In this issue: 2013 Donor Honor Roll

InsideSalk

Where cures begin.

Salk Institute 01|14

UNRAVELING THE MYSTERIES OF AGING TO INCREASE OUR

HEALTHSPAN

January 2014
Inside Salk

One on one with…Jan Karlseder

Next generation: Kevin Curran

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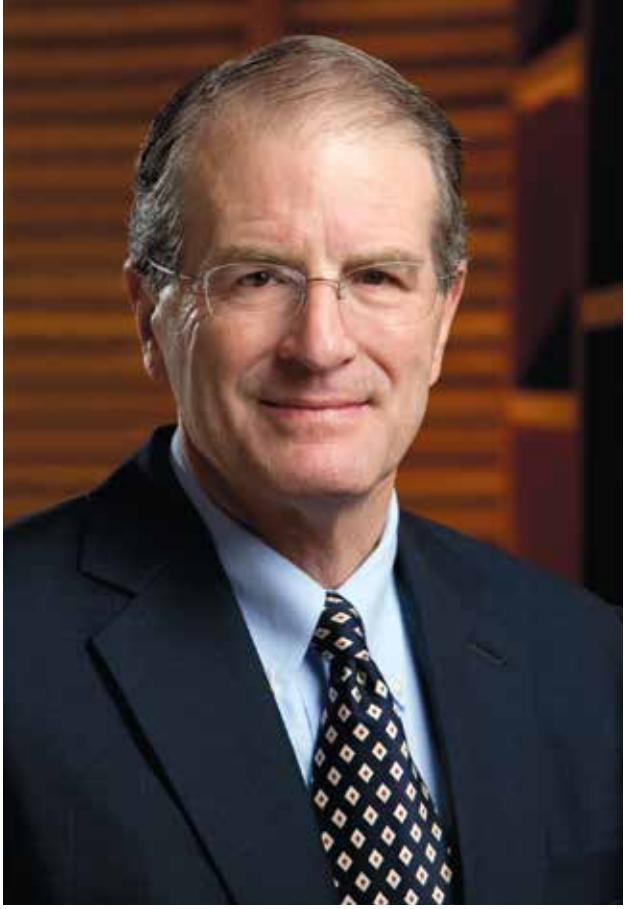


William R. Brody

Dear Friends,

"OLD AGE," THE ACTOR AND ENTERTAINER MAURICE CHEVALIER IS reported to have said, "isn't so bad when you consider the alternative."

And Chevalier, who continued performing until two years before his death at 83, presumably knew a thing or two about aging with grace and good health.

But millions of people stricken with the diseases of old age—Alzheimer's, Parkinson's, cancer, cardiovascular disease and more—are not as lucky. For them, growing older can be fraught with physical and cognitive difficulties that undermine their quality of life. Earlier this year, a government report projected that 13.8 million Americans will develop Alzheimer's disease by 2050, with the associated costs of care reaching $1.1 trillion. And those are the figures for just one condition! Clearly it's critical for society that we develop new interventions for age-related diseases that allow people to remain healthy and vigorous for as long as possible.

This issue of *Inside Salk* celebrates Salk research into healthy aging. We are fortunate to have many scientists at the Institute who are investigating the basic mechanisms behind aging, making important discoveries that are advancing our understanding of growing older. As you probably know, healthy aging is one of the four scientific initiatives underlying the Campaign for Salk, and I think it's safe to say that it's one in which everyone has a stake. I hope you'll enjoy reading about the work of **Martin Hetzer, Juan Carlos Izpisua Belmonte** and **Jan Karlseder** in our cover story and gain a new appreciation for what the campaign means for cutting-edge Salk research.

In fact, it's been a remarkable several months at the Institute, with many of our researchers publishing significant papers in major journals. We are thrilled to report on some of the highlights in the following pages. **Satchin Panda**, for instance, has discovered a new molecule with implications for migraines. **Ed Callaway** has produced novel insights into how specific brain regions interconnect, and **Sreekanth Chalasani** has discovered a previously unknown flexibility in neural circuitry and its influence on behaviors in model organisms. Also in neuroscience, **Joseph Ecker** and **Terrence Sejnowski** have helped elucidate how information in the genomes of cells in the brain is controlled from fetal development to adulthood, and **Tatyana Sharpee** and **John Reynolds** have demonstrated the complexities of decoding images made of both simple and intricate elements. In cell biology, **John Young** and **Greg Lemke** have discovered a new mechanism that may prove effective at clearing viruses from cells, and **Lei Wang** has developed a new tool for protein engineering.

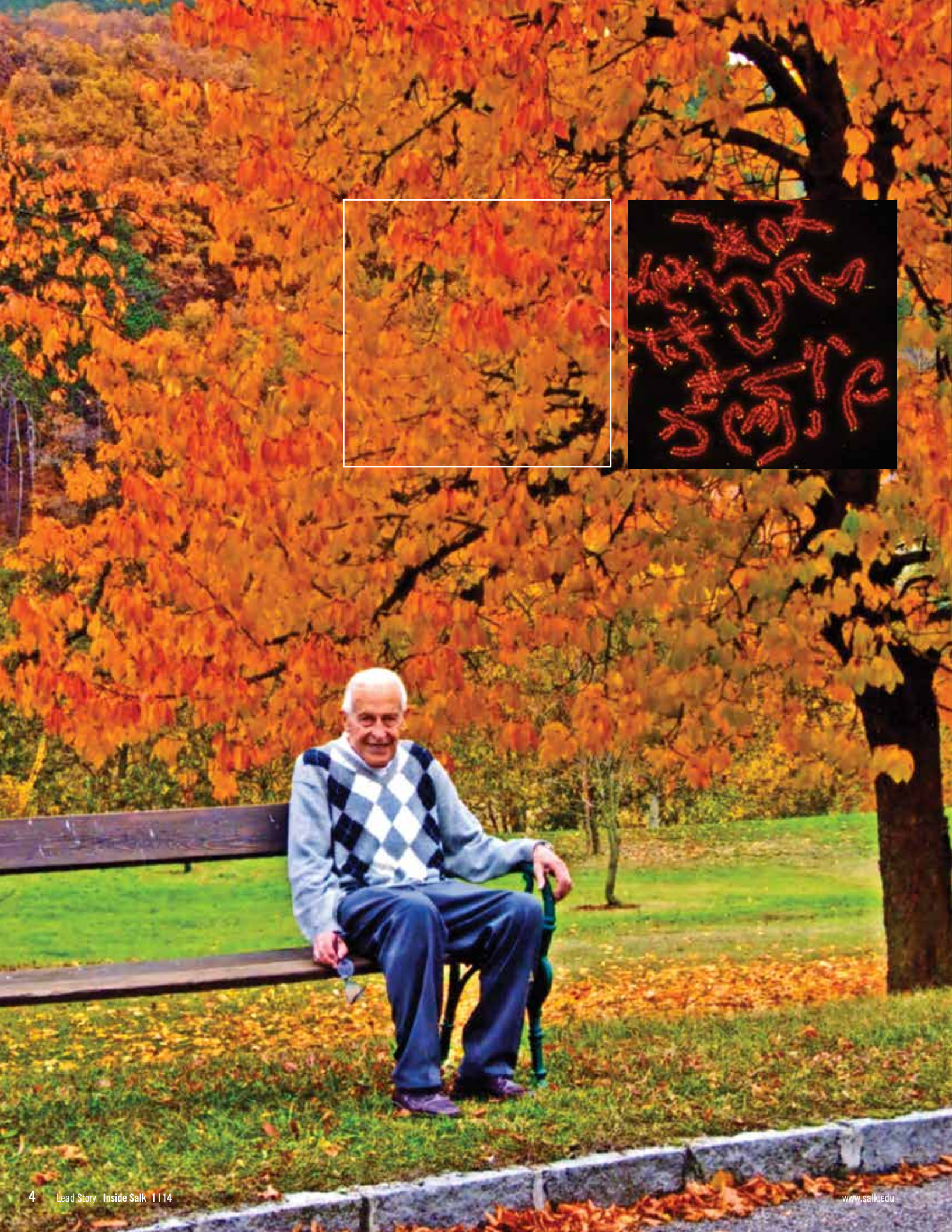
Your friendship and especially your support have been instrumental in these breakthroughs, and as you peruse the magazine, I hope you'll think about what the findings of our scientists may ultimately mean to all of us and how you have helped bring them about. On behalf of everyone at the Institute, thank you for being such an important part of the Salk community.

William R. Brody

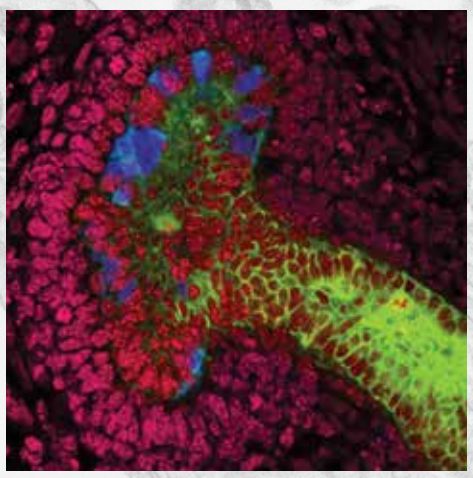
William R. Brody, M.D., Ph.D.
President, Salk Institute
Irwin M. Jacobs Presidential Chair

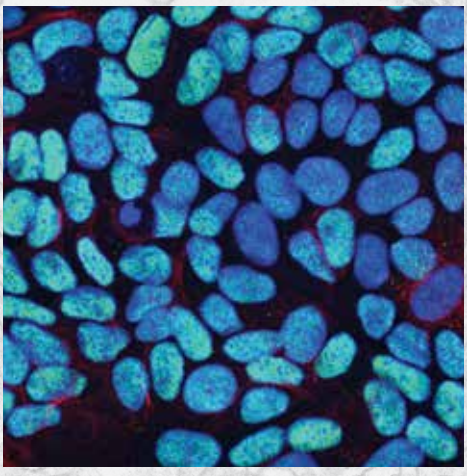
ON THE COVER

A lot changes in our bodies from infancy to our golden years, and science is just now beginning to decipher what it means to age at the molecular level. The goal is to increase our "healthspan," the amount of time during our lives that we remain healthy and active.



Ernest Juller was active and healthy well into his ninth decade. Salk scientists are exploring why some people have such a long 'healthspan.'





THE SCIENCE OF HEALTHY AGING

What was Ernest Juller's secret? In his 97 years, Juller was rarely sick, hardly saw a doctor and, until the very end of his life, remained healthy, active and a gardener of particular persistence. Was it his daily glass of white wine? Was it his regular leisurely walks in the Austrian forest? Or maybe his exceptional vitality stemmed from the same tenacity that kept him, year after year, attempting to grow an alpine forest in lowland Austria.

"He lived in a region situated at a much lower altitude than Alpine plants typically grow," recalls Juller's grandson, **Jan Karlseder**, a professor at the Salk Institute. "He was never completely successful with his Alpine garden, but that didn't deter him. He was a botany professor, and he loved mountain plants. It's impossible to say exactly what kept him healthy and active for so long—maybe it was good genes. If so, I hope he passed them on."

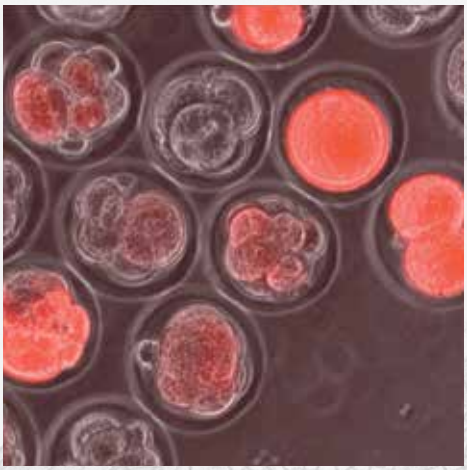
For most of us, explaining the mystery of people like Juller, who live remarkably long and healthy lives, is a matter of making casual observations. We catalog aspects like diet, exercise, sleep and other salubrious elements of a person's life as we attempt to identify their formula for success. For Karlseder and other scientists at Salk, however, deciphering the secrets of healthy aging is a full-time occupation. Equipped with cutting-edge scientific tools, such as high-resolution imaging, whole-genome sequencing and bioinformatics, they are exploring how our bodies age at the molecular level. Line by line, they are filling in the blueprint for the biological mechanisms that maintain our cells and organs, repair damage from injuries and fend off diseases as we get older.

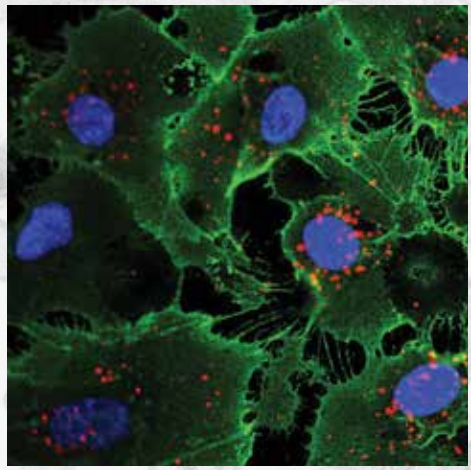
The science of aging has never been more important. Currently, about 40 million Americans are over 65, and by 2030 those numbers are expected to grow to more than 72 million. As the proportion of older people rises, so too does the incidence of age-associated disease, with its attendant personal, social and economic costs. Largely as a result of this trend, healthcare spending is expected to increase by 25 percent by 2030, and Medicare spending will grow from $555 billion in 2011 to $903 billion in 2020.

It is against this backdrop that the Salk Institute has launched its Healthy Aging Initiative as part of the Campaign for Salk, the Institute's first-ever major fundraising campaign. Through support for research on aging, the initiative seeks to explain why aging is the number-one risk factor for conditions such as neurodegeneration, cancer, diabetes and cardiovascular disease. But Salk scientists aren't just asking why aging often leads to illness. The initiative is also a crucial step in developing therapies that target the causes—not just the symptoms—of such diseases and disabilities.

"Every person's medical history stems from a mix of genes, lifestyle and environment, but what we want to find are the common factors—at the molecular, cellular and organismal levels—that allow some people to remain robust late into

From left: Salk scientists Makoto Hayashi, Anthony Cesare and Jan Karlseder





life," says Karlseder, the holder of Salk's Donald and Darlene Shiley Chair. "If we understand these mechanisms, these programs that run our cells and organs, we can use them to help increase the human 'healthspan,' the length of time people stay healthy during their lifetimes."

Karlseder's research centers around telomeres—complexes that cap the ends of chromosomes, the structures that contain our DNA. Telomeres help protect and repair our cells, and they play a central role in cellular aging by shortening every time a cell divides, a molecular method of marking time. When telomeres become too short, they signal the cell to stop dividing and self-destruct, making way for new cells.

Telomeres are also involved in DNA repair, a process by which cells fix damage done from normal physiological wear and tear and environmental factors such as UV light. Because tumors attack the body by bypassing these safeguards, scientists are also actively studying telomeres' involvement in cancer.

Recent discoveries by Karlseder's team explain how telomeres serve as sentries, keeping cells operating in an orderly fashion and protecting our bodies from cells containing damaged DNA. In one study, they showed that telomeres begin to degrade rapidly when a cell takes too long to divide—a sign of genetic damage. This sends a warning signal that tells the cell to shape up or ship out: repair its DNA or self-destruct. It is a crucial check on cellular growth that prevents cells with damaged DNA from propagating. In another experiment, the scientists found that telomeres act as anchors that organize chromosomes as a cell divides. Under a microscope, they observed that telomeres move to the outer edge of a cell's nucleus after the chromosomes are duplicated during cell division.

"Our cells aren't simply bags containing an unorganized mix of chemicals, but rather are complex three-dimensional machines, in which the gears and wires are made up of molecules," Karlseder says. "What we found suggests that telomeres don't just protect our cells; they help orchestrate this molecular machinery in the nucleus, which is the cell's control center."

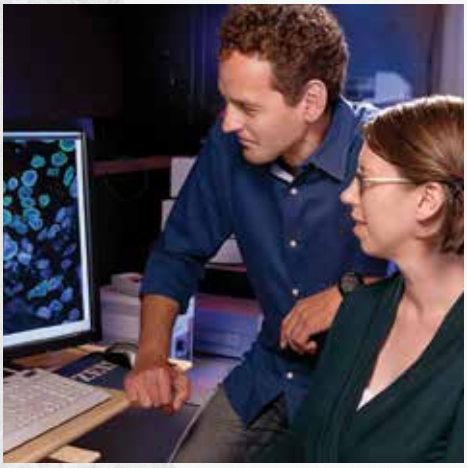
In fact, Karlseder believes that telomeres may play a central role in controlling how our cellular programming—the genetic "software" that runs our cells—changes as we get older. The code that runs these programs is stored in our DNA sequences and in a collection of extra-genetic chemical markers known as the epigenome, which can turn genes on and off, thereby guiding cellular function. Integrated into the chromosomes that house and organize these codes, telomeres are well placed to influence how cells behave.

"The more we learn about telomeres," Karlseder says, "the more they appear to affect gene expression profiles and how the genome morphs over time. By understanding these mechanisms and learning how to influence them, we may be able to intercede in the genomic and epigenomic programming that changes with aging. The idea would be to bolster the cellular programs that protect and renew our bodies and stifle those that lead to premature aging."

The research of **Martin Hetzer**, another Salk professor studying the cellular roots of aging, focuses on another important component of a cell's nucleus: the molecular gates, known as nuclear pores, that allow the genetic control center inside the nucleus to communicate with the cellular machinery outside the nucleus, in the region known as the cytoplasm. These pores also protect the valuable genetic material from toxins found in the cytoplasm.

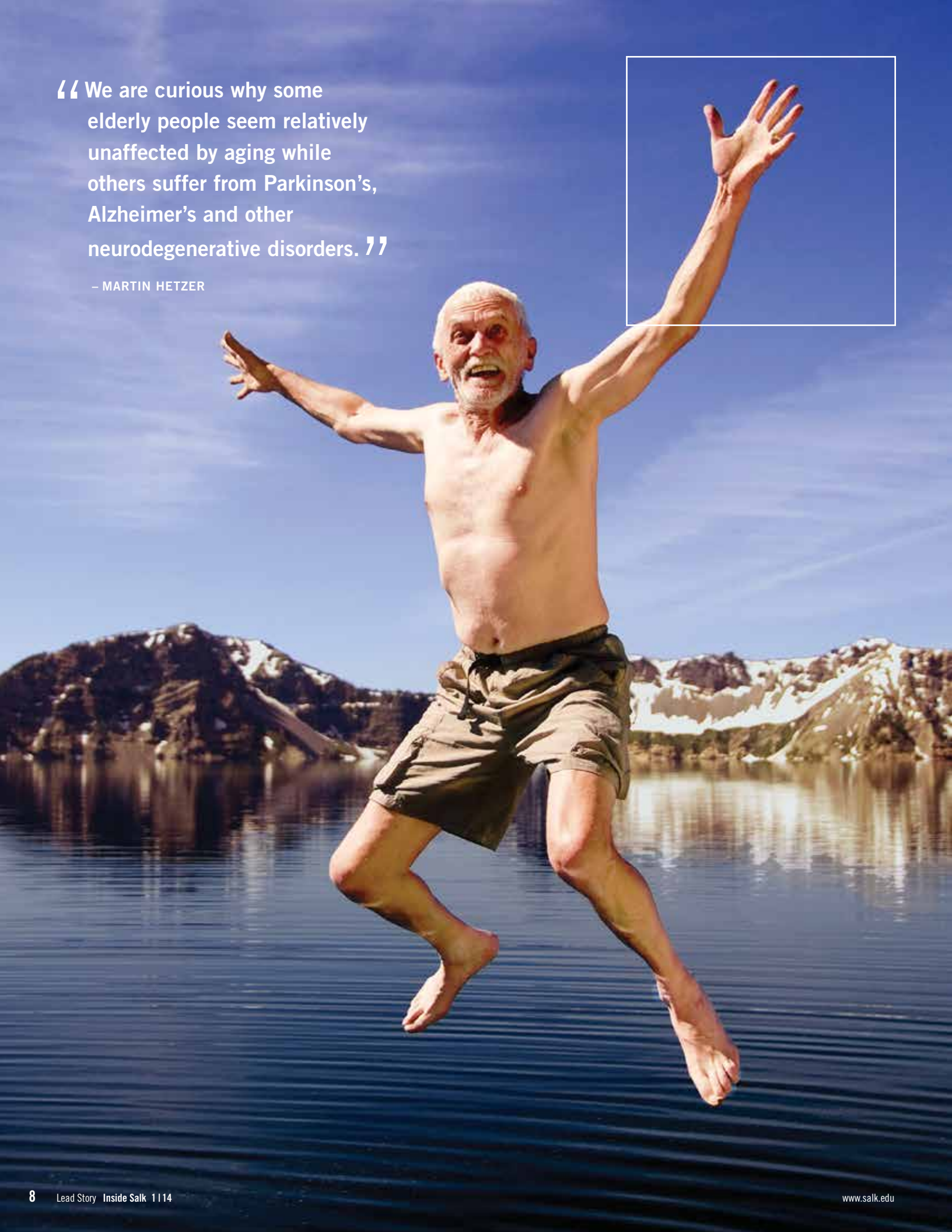
Hetzer's team found that nuclear pores of neurons contain certain proteins—which they dubbed extremely long-lived proteins (ELLPs)—that have a remarkably long lifespan. While most proteins last a total of two days or less, the researchers identified ELLPs in the rat brain that were as old as the organism. This was the first time scientists had discovered an intracellular component made up of molecules of this age, and their results suggested that the proteins lasted an entire lifetime without being replaced.

The longevity of ELLPs may help explain in part why brain function often declines as people age. Previous studies by Hetzer's group showed that the nuclear pores weaken over time, allowing proteins to leak from the cytoplasm into the inner sanctum of the nucleus. For instance, in older cells a protein called tubulin, which should be found only in the cytoplasm, gums up the nucleus with long filaments. Associated with several neurodegenerative diseases, including Parkinson's, the filaments are found in the substantia nigra of many Parkinson's patients, the part of the brain that is involved in dopamine production and that is affected by the condition.

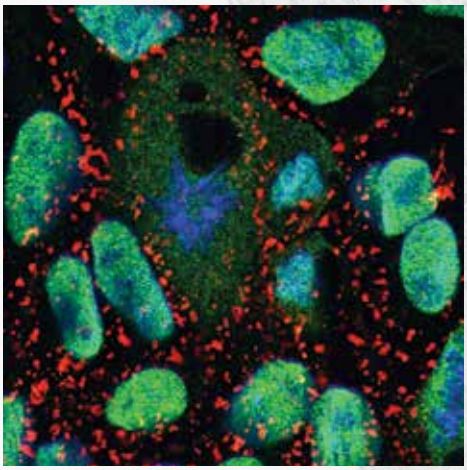


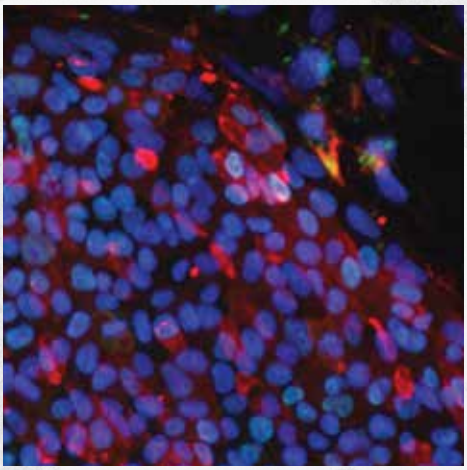
Above: Martin Hetzer, professor, Molecular and Cell Biology Laboratory and Emily M. Hatch, research associate

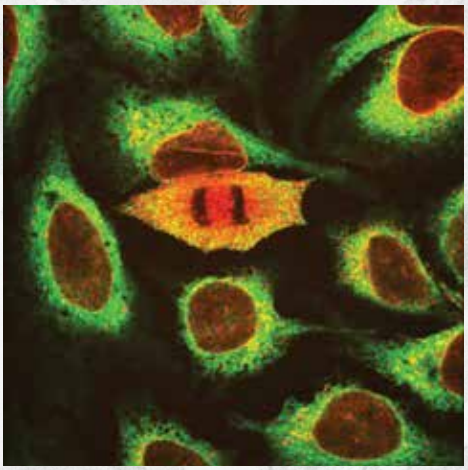
Opposite page, left to right: Martin Hetzer, Juan Carlos Izpisua Belmonte, and Jan Karlseder



> “We are curious why some elderly people seem relatively unaffected by aging while others suffer from Parkinson’s, Alzheimer’s and other neurodegenerative disorders.”
>
> – MARTIN HETZER







"What we think is happening is that ELLPs deteriorate over the years and aren't replaced, which leads to dysfunction and vulnerability," says Hetzer, who holds the Jesse and Caryl Philips Foundation Chair. "It's as if you regularly take your car in for routine maintenance, but one critical component was never replaced or repaired. Eventually, that part will stop working, and that will have a cascade of effects, causing the whole engine to go haywire."

The deterioration of proteins may extend beyond malfunctioning nuclear pores. Unlike cells of the skin or other high-turnover areas of the body, most of our neurons stay with us our whole lives. Other important components of neurons may contain ELLPs and thus may be similarly prone to wear and tear. In addition to being embedded in the membrane surrounding the nucleus, ELLPs are found on the plasma membrane, the outermost surface of the cell. They are also part of the chromatin, the bundles of DNA and proteins found inside the nucleus, which help to organize and control the function of a cell's genetic operations. In each case, ELLPs serve a vital role in coordinating the dizzying array of cellular activity that keeps our nervous system healthy.

"The reason we keep neurons so long is that it's important to have consistency; otherwise we wouldn't be able to learn and remember or to respond quickly to our environment," Hetzer says. "If we had to replace neurons all the time, it would constantly interfere with our ability to function in the world. But stability comes at a cost: it tests the durability of those neurons. We know that genetic activity changes with age, and we think that results in part from deterioration of nuclear pores and other long-lived cellular components."

Like Karlseder, Hetzer is curious why some elderly people seem relatively unaffected by aging, while others suffer from, Parkinson's, Alzheimer's and other neurodegenerative disorders. Through fully understanding how certain people maintain normal function and ward off disease, his team hopes to identify and possibly bolster genetic and epigenetic mechanisms that protect us as we age.

Other Salk scientists, such as **Juan Carlos Izpisua Belmonte**, holder of the Roger Guillemin Chair, are looking to our most immature cells to explain what it means to get old. Izpisua Belmonte's lab studies how stem cells differentiate and give rise to over 200 cell types that constitute the human body. This research not only helps explain how our bodies maintain and heal themselves, but also offers the possibility of using stem cells in regenerative medicine.

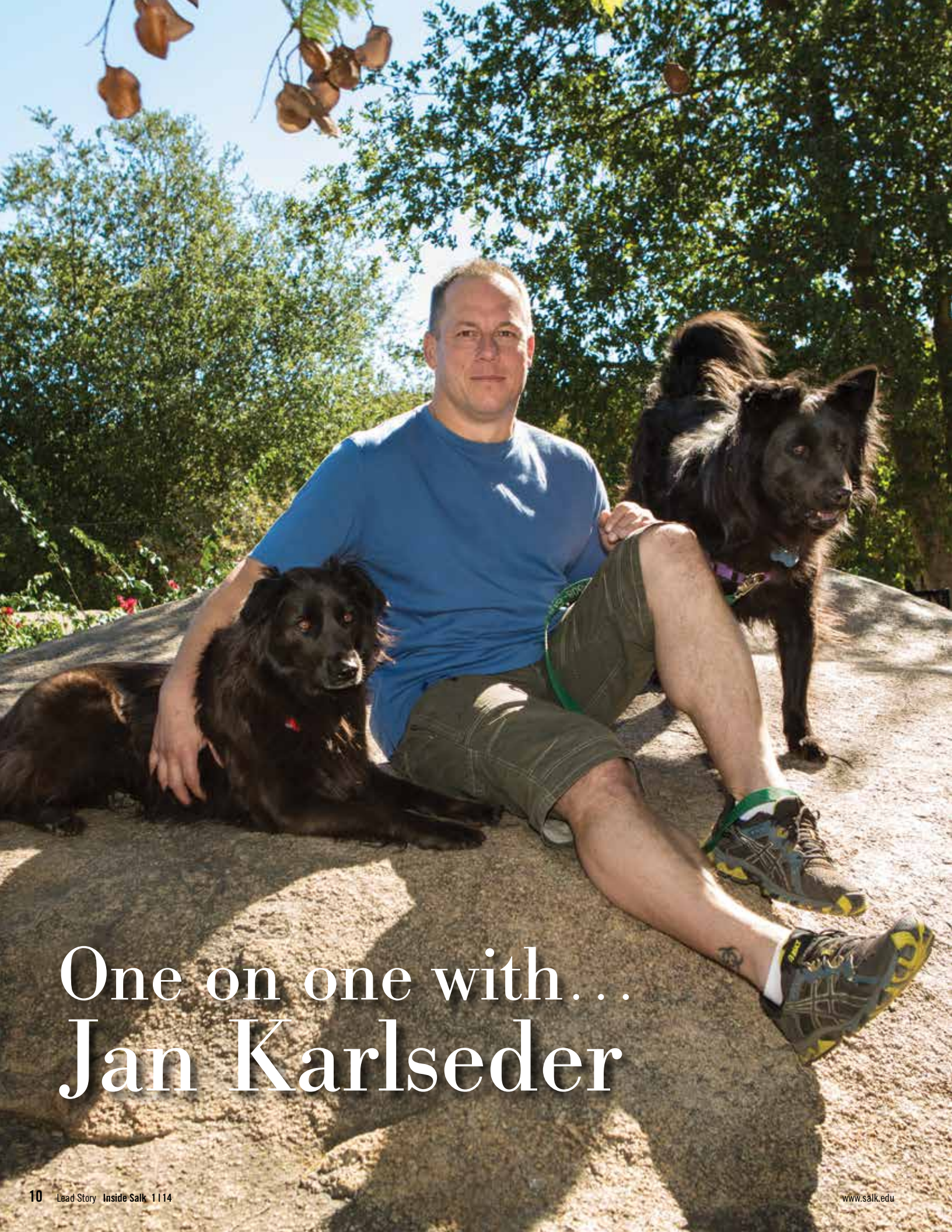
In one study, Izpisua Belmonte's team generated induced pluripotent stem cells (iPSCs) from skin cells obtained from patients with Hutchinson-Gilford progeria syndrome, a condition which causes them to age eight to ten times faster than the rest of us. The Salk scientists then differentiated the stem cells into smooth muscle cells displaying the telltale signs of vascular aging. In addition to providing insight into Hutchinson-Gilford progeria, the study offered a new method for studying age-related disease in the laboratory at an accelerated pace.

More recently, Izpisua Belmonte's group used iPSCs to generate neurons that exhibited characteristics of Parkinson's disease due to mutant genes inserted into the cells' DNA. This allowed them to study the molecular underpinnings of the disorder in the laboratory, overcoming the difficulty of obtaining human neurons for experiments. His lab is also using iPSCs to study Werner syndrome, a premature aging condition that more closely resembles normal aging, compared to Hutchinson-Gilford progeria. Using these laboratory models, he and his team are studying the links between genetic instability, aberrant epigenetic signatures and cellular aging. Like Karlseder and Hetzer, Izpisua Belmonte emphasizes that studying the normal process of aging is crucial to understanding how things can go wrong.

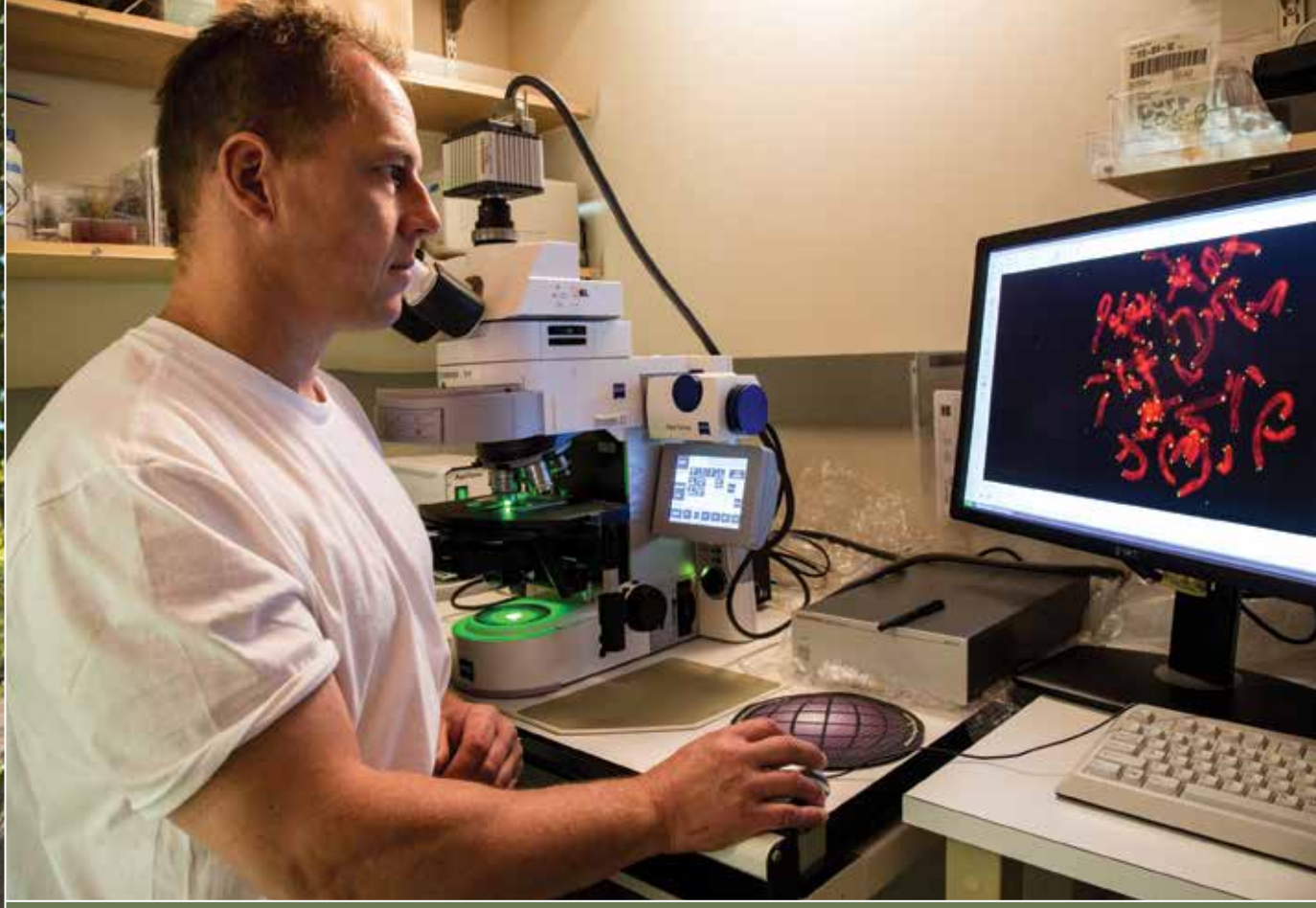
"Pluripotent stem cells give rise to all the tissues and organs in our bodies, and stem cells continue to repair and replace old cells throughout our lives," he says. "If we know precisely how this happens—the exact molecular mechanisms—we might be able to boost this capacity for self-healing."

Karlseder offers Ernst Juller as an example of what could become the norm if the science unravels the mysteries of healthy aging. "Obviously, advances in science and medicine have played a large role in helping us live longer," says Karlseder. "Now we need to focus on keeping us healthy longer. My aspiration is to stay as healthy as my grandfather as I get older, and I think the science we're doing now can help make that happen."

From left: Emmanuel Nivet and Juan Carlos Izpisua Belmonte. Seated: Ignacio Sancho Martinez



One on one with…
Jan Karlseder



JAN KARLSEDER, HOLDER OF SALK'S DONALD AND DARLENE SHILEY CHAIR, STUDIES THE complex relationship between aging and telomeres, the protective ends of chromosomes, as well as such aging-related diseases as cancer.

A professor in Salk's Molecular and Cell Biology Laboratory, Karlseder, along with his team, has discovered that the relationship between telomeres and cancer extends much further than previously believed. Their research has explained the process by which a class of anti-cancer drugs known as mitotic inhibitors kills cells: exposure to mitotic inhibitors causes telomeres to lose their protective function, and the cells respond with stress signals that eventually lead to the death of cancer cells. Karlseder believes that continued research into the telomeres' functions within cells will lead to an ability to influence the aging process and, as a result, to the restriction of cancer cell growth.

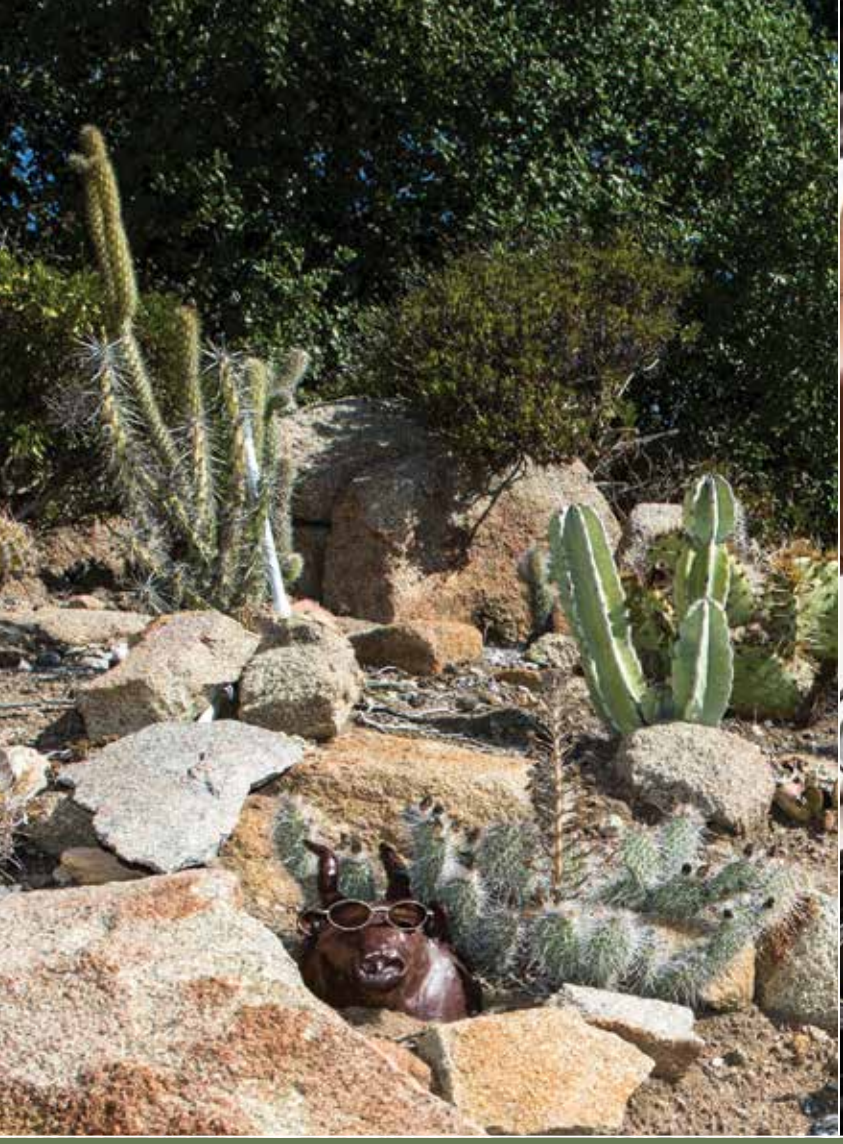
A recent discussion with Karlseder reveals how, in the lab as well as his personal life, he pursues "the bigger picture" by addressing the smallest details.

Your grandfather was a scientist in Austria. Did that influence your decision to go into science?

Yes, definitely. He was a botanist who studied alpine plants. He used to take me and my brother into the forest and tell us about all the plants. It instilled in us a curiosity about the natural world, and both my brother and I still love the outdoors. It also gave us a do-it-yourself mentality. My brother, who still lives in Austria, is a serious mushroom hunter and brews his own schnapps. The schnapps varieties are actually really good.

Your grandfather lived a long, healthy life and stayed active until the very end. Why do some people get so lucky?

These things are very circumstantial. Good genes, probably. He didn't exercise rigorously, but he stayed active walking and gardening. One thing about my grandfather was that stress was unknown to him. He had the attitude that if something couldn't get done today, it could wait until tomorrow. Nearly every day, he drank a glass of the local white wine, for which that area of Austria is famous. But really, it's impossible to know.



Cactus garden at Karlseder's house in Ramona, California.

But your research is helping us to understand aging?

We're learning a lot about how our cells and organs age. Telomeres control a lot more than just the number of times a cell divides. They play a role in arranging chromosomes in a certain order so that they can talk to each other. It's very well-controlled, certainly not random, so there must be a mechanism behind this process. If we can identify this mechanism, then I think we'll be able to address the often coordinated onset of age-associated diseases. I have terrific people working in my lab, and we've shown that the deeper we dig, the more we realize how these very localized processes affect the entire cell and therefore the organ and after that the organism. There's always a bigger picture.

Away from your lab, you spend a lot of free time working on Land Cruisers. What is the attraction?

The attraction came about after moving to San Diego. I fell in love with the southwestern desert and the Mexican desert, and I wanted to explore these areas. I met some others who shared that interest, and the general agreement was that if you don't want to break down out there you must have a Toyota Land Cruiser. If you look at the wildest continents of the world, such as Africa and Australia, you don't see too many Jeeps; you do see a lot of Land Cruisers. They are very durable trucks. So I bought a Land Cruiser and I drove it to Mexico. And of course it broke down. That was because it was old and I didn't know what I was buying. That's when I decided that if I was going to do this, I needed to know a whole lot more about these vehicles. I met a good guy, a sort of hobby mechanic, and we became friends and started working on them together, rebuilding engines, taking transmissions apart and such.

How many Land Cruisers have you built?

Just for my use, at least six. I have one right now that's a diesel. Diesels have become our specialty. They get much better gas mileage, which is important when you're traveling through the remote areas of the desert. And the diesel engines are usually more reliable, too. But they're difficult to get. They were never sold in the U.S. You could get them in Canada for a while but not now. I just put an Australian diesel engine in my 1996 Land Cruiser. Over the past 11 years, I think I've logged about 100,000 miles in Baja.

What was your most harrowing moment?

I took a trip with my brother and a friend. We were going to try a new route from the Pacific Ocean to the Sea of Cortez, and it was through some really high mountains. We had two vehicles, and at one point we overlooked a big rock, and the Toyota Tundra got hung up. That ripped out the rear axle and tore the driveshaft in two. So, there we were in the middle of absolute nowhere, high in the mountains, and we didn't know what we were going to do. We thought about piling all of our stuff into the one vehicle and just driving away, leaving the Tundra. But then we took some time to put up

Karlseder and friend Mike Hein work on one of their overlanding vehicles.

some shade—it was scorchingly hot—and think about the problem, and we decided, "Hey, we can fix this." We had a few tools with us, but some sockets were missing, so I ended up driving to Loreto, which was six hours away. When I got back, we lifted up the rear of the truck and tried to push the axle into place, but it was too heavy. So we put the truck in front wheel drive and drove backward, doing our best to center the truck over the axle. Then we managed to rig up something to bolt it into place. It was on that trip that we discovered the most important tool of all: a really big hammer. We used that to fix the driveshaft. It was a little unbalanced when we were done but it got us back to San Diego without a hiccup. You know, you can work yourself out of a lot of problems if you have at least a remote idea of what you're doing.

What keeps you going back to Baja California?

It is absolutely beautiful there, completely deserted. You have a 1,200-mile stretch of land that no one has spoiled. In many places there is not a single person around, and there probably hasn't been a single person around in a month. It's incredibly peaceful. You can sit on a beach and just think. No email, no cell phones. You know that no one's going to bother you. It's very relaxing.

Do you think about science when you're there?

All the time. You get a distance, you know. And sometimes you actually get some very good ideas just sitting on the beach.

Karlseder estimates that he's logged more than 100,000 miles of driving during his rugged expeditions to Baja.

SYMPHONY at SALK

An enchanting way to support science and education

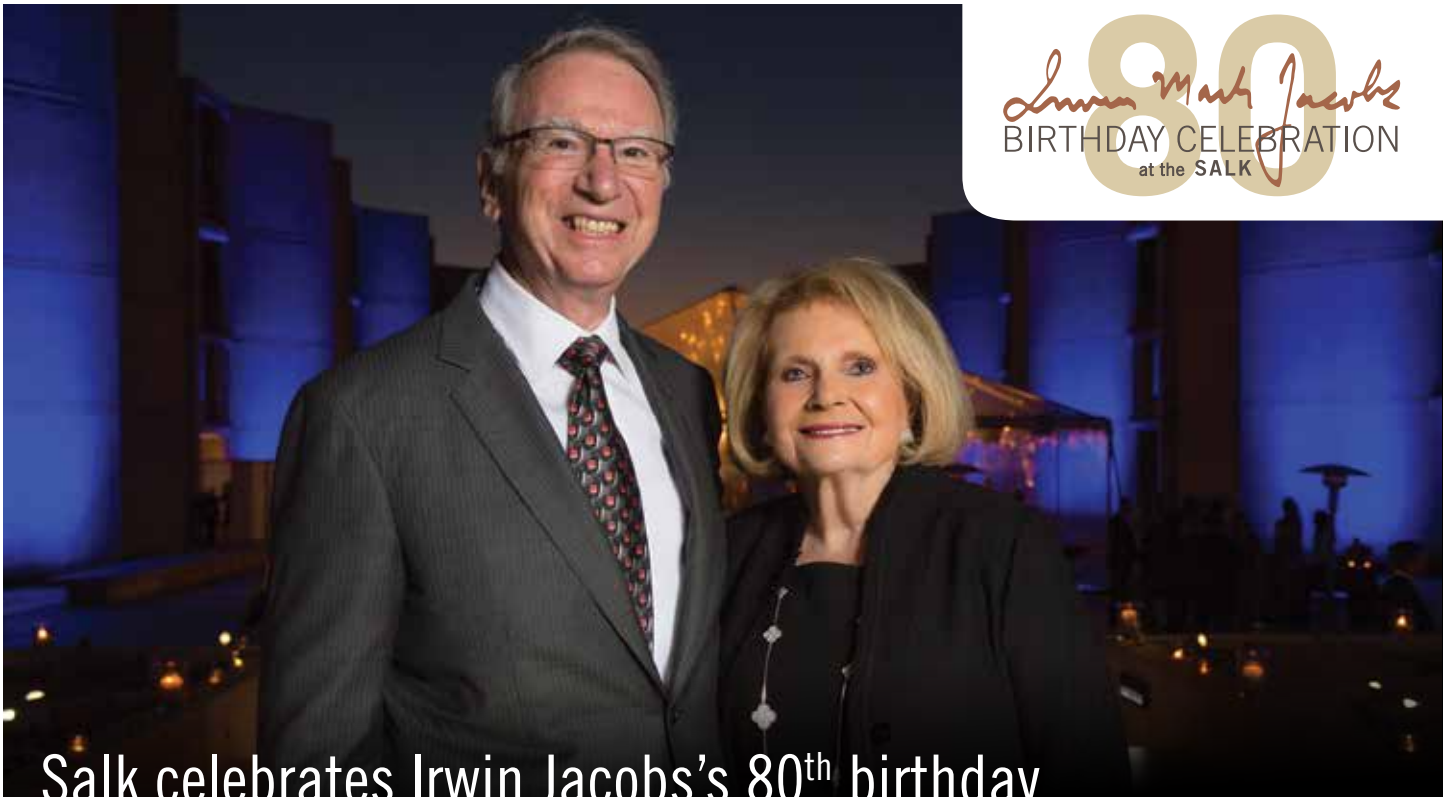
HIGH ABOVE THE PACIFIC OCEAN, UNDER A CANOPY OF STARS, the Institute's famed courtyard was transformed into a spectacular concert venue on August 24, for the 18th annual Symphony at Salk. Award-winning singer and actress Katharine McPhee, the featured guest artist, performed a diverse set of songs ranging from classic Cole Porter to R&B soul and pop music, accompanied by the San Diego Symphony under the baton of returning guest conductor Thomas Wilkins.

Before the concert, guests were treated to a gourmet dinner, created for the event by celebrated chef Jeffrey Strauss, owner of the critically acclaimed Pamplemousse Grille.

The unforgettable evening raised nearly $900,000 for the Institute's scientific research and educational outreach program.

Katharine McPhee and Maestro Thomas Wilkins

Katharine McPhee



Salk celebrates Irwin Jacobs's 80th birthday

ON THE EVENING OF OCTOBER 14, SOME 140 people gathered in the Salk courtyard to celebrate the 80th birthday of board chairman **Irwin M. Jacobs** and recognize his many accomplishments. Those attending included personal friends of Jacobs and his wife, Joan, as well as Salk faculty, donors, trustees and local business leaders.

The celebration capped a daylong symposium in Jacobs's honor, titled "Unraveling Biological Complexity: Transforming Research through Innovation, Leadership and Philanthropy." Some of the Institute's most distinguished researchers spoke about discoveries from their labs, including **Joseph Ecker**, **Inder Verma**, **Fred Gage**, **Joanne Chory**, **Ronald Evans**, **Thomas Albright**, **Juan Carlos Izpisua Belmonte** and **Terrence Sejnowski**. The symposium concluded with a keynote lecture by MIT professor Robert Langer, one of the world's leading researchers in biotechnology.

At the evening's cocktail reception, Verma, serving as master of ceremonies, welcomed the guests and introduced a video highlighting the tremendous impact Jacobs has had during his lifetime, both during his career at Qualcomm, Inc., which he cofounded, and through his numerous philanthropic activities. Salk president **William R. Brody** led the crowd in a toast to Jacobs; then former vice president Al Gore spoke about Jacobs's rise to success.

Executive vice president **Marsha Chandler** introduced the musical performers for the evening: Geoffrey Keezer, a jazz pianist and two-time Grammy nominee who had recently recorded an album at the Jacobs home, and Jesse Palter, a vocalist and composer who performed a number of songs, ending with the classic "Hey, Big Spender." At this point Jacobs was led onto the stage and presented with a birthday cake and a gift specially chosen by Salk faculty—an early edition of Charles Darwin's *On the Origin of Species*.

After Jacobs thanked his friends and family for sharing the special day with him, Verma concluded the evening by reading a poem he'd composed for the occasion. It was a heartwarming tribute to a man who has done so much for the community and for the Salk Institute.

Salk earns third consecutive Charity Navigator four-star rating

FOR THE THIRD STRAIGHT YEAR, CHARITY NAVIGATOR, THE nation's largest evaluator of nonprofit business and financial operations, has awarded Salk a four-star rating for "sound fiscal management." This top designation was determined after a team of professional analysts examined tens of thousands of nonprofit financial documents.

"We are proud to announce that the Salk Institute for Biological Studies has earned our four-star rating for its fiscal health and commitment to accountability and transparency," said Ken Berger, president and CEO of Charity Navigator. "Only 11 percent of the charities we evaluate have received our highest rating three years in a row, indicating that the Salk Institute for Biological Studies executes its mission in a fiscally responsible way and outperforms most other charities in America. This 'exceptional' designation… demonstrates to the public [that] it is worthy of their trust."

Inaugural Wellness Event Ushers in the New Year:

The Art and Science of Cuisine

From left: Professor Ron Evans and Chef Nathan Coulon

Notable chef, author and restaurant owner Su-Mei Yu stirs things up with Salk scientist Geoff Wahl.

FUEL FOR BOTH THE MIND AND BODY WILL BE THE THEME IN January when the Salk Institute introduces The Art & Science of Cuisine, blending the most recent nutritional discoveries with novel culinary concepts.

Guests at the mixer will have the opportunity to meet some of San Diego's most innovative chefs, sample their cooking and learn how to optimize nutrition in home-cooked meals. Complementing the fare will be up-to-the-minute information from Salk scientists about the latest research into the links between nutrition and health, and the role diet may play in disease risk.

San Diego has long been known for its dynamic restaurant scene, and the city regularly tops lists for active living. Many local chefs have made it a priority to serve the freshest, most healthful fare—food that not only pleases the palate but nourishes the body. Deborah Szekely, the honorary chair of the event, cofounded the renowned spas The Golden Door and Rancho La Puerta and at 91 embodies the power of mindful eating. Szekel has written three cookbooks and recently launched Wellness Warrior, a nonprofit organization to champion health issues. Featured chefs at the event will include:

Nathan Coulon—executive chef at True Food Kitchen, who takes popular trends in cuisine and pairs them with healthy living. His menu features seasonal recipes that emphasize locally grown organic ingredients.

Isabel Cruz—owner of three restaurants in San Diego and two in Oregon and known for her innovative blending of Latin and Asian cuisines. Her recipes produce meals that are not only delicious but are good for you.

Joy Houston—a certified Raw Food Nutrition Educator who helps people incorporate more fresh foods into their everyday diet. She has been featured on TV and in magazines for various aspects of healthy eating, raw food, superfoods and juicing.

Denise Roa—chef at Rancho La Puerta, who fuses the culinary and cultural heritages of her own life with the healthful "spa cuisine" dining pioneered by Rancho La Puerta. The resort has never focused on caloric deprivation, but instead celebrates the seasons of its own farm and organic produce suppliers with a cuisine that is colorful, zesty, and satisfying—the kind of food that fuels a life of vigorous activity.

Su-Mei Yu—owner of the popular Thai restaurant Saffron. Yu serves only the freshest seasonal ingredients "to offer food for the body, mind and soul." Host of the TV show *Savor San Diego*, she is a passionate advocate for the local food community.

The Art and Science of Cuisine will take place at the Institute on Wednesday, January 22, 2014. For more information, visit www.salk.edu/cuisine or contact cuisine@salk.edu or call 858-453-4100 ext. 1846.

Awarding-winning pianist Sean Chen played to a sold-out audience at the inaugural Salk Science and Music Series concert held at the Institute on October 6.

Sean Chen

Salk Science and Music Series

Program combining concert performances and scientific talks 'Amaze & Inspire'

INSPIRED BY A MAGNIFICENT GIFT OF A CONCERT STEINWAY PIANO from generous Salk benefactor Conrad Prebys, the Institute has initiated the Salk Science and Music series—an ambitious program that melds both amazing science and inspiring music for the San Diego community. The six-concert series, which debuted on October 6 to a sold out audience, will run through May of 2014. The program provides a venue to feature some of the hottest emerging classical and jazz musicians, and also includes fascinating scientific presentations of the latest discoveries occurring in Salk labs by our world-renowned faculty.

Each concert begins at 4 p.m. With a 40-minute musical performance, followed by a 15-minute scientific talk, and then more music, concluding at 5:45 p.m. For tickets and information: www.salk.edu/music

Fred 'Rusty' Gage presented an intriguing scientific talk at the debut event.

SALK SCIENCE & MUSIC SERIES

2014 FEATURED PERFORMERS

Jan. 26: Pianist Yoonie Han (Fulbright Concerto Competition winner) and scientist **Ron Evans** (Professor and Director, Gene Expression Laboratory)

Feb. 23: Vibraphonist Joe Locke with pianist Geoffrey Keezer and scientist **Tom Albright** (Professor and Director, Vision Center Laboratory)

March 16: Violinist Sean Lee (Paganini Competition winner) with pianist Karen Joy Davis and scientist **Marc Montminy** (Professor and Director, Clayton Foundation Laboratories for Peptide Biology)

May 18: Pianist Fei Fei Dong (Van Cliburn finalist) and scientist **Clodagh O'Shea** (Associate Professor, Molecular and Cell Biology Laboratory)

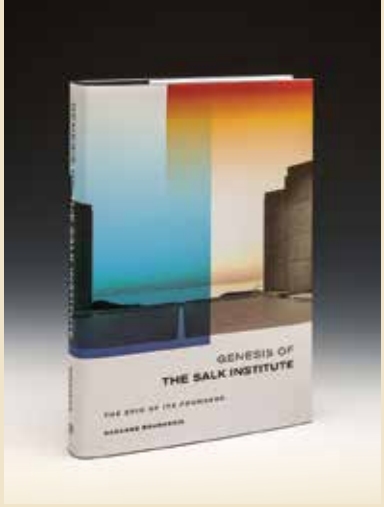
For more information, call (858) 453-4100 ext. 2098; visit salk.edu/music; or email music@salk.edu

President's Club members receive free admission and premier seating to all Salk Science & Music Series concerts and are invited to attend a private reception following each performance hosted by President William Brody and the featured Salk scientist. Visit www.salk.edu/presidentsclub or call 858-453-4100 x 1405 to learn more.

Suzanne Bourgeois

> "Jonas Salk should be recognized for two major achievements: One is the polio vaccine and the other is the Salk Institute."
>
> – SUZANNE BOURGEOIS

A history of the Salk



SUZANNE BOURGEOIS, PROFESSOR EMERITUS AND FOUNDING DIRECTOR of Salk's Regulatory Biology Laboratory, has written a new book documenting the dynamic history of the Institute and the key players who played a part in its creation. Titled *Genesis of the Salk Institute: The Epic of Its Founders*, Bourgeois retells the story of how and why, born far apart, the founders of the Salk Institute eventually gathered in La Jolla in the early 1960s to create an exceptional institution.

"Jonas Salk should be recognized for two major achievements: One is the polio vaccine and the other is the Salk Institute," says Bourgeois. The new book is a personal account of the origins and early years of the Salk, and Bourgeois crafts an engaging study that draws on her involvement with the Institute since its founding and on related archives, interviews and informal conversations. "I think I'm probably the only one who has daily records of what happened," she says.

The volume discusses the people who founded the Institute and built a home for pioneering research—leading scientists of the time as well as non-scientists of stature in finance, politics, philanthropy, publishing and the humanities. The events that brought these individuals together, the historic backdrop in which they worked, their personalities, their courage and their visions, their clash of egos and their personal vanities are woven together in a rich, engaging narrative about the founding of one of the world's premier research institutions. Released last month, the book is available through University of California Press and Amazon.

Salk hosts the second annual 5K Walk for Salk and Explore Salk open house

MARK YOUR CALENDARS FOR APRIL 12, 2014 to join in Salk's second annual Step Into Discovery day. This year the date is especially significant. On April 12, 1955, Jonas Salk announced the discovery of the polio vaccine, forever transforming lives around the world.

Last year's inaugural event drew over a thousand people to the Institute and this year promises to bring even more supporters eager to experience the event.

The day will be filled with activities starting with the 5K Walk for Salk. Participants will start at the courtyard and walk through a coastal trek on Torrey Pines Road that concludes back on the Salk campus.

The fun doesn't end at the finish line. It continues at the Explore Salk open house featuring exclusive behind the scenes tours of science and research labs. The courtyard will be filled with informational booths and hands-on activities for children and adults, including special presentations by the Salk Education Outreach Program.

Step into Discovery supports the Salk's leading edge research and important education outreach programs including the Mobile Science Lab, High School Scholars and High School Science Day—dynamic programs that bring the excitement of scientific discovery to thousands of students and teachers throughout San Diego County.

For more information please visit: www.salk.edu/stepintodiscovery

Step into Discovery

walk for salk Where cures begin explore salk Tours, activities, talks

Axel Nimmerjahn

Innovative research earns Salk scientist EUREKA award

THE NATIONAL INSTITUTES OF HEALTH (NIH) have selected **Axel Nimmerjahn** for a highly selective EUREKA (Exceptional Unconventional Research Enabling Knowledge Acceleration) grant. The EUREKA awards provide support for innovative, high-risk biomedical research initiatives with the potential for achieving significant health impact.

An assistant professor in the Waitt Advanced Biophotonics Center, Nimmerjahn holds the Richard Allan Barry Developmental Chair. The award, totaling $1.38 million over four years, will support his goal of better understanding the relationship between spinal cord physiology and brain activity and behavior. Data from this research should foster development of new treatment and rehabilitation strategies for spinal cord injury, tumors, infections and neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and spinal muscular dystrophy.

The EUREKA program was conceived specifically to help scientists such as Nimmerjahn test new, innovative ideas or tackle major methodological or technical challenges. "EUREKA awards reflect the NIH's continued commitment to funding transformative research, even if it carries more than the usual degree of scientific risk," says NIH director Francis S. Collins, M.D., Ph.D. "The grants seek to elicit those 'eureka moments' when scientists make major theoretical or technical advances."

Nimmerjahn is only the second Salk scientist to be honored with this prestigious award. **Fred Gage**, a professor in the Institute's Laboratory of Genetics, was the recipient of a EUREKA grant in 2009.

Promising new research earns Salk scientist Career Development Award

THE JUVENILE DIABETES RESEARCH Foundation (JDRF) has given Salk scientist **Mark Huising** a five-year, $750,000 Career Development Award for his study on how a novel network of receptors in human islets receives and integrates molecular signals. In preclinical models, activation of these receptors has proven to actually prevent diabetes.

The goal of Huising's study, titled "Urocortin 3 Marks Mature Beta Cells and Prevents Diabetes," is to understand how this protection is accomplished. "Despite years of research," he says, "significant gaps remain in our understanding of the way the islet receives and integrates signals from a wide variety of sources. We envision that among these networks of signaling molecules plenty remain that are unknown and can lead to novel strategies to treat or cure type 1 diabetes."

Type 1 diabetes is a chronic condition in which the pancreas produces little or no insulin. Although the condition, which usually appears during childhood or adolescence, can be managed, it requires a daily juggling act. Food, exercise and insulin must be carefully balanced with scheduled blood sugar checks and insulin injections. A diagnosis of diabetes is also a major risk factor for later complications such as cardiac failure, kidney problems and lower limb amputations. To date, type 1 diabetes has no cure, making Huising's research all the more exciting.

The JDRF is the leading global organization funding type 1 diabetes research. It currently sponsors $530 million in scientific research in 17 countries and particularly seeks researchers who specialize in translational research. The primary purpose of the Career Development Award is to "attract qualified and promising scientists early in their faculty careers and to give them the opportunity to establish themselves" in areas pertinent to diabetes research. Career Development Awards are highly competitive and awarded to only a handful of people each year.

Mark Huising

Salk scientist receives grant for breast cancer research

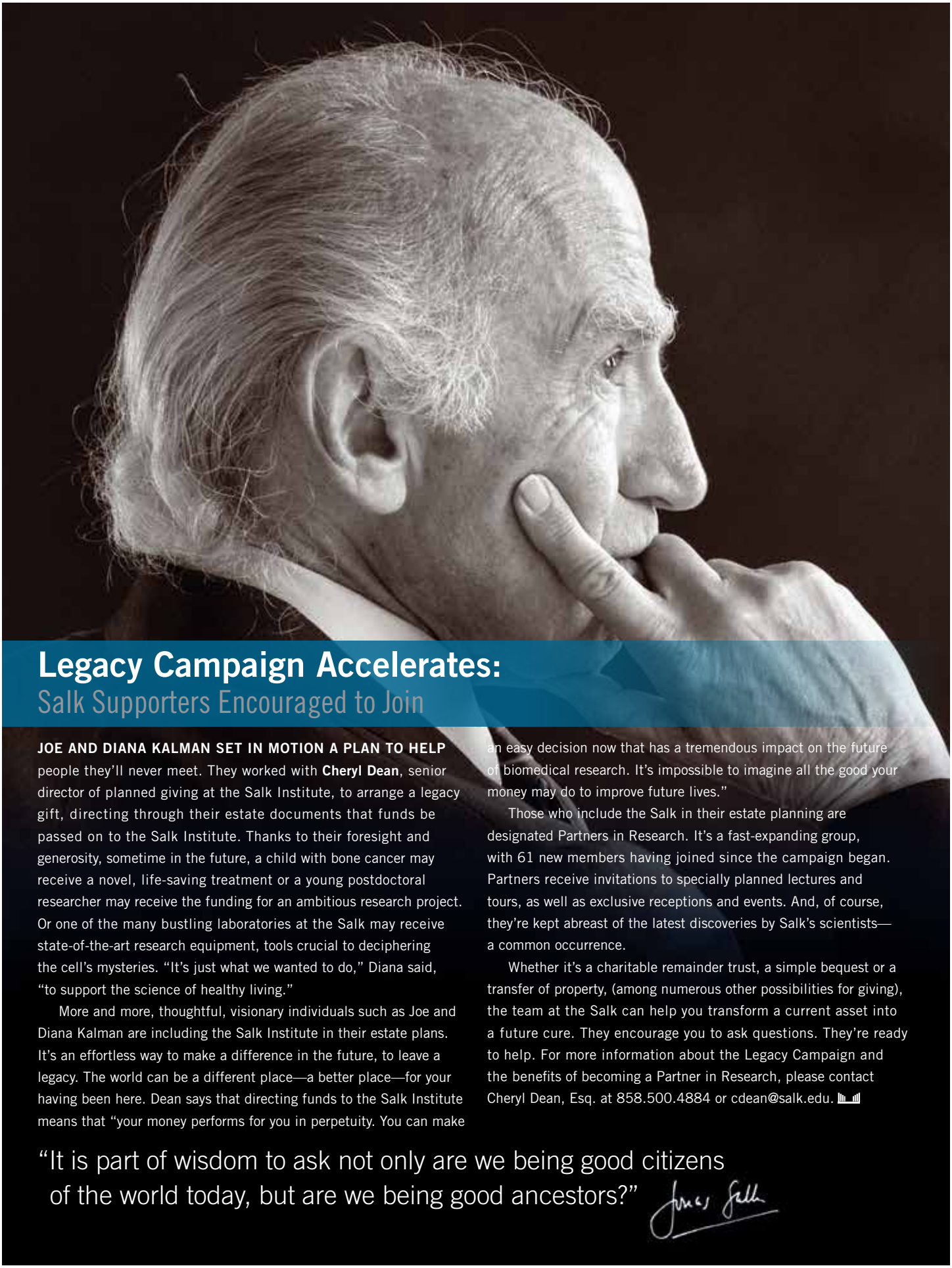
THE SUSAN G. KOMEN FOR THE CURE organization has awarded **Geoffrey Wahl,** professor in the Salk Institute's Gene Expression Laboratory, a $225,000 grant to support his breast cancer research.

Wahl, a Komen Scholar, has been working to identify characteristics in triple negative breast cancer cells. His research seeks to further our understanding about what makes triple negative cancers so dangerous and resistant to traditional therapies. He also hopes to discover new and better ways of eliminating these types of cancers.

The grant is part of $4.5 million in grants recently awarded to California research organizations by Susan G. Komen for research that examines the role that environmental issues play in the development of breast cancer.

Susan G. Komen for the Cure was founded in 1982 and has since invested more than $790 million in breast cancer research, making it the largest nonprofit, non-government cancer research-funding organization in the United States.

Geoffrey Wahl



Legacy Campaign Accelerates:
Salk Supporters Encouraged to Join

JOE AND DIANA KALMAN SET IN MOTION A PLAN TO HELP people they'll never meet. They worked with **Cheryl Dean**, senior director of planned giving at the Salk Institute, to arrange a legacy gift, directing through their estate documents that funds be passed on to the Salk Institute. Thanks to their foresight and generosity, sometime in the future, a child with bone cancer may receive a novel, life-saving treatment or a young postdoctoral researcher may receive the funding for an ambitious research project. Or one of the many bustling laboratories at the Salk may receive state-of-the-art research equipment, tools crucial to deciphering the cell's mysteries. "It's just what we wanted to do," Diana said, "to support the science of healthy living."

More and more, thoughtful, visionary individuals such as Joe and Diana Kalman are including the Salk Institute in their estate plans. It's an effortless way to make a difference in the future, to leave a legacy. The world can be a different place—a better place—for your having been here. Dean says that directing funds to the Salk Institute means that "your money performs for you in perpetuity. You can make an easy decision now that has a tremendous impact on the future of biomedical research. It's impossible to imagine all the good your money may do to improve future lives."

Those who include the Salk in their estate planning are designated Partners in Research. It's a fast-expanding group, with 61 new members having joined since the campaign began. Partners receive invitations to specially planned lectures and tours, as well as exclusive receptions and events. And, of course, they're kept abreast of the latest discoveries by Salk's scientists—a common occurrence.

Whether it's a charitable remainder trust, a simple bequest or a transfer of property, (among numerous other possibilities for giving), the team at the Salk can help you transform a current asset into a future cure. They encourage you to ask questions. They're ready to help. For more information about the Legacy Campaign and the benefits of becoming a Partner in Research, please contact Cheryl Dean, Esq. at 858.500.4884 or cdean@salk.edu.

"It is part of wisdom to ask not only are we being good citizens of the world today, but are we being good ancestors?" Jonas Salk

Elizabeth "Liz" Keadle

David F. Hale

Alan D. Gold

Salk Institute Board of Trustees Elects Three Visionary Business Leaders

THE SALK INSTITUTE IS PLEASED TO announce that Elizabeth Keadle, David F. Hale and Alan D. Gold have been elected to its Board of Trustees.

"Liz, Alan and David each bring outstanding records of entrepreneurial success and business expertise to Salk," said **Irwin M. Jacobs**, Chairman of the Salk Institute Board of Trustees. "We are greatly pleased to have them join our Board of Trustees."

Elizabeth "Liz" Keadle is an alumna of the Institute and worked in the Peptide Biology Laboratory with Salk scientist Wylie Vale while a student at UC San Diego. She started as a volunteer and was hired to work on several research projects, including Vale's work with corticotropin-releasing factor, which his group discovered in 1981. Her experience at Salk led to a career in the biotech business; she eventually joined Swedish biotech supply company Pharmacia AB, where she rose to key technical and business leadership positions. She also became involved in the launch of the local biotech company Invitrogen, which quickly grew to become the world's largest biotech research supply company and went public in 1999. Years later, it was renamed Life Technologies and in 2013 was sold to Thermo-Fisher for $13.6 billion. An ardent supporter of Salk science, Keadle is a longtime Symphony at Salk sponsor and created an endowment in support of the Vale lab. She recently established the Wylie Vale Chair as a lasting legacy to honor the late scientist; **Paul Sawchenko**, professor and head of Salk's Laboratory of Neuronal Structure and Function, currently holds the chair.

David F. Hale is chairman and chief executive officer of Hale BioPharma Ventures, LLC, a private company focused on the formation and development of biotechnology, specialty pharma, diagnostic, and medical device companies. He also serves as executive chairman of Biocept, Inc., a cancer diagnostic company working on the detection and analysis of circulating tumor cells. Previously, he was president and chief executive officer of CancerVax Corporation from October 2000 through its merger in May 2006 with Micromet, Inc., where he served as chairman until its acquisition by Amgen Inc. in 2012. Additionally, Mr. Hale is chairman of Santarus, Inc., and a founding director and chairman of Conatus Pharmaceuticals, Inc. He is a co-founder and chairman of numerous other companies. Mr. Hale currently serves on the board of directors of BIOCOM, which he co-founded, and the San Diego Economic Development Corporation. He is a former member of the board of the Biotechnology Industry Organization (BIO) and the Biotechnology Institute. He is a co-founder and a director of CONNECT, acts as chairman of the board of trustees of Rady Children's Hospital, and is a member of Rady School of Management Dean's Advisory Council.

Alan D. Gold is chairman and chief executive officer of Biomed Realty, a publicly traded REIT specializing in acquiring and managing laboratory properties for lease to the life science industry. Mr. Gold also served as president of BioMed's privately held predecessor, Bernardo Property Advisors, Inc. He was a co-founder and served as president and as a director of Alexandria Real Estate Equities, Inc. He was managing partner of GoldStone Real Estate Finance and Investments, a partnership engaged in the real estate and mortgage business. He also served as assistant vice president of Commercial Real Estate for Northland Financial Company, a full service commercial property mortgage banker, and as Real Estate Investment Officer–Commercial Real Estate for John Burnham Company, a regional full service real estate company. He currently serves on the Campanile Foundation Board supporting San Diego State University.

Tatyana Sharpee

Tatyana Sharpee receives NSF CAREER award

TATYANA SHARPEE, AN ASSOCIATE PROFESSOR IN THE Computational Neurobiology Laboratory, has received a CAREER award from the National Science Foundation (NSF) to fund upcoming research in her lab. The CAREER award supports faculty who exemplify the role of teacher-scholars through outstanding research, excellent education and the integration of education and research within the context of the mission of their organizations.

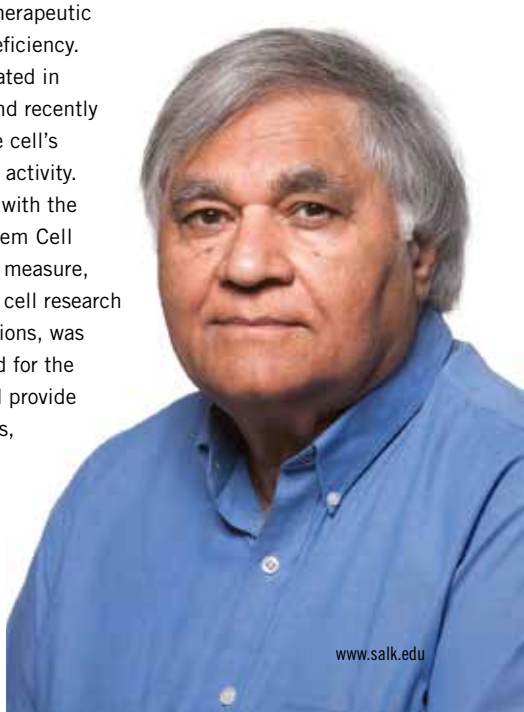
Sharpee will receive $453,000 over the next five years to fund her study "Characterizing feature selectivity and invariance in deep neural architectures." In an effort to help elucidate the principles that make robust object recognition possible, she will explore how an organism's neurons are able to demonstrate both "invariance," which produces a similar response to the same object even when observed from different viewpoints, and "selectivity," which requires different responses to potentially similar objects. The results of her study will help reveal the common principles of sensory processing in the brain and may ultimately lead to improved designs of artificial recognition systems, including sensory prostheses.

Salk scientist receives CIRM award

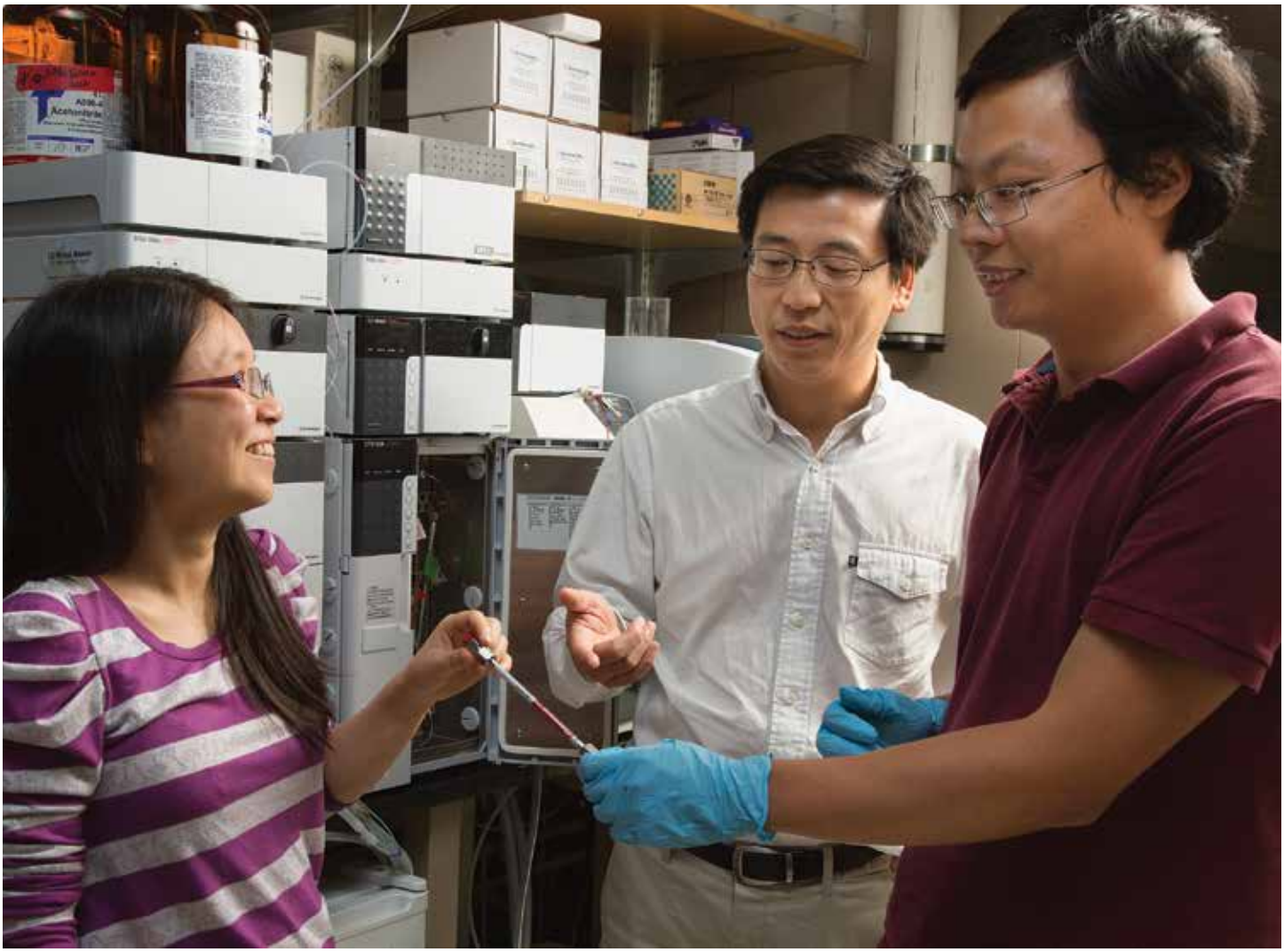
INDER VERMA, PROFESSOR IN THE LABORATORY of Genetics and American Cancer Society Professor of Molecular Biology, received a $2.3 million grant from the California Institute for Regenerative Medicine (CIRM) as part of its Early Translational IV Research awards. The program is designed to fund research that will help shift stem cell research from the laboratory to practical use with the development of new potential drug or patient therapies.

Verma, holder of the Irwin and Joan Jacobs Chair in Exemplary Life Science, is one of the world's leading authorities on the development of viruses for gene therapy vectors. He uses genetically engineered viruses to insert new genes into cells that can then be returned to the body, where they produce the essential protein whose absence causes disease. Verma and Salk colleagues developed a gene therapy vector, based on a stripped-down version of HIV that can deliver genes to non-dividing cells, which constitute the majority of the cells in our bodies. They have used this vector successfully to deliver the clotting factor gene to laboratory animals and to transfer a therapeutic gene to retinal cells to mice with an inborn deficiency. Verma's lab is also studying two genes implicated in familial breast cancer, BRCA1 and BRCA2, and recently demonstrated that their action is linked to the cell's division cycle and that BRCA1 regulates gene activity.

CIRM was established in November 2004 with the passage of Proposition 71, the California Stem Cell Research and Cures Act. The statewide ballot measure, which provided $3 billion in funding for stem cell research at California universities and research institutions, was overwhelmingly approved by voters, and called for the establishment of an entity to make grants and provide loans for stem cell research, research facilities, and other vital research.



Inder Verma



From left: Scientists Haiyan Ren, Lei Wang and Zheng Xiang

Salk scientists add new bond to protein engineering toolbox

PROTEINS ARE THE WORKHORSES OF CELLS, adopting conformations that allow them to set off chemical reactions, send signals and transport materials. But when scientists are designing a new drug, trying to visualize the processes inside cells or probe how molecules interact with each other, they can't always find a protein that will do the job they want. Instead, they often engineer their own novel proteins to use in experiments, either from scratch or by altering existing molecules.

As reported in *Nature Methods*, researchers in the lab of **Lei Wang** have developed a new tool for protein engineering: a way to add strong, unbreakable bonds between two points in a protein or between two proteins.

When a protein folds from a loose chain of amino acid building blocks into its active three-dimensional structure, bonds and chemical interactions naturally form between different parts of the chain to keep the structure assembled. Most are relatively weak, driven by the electrochemical charges of different amino acids. Stronger bonds, called disulfide bridges, occur between pairs of cysteines, one particular amino acid. But for protein engineers, either type of bond has had its own deficiencies. So linking two parts of a protein in a predictable and permanent way has been notoriously hard.

Wang and his team wanted to be able to add strong, irreversible bonds—called covalent bonds—to proteins to alter their shape, make them more stable or attach them to one another. So they began trying to create a new amino acid, different from the 20 that exist naturally.

They created dozens of possible amino acids and tested each one to see if it bound with just the right strength. After a series of tests, they settled on a newly created amino acid called p-2-fluoroacetyl-phenylalanine, or Fact, then designed three proteins using it in their sequences. Tests of the proteins showed that they formed a covalent bond with Fact.

"I think anyone who is working on proteins, or anything related to proteins, could make use of this new technology," says Wang. "It can provide a novel way to control proteins or design proteins to study basic biology."

Discovery Roundup

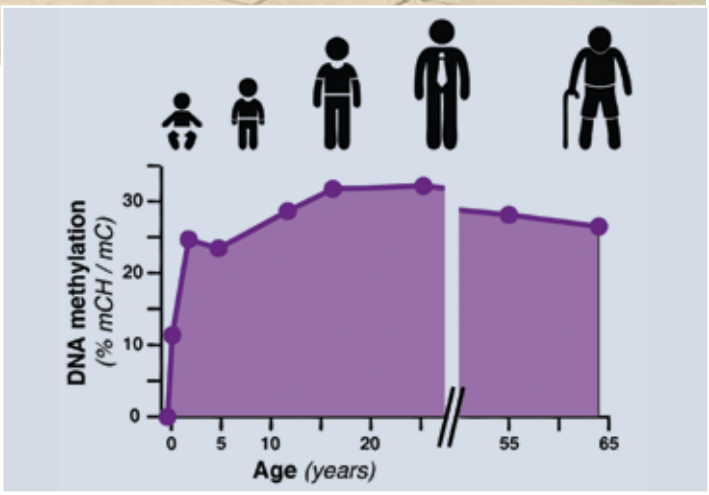
From left: Marga Behrens, Eran Mukamel, Terry Sejnowski, Joseph Ecker

Unique epigenomic code identified during human brain development

THE FRONTMOST PART OF THE BRAIN, THE FRONTAL CORTEX, PLAYS a key role in our ability to think, decide and act. The brain accomplishes all of this through the interaction of special cells such as neurons and glia. We know that these cells have distinct functions, but what gives them their individual identities? The answer lies in how each cell expresses the information contained in its DNA.

Changes in the epigenome, including chemical modifications of DNA, can act as an extra layer of information in the genome and are thought to play a role in learning and memory, as well as age-related cognitive decline. In a recent study, a team led by **Joseph R. Ecker** and **Terrence J. Sejnowski** showed that the landscape of DNA methylation, a particular type of epigenomic modification, is highly dynamic in brain cells during the transition from birth to adulthood, helping to understand how information in the genomes of cells in the brain is controlled from fetal development to adulthood.

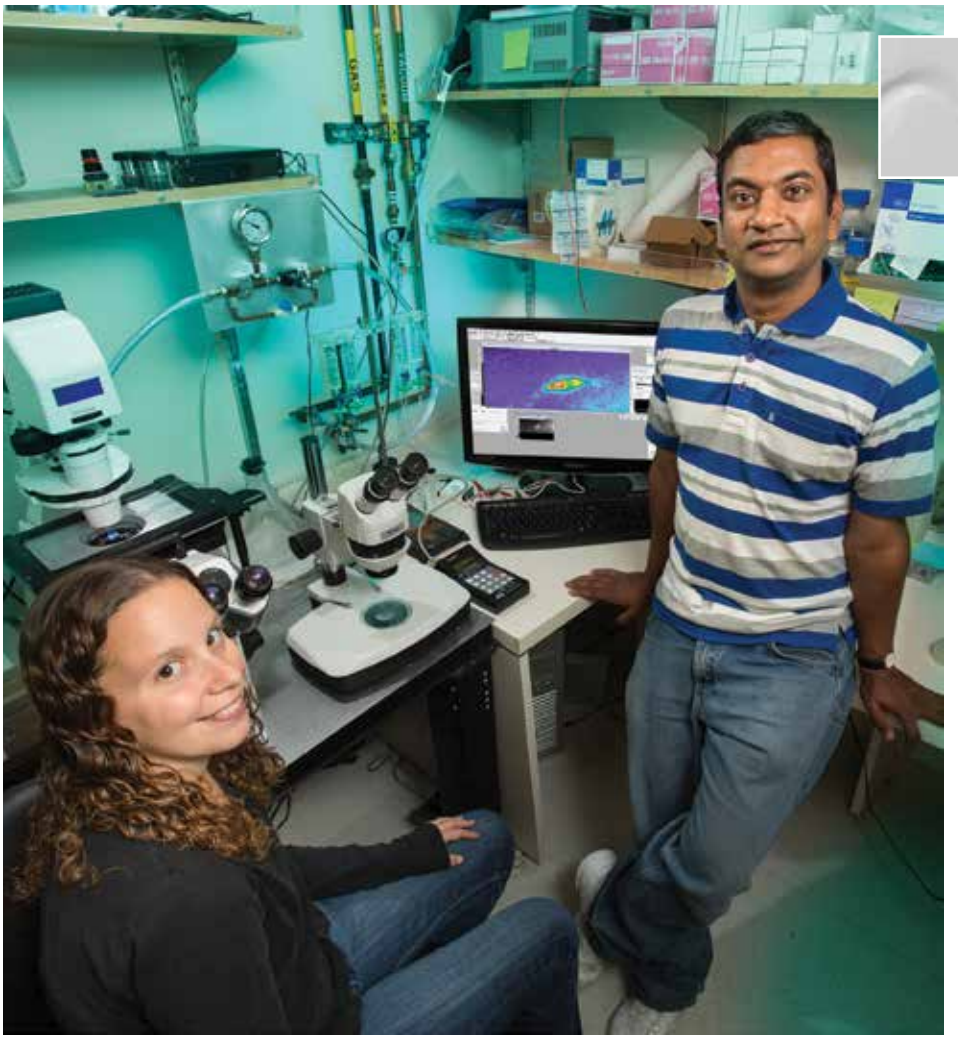
In the study, published in *Science*, the scientists found that the patterns of DNA methylation undergo widespread reconfiguration in the frontal cortex of mouse and human brains during a time of development when synapses are growing rapidly. They identified the exact sites of DNA methylation throughout the genome in brains from infants through adults and found that one form of DNA methylation is present in neurons and glia from birth. Strikingly, a second form of DNA methylation that is almost exclusive to neurons accumulates as the brain matures, becoming the dominant form of methylation in the genome of human neurons.



A new study by Salk researchers provides the first comprehensive maps of epigenomic changes in the brain known as "DNA methylation," a chemical modification of a cell's DNA that can act as an extra layer of information in the genome. The study provides clues as to how specific genes are regulated in fetal, juvenile and adult brain cells, and the findings form a critical foundation to explore whether changes in methylation patterns may be linked to human diseases, including psychiatric disorders.

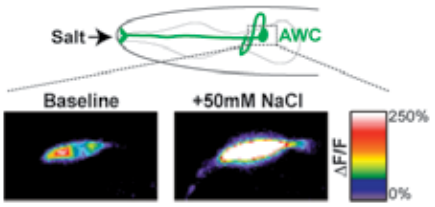
Image courtesy of Eran Mukamel, The Salk Institute for Biological Studies

These results help explain how the intricate DNA landscape of brain cells develops during the key stages of childhood. They also provide the first comprehensive maps of how DNA methylation patterns change in the mouse and human brain during development, forming a critical foundation for exploring whether changes in methylation patterns may be linked to human diseases, including psychiatric disorders.



Salk scientists Sarah Leinwand and Sreekanth Chalasani

Salk scientists found that insulin plays a role in mediating roundworms' perceptions and behaviors. This image shows a *C. elegans*, the species of roundworm the Salk researchers studied.



Top: An odor-sensing neuron (named AWC and shown in green) in the head of the worm was unexpectedly found to respond to salt in the environment. Bottom: Higher magnification images of this neuron before (left) and during (right) salt presentation. The neuron expresses a calcium indicator that causes the neuron to light up (indicated by the white and warmer colors) when it is active; the salt exposure significantly lit up this neuron, which revealed the complexity of the worm's sensory system.

Insulin plays a role in mediating worms' perceptions and behaviors

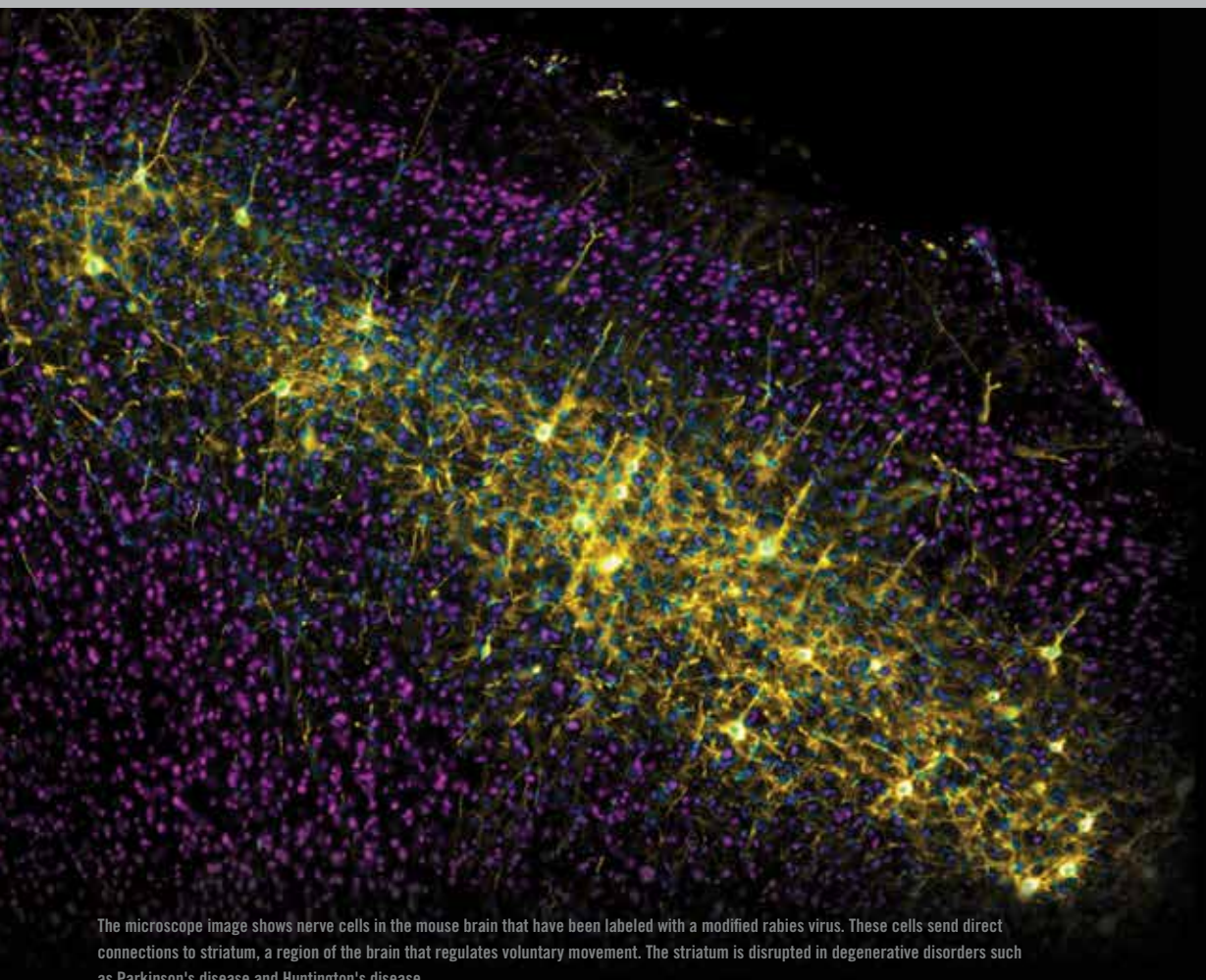
AS IMAGING TOOLS AND TECHNIQUES HAVE IMPROVED, SCIENTISTS have been building a detailed map of neural connections in the human brain, with the ultimate hope of understanding how the mind works. But in order to decode perceptions and behaviors, it is also necessary to know the routes that information takes in the brain. A recent study by **Sreekanth Chalasani**, in collaboration with UC San Diego doctoral student Sarah Leinwand, found a striking example of flexibility in neural circuitry and its influence on behaviors in worms.

In the study, reported in *Nature Neuroscience*, Chalasani's team built on established research on the roundworm *Caenorhabditis elegans* that had identified sensory neurons with distinct roles such as sensing temperature, pheromones, salt and odors. Imaging worms that expressed genetically encoded indicators in their neurons, which caused the cells to light up when active, they found the worms' olfactory sensory neuron lit up after exposure to an attractive but high concentration of salt. This revealed that more than one type of neuron is involved in processing sensory cues; previously it had been thought these were sensed only by single neurons.

Chalasani and Leinwand further showed that the olfactory neuron was crucial for the worm's movement toward salt within a certain concentration range and that a neuropeptide was being released by the salt-sensing neuron to shape the animal's behavior. Tracking olfactory neuron responses to high salt in worms missing specific genes, they found that worms lacking the gene for an insulin neuropeptide known as INS-6 did not respond to increases in salt. Restoring this peptide reinstated the animal's normal responses to high salt.

It was a big surprise that insulin was the main signaling molecule recruiting the olfactory neuron into a salt-sensing circuit. Neuropeptides had been thought to modulate neuronal function over many seconds to many minutes. But in this instance, it appears that the insulin is acting in less than a second to transfer information from the salt-sensing neuron to the neuron that normally responds to odor. Similar neuropeptide communication may create flexible neural circuits that mediate the behaviors of other animals and people, so Chalasani and Leinwand plan to investigate whether other fast neural circuit switches exist in worms, and if so, what signaling mechanisms they use.

Discovery Roundup



The microscope image shows nerve cells in the mouse brain that have been labeled with a modified rabies virus. These cells send direct connections to striatum, a region of the brain that regulates voluntary movement. The striatum is disrupted in degenerative disorders such as Parkinson's disease and Huntington's disease.

Photo courtesy of Nicholas Wall.

High-resolution mapping technique uncovers underlying circuit architecture of the brain

NEUROSCIENTISTS HAVE LONG SOUGHT TO map individual neuronal connections to see how they influence specific brain functions, but traditional techniques have proven unsuccessful. Using an innovative brain-tracing technique, a team led by **Edward Callaway** and Gladstone Institute investigator Anatol Kreitzer has found a way to untangle these networks. Their findings, reported in *Neuron*, offer new insight into how specific brain regions interconnect, while also providing clues to what may happen, neuron by neuron, when these connections are disrupted.

The researchers used a sophisticated tracing technique, pioneered by Callaway and known as the monosynaptic rabies virus system, to assemble brain-wide maps of neurons that connect with the basal ganglia, a region of the brain involved in movement and decision- making. The system uses a modified version of the rabies virus to "infect" a brain region, which in turn targets neurons connected to it. In their study, the investigators activated the tracer genetically, ensuring that it only turned on in specific neurons in the basal ganglia. This huge technological advance enabled them to follow just the networks that connect to particular kinds of cells in the basal ganglia from other parts of the brain.

Last year, Kreitzer and his team published research that revealed clues to the relationship between two types of neurons found in the basal ganglia, which act as opposing forces, with one initiating movement and the other inhibiting it. These neurons are also involved in decision-making, and dysfunctions in them are associated with addictive and depressive behaviors. The findings provided a link between the physical neuronal degeneration seen in movement disorders, such as Parkinson's disease, and some of the condition's behavioral aspects. But the study left unanswered questions about how other brain regions influence the function of these neuron types.

When the monosynaptic rabies virus system was applied in mouse models, the team could see specifically how sensory, motor and reward structures in the brain connected to the two neuron types. The results will help decode how this network guides the vast array of distinct brain functions, as well as how dysfunctions in different parts of this network can lead to different neurological conditions, eventually also suggesting solutions.

From left: John Young, Erin Lew, Greg Lemke, Anna Zagórska, John Naughton

Potent mechanism helps viruses shut down body's defense system against infection

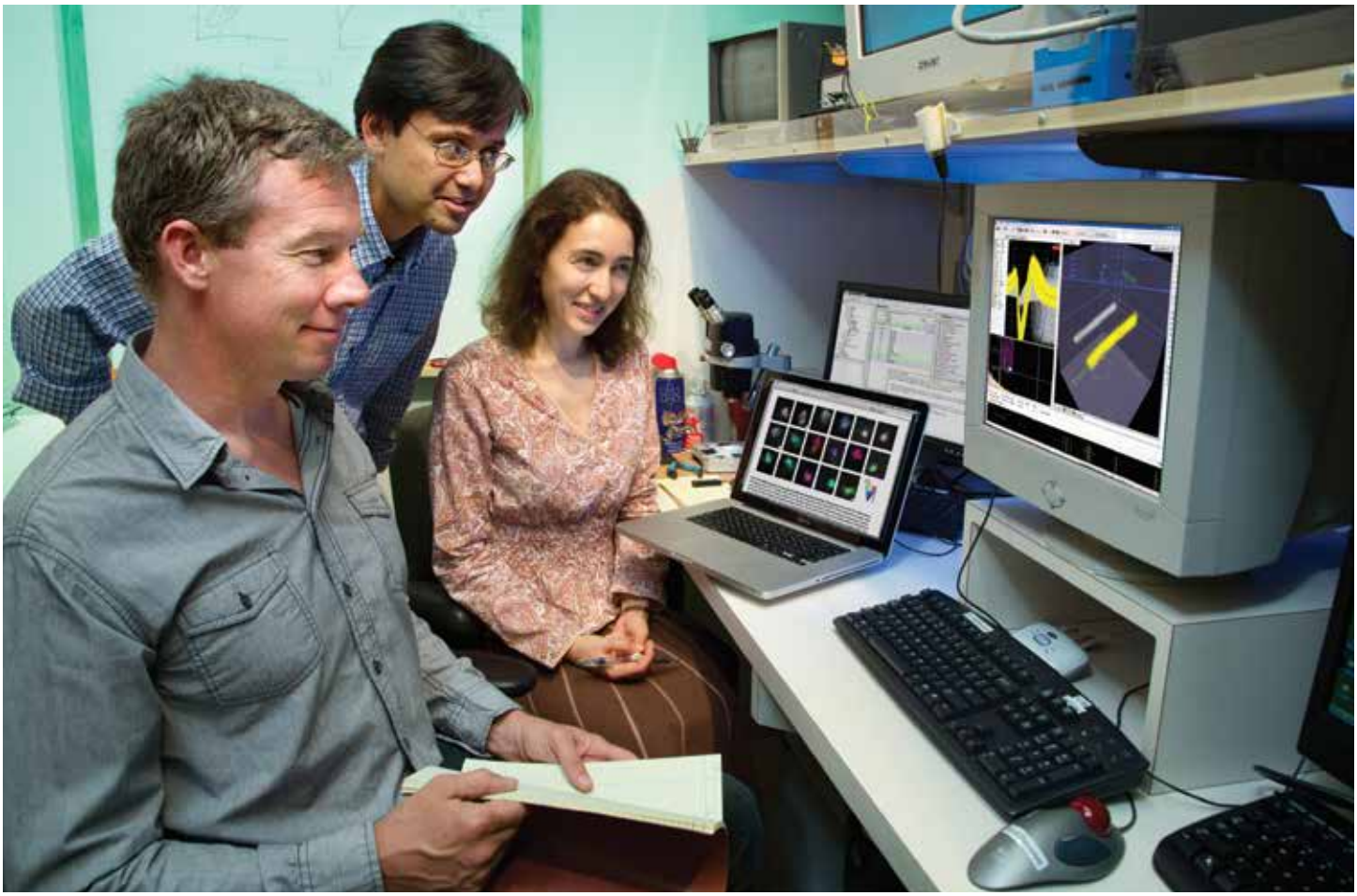
IN THE IMMUNE SYSTEM, TAM RECEPTORS are used by cells such as macrophages and dendritic cells to clean up dead cells. They are also central inhibitors of the body's innate immune response to bacteria, viruses and other pathogens.

As reported in *Cell Host and Microbe*, researchers in the labs of **John A.T. Young** and **Greg Lemke** have discovered that a substance called phosphatidylserine (PtdSer), found on the surface of enveloped viruses (viruses with an outer wrapping of a lipid membrane), binds to extracellular proteins and activates TAM receptors on immune cells. In dendritic cells, a type of immune cell that interacts with T and B cells to initiate the adaptive immune response, TAM receptor activation turns off a set of genes called interferons that play a key role in antiviral defense. The findings suggest a unique way in which TAM receptors contribute to the establishment of viral infection by disabling the interferon response. As a consequence, the interferon-stimulated defense genes are not turned on, rendering the target cell more vulnerable.

This is a previously unknown mechanism for enveloped viruses, which are very common, to inhibit the body's normal antiviral response. Since PtdSer exposure seems to be a general feature of enveloped viruses, the researchers say many different viruses may use the mechanism to counteract the antiviral response in cells with TAM receptors.

Understanding this mechanism will allow researchers to work on developing broad-spectrum antiviral drugs that prevent viruses from shutting down the interferon response in cells by blocking TAM receptor activation. Young and Lemke tested a small-molecule drug initially developed for anti-cancer therapy that does just that, and with other scientists around the country, they are now testing other small-molecule drugs that work, in large part, by blocking the virus's ability to activate TAM receptors, leaving the interferon-mediated antiviral response intact in such viruses as West Nile, dengue, influenza, Ebola, Marburg and hepatitis B. This is a completely novel approach, says Young, and if it works, it may prove effective at clearing enveloped viruses during the acute phase of infection and perhaps in chronic viral infections as well.

Discovery Roundup



From left: Scientists John Reynolds, Anirvan Nandy and Tatyana Sharpee

Scientists help explain visual system's remarkable ability to recognize complex objects

HOW CAN A HUMAN EYE FIGURE OUT twisted and looped letters, like those in the little security tests Internet users are often given on websites? The task is so complex, no one has been able to write computer code that translates these distorted letters the same way that neural networks can. That's why the test is used to distinguish a human response from computer bots that try to steal sensitive information.

Two studies by **Tatyana Sharpee** and **John Reynolds** published in *Neuron* and the *Proceedings of the National Academy of Sciences (PNAS)*, have demonstrated how complex a visual task decoding the test or any image made of simple and intricate elements actually is to the brain. Sharpee and Reynolds sought to figure out how a part of the visual cortex known as area V4 is able to distinguish between different visual stimuli even as the stimuli move around in space.

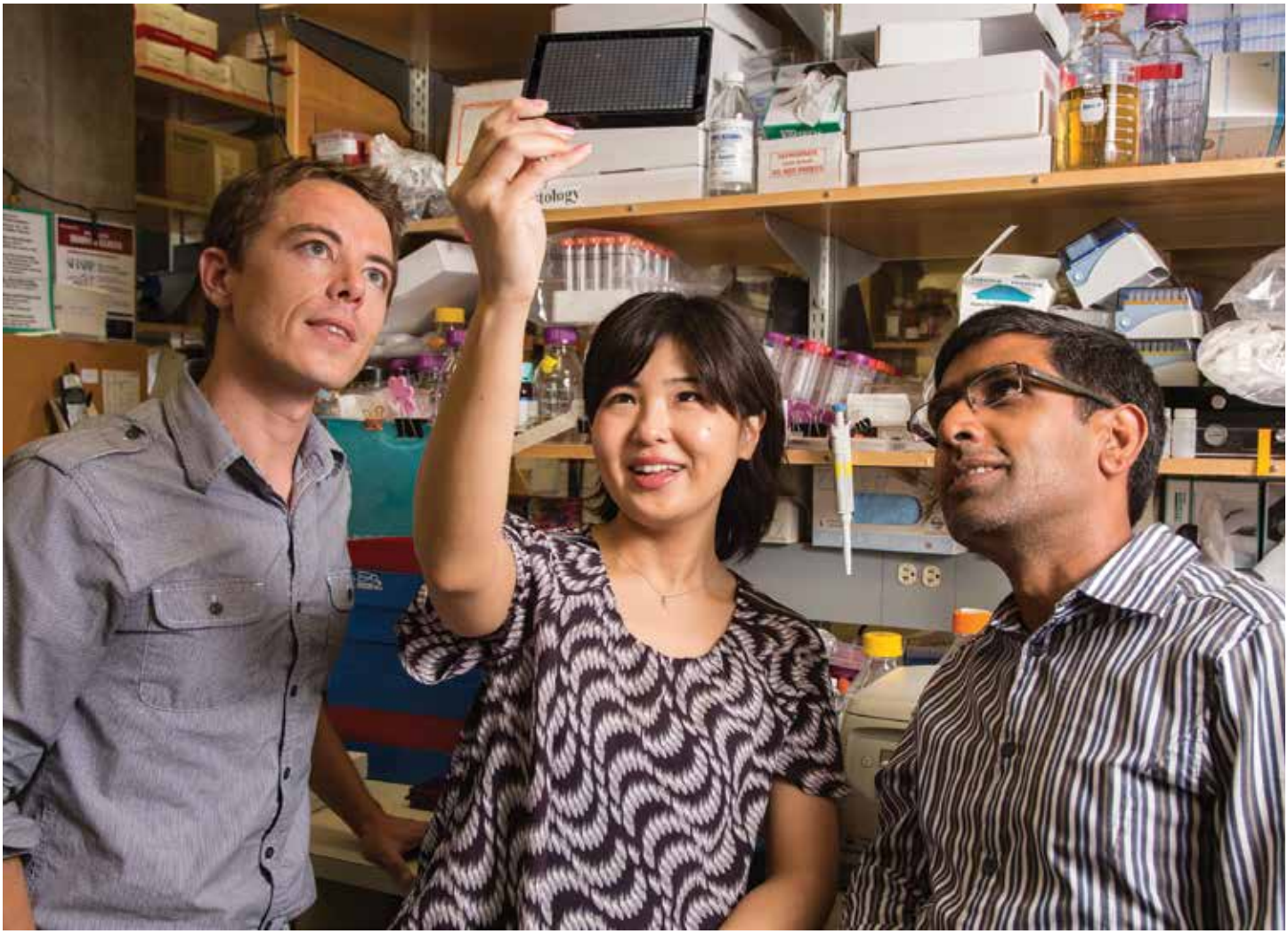
"Neurons in the visual system are sensitive to regions of space—they are like little windows into the world," says Reynolds. In the earliest stages of processing, these windows, known as receptive fields, are small, with access only to information within a restricted region of space.

Neurons in V4 have a larger receptive field that can also compute more complex shapes, such as contours.

Both studies investigated the ability of a neuron to recognize the same stimulus within its receptive field no matter where it is in space, or where it happens to fall within the receptive field. The researchers found that neurons that respond to more complicated shapes need that complicated curve to be in a more restricted range for them to detect it and understand its meaning. On the other hand, neurons in V4 tuned to recognize simpler shapes don't care where the stimulus they are tuned to is as long as it is within their receptive field.

The results indicate that there is a deeper mystery to be solved, Reynolds says. "What we have done is unpack part of the machinery for achieving integration of parts into wholes."

> "Neurons in the visual system are sensitive to regions of space—they are like little windows into the world."
>
> – JOHN REYNOLDS



From left: Scientists Ludovic Mure, Megumi Hirota and Satchin Panda in Salk's Regulatory Biology Laboratory.

Drug blocks light sensors in eye that may trigger migraine attacks

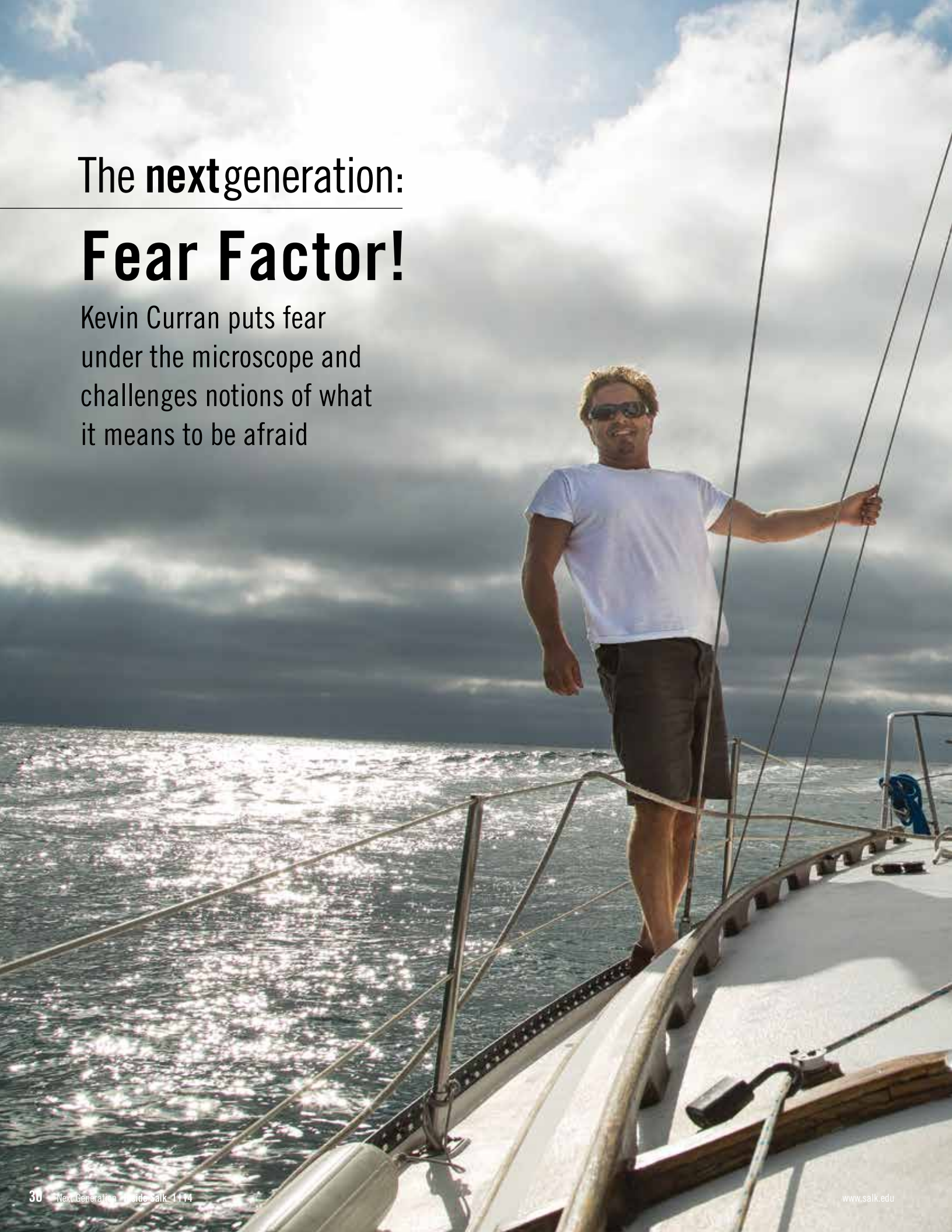
SCIENTISTS HAVE KNOWN FOR NEARLY A CENTURY THAT HUMANS and animals can sense light even when they can't see, and more than ten years ago, **Satchidananda Panda**'s lab discovered that melanopsin, a receptor found in neurons connecting the eyes and brain, is responsible for sensing light independently of normal vision. Since then, researchers have determined that the receptor is vital for maintaining sleep cycles and other circadian rhythms in those with healthy vision, constricting the pupil of the eye in bright light and potentially exacerbating the light-sensitivity associated with migraines. While melanopsin senses light for these non-vision purposes, closely related receptors—rhodopsin and cone opsins—provide vision-forming information to the brain.

In a recent study published in *Nature Chemical Biology*, Panda reported that a new molecule that selectively blocks light-sensitive receptors in the eyes could help people with migraines or circadian rhythm imbalances without affecting normal vision.

Scientists already know of one class of compounds, retinoids, which interact with opsins, but they are non-specific and bind to melanopsin, rhodopsin and a handful of other receptors in the body, causing widespread side effects. Panda wanted something more specific, so for ten years, his group, in collaboration with scientists at the pharmaceutical company Lundbeck, has attempted to find chemical compounds that specifically shut off melanopsin in animals.

In their latest search, Panda and his collaborators turned to Lundbeck's library of compounds. A team at Lundbeck tested whether each chemical from the library turned off melanopsin; several appeared to block its function. None looked like retinoids, and the chemicals, dubbed opsinamides, also showed no interaction with rhodopsin or other opsins. To make sure they were specific to melanopsin and to determine whether they would have a physiological response in addition to binding to melanopsin, Panda's group next looked at whether the drugs affected pupillary constriction in mice. The results showed that the drugs stop melanopsin from signaling the brain when the eyes are exposed to bright light.

The compounds require further optimization in anticipation of clinical testing but are extraordinarily useful for research and as leads in the discovery process.



The **next** generation:

Fear Factor!

Kevin Curran puts fear under the microscope and challenges notions of what it means to be afraid

FOR A MAN WHO STUDIES FEAR FOR A LIVING, Kevin Curran exhibits little of it in his everyday life. The moment he leaves his work at **Sreekanth Chalasani's** Molecular Neurobiology Laboratory at the Salk, he's likely sailing the open ocean, scuba diving or spearfishing. With a wide grin, the postdoctoral researcher readily admits, "I'm an outdoorsy person."

Inside the lab, however, Curran throws himself into challenges of a different kind. "Kevin chose a project that was difficult," Chalasani says, "but in a short time has made a ton of progress. In fact, we are currently writing up the results for what should be a very exciting publication."

The project that Curran adopted is identifying specific molecular pathways that modulate threat avoidance behavior, using *Caenorhabditis elegans*, a nematode, for his subject. Serotonin signaling is markedly well conserved between *C. elegans* and *Homo sapiens*, making it an ideal candidate for focused research. While previous studies acknowledge the link between serotonin circuitry and fear/anxiety behavior, less is known about how serotonin actually modulates neural circuits. This is what Curran is working diligently to identify.

His research has very real application for humans. While the ability to respond appropriately to a potentially harmful situation is critical to an organism's well-being, the behavior can go awry. In humans, for example, malfunctions in this neurobiological process can lead to such debilitating diseases as panic attacks and post-traumatic stress disorder, conditions becoming ever more prevalent in today's fast-paced and competitive society. It's estimated that the cost of treating anxiety disorders in the U.S. exceeds $42 billion a year.

"Actual fear has a tangible stimulant: a person sees something threatening, and the body has an appropriate response, often characterized as fight or flight," Curran explains. "Anxiety, on the other hand, does not have a tangible stimulant, but the body reacts in a similarly heightened manner."

Outward symptoms such as shortness of breath, palpitations and dizziness often lead to insomnia, fatigue and physiological stress across multiple organ systems. "We are seeking to learn which novel pathways are active in *C. elegans* during avoidance behaviors and which chemicals affect those behaviors, with the goal of duplicating our findings in mammalian species."

The research so far has produced some very interesting results, says Chalasani. "In lab experiments we often forget how animals live in the natural world, the challenges they face and the strategies they use to survive and reproduce," he says. "Kevin's unique insights have changed the way we approach this project and are instrumental in us studying some very fundamental behavior. His project is one of the first to show that worms might have a rudimentary form of a very complex (likely emotional) fear-like behavior."

> **“[Kevin’s] project is one of the first to show that worms might have a rudimentary form of a very complex (likely emotional) fear-like behavior.”**
>
> **– SREEKANTH CHALASANI**

In May, Curran was the recipient of the Alumni-Faculty Fellowship, an award that will enable him to conduct a drug screen to further identify which molecular pathways modulate threat avoidance behavior.

Out in the natural world, Curran tests his own ability to respond appropriately to potentially harmful situations again and again, especially on the ocean. While completing his Ph.D. at the University of Washington, he took sailing lessons and upon completion, bought a 30-foot keel hull sailboat named Alizé, French for “trade wind.”

As a personal challenge, he set out on a four-month journey exploring the Alaskan coastline. “I didn’t have a job lined up, so whenever I landed in a port with an Internet café, I’d check the job listings,” he says. “Eventually I came across one for Dr. Chalasani’s lab. I knew him from a presentation he’d given when I was a grad student. His talk was awesome! So I applied for the position. Luckily, Dr. Chalasani remembered me too and invited me down.”

With the winds having landed him at the Salk Institute, Curran now lives aboard his sailboat in the San Diego harbor. “It’s a whole mix of people living on my dock,” he says. “I like the fact that they’re from all walks of life; the unifying thread is that we all love boats.”

After his usual early morning run, it’s off to the lab, where Curran enjoys a vibrant and productive working relationship with “Shrek,” as Chalasani is affectionately known. “He has an amazing capacity to generate ideas,” Curran says of his mentor. “His enthusiasm never wanes.”

When work is finished and the setting sun is polishing the marina’s gleaming white hulls, Curran eagerly returns to the ocean. And while others are stopping at the store to pick up something for dinner, Curran is donning his wetsuit and diving into his own grocery. “I spearfish for sheepshead, kelp bass, rockfish,” he says. “In season, I catch California spiny lobsters with a couple of the other guys here.” Delivering his trademark grin that knows no fear, he says, “It’s a good life!”

Salk Science Leads to Discoveries.

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Scientific discovery at the Salk Institute is made possible through annual contributions from individuals, organizations, corporations and foundations. Your support will accelerate the pace of breakthroughs in understanding disease and pave the way to new drug therapies. To learn more, please visit **www.salk.edu/support** or call 858.453.4100 x1405.

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Unrestricted gifts, in any amount, provide funding where it is most needed and allow our scientists to conduct critical early-stage research. Contributors up to $2,500 receive *Inside Salk* magazine and invitations to annual events.

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The Salkexcellerators program is focused on making Salk science accessible to a younger generation of business professionals, entrepreneurs, and volunteers. Donors receive *Inside Salk* magazine and invitations to private receptions and lectures with Salk's renowned scientists. Salkexcellerators meet in La Jolla and New York City, and engagement ranges from $500 to $5,000.

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President's Club donors fulfill a central role for the Institute and provide the flexibility to respond to Salk's greatest needs. Contributors of $2,500 – $25,000 enjoy unique opportunities to interact with our scientists in the lab and receive Salk publications.

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Chairman's Circle visionary donors support the Institute's mission with unrestricted annual gifts of $25,000 and above. Their generous support fills a vital need for the Institute by providing the world's finest minds in science with the resources to pursue discoveries at the frontier of human knowledge. Donors are invited to exclusive lab tours and special events with senior researchers that provide opportunities to discuss specific areas of interest. Donors receive Salk publications and individual reports on the impact of their gifts.

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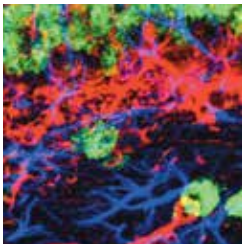
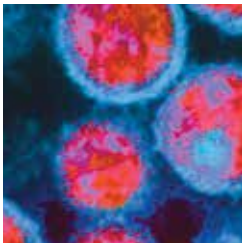
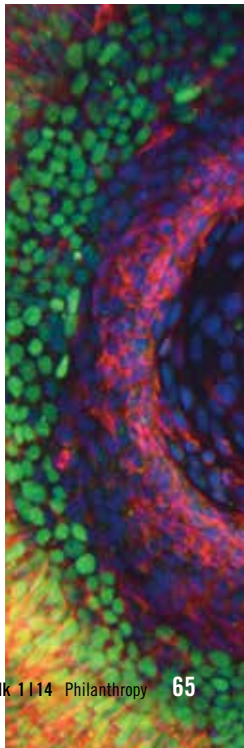
If you have a special interest in one of Salk's areas of research, such as cancer, aging, diabetes, neuroscience, genetics, vision or plant biology, you may designate your gift to support investigations in that field. You may also elect to support the work of a young scientist with a fellowship or Salk's education outreach programs. You will be privy to exclusive updates and invitations.

PARTNERS IN RESEARCH

Salk's legacy society, Partners in Research, welcomes those who have included Salk in their estate plans. Charitable gift planning is a powerful way of ensuring your legacy lives on, and it can maximize tax and other financial benefits to you, your family, and the Institute. Partners in Research members receive special communications and are invited to events throughout the year.







salk women & science
Where cures begin.

Clodagh O'Shea


Ursula Bellugi

Women & Science events entertain and inspire

THE SALK INSTITUTE'S WOMEN & SCIENCE program continues to attract an ever-growing audience, and in recent months presented two thought-provoking events.

On July 23, **Ursula Bellugi**, professor and director of the Laboratory for Cognitive Neuroscience, gave a talk titled "Williams Syndrome: A Model for Linking Genes, Neural Systems and Social Phenotypes." Following an introduction by **Catherine Rivier**, professor emerita of the Clayton Foundation Laboratories for Peptide Biology, Bellugi explained to a crowd of approximately 60 female business and community leaders how she works with individuals with Williams syndrome to further understand the ties between neural and cognitive functions. Those with this rare genetic disorder, though developmentally disabled, possess remarkable verbal abilities and facial recognition skills. Because the genetic deletion is so tiny—of the 20 or so genes missing, just three to six create the cognitive and social effects typical of the condition—Bellugi and her colleagues are beginning to identify the very genes and neural pathways that help determine language and social skills.

Then, on November 6, a crowd of more than 80 gathered to hear **Clodagh O'Shea** speak about her work designing synthetic viruses to combat cancer. During her introduction, **Beverly Emerson**, holder of the Edwin K. Hunter Chair in the Regulatory Biology Laboratory, described the iconoclastic O'Shea as a cross between Grace Kelly, bareknuckle boxer John Sullivan and risk-taking adventurer Edmund Hillary. O'Shea embodied all three as she spoke passionately of her search for a sophisticated anticancer tool that could target tumors without causing the bodily harm of current cancer treatments. In her talk, titled "Designing Viruses that Seek and Destroy Tumor Cells," O'Shea explained how she and her lab are using the common cold virus, the adenovirus, to create synthetic viruses that can act like guided missiles, specifically infecting and replicating in tumor cells before bursting them apart to release thousands of viral progeny. These progeny then seek out and destroy distant metastases while overcoming all possible resistance.

The 2013 Women & Science outreach events have been generously underwritten by Union Bank and by the wealth advisory firm Hoyle-Cohen. For more information on the Women & Science program, contact **Betsy Reis**, director of donor relations, at 858.453.4100 x1426 or by email at breis@salk.edu

From left to right: Ursula Bellugi, Ph.D., Diana Vines, Pamela Ombres

Back to Basics: Spicing up Alzheimer's drug discovery

Back to Basics
LECTURE SERIES at the SALK INSTITUTE

» Webextra: To view the video
www.salk.edu/jan14/video1/

Marguerite Prior

SALK SUPPORTERS GATHERED ON OCTOBER 2 FOR THE latest Back to Basics lecture. Titled "Spicing up Alzheimer's Drug Discovery," it featured **Marguerite Prior**, a research associate in the Cellular Neurobiology Laboratory of **David Schubert**.

In her talk, Prior described how the cognitive decline that characterizes Alzheimer's disease results from the progressive loss of nerve cells in areas of the brain and how Schubert's lab has developed a novel drug discovery scheme that uses living neurons grown in laboratory dishes to test new synthetic compounds for effectiveness at protecting brain cells.

Using this strategy, Schubert's team has identified a potent compound, J147, that shows strong therapeutic potential for Alzheimer's by slowing the disease's progression and rapidly improving memory.

The audience was riveted throughout Prior's presentation, and an animated question and answer session followed.

Prior discusses her research with a Back to Basics attendee.

salkexcellerators

keep up with cutting-edge science

Salkexcellerators are professionals from varied sectors in San Diego and New York City who share a commitment to supporting scientific discovery at the Salk Institute. Members receive invitations to social events throughout the year featuring talks by Salk scientists about some of the most critical health-related issues of our time. Through their support, the Salkexcellerators fund an annual fellowship for talented postdoctoral scholars, like Jonathan Nassi, Ph.D., this year's fellowship recipient.

Two recent events brought together members for thought-provoking evenings with three of the Institute's most innovative faculty, who presented their latest findings.

New York

On October 30, the New York Salkexcellerators gathered at the private Norwood Club in Chelsea for a special evening with **Reuben Shaw**, an associate professor in Salk's Molecular and Cell Biology Laboratory. In his talk, "Cancers Are Addicted to Sugar: Targeting Their Demise with Metabolism Drugs," Shaw shared findings from his lab that could lead to new treatments for cancer using existing diabetes drugs.

Reuben Shaw and New York Salkexcellerators Mark Herschberg and Mitzie Perdue

Salkexcellerators from left to right: George and Greg Katakalidis, Michael and Devra Doiron, Mary Katakalidis

The San Diego Salkexcellerators gathered at the Institute November 13 to hear **Janelle Ayres**, an assistant professor in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis, and **Satchidananda Panda**, an associate professor in the Regulatory Biology Laboratory, speak about two different aspects of diet and health. The evening's program, "Metabolism and Microbial Balance," highlighted discoveries that have changed our thinking about combating disease through eating patterns and stabilizing our immune response with healthy bacteria.

San Diego Salkexcellerators

For more information about joining the Salkexcellerators at events like these year round, contact Megan Shockro at 858-453-4100, ext. 1405, or visit www.salk.edu/salkexcellerators.

PEDAL THeCAUSE.

THE SALK INSTITUTE WAS STRONGLY REPRESENTED in the first annual Pedal the Cause San Diego—a weekend cycling event that took place October 26 and 27 to benefit San Diego's three cancer centers: the Salk, UC San Diego's Moores Cancer Center and the Sanford-Burnham Medical Research Institute. In addition to helping strengthen the bonds between the cancer centers on the Torrey Pines Mesa, the Salk Cancer Center team raised more than $18,000 for research. The Institute is most grateful to everyone who invested in cancer discovery by sponsoring Team SCC.

Team Salk Cancer Center, from left: Henry Juguilon, Mara Sherman, Nicholas White, Michael Sullivan, Maryam Ahmadian, John Reynolds, Sam Pfaff, John Young, Geoff Wahl, Tony Hunter, Mathew Lewsey, Kevin Waldrop

Insider's View

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

YEARS AGO, STANFORD PHYSICIAN DR. JAMES FRIES PROPOSED AN IDEA WHICH HAS been deemed the "compression of illness" hypothesis. According to Fries, the best strategy both for healthy living and lowering medical costs is to delay the time of onset of chronic disease: in other words, slow down the appearance and progression of chronic illness.

When Fries proposed this idea, it was highly controversial. Critics of the strategy suggested that if chronic illness appeared early, longevity would be shortened and overall healthcare costs would be lower, even though the outcome would be worse for the individual patient. In other words, the healthcare costs of dying of a heart attack at age 40 might be lower than living to age 75 with heart failure that occurs at age 65.

Yogi Berra supposedly once said: "In theory there is no difference between theory and practice. In practice, there is!" In this case, subsequent studies appear to validate Fries's theory. Interventions that slow or delay the onset of a chronic illness appear to lead to lower overall healthcare costs incurred by that patient. Of course, addressing the costs of treating chronic illness is still an enormous challenge—one that has become a major concern in recent decades. Unfortunately, chronic illness requires chronic treatment.

Today, formerly acute illnesses, including infection, heart disease and many forms of cancer, have been transformed by medical science into chronic diseases. According to some estimates, Medicare patients with five or more chronic illnesses consume 75 percent of the costs of this important federal program. Common logic dictates that bending the cost curve requires more cost-efficient methods of care for arthritis, heart disease, cancer, stroke, depression, dementia, Parkinson's disease and other chronic illnesses.

The Salk Institute has a lot to offer in addressing this issue. As the feature article on the Campaign for Salk's Healthy Aging Initiative in this issue of *Inside Salk* explains, deciphering how cells change at the molecular level as we get older will help us bolster our ability to fend off age-related illnesses. Similarly, our Genomic Medicine Initiative was also designed to tackle chronic illnesses that undermine our health as we age. The Helmsley Center for Genomic Medicine, established by the largest gift in the Institute's history, has at its core the focus on understanding chronic inflammation and the role that our immune system plays in aging and the development of chronic disease.

Salk scientists believe that there is a common thread to chronic illness and the aging process: chronic, low-grade inflammation. When our body encounters something it considers 'foreign,' like a bacterium, it sends signals to the genome of immune cells that participate in fighting the foreign invader. Unfortunately, as Salk scientists are discovering, sometimes what gets turned on fails to get fully turned off, which can lead to so-called autoimmune diseases, like rheumatoid arthritis and type I diabetes. In addition, there may be other forms of chronic inflammation that keep the immune system activated, albeit at a lower level, and this form of chronic immune response may play a previously undiscovered role in chronic illness as well as the aging process.

Finding the keys to chronic illness will reduce the burden of healthcare costs and at the same time help us stay healthy longer. By 'compressing' illness, Salk science helps people live their lives to the fullest.

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Salk **Calendar**

JANUARY

22 **The Art and Science of Cuisine**
26 **Salk Science & Music Series**

FEBRUARY

13 **Partners in Research Luncheon**
23 **Salk Science & Music Series**
26 **San Diego Salkexcellerators**

MARCH

16 **Salk Science & Music Series**
18 **Women & Science Reception**
25 **Back to Basics**
26 **San Diego Salkexcellerators**

APRIL

12 **Second Annual Step into Discovery**

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The Art and Science of Cuisine

will take place at the Institute on
Wednesday, January 22, 2014.

For more information visit the website at www.salk.edu/cuisine/

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