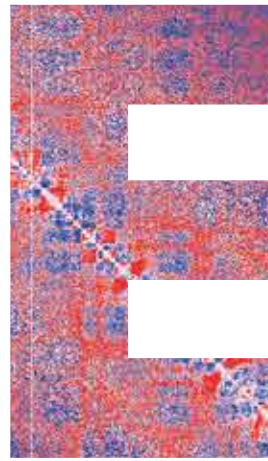
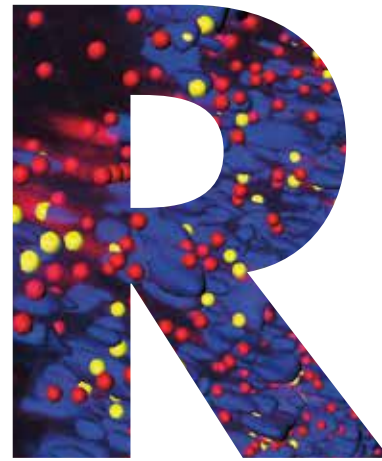


In this issue: 2015 Donor Honor Roll

InsideSalk

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Salk Institute 12|15



PHILOSOPHY

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December 2015

Inside Salk



One on one with...Ed Callaway



Next generation: Conchi Estarás



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CALENDAR

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Dear Friends,

STAR PERFORMERS ON STAGE OR SCREEN MAY RECEIVE THE applause, but no complex production comes to fruition without an extensive team of skilled individuals working behind the spotlight. So it is with science.

While notable discoveries in Salk laboratories make headlines, enabling these achievements is the provenance of our scientific core facilities. We like to call them “idea factories” because they provide the cutting-edge technology and expertise that allow our scientists to perform the novel experiments they envision. In this issue they’re getting a well-deserved turn in the spotlight.

Also receiving recognition are three Salk faculty members who have been awarded chairs. **John Reynolds** is the inaugural holder of the Fiona and Sanjay Jha Chair in Neuroscience. **Ursula Bellugi** will hold another new chair, the Salk Founders’ Chair. And **Alan Saghatelian** has been named holder of the Dr. Frederik Paulsen Chair.

Discoveries at the Institute continue to pour forth at an impressive pace. **Sam Pfaff** and his team have developed a technique that lets researchers watch—for the first time—motor neuron activity in the spinal cord. **Terrence Sejnowski**’s group has linked a particular receptor in the mouse brain to aberrant behavior. Research with cellular proteins in **Martin Hetzer**’s lab is revealing how age affects organs in strikingly different ways. And **Björn Lillemeier** and his team are uncovering ways to harness the immune system.

Other notable findings at the Institute are advancing our understanding of cancer. **Geoff Wahl**’s lab identified a key molecular mechanism underlying deadly behavior in some breast cancers. A group led by **Jan Karlseder** showed how disabling a chromosome’s telomeres could



William Brody

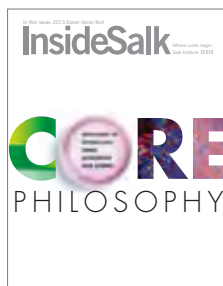
aid chemotherapy. **Reuben Shaw**’s team, in collaboration with scientists at Sanford Burnham Prebys Medical Discovery Institute, developed a drug that blocks cancerous cells from obtaining nutrients. And novel research in **Clodagh O’Shea**’s lab is paving the way for cancer-selective viral therapies.

Critical to all these accomplishments are Salk’s loyal donors and we take pleasure in honoring them in this issue in our annual Donor Honor Roll. Much like the go-to experts in our core facilities, donors are part of the team behind the scenes who make revolutionary science possible.

This is my last message as President of the Salk Institute, as I will be stepping down at the end of December. It has been my privilege to work among such prodigious talent. Salk is in good shape and in good hands, and the future looks bright indeed. I wish you all well. 🙏

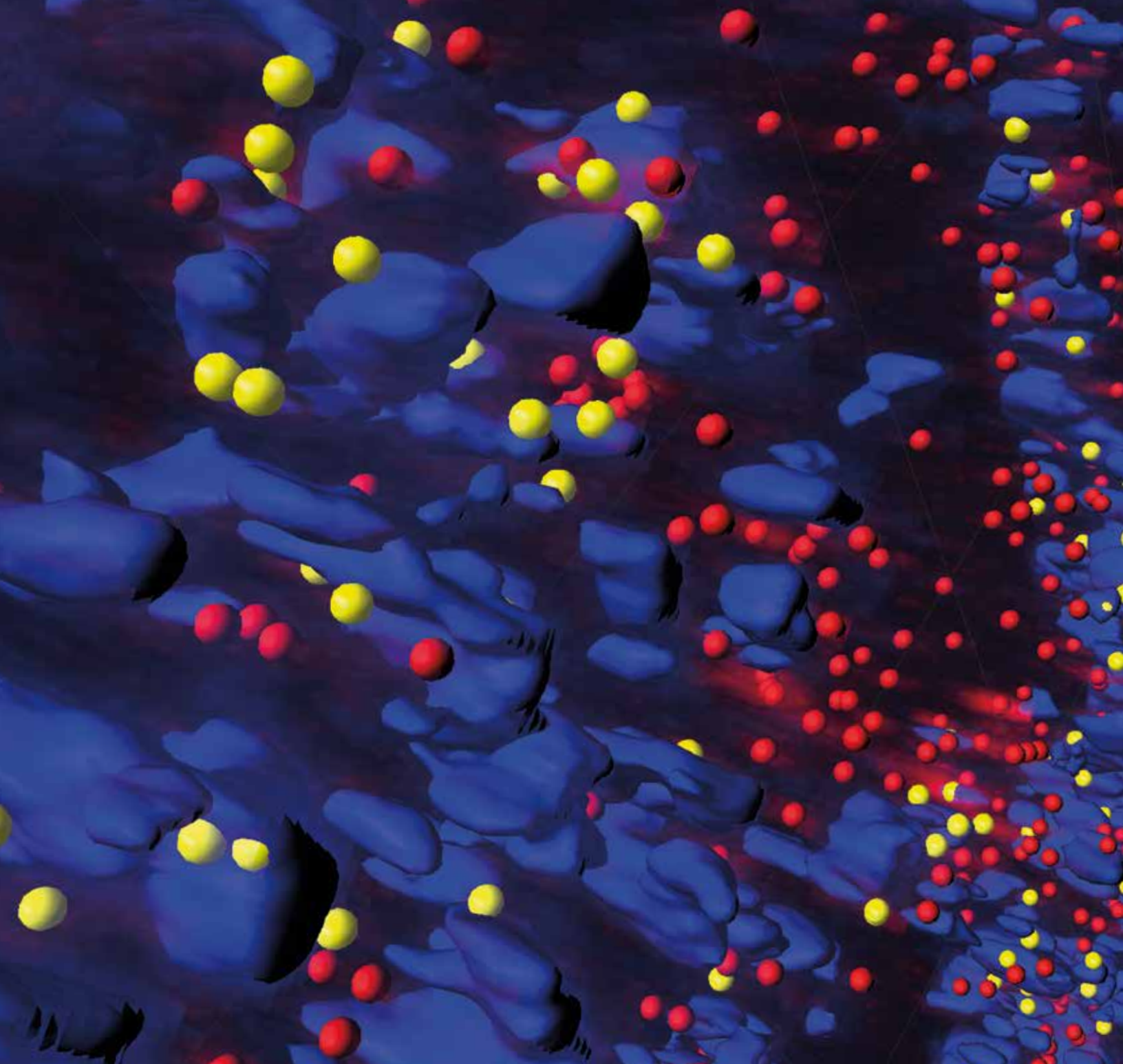
A handwritten signature in black ink that reads "William R. Brody". The signature is fluid and cursive.

William R. Brody, MD, PhD
President, Salk Institute
Irwin M. Jacobs Presidential Chair

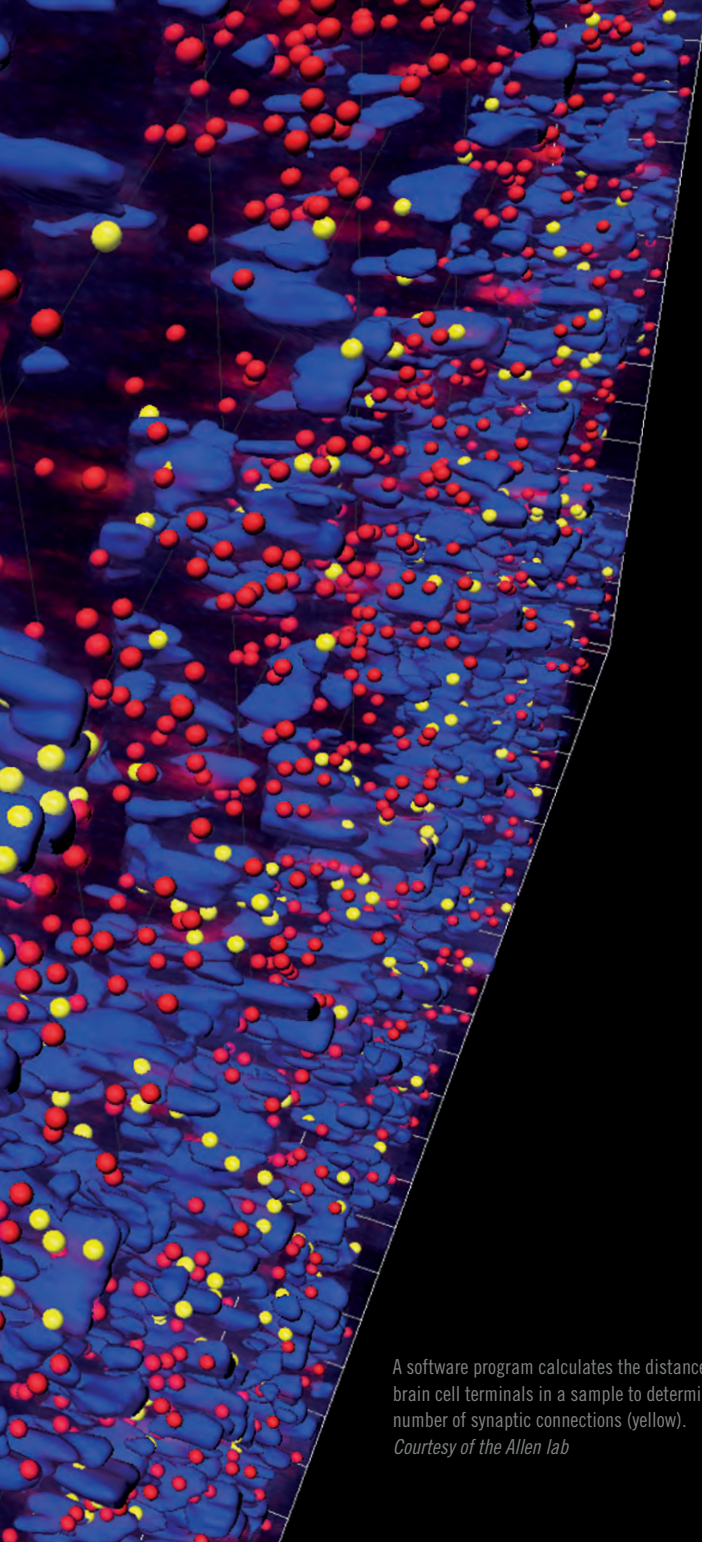


ON THE COVER

Salk’s 13 shared scientific facilities, or cores, enable discoveries and innovative breakthroughs to Salk labs. The cores offer state-of-the-art technology and expertise on everything from stem cells to analyzing genomic data.



SUPPO



A software program calculates the distance between brain cell terminals in a sample to determine the number of synaptic connections (yellow).
Courtesy of the Allen lab

IT'S FEEDING TIME AT THE MICROSCOPIC ZOO.

In a small, brightly lit room, scientists sit or stand at counters, carefully pouring liquid food into round petri dishes. The dishes, which contain tiny specks of stem cells, turn yellow (a result of the cells' waste) when it's time to feed them. The dishes turn a happier crimson when the cells are given their daily cocktail of vitamins and sugars.

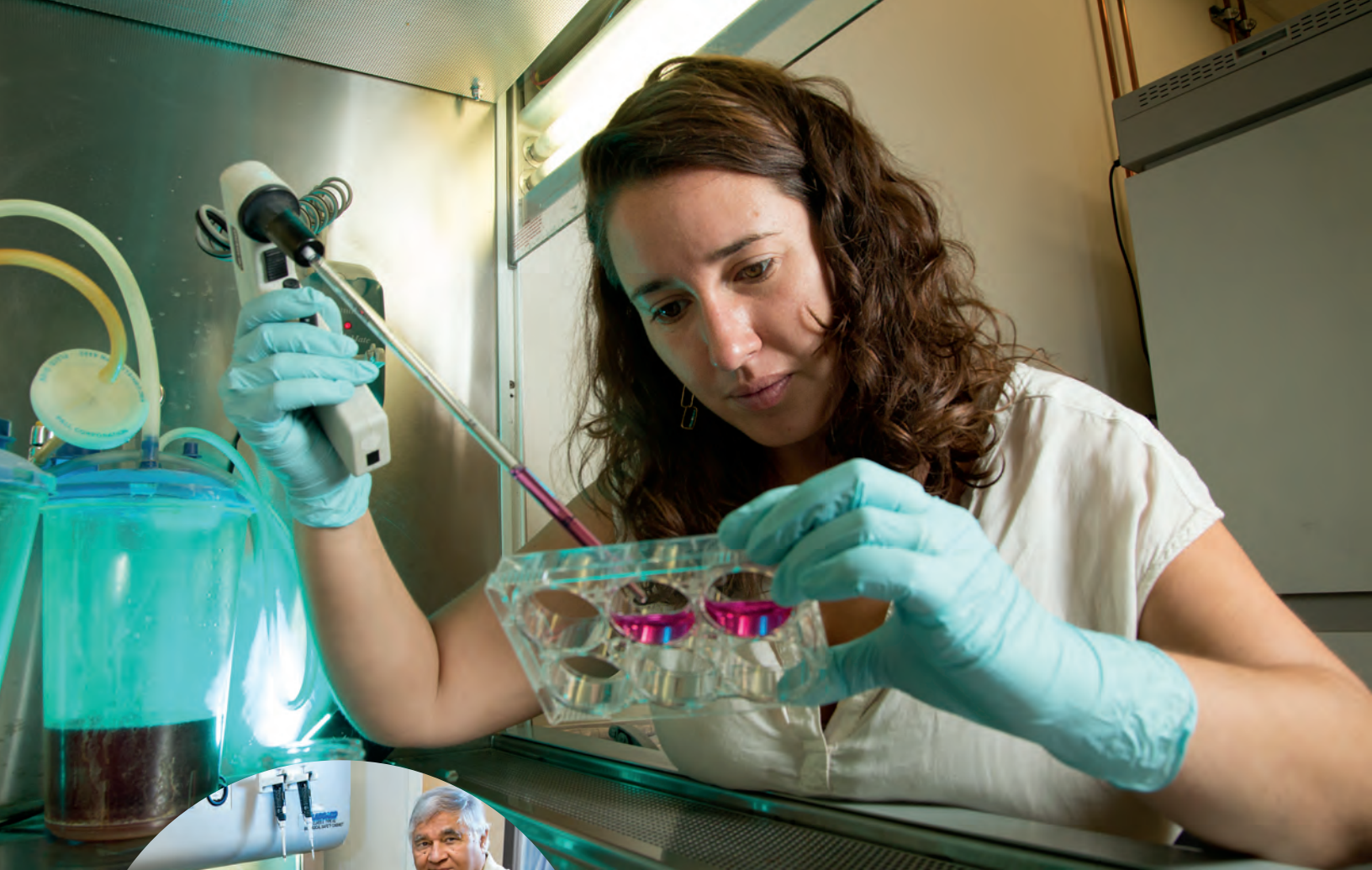
Stem cells are incredibly fickle, requiring precise, often daily, care to survive. But the effort has a potentially big payoff, as the cells are a powerful way to study diseases ranging from autism to cancer and hold the key to life-saving regenerative therapies.

The most sophisticated research technologies—from stem cell protocols to genome sequencers—demand dedicated expertise and thorough understanding of their complexities, limitations and possibilities. This specialized knowledge is often beyond the purview of the average research lab, as are the expenses associated with purchasing, operating and maintaining the very latest in equipment and supplies.

That's where shared scientific facilities called cores, like the Salk Stem Cell Core, come in. As part of Salk's first major fundraising campaign, the Institute has secured support to expand its core facilities in recent years. The Institute currently has 13 core facilities providing leading-edge scientific technologies and expertise. Far from being just service stations, the cores are idea factories spurring collaboration and pushing the limits of technology to enable breakthroughs.

"To do big science, you need big technology," says **Travis Berggren**, senior director of Salk's scientific core facilities. "The continued advancement and cost of technology, as well as the need for trained experts, are the drivers for creating these structured, shared resources between the labs."

PRINTING SCIENCE AND TECHNOLOGY



Leah Boyer, director of Salk's Stem Cell Core, uses a pipette to transfer medium into stem cell dishes.



Travis Berggren and Inder Verma

“To do big science, you need big technology.”

– Travis Berggren

Inder Verma, a Salk professor and faculty advisor for the Stem Cell and Next Generation Sequencing cores, argues that research in modern biological sciences requires expertise in a range of pioneering technologies, including imaging, genomic sequencing, proteomics and much more.

“No single scientist can have these specialized technologies in their laboratory,” says Verma. “The most efficient and productive way to do cutting-edge science is to have the resources to not only run, but continuously upgrade, shared facilities. We are very fortunate here at Salk to have state-of-the-art cores.”

While many academic institutions have shared facilities, Salk's cores have been particularly effective at catalyzing discovery because of both the size and structure of the Institute. “At other institutes, this kind of equipment is only accessible to a select group of influential researchers. We're at the optimal size to have great resources and share them equally,” says Berggren. Indeed, all 48 active labs are able to use the cores for needs that include biophotonic expertise, stem cell culturing and genomic sequencing, to name a few.

But perhaps even more important than equal access, Salk's cores serve as connecting ligaments between the diverse and varied scientific labs. By working with many researchers, the core staff has the perspective to see what works and what doesn't. The cores also advise labs on best practices; offer scientific consultations; engage in teaching, training and outreach to scientific and lay audiences; and standardize procedures across the Institute. This support bolsters the Institute's foundational and translational science and helps make groundbreaking discoveries that point to ways to tackle some of today's most devastating diseases.



NURTURING COY CELLS

“Stem cells play hard to get,” says **Leah Boyer**, director of Salk’s Stem Cell Core, which opened in 2008 and serves approximately half of the labs at Salk. Many of these users are in neuroscience, a field that has benefited greatly from the ability to grow neurons from stem cells derived from skin cells—a technological advance developed less than a decade ago. Boyer’s own interest in neuroscience began, in part, after witnessing her grandmother’s battle with Parkinson’s disease.

“For 20 years I watched my grandmother’s disease unfold, transforming her from an independent pharmacist, keen on crosswords and puzzles, into a woman shamed by the helmet and kneepads she had to wear in public,” says Boyer. “She is the reason why I am in San Diego, a neuroscience stronghold, and why I am a stem cell biologist.”

Developments in stem cell science have the ability to model and potentially treat a wide range of diseases: not only Parkinson’s and other neurological disorders, but also threats ranging from cancer to organ failure. Labs that study cancer mechanics, cellular aging and many other topics rely on stem cell research to make discoveries.

The core offers a “choose-your-own-adventure” experience for the labs, says Boyer, with access to reagents, project consultation, hands-on-training and additional space. It also generates pluripotent stem cell lines for Salk researchers and has developed over 300 stem cell lines with a 92 percent success rate—numbers that are jaw-dropping to other stem cell cores, many of which have developed 20-some stem cell lines, says Boyer. Additionally, the core tests novel protocols and buys reagents in bulk for the entire Institute, a process that helps keep all of the labs up to date on the latest advances in stem cell research at a fraction of the cost. And it does all of this with only a staff of three.

“We’re like researchers’ labs outside a lab,” says Boyer, who joined the core after working in a Salk neuroscience lab and Harvard’s Stem Cell Institute. “Small labs literally could not do this research if we weren’t here.”

Aside from assisting smaller labs that don’t have experience in stem cell work, the core also helps larger stem cell labs that need access to more advanced equipment, qualified reagents and additional space.

In one instance, the lab of **Juan Carlos Izpisua Belmonte** was able to use custom resources provided by the Stem Cell Core to help prepare experimental stem cell conditions that led to the first reliable method

SALK’S TECHNOLOGY CORES

Waite Advanced Biophotonics Center Core

Provides technical and logistical access for advanced fixed and live cell fluorescence imaging and charged particle imaging methods

Behavior Testing Core

Offers comprehensive resource for behavioral phenotyping and standardized neurobehavioral testing

Flow Cytometry Core

Advances research projects requiring cell sorting and/or analysis of cell populations by flow cytometry

Functional Genomics Core

Provides gene expression profiling using standard Affymetrix arrays and custom cDNA or oligo arrays

Genome Manipulation Core

Generates homologous recombination-base gene targeted mouse embryonic stem cell lines

Gene Transfer, Targeting and Therapeutics Core

Contributes design, consultation and production services for retrovirus, lentivirus, adeno-associated virus, adenovirus, rabies virus and vesicular stomatitis virus-based viral vector systems

Razavi Newman Integrative Genomics and Bioinformatics Core

Focuses on the analysis of next-generation sequencing and other genomics data as well as develops novel analysis algorithms

Mass Spectrometry Core for Proteomics and Metabolomics

Offers an array of services from protein identification and proteomic profiling to more complex studies using state-of-the-art instrumentation

Media Preparation Core

Provides routine and specialized cell culture media

Peptide Synthesis Core

Carries out the synthesis of inexpensive peptides and provides unmodified, biotinylated, acetylated or phosphorylated peptides

The H.A. and Mary K. Chapman Charitable Foundations Genomic Sequencing Core

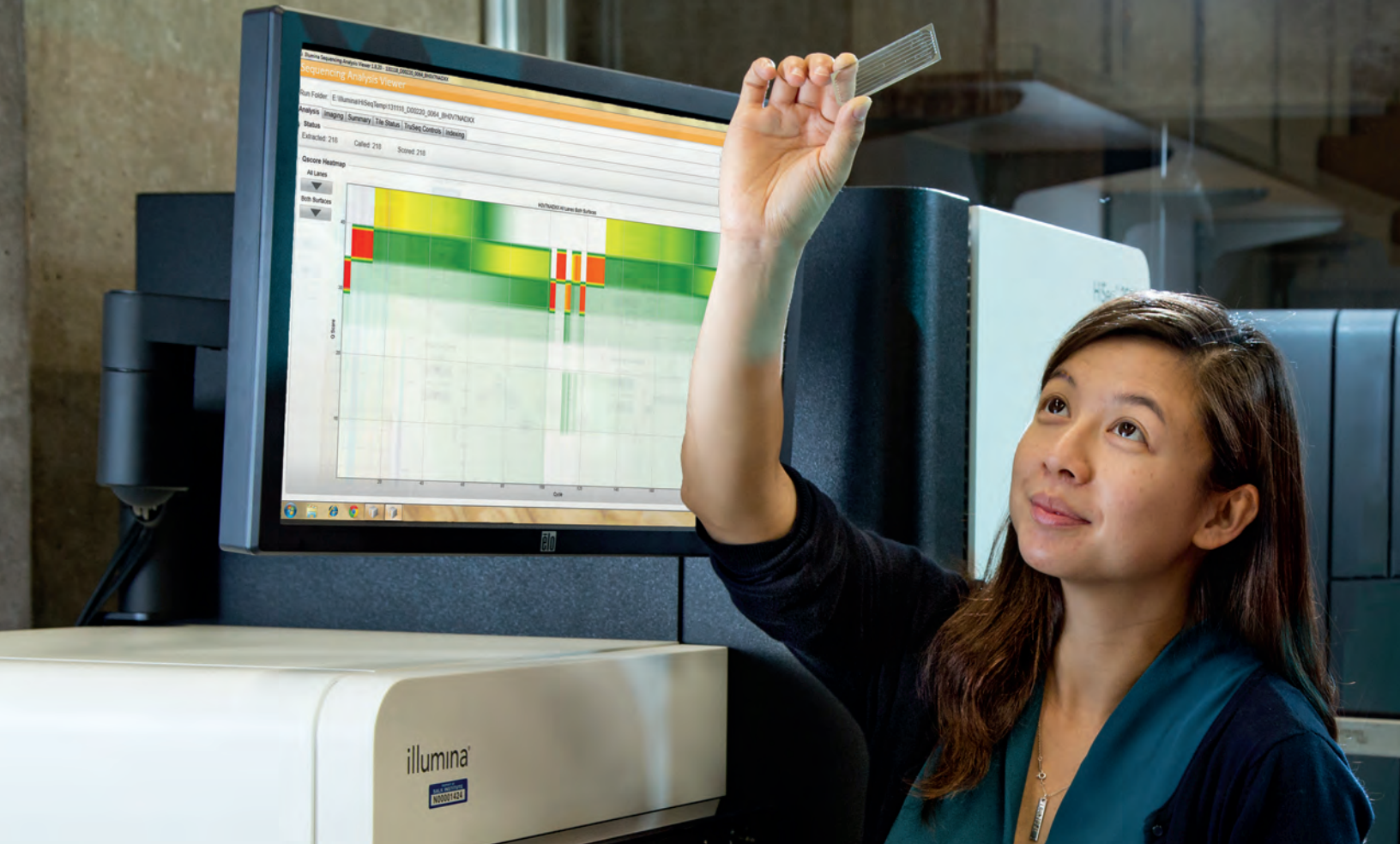
Provides low-cost, rapid-turnaround, high-throughput sequencing services, offers consultation and training in next-generation sequencing-based methods and assists in method development

Helmsley Stem Cell Core

Supports the needs for human ES and reprogrammed IPS cell culture and offers training and the physical space to carry out experiments using pluripotent cell types

Transgenic Core

Supplies services to create transgenic and knockout mouse models



Manching Ku, director of Salk's Next Generation Sequencing Core, holds a flow cell containing samples of DNA, which will be entered into a sequencer for decoding.

for integrating human stem cells into nonviable mouse embryos in a dish. The work, published in the journal *Nature* in May 2015, garnered international attention for being a critical precursor to regenerative therapies.

"The core's state-of-the-art technical support for projects involved with the routine maintenance, characterization and differentiation of human pluripotent stem cells was critical to this work," says **Jun Wu**, first author of the *Nature* paper and postdoctoral researcher in the Izpisua Belmonte lab. "The customized basal media provided by the Stem Cell Core was one of the key components for generating these human region-selective pluripotent stem cells."

The discovery prompted much interest from other labs at Salk, to the point where Boyer acquired the chemicals and protocol for the technique so that everyone could use it. She is currently working with Wu to optimize and outline an easy-to-use protocol.

"The cores are facilitators of research and the hubs of collaboration—we make science more cost-effective, time-efficient and robust," says Boyer.

DECODING THE BOOK OF LIFE

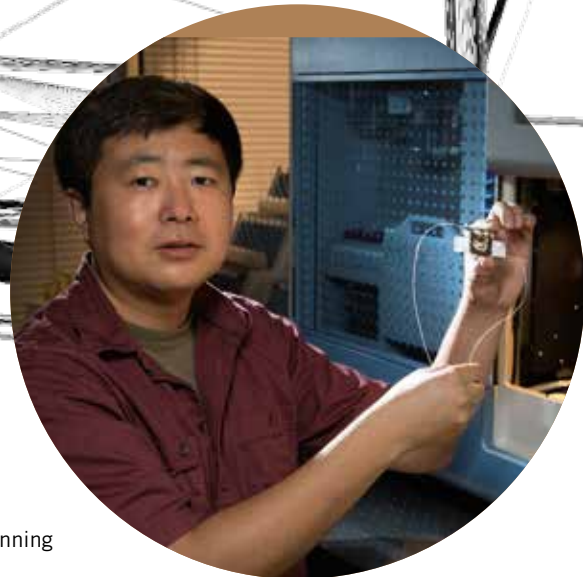
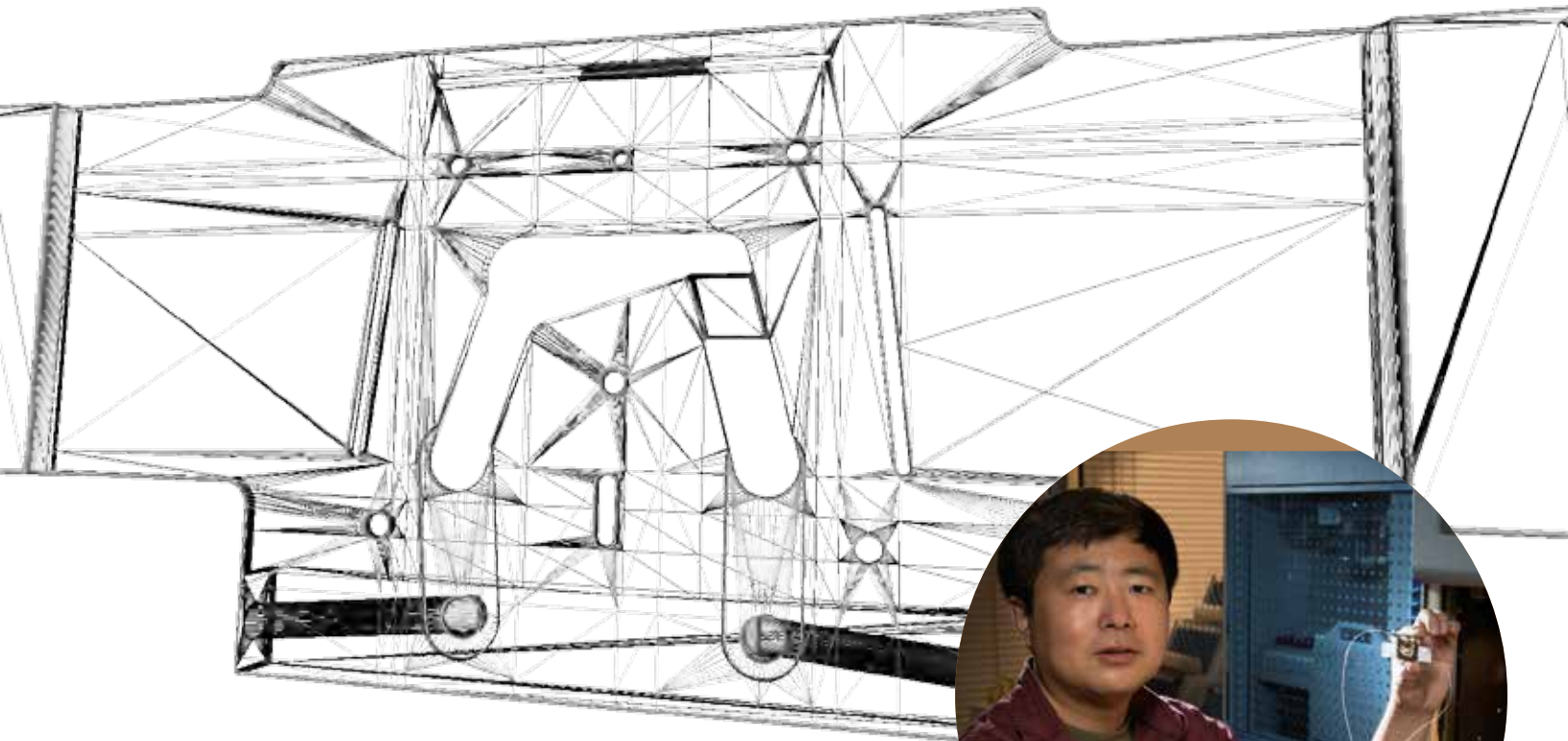
Manching Ku holds out what looks like a glass business card with four pencil-thin lines running across it. Each line is a channel that can hold up to about 150 million fragments of DNA from samples such as, for example, a diseased brain and a healthy brain.

After one side of the double-stranded DNA is stripped off, the sample-laden card—known as a flow cell—is fed into a box-shaped machine called a sequencer. The sequencer reloads matching molecules, sequences of four nucleotides (adenine, thymine, cytosine and guanine) onto the DNA. But these replacement A, T, C and G nucleotides are tagged with colors, allowing a camera inside the machine to capture a snapshot of the newly colored DNA and decode what exactly those sequences are.

Despite only being made up of four letters, so to speak, our DNA—and all the accompanying bits that hang onto it—is still a puzzle to read. It has been described as a book in which there are no spaces or punctuation marks and with letters thrown in at random. But decoding this book is the key to understanding disease and health, development and aging.



A flow cell can hold several million fragments of DNA samples.



Next generation sequencing took off about 10 years ago, thanks to new technology that allowed comparisons of smaller, multiple samples. This high-throughput screening enables scientists to better understand diseases like cancer by showing what groups of genes are overexpressing on a DNA strand. Many areas of research, like studies in metabolism, epigenetics and plant biology, also look to next generation sequencing to uncover how and why disease progresses.

“We are like the glue of the Institute,” says Ku, director of the Next Generation Sequencing Core. Ku came to Salk in 2013 after honing her expertise at the Broad Institute in Cambridge, Massachusetts. “We have a common technology that everyone is able to use no matter what type of organism or system they’re studying, from fruit fly to human tissue samples.”

Nearly all of the Salk labs use the sequencing core. One of the benefits of having it onsite and accessible to researchers is that Ku is constantly doing project consultations and advising researchers when something looks amiss.

“At other places you might send a sample off-site and not hear back for months,” she says.

“Here, we can troubleshoot from the beginning and give immediate feedback.”

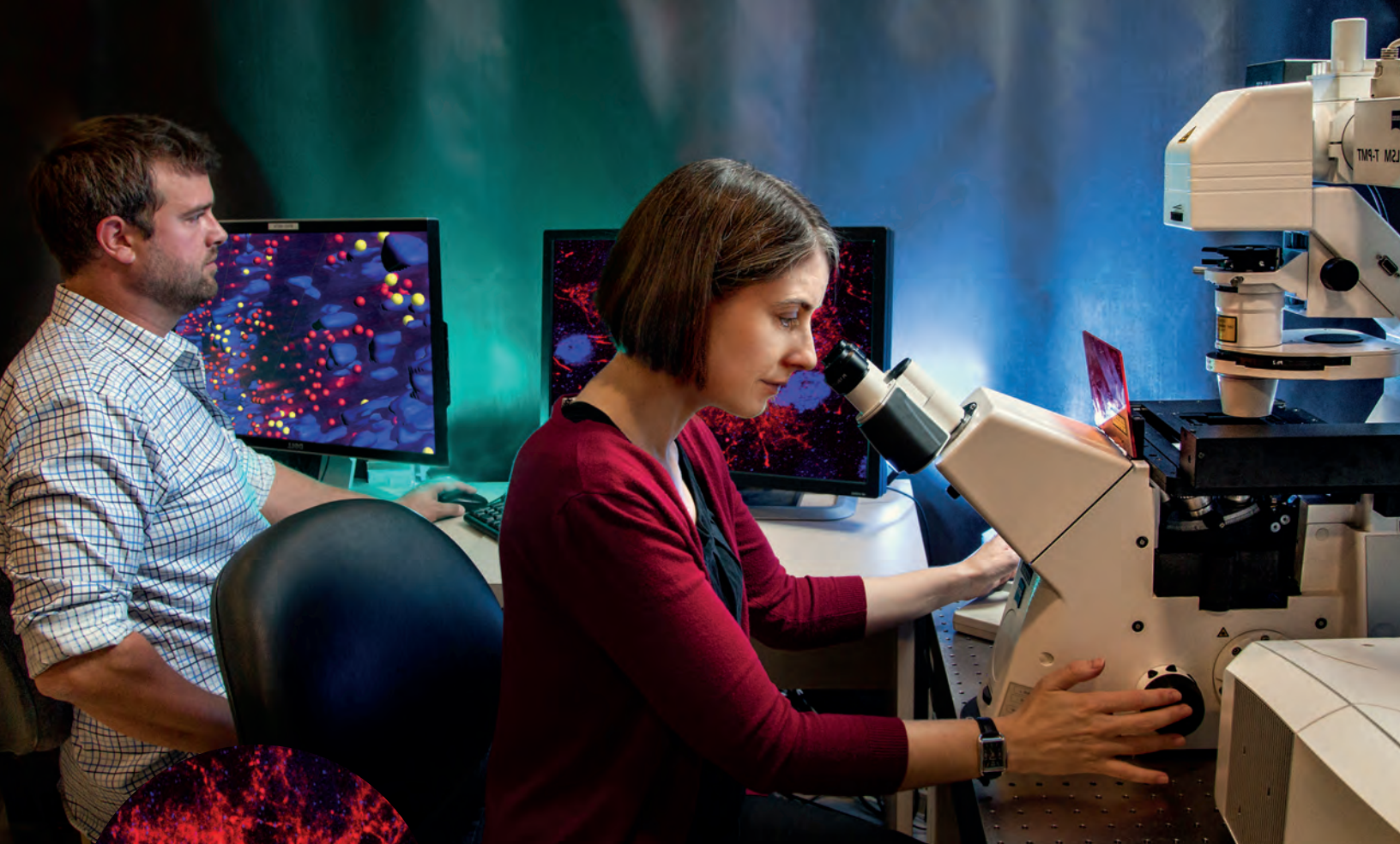
The core is also a knowledge platform, says Ku, who recommends (with permission) one researcher’s technique to another. This open exchange makes science more efficient, adds Ku, because researchers don’t have to waste time or resources trying attempts that others have already worked through. “Salk is already really collaborative, but the cores make it more so,” she says. “No one is forced to reinvent the wheel.”

Aside from providing expertise and training, Ku also works with faculty to push the boundaries of the technology. In one collaboration, Ku and **Hu Cang**, assistant professor, are trying to find a way to capture the three-dimensional information in a cell by reverse-engineering a common genetic sequencer and combining it with a microscope. Their goal is to capture the spatial information of packages of DNA (chromatin) within a cell, the shape of which may have many implications for disease.

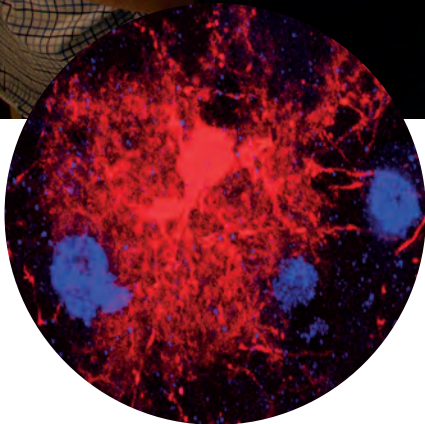
“In traditional sequencing, you break apart the cell and harvest the genetic material, but you lose all of the spatial information about that

Hu Cang uses a 3D printer to create his own flow cells (below) for use in a hacked gene sequencer. The new technology aims to capture the spatial information of biological samples.





Michael Adams and Nicola Allen



Brain cells called astrocytes are pictured in red, neuronal nuclei in blue.
Courtesy of the Allen lab

cell,” says Cang, who was awarded a Waitt Advanced Biophotonics Imaging Tools and Technologies Seed Grant to pursue this work. “We want to be able to put the entire tissue onto a flow cell, amplify the genes of interest and do the sequencing without destroying its structure.”

The duo used a 3D printer to make custom flow cells that would work with this hacked sequencer and hopefully retain—and image—the shape of the chromatin. Ideally, the hacked sequencer would be able to look at a tumor and record the individual transcription of each cell, showing how the cancer develops drug resistance.

“Right now the spatial information of those cells is very hard to quantify and measure,” Cang says. He is also in talks with other potential collaborators to use this technique to quantify latent HIV genetic material inside cells, something that is currently hard to pinpoint.

A collaboration like this, adds Cang, wouldn’t have happened anywhere else. “I don’t know anyone who is pushing sequencing this far,” he says. “You need someone with the biological and technical experience like Manching and the engineering background like me, and an environment that supports doing something risky but is also collaborative, like Salk.”

IMAGING THE UNSEEN

Salk Assistant Professor **Nicola Allen** wanted to find the answer to the question: how many neuronal connections are there in a developing brain? While it’s easy enough to take a snapshot of dyed brain cells, figuring out the number of synapses—specialized connections that neurons use to communicate—was a much bigger computational problem, but one that could help to understand how the brain develops and what happens when things go awry.

She found a solution in a collaboration with **Michael Adams**, a Biophotonics Core staff scientist and physicist. Adams developed a software program to count the number of synaptic connections in a volume of brain tissue. This work will let the Allen lab ultimately investigate if altering the function of other brain cells, known as astrocytes, affects the formation of these synapses in developing and mature brains.

“The Biophotonics Core helped us beyond what we could do on our own,” says Allen, who has used most of the Salk cores to advance her neuroscience research. “It’s not just about training you on how to use a confocal microscope; the core staff talks to you about your experiments and their design to do science most effectively.”

Salk’s Biophotonics Core was founded in 2011 as part of the Waitt Advanced Biophotonics Center, which was established with a \$20 million gift from the Waitt Foundation. With a staff of only a few, this core remains one of the most heavily used shared resources at the Institute.

About 40 labs rely on the two dozen state-of-the-art imaging platforms it houses, including



In this network representation of genes involved in lymphoma, each circle is a gene and the connections indicate a variety of biological interactions. Darker colors indicate a stronger association with the disease.

Image courtesy of Max Chang, Integrated Genomics Core

light fluorescent and electron microscopy—a broad range of availability not common in a single core. This range allows what’s called multi-scaled imaging: a researcher can not only image a whole organism (e.g., the brain of a worm) but can go down to single cells and molecules to understand what happens in genes and proteins and how they impact the whole organism in disease.

The core focuses not just on the development of new microscopes, but rather new computational methods to analyze images. The field of microscopy and imaging has become, like other technologies, data-driven science, as a single image can produce a terabyte or more of data to analyze.

“We very much see this as not a classic core where a staff of technicians assists scientists, but rather a center actively involved in developing new technology to enable people to do experiments that they couldn’t otherwise do,” says **Martin Hetzer**, Salk professor and faculty director of the biophotonics center. “Biophotonics is one of the hottest and most rapidly developing areas in biomedical research. Our ability to visualize things in animals and cells is improving through techniques in physics and optics, allowing us to dig deeper into cells.”

This core also has a unique model: it operates under the Waitt Advanced Biophotonics Center, which includes a group of award-winning

faculty whose specialties span many fields: biomedicine, physics, chemistry and engineering.

“The center really enabled the core to take off,” says Hetzer. “The idea was to have a core with the broadest impact on the Institute, while the biophotonics faculty—**Hu Cang**, **Björn Lillemeier** and **Axel Nimmerjahn**—push the new technology and develop imaging approaches that don’t exist yet.”

INTEGRATING DATA

As technology becomes more advanced, so does the need to contextualize new data. The Integrative Genomics and Bioinformatics Core, started in 2012, processes raw data from sequencing and develops techniques to combine different types of genomics data, such as linking mutations to the molecular pathways and epigenetic changes involved in research. In addition to providing technological tools, it also offers innovative methods in bioinformatics, network analysis, molecular dynamics and computational data integration.

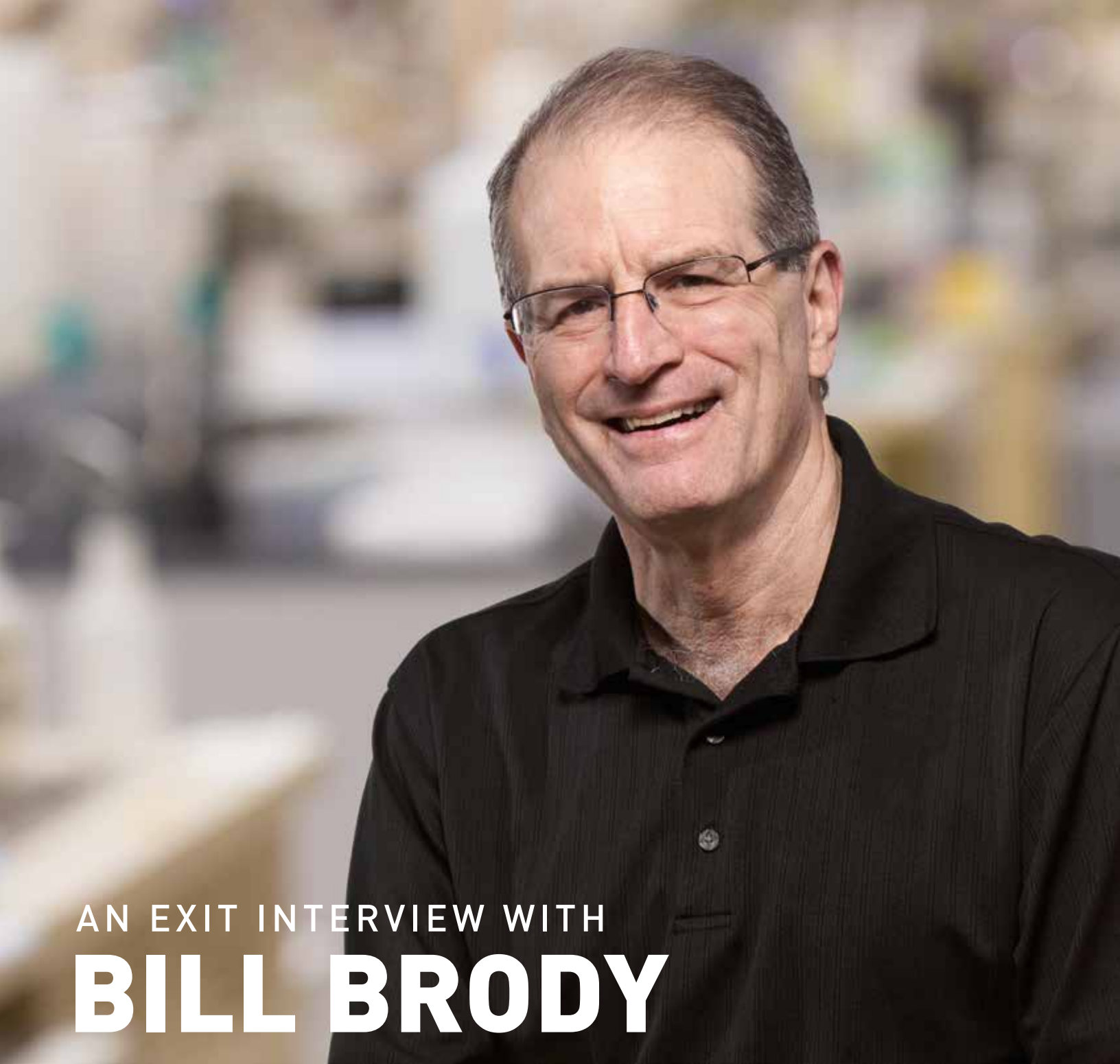
“Over the course of the last three years, I’ve learned how to analyze sequencing data through this core,” says **Julie Law**, a Salk assistant professor who studies the genome of plants to better understand epigenetic regulation and DNA packaging. “I started with a cursory understanding of genomics analyses, and after working with the core my lab is now at a point where we can do more

sophisticated interpretations of sequencing data to maximize what we can learn from the experiments we do.”

Researchers who are doing anything with big data—whether it’s next generation sequencing, mass spectrometry, proteomics or biophotonics—need new ways to interpret the reams and reams of information. For scientists that have huge data sets, a regular, off-the-shelf computer cannot process—let alone organize—the information within a reasonable time-frame. “Expanding in this area, and relatedly, high-performance computing in general, is one of our biggest needs for the future,” says Berggren.

A data resource center at Salk has already been constructed, with high-end fiber optic data transmission cables and other infrastructure that supports moving and analyzing data for the cores and labs. The next steps, says Berggren, are to secure equipment and, most importantly, staff who not only understand biological research questions, but are also able to leverage the latest approaches in computer science and informatics.

“We have a truly dedicated group of some 40 scientists and core staff researchers that routinely give that extra effort,” says Berggren. “It’s that extra effort, combined with powerful new technologies, that makes core facilities at Salk such exceptional standouts.”



AN EXIT INTERVIEW WITH
BILL BRODY

As Bill Brody prepares to step down as president after six years of leading the Salk Institute, he shares his perspective on the Institute, science and what it's like to play piano with the San Diego Symphony.



Bill Brody and Irwin Jacobs, chairman of Salk's Board of Trustees

WHEN BILL BRODY RETIRES AS PRESIDENT OF the Salk Institute at the end of December 2015, it will mark the close of a fruitful chapter for the Institute and the beginning of a new era. An acclaimed physician-scientist entrepreneur and university leader, Brody joined Salk in 2009 after serving 12 years as president of Johns Hopkins University. During Brody's six years of leadership at Salk, he navigated the Institute through challenging waters, weathering a global financial crisis while launching Salk's first major fundraising campaign. The Campaign for Salk significantly boosted the Institute's outreach efforts to raise its profile and attract private philanthropic support. This included a number of new public events, including the Salk Science & Music Series, Brody's brainchild and an offshoot of his classical piano training.

As Brody steps down as president this month, the campaign comes to a close, having exceeded the goal of raising \$300 million and more than doubling the Institute's endowment from \$132 million in 2009 to \$356 million in 2015—laying a financial foundation critical to long-term stability and flexibility.

In addition to shoring up its financial footing, the Institute has boasted a run of scientific successes during Brody's tenure, including recruiting a new cadre of highly sought-after faculty and expanding its research facilities, outfitting them with the most cutting-edge scientific technologies. Most important of all, Salk's scientists continue to produce a steady stream of remarkable scientific discoveries that are changing how we see the world and how we tackle the many challenges facing humanity, from climate change to Alzheimer's disease to cancer.



“THE FUTURE ALWAYS HOLDS OPPORTUNITIES AND CHALLENGES.”

– BILL BRODY

What do you see as the best opportunities for the Salk Institute?

We have so many opportunities—too many, really. We're living in a renaissance of biomedical science. People say this is the 'era of stem cells' or 'neuroscience' or 'cancer.' And that's all true. One challenge at Salk is all the technologies we have to deal with. We are the Salk Institute for Biological Studies—not technological studies—but it's critically important that we invest in technology. Technology is really driving the science now. Another promising trend I've seen at Salk is the merging of basic and translational research. It used to be that someone who discovered



Robert Redford and Bill Brody at Salk's June 2014 premiere of Redford's film *Cathedrals of Culture*

a fundamental biological mechanism would rely on pharmaceutical companies to turn the discovery into a drug. The problem is that there is traditionally a gap between discovery science and translational science—really promising ideas can fall into this gap and never emerge. A number of Salk scientists are now conducting the initial translational experiments based on their previous discoveries, looking for specific drug targets and even developing initial drug candidates. It's exciting, because it means the people who have the deepest understanding of the biology are getting more involved in making sure the knowledge helps people.

What are the biggest challenges for the Institute?

I think we're in really good shape. We've had a wonderful fundraising campaign and we exceeded our goal. But funding is still scarce. Finding support for the research is key to the long-term success of Salk. That isn't going to change. And it shouldn't change. We need to have people who are hungry and can compete for grants. In applying

for grants, the science gets honed. You see, here at Salk, we play a high-risk game called science. We ask people to take these crazy-sounding ideas and see if they're real or not. It often takes the establishment a number of years to realize that what Salk scientists have found is true. To our credit, although we work with a small staff, these people are always willing to go the extra mile. So we must be efficient, effective and hungry.

Is that what makes Salk "Salk"—the people?

You can have all the money in the world, and it's still the people that make an organization. The very best thing about Salk is the people. They are the secret sauce. We are not a large organization so we don't have a lot of reserves nor a deep bench. While a big organization can tolerate a certain amount of mediocrity, there's simply no room for it at Salk. We have to have the highest quality people—and we do. It's imperative that we keep making investments in quality faculty and staff.



From left: Tim Ball, Sr. Director of Facility Services, Bill Brody and Irwin Jacobs

You've had a long and fascinating career. You were a surgeon, inventor and head of one of the world's great universities. Did you learn anything new over the past six years in La Jolla?

When I was a medical student at Stanford and also enrolled in the PhD program in electrical engineering, I took the biochemistry course taught by Nobel laureates Arthur Kornberg and Paul Berg (the latter having been previously a scientist at Salk) and became so intrigued with biochemistry and the emerging field of molecular biology, I almost changed my major to biochemistry. It was probably a good thing I didn't, but when I was invited to come to the Salk Institute I viewed it as an opportunity to learn about modern molecular biology. I have been a voyeur watching some of the world's most amazing discoveries unfold before my eyes.

What are the three most important things you would tell the next president of the Institute?

Continue to recruit the best and brightest minds to the Salk Institute. Expand our reach to more individuals and foundations that can support Salk research in the face of scarce government research funds. Keep the Institute lean and effective.

For Symphony at Salk 2014 you played piano on stage with the San Diego Symphony. Were you nervous?

No, of course not, how could I be nervous... the night before the event, I slept like a baby...waking up screaming every two hours! I had never played with a symphony before, so it was a high-risk endeavor. I told Maestro Thomas Wilkins that if I failed, people would say, 'Well, what do you expect? He's a scientist not a musician. But what was Maestro Wilkins thinking when he decided to have Dr. Brody perform with the Symphony?'



Bill Brody and Maestro Thomas Wilkins

What are you going to do in retirement?

Less! That's the short answer to that question. I love playing the piano, so I'll probably spend more time practicing and playing for fun. I also mentor younger people in academia and in small companies, something that is very enjoyable. I look forward to maintaining a presence at Salk; a piece of my heart is here. It's been a real privilege to work at the Institute, to be greeted each morning by incomparably talented people. It's a superb organization.

Now, it's time to pass the baton. The next president will come up with new ideas, install new ways, bring a new energy. There's a buzz about Salk among researchers that Salk is a great place to be. And it is! 🏢



One on one with...

Ed Callaway

ED CALLAWAY CAN'T RESIST A PUZZLE. WHETHER IT'S PERFECTING HIS golf swing, playing poker or trying to unravel the most complicated conundrum in existence—the human brain—Callaway finds bliss in those moments when he's completely immersed in solving a problem. And when it comes to studying the brain, his penchant for puzzles has paid off.

Callaway, a professor in Salk's Systems Neurobiology Laboratories and holder of the Audrey Geisel Chair in Biomedical Science, focuses on deciphering circuits in the cerebral cortex, the brain's outer layer, that process visual information. In one major breakthrough, he developed a way to use a modified rabies virus to trace single connections between neurons. This method and others are used by labs all around the world to map connections related to numerous nervous system functions and diseases such as schizophrenia, autism, Parkinson's and Huntington's.

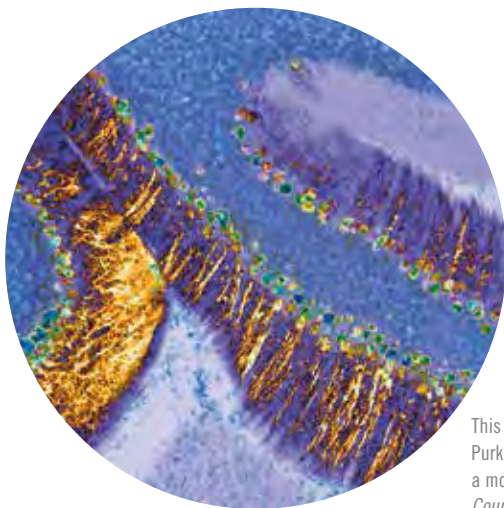
Inside Salk sat down with Callaway to discuss his work and family, why he retired his putter, and the time he won a big poker pot without even trying.

Your father was an engineer. Did that have anything to do with your career choice?

My father was an electrical engineer and designed the infrared radiometers used on one of NASA's Pioneer spacecraft to explore the solar system. We helped him wrap wire coils around metal rods to make electromagnets for one of his projects. It taught me you could build your own technologies, which is really important for science, because the tools you need to really push the edge often don't exist. We also always had lots of animals in the house when I was a kid: lizards, snakes, hamsters. A hamster once snuck into my sock drawer and had a litter of pups. It was eye opening.

When I was an undergraduate in college learning about the brain and neurons, it struck me that it's really a lot like electrical engineering, that our brains are electrochemical devices. But this living device makes our experience of life possible. I thought, 'Wow. I want to study that.'

“I like a challenge and meeting the challenge often requires a team working together rather than in competition.” – Ed Callaway



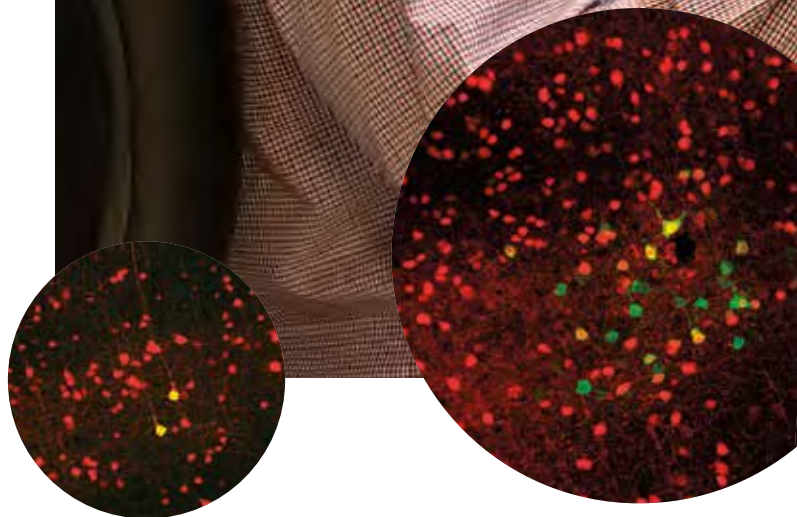
This microscope image shows Purkinje cells in the cerebellum of a mouse's brain.
Courtesy of Nicholas Wall

You and your wife, Amy Freeman, have three children (Jackson, 25; Perri, 21; and Marin, 19). Did you push them to go into science?

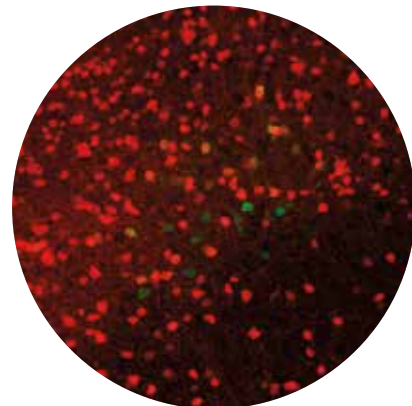
I tried not to bring the work home with me. Perri is studying biology at Barnard, focusing on infectious disease, and she worked in **Greg Lemke's** lab at Salk when she was home from college last summer. Jackson studied computer science at the University of California, San Diego and now works in San Francisco, and Marin is studying international relations at Stanford. I'm sure I've had some influence, but really they've all chosen their own path. I didn't bring the science home for my own benefit as well. You need to take a break from it. I find that when I take my conscious mind off my research by doing something completely different, my unconscious mind seems to do its best work. That's when I get ideas that are less controlled and more creative.

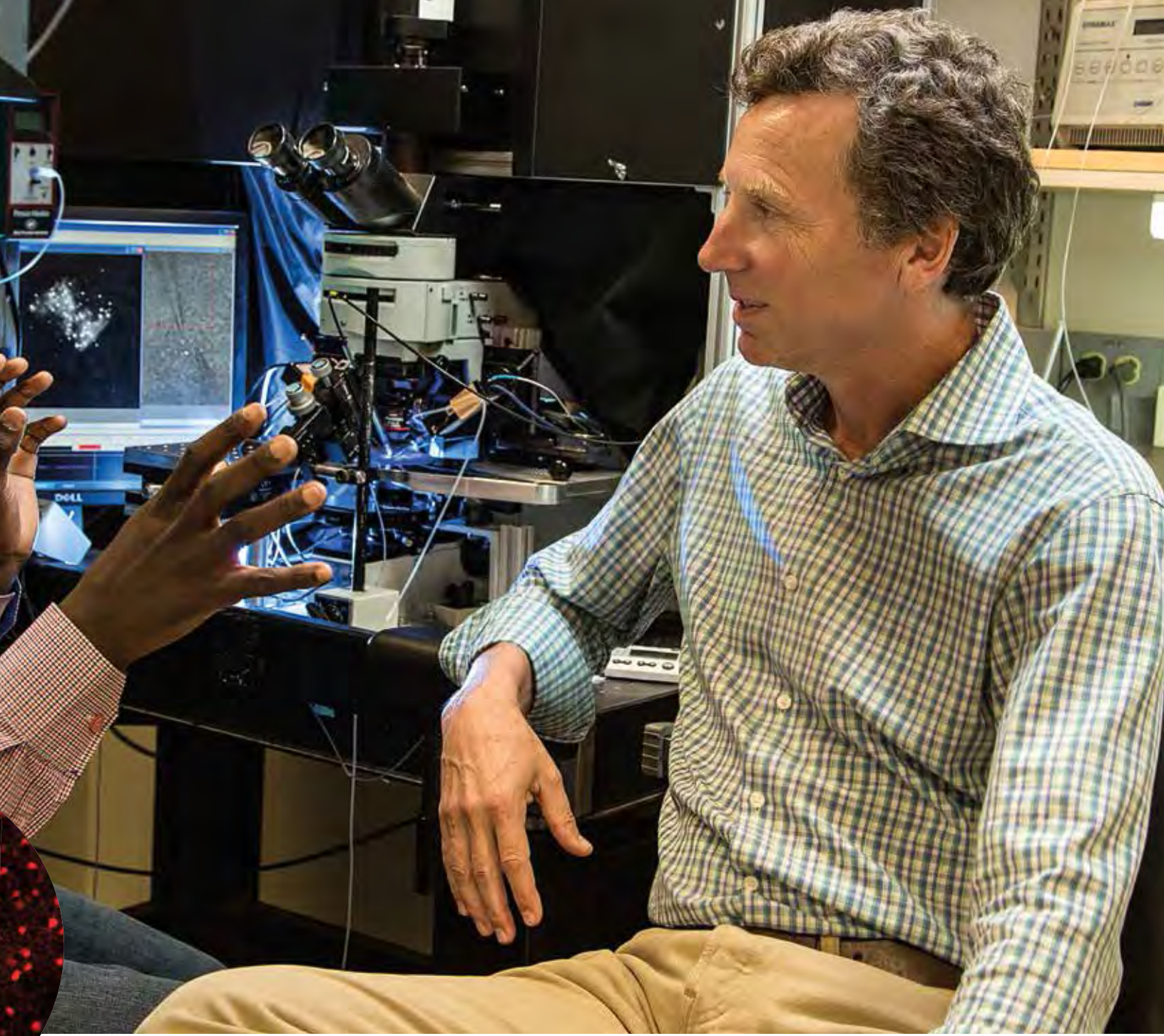
How do you get your mind off your research?

I took up golf a few years ago and got obsessed with it. It's really hard—kind of like science—so it took all my concentration to learn and improve. I grew up with three brothers, so I've always been very competitive. Golf appealed to me. At one point, though, I realized I'd plateaued at golf and was getting frustrated and the time commitment to get past it was just too much. It was either golf or time spent with my family and in the lab. So one day, I just quit cold turkey. I was a long distance runner and scholarship athlete in college, so after I quit playing golf, I started running again. It's another good way to rest the mind. I also play poker occasionally. There, the challenge is really reading your opponents, which is another kind of puzzle. Once, I was playing with Florian Engert from Harvard and Mike Ehlers who's now at Pfizer and I had a straight flush. I knew there was no hand that could beat me and I told them so. They kept raising me, and I told them, 'Really guys, you don't want to raise me.' But they thought I was bluffing and they just kept going. I won a lot that night.



Ed Callaway developed a technique for tracing connections between brain cells using a modified virus. The glowing green neurons in these images are connected to each other.
Courtesy of Euisook Kim





Espoir Kyubwa and Ed Callaway

Science is also very competitive. Does that appeal to you?

I wouldn't say that it necessarily appeals to me, but it sometimes influences the work. I think it did more so earlier in my career. I'm still competitive, but now it's more about solving the problems I see in front of me. I like a challenge and meeting the challenge often requires a team working together rather than in competition. For example, there's the challenge of running a lab, which means solving the puzzle of funding the lab and really understanding the people I'm working with. If you want to do the best science, you've got to hire the best people. And everybody has their strengths and weaknesses, so figuring out what projects are best for a certain person or who they should work with is really important. Ultimately, if you hire great people, the best thing you can do is get out of their way. For instance, one of my former grad students, Ian Wickersham, played a big part in the viral tracing methods we've developed.

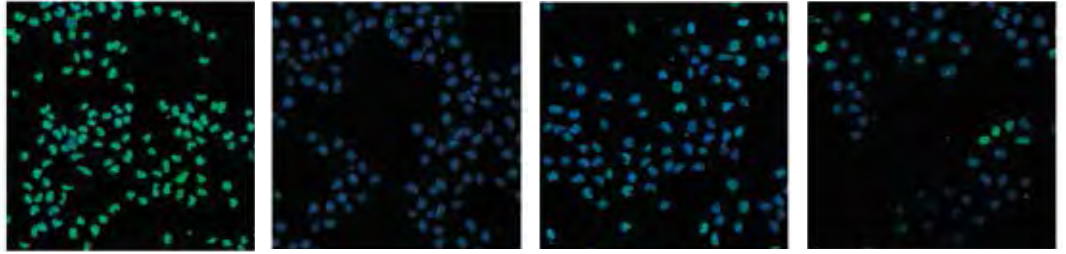
What's most exciting in neuroscience now?

The brain is so complicated, but suddenly we got these incredible tools. The viral tracing technology we developed is helping us map neural circuits at a level of detail that was unthinkable just a few years ago. Optogenetic tools that let us control neural activity with light are another huge advance. The combination of the ability to trace connections between types of neurons and the ability to control them is really powerful. We can now decode how these networks of neurons guide the vast array of very distinct brain functions, as well as determine how dysfunctions in various parts of these networks can lead to different neurological conditions. If we can pinpoint distinct network disruptions in distinct types of diseases, we can significantly improve our understanding of the underlying molecular mechanisms of these diseases—and get even closer to developing solutions for them. 📌



Next generation:

Conchi Estarás



In early-stage cell nuclei (blue), developmental genes (green) must be turned on for the cell to develop. When the two cellular processes, Wnt and Activin, work together (first panel), genes are activated to a much greater degree than when neither process is active (second panel). When just a single pathway is active (Wnt, third panel, Activin, fourth panel), only a few genes are turned on.

The machinery behind the magic:

Conchi Estarás unlocks the mysteries of cellular mechanism

MALLORCA, A STUNNINGLY BEAUTIFUL ISLAND LYING OFF the east coast of Spain, is known for several distinctive exports. The red sausage *sobrasada*. Tennis great Rafael Nadal. Father Junípero Serra, who left the island in 1749 to make his mark in what would become California.

Now, some 240 years later, another ambitious Mallorcan has arrived on California's shores: Salk postdoctoral researcher **Conchi Estarás**. She's here to explore the inner workings of cellular machinery.

"I've always been curious," Estarás says with an infectious laugh, "even from the time I was a child. The telephone, the television—how does this work? I would always ask this. Then later, when I watched a caterpillar transform into a butterfly, I was completely fascinated. Metamorphosis is like magic for me. But tell me how it works!"

She's had to blaze that educational path for herself. No one in her family was interested in science: Estarás' mother is a seamstress and her father works in construction. None of her three sisters has a bent for research. But Estarás, with her unflagging curiosity, simply had to know more.

So after excelling in her undergraduate schooling, she went on to earn her doctorate at the Universitat de Barcelona in Spain. That's where she discovered that her innate curiosity was well suited to the field of molecular biology. "What I do is very mechanistic,"



she explains. "I like to learn how all the parts work together and to understand how one part directly influences another. In my studies I try to understand how everything works inside the cell."

Ever eager to expand her education, Estarás eventually packed her bags for the Salk Institute, where she found a mentor to guide further exploration: **Kathy Jones**, professor in the Regulatory Biology Laboratory. "Kathy has been wonderful," says Estarás. "She supported me in pursuing a new line of research within her lab."



That research culminated in a paper, recently published in *Molecular Cell*, with Estarás as the first author. In it, Jones and Estarás describe new details about stem cell growth that could bolster regenerative therapies to, for instance, create tissues for organ replacement, stroke victims and patients of other diseases.

They unveiled specifics about two cellular processes made up of clusters of signaling proteins, collectively called the Wnt and Activin pathways. These two processes work together to activate about 200 genes essential for stem cells to differentiate into cell precursors of a particular tissue, such as liver. The Wnt pathway initiates transcription and the Activin pathway increases the speed and efficiency of the cellular machinery. The team also learned that the Activin pathway was not effective unless the stem cells were first exposed to the Wnt signal. Additionally, they identified a connection to a third cellular signaling process, Yap, known to control tissue growth and organ size. Yap appears to buffer the effects of Activin in a late step of transcription. Better understanding these cellular processes will offer guidance for improving stem cell therapies to, for example, create effective replacement tissue for the lungs or pancreas.

“It’s been a delight to work with Conchi to explore this emerging area of science,” says Jones, “and amazing to see how quickly she has been able to discern unique aspects of the transcriptional environment.”



**“It doesn’t matter what you do.
The important thing is just to
try your hardest.” – Conchi Estarás**

The team’s study has implications for cancer research as well. Wnt is known to turn on very early in human colon cancer, for example, and Activin-related transforming growth factor beta (TGF- β) is tied to the metastasis of many cancers. Unraveling each gene’s role in cancer could point the way to new therapies. “There is great interest in developing transcription-based inhibitors of the Wnt pathway,” says Estarás, “because these would have strong anticancer activity for many tumor types.”

In her free time—what little there is of it—Estarás will sometimes indulge in reading a mystery (no surprise there!) such as Isabel Allende’s *Ripper*. She communicates regularly with her niece and nephews in Mallorca, claiming them as her “favorite hobby.” And she also enjoys cooking. True to her independent nature, though, she doesn’t follow a recipe. “I recently made *moussaka*,” she says, “or at least, my version of it. I’m sure they do it differently in Greece. But people like mine a lot!” When

asked if she finds similarities between cooking and scientific research, a mischievous gleam sparks her eyes. “First, I say ‘no,’ because that would mean that I don’t follow protocol. But the truth is, when you get a protocol from someone else, you need to make it yours. You need to adapt it to your system and to your tools. So maybe the answer is ‘yes.’”

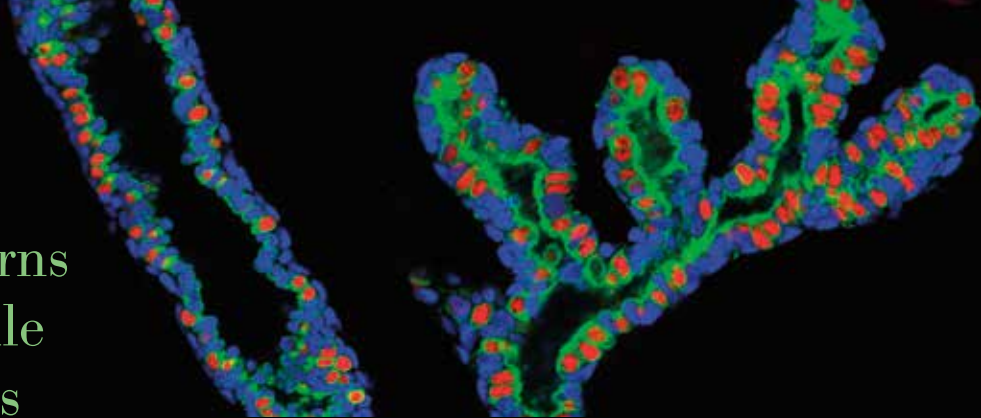
She finds puttering in the kitchen to be relaxing, one of the few times of day she doesn’t have to think about science. But often that’s when breakthroughs happen. “Sometimes I’m in the lab 10 or 12 hours and I don’t get any ideas,” she says. “But when I go home and start cooking, it’s suddenly like ‘I know! I know!’ And then I realize I do know how to further my project.”

If her brain is sometimes resting, her vibrant personality is not. “I like going to work,” she says. “The days I have more work are the days I enjoy better. But as the day progresses and there are failures, I start feeling like ‘I don’t want to do this anymore.’ And by night I’m disappointed about everything. But the next day I wake up and think, ‘Okay, maybe I can find a solution to this. Let’s give it another try.’”

That sort of genial persistence might be a Mallorcan trait. Father Serra had it. Estarás’ parents teach it. “You have to try to be the best at whatever you choose to do. That is what my parents always told me. It doesn’t matter what you do. The important thing is just to try your hardest.”

And that’s what she’s doing in her laboratory at the Salk Institute. “There’s no place like Mallorca!” she proclaims. “But Salk is a wonderful place to make discoveries.” 🏠

Errant gene turns cells into mobile cancer factories



A SINGLE STEM CELL HAS THE POTENTIAL to generate an animal made of millions of different types of cells. Some cancers contain stem-like but abnormal cells that can act like mini factories to rapidly churn out not only more copies of themselves, but also variants that are able to better survive in the challenging and changing environments to which cancers are exposed. Worse still, these stem cell-like cancers can spread to other tissues in the body, causing metastasis.

Researchers at the Salk Institute demonstrated how a single master gene, called Sox10, controls if—and to what extent—cells turn into these potentially dangerous factories. This new understanding of Sox10 could help point the way to more efficient therapies for drug-resistant cancers.

“One of the problems with a cancer mass is that it isn’t uniform. You might think of it like the microclimates leading from the Salk Institute down to the beach: some areas have rain and lots of plants while others get sun and look like a desert. Just like plants adapting to different environments, the cancer cells do the same, making some sensitive and others

resistant to treatments. We have to be able to confront this tumor heterogeneity to fight cancers more effectively,” says **Geoffrey Wahl**, professor of Salk’s Gene Expression Laboratory and senior author of the work, published September 10, 2015 in *Cell Reports*. “We’ve found that Sox10 is one type of master regulator able to unlock the cell fate door to enable cells to adopt different identities to adapt to different tumor microenvironments.”

For example, this stem cell-like ability is present in an aggressive form of the disease known as triple negative breast cancer (TNBC). TNBC lacks three of the most common targets for breast cancer therapy and makes up about 20 percent of breast cancers in the United States; it also has overactive levels of Sox10. Other labs have shown that high levels of Sox10 are also present in melanoma, another highly metastatic disease.

In the new work, the team looked for genes that were present at high levels in both normal mammary stem cells and breast cancer tissue. One gene that stood out was Sox10, which is part of a group of genes known to control how cells differentiate into mature tissues.

Christopher Dravis, a Salk research associate and the lead author of the study, found that specialized mammary cells with the greatest ability to create different cell types, known as plasticity, had higher levels of Sox10 expression. When Sox10 was removed, the cells lost that ability.

Aside from determining how powerful a factory these cells became, high levels of the Sox10’s protein in the right conditions caused a totally unexpected property to arise: the cells became mobile and invaded surrounding areas.

“We have functional evidence linking Sox10 to all of the most dangerous aspects of tumor progression—growth potential, plasticity and spreading, which indicates that Sox10 may be driving these same deadly functions in breast cancers,” says Dravis.

The group plans to test whether eliminating the function of Sox10 could be a way to fight the disease and block metastasis. “Our hope is that continued study of this critical gene will identify other signaling pathways we can inhibit to block the breadth of functions induced by Sox10 that appear to favor tumor progression,” says Dravis.

Another potential application, adds Wahl, is that Sox10 could act as a light bulb to help researchers see the cells that are beginning to move, acting as a faster test for metastatic breast cancer.

“This type of curiosity-driven science aims to understand the basic principles of how an organism is formed and then apply those findings to a very important disease,” says Wahl, who holds Salk’s Daniel and Martina Lewis Chair. “We hope every day we can bring this work out of the lab to the clinic because it is the patient who we feel ultimately responsible to.”



Christopher Dravis and Geoffrey Wahl

» **View video:** www.salk.edu/insidesalk/1215/wahl

Targeting telomeres, the timekeepers of cells, could improve chemotherapy

TELOMERES, SPECIALIZED ENDS OF OUR CHROMOSOMES THAT dictate how long cells can continue to duplicate themselves, have long been studied for their links to the aging process and cancer. Now, a discovery at the Salk Institute shows that telomeres may be more central than previously thought to a self-destruct program in cells that prevents tumors, a function that could potentially be exploited to improve cancer therapies.

When cells replicate in a process called mitosis, their telomeres get a little shorter each time. Eventually, after many cell divisions, telomeres become critically short, signaling the cell to stop dividing. This normal process functions as a barrier against cancer. Cells that have defects in the signaling pathway, however, continue past this stage to self-destruct.

This process of cell destruction, called crisis, typically prevents genetically unstable or damaged cells from replicating. But many types of cancer cells circumvent crisis by protecting the telomeres to hamper the self-destruct signal and allow cells to continue to proliferate.

“We set out to understand the mechanism of cell death in crisis and found a much more active role of telomeres as barriers to tumor development than previously thought,” says **Jan Karlseder**, Salk professor in the Molecular and Cell Biology Laboratory and senior author of the work. “It started when we saw that mitosis is longer in cells approaching crisis.” The work was detailed in *Nature* on June 24, 2015.

While regular mitosis is typically about 30-45 minutes, cells about to go into crisis have a mitosis that lasts 2-20 hours or more. Observing this reminded the researchers of a 2012 discovery where they artificially lengthened the mitosis process. Typically, telomeres have a protein protecting them from being identified as damaged DNA by the cell and thus prevented them from proceeding to cell death. But during artificially lengthened mitosis, telomeres lost the protein, spurring a DNA damage signal that pushed the cells to self-destruct.

To their surprise, the scientists found that exactly the same thing was happening in the natural crisis state. In this new work, the researchers did real-time imaging of cells in a dish to track the cells’ fate through one or more mitotic cycles. They found that a type of cellular stress called telomere fusion could evoke a prolonged mitosis and eventually crisis. Cells in this state lost their telomere-protecting protein and activated the self-destruct sequence.

“There was a long-standing hypothesis that turned out to be incorrect: that cells simply start to fuse chromosomes and break apart, generating instability and cell death,” says Karlseder, who is also the holder of Salk’s Donald and Darlene Shiley Chair. “What we show instead is it is



This cover of *Nature* shows an illustration by the Salk Institute where mitotic chromosomes (blue), telomeres (green) and a DNA damage marker (red) indicate that telomeres are recognized as damage in cells that spontaneously arrest in mitosis during crisis. These findings might offer a clinical opportunity to make cancer more susceptible to certain drugs that affect mitosis.

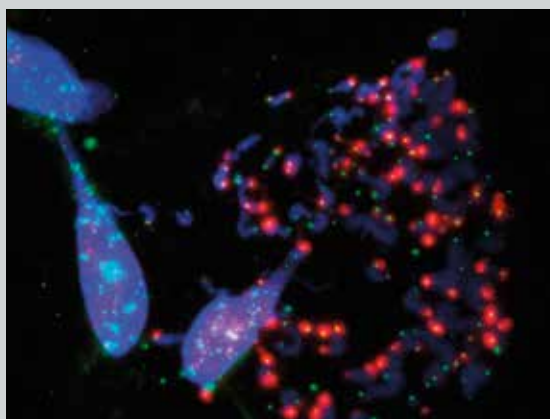
a much more targeted pathway that really only takes one cell cycle to cause crisis—it has nothing to do with the slow and steady accumulation of genomic instability.”

Anthony Cesare, Head of the Genome Integrity Group at Children’s Medical Research Institute in Australia and a contributor to the work, said it was unexpected to see how events early in the cell cycle, telomere fusions, are passed to a later stage of the cell cycle, mitosis. “This opens up new avenues for understanding how telomeres control cell growth and the implications of telomere biology in chemotherapy,” he says.

Several chemotherapies—such as Taxol for breast cancer—seek to stop cancer by interrupting mitosis so cancer cells can no longer divide.

The researchers hypothesize that they can enhance these mitotic inhibitors by, for example, deprotecting telomeres first to make the cells more susceptible to drugs. It might also be possible to see if cells from a particular tumor had shorter or deprotected telomeres and, if so, expect that tumor to be much more sensitive to mitotic inhibitors. 📺

» [View video: www.salk.edu/insidesalk/1215/karlseder](http://www.salk.edu/insidesalk/1215/karlseder)



Salk researchers show how the disabled protection of ends of chromosomes (blue) called telomeres (green) during cell division (mitosis) prompts cell death. This happens when the telomere-protecting protein, TRF2, is inhibited. This image shows an exacerbation of telomeric deprotection (red) during mitotic arrest by artificial manipulation of TRF2.

Cell recycling (shown in green) is elevated in lung cancer cells treated with an established cancer drug. Recycling is suppressed upon co-treatment with a newly discovered enzyme inhibitor.



New drug squashes cancer's last-ditch efforts to survive

AS A TUMOR GROWS, ITS CANCEROUS cells ramp up an energy-harvesting process to support its hasty development. This process, called autophagy, is normally used by a cell to recycle damaged organelles and proteins, but is also co-opted by cancer cells to meet their increased energy and metabolic demands.

Salk Institute and Sanford Burnham Prebys Medical Discovery Institute (SBP) scientists have developed a drug that prevents this process from starting in cancer cells. Published June 25, 2015 in *Molecular Cell*, the new study identifies a small molecule drug that specifically blocked the first step of autophagy, effectively cutting off the recycled nutrients that cancer cells need to live.

“The finding opens the door to a new way to attack cancer,” says **Reuben Shaw**, a senior author of the paper, professor in the Molecular and Cell Biology Laboratory at the Salk Institute and a Howard Hughes Medical Institute Early Career Scientist. “The inhibitor will probably find the greatest utility in combination with targeted therapies.”

Besides cancer, defects in autophagy have been linked with infectious diseases, neurodegeneration and heart problems. In a 2011 study in the journal *Science*, Shaw and his team discovered how cells starved of nutrients activate the key molecule that kicks off autophagy, an enzyme called ULK1.

Reasoning that inhibiting ULK1 might snuff out some types of cancer by stifling a main energy supply that comes from the recycling process, Shaw's group and others wanted to find a drug that would inhibit the enzyme. Only a fraction of such inhibitors that show promise in a test tube end up working well

in living cells. Shaw's group spent more than a year studying how ULK1 works and developing new strategies for screening its function in cells.

A key breakthrough came when Shaw met the paper's other senior author, Nicholas Cosford, a professor in the NCI-Designated Cancer Center at SBP. Cosford had been investigating ULK1 using medicinal chemistry and chemical biology, and had identified some promising lead compounds using rational design. The two labs combined efforts to screen hundreds of potential molecules for ULK1 inhibition, narrowing the list down to a few dozen, and eventually one.

“The key to success for this project came when we combined Reuben's deep understanding of the fundamental biology of autophagy with our chemical expertise,” says Cosford. “This allowed us to find a drug that targeted ULK1 not just in a test tube but also in tumor cells.”

The result was a highly selective drug they named SBI-0206965, which successfully killed a number of cancer cell types, including human and mouse lung cancer cells and human brain cancer cells, some of which were previously shown to be reliant on cellular recycling.


Interestingly, some cancer drugs (such as mTOR inhibitors) further activate cell recycling by shutting off the ability of those cells to take up nutrients, making them more reliant on recycling to provide all the building blocks cells need to stay alive. Rapamycin, for example, works by shutting down cell growth and division. In response, the cells launch into recycling mode by turning on ULK1, which may be one reason why,

rather than dying, some cancer cells seem to go into a dormant state and return—often more drug resistant—after treatment stops.

“Inhibiting ULK1 would eliminate this last-ditch survival mechanism in the cancer cells and could make existing anti-cancer treatments much more effective,” says **Matthew Chun**, one of the study's lead authors and a postdoctoral fellow in the Shaw lab at Salk. Indeed, combining SBI-0206965 with mTOR inhibitors made it more effective, killing two to three times as many lung cancer cells as SBI-0206965 alone or the mTOR inhibitors alone.

Drugging the autophagy pathway to combat cancer has been tried before, but the only drugs that currently block cell recycling work by targeting the cell organelle known as the lysosome, which functions at the final stage of autophagy. Although these lysosomal therapies are being tested in early-stage clinical trials, they inhibit other lysosomal functions beyond autophagy, and therefore may have additional side effects.

Comparing equivalent concentrations of the lysosomal drug chloroquine with SBI-0206965, in combination with mTOR inhibitors, the scientists found that SBI-0206965 was better than chloroquine at killing cancer cells.

“An important next step will be testing this drug in other types of cancer and with other therapeutic combinations,” says Shaw, who is deputy director of Salk's NCI-Designated Cancer Center. 

» **View video:** www.salk.edu/insidesalk/1215/shaw

The DNA damage response goes viral: a way in for new cancer treatments

EVERY ORGANISM—FROM A SEEDLING TO A PRESIDENT—MUST protect its DNA at all costs, but precisely how a cell distinguishes between damage to its own DNA and the foreign DNA of an invading virus has remained a mystery.

Now, scientists at the Salk Institute have discovered critical details of how a cell's response system tells the difference between these two perpetual threats. The discovery could help in the development of new cancer-selective viral therapies and may help explain why aging and certain diseases seem to open the door to viral infections.

"Our study reveals fundamental mechanisms that distinguish DNA breaks at cellular and viral genomes to trigger different responses that protect the host," says **Clodagh O'Shea**, associate professor and senior author of the work, which was published in *Cell* on August 27, 2015. "The findings may also explain why certain conditions like aging, cancer chemotherapy and inflammation make us more susceptible to viral infection."

Many factors (such as radiation) can cause a break in our DNA. The team detailed how a cluster of proteins—collectively called the MRN complex—detects both DNA and viral breaks and amplifies its response through histones, packaging proteins that wrap genetic material into small bundles like Styrofoam peanuts. MRN starts a domino effect, activating histones on surrounding chromosomes, which summons a cascade of additional proteins, resulting in a cell-wide, all-hands-on-deck alarm to help mend the DNA.

If the cell can't fix the DNA break, it will induce cell death—a self-destruct mechanism that helps to prevent mutated cells from replicating (and thus prevents tumor growth). "What's interesting is that even a single break transmits a global signal through the cell, halting cell division and growth," says O'Shea. "This response prevents replication so the cell doesn't pass on a break."

When it comes to defending against DNA viruses, however, the Salk team found something interesting: the cell's response system begins the same way (with MRN detecting either DNA or viral breaks) but never progresses to the global alarm signal in the case of the virus.

Typically, a common DNA virus enters the cell's nucleus and turns on genes to replicate its own DNA. The cell detects the unauthorized replication and the MRN complex grabs and selectively neutralizes viral DNA without triggering a global response that would arrest or kill the cell. The difference in the intensity of its response, say the Salk researchers, is akin to sending a text message for a local flood warning (in the case of the DNA virus) versus a citywide tsunami siren (DNA break). The MRN response to the virus stays localized and only selectively prevents viral, but not cellular, replication. If every incoming virus spurred a similarly strong response, points out O'Shea, our cells would be frequently paused, hampering our growth.

And when both threats to the genome are present, MRN will activate the massive response at the DNA break; no MRN is left to respond to the virus. This means the virus is effectively ignored while the cell responds to the more massive alarm.

"The requirement of MRN for sensing both cellular and viral genome breaks has profound consequences," says O'Shea. "When MRN is recruited to cellular DNA breaks, it can no longer sense and respond to incoming viral genomes. Thus, the act of responding to cellular genome breaks inactivates the host's defenses to viral replication."

O'Shea says this may explain why people with conditions resulting in high levels of cellular DNA damage (e.g., cancer, chemotherapy, inflammation and aging) are more susceptible to viral infections.

"Having damaged DNA compromises our cells' ability to fight viral infection, while having healthy DNA boosts our cells' ability to catch viral DNA," says **Govind Shah**, first author of the new work and a former research associate at the Salk Institute. "Our work implies that we may be able to engineer viruses that selectively kill cancer cells."

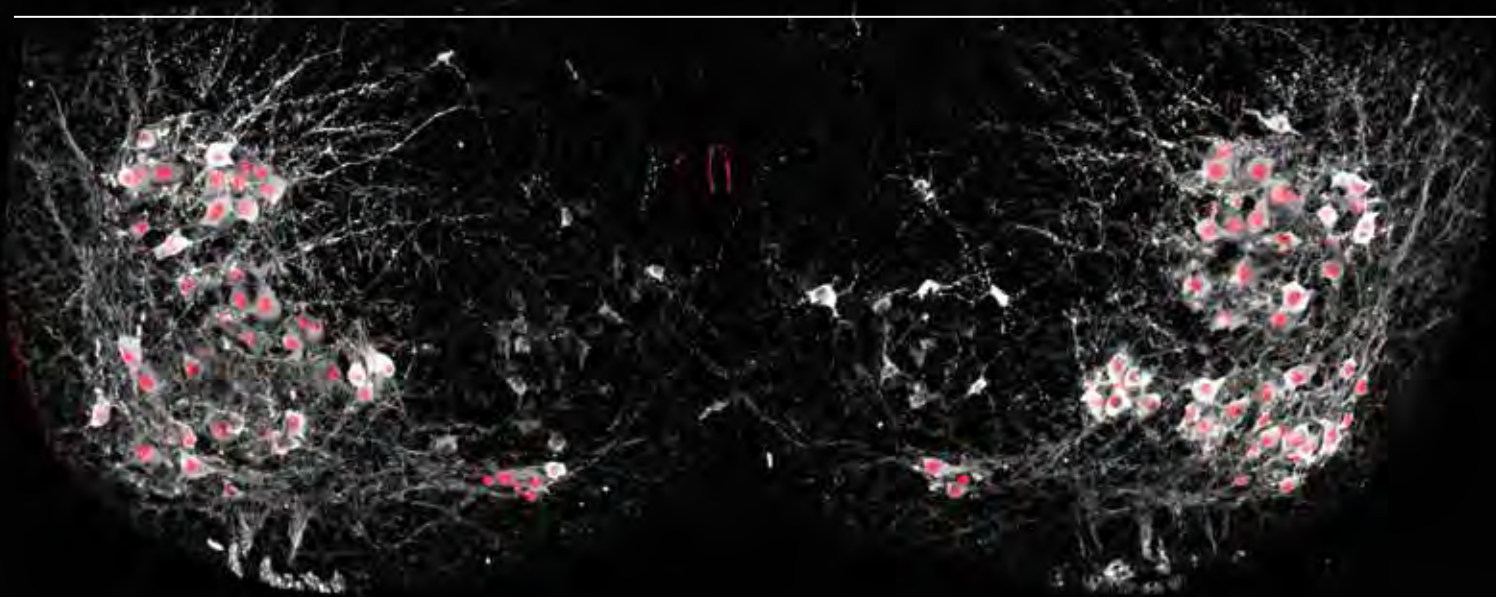
The O'Shea lab aims to use this new knowledge to create novel viruses that are destroyed in normal cells but replicate specifically in cancer cells. Unlike normal cells, cancer cells almost always have very high levels of DNA damage. In cancer cells, MRN is already so preoccupied with responding to DNA breaks in cancer cells that an engineered virus could sneak in undetected.

"Cancer cells by definition have high mutation rates and genomic instability even at the very earliest stages, so you could imagine building a virus that could destroy even the earliest lesions and be used as a prophylactic," says O'Shea. 📄



Clodagh O'Shea and Govind Shah

» [View video: www.salk.edu/insidesalk/1215/oshea](http://www.salk.edu/insidesalk/1215/oshea)



Salk scientists were able to selectively add fluorescent proteins to the nuclei of motor neurons (red) using cutting-edge genetic techniques to show how cells in the spinal cord synchronize many neurons at once to allow complex movements.

Scientists see motor neurons ‘walking’ in real time

WHEN YOU'RE TAKING A WALK AROUND THE BLOCK, YOUR body is mostly on autopilot—you don't have to consciously think about alternating which leg you step with or which muscles it takes to lift a foot and put it back down. That's thanks to a set of cells in your spinal cord that helps translate messages between your brain and your motor neurons, which control muscles.

Now, for the first time, researchers have created a method to watch—in real time—the activity of those motor neurons. The new technology, developed by Salk scientists and published in *Neuron* on September 2, 2015, is helping researchers understand how spinal cord cells make connections with motor neurons, and how clinicians might be able to repair those connections in patients with spinal cord injuries or neurodegenerative diseases like amyotrophic lateral sclerosis (ALS).

“Using optical methods to be able to watch neuron activity has been a dream over the past decade,” says **Samuel Pfaff**, a professor in Salk's Gene Expression Laboratory. “Now, it's one of those rare times when the technology is actually coming together to show you things you hadn't been able to see before.”

In the past, to measure the activity of neurons—whether in the brain or extending throughout the body—scientists relied on electrodes that could detect the change in electrical voltage inside a cell when it's activated. But it is tricky to use electrodes to simultaneously record the activity of many different neuron types to study how their activity is synchronized.


To get around this shortcoming of electrode readings, Pfaff's team used a fluorescent sensor protein called GCaMP6f that lights up whenever a neuron is activated. Unlike the electrodes, the protein could easily be added to many different cells at once. When Pfaff and his colleagues added GCaMP6f to motor

neurons, they could watch with a microscope which cells were activated in a mouse spinal cord when chemicals that turn on walking circuits were added.

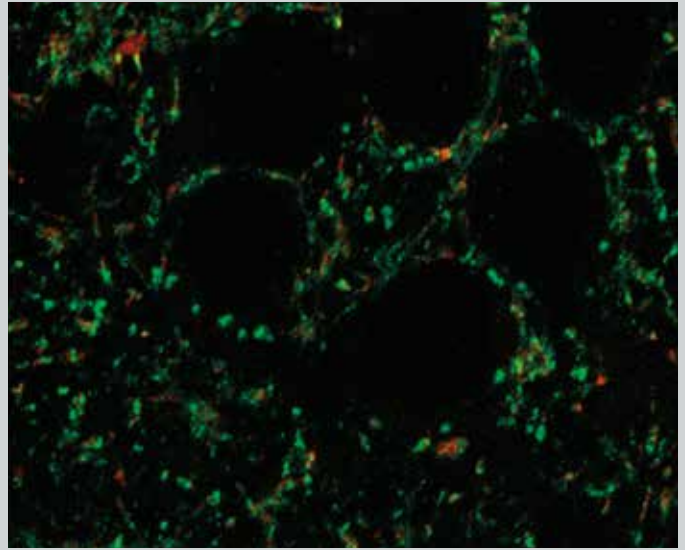
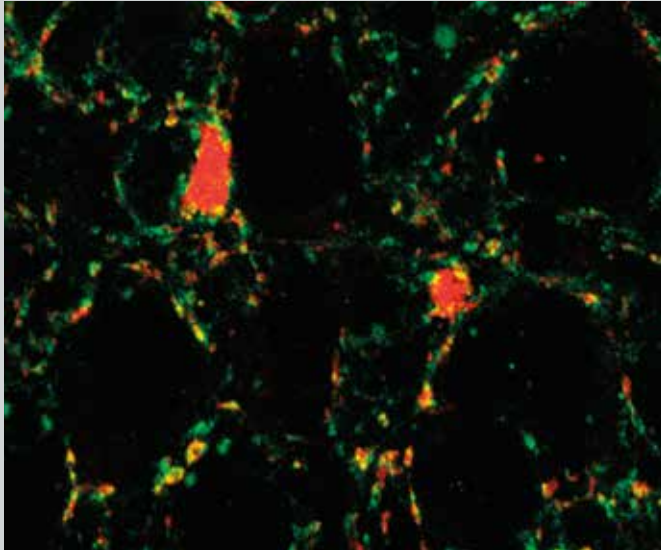
“You don't need to do any kind of post-image processing to interpret this,” says Pfaff. “These are just raw signals you can see through the eyepiece of a microscope. It's really a jaw-dropping kind of visualization for a neuroscientist.”

Pfaff's group used the new method to answer a long-standing question about how a collection of cells in the spinal cord, called the locomotor central pattern generator (CPG), connects to the right motor neurons to allow movements like walking. The CPG, Pfaff says, is where relatively simple signals from the brain—to walk forward, or move your hand off a hot stove—are translated into more complex instructions for motor neurons to control muscles.

Normal movement requires that CPG neurons in the spinal cord connect to and control when motor neurons fire. But, until now, researchers didn't know exactly how the CPG cells forged these connections.

By tweaking the locations and identities of motor neurons, and then watching the resulting patterns of activation using their new fluorescent technique, **Chris Hinckley** in the Pfaff laboratory found that the CPG didn't rely solely on the cells' locations to connect to them. Instead, the genetic identity of each subtype of cells—what makes those that control the quadriceps muscle different from those that control the calf muscle, for instance—is also important. This finding will help scientists further understand how to treat spinal cord injuries and ALS. 

» [View video: www.salk.edu/insidesalk/1215/pfaff](http://www.salk.edu/insidesalk/1215/pfaff)



When mice are engineered to lack the mGluR5 receptor in parvalbumin cells (right), they have fewer inhibitory (red) connections controlling the activity of excitatory neurons.

Receptors in brain linked to schizophrenia, autism

THE LOSS OF A CRITICAL RECEPTOR

in a special class of inhibitory neurons in the brain may be responsible for neurodevelopmental disorders including autism and schizophrenia, according to new research by Salk scientists.

The importance of the receptor, called mGluR5, in other areas of the brain had been previously established. Until now, however, no one had studied its specific role in a cell type known as parvalbumin-positive interneurons, thought to be important in general cognition and generating certain types of oscillatory wave patterns in the brain.

“We found that without this receptor in the parvalbumin cells, mice have many serious behavioral deficits,” says **Terrence Sejnowski**, head of Salk’s Computational Neurobiology Laboratory, which led the research published in *Molecular Psychiatry* on August 11, 2015. “And a lot of them really mimic closely what we see in schizophrenia.”

Scientists had previously discovered that when molecular signaling was disrupted in these cells during development, the brain’s networks didn’t form correctly. Separate studies have revealed that

mGluR5 receptors, which transmit glutamate signaling in the brain, are linked to addiction disorders, anxiety and Fragile X Syndrome. But, in these cases, mGluR5 is affected in excitatory cells, not inhibitory cells like the parvalbumin-positive interneurons.

The Salk team wondered what the role of mGluR5 was in the parvalbumin cells since the cells were deemed so important in brain development. They partnered with Athina Markou’s team from the Department of Psychiatry at the University of California, San Diego, to examine what happened when the receptor was selectively deleted from these cells after the brain’s initial formation. Without the receptor in these cells, they found, mice had a host of developmental problems, including obsessive, repetitive grooming behavior and anti-social tendencies. Moreover, the patterns of activity in the animals’ brains resembled those seen in humans suffering from schizophrenia.

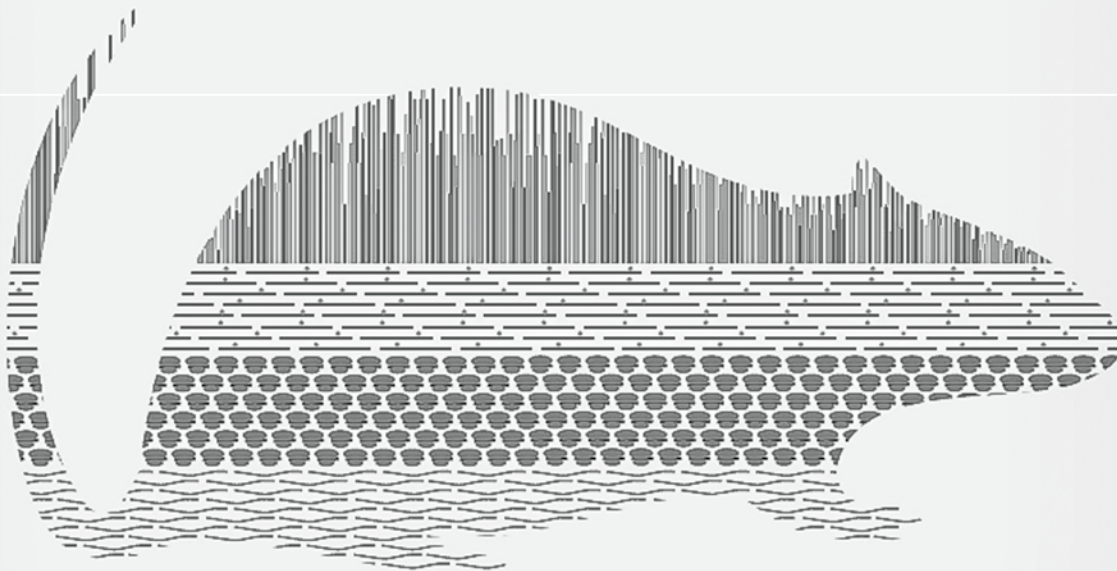
“This discovery implies that changes after birth, not just before birth, are affecting the way the network is set up,” says **Margarita Behrens**, corresponding author and Salk staff scientist.

The results suggest that an alteration in the mGluR5 receptor in these brain cells may be a critical step in the formation of some neurodevelopmental disorders, adds Sejnowski. It’s good news, he says, because the molecular change is potentially reversible.

“The cells are still alive, and if we can figure out how to go in and change some of these molecular switches, we might actually be able to put the cells back into healthy, functioning states,” he says.

Behrens says the study also should be a signal of caution to the pharmaceutical industry to be wary of drugs that affect mGluR5 throughout the whole brain. “There are a lot of clinical trials ongoing looking at modulating mGluR5 for anxiety and Fragile X Syndrome,” she says. “But our results suggest that if you affect parvalbumin neurons, you might get behavioral changes you weren’t expecting.”

More research is needed to show whether the parvalbumin cells’ mGluR5 receptors are linked to disease in humans and, if so, what causes the loss or disruption to the receptors. [Read more](#)



Scientists provide the first comprehensive view of how cellular proteins age in different organs, revealing major differences between the liver and brain in young and old rats.

Not all organs age alike

Study shows first comprehensive view of how proteins age in different organs

AGING IS TYPICALLY THOUGHT OF AS THE GRADUAL DECLINE of the whole body, but new research shows that age affects organs in strikingly different ways. A study published September 17, 2015 in *Cell Systems* provides the first comprehensive view of how cellular proteins age in different organs, revealing major differences between the liver and brain in young and old rats. The findings suggest that how an organ ages may depend on its unique cellular properties and its physiological function in the body.

“Our study showed that organs have different aging mechanisms and that aging is largely driven by changes in protein production and turnover,” says co-senior author **Martin Hetzer**, Salk professor and holder of the Jesse and Caryl Philips Foundation Chair.

“Changes that occur in aging can be diverse and difficult to pin down, and looking simply at one parameter might result in not seeing the whole picture,” says co-first author **Brandon Toyama**, Salk research associate. However, harnessing the power of several state-of-the-art technologies has let the group see age-dependent changes that could not be seen before. The result, according to Toyama, is “a rich resource that should stimulate the generation of new experimentally testable hypotheses, leading to a better understanding of aging on the organism level.”

Aging causes the progressive deterioration in the function of organs, as well as the functions of cells and proteins within them. Past studies have shown that the activity level of genes also changes with age, with most genes showing similar changes in expression across organs. However, a recent large-scale study showed that the vast majority of proteins across different organs don’t change in abundance during aging. These findings have left it unclear how aging affects cellular proteins and whether age-related changes that affect proteins differ across organs.


To answer these questions, Toyama and Hetzer, along with co-first author Alessandro Ori of the European Molecular Biology Laboratory (EMBL), and senior authors Nicholas Ingolia of the University of California, Berkeley and Martin Beck of EMBL took an integrated

“omics” approach instead of focusing on one isolated aspect of gene expression as in past studies. The combination of genomics and proteomics allowed them to simultaneously analyze changes in transcription, translation, protein levels, alternative splicing and protein phosphorylation to gain a comprehensive and quantitative view of protein differences in the liver and brain of young and old rats.

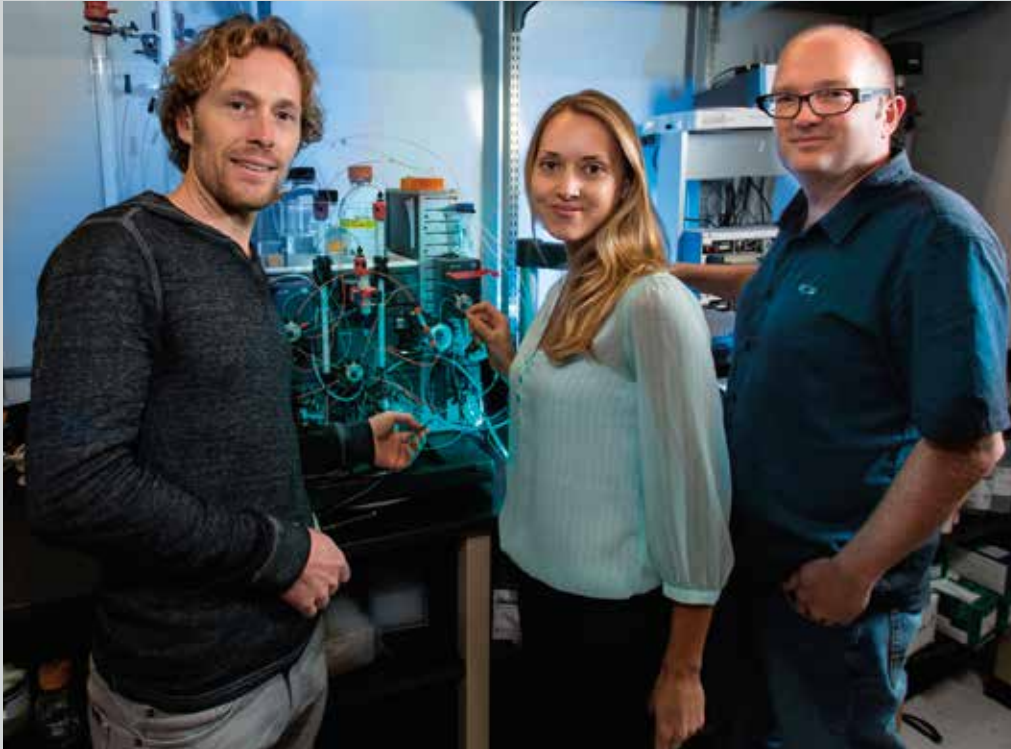
They identified 468 differences in protein abundance between young and old animals, mainly due to changes in protein synthesis. Another set of 130 proteins showed age-related changes in their location within cells, phosphorylation state, or splice form—changes expected to affect the activity level or function of the proteins.

Strikingly, most of these age-related protein differences were specific to one organ. The protein aging patterns seem to relate to the organ’s specific cellular properties or function. Because cells in the liver are frequently replaced throughout adulthood, this organ has ample opportunity to replenish its proteins. By contrast, most neurons in the adult brain are non-dividing cells that must survive for an organism’s entire lifetime, so the longer-lived proteins in the brain are more vulnerable to the accumulation of damage and loss of function over time.

As a result, a larger fraction of proteins was affected by aging in the brain compared to the liver. In the brain, aging altered proteins involved in neuronal plasticity and memory formation, whereas several metabolic networks were altered in the liver. “Based on our findings, we would define aging as an organ-specific deterioration of the cellular proteome,” says Hetzer.

In future studies, the researchers will analyze other organs, such as the heart, to further examine the general and organ-specific effects of aging, and investigate how and why these changes occur. 

As seen in **The Boston Globe**



From left: Christian Klammt, Lucie Ridlon and Björn Lillemeier

New insight into how the immune system sounds the alarm

T CELLS ARE THE GUARDIANS OF OUR bodies: they constantly search for harmful invaders and diseased cells, ready to swarm and kill off any threats. A better understanding of these watchful sentries could allow scientists to boost the immune response against evasive dangers (e.g., cancer or infections), or to silence it when it mistakenly attacks the body itself (e.g., autoimmune disorders or allergies).

Now, scientists at the Salk Institute have discovered that T cell triggering relies on a dynamic protein network at the cell surface, as reported in August 3, 2015, in *Nature Immunology*.

“This is a completely new principle for how T cell activity is controlled—whether it ignores or responds to a threat,” says senior author **Björn Lillemeier**, an assistant professor in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis and the Waitt Advanced Biophotonics Center at the Salk Institute.

T cells become active when a signal—often from a virus or bacterium—triggers molecular sensors on their surface, namely T cell receptors. Previously, scientists believed that additional molecules that bind T cell receptors and help the cell to perceive this signal were like grapes hanging from a vine, occasionally dropping away or joining to begin the process. In contrast, the new discovery shows that T cell receptors are incredibly active—more like a bustling train station, with molecules rapidly coming and going at different intervals of time, says Lillemeier.

A protein called ZAP-70 is well known as a crucial player for kicking the T cell into action. Until now, scientists assumed that a silent form of ZAP-70 floats around inside the T cell until a threat is detected, which recruits ZAP-70 to the cell surface and activates it. By analyzing mutant forms of ZAP-70, Lillemeier’s group discovered that instead of ZAP-70 staying bound to the T cell receptor, it comes in contact with the receptor sporadically.

Each time this happens, ZAP-70 has to adopt an unfavorable shape that forces it back inside the cell. This cycle continues until a second molecule, called Lck, helps it to remain with the T cell receptor. The prolonged stay at the cell surface activates ZAP-70 and prompts the T cell to attack invaders and diseased cells.

This study shows that the steps underlying T cell activation are much more dynamic compared with the less mobile modes that scientists had suspected before. The new study highlights how ZAP-70 and other molecules communicate in space and time, which is crucial for controlling the ultimate activity of a T cell. By understanding this process, Lillemeier says, “We might be able to encourage the immune system to be a little more sensitive in order to recognize and eliminate diseases.” 📺

» **View video:**
www.salk.edu/insidesalk/1215/lillemeier

In first, Salk scientists use sound waves to control brain cells

SALK SCIENTISTS HAVE DEVELOPED A NEW WAY TO

selectively activate brain, heart, muscle and other cells using ultrasonic waves. The new technique, dubbed sonogenetics, has some similarities to the burgeoning use of light to activate cells in order to better understand the brain.

This new method—which uses the same type of waves used in medical sonograms—may have advantages over the light-based approach—known as optogenetics—particularly when it comes to adapting the technology to human therapeutics. It was described September 15, 2015 in the journal *Nature Communications*.

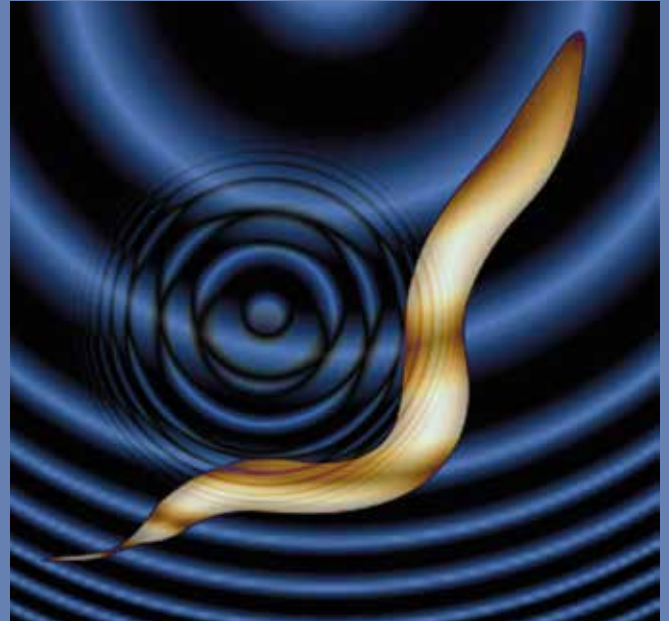
“Light-based techniques are great for some uses and I think we’re going to continue to see developments on that front,” says **Sreekanth Chalasani**, an assistant professor in Salk’s Molecular Neurobiology Laboratory and senior author of the study. “But this is a new, additional tool to manipulate neurons and other cells in the body.”

In optogenetics, researchers add light-sensitive channel proteins to neurons they wish to study. By shining a focused laser on the cells, they can selectively open these channels, either activating or silencing the target neurons. But using an optogenetics approach on cells deep in the brain is difficult: typically, researchers have to perform surgery to implant a fiber optic cable that can reach the cells. Plus, light is scattered by the brain and by other tissues in the body.

Chalasani and his group decided to see if they could develop an approach that instead relied on ultrasound waves for the activation. “In contrast to light, low-frequency ultrasound can travel through the body without any scattering,” he says.

“This could be a big advantage when you want to stimulate a region deep in the brain without affecting other regions,” adds **Stuart Ibsen**, a postdoctoral fellow in the Chalasani lab and first author of the new work. Chalasani and his colleagues first showed that, in the nematode *Caenorhabditis elegans*, microbubbles of gas outside of the worm were necessary to amplify the low-intensity ultrasound waves. “The microbubbles grow and shrink in tune with the ultrasound pressure waves,” Ibsen says. “These oscillations can then propagate noninvasively into the worm.”


Next, they found a membrane ion channel, TRP-4, which can respond to these waves. When mechanical deformations from the ultrasound hitting gas bubbles propagate into the worm, they



cause TRP-4 channels to open up and activate the cell. Armed with that knowledge, the team tried adding the TRP-4 channel to neurons that don’t normally have it. With this approach, they successfully activated neurons that don’t usually react to ultrasound.

So far, sonogenetics has only been applied to *C. elegans* neurons. But TRP-4 could be added to any calcium-sensitive cell type in any organism including humans, Chalasani says. Then, microbubbles could be injected into the bloodstream, and distributed throughout the body—an approach already used in some human imaging techniques. Ultrasound could then noninvasively reach any tissue of interest, including the brain, be amplified by the microbubbles, and activate the cells of interest through TRP-4. And many cells in the human body, he points out, can respond to the influxes of calcium caused by TRP-4.

“The real prize will be to see whether this could work in a mammalian brain,” Chalasani says. His group has already begun testing the approach in mice. “When we make the leap into therapies for humans, I think we have a better shot with noninvasive sonogenetics approaches than with optogenetics.”

Both optogenetics and sonogenetics approaches, he adds, hold promise in basic research by letting scientists study the effect of cell activation. And they also may be useful in therapeutics through the activation of cells affected by disease. However, for either technique to be used in humans, researchers first need to develop safe ways to deliver the light or ultrasound-sensitive channels to target cells. 

» **View video:** www.salk.edu/insidesalk/1215/chalasani

As seen in **Forbes** **BBC** **The New York Times**

Mobile app records our erratic eating habits

BREAKFAST, LUNCH AND DINNER? FOR too many of us, the three meals of the day go more like: morning meeting pastry, mid-afternoon energy drink and midnight pizza. In *Cell Metabolism* on September 24, Salk scientists presented daily food and drink intake data collected from over 150 participants of a mobile research app over three weeks. They showed that a majority of people eat for 15 hours or longer, with less than a quarter of the day's calories being consumed before noon and over a third consumed after 6 p.m.

The purpose of the app is to pilot a way to objectively study the effects of timing food intake in humans. Primed with evidence of how long people eat each day, senior author **Satchidananda Panda**—an associate professor in the Salk Institute's Regulatory Biology Laboratory—along with first author Shubhroz Gill, a former postdoctoral researcher, were able to test whether reducing this daily duration impacts health. In addition to cutting out some bad habits, the authors

hypothesized that a timed feeding schedule could prevent “metabolic jetlag”—when differences in day-to-day or weekday/week-end meal times cause metabolic organs to become out of sync with the body's overall circadian rhythms.

Past experiments in mice from Panda's lab have shown that changing eating duration could protect against obesity and disease.

To begin to explore these implications in people, Gill and Panda designed a mobile app that could be used to collect, analyze and interpret patterns of food intake in humans. They kept the app simple, only requiring users to send pictures of everything they ate or drank, whether it was an entire water bottle or a few bites of a cookie. Each click also captured metadata (such as the location where food was consumed) and recorded a timestamp. Food data were not stored in the app, and reminders were sent about once a day to sustain compliance.

The data revealed cultural food practices, such as Americans' consumption of coffee and milk in the morning, alcohol in the evening, and tea throughout the day. Yogurt was a morning food, sandwiches and burgers were primarily reserved for lunchtime, while vegetables and ice cream were saved for the evening. Photos of chocolate and candy were recorded from pretty much 10 a.m. onward. Larger studies that collect data from patients, shift workers, and different socioeconomic groups will be necessary to offer a more complete picture and to study socio-economic variations.



The researchers also tested whether the app could assist people who wished to adapt to time-restricted feeding, for example, eating for fewer and consistent hours every day. Eight overweight individuals who used to eat for more than 14 hours every day were selected to eat for a 10–11 hour period each day without any recommendation for altering their normal diet. After 16 weeks, assisted by a weekly “feedogram” showing their dietary intake patterns, each lost an average of 3.5% of their excess body weight and reported feeling more energetic and having slept better.

“The study is about developing methods and offers some preliminary insight into what and when people eat,” Panda says. “One should not take away the message that changing the eating duration is the only method to improve health. This may also be risky for individuals with undiagnosed fasting hypoglycemia.”

The smartphone app is available for anyone willing to contribute his/her data to a Salk Institute IRB-approved study at www.mycircadianclock.org. 📱

» **View video:**
www.salk.edu/insidesalk/1215/panda



As seen in **Smithsonian**





Salk-Helmsley Fellow brings new gene-editing technologies to the Salk Institute

THE SALK INSTITUTE IS pleased to announce the appointment of bioengineer **Patrick Hsu** in the innovative Salk Fellows Program. Hsu, who hails from Harvard University and MIT's Broad Institute, aims to develop the next generation of medical

therapeutics by harnessing the gene editing technology known as CRISPR. A gene editing technique originally derived from bacterial immune systems, CRISPR has recently made headlines for its use in modifying DNA with unprecedented ease and accuracy.

"Patrick Hsu will use genome engineering technologies to bring novel insight and therapeutic strategies to a wide range of diseases, particularly neurodegenerative and genetic disorders," says **Inder Verma**, who, along with fellow professors **Rusty Gage** and **Ronald Evans**, is currently leading the program.

The Salk Fellows Program, which was started in 2014 to bring together scientists from different disciplines to tackle big problems in biology, has already seen success. "So far, the program has spurred exciting research and new collaborations that complement many studies currently going on at the Institute," Verma says.

Hsu recently made *Forbes'* coveted "30 under 30" list in 2015 for his contributions to genome engineering, co-authoring peer-reviewed publications in *Cell*, *Nature Biotechnology*, *Nature* and *Science*. He received his BA from the University of California, Berkeley and PhD degree from Harvard University, where he was both a James Mills Pierce Fellow and Harvard Merit Fellow. Working with Feng Zhang and Xiaowei Zhuang at the Broad Institute and the McGovern Institute for Brain Research at MIT, Hsu played a key role in developing the CRISPR-Cas9 genome engineering technologies for efficient and precise application in eukaryotic cells. As a lead scientist at Editas Medicine, he also directed preclinical discovery projects to translate these tools for treating human genetic disorders.

"I am very excited to join the Salk Institute, where my group will focus on developing diverse approaches from synthetic biology, genomics, and neuroscience for the high-throughput interrogation and control of transcriptional and epigenetic cell states," says Hsu. "In collaboration with the world class research community at Salk, I look forward to exploring the biological mechanisms behind neurodegenerative disease and complex genetic disorders, as well as developing novel technologies and therapeutic strategies for their treatment."

Hsu, who is supported by the Leona M. and Harry B. Helmsley Charitable Trust through the Helmsley Center for Genomic Medicine at Salk, joined the Institute in November 2015. 📄

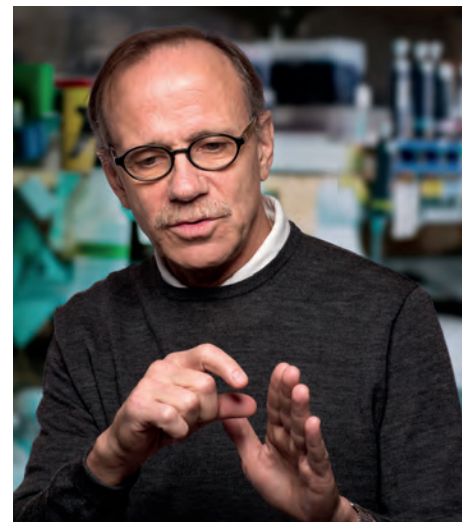
Rusty Gage receives Allen Distinguished Investigator Award to reveal biology of Alzheimer's disease

IN JULY, RUSTY GAGE, PROFESSOR IN THE Laboratory of Genetics, was named one of five recipients of the Paul G. Allen Family Foundation's Allen Distinguished Investigator (ADI) program and will be awarded \$1.5 million to conduct his research. All five of the selected researchers have projects aimed at uncovering the elusive biological foundations of Alzheimer's disease. The projects are funded at a total of \$7 million over three years.

Gage, who holds the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease, studies the underlying cellular and molecular mechanisms of neurogenesis and neurodegeneration to develop avenues to repair damaged or aging brains, such as in Alzheimer's. The goal of Gage's research effort with this award is to separate out the role of aging from the role of disease

in Alzheimer's progression. Gage will use cutting-edge cell culture methods capable of developing patient-specific neurons, as well as high-throughput RNA sequencing and bioinformatics analysis, to compare changes in gene expression due to age with changes specific to Alzheimer's disease. Since both aging and disease impact neuron function, synapses and network function, this work will provide valuable insights into the role of normal aging in disease progression.

"We cannot hope to fight Alzheimer's until we understand the basic biology that underlies the onset and progression of disease," says Tom Skalak, executive director for Science and Technology for the Paul G. Allen Family Foundation. "The Allen Distinguished Investigator projects will provide crucial fresh direction in Alzheimer's disease research,



in part because they include team member perspectives both from within and outside the Alzheimer's field. We know that these kinds of creative, cutting-edge projects will produce new diagnostics, treatments or even cures for this devastating disease." 📄

Julie Law named Rita Allen Foundation Scholar


JULIE LAW, ASSISTANT PROFESSOR in Salk's Plant Molecular and Cellular Biology Laboratory, was named a Rita Allen Foundation Scholar in July. She is one of just seven researchers in 2015 to receive the distinction, which is given to early-career biomedical scientists whose research holds exceptional promise for advancing the frontiers of knowledge about how biological systems function in health and disease.

Law, who holds the Hearst Foundation Development Chair, will receive grants of up to \$110,000 per year for a maximum of five years to conduct innovative research on brain development, antiviral immunity, gene regulation mechanisms, and the interplay

of cancer, inflammation and chronic pain. She joins nearly 150 scientists who have been selected as Allen scholars since the program's inception in 1976.

Law's research focuses on chromatin, the combination of proteins, small RNAs and other molecules that surround genomic DNA and play key roles in controlling gene expression and stability. To investigate how chromatin modifications impact genome stability and development, Law and her team genetically manipulate chromatin components in the plant *Arabidopsis thaliana* by combining classical genetics with fluorescence imaging and new gene-editing techniques.



"We hope that a greater understanding of these processes will ultimately lead to the development of new tools that can be used to correct chromatin defects," Law says. 

Geoffrey Wahl named recipient of National Cancer Institute Outstanding Investigator Award

PROFESSOR GEOFFREY WAHL HAS BEEN named a recipient of the National Cancer Institute (NCI) Outstanding Investigator Award (OIA), which encourages cancer research with breakthrough potential. Wahl, a professor in Salk's Gene Expression Laboratory, will receive \$7.9 million over seven years to further his research. NCI anticipates funding approximately 60 OIAs from the first round of applications submitted in 2015.

Wahl is a past president and elected Fellow of the American Association for Cancer Research, as well as a Fellow of the American Academy of Arts and Sciences and the American Association for the Advancement of Science. He has been involved in various aspects of cancer research for his entire 40-year career.


Currently, Wahl, who holds the Daniel and Martina Lewis Chair, is developing innovative strategies to chart the molecular and genetic underpinnings of breast and other cancers in his effort to discover novel treatments for these complex diseases. With support

from the award he will be able to create new models of basal-like breast cancer (BLBC), a cancer notorious for resisting chemotherapy and for which no targeted therapies currently exist. He will use a suite of cutting-edge tools and techniques—including the latest in gene editing, single cell genomic analysis and bioinformatics—to explore unknown targets of this cancer and reveal more about how common cancer mutations (such as p53 and BRCA1) contribute to BLBC.

Wahl's lab will also examine how environmental stressors, like inflammation, or conditions such as obesity, tie into the disease. His goal is to move the field closer to a new understanding of how cancers initiate and progress, and to develop more effective treatment strategies. This award will give him the long-term support that is required to embark upon projects of unusual potential in cancer research.

"The NCI Outstanding Investigator Award addresses a problem that many cancer researchers experience: finding a balance



between focusing on their science while ensuring that they will have funds to continue their research in the future," says Dinah Singer, director of NCI's Division of Cancer Biology. "With seven years of uninterrupted funding, NCI is providing investigators the opportunity to fully develop exceptional and ambitious cancer research programs." 




Janelle Ayres receives Young Faculty Award (YFA) from DARPA

SALK SCIENTIST JANELLE AYRES HAS RECEIVED AN AWARD of \$500,000 over two years, with the possibility of an additional \$500,000 for a third year, from the Defense Advanced Research Projects Agency (DARPA) to further her research on bolstering a person's microbiome to help their body overcome an infection. Ayres, assistant professor in Salk's Nomis Foundation Laboratory for Immunobiology and Microbial Pathogenesis, is one of 24 to receive DARPA's Young Faculty Award (YFA).

"There is a disconnect between our methods for treating infectious disease and our understanding of the mechanisms that keep us healthy during infection," says Ayres. "With DARPA's support, I hope to develop a better understanding of how the body's microbiome helps defend it against infections and how these mechanisms might be enhanced to improve disease tolerance."

DARPA, which is part of the US Department of Defense (DoD), is proposing a new approach for medical countermeasures against biological threats by shifting away from eradicating pathogens and instead finding therapies for disease tolerance. "Support for basic biomedical research that is aimed at identifying new ways to combat infectious diseases rather than the traditional antimicrobial-based strategies is important and timely, especially given the rate at which infectious diseases are evolving resistance to traditional methods," Ayres says.

In pivotal studies, Ayres was one of the first to demonstrate that animals encode disease tolerance defense strategies and that these defense mechanisms are crucial for survival of lethal infections. A main goal of Ayres' research is to elucidate disease tolerance mechanisms by studying how the body controls and repairs the collateral damage generated during interactions with bad microbes. She is taking an innovative approach grounded in mathematical and evolutionary predictions that uses the beneficial microbes that inhabit our digestive system for damage-control therapeutics.

In September, DARPA hosted a one-day site visit at West Point Military Academy for YFA recipients. A number of such visits are hosted by DARPA around the nation each year to give awardees the opportunity to learn more about DoD research and technology used in the field. YFA recipients and the West Point faculty gave presentations about their work. "The experience was quite unique for a biomedical scientist," says Ayres. "I was exposed to cutting-edge research conducted by scientists in fields distant to my own, including engineering and robot science. Bringing together such distinct researchers will certainly facilitate powerful collaborations." 



Salk Assistant Professor Janelle Ayres and other Young Faculty Award recipients were given a historical tour of the West Point Military Academy campus. From left: Ayres and fellow YFA recipient, Srabanti Chowdhury.



From left: Rusty Gage, Ursula Bellugi, William Brody, Joan Jacobs and Irwin Jacobs



From left: Anirvan Nandy, Sanjay Jha, John Reynolds, Catherine Williams and Zac Davis

Three Salk faculty honored as recipients of senior scientist chairs

SALK SCIENTISTS URSULA BELLUGI, John Reynolds and Alan Saghatelian have been honored with the dedication of three chairs in acknowledgement of their outstanding contributions and commitment to scientific research. Bellugi and Reynolds were named inaugural holders of two newly established chairs—the Salk Founders' Chair and the Fiona and Sanjay Jha Chair in Neuroscience, respectively. Saghatelian received the Dr. Frederik Paulsen Chair.

Bellugi has been professor and director of the Laboratory for Cognitive Neuroscience since its inception in 1970. She received the distinguished honor of being named the inaugural recipient of the Salk Founders' Chair, given on behalf of Salk's president. Bellugi, a pioneer in the study of biological foundations of language and cognition, is regarded as the founder of the neurobiology of American Sign Language. She was the first to discover the principles of naturally occurring signed languages. Her work led to new discoveries about the functional organization of the brain for language, whether spoken or signed, and provides a striking demonstration of neuronal plasticity. Bellugi has also pioneered the study of individuals with Williams syndrome (WS), a rare neurogenetic disorder which gives rise to unusual prosocial behavior. Her program examines links across levels, from behavior to brain imaging and genetics.

Salk President **William R. Brody** says, "Professor Bellugi has had more than a lifetime of amazing achievements in the field of neuroscience. She has been a stalwart contributor to the ambience of the Salk Institute

and it is a wonderful tribute to her that she will be the inaugural recipient of the Salk Founders' Chair."

Reynolds, professor in the Systems Neurobiology Laboratory, was honored with the Fiona and Sanjay Jha Chair in Neuroscience, which was created through the Joan Klein Jacobs and Irwin Mark Jacobs Senior Scientist Endowed Chair Challenge. In 2008, the Jacobses created a challenge grant to establish endowed chairs for senior scientists. For every \$2 million that a donor contributes toward an endowed chair at the Institute, the couple will add \$1 million to achieve the \$3 million funding level required to fully endow a chair for a Salk senior scientist.

Reynolds seeks to understand how and why neural computations fail in brain disease—research that is essential to developing treatments for disorders in which attention and vision are impaired, such as visual agnosia, Bálint's syndrome, autism, schizophrenia and Alzheimer's disease.

Sanjay Jha, CEO of GlobalFoundries and a Salk Institute trustee, says, "It is our great pleasure to support Salk's phenomenal research, particularly in neuroscience, so we can advance our understanding of the basis for neurological diseases such as Alzheimer's and depression, and forge new frontiers in neuronal computation."

Saghatelian, professor in the Clayton Foundation Laboratories for Peptide Biology, received the Dr. Frederik Paulsen Chair. Dr. Frederik Paulsen, board chairman

of Ferring Pharmaceuticals and a trustee of the Salk Institute, established the chair in 1999 in memory of his father, Dr. Frederik Paulsen, Sr. It was first appointed to Salk emeritus **Jean Rivier**.

Saghatelian's lab focuses on the discovery and characterization of novel peptides and their role in diseases such as diabetes, cancer and autoimmune disease. He has pioneered the use of mass spectrometry-based approaches to discover hundreds of new human peptide genes. His lab strives to understand the function and regulation of these peptides in human biology and disease.

Dr. Paulsen says, "We are proud to support the Salk Institute and the exceptional faculty whose groundbreaking research leads to discoveries that have a global impact on human health." 🏢



From left: William Brody, Joan Jacobs, Alan Saghatelian and Irwin Jacobs

Salk supporter Edwin K. Hunter appointed to Salk Institute board of trustees

LONGTIME SALK INSTITUTE SUPPORTER

Edwin K. Hunter, who is president of Hunter, Hunter & Sonnier, LLC, was named to the Salk Institute Board of Trustees in August.

“Edwin’s expertise in tax law, estate planning and philanthropy make him a valuable asset to our board,” says Salk Board Chairman Irwin M. Jacobs. “In addition, he comes into this role with a great deal of familiarity with the Institute having served as chairman of Salk’s yearly Tax Seminar for the past five years, and establishing the Edwin K. Hunter Chair in Molecular Biology in 2013.”

Hunter currently practices law in Louisiana and is a member of the Louisiana, Texas and

District of Columbia bars. As a board certified tax attorney, he conducts talks on tax law, estate planning and philanthropy, and is a published author on these topics. In addition, Hunter has served as a director of companies in the fields of cardiology, orthopedics, stem cell research and nutraceuticals. He is also a founding director of the Community Clinic of Southwest Louisiana and the Community Foundation for Southwest Louisiana.

Hunter serves as a trustee for the Joe W. and Dorothy Dorsett Brown Foundation, the Fritz Lang Foundation, the Olive Tupper Foundation and the Chambers Medical Foundation. He is past chair of the Section on Taxation of the Louisiana State Bar Association, a member



of the Louisiana Educational Television Authority, a member of the Governor’s Commission on Public Broadcasting, and counsel for the Louisiana Commissioner for Indian Affairs. [L](#)

Education Outreach recipient of generous grants

SALK’S EDUCATION OUTREACH PROGRAM IS THE RECIPIENT OF two grants that will help expand its offerings to share groundbreaking biological research with the San Diego community.

Neal Blue, chairman and CEO of General Atomics, has given \$500,000 to Salk’s endowment earmarked for Education Outreach programs such as the Mobile Science Lab and SciChats@Salk. The gift is in memory of Blue’s late wife, Anne, who was an early champion of Education Outreach through the Salk Institute Association and a founder of the annual March of Dimes High School Science Day at Salk.

The Stavros Niarchos Foundation has also given a \$300,000, three-year matching grant to support, develop and expand Education Outreach programs. The funding will support Salk scientists who participate in Education Outreach, as well as help develop new and innovative curricula using the latest technology.

For more information about Education Outreach, contact **Claire Grezemkovsky**, associate director of Foundation Relations, at (858) 453-4100 x2062. [L](#)



Education Outreach’s Dona Mapston (foreground) and Ellen Potter demonstrate how to use a pipette at a local San Diego library.



AFP honors Newman

REBECCA NEWMAN, SALK'S VICE PRESIDENT OF EXTERNAL RELATIONS, HAS BEEN named the 2015 Outstanding Development Professional by the Association of Fundraising Professionals, San Diego Chapter. She was chosen for her overall financial development career as well as her successful leadership of the Campaign for Salk, which exceeded its \$300 million goal a year ahead of schedule.

Newman was honored at an AFP awards luncheon on National Philanthropy Day, November 9, 2015. She was also recently profiled in the *La Jolla Light's* "10 Questions" column. 📖



Pedal pushers: The mercury hovered near 100 degrees, but the SCC-Salk Cancer Center Team suited up and pedaled in the third annual Pedal the Cause San Diego cycling fundraiser September 18-20. The 16-member Salk team traversed courses from 10 to 75 miles through San Diego and Temecula to help raise funds for cancer research at Salk, the UC San Diego Moores Cancer Center, the Sanford Burnham Prebys Medical Discovery Institute and Rady Children's Hospital.



New Salk website

THE SALK INSTITUTE LAUNCHED ITS REDESIGNED website in November and invites you to check out all the new and expanded features. The site was built with form following function and a high priority given to ensuring users can navigate and view content as easily on smartphones and tablets as on a desktop screen. The new site was designed to chronicle the Institute's remarkable beginnings as well as showcase Salk's renowned scientists and their breakthrough research that is making headlines today.

salk.edu

FOLIO: magazine award sweep

INSIDE SALK RECEIVED HONORS FROM THE MAGAZINE

publishing company FOLIO:, which recognizes excellence in online and print magazines through yearly editorial and design awards.

Inside Salk won best cover for the December 2014 "Brain Gain" issue in the "nonprofit/consumer" category, which featured a design based on neuroscience research by **Tom Bartol**, **Terrence Sejnowski** and colleagues. The magazine also received five honorable mentions in the following categories: series of articles ("Next Generation"); single article ("Brain Gain," December 2014); feature design ("The Legacy of Jonas Salk," August 2014); overall design (December 2014 issue); and photography ("Next Generation: Avani Wildani," December 2014). For more information, please visit: www.folioawards.com.





Dr. Frederik Paulsen and Rusty Gage



Irwin Jacobs and Dr. Frederik Paulsen



Irwin and Joan Jacobs



Dr. Frederik Paulsen and Rebecca Newman

Venice offers picturesque setting for inaugural Salk Summit

VENICE, THE CITY OF BRIDGES, SERVED AS A beautiful backdrop for this year's inaugural Salk Summit, which was graciously underwritten by Dr. Frederik Paulsen. The four-day summit, which took place June 14-17, included scientific presentations and interactive discussions with eight of Salk's esteemed faculty, as well as talks by Salk leadership about the future of the Institute.

Riveting scientific presentations given throughout the summit ranged from "Human Disease Modeling and Aging" and "Policing the Immune System" to "New Frontiers in Cancer" and "Technology, Cells and Organogenesis." Open discussion sessions with Salk faculty were incorporated into the program, providing a unique platform for conversations on a variety of science-related topics. Presenting Salk faculty included: **Janelle Ayres, Rusty Gage, Martin Hetzer, Juan Carlos Izpisua Belmonte, Greg Lemke, Clodagh O'Shea, Alan Saghatelian and Reuben Shaw.**

The Salk Summit was open to major individual and foundation donors who, through their ongoing support, have helped make the Campaign for Salk extraordinarily successful. ■■■





Remembering PAVAROTTI

BENEFITING PANCREATIC CANCER RESEARCH AT THE SALK INSTITUTE

More than 3,000 people attended “Remembering Pavarotti,” a star-studded concert to benefit the Salk Institute’s pancreatic cancer research on September 25 at the Dorothy Chandler Pavilion in Los Angeles. Thanks to the leadership and dedication of host William Isacoff, the event was a resounding success.



From left: Ronald Evans of Salk, soprano Renée Fleming, tenor Andrea Bocelli and William Isacoff

MANY THANKS TO THE FOLLOWING SPONSORS:

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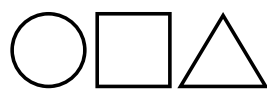
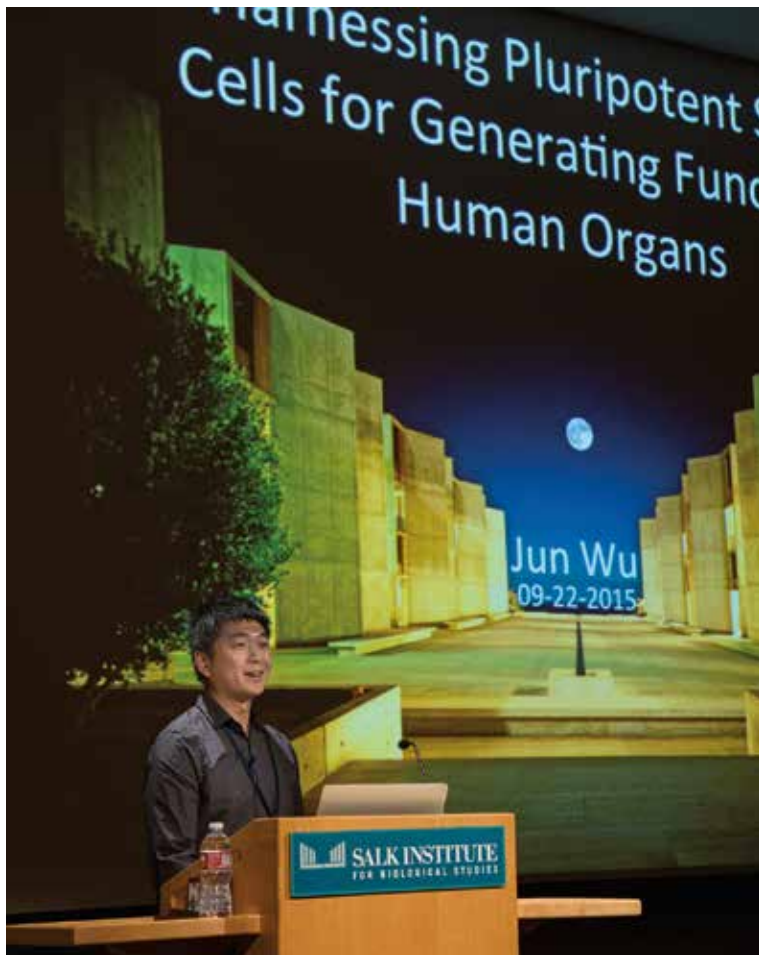
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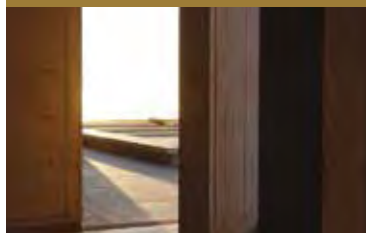


Back to Basics
LECTURE SERIES at the SALK INSTITUTE

Back to Basics lecture profiles pluripotent stem cells

SALK RESEARCH ASSOCIATE JUN WU CAPTIVATED A Back to Basics audience of more than 160 people in September with his talk on harnessing pluripotent stem cells to generate functional human organs. Wu, who works in the lab of **Juan Carlos Izpisua Belmonte**, explained how human pluripotent stem cells offer the hope to eradicate donor organ shortages owing to their unlimited proliferation and ability to generate any tissues in the body; however, these stem cells have yet to be harnessed to attain this goal. A lively conversation continued during the reception that followed.

The Back to Basics program is offered twice a year to the public interested in learning more about the dynamic research conducted at the Salk Institute. There is no cost to attend. For more information about the next Back to Basics event, which will be held March 22, 2016, please contact **Jennifer Rothrock** at (858) 500-4881 or jrothrock@salk.edu. 📞



PIANIST VADYM KHOLODENKO, WHO earned the gold medal at the 2013 Van Cliburn Competition, gave a stellar performance on October 11, the first concert in the six-part Salk Science & Music Series. This is the third season of the music series, which features performances by established and emerging classical and jazz musicians, as well as riveting talks on the latest scientific discoveries by Salk scientists.

WWW.SALK.EDU/MUSIC



Sizzling evening of jazz makes for an unforgettable 20th annual Symphony at Salk

OVER 750 SALK SUPPORTERS AND MUSIC LOVERS were fêted with an unforgettable 20th annual Symphony at Salk on August 29. The event, which sold out weeks in advance, included dinner by acclaimed chef Jeffrey Strauss of Pamplemousse Grille and a sizzling music program featuring the San Diego Symphony, jazz guitarist John Pizzarelli and trumpeter Chris Botti. The event raised over \$900,000, which will support Salk's scientific research and education outreach efforts.

Maestro Thomas Wilkins, one of the country's most distinguished conductors, returned to lead the San Diego

Symphony for the 11th consecutive year. Wilkins brought an energy and excitement all his own, making him a perennial favorite at Symphony at Salk. Pizzarelli, also a Salk favorite, made his second guest appearance, having first performed at Symphony at Salk in 2008. He opened with a beautiful rendition of "They Can't Take That Away From Me." Leading off the second half of the show was a spectacular performance by Grammy award-winning trumpeter Botti, who left the audience breathless.

Another highlight of the night was a special tribute to Symphony at Salk's longtime honorary chair, Françoise





Gilot-Salk. For the past 20 years, Gilot-Salk has contributed one of her paintings for the event's visual theme. Concertgoers had the opportunity to view a colorful display of Gilot-Salk's posters from the past 20 years lining the entrance to the courtyard.

This magical evening would not have been possible without the support of title sponsor Conrad Prebys and Debra Turner, along with Audrey Geisel, Joan and Irwin Jacobs, Liz Keadle, Martina and Daniel Lewis, Becky and Ralph O'Connor and Carole and Jerome Turk, plus a host of sponsors who return each year. All together, it was a stellar night for the Institute, and a wonderful way to celebrate 20 years of this time-honored event. 🎵



Françoise Gilot-Salk
SYMPHONY AT SALK HONORARY CHAIR





Insider's View

William R. Brody, MD, PhD
President, Salk Institute
Irwin M. Jacobs Presidential Chair

Salk discoveries will empower precision medicine

IN HIS 2015 STATE OF THE UNION ADDRESS, PRESIDENT OBAMA announced that he's launching the Precision Medicine Initiative—a bold new research effort to revolutionize how we improve health and treat disease.

Obama noted that most medical treatments have been designed for the average patient, a one-size-fits-all approach that can be very successful for some diseases but not for many others. "Precision medicine, on the other hand, is an innovative approach that takes into account individual differences in people's genes, environments and lifestyles," he said.

Precision medicine is particularly applicable to patients with cancer, and, in fact, has been applied for the past decade to thousands of patients with malignancies. Regardless of the cause, the accumulated effect of one or multiple genomic alterations is the proliferation of cancer cells that appear to have immortality and can migrate and divide rapidly.

Before precision medicine, drug therapy for cancerous tumors consisted of cytotoxic drugs, such as Cytoxan, Temodar and Matulan that non-specifically killed rapidly dividing cells. Because most cancers divide rapidly, they were highly susceptible to these agents, but so were other rapidly dividing cells such as those lining the intestine and bone marrow cells that produce blood cells—which resulted in serious side effects.

One form of blood cancer, chronic myelogenous leukemia (CML), was first recognized in 1845 and the first attempt at treatment using arsenic trioxide was reported in 1865, then 'rediscovered' in the 1930s. Little progress was made until 1960, when scientists Nowell and Hungerford discovered an altered chromosome, called the Philadelphia chromosome (Ph+), associated with certain forms of leukemia, especially CML.

In the late 1970s, Salk scientist **Tony Hunter** discovered an enzyme (protein) called tyrosine kinase that was associated with cancers in animals. Over the next several decades, Hunter and colleagues around the world discovered and described alterations in a family of over 500 protein kinases, about half of which have been implicated in various forms of cancer.

In 1973, scientist Janet Rowley reported that the Philadelphia chromosome resulted from segments of DNA on chromosome 9 that essentially traded places with segments on chromosome 22.

Over the next few years, the work of several researchers, including Salk Non-Resident Fellow David Baltimore, showed that the swapping of genes created a defective gene. The gene produced an altered tyrosine kinase that drove overproduction of defective white blood cells seen in CML. Shortly thereafter, scientists at Novartis and the Oregon Health and Science University developed a new drug called imatinib that inactivated the altered kinase enzyme. Many other scientists were involved in the chain of discoveries that lead to imatinib.

In CML patients who had the Philadelphia chromosome, imatinib was 97 percent successful in stopping the growth of the tumor. Results of this spectacular nature were previously unheard of in the annals of cancer medicine, and following FDA approval, Novartis marketed the drug under the name Gleevec. Many CML patients who started taking the drug in 2001 when the FDA approved it are still taking the drug and are healthy today.

Subsequent to the dramatic success of Gleevec, Novartis and other drug companies went on to develop drugs against many of the other altered forms of tyrosine kinases. Today, there are more than 100 drugs, either approved or in clinical trials, to target protein kinases, mostly for cancer therapy.

What we have learned is that the more detailed molecular knowledge we obtain from basic scientific studies about the nature of various forms of cancer the better we can evaluate a tumor's strengths and weaknesses. There are a myriad of changes that can occur following genetic alterations in cancer—these can affect enzymes, metabolic pathways (or networks of pathways) as well as regulatory genes, such as oncogenes or tumor suppressor genes. Analysis of these changes, called *polyomics*, creates a wealth of data that can inform the development of new therapies and the tailoring of treatment selections to an individual patient.

This, then, is the future potential of precision medicine: bringing together a wealth of information gained from basic scientific studies on cancer with polyomic analysis of an individual patient. There are many challenges to the widespread adoption of precision medicine for cancer, but in highly specialized cancer treatment centers—thanks to the foundational science of the past few decades—the future is already here. 🏗️

Salk Science Leads to Discoveries

IMPACTING HUMAN HEALTH BEGINS AT THE SALK

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 x1521.

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SALKEXCELLERATORS

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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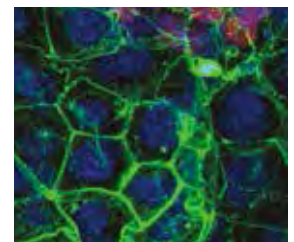
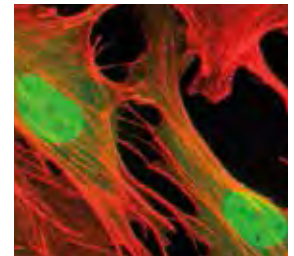
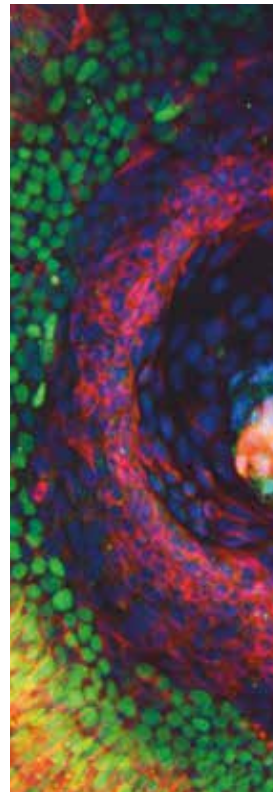
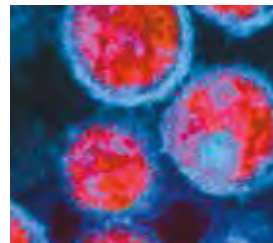
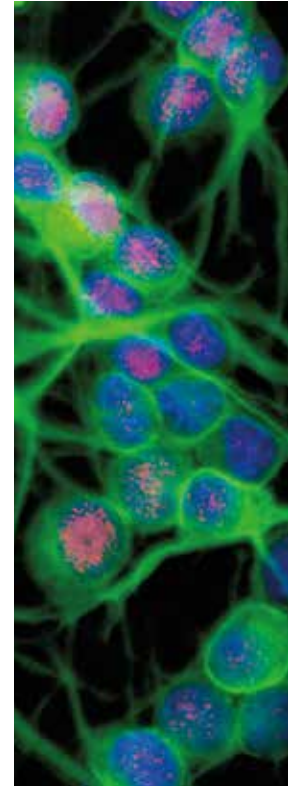
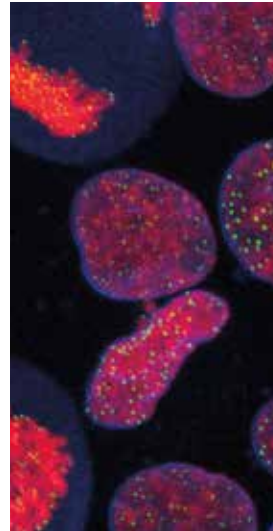
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SPECIAL PROJECTS

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.

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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.



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Salk Calendar

JANUARY

- 24 Salk Science & Music Series
featuring the Victor Goines Quartet
- 27 San Diego Salkexcellerators Lecture

FEBRUARY

- 21 Salk Science & Music Series
featuring Cicely Parnas

MARCH

- 20 Salk Science & Music Series
featuring Julia Bullock
- 22 Back to Basics Lecture
- 30 Salk Women & Science Lecture

APRIL

- 16 Explore Salk Open House
- 24 Salk Science & Music Series
featuring Sean Chen & Karen Joy Davis



2015-2016 SEASON



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