a normal human epithelial cell. Centrosomes are pictured in red, tublin in green and chromosomes in blue. The "mirrored" image in the Sputnik satellite is a confocal microscopic image. Center: a mathematical reconstruction of the confocal image to resolve the tubulin fibers and the individual chromosomes.

Image: Quan Zhu (confocal image); Jamie Simon (composition), Salk Institute for Biological Sciences; James Fitzpatrick (reconstructed image) Waitt Advanced Biophotonics Center.

Researchers near goal of using a patient's own cells to make stem cells

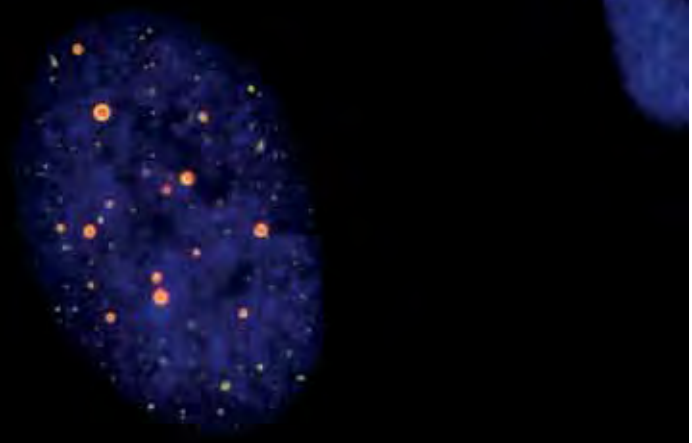
A TEAM IN THE LAB OF INDER VERMA HAS developed an improved technique for generating large numbers of blood cells from a patient's own cells. The new technique, published in the journal *Stem Cells*, will be immediately useful in further stem cell studies and when perfected, could be used in stem cell therapies for a wide variety of conditions, including cancers and immune ailments.

Stem cell researchers have been racing toward this goal since 2006, when techniques for turning ordinary skin cells into induced pluripotent stem cells (iPSCs) were first reported. In principle, iPSCs mimic the embryonic stem cells (ESCs) from which organisms develop. However, researchers don't know yet how to induce iPSCs to become tissue-specific stem cells or mature tissue cells with high efficiency.

Like many other laboratories, the Verma lab has been seeking more efficient ways to turn iPSCs into blood-forming hematopoietic stem cells (HSCs). These may be more valuable medically than any other tissue-specific stem cell because they can supply not only oxygen-carrying red blood cells but also all the white blood cells of the immune system.

In this study, the research team took seven lines of human ESCs and iPSCs and experimented with different combinations and sequences of growth factors and other chemical compounds that are known to be present as ESCs move to the HSC state in a developing human. Applying cocktails of these factors, the researchers induced the iPSCs and ESCs to form colonies of cells that bore the distinctive molecular markers of blood cells. With their best such cocktail, they were able to detect blood-specific markers on 84% of their cells after three weeks—a big jump in efficiency from just a few years ago.

Although the technique still has room for improvement—the researchers detected progenitor cells and mature cells from only one category or lineage, and the blood cell population they produced from ESCs and iPSCs contained no indefinitely renewing, transplantable HSCs—Verma notes, "We're now tantalizingly close to our ultimate goal."



About 10 percent of tumor cells use a mechanism called ALT, short for alternative lengthening of telomeres, to keep their chromosomes ends intact. PML bodies that contain telomeric DNA and associated telomere-binding proteins (shown in orange) are highly characteristic of ALT tumor cells.
Image: Liana Oganesian, Salk Institute for Biological Studies.

A new ending to an old "tail"

IN STARK CONTRAST TO NORMAL CELLS, WHICH ONLY DIVIDE A FINITE number of times before they enter into a permanent state of growth arrest or simply die, cancer cells never cease to proliferate. Scientists in the lab of **Jan Karlseder** have uncovered an important clue to one of the mechanisms underlying cancer cell immortality. Their findings reveal an unanticipated structure at chromosome ends, which could be a key ingredient in the biological "elixir of life."

"How tumor cells evade cell death is still baffling to us, but we think we may have solved a small piece of this puzzle," says Karlseder.

A linchpin to the immortality of malignant cells is the ability to maintain telomeres, the specialized ends of chromosomes. Like slow-burning fuses, telomeres become shorter each time a cell divides, acting as a kind of cellular clock ticking down a cell's age. Eventually they are depleted, and the cell enters a permanently arrested state called senescence. To escape this inevitable demise, about 90 percent of human tumors rely on a huge boost in the levels of an enzyme called telomerase, which adds DNA to telomeres, thus turning the clock back. The remaining 10 percent use a mechanism known as ALT, short for alternative lengthening of telomeres. Understanding ALT is essential since tumors can evade anti-cancer therapies aimed at inhibiting the activity of telomerase through the activation of ALT.

Trying to learn more about the biological tools that ALT tumors use to sustain their immortal status, Karlseder and his team uncovered a new structural beacon, called the C-tail—a string of DNA rich in the base cytosine (C) that hangs over the very tip of telomeres. The finding came as a big surprise since conventional wisdom had it that mammalian cells normally terminate both ends of every chromosome with a single-stranded stretch of DNA rich in the base guanine (G).

When postdoctoral researcher **Liana Oganesian** carefully looked at chromosome ends, however, she discovered that about half of all telomeres in ALT tumors bore a C-tail, while the presence of such a tail in normal human cells was several hundredfold less prevalent.

"This piece of DNA is conspicuously absent in tumors that use telomerase, suggesting that C-tails are a unique feature of ALT tumors," she says, and potentially opening up new therapeutic avenues to cut the life of a cancer cell short.

Aging, interrupted

WE LIVE IN A SOCIETY OBSESSED WITH AGING (and how to slow it down), but surprisingly little is known about the human aging process because lifespans of eight decades or more make it difficult to study. Researchers in the lab of **Juan Carlos Izpisúa Belmonte** recently replicated premature aging in the lab, however, allowing them to study aging-related disease in a dish.

In their study, published in the journal *Nature*, Izpisúa Belmonte and his team successfully generated induced pluripotent stem (iPS) cells from skin cells obtained from patients with Hutchinson-Gilford progeria, who age eight to ten times faster than the rest of us, and differentiated them into smooth muscle cells displaying the telltale signs of vascular aging. Progeria's striking features resemble the aging process put on fast-forward, and afflicted people rarely live beyond 13 years. Almost all patients die from complications of arteriosclerosis—the clogging or hardening of arteries or blood vessels caused by plaques—which leads to heart attack and stroke. Scientists are particularly interested in progeria in the hope that it might reveal clues to the normal human aging process. The disease is exceedingly rare, however, and only 64 children living with progeria are known, making access to patients very difficult.

Progeria stems from a mutation that leads to the production of a truncated version of the protein known as progerin. Cells from progeria patients have misshapen nuclei and a range of other defects. Yet despite their "old" appearance and against all predictions, it turned out that these cells could be readily converted into iPS cells. The reprogramming process erased all apparent defects, and the rejuvenated pluripotent cells looked and acted like perfectly normal healthy cells. But as soon as Izpisúa Belmonte's group differentiated progeria-derived iPS cells into smooth muscle cells, the evidence of premature aging reappeared.

This suppression of progerin expression by reprogramming and subsequent reactivation during differentiation provides a unique model system to study human premature aging pathologies, notes Izpisúa Belmonte, and having a human model of accelerated aging may provide new insights into how we age.

In a later study, published in *Cell Stem Cell*, Izpisúa Belmonte's team successfully edited a diseased gene in patient-specific iPS cells as well as adult stem cells, demonstrating that the gene-editing approach they developed provides an efficient and safe tool for cell engineering and opens the way for gene editing–based stem cell therapies suitable for clinical applications.

San Diego **salk**ex**cell**erators spend special evening with Dr. Geoff Wahl

San Diego salkexcellerators gathered at the Institute on May 4 for a private reception and scientific lecture by regarded Salk scientist **Geoff Wahl**, titled "Are We Winning the War on Cancer?"

IN HIS PRESENTATION, WAHL EXPLAINED how his research tries to determine, at the molecular level, the various ways cancer originates and progresses and why tumors become resistant to even the most powerful anti-cancer drugs—research that could lead to new strategies and drugs to treat and even cure the disease. A professor in the Gene Expression Laboratory and former president of the American Association for Cancer Research, Wahl offered unique insights into the disease, which is the second leading cause of death in the U.S., declaring, "I see significant opportunities for advances in cancer prevention, diagnosis and treatment as our knowledge of the molecular biology of cancer increases."

San Diego salkexcellerators are the next generation of business professionals, entrepreneurs, and volunteers committed to supporting the groundbreaking research conducted at the Salk Institute. Join our community at special events year-round that include opportunities to engage with Salk's renowned scientists.

For more information visit www.salk.edu/support or call (858) 453-4100, ext. 1405.

From left: Leanne Jones, Ramin Pourteymour and Geoff Wahl

SALK in the city... NEW YORK

Salk leaves mark on Big Apple

SALK SCIENCE WAS THE FOCUS IN APRIL, WHEN NEW YORK FRIENDS, supporters and guests of the Institute gathered at two separate events for updates on research, to socialize and to become better acquainted with Salk.

The first event, NY salkexcellerators, took place Wednesday evening, April 27, at the law offices of Covington & Burling, LLP. Salkexcellerators are the next generation of business professionals, entrepreneurs and volunteers committed to supporting the groundbreaking research conducted at the Salk Institute, and some 50 members and guests convened for cocktails and conversation. The featured attraction was Salk professor **Samuel Pfaff**, who gave a presentation titled "From Discovery to You: The Neuronal Pathway." Salkexcellerators cabinet member **Carrie Hamerslag** opened and closed the program, which in addition to Pfaff featured Salk president **William R. Brody**, executive vice president **Marsha A. Chandler** and trustee **Howard Newman**. A wine tasting was sponsored by Alex Elman Wines.

The following day, approximately 70 people, including many members of the Salk President's Club and Partners in Research, met at the historic 21 Club for the biannual Salk in the City luncheon and talk, which again featured Pfaff. The event was hosted by **Mary Jane Salk**, widow of Jonas Salk's brother Lee, to commemorate the anniversary of the discovery of the polio vaccine—a tradition that the brothers established and continued for many years at the same venue. Also present were representatives from the Christopher Reeve Foundation, which significantly supports Pfaff's research; **John** and **Anne Codey** from the Helmsley Foundation, which has made several major grants to the Institute; and **Francoise Gilot-Salk**, Jonas Salk's widow, who will celebrate her 90th birthday next year. Salk board chair **Irwin Jacobs** was on hand as well to welcome the guests, as were Brody and Chandler.

*Interest in Salk Institute research and support for the Salk mission have been growing steadily in New York. For information about the Institute's upcoming New York events, contact **Betsy Reis** at 858-452-8051 or breis@salk.edu.*

Samuel Pfaff

Second Annual Golf Tournament raises funds to support scientific discovery

MORE THAN 65 GOLFERS HIT THE LINKS AT THE beautiful Del Mar Country Club on May 10 to participate in the 2nd annual Salk Institute Golf Tournament.

The teams, made up of corporate sponsors, foundation representatives and loyal Salk supporters, enjoyed a lively day of golf and raised over $64,000 at the fundraiser to support the Institute's basic biological research. After the last round was completed, the players enjoyed a delicious dinner and raffle.

"This tournament gives the local golfing community a great opportunity to play on the beautiful greens at the Del Mar County Club while contributing their support to further the transformative scientific discoveries of this world-renowned institute," explains **Seth Schechter**, Salk's senior director of foundation relations, who launched the golf tournament last year.

From left: Salk supporters Dave Jesme (Rudolph & Sletten), Jim Carson (Rudolph & Sletten), Phil Petersen (Dynalectric), and Howard Mills (Rudolph & Sletten) strike a pose on the greens at the Del Mar Country Club.

Tax seminar attendees dine al fresco at the beautiful Lodge at Torrey Pines.

Foundation leaders convene at 39th Salk Tax and Management Seminar

BUILDING ON ALMOST FOUR DECADES OF SUCCESS, the Institute's 39th annual Tax and Management Seminar, held May 11–13, drew scores of prominent representatives from national and international foundations to the Salk campus for three days of presentations and discussions by authorities in foundation tax law and prominent leaders in foundation management. World-renowned philanthropist Bill Gates, Sr., co-chair of the Bill & Melinda Gates Foundation, delivered the keynote address.

Bill Gates, Sr., delivers the keynote address to the audience at the 39th annual Salk Tax and Management Seminar.

Diana Kalman looks through a microscope in Leanne Jones's lab.

Chaired by Edwin K. Hunter, an attorney with the firm of Hunter, Hunter & Sonnier (LLC) in Lake Charles, LA, and a trustee of the Joe W. and Dorothy Dorsett Brown Foundation, among others, the seminar featured two separate tracks of presentations by distinguished experts in their fields. Hunter led the tax track, while Valerie Jacobs, founder of Valerie Jacobs Consulting, led the trustee management and governance track. Introduced at the 2010 seminar, this second track was so well received that it was again incorporated into this year's event.

"The Salk Institute tax seminar has proven to be a great resource that provides a wealth of pertinent and timely information about the applicable tax rules and regulations affecting foundations," says **Seth Schechter**, Salk's senior director of foundation relations. "It enhances the power of philanthropy by providing donors, trustees and professionals with peer learning opportunities, along with a chance to ask questions of top tax authorities."

Launched in 1972, the tax seminar attracts attorneys from the nation's top law firms and leading consultants from many U.S. foundations and nonprofit organizations, large and small, including the Leona H. and Harry B. Helmsley Charitable Trust, the Bill & Melinda Gates Foundation, the Henry L. Guenther Foundation, the H.A. and Mary K. Chapman Charitable Foundations, and the H. N. and Frances C. Berger Foundation, to name just a few.

Meeting of the minds: Partners in Research gather for luncheon and lecture

THIRTY FRIENDS OF THE INSTITUTE ATTENDED THE MAY 25 PARTNERS in Research luncheon at the Salk Institute, where they enjoyed a lecture titled "In the Spotlight: The Brain's Silent Majority," presented by **Axel Nimmerjahn**, assistant professor in the Waitt Advanced Biophotonics Center and holder of the Richard Allan Barry Developmental Chair. The discussion focused on glia, a set of mostly silent cells that make up the bulk of our brain and whose role in health and disease still remains largely unknown. Biophotonics—the science of using and manipulating light to interrogate biological function—is now beginning to shed light on the part this "silent majority" plays in brain function.

Partners in Research are a visionary group that invests in the future of science by incorporating philanthropic support for the Salk Institute into their estate plans. If you or someone you know is interested in attending future events or in supporting the Salk Institute thorough a planned gift, contact Cheryl H. Dean, Esq., at 858. 453. 4100 x1228 or cdean@salk.edu.

Irwin and Joan Jacobs increase Chair Challenge with $5 million contribution

In 2008 the Jacobses stepped forward with 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. Due to the success of the Chair Challenge, the Jacobses have committed to add five more chairs to the challenge, for a total of 15 endowed chairs. To date, 11 chairs have been established and are recognized on the new Donor Wall in the Salk Institute's East Courtyard.

Insider's View

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

Serendipity and science

For our readers who are not scientists, I am going to let you in on a big secret ingredient that underlies many major scientific discoveries. One short word describes this ingredient, and it is simply this: **luck**

Not only luck, but hopefully good luck. While most of us were taught in school about the scientific method—rational thinking, deductive and inductive reasoning—and these are indeed important ingredients, the fact is, chance plays a significant role in scientific discovery. Sometimes it is an experiment that goes awry and produces unexpected (and sometimes unwanted) results that ultimately lead to a whole new paradigm. This was the situation for Alexander Fleming in 1928, when he left a stack of bacterial cultures in Petri dishes in his lab to be discarded while he went on vacation. By mistake, they were not discarded, and when he returned from vacation, he noticed that a fungus had grown in one of the dishes, and where there was fungus, the bacteria failed to grow. This chance observation led to the discovery of penicillin.

Professor **Ed Callaway**, a neuroscientist at Salk, was studying the electrical behavior of single neurons in the brain and wanted to know which other neurons in the cortex were sending signals to a particular neuron. This difficult challenge had never been solved, but a chance conversation between Callaway and Salk professor **John Young**, a virologist, led to an intriguing idea. Young theorized that the rabies virus, because it infected neurons in the brain by traveling along the axon sheath (the "cable" that transmits signals from one neuron to another), could be used as a sophisticated agent to identify the connections between nerve cells.

In order to get the virus to infect the single neuron, it required substantial genetic modification. A series of steps, including inserting a snippet of DNA that would allow the virus to become fluorescent green, ultimately allowed Callaway to identify a single neuron, record its electrical activity and then shine a laser on the brain. Amazingly, the connected neurons show up as bright green spots in the microscope.

The "secret sauce" of Salk scientific discovery is the unique character of our institute. Because there are no departments or divisions and also because the architectural design of the Salk facilitates interaction among scientists in the laboratory, discussions such as the one between Callaway and Young are commonplace. Facilitating interaction among the best minds in seemingly unrelated fields is one important aspect of scientific (or should I say "serendipitous") discovery.

Of course, luck is no substitute for expertise and hard work, leading to two corollaries of scientific discovery that are also important:

From Louis Pasteur: "Chance favors the prepared mind."

And from an anonymous source: "The harder I work, the luckier I get!"

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**

DECEMBER 2011

1 **Loyal Donor Lunch**

FEBRUARY 2012

1 **San Diego salkexcellerators Lecture**

15 **Partners in Research**

MARCH 2012

14 – 16 **Tax and Management Seminar**

Follow us on:

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

More than 200 students and teachers from the San Diego region spend a Saturday at the Salk Institute for the annual March of Dimes High School Science Day (MODHSSD), a half-day community outreach event designed to get youngsters interested in considering an exciting career in research. The next MODHSSD will be on Saturday, March 3, 2012. For more information, contact **Dona Mapston** at mapston@salk.edu.