

InsideSalk

Where cures begin.
Salk Institute 11|12

Investing in Discovery

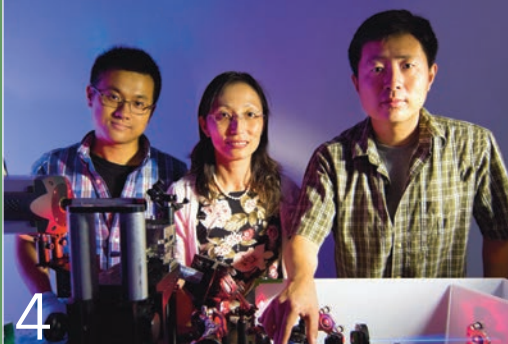
Private philanthropy redraws the landscape
of Salk Science

ALSO IN THIS ISSUE:

2011-2012 DONOR HONOR ROLL

November 2012

Inside Salk



Investing in discovery



One on one with... Tony Hunter



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

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

Rebecca Newman
Vice President,
External Relations

Stacie Spector
Chief Communications Officer

Christopher Emery
Director, Scientific Communications

Andy Hoang
Director, Media Relations

Karen Heyman
Staff Writer

Sarah Lifton
Staff Writer

Scott Edwards and Renee Twombly
Contributing Writers

Liz Hincks
Web Editor

Joe Belcovson and Kent Schnoeker
Photographers

Mike Sullivan
Videography

Kat Kearney
Media Specialist

Rhiannon Bruni
Contributing Writer

Sarah Loffler
Design and Production

studio L.
Graphic Design

Visit the Salk Institute at www.salk.edu

3 EXECUTIVE MESSAGE

LEAD STORY

4 Investing in discovery

INSTITUTE NEWS

12 One on one with... Tony Hunter

16 Salk professors awarded chair appointments

18 Salk professor receives Howard Hughes Medical Institute Collaborative Innovation Award

Salk recruits two outstanding scientists

19 Salk celebration honors Ron Evans as winner of 2012 Wolf Prize in Medicine

Daniel C. Lewis joins Salk Institute board of trustees

20 Singing sensation LeAnn Rimes performs at 17th annual Symphony at Salk

21 Merci, Françoise Gilot-Salk exhibit draws to a close

22 Women & Science

23 Salk investigator Terrence Sejnowski wins IEEE Frank Rosenblatt Award

A grand gift

DISCOVERY ROUNDUP

24 Discovery of plant proteins may boost agricultural yields and biofuel production

25 Salk study may offer drug-free intervention to prevent obesity and diabetes

Salk scientists discover molecular link between circadian clock disturbances and inflammatory diseases

26 Planting the seeds of defense

27 "Magical state" of embryonic stem cells may help overcome hurdles to therapeutics

28 "Trust" hormone oxytocin found at heart of rare genetic disorder

29 Speeding up discovery with rapid 3D mapping of proteins

NEXT GENERATION

30 Gerald Pao's eclectic life

33 GEAR UP program

34 The heat is on: Salk 2012 Summer Scholars Program

PHILANTHROPY NEWS

35 2012 Donor Honor Roll

73 Insider's View

CALENDAR

Back Cover

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.



“I firmly believe that private contributions to Salk represent the very best of human nature in service to the very best in science.”

Dear Friends,

THIS ISSUE OF *INSIDE SALK* CELEBRATES THE ROLE THAT PRIVATE philanthropy has played at the Salk Institute—a role that is assuming ever increasing importance as funding from the National Institutes of Health and other federal agencies is shrinking and competition for grants to fund Salk research is intensifying. Our cover story presents compelling voices from the Salk discussing how private giving has shaped the cutting-edge science for which we are renowned and how it will accelerate discovery in the future.

The theme of philanthropy is woven throughout the contents of this issue, whether in announcements about new endowed chairs or a new faculty appointment to an existing chair, both demonstrating the impact and the timelessness of a gift to endowment, or an account of our long-standing Salk High School Scholars program, which is entirely supported by private gifts.

This issue's Discovery Roundup includes key research findings that help improve the human condition and were in part made possible by private donations and would not have advanced as rapidly without them. There have been many significant discoveries in neuroscience, cell biology, plant biology, stem cells and metabolism, but I would especially like to cite the two fascinating studies of circadian rhythms. Also on the science front, I think you will find the “One on one” with **Tony Hunter** particularly compelling. Tony is not only one of the Institute's most accomplished scientists but a generous donor in his own right, and he talks about why he feels it is so important to give back to the Institute.



ON THE COVER

A scanning electron micrograph showing the size and shape of the epidermis cellular ultrastructure of the stem of an oilseed crop, *Brassica raps*. Image courtesy of Matthew Joens, Waitt Advanced Biophotonics Core Facility, and Carl Procko, Plant Molecular and Cellular Biology Laboratory.



William R. Brody

Each of these articles draws a direct line from philanthropic support to the high-impact scientific advances that are our stock in trade, so it is only appropriate that we also pay homage to the very generous individuals and organizations who supported us this past year, in the accompanying Donor Honor Roll.

I hope you'll enjoy reading about the many facets of philanthropy at the Salk Institute and perhaps even take this opportunity to renew a gift or make a new one. I firmly believe that private contributions to Salk represent the very best of human nature in service to the very best in science.

As always, thank you so much for your continued support. It is one of the cornerstones of our success. 🏠

William R. Brody

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

INVESTING IN DISCOVERY

Private philanthropy redraws the landscape of Salk science

VISIONARY DONORS HAVE LONG RECOGNIZED THE UNIQUE

character of the Salk Institute and come forward with contributions, large and small, to advance its mission of discovery. With their generous support, the Institute attracts the best scientific minds in the world to work in open collaboration, conducting innovative research, making discoveries and mapping the blueprints to enable cures to be developed anywhere.

It is this generosity—and the environment it creates—that brought together **Quan Zhu** and **Hu Cang** to work on a bold new idea.

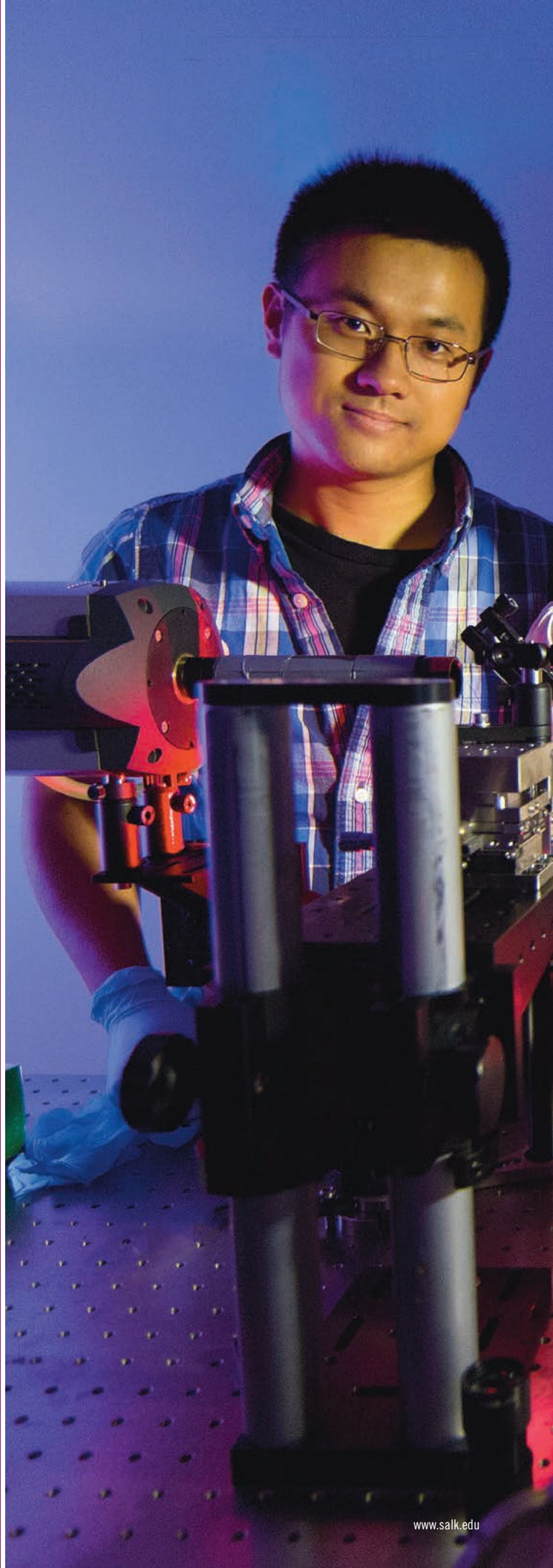
When Zhu, a molecular biologist, wanted to see how cancer cells interpret genetic instructions, she turned to Cang, a physicist. Combining their expertise in two very different fields, the two Salk scientists are using microscopes to visualize in unprecedented detail how DNA in living cells is bundled inside the nucleus. They are helping to explain how genetic regulation in cancer cells and stem cells is different than it is in other cells—research essential to developing new regenerative medicine and cancer therapies.

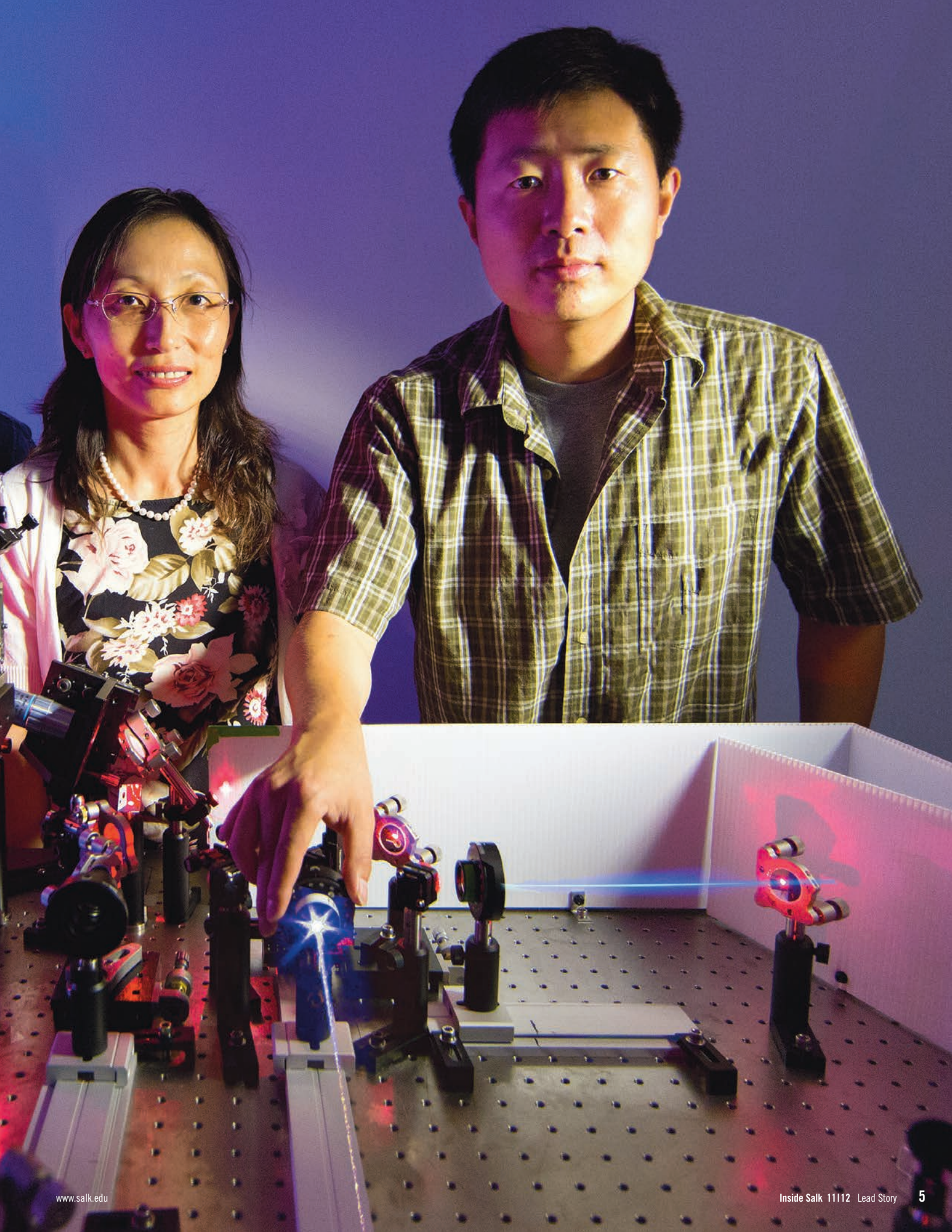
“This has bridged a chasm in studying how our genome is regulated,” says Zhu, a research associate in the lab of **Inder Verma**, a professor in the Laboratory of Genetics. “If you can see with your own eyes, you can learn things that aren’t otherwise possible.”

Since the Salk Institute’s inception in the 1960s with a landmark gift from the March of Dimes, the generosity of those who believe in Salk has supported the Institute’s ambitious research. Today that spirit of giving is more critical than ever. Zhu and Cang’s success is a testament to the growing importance of private philanthropy in supporting the kind of groundbreaking biomedical research for which the Salk Institute is known. Their work is drawing on the resources available in the Waitt Advanced Biophotonics Center, a cutting-edge microscopy center established at Salk with a \$20 million gift from **Ted Waitt**, Vice Chair of Salk’s board of trustees. In fact, Cang joined the Salk faculty in large part because of the biophotonics center.

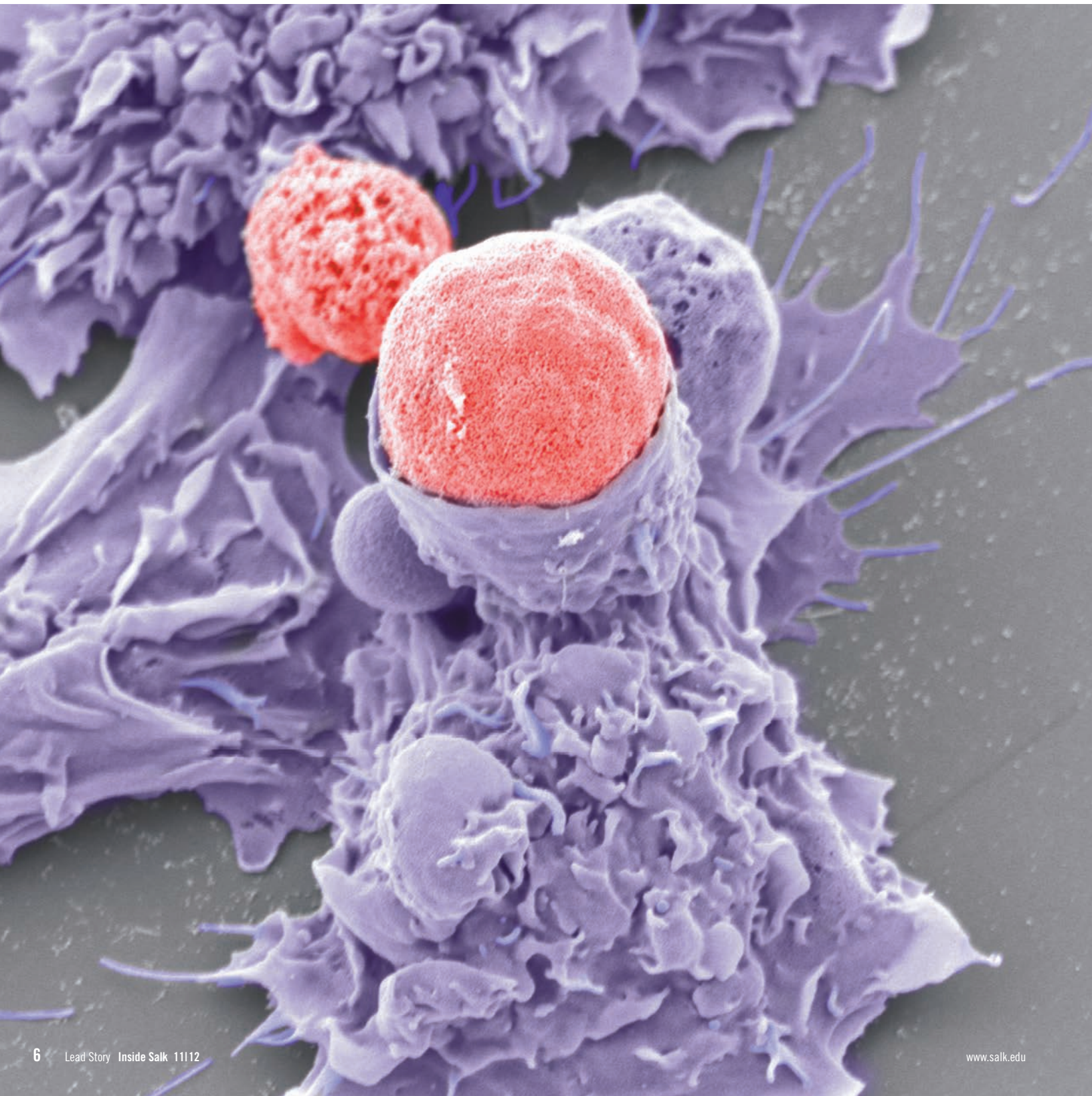
Waitt’s generous support and that of other philanthropists has been crucial in allowing Salk to capitalize on powerful new imaging technologies, methods for measuring chemical changes and genetic activity in cells, and computational methods for analyzing the massive amount of data these approaches produce. These remarkable advances are proceeding against a backdrop of declining federal funding for basic biomedical research, making private philanthropy essential to developing new therapies against a range of diseases.

Hu Cang (center) and Quan Zhu (right) have developed a method for imaging how DNA bundles inside a cell’s nucleus. Ying Hu (left), a postdoctoral researcher in Cang’s lab, also contributed to the research.





“Generous gifts from individuals and foundations have continued to provide the margin of excellence for the Salk. By supporting risk-taking and innovation, philanthropy enables Salk scientists to do what they do best—make the high-impact discoveries that lay the groundwork for new therapies and cures.” Marsha Chandler, Executive Vice President, Salk Institute



By all accounts, the biophotonics center has transformed how science is done at Salk. Three sought-after new faculty members, including Cang, have joined the center since it opened in early 2011. “Biology has become an extremely interdisciplinary field, and the center has allowed us to recruit people with bioengineering and biophysics backgrounds that we couldn’t have otherwise attracted,” says **Martin Hetzer**, a Salk professor and director of the center.

The center’s core facility is equipped with some of the most advanced imaging and microscopy instrumentation in the country. More than 40 Salk laboratories use the facility, with about 300 Salk researchers using the imaging equipment on a daily basis. So far, at least 15 high-impact research papers by Salk scientists have resulted from experiments that relied on the facility’s expertise and equipment.

Waite, who founded Gateway, Inc., and has gone on to form multiple enterprises since his retirement from the company, has been gratified by the results of supporting the biophotonics center.

“Science, like technology, is always changing and advancing,” he says. “I wanted to give Salk’s phenomenal scientists the tools they needed to take advantage of these new imaging technologies to take their science one step further. Already I’ve seen remarkable discoveries emerging from that investment—findings that are changing our understanding of life and disease.”

passion they bring to the discovery process, and we are proud to support their work.”

The Jacobses, along with many other private donors, have also given generously to Salk’s Innovation Grants Program, a fund that supports promising studies that would have difficulty garnering federal funding, which favors more established traditional lines of research. By helping researchers establish proof-of-concept data, the program allows them to then leverage outside support to expand on the studies.

“Federal funding has traditionally provided the lion’s share of funding for research that has improved medicine with each generation, but that support is declining,” says Salk president **William R. Brody**.

Since the 1960s, funding for basic science in the United States has dropped from approximately 1.9 percent of the gross domestic product to around 0.7 percent, less than half that of the peak. Since 2003, the National Institutes of Health budget has declined in constant dollars—with the exception of the two-year American Recovery and Reinvestment Act, which has now expired.

“The success of Salk and other biomedical research institutions will rely more and more upon private individuals and foundations with the foresight to understand the impact their giving has on this critical work,” Brody says.

Fortunately, as the need is growing, so too is giving. From 2003 to 2012, philanthropic contributions to the Salk grew annually from \$19.8

“I think any way that you can further science you, in effect, change the world.”

Elizabeth Keadle, Salk Donor

Verma, who helped establish the biophotonics center, credits its success in large part to Waite’s involvement in determining early on what technologies and expertise were most needed. “It was really a joint effort,” Verma says. “Ted really understood the power of the technology, but he also actively participated in building the center. He continuously pushed us to get it right.”

Verma also cites gifts by **Irwin Jacobs**, chairman of Salk’s board, and his wife, **Joan**, as examples of philanthropic giving that have made a big difference at Salk. Among other generous investments in Salk science, the Jacobses created a challenge grant to encourage donors to establish endowed chairs for senior scientists at Salk. For every \$2 million that a donor contributes toward a chair, Joan and Irwin Jacobs add \$1 million to achieve the \$3 million required to fully endow the chair. To date, 15 chairs have been established.

“Salk’s highly talented cadre of scientists continues to make important contributions to our understanding of biology and disease,” Irwin Jacobs says. “Joan and I are deeply impressed by the commitment, creativity and

million to \$50 million, a 150 percent increase in less than ten years. This unprecedented growth has helped the Institute hire and retain top-notch faculty, postdoctoral researchers and staff; acquire new research technologies; and fund innovative experiments.

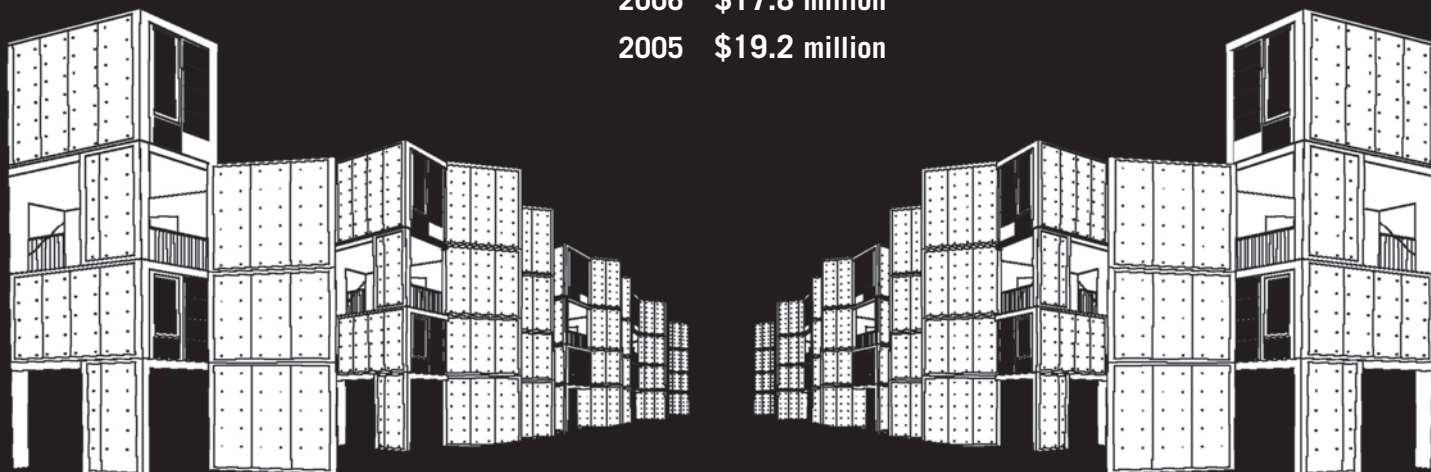
Rebecca Newman, Salk’s vice president, external relations, credits this success in part to growing awareness among donors of the importance of basic biological research in laying the groundwork for cures to diseases and other human health issues. Building strong development and communications teams at Salk, she says, has proved crucial to attracting increased support for the Institute’s work.

“We’ve been much bolder in explaining the importance of Salk science as the bedrock for clinical science,” she says. “Clinicians will tell you that they can’t do their work at the patient’s bedside without the work done at the Salk. Our donors understand that they are supporting the first, indispensable step in this process of discovery and its impact on human health.”

The image shows a macrophage in culture (purple) engulfing a dead cell (red).

Philanthropic Giving to Salk since 2005:

2012	\$50.6 million
2011	\$39.1 million
2010	\$31.2 million
2009	\$30.6 million
2008	\$45.5 million
2007	\$16.3 million
2006	\$17.8 million
2005	\$19.2 million



This sentiment is echoed by **Elizabeth Keadle**, a loyal donor to Salk who once worked in the laboratory of the late Salk professor **Wylie Vale**. She continued to follow the work of Vale's laboratory over the years and has been particularly intrigued by the Institute's research in plant biology, neuroscience and metabolism.

"I think any way that you can further science you, in effect, change the world," Keadle says. "Very few of us have the abilities that the scientists at Salk possess. Supporting them is an honor and an opportunity to be a small part of their amazing work."

2009 with a \$5.5 million grant from the Leona M. and Harry B. Helmsley Charitable Trust. The center employs a molecular approach to nutrition and the role of metabolism in diabetes, obesity, cancer, exercise physiology and lifespan, thereby expanding our understanding of how nutrients affect health. It includes a metabolic core facility and an interdisciplinary fellows program.

The center has allowed Evans to work closely with two other Salk professors, **Marc Montminy** and **Reuben Shaw**, by providing them with research technologies that bridge their areas of expertise. Together, the trio has made key

in physiology and disease," says Evans. "The center allows experts in cellular genetics and genomics to team up with experts in the physiology of disease. Federal funding mechanisms support projects that remain squarely in one of these areas, but not the kind of cross-disciplinary research we're undertaking in the center."

The initial Helmsley Trust grant was followed in 2010 with a \$15 million grant to create a collaborative stem cell project involving Salk and Columbia University. This program was designed to fast-track the use of induced pluripotent stem cells to gain new insight into disease

“Our philanthropic investment has produced tangible and impactful results, and we have forged lasting friendships with Salk researchers and staff members.”

John Codey, Leona M. and Harry B. Helmsley Trust

Ronald Evans, a professor in Salk's Gene Expression Laboratory, says philanthropic support has funded creative, high-risk projects at Salk that wouldn't have received federal government funding.

Evans is a member of the Salk Center for Nutritional Genomics, which was established in

discoveries regarding genetic switches that potentially point to new ways of controlling the body's production of glucose, the simple sugar that is the source of energy in human cells and the central player in diabetes.

"We want to understand what's happening at the genetic level and how this leads to changes

mechanisms and screen for novel therapeutic drugs. The funding helps Salk's Stem Cell Core facility support over 15 laboratories working on regenerative medicine.

John Codey, a trustee for the Helmsley Trust, said his organization is proud of its long and successful partnership with the Salk Institute.

“Already I’ve seen remarkable discoveries emerging from that investment—findings that are changing our understanding of life and disease.” Ted Waitt, Salk Trustee

He adds that the trust has supported Salk research because basic research is the foundation for cures for devastating diseases like cancer and metabolic and neurodegenerative disorders.

“Our philanthropic investment has produced tangible and impactful results, and we have forged lasting friendships with Salk researchers and staff members,” Codey says. “The Helmsley Trust’s philanthropy has helped plant the seeds that will grow and develop into clinical treatments and cures, and we look forward to many more years of partnering with Salk to improve human health.”

Just as the Helmsley Trust support made the collaboration between Evans, Montminy and Shaw possible, the Waitt Center for Advanced Biophotonics paired the unlikely team of **Hu Cang** and **Quan ZHu**—the physicist and molecular biologist working together to develop a powerful imaging technique.

Their work is providing the sharpest live-cell images ever taken of chromatin, the combination of proteins and DNA that form bundles in a

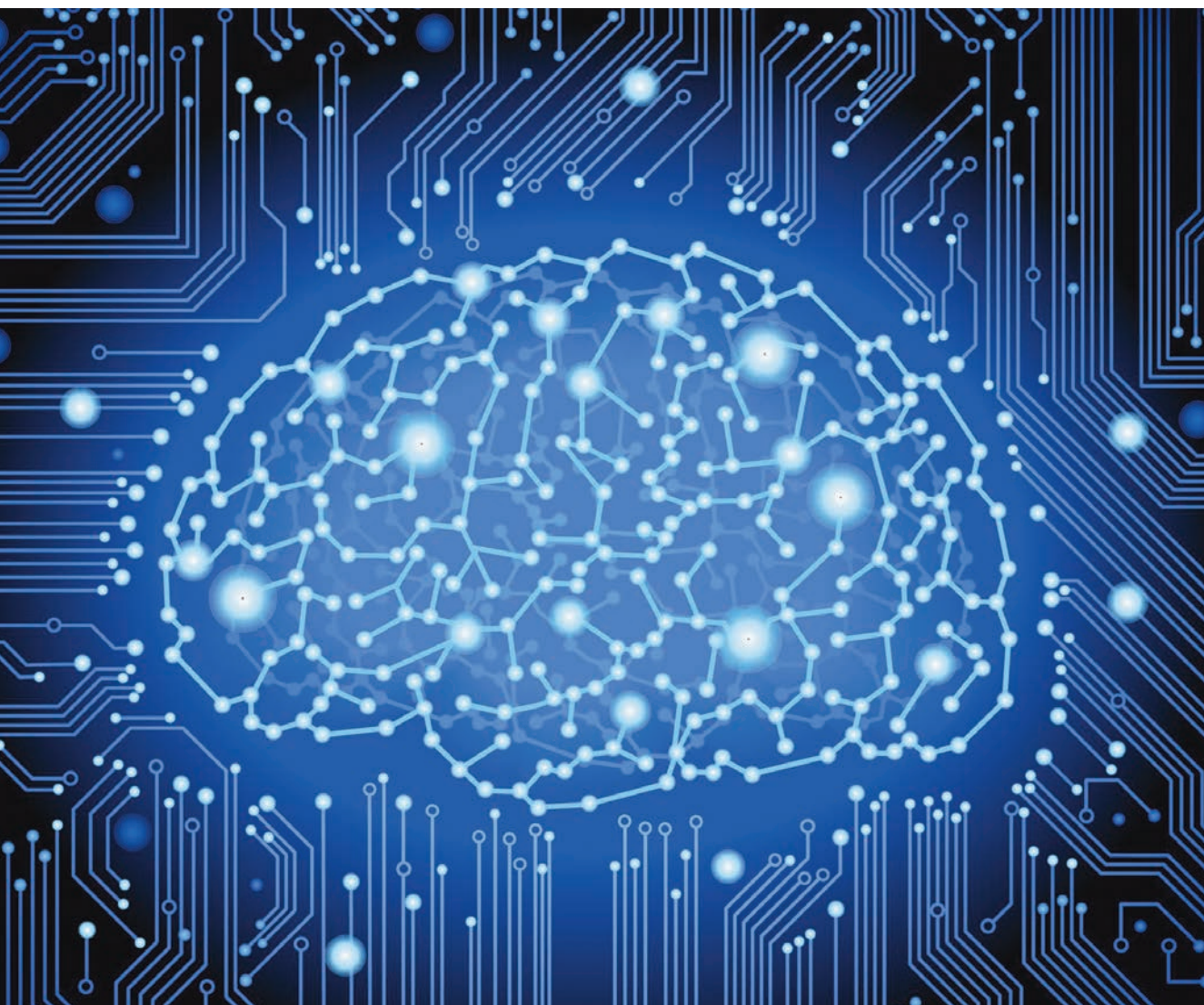
cell’s nucleus. Chromatin plays a key role in determining which genes in a cell are expressed, and understanding the chemical modifications to chromatin that control this process is the basis of a hot new field known as “epigenetics.” The ability to visualize chromatin bundles in high resolution in living cells is allowing Zhu and Cang to map how epigenetic changes alter cellular function. Imaging chromatin structure might even be used to identify cellular pathologies in the same way a pathologist currently uses the shape of a cell nucleus to diagnose a disease.

Ultimately, Zhu and Cang’s work is nourished by the same wellspring of generosity and vision that helped launch the Institute a half-century ago and that will allow inspired science to thrive well into the future. “If it wasn’t for private philanthropy, I couldn’t have come to the Salk and had this close relationship with biologists,” Cang says. “This is a great place for pushing engineering into biology in a way that really makes a difference, and that’s only the case because of the vision and generosity of a private donor.”

Martin Hetzer (left) heads the Waitt Advanced Biophotonics Center, which was launched with a gift from Ted Waitt (right).




THE GIFTS OF DISCOVERY



Using viruses to map the brain

SUPPORT FROM THE SALK'S INNOVATION GRANTS PROGRAM, WHICH IS FUNDED THROUGH PRIVATE PHILANTHROPY, allowed **Edward Callaway** and his collaborators to show that a modified rabies virus could be used to label partner cells across neuronal synapses, the connections between neurons.

The innovation was the result of a conversation between Callaway and **John Young**, a professor in Salk's Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis. Together, they applied the modified rabies virus, which had been given the ability to make infected neurons fluoresce green, to mapping the brain. The result was spectacular: as expected, these cells were selectively infected by the virus, which spread to hundreds of surrounding cells, turning them brilliant fluorescent green.

Callaway went on to develop a new project expanding the use of these techniques in collaboration with Salk professor **Martyn Goulding**, who also received funding from the program. They were then able to secure a \$3 million grant from the National Institutes of Health to use the technique to map the mammalian nervous system, a crucial step in understanding and treating neurological diseases and injuries. To date, the Innovation Grants Program has provided \$5.4 million to 46 research projects ranging from neuroscience to cancer research. 




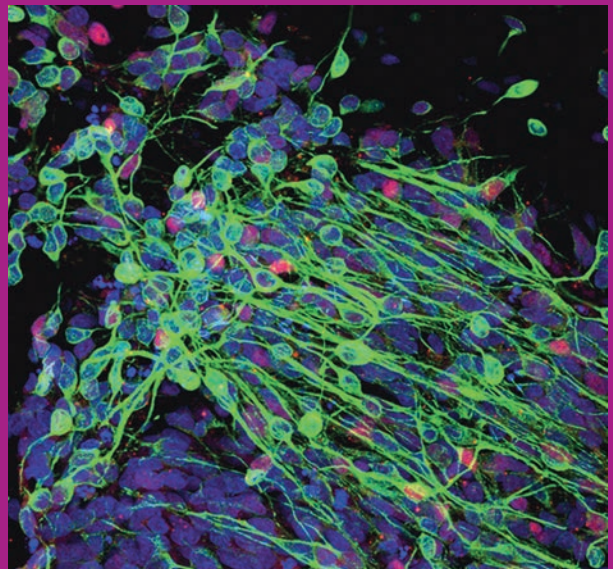
Carol Marchetto, a Salk senior staff scientist, and Mo Li, a postdoctoral researcher, helped discover a way to convert cord blood cells to neurons.

Neurons derived from cord blood cells may represent new therapeutic option

FOR MORE THAN 20 YEARS, DOCTORS HAVE BEEN USING CELLS FROM blood that remains in the placenta and umbilical cord after childbirth to treat a variety of illnesses, from cancer and immune disorders to blood and metabolic diseases. With support from several foundations, scientists at the Salk have found a new way—using a single protein, known as a transcription factor—to convert cord blood (CB) cells into neuron-like cells that may prove valuable for the treatment of a wide range of neurological conditions, including stroke, traumatic brain injury and spinal cord injury.

The researchers demonstrated that these CB cells, which come from the mesoderm, the middle layer of embryonic germ cells, can be switched to ectodermal cells—outer-layer cells from which brain, spinal and nerve cells arise. “This study shows for the first time the direct conversion of a pure population of human cord blood cells into cells of neuronal lineage by the forced expression of a single transcription factor,” says **Juan Carlos Izpisua Belmonte**, a professor in Salk’s Gene Expression Laboratory, who led the research team.

The study, a collaboration with **Fred H. Gage**, a professor in Salk’s Laboratory of Genetics, and his team, was supported in part by The Lookout Foundation, the G. Harold and Leila Y. Mathers Charitable Foundation, the Leona M. and Harry B. Helmsley Charitable Trust and the JPB Medical Foundation. 



This microscope image shows a colony of neurons derived from cord blood cells using stem cell reprogramming technology. The green and red glow indicates that the cells are producing protein markers found in neurons, evidence that the cord blood cells did in fact morph into neurons. The blue glow marks the nuclei of the neurons.

Image: Courtesy of Alessandra Giorgetti



The human kinome overlaid on the Grand Canyon.

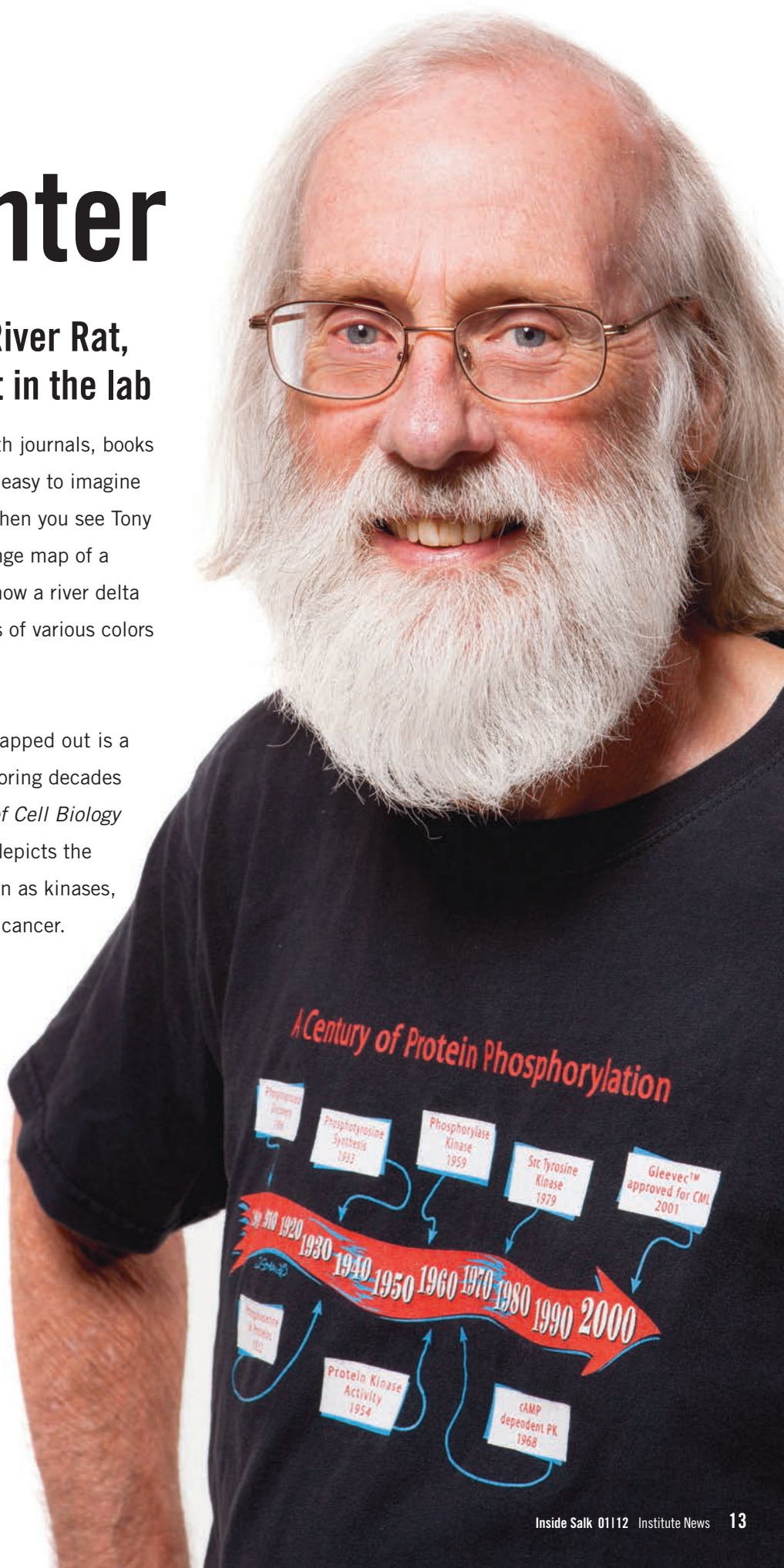
One on one with...

Tony Hunter

For the Kinase King and River Rat, the challenges aren't just in the lab

In an office filled nearly floor to ceiling with journals, books and papers from a four-decade career, it's easy to imagine you're visiting with a wizard—especially when you see Tony Hunter's flowing white beard and the strange map of a watery kingdom on his wall. It seems to show a river delta spreading in all directions, with tributaries of various colors that look like elongated runes.

In fact, what has been so meticulously mapped out is a cellular landscape that Hunter began exploring decades ago—a quest that prompted the *Journal of Cell Biology* to dub him “The Kinase King.” The map depicts the “kinome,” the collection of enzymes known as kinases, which are crucial to life and play a role in cancer.





Tony Hunter (in yellow life vest) running the Lava Falls rapids in 1987. Photo credit: Carlisle Landel

Louis Pasteur once said, “Fortune favors the prepared mind,” and it aptly describes the discovery that Tony Hunter made in 1979. Hunter ran an experiment on tumor viruses and then ran it again, expecting the same result. Yet the results didn’t match. Someone else might have dismissed this as just an annoying glitch, but Hunter’s biochemistry background alerted him that an extremely subtle difference in the ingredients had exposed a significant finding. He discovered that a certain enzyme – known as a “kinase”– specifically targeted the amino acid tyrosine, which among other essential functions, regulates cellular growth, and thus, the spread of certain cancers. Two decades later, the drug Gleevec, which is highly effective against two cancers, was developed based in part on Hunter’s keen observation.

His research has led to a cancer drug and caused textbooks to be rewritten, but what Tony Hunter is equally proud to show off is a video of a whitewater rafting trip he took in the summer of 2010, his ninth through the Grand Canyon. He’s in a raft on the Colorado River with his two sons, steering through the Lava Falls rapid, a whirling pit of bucking water so technically challenging that the Colorado’s premier explorer, John Wesley Powell, opted to walk. As they run it, their raft plunges in and out of colliding waves and arcing froth that hits with the force of fastballs. They swerve into a huge claw of water, and Hunter is swept overboard.

But fortune, it seems, favors the prepared body as well. A few frames later, Hunter can be seen back inside the raft, enjoying the rest of the ride. After all, how else would you spend your vacation when you’re 67 years old?

Did anyone at the Institute ever suggest you might consider a safer hobby?

No one told me that, but one summer in 1975, just after I got back from spending a month river rafting, Walter Eckhart, a faculty colleague at Salk, said, “Tony, I think you should spend more time in the lab!”

Many scientists seem to have extreme outdoor hobbies, like mountain climbing....

Well, they’re crazy! I think river running is safer than mountain climbing. The rush you get running through a big rapid is tremendous—and the relief when you get out the other side. If you’re concerned, you can take a trip on big tourist rafts that are almost bullet-proof safe. However you do it, a trip through the Grand Canyon by raft is an amazing experience. Seeing it from the bottom is very different from seeing it from the top.

Speaking of safety, we hear that early in your career you burned down a lab.

Yes, when I was back in Cambridge. The picture’s right there on the wall. [He casually points to a framed black-and-white photograph of charred ruins.] I’ve still got some of the lab notebooks. We’re not sure what started the fire, but because the notebooks were so tightly stacked against one another, the fire had no oxygen to burn them.

But wouldn’t most people have seen those ruins and given up in despair?

Well, we were young—nothing was going to deter us! We were lucky there was extra lab space in a building next to the famous Laboratory of Molecular Biology where Francis Crick worked in Cambridge. We were given dining rights there, which produced a silver lining to the fire. Because the unwritten rule was that you were supposed to sit at a table with people other than your lab mates, we started discussions with a group there working on tobacco mosaic virus and set up a collaboration. This resulted in a very nice paper that came out in *Nature*, so that was a totally new direction that came out of a disastrous event.

“Cancer is not a single disease.” Tony Hunter

What are “kinases” and why are they important?

Let me take it back a step. Most processes in the cell occur because proteins signal to each other in a relay chain. But protein signaling is as restrictive as dominoes—the ends must match exactly. Kinases are enzymes that add chemical components known as phosphate groups onto proteins, a process called phosphorylation. Phosphates are very versatile—it's analogous to putting on a blank domino—so through phosphorylation, you vastly increase the number of links a protein can have.

Thus, kinases are important for continuing—or breaking—the chain. In a cancer cell, you want to say to a kinase, “Stop! Don't make the link that lets that cell divide.”

You discovered a previously unknown kinase that acted on a building block of proteins called tyrosine. Was the reaction in your field, “Of course, it's only logical,” or “Oh my God!”?

I think it was more of the latter, although surprisingly, there wasn't any skepticism. Often when you make an unexpected discovery, people say, “Oh, that can't be right; they must've done something wrong.” Instead, it was very quickly adopted. Within a year of our beginning to talk about it, there were four or five papers from other groups reporting that their kinases were also tyrosine kinases.

There is a lesson here: however logical you are, the experiment doesn't always give you the expected results, and once you rule out the obvious, you've got to spend some time investigating what the new result means.

What is the kinome, and what does it tell you?

Once we realized protein phosphorylation was such a prominent cellular mechanism and that there were going to be such a large number of protein kinases, it clearly became important to try to determine exactly how many there really were, so we could understand the extent of the landscape.

Using the complete sequence of the human genome, **Gerard Manning**, a former staff scientist here at Salk, did most of the work to find out how many genes coded for protein kinases. Originally, we came up with the number of 518, but this is about to be revised upward to about 540.

It's been very useful because mapping the kinome does suggest that certain kinases will have similar properties. Knowing this gives you a starting point for developing drugs that can target processes involved in diseases like cancer.

If we can land a robot on Mars, why can't we cure cancer?

First, cancer is not a single disease. Each cancer undergoes genetic changes that are unique to that cancer. Because of those differences, we actually have had success with certain cancers, such as chronic myeloid leukemia, but not with others, such as pancreatic cancer, which remains especially challenging because the cancer develops a peculiar vasculature that makes it very difficult to deliver drugs.

As for putting a robot on Mars, it turns out biology is much more complicated than physics. The human body has evolved over billions of years to be very robust—you push on one thing, and another one changes in ways that you couldn't necessarily know. Particularly with cancer cells, if you target one thing you know that a cancer cell needs to grow, what you find is that something else pops up to take its place.

We're all hoping that if we understand the pathways that are switched on in cancer cells by genetic mutation and could block two or three of them simultaneously, then we would stand a much better chance. If you only block one, then the cell finds a way around it. If you can also take out its backup strategies as well, then treatment is more likely to be successful.

You're a senior editor of the new journal *eLife*. Why is it important to you?

It's a journal for scientists, run by scientists. The decisions are made by scientists in the field instead of professional editors, who increasingly rely on the referees to make the decisions instead of making their own decisions.

In addition, the whole reviewing process is made easier for authors; there's just a single round of revision allowed. You receive one letter back, which outlines what needs to be done, rather than the current practice of having to answer multiple suggestions and objections from several separate reviewers. We're hoping it will become the new model for how scientific journals are run. It's going to be a lot of work, obviously.

You not only work at Salk but also support the Institute financially. Why do you choose to contribute to Salk?

I owe an enormous debt to the Salk for having been the place that enabled me to establish my career and that gave me the environment to do the best science. When I was appointed an assistant professor in 1975, I joined a group of young faculty members in the Tumor Virology Laboratory, which was created in the early '70s, and it was a fantastic place to work. I give money to the Salk because I think science is still fascinating, and there is lots more to do. Salk is a really important biomedical research institution, and I want to see it survive and succeed because we know the Institute can't survive on federal funding alone.

How does funding change the way science is done?

Your research can be restricted if the grant money is dedicated only to a specific purpose. But sometimes this can also open up opportunities. In fact, the reason I'm a cancer biologist is because I came to the Salk to do a postdoc with Walter Eckhart, who had money from the Special Virus Cancer Program at the National Cancer Institute. That program brought a lot of very talented people into the cancer field because the money was available. Nowadays, private donors are very important to provide that kind of support. ■■■

Salk professors awarded chair appointments


Leading philanthropists recognize outstanding scientists with endowed faculty chairs

IT WAS A NIGHT OF CELEBRATION ON AUGUST 23, AS SCIENTISTS, colleagues and patrons gathered at Salk to honor four faculty members who were appointed to endowed chairs. Professors **E. J. Chichilnisky**, **Jan Karlseder**, **Greg Lemke** and **Kuo-Fen Lee** were acknowledged for their scientific excellence and contributions to biological research at the board of trustees reception and chair recognition ceremony.

The **Ralph S. and Becky O'Connor Chair**, the **Donald and Darlene Shiley Chair** and the **Françoise Gilot-Salk Chair** were all created as part of the **Joan Klein Jacobs and Irwin Mark Jacobs Senior Scientist Endowed Chair Challenge**. In 2008, the Jacobses created a challenge grant to encourage donors to establish endowed chairs for senior scientists. For every \$2 million that a donor contributes toward an endowed chair at the

Institute, Joan and Irwin Jacobs add \$1 million to achieve the \$3 million funding level required to fully endow a chair for a Salk senior scientist. To date, 15 chairs have been established.

In addition to the challenge grant chairs, Kuo-Fen Lee was appointed to the **Helen McLoraine Chair** in Molecular Neurobiology.

"This is a well-deserved honor for these exceptional investigators," said Salk president **William R. Brody**. "Endowed chairs enable scientists to explore the most creative and innovative science for which they are known. It is impossible to overstate the gratitude we feel toward the donors of the newly established chairs. We are celebrating a legacy that crosses generations and a good that will live on in perpetuity." 



Ralph S. and Becky O'Connor, E.J. Chichilnisky

E. J. Chichilnisky, professor in the Systems Neurobiology Laboratory, was named the inaugural holder of the Ralph S. and Becky O'Connor Chair. Ralph O'Connor, who serves on the Salk board of trustees, and his wife, Becky, are generous supporters of the Institute and created the chair as an "investment that has the potential for maximum impact on human health."

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 traced, 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.



Darlene Shiley, Jan Karlseder

Jan Karlseder, professor in the Molecular and Cell Biology Laboratory, was appointed the inaugural holder of the Donald and Darlene Shiley Chair. Darlene Shiley is vice chair of the Salk board of trustees and a dedicated philanthropist who, along with her late husband, Donald, is well known for donating time and support to many organizations throughout San Diego. The chair will provide funding for the interdisciplinary and groundbreaking research that takes place at the Salk.

Karlseder's research centers on understanding the functions of telomeres, the protective protein-DNA complexes at the ends of chromosomes. Various diseases associated with aging, including cancer and a number of premature aging syndromes, are characterized by critically short or otherwise non-functional telomeres. Karlseder and his team explore how cells keep tabs on their telomeres and, most importantly, prevent catastrophic meltdowns. Their studies uncovered how telomeres signal the approach of cell death, and they were the first to show that progressive telomere shortening plays a key role in cellular aging by changing the way chromosomes entwine with histones, so-called epigenetic changes. Karlseder believes that a better understanding of the interplay between telomeres and cellular functions that play a key role in the aging process may begin to explain why some individuals have long, healthy lives; at the same time it may also lead to new therapies to mitigate age-related diseases.



Dr. Frederik Paulsen,
Ferring Pharmaceuticals board
chairman and Salk board member.



Françoise Gilot-Salk, Greg Lemke

Greg Lemke was named the inaugural holder of the Françoise Gilot-Salk Chair, which was established by Ferring Pharmaceuticals, a global specialty biopharmaceuticals company, in honor of Françoise Gilot-Salk—the internationally acclaimed artist and widow of Jonas Salk.

Lemke, a professor in the Molecular Neurobiology Laboratory, is renowned for his distinguished contributions to understanding the roles that receptor tyrosine kinase (RTK) pathways play in regulating nervous system development and immune system function. The endowment will help support his research into the role that TAM receptors play in immune regulation. These receptors, which were discovered in his lab, are central inhibitors of the innate immune response to bacteria, viruses and other pathogens. Diminished activity of the TAM system is associated with systemic lupus, multiple sclerosis, rheumatoid arthritis and other human inflammatory syndromes, while TAM activation facilitates viral infection. He is currently investigating agents that either activate or inhibit TAM receptor signaling to develop new therapeutic approaches to the treatment of human autoimmune diseases and viral infections.



Eudoria Lee, Kuo-Fen Lee, Joan Ho, Marsha Chandler

The Helen McLoraine Chair in Molecular Neurobiology, awarded to **Kuo-Fen Lee**, a professor in the Clayton Foundation Laboratories for Peptide Biology, was created through the estate of Helen McLoraine to support neurobiological research. Her commitment to science and education as a passionate supporter and friend of the Salk Institute led her to establish endowments to ensure future generations of Salk scientists the needed resources to continue their research.

Lee studies the genes and molecules that guide brain cell development, using gene-targeting technology to observe the physiological effects of specific genes on nervous system function. His lab focuses on how disruptions in the development and maintenance of nerve cells and their supporting cells can contribute to neurodegenerative conditions, such as Alzheimer's disease; neuroendocrine diseases, such as anxiety; and neuromuscular diseases. His research will help accelerate discovery of how abnormalities occur in the way brain cells communicate with each other, with the aim of developing new therapies that prevent brain cell death and can treat many disorders.


Salk professor receives Howard Hughes Medical Institute Collaborative Innovation Award

EDWARD CALLAWAY, PROFESSOR IN THE Salk's Systems Neurobiology Laboratories, has been selected as a participating investigator by a team that is the recipient of a Howard Hughes Medical Institute (HHMI) Collaborative Innovation Award (HCIA).

Callaway will work together with project leader Dr. Liqun Luo, an HHMI investigator at Stanford University, on a collaborative research study entitled "Mapping Global Patterns of Connectivity in the Mammalian Brain." The team plans to develop a suite of tools for mapping neuronal connections in the complete mouse brain, including those that extend across long distances, and use those tools to study the organization of neural circuits and how they are affected by specific neurotransmitters.

Launched by the HHMI in 2008 as part of a four-year, \$40 million pilot project, the HCIA program supports projects led by heads of its

research laboratories that have the potential of being transformative and solving important scientific problems. The goal is to allow groups of scientists to devote substantial time and energy to pursuing collaborative research. The award is intended to encourage both HHMI investigators and participating scientists to undertake projects that are new and so large in scope that they require a team of collaborators with a range of expertise.

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




Salk recruits two outstanding scientists

Building on its international reputation as a home to world-class faculty, the Salk Institute announced the appointment of two new assistant professors, each of whom brings impressive credentials to their areas of expertise.



JULIE LAW, ASSISTANT PROFESSOR IN THE PLANT Biology Laboratory, is interested in understanding how epigenetic modifications are recognized by the cell and translated into stable expression states. To this end, Law focuses on the characterization of several newly identified families of chromatin-binding proteins. By employing genetic, biochemical and genomics approaches, she seeks to determine the epigenetic modifications recognized by these protein families,


identify their interacting partners and determine their effects on gene expression and higher-order chromatin structure, providing a holistic view of how epigenetic modifications control gene expression. Law's studies will help expand current knowledge of epigenetic gene regulation and increase scientists' ability to understand and control the expression of existing and newly introduced genes—research that has broad implications in both agriculture and gene therapy.

Law received a B.S. in biochemistry and biophysics from Oregon State University and attended graduate school at The Johns Hopkins University School of Medicine in Baltimore. She most recently conducted postdoctoral research that explores the mechanism through which small RNAs target DNA methylation in *Arabidopsis thaliana*. 



JANELLE S. AYRES, ASSISTANT PROFESSOR in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis, will focus on understanding the defense strategies that enable a host to survive and even thrive when interacting with microbes. Ayres provided some of the first evidence that tolerance is crucial for defense against infections in animals. Using fruit flies infected

with lethal bacteria, she identified genes and environmental factors, such as diet, that are important in order to tolerate and, ultimately, survive infections. She also demonstrated that a single gene could influence both resistance and tolerance so that conditions that enhance tolerance against one type of infection also can influence resistance against a different pathogen. Her work will advance knowledge of these defense mechanisms and could lead to new therapeutic approaches for treating infectious and inflammatory diseases.

Ayres earned her B.A. from the University of California, Berkeley, in molecular and cell biology and received a Ph.D. in microbiology and immunology from Stanford University. Most recently, she has conducted postdoctoral research at UC Berkeley that explores how certain symbiotic relationships in mammals contribute to health and disease. 



William R. Brody, Marsha Chandler, Ron Evans, Gil Artzyeli, Deputy Consul General of Israel in Los Angeles, and Irwin Jacobs

Salk celebration honors Ron Evans as winner of 2012 Wolf Prize in Medicine

A SPECIAL DINNER WAS HELD AT THE INSTITUTE ON JUNE 5 TO acknowledge **Ron Evans** as the most recent winner of the prestigious Wolf Prize in Medicine, Israel's highest honor for achievements benefiting mankind and one of the world's top science awards. The certificate was on display in the Foyer, where friends and colleagues gathered to congratulate Evans on this major accomplishment.

Evans, professor and head of the Salk Institute's Gene Expression Laboratory and holder of the March of Dimes Chair in Molecular and Developmental Biology, was selected for the prize for his discovery of the gene super-family encoding nuclear receptors and elucidating the mechanism of action of this class of receptors. The official ceremony took place at the Knesset, the House of Representatives for the state of Israel, in Jerusalem, on May 13, 2012. 📄

Daniel C. Lewis joins Salk Institute board of trustees

DANIEL C. LEWIS, A WELL-KNOWN LEADER in the global transportation, defense and aerospace industries, has been named a member of the Salk Institute board of trustees.

Lewis served as president and as senior vice president at Booz & Company, the renowned global management consulting firm, with a career spanning over 30 years. He has an extensive track record of successfully managing complex multidisciplinary transformation programs that encompass business strategy, operations, engineering and organization for clients worldwide. Before joining Booz, Lewis

was director of materials management and purchasing at Warner-Lambert Corporation.

A longtime member of Salk's International Council, Lewis and his wife, Martina, recently established the Daniel and Martina Lewis Chair, which is currently held by **Geoff Wahl**, professor in the Institute's Gene Expression Laboratory.

Lewis also serves on the President's Council and the Dean's Executive Council at Purdue University's College of Technology and sits on the Finance, Audit, and Budget Committee at Fairleigh Dickinson University. He is a



Daniel C. Lewis, William R. Brody, Wendy Brody, and Martina Lewis

member of the World Economic Forum, has served on the Aviation and Travel and Tourism Board of Governors and is a prior board member of Aviation Distributors, Inc. 📄



Singing sensation LeAnn Rimes performs at 17th annual Symphony at Salk

Sold-out show raises over \$900,000 for research and education outreach

WHAT BETTER WAY TO SAVOR A SAN DIEGO summer night? On the evening of August 25, the audience that gathered at the Salk Institute would have answered that question with a unanimous response—Symphony at Salk: a Concert Under the Stars.

For 17 summers now, the annual fundraiser has brought scores of music lovers and science supporters to the Institute for an unforgettable evening. Guests began this year's event sipping champagne at an outdoor reception on the magnificent Salk courtyard, followed by a gourmet dinner specially prepared by award-winning chef Jeffrey Strauss, owner of the critically acclaimed Pamplemousse Grille.

As the sun set over the ocean-view terrace, the San Diego Symphony took the stage, once again led by special guest conductor

Thomas Wilkins, who with one wave of his baton began an extraordinary show. The musicians played a rousing set of country-inspired classics to set the mood for the concert's much-anticipated headliner, award-winning singer LeAnn Rimes. From the moment Rimes walked on stage until the last note of the night, she held the rapt attention of the crowd as she performed a selection of her hits, including "Can't Fight the Moonlight" and "How Do I Live." Rimes brought the evening to a close with an incomparable rendition of "Amazing Grace."

More than 700 people attended the sold-out gala, which raised over \$900,000 to benefit Salk scientific research and educational outreach programs. 🎵

» **View video and photos**


www.salk.edu/isnov12/video3





Merci, Françoise Gilot-Salk exhibit draws to a close

FROM MARCH THROUGH NOVEMBER, THE SALK COMMUNITY AND visitors to the Institute had the exclusive opportunity to view 11 pieces of art created by Françoise Gilot-Salk, the internationally renowned artist and widow of Jonas Salk. Adorning the walls in the Foyer, the collection included works in gouache, ink and acrylic on canvas, as well as original prints. These pieces from the last 50 years have rarely been exhibited and highlighted Gilot-Salk's interest in color relationships and her mastery at blurring the boundaries between the figurative and the abstract.

Gilot-Salk, who celebrated her 90th birthday this year, continues to paint every day, more than seven decades after she began her artistic career. She is an active supporter of the Institute and has graciously served as honorary chair of Symphony at Salk for the last 17 years. Her paintings have also been featured as the signature artworks for each of the concerts since the event's inception in 1996. 





Salk Professor Vicki Lundblad speaks about her research at the Women & Science event.


Women & Science

ON JULY 24TH, MORE THAN 30 WOMEN business and community leaders in San Diego attended the inaugural Salk Women & Science event to hear about ground-breaking research being conducted by female faculty at the Salk Institute. The event was a unique opportunity to learn how novel approaches to basic research are shaping future discoveries.

Joanne Chory, director of the Plant Molecular and Cellular Biology Laboratory and holder of the Howard H. and Maryam R. Newman Chair in Plant Biology, welcomed guests to the reception and lecture. The theme of the wine and cheese reception was continued in the talk by **Vicki Lundblad**, professor in the Renato Dulbecco Laboratories for Cancer Research, entitled "Of bread and wine: the influence of science on biology and life." She explained

how research in her laboratory, studying chromosomes in the yeast used to make bread and wine, has led to unexpected insights about both aging and cancer.

"The vision of the Salk Women & Science program is to create an ongoing engagement between women in the community and leaders in biological science and technology," said **Rebecca Newman**, vice president of external relations. "We want to provide a dynamic and vibrant forum in which community and business leaders and Salk's women of science have an opportunity to gather as friends, entrepreneurs and researchers to discuss the latest discoveries in science and technology while inspiring more women to embrace scientific research as a focus of personal and philanthropic interest."

At the next Salk Women & Science event on November 27th, **Catherine Rivier**, a professor in the Clayton Foundation Laboratories for Peptide Biology at the Institute, will discuss her remarkable research on hormones. Dr. Rivier investigates the way that information regarding the occurrence of stressors, such as exposure to alcohol or stimulation of the immune system, is transmitted to the brain; where it is received in the brain; and how the brain mounts appropriate endocrine responses. She will also briefly discuss how perturbations such as adolescent exposure to alcohol interfere with these responses. For more information please contact **Betsy Reis**, Director of Donor Relations at (858) 453-4100 x1426 or via email at breis@salk.edu. 

“The vision of the Salk Women & Science program is to create an ongoing engagement between women in the community and leaders in biological science and technology.”





Salk investigator Terrence Sejnowski wins IEEE Frank Rosenblatt Award


THE INSTITUTE OF ELECTRICAL AND Electronics Engineers (IEEE), the world's largest professional association dedicated to advancing technological innovation and excellence for the benefit of humanity, has chosen Salk researcher **Terrence Sejnowski** as the recipient of the 2013 IEEE Frank Rosenblatt Award "for contributions to the advancement of the design, practice, techniques or theory in biologically and linguistically motivated computational paradigms."

Sejnowski, professor and head of the Computational Neurobiology Laboratory, was selected for the honor in recognition of his outstanding contributions to computational neuroscience. A leader in the field, he conducted trailblazing work that helped spark

the neural networks revolution in computing in the 1980s. He is also recognized for his important contributions to artificial and real neural network algorithms and applying signal-processing models to neuroscience.

A physicist by early training and a pioneer in using computers to understand brain function, Sejnowski models how interactions among groups of neurons are able to produce complex behavior; he has also used this understanding to develop particular computer algorithms—called artificial neural networks—that are able to solve practical engineering problems, including methods to reduce background noise in cellphone conversations and headphones. Sejnowski has focused his recent studies on how the brain is capable of learning and stor-


ing memories and exploring the brain mechanisms responsible for triggering plasticity at synapses between neurons—research that may also provide critical clues to how memories are consolidated during sleep states.

The IEEE Frank Rosenblatt Award is named in honor of Frank Rosenblatt, who is widely regarded as one of the founders of neural networks. His work influenced and anticipated many modern neural network approaches. For nearly a century, the IEEE awards program has paid tribute to technical professionals whose exceptional achievements and research have made a lasting impact on technology, society and the engineering profession. 

A grand gift

THANKS TO THE GENEROSITY OF CONRAD PREBYS, TRUSTEE AND DEDICATED

Salk supporter, the Institute is now home to a one-of-a-kind Steinway concert grand piano. Once part of an elite "piano bank," where an exclusive inventory of concert grand pianos was maintained for the use of performing artists, this particular Steinway was well known as number 191—a highly sought-after instrument regularly requested by local and visiting world-class pianists performing in San Diego. The piano has graced stages throughout the county and has a long, rich history of being played by some of the best musicians in the world.

"Having this exceptional piano at the Salk can offer new opportunities to reach out to musicians and the community alike with music," said **William R. Brody**, president of Salk and an accomplished musician in his own right. "We are extremely grateful and appreciative of Conrad's generosity with this wonderful donation." 

Salk president Bill Brody, a classically trained pianist, takes a seat at #191—a spectacular Steinway concert grand piano.



Discovery Roundup



Gordon V. Louie, Ryan N. Philippe and Marianne E. Bowman.

Discovery of plant proteins may boost agricultural yields and biofuel production

PLANT OILS ARE COMPOSED PRIMARILY OF triglycerides, formed by linking together three fatty acid molecules, and are stored mostly in seeds, where they are used for energy during germination. Seeds are crucial sources of oils for nutrition, flavoring and industrial applications, such as the manufacturing of soap and cosmetics and for biofuels. With growing concerns about global climate change and petroleum security, producing biofuels for use in transportation and energy generation is a burgeoning industry.

Now, scientists at Salk and Iowa State University, led by Salk professor **Joseph Noel**, have discovered a family of plant proteins that play a role in the production of seed oils.

Scoring a rare scientific hat trick, the

researchers identified three related proteins in thale cress plants (*Arabidopsis thaliana*) that regulate the metabolism of fatty acids, chemical components of all cell membranes and vegetable oils. They found that the proteins, FAP1, FAP2 and FAP3, bind fatty acids, including the major plant omega-3 fatty acid, an important nutritional component found in certain seeds.

"They say a picture is worth a thousand words, and that is certainly the case for these FAPs," says **Gordon Louie**, a researcher in Noel's laboratory, who determined the three-dimensional arrangement of the FAPs holding onto their fatty acid cargo.

The proteins were found in the chloroplasts, the site of fatty acid production and photosynthesis in plant cells. This suggested that these

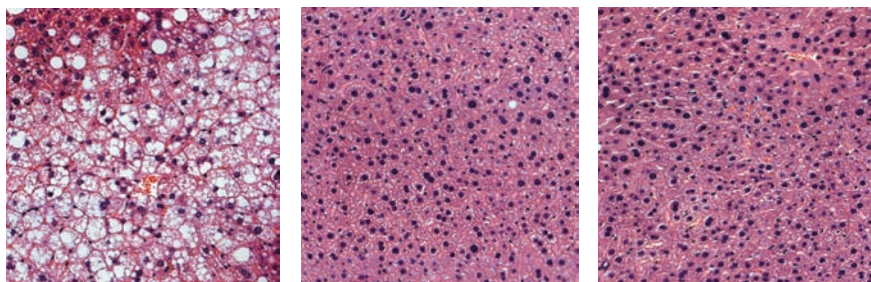
proteins play a role in the metabolism of fatty acids and thus in the production of fatty acids for plant membranes and oils.

The findings, reported in *Nature*, may lead to the development of crops yielding higher qualities and quantities of oils, helping to address growing demands for food and fuel and the consequent environmental pressures on the world's ecosystems.

"This work has major implications for modulating the fatty acid profiles of plants, which is terribly important, not only to sustainable food production and nutrition but now to biorenewable chemicals and fuels," says Joseph Noel. 📺

» **Watch the video**

www.salk.edu/isnov12/video4



» Watch the video

www.salk.edu/isnov/video2

These images of liver tissue show the difference in fat accumulation between two groups of mice fed a high-fat diet. A mouse allowed to eat 24 hours a day (left) had much higher levels of liver fat (white) than one restricted to an 8-hour daily feeding window (right).

Salk study may offer drug-free intervention to prevent obesity and diabetes

IT TURNS OUT THAT WHEN WE EAT MAY BE AS IMPORTANT AS WHAT we eat. Scientists at Salk have found that regular eating times and extending the daily fasting period may override the adverse health effects of a high-fat diet and prevent obesity, diabetes and liver disease in mice.

In a paper published in *Cell Metabolism*, a team led by **Satchidananda Panda** reported that mice limited to eating during an eight-hour period are healthier than mice that eat freely throughout the day, regardless of the quality and content of their diet. The study sought to determine whether obesity and metabolic diseases result from a high-fat diet or from disruption of metabolic cycles.

"It's a dogma that a high-fat diet leads to obesity and that we should eat frequently when we are awake," says Satchidananda Panda. "Our findings, however, suggest that regular eating times and fasting for a significant number of hours a day might be beneficial to our health."

Panda's team fed two sets of mice that shared the same genes, gender and age a diet comprising 60 percent of its calories from fat (like eating

potato chips and ice cream for all your meals). One group of mice could eat whenever they wanted, consuming half their food at night (mice are primarily nocturnal) and nibbling throughout the rest of the day. The other group was restricted to eating for only eight hours every night—in essence, fasting for about 16 hours a day. Two control groups ate a standard diet comprising about 13 percent of calories from fat under similar conditions.

After 100 days, the mice who ate fatty food frequently throughout the day gained weight and developed high cholesterol, high blood glucose, liver damage and diminished motor control, while the mice in the time-restricted feeding group weighed 28 percent less and showed no adverse health effects despite consuming the same amount of calories from the same fatty food. Further, the time-restricted mice outperformed the ad lib eaters and those on a normal diet when given an exercise test.

"The take-home message," says Panda, "is that eating at regular times during the day and overnight fasting may prove to be beneficial, but we will have to wait for human studies to prove this." ■■

Salk scientists discover molecular link between circadian clock disturbances and inflammatory diseases

SCIENTISTS HAVE KNOWN FOR SOME TIME that throwing off the body's circadian rhythm can negatively affect body chemistry. In fact, workers whose sleep-wake cycles are disrupted by night shifts are more susceptible to chronic inflammatory conditions such as diabetes, obesity and cancer.

Salk researchers have now found a possible molecular link between circadian rhythm disturbances and an increased inflammatory response. In a study published in *Proceedings of the National Academy of Sciences*, the Salk team found that the absence of a key circadian clock component called cryptochrome (CRY) leads to the activation of a signaling system that elevates levels of inflammatory molecules in the body.

Cryptochrome serves as a brake to slow the circadian clock's activity, signaling our biological systems to wind down each evening. In the morning, CRY stops inhibiting the clock's activity, helping our physiology ramp up for the coming day.

"There is compelling evidence that low-grade, constant inflammation could be the underlying cause of chronic conditions such as diabetes, obesity and cancer," says senior author **Inder Verma**. "Our results strongly indicate that an arrhythmic clock system, induced by the absence of CRY proteins, alone is sufficient to increase the stress level of cells, leading to the constant expression of inflammatory proteins and causing low-grade, chronic inflammation."

The researchers demonstrated that a lack of cryptochrome activates proinflammatory molecules, indicating a potential role for cryptochrome in the regulation of inflammatory cytokine expression. They also found that a lack of CRY activated the NF-κB pathway, a molecular signaling conduit that controls many genes involved in inflammation.

"Every time this pathway is turned on, there is a residual amount of inflammation left in the body," says **Rajesh Narasimamurthy**, a research associate in Verma's laboratory and the paper's



first author. "That adds up over time, contributing to inflammation-related conditions like obesity and diabetes."

The researchers say the goal now is to find out how to suppress NF-κB activation in the short term to treat diseases like diabetes. They caution that any long-term suppression of the pathway could lead to chronic infection. "We would like to find molecules that modify this activity and focus on those small-molecule inhibitors to treat disease," Verma adds. ■■

Discovery Roundup



Salk researchers Joe Ecker and Hong Qiao infected two lines of plants with bacteria to determine whether methylation, a type of epigenetic chemical modification to DNA, plays a role in a plant's response to stress. Image: Courtesy of Robert H. Downen

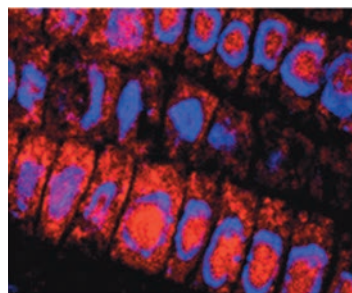
Planting the seeds of defense

IT WAS LONG THOUGHT THAT METHYLATION, A CRUCIAL PART OF normal organism development, was a static modification of DNA that could not be altered by environmental conditions. New findings by **Joseph Ecker**, however, suggest that the DNA of organisms exposed to stress undergoes changes in DNA methylation patterns that alter how genes are regulated.

Ecker and his team found that exposure to a pathogenic bacterium caused widespread changes in a plant's epigenetic code, an extra layer of biochemical instructions in DNA that help control gene expression. The epigenetic changes were linked to the activity of genes responsible for coordinating a plant's response to stress, suggesting that the epigenome may help organisms develop resistance to pathogens and other environmental stressors.


"This means the epigenome may not just be a static set of instructions, but also a way of rewriting those instructions based on experience," says Joseph Ecker. "Our findings, combined with other researchers' findings, build the case that life experiences leave an imprint on our DNA."


In the study, published in the *Proceedings of the National Academy of Sciences*, Ecker and his colleagues explored how DNA methylation regulates the immune system of *Arabidopsis thaliana*, a flowering plant



» [Watch the video](http://www.salk.edu/isnov12/video1)
www.salk.edu/isnov12/video1

in the mustard family. Methylation is a biochemical process that, among other things, suppresses the expression of "jumping genes," called transposons, that have been incorporated into the genome over time. Using genome-wide sequencing technologies, the researchers found a wide range of methylation changes in the plant's response to a bacterial infection and performed a variety of analyses to determine how these methylation changes alter gene expression.

The findings may have broad implications for agriculture, including engineering the DNA methylation patterns of plants to generate pathogen-resistant crops and minimize pesticide exposure. These application technologies are of intense interest, as more than 30 to 40 percent of annual crops are lost to pathogens each year, at a cost of some \$500 billion. 



Red fluorescent “reporter” molecules highlight cells in the totipotent state.

“Magical state” of embryonic stem cells may help overcome hurdles to therapeutics

WITH THEIR POTENTIAL TO TREAT A WIDE range of diseases and uncover fundamental processes that lead to those diseases, embryonic stem (ES) cells hold great promise for biomedical science. A number of hurdles, both scientific and non-scientific, however, have precluded scientists from reaching the holy grail of using these special cells to treat heart disease, diabetes, Alzheimer’s and other diseases.

In a paper published in *Nature*, Salk scientists report discovering that ES cells cycle in and out of a “magical state” in the early stages of embryo development, during which a battery of genes essential for cell potency (the ability of a generic cell to differentiate, or develop, into a cell with specialized functions) is activated. This condition, called totipotency, gives ES cells their unique ability to turn into any cell type in the body, which may make them useful for therapies.

“These findings,” says senior author **Samuel L. Pfaff**, a professor in Salk’s Gene

Expression Laboratory, “give new insight into the network of genes important to the developmental potential of cells. We’ve identified a mechanism that resets embryonic stem cells to a more youthful state, where they are more plastic and therefore potentially more useful in therapeutics against disease, injury and aging.”

ES cells are like Silly Putty that can be induced, under the right circumstances, to become specialized cells in the body—for example, skin cells or pancreatic cells. In the initial stages of development, when an embryo contains as few as five to eight cells, the stem cells are totipotent and can develop into any cell type.

Pfaff and his colleagues performed RNA sequencing (a new technology derived from genome sequencing to monitor what genes are active) on immature mouse egg cells, called oocytes, and two-cell-stage embryos to identify genes that are turned on just prior to and immediately following fertilization. Pfaff’s team discovered a sequence of genes tied to this

privileged state of totipotency and noticed that the genes were activated by retroviruses adjacent to the stem cells.

It is too early to tell if this “magical state” is an opportune time to harvest ES cells for therapeutic purposes. But by forcing cells into this privileged status, scientists might be able to identify genes to assist in expanding the types of tissue that can be produced.

“There’s tremendous hype over the practical applications of embryonic stem cells in clinical situations,” Pfaff says. “The struggle in labs throughout the world is that the smallest changes in environmental conditions could subtly and unpredictably have an effect on these cells. So, the more we know about the basic requirements needed for these cells to be able to generate a full range of tissue types, the better off we’ll be.” 📖

Discovery Roundup



Kirsten Gilham, a young woman with Williams syndrome, undergoes an ERP (event related potential) test. The test measures the electrical activity of the brain.

“Trust” hormone oxytocin found at heart of rare genetic disorder

THE HORMONE OXYTOCIN—OFTEN REFERRED TO AS THE “TRUST” hormone or “love” hormone for its role in stimulating emotional responses—plays an important role in Williams syndrome (WS), according to a study published in *PLoS ONE*.

The study, a collaboration between scientists at Salk and the University of Utah, found that people with WS were flushed with the hormones oxytocin and arginine vasopressin (AVP) when exposed to emotional triggers.


“Williams syndrome results from a very clear genetic deletion, allowing us to explore the genetic and neuronal basis of social behavior,” says **Ursula Bellugi**, director of Salk’s Laboratory for Cognitive Neuroscience and a co-author on the paper. “This study provides us with crucial information about genes and brain regions involved in the control of oxytocin and vasopressin, hormones that may play important roles in other disorders.”

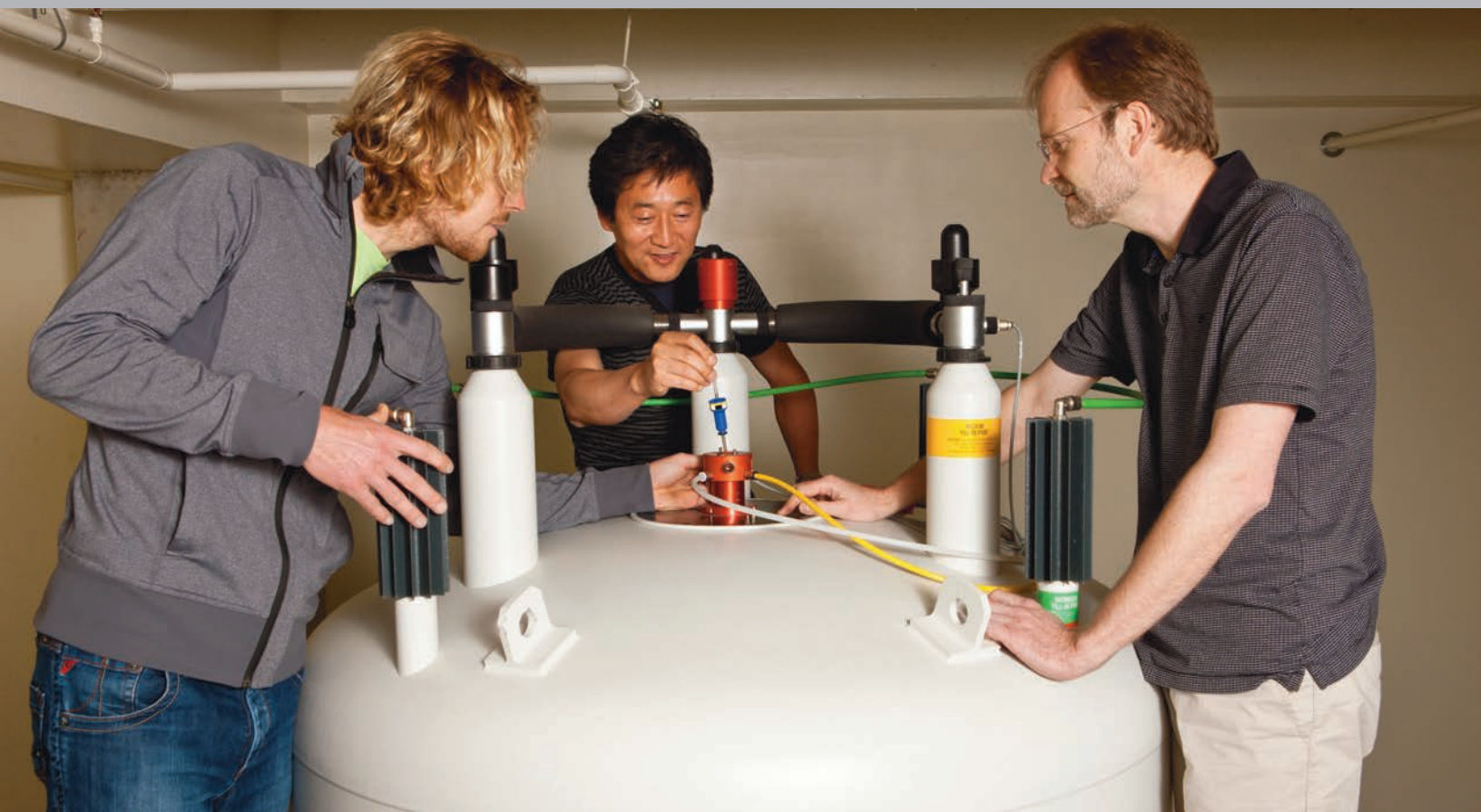
WS arises from a faulty recombination event during the development of sperm or egg cells. As a result, virtually everyone with WS has exactly the same set of genes missing (25 to 28 genes are missing from one of two copies of chromosome 7). There also are rare cases of individuals who retain one or more genes that most people with the disorder have lost.

To children with WS, people are much more comprehensible than inanimate objects. Despite myriad health problems, they are extremely

gregarious, irresistibly drawn to strangers and insistent upon making eye contact. They have an affinity for music. But they also experience heightened anxiety, severe spatial-visual problems and have an average IQ of 60, as well as suffer from cardiovascular and other health issues. Despite their desire to befriend people, they have difficulty creating and maintaining social relationships.

The results of the new study indicate that the missing genes affect the release of oxytocin and AVP through the hypothalamus and the pituitary gland. About the size of a pearl, the hypothalamus is located just above the brain stem and produces hormones that control body temperature, mood, sex drive, sleep, hunger and thirst, and the release of hormones from many glands, including the pituitary. The pituitary gland, about the size of a pea, controls many other glands responsible for hormone secretion.

The researchers’ findings may help in understanding human emotional and behavioral systems and lead to new treatments for devastating illnesses such as WS, post-traumatic stress disorder, anxiety and possibly even autism. 



From left: Christian Klammt, Senyon Choe and Innokentiy Maslennikov used their new rapid technique to generate the structure of a hIMP known as TMEM14A, shown here in multiple three-dimensional conformations.

Speeding up drug discovery with rapid 3D mapping of proteins

A new method for rapidly solving the three-dimensional structures of a special group of proteins, known as integral membrane proteins, may speed drug discovery by providing scientists with precise targets for new therapies.

The technique, developed in the lab of **Senyon Choe** and reported in *Nature Methods*, provides a shortcut for determining the structure of human integral membrane proteins (hIMPs), molecules found on the surface of cells that serve as the targets for about half of all current drugs.

Knowing the exact three-dimensional shape of hIMPs allows drug developers to understand the precise biochemical mechanisms by which current drugs work and to develop new drugs that target the proteins.


"Our cells contain around 8,000 of these proteins, but structural biologists have known the three-dimensional structure of only 30 hIMPs reported by the entire field over many years," says Choe. "We solved six more in a matter of months using this new technique. The very limited information on the shape of human

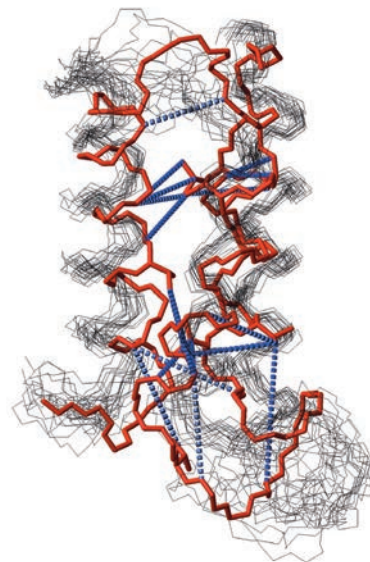
membrane proteins hampers structure-driven drug design, but our method should help address this by dramatically increasing the library of known hIMP structures."

Integral membrane proteins are attached to the membrane surrounding each cell, serving as gateways for absorbing nutrients, hormones and drugs, removing waste products, and allowing cells to communicate with their environment. Many diseases, including Alzheimer's, heart disease and cancer, have been linked to malfunctioning hIMPs, and many drugs, ranging from aspirin to schizophrenia medications, target these proteins.

Choe's team created an outside-the-cell environment, called a cell-free expression system, to synthesize the proteins. They used a Plexiglas® chamber that contained all the biochemical elements necessary to manufacture hIMPs as if they were inside the cell. This system provided the researchers with enough of the proteins to conduct structural analysis.

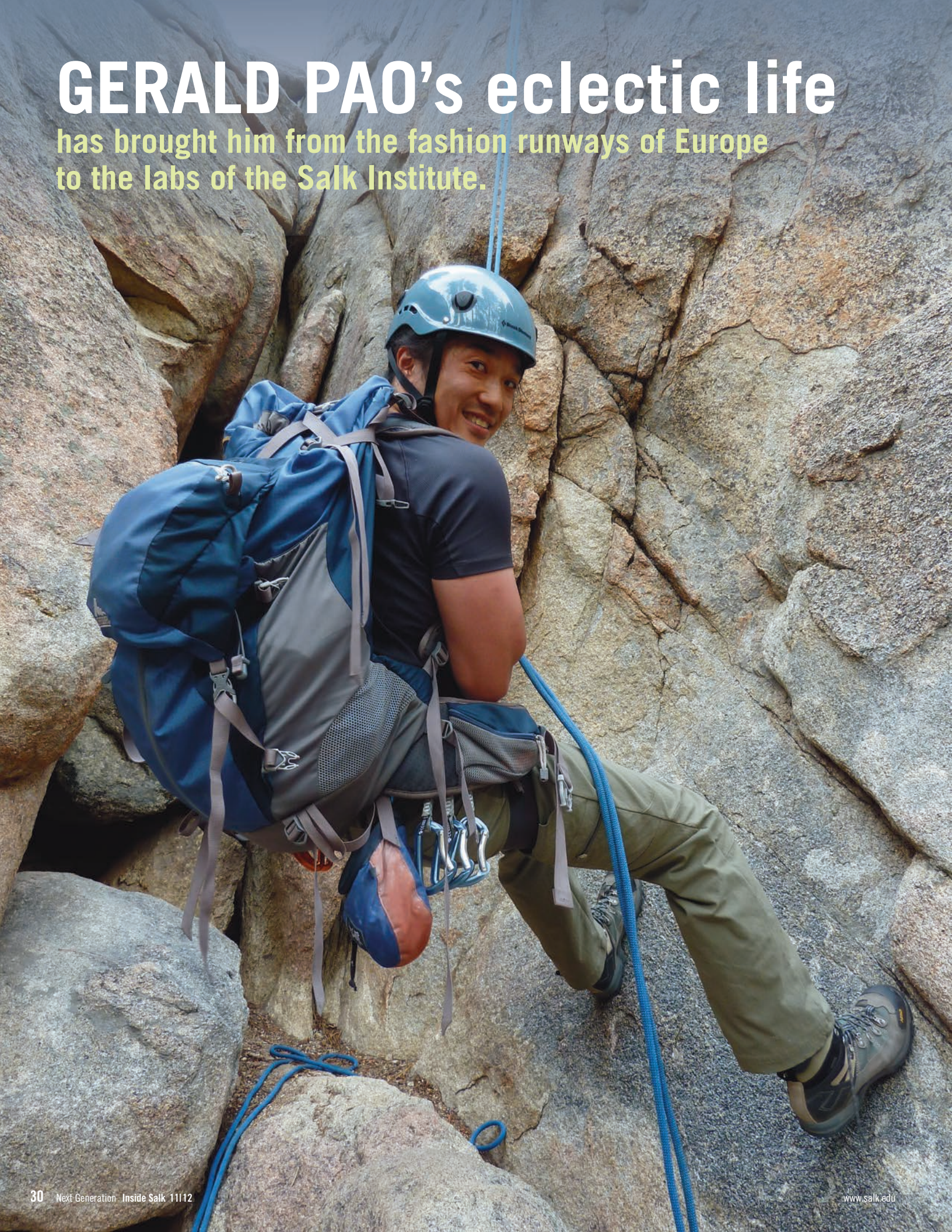
Prior methods might take up to a year to determine a single protein structure, but using

their new method, the Salk scientists determined the structure of six hIMPs within just 18 months. They have already identified 38 more hIMPs that are suitable for analysis with their technique, and expect it will be used to solve the structure for many more. 



GERALD PAO's eclectic life

has brought him from the fashion runways of Europe
to the labs of the Salk Institute.



The senior research associate in Inder Verma's Laboratory of Genetics is of Chinese and Caucasian descent, but was born in Spain, where his father was a diplomat and also worked with the counterintelligence agency. He spent his childhood and teenage years in Madrid and experienced everything from modeling for the United Colors of Benetton to fighting off schoolyard bullies. He discovered a love for science in first grade. Along the way, he became fluent in five different languages.

These experiences shaped his future as an accomplished scientist. Pao dedicated nearly ten years of his life to one study and recently published his findings in the journal *Nature*. The results? A dramatic discovery with the BRCA1 gene that could pave the way to detecting breast and ovarian cancers earlier in patients.

Your childhood is like something out of a movie. How does a Chinese boy born in Spain learn how to speak five different languages fluently?

My parents originally came from two different regions of China, and my mother spoke Cantonese and my father Mandarin. To understand each other, they spoke English until my mother learned Mandarin. They both spoke Spanish, as we were living in Spain, but they wanted to preserve the ancestral languages, so they refused to let us speak Spanish at home. For my siblings and me, schooling was completely done in German from kindergarten to 12th grade. Our parents sent us to German school because they believed it was a better educational system, less focused on memorization and with a greater emphasis on causal analysis, compared to Spanish schools.

Some people may think growing up in Madrid sounds exotic and fun, but what was it really like for you?

It was definitely difficult without any Asians around, mostly because racism at that time was so ingrained in society, people did not even know they were discriminatory when they were. I had accepted the xenophobic behavior of many Spanish people as a fact of life and thought it to be the normal baseline. I did not realize it was a discriminatory behavior until I came to San Diego for college at UCSD and experienced the difference of living in a truly multicultural society that aims at integration.

Your father did some work in military counterintelligence. Did you ever see him bring his work home? Anything similar to a Jason Bourne movie?

On two occasions we met up with the CIA station chief in Madrid and his wife in a Chinese restaurant that a friend of my father owned. They exchanged information on individuals, showing each other pictures of people they were tracking. On another occasion I remember going with my father to some diplomatic function. He was pointing out that almost every military attaché was indeed a spy. From what I saw, the real-life version had nothing of the excitement of the Bourne movies.

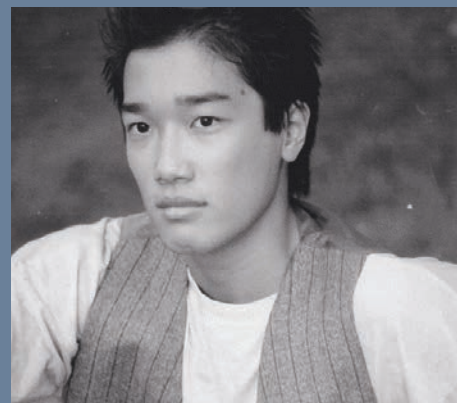
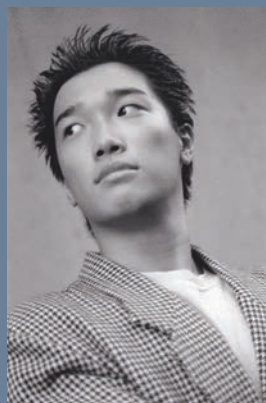


What motivated you to go into science, and when did you realize that you wanted to become a researcher?

My father wanted me to become an architect, but I had no desire to pursue anything that I considered “artificial” in the sense that it was man-made as opposed to naturally occurring objects in nature. My interest was first in animals throughout kindergarten and into first grade. While in second grade, I studied a subject called *Sachkunde*, which is an amalgamation of natural science that literally means “the study of things.” From then on, my interest was broadened from zoology to chemistry, physics and astronomy. By the time I was in fifth grade, I was trying to decide whether I wanted to become a physicist or a biologist. It was finally a computer graphical representation of DNA replication displayed in Carl Sagan's documentary *Cosmos* that made me decide to become a molecular biologist. I was 12 years old.

How did your father's political connections help you explore your thirst for science?

Neither of my parents had a background in science. My mother studied English philology/linguistics and philosophy, and my father had law degrees. At foreign service school, which was the training ground for most of the Spanish foreign ministry, my father was well connected with the political elites. When I told my father that I wanted to do molecular biology, he sent me to his friend, the minister of education and science, who introduced me to the director of Spain's molecular biology institute. I would then meet Gines Morata, a faculty member at the institute. He encouraged me to read college-level textbooks and told me to specifically come to UCSD and the Salk once I graduated from high school.



Before he became a scientist, Gerald Pao was a fashion model in Spain.

Most teenagers find their first job at the local mall or the fast-food drive-through window. What was your first job, and where was it?

My first job was actually as a stunt man for commercials. In high school I was doing gymnastics, and a booker of Maroe, the oldest modeling agency in Madrid, asked me to do a few commercials.

Rumor has it that you did some fashion runway modeling and some campaigns for Adidas and the United Colors of Benetton.

After I showed up at the agency a few times, my booker introduced me to the owner of the agency. She placed me on the fashion side of the agency, so I ended up working as a model for various commercials, including print. Among them, for a couple years, I did runway every season for Benetton, being the only Asian around, despite the fact that I was just a little too short to make the 6'0" height cutoff for men.

What are the main areas and focus of your research at the Salk?

My main area of work at the Salk is the breast and ovarian cancer gene BRCA1 and its function. I have been working on this since my Ph.D., which I also did at the Salk. We found that BRCA1 is responsible for maintaining the most silent regions of the genome, and loss of this silencing can lead to making too much of a molecule called satellite RNA. This satellite RNA, when in excess, is able to break DNA and presumably cause the mutations that are the ultimate cause of cancer. So in the end we have worked out what BRCA1 really does at the molecular level. I also work on stem cells, and right now we are most interested in how stem cells get generated and why cloning works from an evolutionary perspective. Essentially, I am looking for the "reset button" of the biological program that makes stem cells.

You recently discovered how the mutation of the BRCA1 gene leads to breast and ovarian cancer. How may this finding help physicians detect cancer earlier in patients?

As mentioned before, the loss of BRCA1 leads to making too much of a molecule called satellite RNA. If we were able to track this molecule—let's say in a blood sample—we could in theory track the progression of cancer. Whether this is really possible we will have to test in experiments. Current technology only determines whether someone is predisposed to cancer—i.e., if you have the bad versions of BRCA1, chances are at some point in

your life (if you are a female with a BRCA1 mutation), you will develop a breast or ovarian cancer, but when exactly is unknown. This test would tell you in theory if the cancer is starting to develop.

So this discovery could allow clinicians to follow the cancer in real time?

In theory it would be something similar to the PSA test for prostate cancer, in which you regularly take blood tests, and if the levels of PSA, or in this case satellite RNA, spike, then you need to have follow-ups to find out where the cancer is and surgically excise it.

You spent nearly ten years on this research. What drives you? Why have you chosen a life dedicated to science?

I never considered any occupation other than science. Everything else will be more or less recapitulating something that someone has already done before. I just find it more satisfying to work out something that has not been done before and solve problems that were neglected or ignored by others because the time or the technology was not ready when the questions were first posed.

What do you hope your scientific legacy will be?

I hope that one day I will uncover an elegant fundamental insight that ties together a large number of observations—something that will be unifying under a single elegant principle, much like what physicists aim to do. I am still far from it, but it does not hurt to dream about it.

What are your top five essentials? Things you can't live without for your work and personal life?

I guess for me there are only three sine qua nons: science; physical exercise, especially rock climbing; and occasionally trance, house and techno music. 🎧



GEAR UP program

THE SALK INSTITUTE WAS THE SITE OF A SPECIAL FIELD trip on Friday, July 20, for nearly 70 middle school students from Palomar College's GEAR UP program. The young people learned about basic research, discoveries at the Salk and the path it takes to become a scientist. For many of them, it was their first time visiting a biological research institute.

The GEAR UP program is dedicated to enhancing a college-going culture by improving academic performance, increasing high school graduation rates and giving students opportunities to learn and explore new career fields, such as science. 📊





Standing, from left to right: Toriana Dabkowski (Panda lab), Jocelyn Ramirez (Lundblad lab), Hye-In "Sarah" Lee (du Lac lab)

Seated, from left to right: Seung Mi "Lucy" Oh (Panda lab), Kate Chamberlain (Young lab), Catriona Lewis (Chory lab), Jane Ly (Evans lab), Miguel Espinosa (Chory lab), Chris Collins (Sharpee lab)

The heat is on

High school interns deliver 2012 Salk Summer Scholars program presentations

THE TRUSTEES ROOM WAS FILLED WITH ANTICIPATION ON AUGUST 9th as the students who took part in the Salk Summer Scholars program assembled to deliver their findings.

Enormously popular, the Salk Summer Scholars program offers select high school students from throughout San Diego the opportunity to become immersed in a research topic for eight weeks and experience the intellectual and collaborative spirit of scientific investigation at the Institute.

Interns spent the summer pursuing a full-time project under the mentorship of a Salk scientist, which allowed them to perform hands-on work in a laboratory and explore the possibility of a career in science. The students learned how to formulate and test hypotheses, prepare experiments and draw conclusions from their studies in addition to taking part in regular lab meetings and group discussions. The program culminated with participants presenting their research studies to their mentors, lab members and families. 📊



Insider's View

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

Philanthropy comes from the heart

I HAVE BEEN ASKED ON MANY OCCASIONS TO NAME THE MOST SIGNIFICANT GIFT


I received as the head of a large research university where philanthropic gifts totaled in the hundreds of millions of dollars annually. Without question, one of the most moving and significant donations came from a ten-year-old boy, Conor Griffin Goetz.

Conor's father, John Griffin, had developed cancer and was treated over a long period of time at the Kimmel Cancer Center at Johns Hopkins in Baltimore. Unfortunately, despite the best available therapy at the time, the tumor spread throughout John's body, and he eventually succumbed to the cancer.

Conor was impressed with the treatment, but heartbroken by its inability to save his father's life. He wrote a short note to the Cancer Center: "Use this money to cure cancer." Tucked inside the handwritten note was \$55, his entire savings. With these few short lines, he gave voice to all the children, mothers and fathers whose lives have been forever changed by cancer.

One would think that such a small gift, too small even to be a rounding error in the over 20,000 gifts that are made annually to the Kimmel Cancer Center, would go unnoticed. Yet that gift, in relationship to the net worth of the donor, was as meaningful as any seven- or eight-figure donation. It demonstrated a level of passion and commitment by a boy whose maturity far exceeded his chronological age.

The Salk Institute is dedicated to improving the lot of humankind. We do this by understanding the fundamental mechanisms that determine how the cells and genes of plants, microscopic organisms, animals and humans function normally and when perturbed by certain disease states. And cancer is one of those important diseases whose prevention or cure comes from a profound understanding of how tumors are able to hijack cells in order to replicate uncontrollably.

Fifty years of amazing discoveries by Salk scientists—in cancer, genetics, aging, stem cells, neuroscience, plant biology and many other fields—have been enabled by gifts, large and small, from passionate and committed people like Conor. As we enter the next 50 years of Salk science, we will depend even more on our generous supporters—forward-looking people who recognize how science can ultimately contribute to the public good. 

STREET ADDRESS

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

Telephone: 858.453.4100

Fax: 858.552.8285

www.salk.edu

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

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

NOVEMBER

27 Salk Women & Science

DECEMBER

6 President's Club Luncheon

13 Glenn Symposium

JANUARY 2013

23–25 International Council Meeting
at the Salk Institute

FEBRUARY

13 Partners in Research Luncheon

20 San Diego Salkexcellators Reception
& Scientific Presentation

APRIL

3 Back to Basics

12 Salk Polio Vaccine Anniversary

13 Walk for Salk 5k
Campaign For Salk Open House



salk employee photo contest

Salk Employee Photography Contest

Exhibit now on display in the Foyer

Follow us on:



facebook.com/salkinstitute

twitter.com/salkinstitute

