



InsideSalk

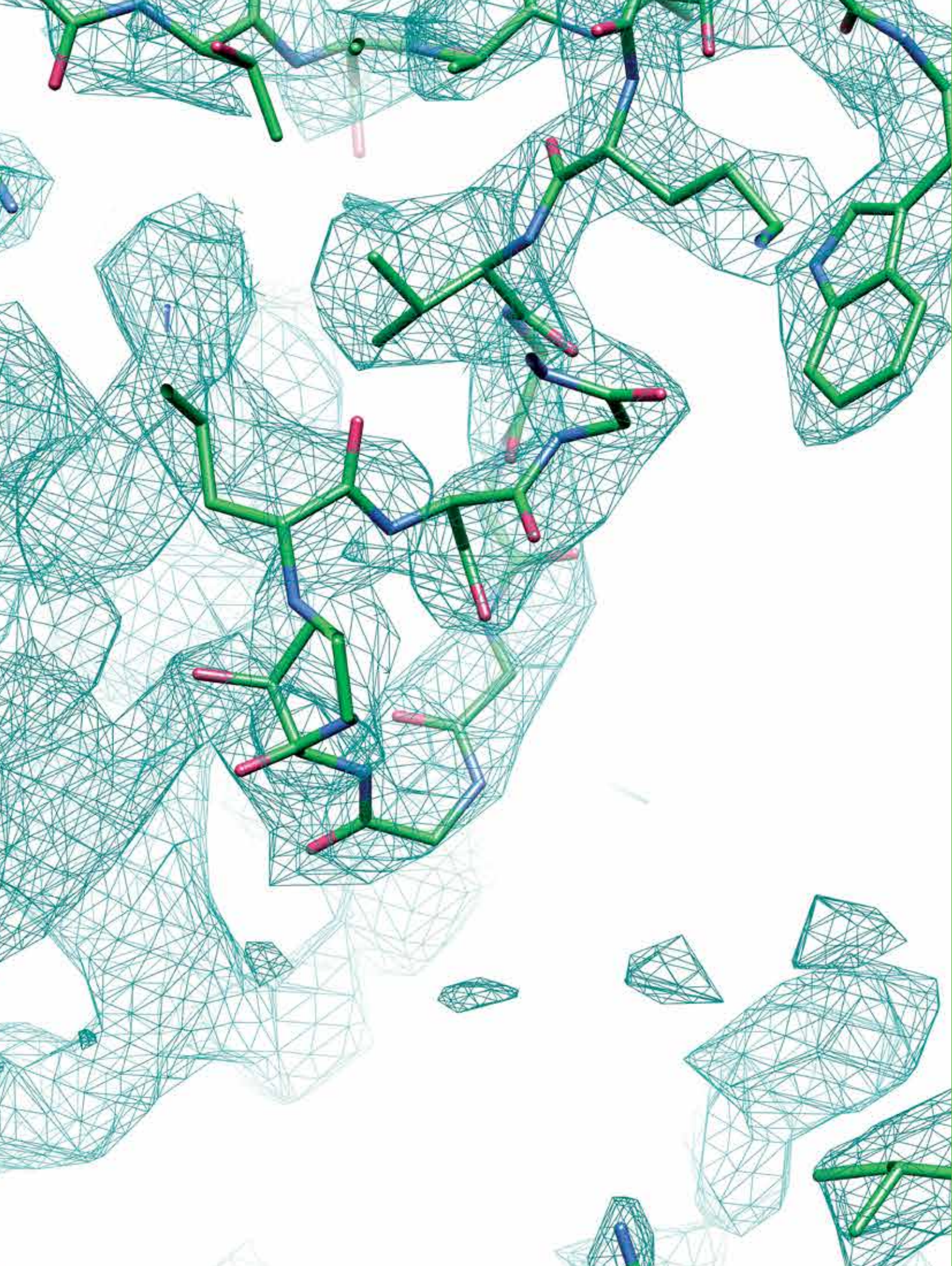
Where cures begin.
Salk Institute 04 | 15

THE POWER OF CONNE CTIONS



LECTIONS

New collaborators from divergent fields are tackling
some of biology's biggest questions



April 2015

Inside Salk



One on one with... Jean Rivier



Next generation: Zuyu Zheng and Yongxia Guo



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Dear Friends,

THE MOST INNOVATIVE IDEAS OFTEN COME FROM SURPRISING places—and that's especially true in science. Biologists and computer scientists, for instance, see the world in very different ways, but the happy collision of those worldviews can lead to something entirely new. The Salk Institute has always embraced and encouraged such cross-pollination, and Salk scientists often mention this “culture of collision”—to coin a phrase—as a big part of why they chose to come here.

The feature story in this issue of *Inside Salk*—“The Power of Connections”—examines some significant advancements produced by these interdisciplinary partnerships. **Alan Saghatelian** and **Reuben Shaw**, for example, are uniting their respective expertise in biology and chemistry to better understand cancer metabolism. In our “Next Generation” article, you’ll learn how Salk researchers and spouses **Zuyu Zheng** and **Yongxia Guo**, though working in separate labs, collaborate to study plant survival mechanisms, an issue vital to future crop production. And you’ll see how rewarding partnerships often extend beyond the Salk campus. A case in point is **Martyn Goulding**, who recently teamed up with researchers at Harvard Medical School to identify a neural mechanism in the spinal cord that appears to be implicated in sending erroneous pain signals to the brain, a major discovery that could benefit patients who suffer from such disorders as fibromyalgia and phantom limb pain.

A number of other notable discoveries are featured in the “Discovery Roundup” section. **Beverly Emerson** has uncovered details about how cancer uses a diversification strategy to develop drug resistance and **Geoffrey Wahl** has found a way to identify previously undetectable protein interactions, which could provide new targets for cancer therapeutics. **Katherine Jones**, also investigating proteins, has identified a protein integral to active HIV replication and one that enables the disease to strike the immune system years after lying dormant. Two discoveries, from the labs of **Ronald Evans** and **Satchidananda Panda**, drew worldwide attention.



William Brody

Panda’s study found that confining caloric consumption to an 8- to 12-hour period—as people did just a century ago—might stave off high cholesterol, diabetes and obesity. Evans’ team developed a new compound, fexaramine, that can trick the body into thinking it has consumed calories and burned calories, thus raising hopes of a successful diet pill.

No scientific advancement occurs without tremendous teamwork and one partnership I am cognizant of on a daily basis is the one we share with you. Your interest in and support of fundamental biological research buoys our determination and drives our discoveries. For that, we are all thankful. 🏠

William R. Brody

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



ON THE COVER


The field of single-particle cryo-electron microscopy (cryoEM) enables researchers to reconstruct biological macromolecules in 3D, revealing more about their form and function. This image shows a small portion of a 3D reconstruction of a large ribosomal subunit of a multi-protein complex responsible for cellular protein synthesis.

The wire mesh displays reconstructed density from cryoEM data. The data can be interpreted in terms of atomic coordinates, which are displayed in ball-and-stick form. Regions displayed without an atomic model are areas that have not yet been modeled and require further interpretation.

Courtesy of Dmitry Lyumkis

A man with dark, curly hair, wearing a light blue and white striped button-down shirt and dark grey trousers, stands in a laboratory. He is leaning his right hand on a piece of equipment. The background is filled with various lab instruments, including what appears to be a microscope and other scientific equipment. The lighting is bright, and the overall atmosphere is professional and scientific.

ECTIONS



New collaborators from divergent fields are tackling some of biology's biggest questions

THE POWER OF CONNECTION

IF THE UNITED STATES CAN BE DESCRIBED AS THE “MELTING POT” OF countries, the Salk Institute might be called the “reaction flask” of scientific institutes: its mix of scientists from varying fields produces surprising—and even life-changing—results.

Since its inception, the Institute has demonstrated that intellectual collisions between scientists from different fields can spark remarkable discoveries. Bringing together first-rate researchers in physics, behavioral psychology, genetics, plant science and other fields has led to everything from cancer drugs to a new understanding of the biological basis of language.

Now, Salk is doubling down on this strategy. Rapid technological advances are allowing scientists to connect across fields in ways that were never before possible. With this rise in technological capability has come a new generation of scientists who are experts in working across multiple fields. In recent months, the Salk Institute has recruited a new batch of such researchers to tackle major problems in biology from entirely new perspectives.

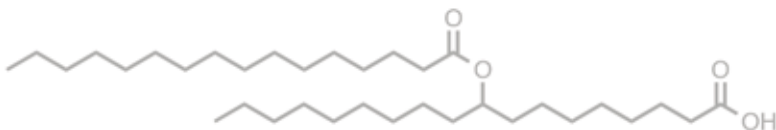
These incoming experts in chemistry, computer science and imaging aren't just providing savvy technical know-how to other labs, but are offering unique approaches that, when partnered with traditional biology, could help solve fundamental problems in human health.

Consider **Alan Saghatelian**, for instance. Saghatelian joined Salk last summer, bringing with him a perspective from outside molecular biology that is already yielding new insights ranging from cancer research to DNA visualization.

Saghatelian first began to move into the field of biochemistry while a chemistry undergraduate at the University of California, Los Angeles. He approached his fourth year wanting to do more than just develop new methods to create chemicals.

“In chemistry, you engineer a molecule and you're done. In biology, you make discoveries and it becomes a first step in a long journey,” says Saghatelian. “I didn't want to be the guy waiting for someone to make a cool discovery and then make the drug. I wanted to be part of the discovery to help uncover the unknown.”

Eventually, Saghatelian found himself in a unique position to contribute to that discovery process. He became an expert in mass spectrometry, a technology that charts the weight of molecules and can reveal the thousands of molecules present in cell or tissue samples. While many scientists use mass spectrometry routinely, Saghatelian is pushing this technology to new limits to solve problems for which no other solution exists.



» View video: www.salk.edu/saghatelian

From left: Reuben Shaw and Alan Saghatelian

Capturing small molecules for

Tiny molecules can provide a completely different view of biology from the more common sequencing methods (which focus on DNA and RNA) and may help uncover new avenues to treat disease. Even so, many of these small molecules are still relatively unknown.

Leveraging his chemistry background and the latest mass spectrometry technologies, Saghatelian is taking a closer look at small molecules. By seeing how they change between samples—for example, between cancerous and noncancerous tissues—he can find molecules of interest that could point to potential treatments for disease.

Identifying and synthesizing a previously unknown small molecule is slow and difficult, but there have been payoffs. As an assistant professor at Harvard University, Saghatelian partnered with a local medical center to discover an entirely new class of lipids, called FAHFAs. The group found that, when they administered FAHFAs to mice with the equivalent of type 2 diabetes, the elevated blood sugar in the mice dropped. The lipids also show up in normal human tissue and less so in at-risk patients, hinting at their use for a potential diabetes therapy.

In a collaboration that spins off of his research in metabolism, Saghatelian is also partnering with Salk Professor **Reuben Shaw** to look for weaknesses in cancer. Shaw's lab has been able to show that genes that are critical in cancer are also key players in metabolism. Shaw and Saghatelian are trying to use the links between cancer genes and metabolism to identify specific small molecules that cancer cells need to grow.

Now, they will use mass spectrometry to detect and quantify thousands of small molecules in cells where cancer genes are turned on in the hopes of uncovering—and eventually blocking—the molecules and pathways cancer uses to grow.

“Alan has cutting-edge techniques to discover brand new natural lipids in our bodies that regulate metabolism and may fight diabetes,” says


Shaw. “But these same methods can be used to study what lipids and other metabolites are different between cancers with one type of gene mutation versus the same type of cancer, but bearing a different gene mutation.” By decoding the metabolic changes in closely related cancers, they may be able to discover opportunities for new precision cancer treatments and cancer diagnostics.

In another collaboration—spurred on after informal conversations—Saghatelian is partnering with Associate Professor **Clodagh O'Shea** to better image critical protein-protein and protein-DNA interactions within living cells.

“The idea came about right at that bleeding edge of biology and chemistry,” says O'Shea, holder of Salk's William Scandling Developmental Chair. O'Shea—who also works with Saghatelian to tag cancer-killing viruses with small molecules—credits many factors to these and other exciting collaborations that are commonplace at the Salk Institute. “You don't have 10 researchers in the same field competing against each other. Instead, you have the best-of-the-best from their respective fields working together. Everyone here is a singularity, experts in their particular areas, but with converged themes,” she says.

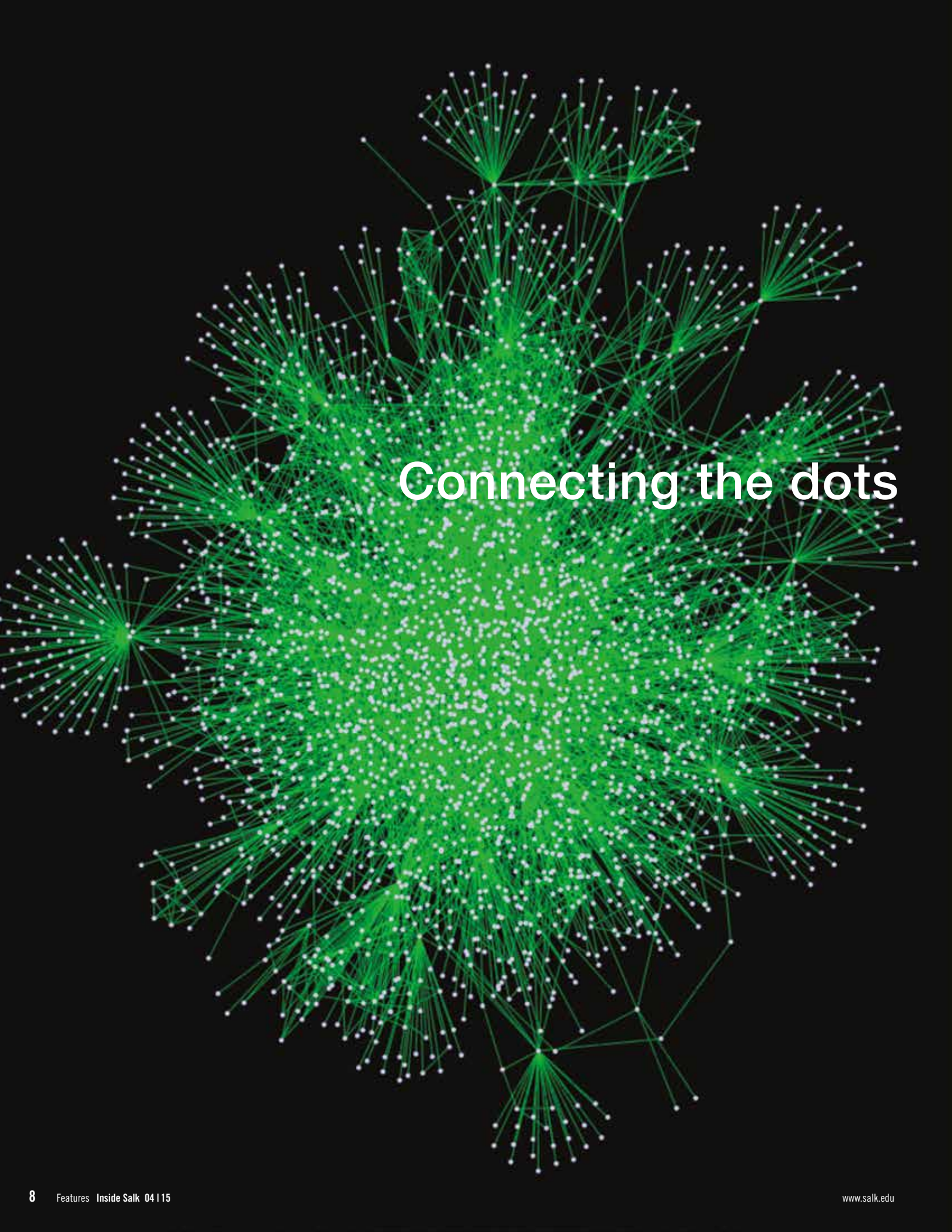
Saghatelian is also working with other Salk labs to understand jumping genes and genetic mosaicism; distinguish how stem cells may differ from each other more than expected; find out how cells in the brain known as astrocytes contribute to Alzheimer's disease; and uncover the connection between metabolism and the cancer gene p53, to name a few.

“The integration of mass spectrometry into the Salk will enable new questions to be asked and answered in all fields, including cancer, metabolism and neurodegenerative disease,” says Saghatelian. “These exciting collaborations are just the beginning.”



big answers.

In this close-up look at a mass spectrometer, molecules are being ionized from samples of interest, revealing their molecular weights.



Connecting the dots



From left: Ullas Pedmale and Saket Navlakha

between biology and computing

What does stomach flu have in common with an anti-government hacker? What can Google's server system teach us about how the brain handles sleep deprivation? And how can a classic game theory quandary explain plant growth?

Assistant Professor **Saket Navlakha** is exploring such questions by striving to uncover algorithms in nature—strategies of how molecules, cells and organisms solve computational problems without a central commander. Discovering shared principles can help advance the fields of both computer science and biology, leading to improved computing algorithms and a better understanding of large, distributed biological systems.

While computer science and biology have had a long history of collaboration, computer scientists working in biology have typically been limited to analyzing troves of experimental information (e.g., imaging or sequencing data) to uncover patterns. Now, computing experts are doing more than just mining information, says Navlakha. Advances in “big data” and jumps in technology in the last few years have triggered this shift.

“There’s been a resurgence of computer science interfacing with biology because now we can really manipulate biological systems in ways we couldn’t before,” says Navlakha, who began his research in computing and graph theory but moved to exploring biological networks at the encouragement of his advisor at the University of Maryland, College Park. “We can get into finer details of biological processes instead of staying at a broad, abstract level.”

Armed with new algorithmic and computational technologies, Navlakha, who recently joined the Salk Institute, has already begun to explore potential collaborations that cover the spectrum of biological questions. Like Saghatelian, Navlakha’s expertise can apply to virtually all areas of biology, from protein interactions to disease outcomes, plant growth to brain development.

Groundbreaking work by Salk Assistant Professor **Janelle Ayres**, for example, suggests that killing a pathogen with antibiotics might not be the most efficient way to treat an infection. Rather, she predicts that

developing therapeutics aimed at the collateral damage done to an organism (rather than the pathogen itself) would lead to new infectious disease treatments that pathogens will not evolve resistance to.

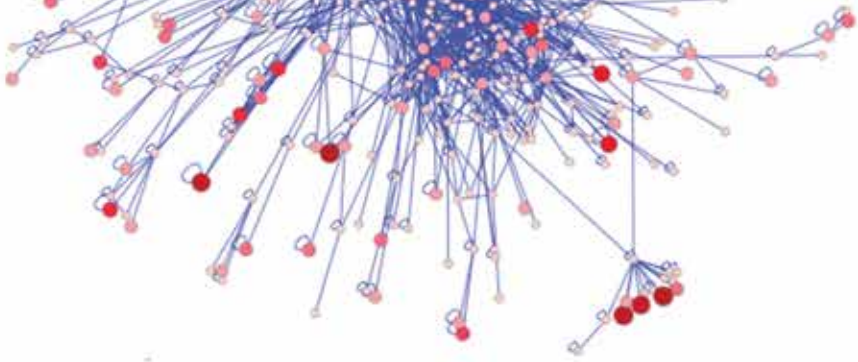
In conversations with Ayres, Navlakha saw parallels in how governments or companies handle security breaches by hackers. When faced with a digital invasion, organizations must decide if they will use their resources to aggressively go after the hackers (pathogens) or focus on stabilizing their system and minimizing collateral damage. The two researchers began to collaborate to develop computational analyses that encompass the principles of both host-pathogen interactions and hacker defense.

“My lab has the expertise to experimentally test our predictions at the level of a single individual and within model populations, but it will be important to predict within an epidemiological context how our approaches to treating infectious diseases will impact the emergence and spread of resistant pathogens,” says Ayres. “In our collaboration with the Navlakha lab, we will be able to execute such computational analyses.”

Navlakha adds, “We’re interested in seeing if there are analogies in the way tradeoffs are made in host-pathogen interactions that might be similar in network engineering and security.” Finding such parallels could also help both fields develop efficient ways to deal with cyber or biological invasions.

“The ability to participate in interdisciplinary collaborations with such ease is the beauty of Salk,” says Ayres. “It is only through such collaborations that science can be pushed into new and unexpected directions, which ultimately leads to the most exciting discoveries.”

In addition to this work, Navlakha plans to connect with neuroscientists to explore intriguing parallels between the brain and computers. When you do a search on Google, a central commander selects one of thousands of servers with a low activity load to take on that request. By evenly distributing requests for work, the system is able to quickly provide accurate answers to users. The brain also does its own “load balancing” (called homeostasis) to generate responses in a timely manner. The brain, however, does all of this without a central commander.



“The big theme of all of these collaborations is in trying to develop a computational understanding of life.”

— Saket Navlakha

“Every neuron is active on its own, but emergently from the brain’s actions you get a very robust and load-balanced system,” says Navlakha. “It would be really cool to study this process of how neurons solve the load-balance problem and use that insight to improve the fault tolerance and performance of distributed networks, like the Internet.”

A better understanding of how load balancing in the brain works could point to ways to alleviate disturbances, which often happen in mental illness and potentially even in sleep deprivation, where overworked neurons are not able to rebalance work loads. To explore this and other questions related to the brain, Navlakha has begun conversations on potential neuroscience collaborations with Salk faculty, such as **Kenta Asahina**, **Xin Jin** and **Charles Stevens**.

Navlakha is also talking with Salk’s plant biologists to try to better understand how plants cooperate or compete for available sunlight. In economics, a hypothetical scenario called the prisoner’s dilemma explores the payoffs of cooperation versus competition. If two suspects are arrested for a crime, kept in separate rooms and individually asked who was responsible, they can each choose to stay loyal and not give up any information (cooperate) or betray each other (compete). If both remain loyal to each other (cooperate) by staying silent, they get light sentences; but if both blame each other (compete), they are deemed liars and given a medium sentence. Finally, if only one points the finger and the other stays silent, the betrayer (competitor) goes free while the betrayed (cooperator) gets a long sentence.

While talking with Salk plant researcher **Joanne Chory**, Navlakha discovered that plants have a similar quandary. If two plants are growing in the same space, a few outcomes can occur: both might grow normally and share the sunlight (cooperate); both could grow aggressively in hopes of shading the other plant (compete); or one could grow more aggressively than the other, dooming the smaller plant. Competing uses up precious resources the plants have, so it’s not always in their best interest to grow aggressively.

“When I first met Saket last year, my lab had been studying shade avoidance for about 10 years,” says Chory, a Howard Hughes Medical Institute investigator and the Howard H. and Maryam R. Newman Chair in Plant Biology. “We had learned quite a bit about the process—just enough to know that we had reached a bottleneck. We needed help because our models for how plants alter their growth rates in the shade were becoming more complex when ideally they should become simpler.”

Chory and her postdoctoral researcher, **Ullas Pedmale**, met with Navlakha to discuss how to analyze the large amounts of gene expression data the lab had gathered and derive a network model for how plants grow. “Saket’s questions about whether plants cooperate or compete got us to think about shade avoidance in a totally different way,” says Chory.

By studying how and why plants cooperate or compete with each other for sunlight in the framework of the prisoner’s dilemma, Navlakha hopes to quantify how nature evolved these strategies in plants. Such an understanding could provide valuable knowledge to the field of agriculture by suggesting which species to plant next to each other—and at what times and conditions—to control growth yields.

“The big theme of all of these collaborations is in trying to develop a computational understanding of life,” says Navlakha.





an edge across the cut, existing with probability q (via a lateral edge, existing with probability $1-q$) that is distance $d-1$ from s . Thus

$$\begin{aligned} F_{S,d} &= (1-q)F_{S,d-1} \\ F_{T,d} &= (1-q)F_{T,d-1} \end{aligned}$$

The base case for these recurrences in $\mathcal{H}(S)$ is at distance 0 and $F_{T,0} = 1$ (i.e. every node in

$\mathcal{H}(S)$ is at distance 0 from s). The probability that s is at distance d from t is $F_{S,d} - F_{S,d-1}$. The expected distance between s and t is

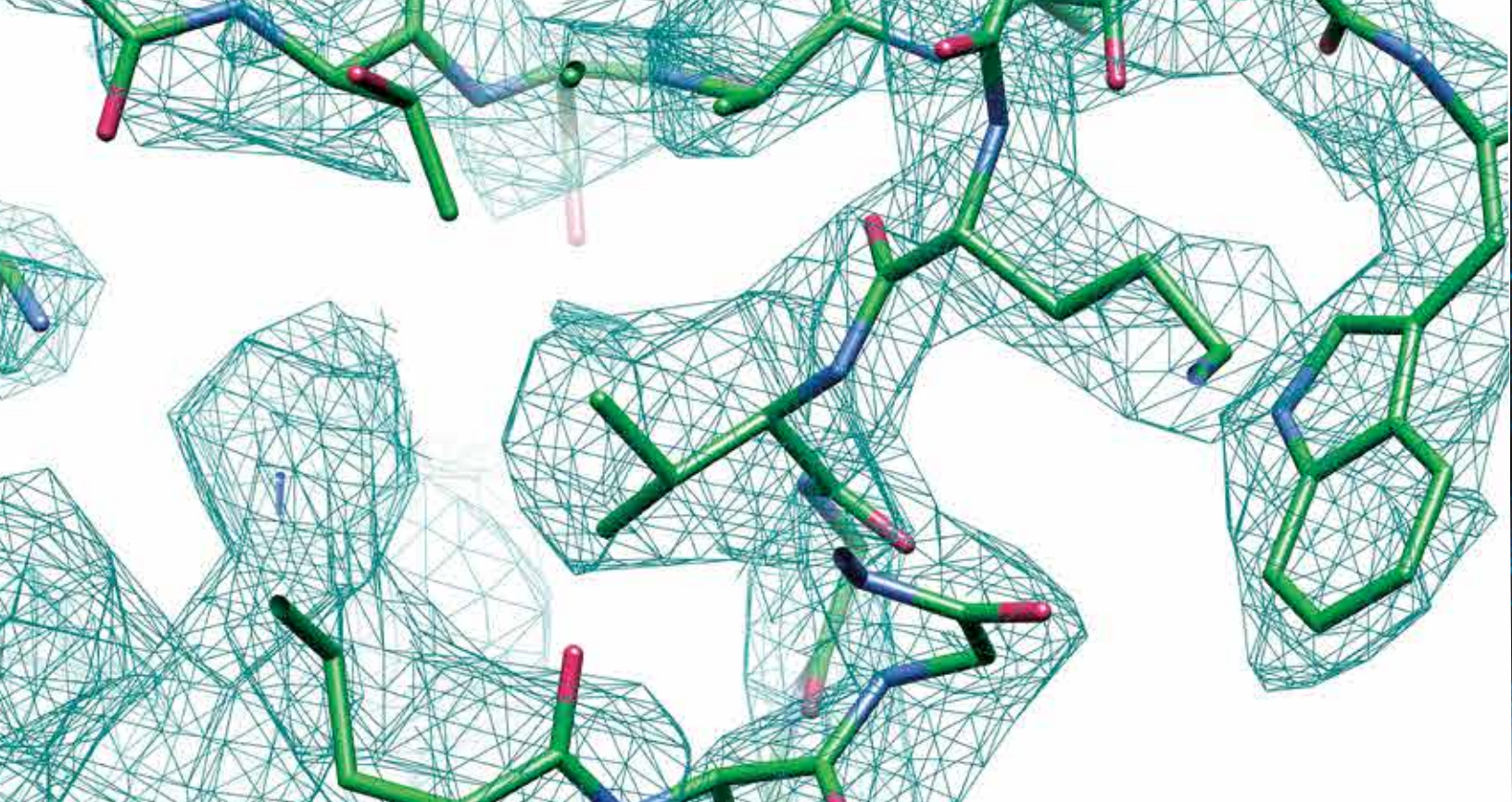
$\sum_{d=0}^{\infty} d(F_{S,d} - F_{S,d-1})$. This is the expected distance between s and t in $\mathcal{H}(S)$. The first factor corrects for the probability that s is not connected to any node in $\mathcal{H}(S)$ (which is $1 - (1-q)^{n_S}$). The second factor corrects for the probability that s is not connected to any node in $\mathcal{H}(T)$ (which is $1 - (1-q)^{n_T}$). We therefore have the following relation:

When these relations are combined, we obtain a formula for the expected distance between s and t in $\mathcal{H}(S)$ and $\mathcal{H}(T)$.

To test the correspondence between theory and practice, we generated random $\mathcal{H}(S)$ and $\mathcal{H}(T)$ graphs with various ratios of n_S/n_T such that the expected number of edges is approximately 500000 with $n_S=1000$. For each ratio, we computed the average distance between random s - t pairs and compared these values with those predicted by our theoretical results above and found very close correspondence (Figure \ref{fig:thy}).

Figure 5.5: Theoretical results for network optimization. (A) Example edge distribution using decreasing pruning rates and the 2-patch distribution. (B) Prediction of final network n_S/n_T ratio given a pruning rate. Bold bars indicate simulated ratios, and hashed bars indicate theoretical predictions. (C) Prediction of source-target efficiency given n_S/n_T ratio. \label{fig:thy}

For each ratio, we computed the average edge connectivity between 500 random s - t pairs. We also computed the number of unrouteable pairs (pairs for which no s - t path exists). We compared these values with those predicted by our theoretical results above, as well as the actual values from our model for the three different pruning strategies (Figure \ref{fig:thy}). We currently do not have theoretical results predicting the edge-connectivity between random



Unraveling structures

If Saghatelian's small molecules are equivalent to a 6-foot human, the protein complexes **Dmitry Lyumkis** studies, termed macromolecules, are on the order of several White Houses stacked next to each other.

For a long time, understanding the active areas of these macromolecules—which can have anywhere from just a few to as many as several hundred intermingled proteins on average—was limited by imaging technology. But a recent breakthrough in the resolution of a specialized microscopy has catapulted forward the imaging of large macromolecules, which could speed up drug discovery related to a number of diseases. Lyumkis, a scientist who came to the Institute under a new cross-disciplinary initiative called the Salk Fellows Program, brings this technology and expertise to explore key macromolecular complexes related to human disease.

Established in 2014, the Salk Fellows Program aims to specifically encourage connections across fields. "The interdisciplinary partnerships among the Fellows and faculty that the program facilitates will continue to add to our environment of innovative collaborations and create future intellectual leaders in the biological sciences," says Salk Professor **Inder Verma**, who is, along with Professors **Fred Gage** and **Ronald Evans**, currently leading this program.


Lyumkis, the inaugural Helmsley-Salk Fellow, uses a cutting-edge technology that images large proteins and macromolecular complexes in more resolution than ever before to build three-dimensional models of the imaged objects. The resulting recreations provide a better understanding of protein function and sometimes reveal long sought-after clues in structural biology.

"An image is worth a thousand words," says Lyumkis. "Apart from understanding how the complexes work from a basic research perspective, imaging these structures can make it much easier to generate drugs that target proteins of interest."

He is discussing potential collaborations with multiple Salk laboratories that can benefit from the technology. In particular, he plans to work with other Salk researchers to target a macromolecule that plays a major role in different types of cancer and inflammatory disease. If Lyumkis can uncover its structure, he and collaborators can test mutations in areas where the subunits interact to develop targeted therapies for cancer.

"Though we've had this breakthrough in resolution, there's still a lot to be improved in the technology," says Lyumkis, who is improving the existing methods for analyzing the image data and building more accurate three-dimensional representations of typically heterogeneous objects. "My long-term goal is to spearhead methods that will allow us to solve increasingly more complicated molecular structures that may contain many different mobile components, and then apply these tools to better understand and potentially treat human disease."

The second Fellow in the program, **Jesse Dixon**, who will join the Institute in August 2015, is also looking at large molecular structures. He will work with Salk researchers to more closely examine the three-dimensional packaging of DNA that O'Shea and others are interested in, and determine what those structures mean for basic biological processes, cancer and evolution. Both fellows are supported by the Leona M. and Harry B. Helmsley Charitable Trust through the Helmsley Center for Genomic Medicine at Salk.

"Salk is a wonderful example of the benefits of collaboration among researchers, where we share equipment, infrastructure and ideas," says Verma, who is also the American Cancer Society Professor of Molecular Biology and the Irwin and Joan Jacobs Chair in Exemplary Life Science. "More importantly, collaborations across fields can expand scientific endeavors and, as we have seen time and time again, pave the way for new discoveries." 



to combat disease



From left: Senior Director of the Biophotonics Core James Fitzpatrick; Salk Fellow Dmitry Lyumkis; and Senior Director of IT Operations Frank Dwyer in Salk's Computing Core. The computational power and server set-up needed to successfully image molecules requires collaboration across departments.

**“Imaging these structures
can make it much easier
to generate drugs that
target proteins of interest.”
— Dmitry Lyumkis**

» [View video: www.salk.edu/insidesalk/apr15/lyumkis](http://www.salk.edu/insidesalk/apr15/lyumkis)

A Conversation

With Polio Survivor and Violinist

ITZHAK PERLMAN

JONAS SALK AND ITZHAK PERLMAN BOTH OVERCAME polio in different yet profound ways. Salk developed the first effective polio vaccine, lifting a shadow of fear from the world. Although he contracted polio at the age of four, Perlman refused to allow the disease to define him or undermine his gift for music, and went on to become a world-renowned violin virtuoso and conductor. Six years after he contracted polio, Perlman gave his first public performance and he appeared on *The Ed Sullivan Show* at age 13. Now in his late sixties, he continues to perform worldwide and remains one of the most recognizable names in classical music today.

It was particularly fitting, then, that Perlman gave a private recital at the Salk Institute last November to honor Jonas Salk's 100th birthday. Joined by Rohan De Silva on the piano, Perlman performed several classical works, including Robert Schumann's "Three Fantasies" and John Williams' hauntingly beautiful theme to *Schindler's List*.

THE SALK INSTITUTE



COMMEMORATES
JONAS SALK
100 YEARS





World-renowned violinist Itzhak Perlman is accompanied by pianist Rohan De Silva at the Salk Institute.

During his visit, Perlman, who is a diligent advocate of efforts to eradicate polio in those countries where it still exists, received the Salk Medal for Public Service. Irwin Jacobs, Salk's board chairman and a previous recipient of the Salk Medal, presented the award. Perlman is only the fifth person to receive the Salk Medal, which is given to individuals who have contributed to the fields of science, medicine, public health or public service.

In a conversation with Salk President **William Brody**, Perlman spoke about his passion for the violin and the importance of hearing what others might miss.

WB: I understand you began playing the violin at age three. What made you choose that instrument?

IP: The sound from the radio. I heard it and that was that.

WB: And the rest is history, as they say.

IP: Well, there was a little interruption. I had polio when I was four. I was in kindergarten at the time and I told my parents, 'My legs feel very weak and I can't walk.' So then I was in the hospital for two to three weeks. After that, life proceeded. There was the violin, there were braces and there were crutches. That was my life.

WB: How did your career develop?

IP: I began in the Conservatory in Israel. Then I was on *The Ed Sullivan Show* in the U.S. and then I went to study at The Juilliard School. It was a pretty normal development for an abnormal situation. Yes, polio was there but it was not an issue. People say, 'Oh what you've done is so amazing.' But it's not that I succeeded 'despite polio'—the talent is there or it is not.

WB: One of my favorite quotes is by Nobel laureate Szent-Györgyi who said, 'Discovery consists of seeing what everybody else has seen, and thinking what nobody else has thought.' That is true for much of science. Does it apply to music?

IP: It does. You have to listen, almost with an X-ray ear. You have to hear what to do both before you play and as you play. The more you develop that sense of hearing, the better your playing. And I think that talent gets better as you get older.

WB: So, do you play differently now than you did when you were younger?

IP: The difference in how I play now versus how I played 30 years ago is that I hear better. The actual playing is not as important. It's already there; it's automatic. And this is what I tell my students: After a while, stop playing. You know how to play. Now you have to hear. Just listen now and talk the music.

“Yes, polio was there but it was not an issue. People say, ‘Oh what you’ve done is so amazing.’ But it’s not that I succeeded ‘despite polio’—the talent is there or it is not.”



From left: Salk Board of Trustees Chairman Irwin Jacobs, Itzhak Perlman and Salk President William Brody

WB: Talk the music?

IP: Yes. Sometimes I have my students read a paragraph with me. For example: ‘One very beautiful morning the sun was shining bright and we were walking on the beach.’ I go over the words with them until they express the emotion in that moment. It is the same with the music. If you hear a harmony that is especially meaningful to you, you must express that harmony to the audience. You must talk the music.

WB: Jonas Salk believed that art and science have more to give to each other than people think. Did you ever meet him?

IP: No, I didn’t meet him, but I met Albert Sabin (who developed another form of polio virus after Salk). I received an honorary medical degree from the University of South Carolina in 1982 and Dr. Sabin, who was retiring from the university, gave the speech. He said, ‘The reason we are giving you a medical degree is because your music is medicine.’ I like that. 🎵

THE SALK INSTITUTE MEDAL FOR PUBLIC SERVICE



THE SALK INSTITUTE MEDAL FOR PUBLIC Service is given to an individual who has made significant contributions to world health and humankind in a manner that is consistent with Dr. Salk’s humanitarian interests and accomplishments. The award is given to individuals who have contributed to science, medicine, public health or public service, or to the support of these enterprises through their business, government, creative or philanthropic activities. Previous recipients of the medal were Paul Farmer, Don Metcalf, Irwin Jacobs and Robert G. Roeder.

The Tiffany Inc. medal was designed by Paloma Picasso.

One on One with... Jean Rivier



Rivier's "worry woods" are one of his solutions for alleviating the stress of everyday life.

ON THE DESK IN JEAN RIVIER'S STUDY AT THE SALK INSTITUTE lies a palm-sized piece of ironwood—a talisman that speaks to both his extracurricular and professional passions. The espresso-colored chunk of wood has served, like a worry stone, as an outlet for anxious energy, evidenced by a thumb-wide groove worn into one side from years of rubbing.

Most surfaces in his office are covered with similar wooden objects, such as small figurines—dolphins, owls and other animals—carved by indigenous peoples in Mexico and collected during his visits to the country. Inspired by these works, he started making sculptures himself from scraps of hardwoods found during his hikes in the mountains east of San Diego. That Rivier designed a piece of wood as a stress reliever suggests his hobby aligns with his scientific research, which has focused largely on understanding how stress manifests itself in the body at a molecular level and on searching for a drug to neutralize the effects of pathogens, both physical and emotional.

Rivier has spent his career as a Salk professor studying a class of stress hormones called corticotropin-releasing factors (CRFs). He showed that CRFs are responsible for many of the body's reactions to stress, including disabling the immune system in irritable bowel syndrome (IBS). In an attempt to develop treatments for these conditions, he designed peptide molecules that block CRF receptors. In the process of studying these CRF-blocking molecules, Rivier discovered that they also restore hair growth and even prevent hair loss in mice that normally go bald quite early in life due to overproduction of CRF. He recently founded a company called Sentia Medical Sciences Inc. and obtained exclusive rights to CRF-targeted molecules from the Salk Institute. Aside from his contributions to understanding stress, his work has resulted in eight drugs used to diagnose and treat neuroendocrine tumors, prostate cancer, hypogonadism, pituitary dwarfism and intractable pain.



Rivier acquired a piece of this felled dead cedar tree from Cuyamaca Rancho State Park. He put together a scaffolding to offload the enormous piece of wood, which he carved into a chair and two boards (so far).





*Use nature for inspiration
Use experimentation for creation
Use perseverance for accomplishments
Find pleasure in leisure*

–Jean Rivier

How did you start collecting wooden figurines?

It was during a Christmas trip to Bahia Kino with my family. I saw these striking ironwood figures carved by the Seri Indians, who have been confined for more than a century in two reservations along the western coast of the Sea of Cortez. Inspired by their commercial success, more than 200 Mexican artists started to mass produce such carvings that they sold to tourists—including me, until they ran out of wood 10 years ago.

You carve wood yourself. What's the appeal?

Wood is malleable, but when you shape it, you need to work with the grain. It reminds you that you are part of nature. There is a connection between emotion and touch. There is something atavistic in working with wood. You return to a simpler rung on the evolutionary ladder. We take for granted the beauty of nature, and working with wood brings you back to that. Spiders make beautiful webs and birds make these amazing nests. Modern humans live in highly artificial surroundings, and sometimes we need to return to a simpler time, to get away from the chronic stress of the modern world.

Are we more stressed than we used to be?

I think so. Not necessarily in terms of intensity but definitely in terms of duration, unpredictability and inescapability. Our ancestors had a lot to

worry about, but much of their stress was acute—it came and it went. On the whole, we now deal with chronic stress that we aren't adapted for. Job pressures, long commutes, economic slumps, mobile phones beeping at us 24 hours a day, you name it, it's nonstop.

When you are stressed, your body copes through the fight-or-flight response, which alters and compromises your metabolism and your immune, reproductive and cardiovascular systems, among other things. When stress is chronic, it puts you at risk for severe anxiety disorders. Our hypothesis is that neutralizing the effects of stress will restore the systems' homeostasis and health.

Why has it been so difficult to develop drugs that effectively target chronic stress?

There are several reasons, in part, because the pharmaceutical industry has focused on the symptoms of stress-related diseases and not the underlying causes. People had high blood pressure, so industry developed beta-blockers. People had acid reflux, so industry developed pH buffers. Also, the pharmaceutical industry stubbornly believed that drugs must be orally active, which excluded the vastly untapped potential of peptides that are commonly destroyed in the stomach.



From left: Joachim Spiess, Catherine Rivier, Jean Rivier and Wylie Vale at the Salk Institute in 1980 after isolating CRF.

It's only in the very recent past that some companies have realized the power of a healthy immune system to beat cancer as an alternative to chemotherapy and radiation. Whereas they came up with “omic” (expensive) solutions, they still ignore the use of CRF peptide antagonists shown to be effective in inducing homeostasis. Despite decades of research, stress has not been conquered. By contributing to the design of potent CRF receptor-selective antagonists that were shown to beat IBS symptoms in early weaned piglets, and preliminarily in humans, I'm confident that sometime in the future, we will have such a drug for treatment in humans.

You started your own company to develop CRF-targeted drugs, right?

That's right. Salk is “Where cures begin” but you have to take the next step. I founded Sentia to take the CRF antagonists we developed to the clinical trial stage. We worked with Salk's Office of Technology Development on filing patents and obtaining licensing. The next step is finding investors and testing the drugs in clinical trials.

In the meantime, how do we cope with our “age of anxiety” in today's world?

In my view, eating right, exercising, practicing yoga, meditating, being hypnotized and having many friends are examples of ways to cope. Psychotherapy may be helpful. I will keep up woodworking. I like to say that ‘worry wood whittles stress away.’ 🪵



Bottles of different forms of atresin, a class of CRF-antagonist drug candidates that Rivier developed to target the body's stress system.



Next generation:

A marriage between labs nurtures the seeds of discovery

Salk couple Zuyu Zheng
and Yongxia Guo team up
to dig for answers to
plant survival mechanisms

PALE GREEN SEEDLINGS OF *ARABIDOPSIS THALIANA* HAVE EMERGED from the soil. They stretch toward the artificial light in the Salk growing room, ready to flourish. Then **Zuyu Zheng** installs a shade device above the young plants, limiting their light. What will the seedlings do? Because survival instincts are strong, the plants immediately begin growing faster, searching for life-giving light. Faced with adversity, they exhibit resilience.

That's a trait shared by both Zheng and his wife and research partner, **Yongxia Guo**. Together, they study plants in adverse situations, tenaciously seeking to understand the mechanisms by which plants adapt and survive. The work can be littered with obstacles.

"That's why they call it research," says Zheng, a postdoctoral researcher in Salk Professor **Joanne Chory**'s laboratory. "You search and then you research. It can be frustrating, but you can't give in."

The interest in plants comes naturally. Both Zheng and Guo were raised on family farms in central China.



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“Our parents grew corn and wheat,” says Zheng, “and we had a vegetable garden. So learning about plants was important.”

Today, however, those family farms no longer exist. Like so many agricultural enterprises around the world, they’ve fallen victim to urban sprawl.

“People don’t realize how much arable land is giving way to development,” says Guo, a postdoctoral researcher in Salk Professor **Joseph Noel**’s laboratory. “More and more, plants are forced to grow in difficult situations, either in poor soil or in greater density. What’s going to happen?”

It’s a critically important question. With the world’s population expanding and arable land diminishing, the research that Zheng and Guo perform directly affects future food supplies. How can they help plants compete for light in dense populations while in poor soil? How can they engineer plants that are more resilient?

Their solution: collaboration. It’s a partnership they’ve been perfecting since they first met as students at Henan Agricultural University in Zhengzhou, China. Since 2008, they’ve been at the Salk Institute, working in separate labs but together. “Our labs have a tradition to collaborate,” Guo explains, “so that was good for how Zuyu and I work.”

Chory, professor and director of the Plant Molecular and Cellular Biology Laboratory, recalls how Zheng and Guo advanced her lab’s research into how plants outcompete nearby rivals for sunlight by making more of the plant hormone auxin.

“Zuyu performed a simple, yet elegant, genetic screen from which he identified an enzyme, an aminotransferase, that not only regulated levels of auxin, a growth hormone, but also regulated ethylene, a different plant hormone,” says Chory. “This is one of the first examples of direct metabolic coupling. Zuyu and Yongxia then took these studies from a genetic screen, through protein purification and X-ray crystallography. They make a very nimble and multi-talented team.”

Such teamwork spills into their personal lives. They talk about their work at home—a lot, both admit. The ongoing conversation has led them down paths of discovery and produced a number of published papers. One paper describes how a dying plant generates a chemical message for the next generation, alerting dormant seeds to sprout after a fire. Another, related to their current shade response studies, offers a new understanding of how hormones regulate growth.

“But there are still so many questions to be answered,” says Zheng. So the dinner conversations will continue.

As much as possible, though, free time is family time, spent with their two children, Emily, eight, and Eric, six. Together, they hike, play ping pong or challenge each other to games of chess. Not surprisingly, the children share their parents’ interest in science.

“Eric wants to be a paleontologist,” says Guo, “so he can drive a blue Jeep and wear gloves. And Emily lectures him on her hypotheses about dinosaur extinction. She thinks a volcano erupted and created so much smoke and ash that all the vegetation died. Then the dinosaurs, which were plant-eaters, had nothing left to eat.”



Given the vital connection between plants and survival, back then as well as today, one has to wonder why plant research doesn't draw more interest—and funding.

"Many people here have never been hungry," says Guo. "Everyone knows someone who has died of cancer or who has diabetes. But no one here knows someone who has died of hunger. In China, however, people of my parents' age have confronted their frustration for no food. They remember being hungry. So, in China, plant research is well-funded."

Zheng adds, "Joanne tells a story of how students at Harvard were asked where bread comes from and they didn't know. People don't think about it. They take food for granted."

"There's no transgenerational memory," says Guo.

Zheng adds that, with the support of the National Institutes of Health, their goal is to study—and genetically modify—the mechanisms plants use to adapt to stress.

"We want to keep the plants growing fast but strong and to help them produce a high yield of fruit and seed," he says.

In the Salk growing room, the tenacity and passion of the two researchers comes readily to light. Noticing a mutant phenotype, Guo immediately bends over a seedling, commenting to her partner on its unique traits. Zheng points out another.

"This one is exhibiting transgenerational memory," he says, adding that, in response to environmental stress, a plant's epigenome (chemical changes that modify an organism's DNA) can actually change so that a future generation is better equipped to handle that stress. It's essential to adaptation and survival.

In another part of the lab, a researcher is painstakingly examining a dish of tiny seedlings, separating those showing the desired phenotype and transplanting them into soil. The subject is again *Arabidopsis thaliana*, a model organism that grows rapidly and has its entire genome sequenced. Still, the process is tedious and often frustrating.

"You have to zigzag and always look for another approach, another way to get to the answer," says Guo.

"Most experiments fail but you can't give up," adds Zheng. "You hope that one day you will find something important for the field and that it will change people's quality of life. This kind of hope keeps me going." 📊



Trailblazing Salk research on “imaginary meal” pill draws worldwide attention

RONALD EVANS, DIRECTOR OF THE GENE Expression Laboratory, and his team pioneered a new type of pill that tricks the body into thinking it has consumed calories, causing it to burn fat. Details of the new compound made headlines across the globe and drew widespread interest from the scientific community and the public for effectively stopping weight gain, lowering cholesterol, controlling blood sugar and minimizing inflammation in animals.

The work was published January 5, 2015 in *Nature Medicine* and was quickly picked up by *USA Today*, *TIME*, *CBS News*, *NPR*, *The Washington Post*, the *Los Angeles Times*, *The Guardian* and *Public International Radio's Science Friday*, among many others. The story also prompted thousands of social media shares and even a skit on *The Late Show with David Letterman*. Unlike most diet pills on the market, the new compound, called fexaramine, doesn't dissolve into the blood like appetite suppressants or caffeine-based diet drugs, but remains in the intestines, causing fewer side effects.

“This pill is like an imaginary meal,” says Evans. “It sends out the same signals that normally happen when you eat a lot of food, so the body starts clearing out space to store it. But there are no calories and no change in appetite.”

Evans' laboratory has spent nearly two decades studying the farnesoid X receptor (FXR), a protein that plays a role in how the body releases bile acids from the liver, digests food and stores fats and sugars. The human body turns on FXR at the beginning of a meal, Evans and others have shown, to prepare for an influx of food. FXR not only triggers the release of bile acids for digestion, but also changes blood sugar levels and causes the body to burn some fats in preparation for the incoming meal.

Pharmaceutical companies aiming to treat obesity, diabetes, liver disease and other metabolic conditions have developed systemic drugs that activate FXR, turning on many pathways that FXR controls. But these drugs affect several organs and come with side effects. Evans wondered whether switching on FXR only in the intestines—rather than the intestines, liver, kidneys and adrenal glands all at once—might have a different outcome.

“When you eat, you have to quickly activate a series of responses all throughout the body,”

says Evans. “And the reality is that the very first responder for all this is the intestine.”

Evans and his colleagues developed the fexaramine compound by departing from the drug scaffold that most pharmaceutical companies typically pursue when targeting FXR. “It turns out that when we administer this orally, it only acts in the gut,” explains **Michael Downes**, a senior staff scientist at Salk and co-corresponding author of the new work. Giving one such drug in a daily pill form that only reaches the intestines—without transporting into the bloodstream that would carry the drug throughout the body—not only curtails side effects but also made the compound better at stopping weight gain.

When the group gave obese mice a daily pill of fexaramine for five weeks, the mice stopped gaining weight, lost fat and had lower blood sugar and cholesterol levels than untreated mice. In addition, the mice had a rise in body temperature—which signals metabolism ramping up—and some deposits

of white fat in their bodies converted into a healthier, energy-burning beige form of the tissue. Even the collection of bacteria in the guts of mice shifted when they received the drug, although what those changes mean isn't clear yet.

Since fexaramine doesn't reach the bloodstream, it is also likely safer in humans than other FXR-targeting drugs, the researchers hypothesize. They're already working to set up human clinical trials to test the effectiveness of fexaramine to treat obesity and metabolic disease. Ideally the drug, administered under a doctor's guidance, would work in conjunction with diet and lifestyle changes, similar to weight-loss surgeries or other obesity or diabetes drugs. 📺

» View videos:

www.salk.edu/insidesalk/apr15/evans

www.salk.edu/insidesalk/apr15/fexaramine



The lab of Ronald Evans developed a compound called fexaramine that acts like an imaginary meal, prompting the body to react as if it has consumed calories.

A new dent in HIV-1's armor

Salk scientists identify a promising target for HIV/AIDS treatment

LIKE A SLUMBERING DRAGON, HIV CAN LIE dormant in a person's cells for years, evading medical treatments only to wake up and strike at a later time, quickly replicating itself and destroying the immune system.

Scientists at the Salk Institute have uncovered a new protein that participates in active HIV replication, as detailed in the latest issue of *Genes & Development*. The new protein, called Ssu72, is part of a switch used to awaken HIV-1 (the most common type of HIV) from its slumber.

More than 35 million people worldwide are living with HIV and about a million people die a year due to the disease, according to the World Health Organization. There is no cure, and while regular medication makes the disease manageable, treatment can have severe side effects, is not readily available to everyone and requires a regimen that can be challenging for patients to adhere to.

The team began by identifying a list of 50 or so proteins that interact with a well-known protein HIV creates called Tat.

"The virus cannot live without Tat," says **Katherine Jones**, Salk professor in the Regulatory Biology Laboratory and senior author of the study.

Tat acts as a lookout in the cell for the virus, telling the virus when the cellular environment

is favorable for its replication. When the environment is right, Tat kicks off the virus' transcription, the process by which HIV reads and replicates its building blocks (RNA) to spread throughout the body.

One of the proteins on the list that caught Jones' eye was Ssu72 (a phosphatase). This enzyme had been shown in yeast to affect the transcription machinery. Sure enough, her team found that Ssu72 binds directly to Tat and not only begins the transcription process, but also creates a feedback loop to ramp up the process.

"Tat is like an engine for HIV replication and Ssu72 revs up the engine," says **Lirong Zhang**, one of the first authors and a Salk researcher. "If we target this interaction between Ssu72 and Tat, we may be able to stop the replication of HIV."

The findings were surprising to the team because Tat, a relatively small protein, was previously thought to have a simpler role. Jones' lab previously discovered the CycT1 protein, another critical protein that Tat uses to begin the steps of replicating the virus.

"After all these years, we thought that Tat only had this one partner (CycT1), but when we looked at it a bit harder, we found that it also binds and stimulates the Ssu72 phosphatase, which controls an immediately preceding step to switch on HIV," she said.

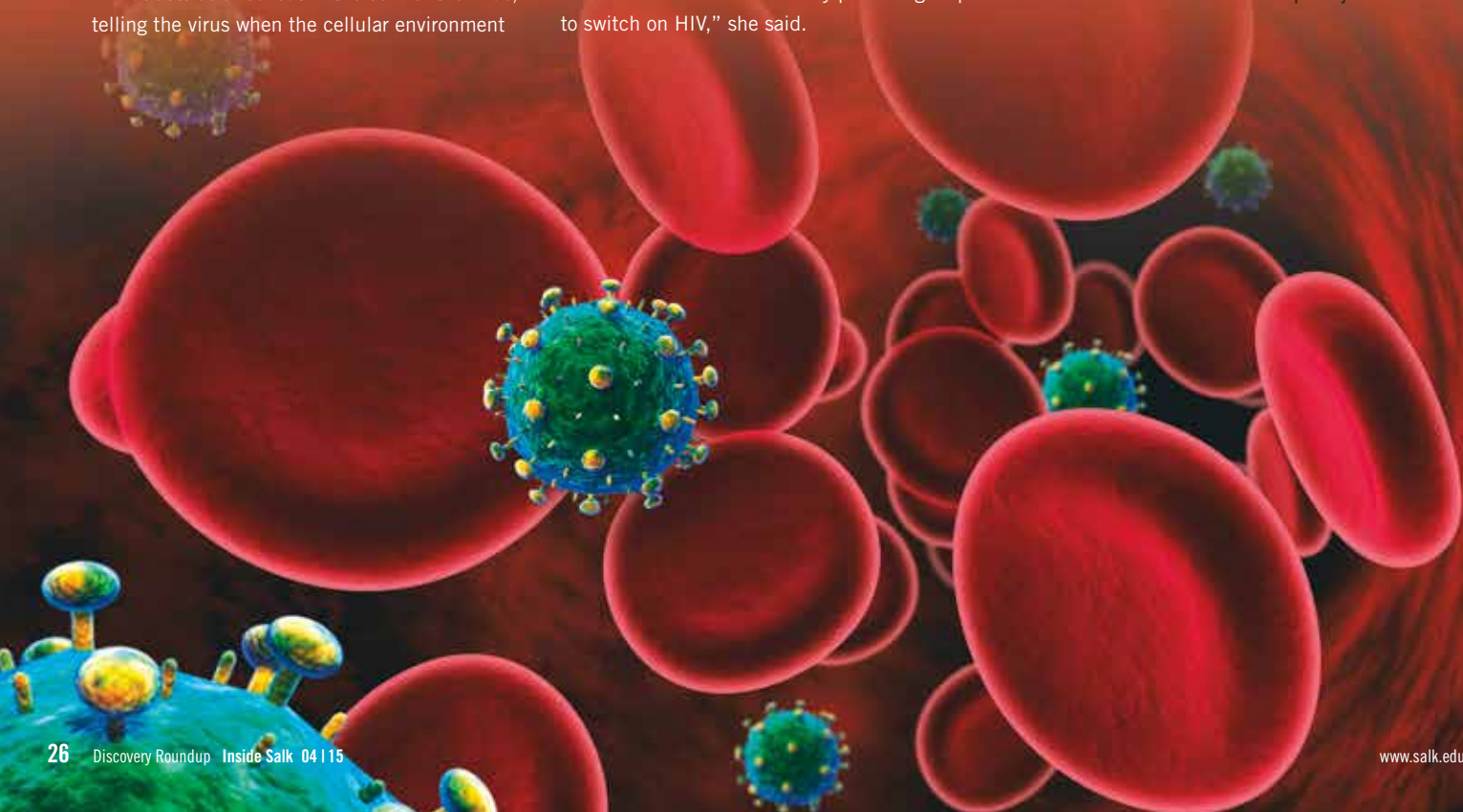
CycT1 is needed for normal cell function, so it may not be an ideal anti-viral target. However, the team found that Ssu72 is not required for making RNA for most host cell genes in the way it is used by HIV, making it a potentially promising target for drug therapy.

"Many proteins that Tat interacts with are essential for normal cellular transcription so those can't be targeted unless you want to kill normal cells," says co-first author **Yupeng Chen**, a Salk researcher. "Ssu72 seems to be different—at least in the way it is used by HIV."

Now that the team knows the protein is specifically required for HIV transcription, they next plan to investigate how they can target the protein, for example by inhibiting Ssu72's ability to kick off the transcription process. They are also examining whether latent HIV infections result from low levels of Ssu72 in resting T cells. And stay tuned: the lab is excited about checking other new host cell partners of Tat that were identified in this study. 📺

» **View video:**

www.salk.edu/insidesalk/apr15/jones



Salk researchers unveil powerful method to speed cancer drug discovery

The new method lets researchers identify weak and previously undetectable interactions between proteins inside living cells

FOR DECADES, RESEARCHERS HAVE struggled to translate basic scientific discoveries about cancer into therapeutics that effectively—and with minimal side effects—shrink a tumor.

One avenue that may hold great potential is the development of drugs that interfere with interactions between proteins, which are often disrupted during the formation and spread of cancer. Deciphering these interactions, however, has proven difficult and time consuming, leading to doubts about the practicality of this approach as a route to new therapies.

Now, Salk scientists have developed a highly sensitive, new method that enables them to detect fleeting protein interactions that play critical roles in the development of many diseases including cancer. The approach, published November 20 in *Cell Reports*, could dramatically accelerate the identification of many potential new drug targets and provide an immediate platform to screen for badly needed new drug candidates that disrupt abnormal protein interactions.

“The number of protein functions that are currently targeted by drugs is incredibly small compared to the total number of protein interactions that could be targeted for therapeutic benefit,” says **Geoffrey Wahl**, a professor in Salk’s Gene Expression Laboratory. “If we can crack the nut of screening for drugs that disrupt cancer-relevant protein interactions, this will be an enormous breakthrough and could have implications for many other fields as well.”

Yao-Cheng Li, a staff scientist in Wahl’s lab and first author of the new paper, explains that their method focuses on one of the two kinds of protein-protein interactions. “One type generates very stable protein complexes that remain together,” he says. “But many other proteins display a touch-and-go kind of interaction—they bind, then fall apart. It’s these latter interactions that have been the most difficult to detect.”

To help visualize these brief, transient interactions, Li and Wahl turned to a molecule called luciferase, an enzyme that generates

bioluminescence of the sort used by fireflies to make their bodies glow. The scientists adapted an old method in which luciferase is split in half to make two non-functional fragments. The scientists attached each half of the luciferase to two proteins of interest so that if the proteins associate for any period of time, luciferase’s two halves are brought together and emit light. The secret to the new method comes in the many tweaks and improvements that Li added to the system, which is symbolized by the acronym he and Wahl apply to the method—ReBiL—which indicates “recombinase enhanced bi-molecular luciferase complementation.”

“It works like a bulb and a lamp,” says Wahl, who is also the holder of Salk’s Daniel and Martina Lewis Chair. “Neither one lights up without the other. The ReBiL method provides a very fast and easy way of seeing whether the bulb will fit into the lamp socket.”

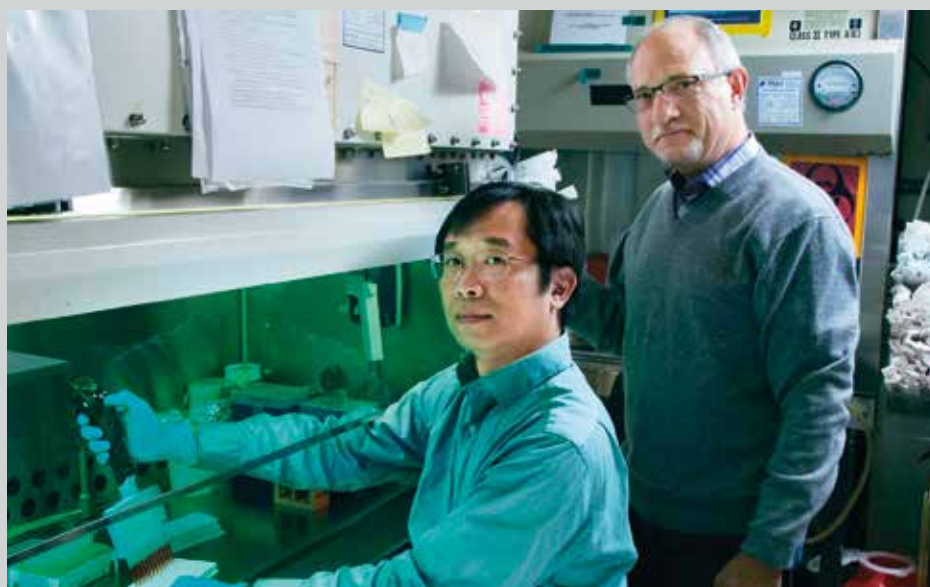
To test the method, Wahl and Li applied it to the interaction between two proteins, Ube2t and FANCL, that’s been notoriously hard to observe and had never been seen in living mammalian cells. These proteins are important because they are involved in the cell’s ability to detect and repair DNA damage, a function that is often disrupted in diseases. Mutations in FANCL, for instance, cause rare blood disorders and dispose people to cancer. The ability of ReBiL to reveal the stealthy FANCL-Ube2t

reaction suggested the method could be a powerful technique for observing other similarly challenging interactions.

The Salk scientists then used ReBiL to study a promising target for cancer, the interaction between the proteins p53 and Mdm2. The function of p53 is affected in almost all cancers and, in many cancers, too much Mdm2 prevents p53 from functioning properly. Hence, a major goal of cancer scientists has been to develop drugs that prevent Mdm2 from binding to p53, and to thereby activate p53 to kill the tumor cell.

Wahl, Li and their colleagues used ReBiL to confirm that some drugs work as expected to prevent Mdm2 from binding to p53. On the other hand, when they applied their method to a new class of promising drugs called stapled peptides, they found that the drugs had difficulty entering cells and had the unexpected and unintended ability to kill cells by punching holes in their protective covering (the membrane). Despite spending millions of dollars to develop these drugs, this dangerous side effect was not observed because previous methods did not reveal it. ReBiL provides a fast and simple way to try to improve stapled peptides to enable them to get into the cell, bind to their targets and kill cells by the specific route they were designed to use.

“The method has applications from understanding many growth regulatory pathways and for understanding critical processes that should lead to the identification of the targets needed for the development of new therapies,” says Wahl. 



From left: Yao-Cheng Li and Geoffrey Wahl

» **View video:**
www.salk.edu/insidesalk/apr15/wahl



From left: Yelena Dayn, Fernando Lopez-Diaz and Beverly Emerson

Findings point to an “off switch” for drug resistance in cancer

Salk research indicates a potential mechanism for cancer cells’ adaptability

LIKE A COLONY OF BACTERIA OR SPECIES of animals, cancer cells within a tumor must evolve to survive. A dose of chemotherapy may kill hundreds of thousands of cancer cells, for example, but a single cell with a unique mutation can survive and quickly generate a new batch of drug-resistant cells, making cancer hard to combat.

Now, scientists at the Salk Institute have uncovered details about how cancer is able to become drug resistant over time, a phenomenon that occurs because cancer cells within the same tumor aren’t identical—the cells have slight genetic variation, or diversity. The new work, published October 20 in *PNAS*, shows how variations in breast cancer cells’ RNA, the molecule that decodes genes and produces proteins, help the cancer to evolve more quickly than previously thought. These new findings may potentially point to a “switch” to turn off this diversity—and thereby drug resistance—in cancer cells.

“It’s an inherent property of nature that in a community—whether it is people, bacteria or cells—a small number of members will likely survive different types of unanticipated

environmental stress by maintaining diversity among its members,” says the senior author of the new work, **Beverly Emerson**, professor of Salk’s Regulatory Biology Laboratory and holder of the Edwin K. Hunter Chair. “Cancer co-opts this diversification strategy to foster drug resistance.”

Instead of looking at a single gene or pathway to target with cancer therapies, lead author **Fernando Lopez-Diaz**, Salk staff scientist, and the team aim to uncover the diversification “switch” by which cancer cells replicate but vary slightly from one another. Turning off this cellular process would strip cancer’s ability to survive drug treatment.

“Cancer isn’t one cell but it’s an ecosystem, a community of cells,” says Emerson. “This study begins the groundwork for potentially finding a way to understand and dial back cell diversity and adaptability during chemotherapy to decrease drug resistance.”

To uncover how groups of cancer cells achieve functional diversity (through RNA) to survive chemotherapy, Lopez-Diaz dosed dishes of human pre-cancer and metastatic breast cancer cells with the cancer drug paclitaxel

» **View video:**

www.salk.edu/insidesalk/apr15/emerson

for a week and then removed the drug for a few weeks, mimicking the treatment cycle for a cancer patient. Surviving cells—usually one or two out of millions—began to repopulate but with subtle changes in their RNA, presumably enabling them to survive future doses of the cancer drug.

By pushing the boundaries of bioinformatics, a collaboration led by Mei-Chong Wendy Lee and Nader Pourmand at the University of California, Santa Cruz charted more than 80,000 pieces of RNA per new cancer cell—typically, single-cell studies by other approaches look at hundreds or so RNA pieces to distinguish fairly different cells from one another. This unusually thorough list helped the researchers tease out subtle differences between generations of same cancer cells treated with chemotherapy and chart how the cancer cell community increased diversity among its members through RNA.

“We found an overwhelming return to diversity after chemotherapy treatment that couldn’t be explained by expected mechanisms,” says Lopez-Diaz. “There is something else going on here, a ‘philosopher’s stone’ to cancer cell diversity that we now know to look for.”

And when the team analyzed the gene expression profiles of the surviving cancer cell line, they were again surprised. “We thought they’d look like stressed cells with a few changes,” says Emerson. “Instead, after a few population doublings they go back to the normal gene expression pattern and rapidly reacquire drug sensitivity.” This adaptive behavior, Emerson speculates, lets the group of cancer cells prepare for the next unanticipated threat.

Another intriguing finding of the paper was that a high percentage of precancerous cells that underwent chemotherapy survived and proliferated, more so than either normal or cancerous cells. This led the pre-cancer cells to become more drug tolerant once they became a tumor. “The pre-cancer cells, when exposed to chemotherapy, evolved much faster and create a more drug-resistant state,” says Lopez-Diaz. “This and other findings can now be explored into greater detail using the knowledge and perspective we have gained here.”

Another case against the midnight snack

Salk researchers tinker with a time-restricted diet in mice and find that it is remarkably forgiving

THESE DAYS, WITH THE ABUNDANCE OF ARTIFICIAL LIGHT, TV, tablets and smartphones, adults and children alike are burning the midnight oil. What they are not burning is calories: with later bedtimes comes the tendency to eat.

A new study by researchers at the Salk Institute cautions against an extended period of snacking, suggesting instead that confining caloric consumption to an 8- to 12-hour period—as people did just a century ago—might stave off high cholesterol, diabetes and obesity. Coverage of the study swept headlines and made the “Most Viewed” and “Most E-mailed” lists on *The New York Times*.

The results, published December 2, 2014 in the journal *Cell Metabolism*, add to mounting evidence suggesting that it's not just what we eat but when we eat it that matters to our health. Although the intervention has not yet been tested in humans, it has already gained visibility as a potential weight loss method—and, in mice, it may reveal what causes obesity and related conditions in the first place.

In 2012, **Satchidananda Panda**, a Salk associate professor, showed that mice which were fed a high-fat diet, but allowed access to that diet for only eight hours per day, were healthier and slimmer than mice given access to the same food for the whole day, even though the two groups consumed the same number of calories. The new study shows the benefits of time restriction is surprisingly more profound than initially thought and can reverse obesity and diabetes in animal models.

The authors demonstrated that time restriction better synchronizes the function of hundreds of genes and gene products in our body with the predictable time of eating.

“These days, most of the advice is, ‘You have to change nutrition, you have to eat a healthy diet,’” Panda says. “But many people don’t have access to healthy diets. So the question is, without access to a healthy diet, can they still practice time-restricted feeding and reap some benefit?”

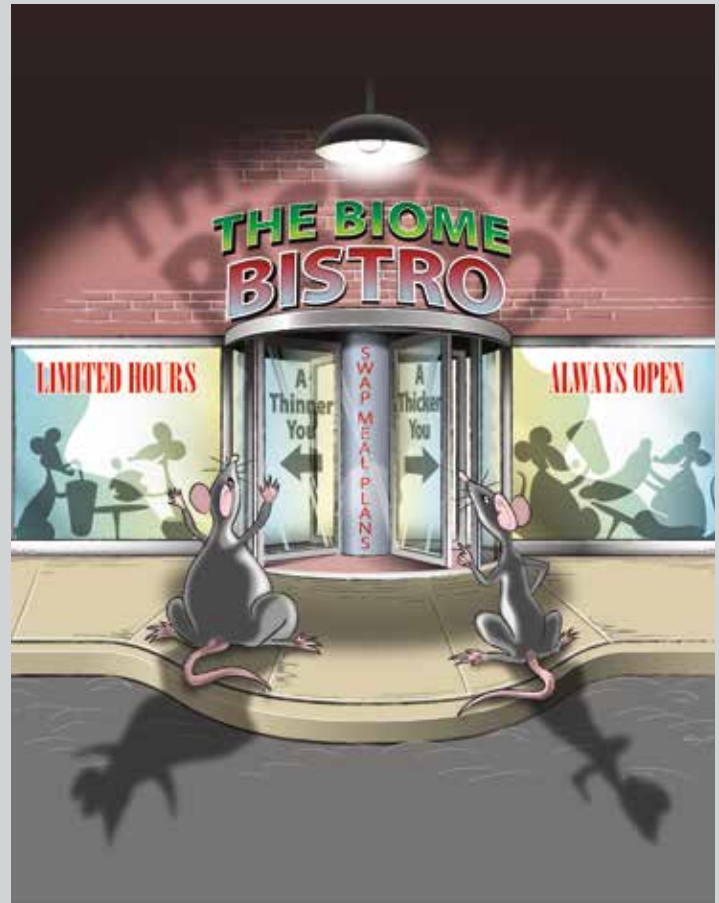
Panda and his researchers, who study the body’s 24-hour rhythms, wanted to know how forgiving time-restricted feeding was.

In the new study, Panda’s group subjected nearly 400 mice, ranging from normal to obese, to various types of diets and lengths of time restrictions. They found that the benefits of time-restricted feeding showed up regardless of the weight of the mouse, type of diet and length of the time restriction (to some degree).

Regardless of whether their diets were high in fat, fat and sucrose or just fructose, mice that were given time restrictions of 9 to 12 hours—and consumed the same amount of daily calories as their unrestricted counterparts—gained less weight than the controls, researchers found.

In particular, variations in the time window in which the mice were allowed to eat a high-fat diet—including 9-, 10- and 12-hour periods—all resulted in similarly lean mice. For a 15-hour group, the benefits conferred by time restriction became more modest.

Researchers gave some of the time-restricted mice a respite on weekends, allowing them free access to high-fat meals for these two days. These mice had less fat mass and gained less weight than the mice given




Cell Metabolism featured the new work on its December cover, designed by Salk’s Jamie Simon.

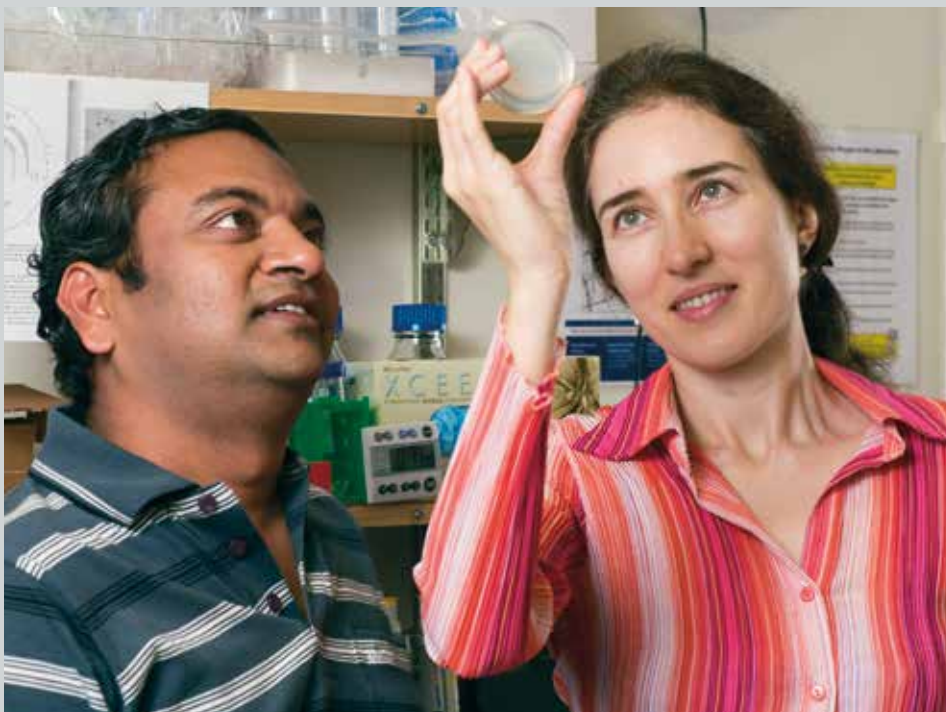
a freely available, high-fat diet the whole time. In fact, the mice that were freely fed just on weekends looked much the same as mice given access to food 9 or 12 hours a day for seven days a week, suggesting that the diet can withstand some temporary interruptions.

“The fact that it worked no matter what the diet, and the fact that it worked over the weekend and weekdays, was a very nice surprise,” says the study’s first author **Amandine Chaix**, a postdoctoral researcher in Panda’s lab.

More importantly, for the mice that had already become obese by eating a freely available high-fat diet, researchers restricted their food access to a nine-hour window. Although the mice continued to consume the same number of calories, they dropped body weight by five percent within a few days. Importantly, eating this way prevented the mice from further weight gain (by about 25 percent by the end of the 38-week study) compared to the group kept on the freely available high-fat diet.

A comprehensive analysis of the blood metabolites in time-restricted mice revealed that multiple molecular pathways that go awry in metabolic disease are turned back to normal, Chaix adds. Next steps include looking more in-depth at these pathways, as well as investigating the effects of time-restricted eating in humans. 

» View video:
www.salk.edu/insidesalk/apr15/panda



Srekanth Chalasani and Tatyana Sharpee

Worms' mental GPS helps them find food

Salk scientists develop a theory to explain how animals gather information and switch attention

YOU'VE MISPLACED YOUR CELL PHONE. YOU start by scanning where you remember leaving it: on your bureau. You check and double-check the bureau before expanding your search around and below the bureau. Eventually, you switch from this local area to a more global one, widening your search to the rest of your room and beyond.

When it comes to animals and food, a similar strategy is used to search for food ("foraging"). Now, Salk scientists have developed a mathematical theory—based on roundworm foraging—that predicts how animals decide to switch from localized to very broad searching. This new

theory could begin to explain animal behavior in a more unified way, laying the groundwork for general rules of behavior that could help us understand complex or erratic attention-related behaviors, such as attention deficit hyperactivity disorder (ADHD), and even let us predict how extraterrestrials might behave.

"How do you decide which route to take home or which problem to work on? This theory is exploring what ultimately makes us human—how we make decisions based on partial information affects all aspects of our lives," says **Tatyana Sharpee**, associate professor of Salk's Computational Neurobiology Laboratory and senior author of the paper, which was published in *eLife* on December 9, 2014.

Worms and other animals often follow a chemical trail (a scent, for example) to find their food. But when no chemicals are present they switch to an "infotaxis" search where information gathering happens in more discrete local and global stages.

"What is surprising is that these simple organisms with a very small nervous system

perform—or approximate—fairly complex, multistep, long-term planning strategies," says Sharpee.

This type of search is like looking for a friend at a crowded beach, says **Srekanth Chalasani**, assistant professor of the Molecular Neurobiology Laboratory, holder of Salk's Helen McLoraine Developmental Chair in Neurobiology and co-senior author of the work. If you think the friend is under a blue umbrella, you won't necessarily charge to the first blue umbrella you see. You'll probably first conduct a more global survey of the scene, glancing at all the umbrellas and ruling out areas where blue does not appear. If you still can't find your friend, you would expand your search to include other locations in addition to under blue umbrellas. Even though you waste some time, you still obtain a lot of information about where this person is likely to be by focusing on things not directly related to your target.

"Seeking information about a target is often better than seeking the target itself," says Chalasani. "And what this paper confirms in a theoretical model is that you don't need lots of neurons to perform these searches that include switching from a local to a global search—you can approximate it by using just three neurons, as in the roundworm *C. elegans*."

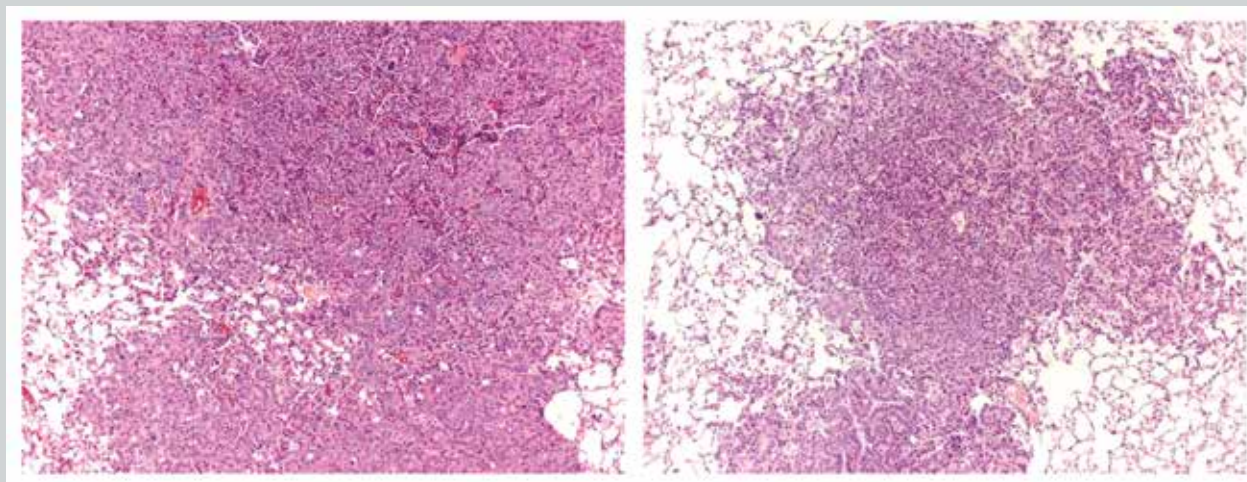
Successfully seeking food is critical to an animal's survival. Previously, *C. elegans* worms have been shown to conduct an intense search of an area where they believe food to be located. After 15 minutes or so, they turn less and explore a more extended area. Since the worms didn't have a chemical gradient to follow, the team wanted to explore the underlying strategy of the worms' behavior. Using data from Chalasani's experimental studies, Sharpee's lab developed virtual simulations of the worms to model their behavior.

Though this information-maximizing theory has been tested in a few types of behavior, Sharpee and others believe it could provide a basis for a larger, unified framework for understanding different types of behavior across species, cells, neurons and even larger scale phenomena, such as resource allocation.

Next, the researchers plan to see whether the roundworm can—and to what extent—maintain a mental map of its food search and explore the energy costs and benefits of information searching. 📊



Animals search a local area intensively (top panel) before switching to exploring the larger "global" area (bottom panel).



Mutation of the KRAS gene leads to a common and hard-to-treat lung cancer. A new combination therapy (lipophilic bisphosphonate and rapamycin) administered to mice for 40 days resulted in shrunken tumor size (right).

Salk scientists deliver a promising one-two punch for lung cancer

A combination of two unexpected drugs targets tumors

SCIENTISTS AT THE SALK INSTITUTE HAVE DISCOVERED A POWERFUL one-two punch for countering a common genetic mutation that often leads to drug-resistant cancers. The dual-drug therapy—with analogs already in use for other diseases—doubled the survival rate of mice with lung cancer and halted cancer in pancreatic cells.

Lung cancer, which affects nonsmokers as well as smokers, is the most common cancer worldwide, causing 1.6 million deaths a year, far more than pancreatic, breast and colon cancer combined. About 30 percent of the most common type of lung cancer (non-small) contains a mutation in a gene called KRAS. This mutation can also lead to hard-to-treat cancer in the pancreas, thyroid and colon.

“There really have been no effective treatments to target the KRAS mutation so far,” says **Inder Verma**, a professor in the Laboratory of Genetics and American Cancer Society Professor of Molecular Biology. “We found a drug combination that successfully targets KRAS and stops tumor growth in the mouse model.”

The new discovery, detailed November 19, 2014 in *Science Translational Medicine*, shows how the two-pronged attack successfully hindered KRAS and other cellular processes to halt or shrink tumor growth.

When activated, mutated KRAS clings to cell membranes and recruits proteins to ramp up cancer growth. Researchers have developed drugs to disable enzymes that tether KRAS to the cell membrane, but these drugs typically end up being toxic because those enzymes are needed in the body for normal functions.

“The Achilles’ heel of KRAS is its movement to the membrane,” says Verma, who is also holder of Salk’s Irwin and Joan Jacobs Chair in Exemplary Life Science.

The researchers took a new approach to targeting this membrane interaction when they noticed that a drug called Zometa, typically used to stop the breakdown and growth of cells in bone disease, also interfered with cell membrane interactions. In previous work, the team added carbon chains to a molecule similar to Zometa to create a lipophilic bisphosphonate (BP) that blocked KRAS from attaching to the cell membrane.

“For the first time, we had the ability to interfere with KRAS without being completely toxic,” says Verma.


This, however, wasn’t enough. Tumors were still proliferating, in part because the new BP led to failed attempts of a process called autophagy, where cells, under stress, self-destruct and break down into nutrients that can be used by other cells.

Autophagy can be both good and bad in fighting cancer: in some cases, autophagy prompts cancer cells to die; in other settings, it creates a cellular environment that helps tumors thrive. With the BP treatment, cells began the process of autophagy but failed, leading to junk protein accumulation and an inflamed environment that helped the tumors to survive.

But, as demonstrated in the new work, when the researchers added a chemical called rapamycin, cells were able to carry out autophagy successfully and prevented tumor cells from proliferating. Rapamycin, discovered in the 1970s, is used in the clinic for preventing organ rejection and has also been linked to anti-cancer effects.

“We found if we also activated autophagy—with the rapamycin—and combined it with the inhibitor of the cell membrane—the BP—there were significant cell deaths in the tumors,” says **Yifeng Xia**, Salk researcher and first author of the new work.

When they injected the combination in mouse lung tumors, tumors shrunk or stopped growing. The study also found that a pancreatic cancer cell line responded to the dual treatment. Next, the team plans to test toxicity of the new BP. The group is also working with the University of California, San Diego, Moores Cancer Center to design human clinical trials to test the dual therapy.

“Those two drugs have not been used together as far as we know for KRAS-related cancer treatment,” adds Xia. “We are excited about the potential and that these molecules are already being used in clinical trials in some form.” 

» View video: www.salk.edu/insidesalk/apr15/verma

Salk and Harvard scientists chart spinal circuitry responsible for chronic pain

Findings could lead to new therapeutics for disorders such as fibromyalgia and phantom limb pain

PAIN TYPICALLY HAS A CLEAR CAUSE—BUT not always. When a person touches something hot or bumps into a sharp object, it's no surprise that it hurts. But for people with certain chronic pain disorders, including fibromyalgia and phantom limb pain, a gentle caress can result in agony.

In a major breakthrough, a team led by researchers at the Salk Institute and Harvard Medical School have identified an important neural mechanism in the spinal cord that appears to be capable of sending erroneous pain signals to the brain.

By charting the spinal circuits that process and transmit pain signals in mice, the study, published online November 20, 2014 in *Cell*, lays the groundwork for identifying ways to treat pain disorders that have no clear physical cause.

"Until now, the spinal cord circuitry involved in processing pain has remained a black box," says **Martyn Goulding**, Salk professor in the Molecular Neurobiology Laboratory and a co-senior author of the paper. "Identifying the neurons that make up these circuits is the first step in understanding how chronic pain stems from dysfunctional neural processing."

In many instances, people who suffer from chronic pain are sensitive to stimuli that don't normally cause pain, such as a light touch to the hand or a subtle change in skin temperature. These conditions, referred to generally as forms of allodynia, include fibromyalgia and nerve damage that is caused by diseases such as diabetes, cancer and autoimmune disorders.

In other instances, the mysterious pain arises after amputation of a limb, which often leads to discomfort that seems to be centered on the missing appendage. These sensations often subside in the months following the amputation, but may linger indefinitely, causing long-term chronic pain for the sufferer.

"These disorders are extremely frustrating for patients, because there is still no effective treatment for such chronic pain disorders," says Qiufu Ma, a professor of neurobiology at Harvard Medical School and co-senior author on the paper.


Scientists have long theorized that pain signals are sent from sensory neurons in the limbs and other extremities to transmission neurons in the spinal cord, which then relay the information to the brain. At each of these three sites—extremities, spinal cord and brain—the pain information can be altered or even blocked before being relayed onward through the nervous system to the brain. The circuitry in the spinal cord is particularly important, as it is able to gate painful stimuli, thereby acting as a checkpoint between the body and the brain to make sure that only the most important pain signals are transmitted.

Previous studies had determined that two types of sensory neurons appeared to be involved in these circuits: pain receptors and touch receptors.

In their new study, the Salk and Harvard researchers set out to precisely identify the spinal neurons involved in these circuits. They deciphered the role each of two neuronal cell types plays in the processing of pain signals in the dorsal horn, the location where the sensory neurons connect with the spinal cord.

The scientists discovered that a class of mechanoreceptors in the skin that detect painful mechanical stimuli are part of a feedback circuit in which excitatory neurons that produce the hormone somatostatin are inhibited by neurons that synthesize dynorphin (a natural analgesic molecule that produces effects similar to opiates). The inhibitory neurons they identified appear to control whether touch activates the excitatory neurons to send a pain signal to the brain.

This finding begins to explain how a light touch can cause discomfort in someone with allodynia: if something is awry in the pain circuitry, then the sensation of touch that normally travels through the mechanoreceptors could instead activate other neurons that trigger a pain signal. Similarly, mechanoreceptor fibers that project to the spinal cord from a missing limb might spur erroneous pain signals.

"Normally, only pain receptors are involved in sending pain signals to the brain, but when the spinal dynorphin inhibitory neurons are lost, touch sensations are now perceived as painful," says Goulding, holder of Salk's Frederick W. and Joanna J. Mitchell Chair. "This really opens the door to understanding what's happening in these pain disorders where the cause of the pain is seemingly innocuous or not known. It could be that something has gone awry in how this spinal circuitry is operating, so sensations become jumbled together and emerge as pain." 



From left: Martyn Goulding and Jovanny Bourane



From left: Inder Verma, Gary Nabel, Vincent Racaniello, Alfred Sommer, Rino Rappuoli and Paul Offit

GLOBAL HEALTH SYMPOSIUM

FEATURED LEADING EXPERTS ON VIRUSES, VACCINES AND PANDEMICS

THE SALK INSTITUTE CELEBRATED ITS founding father's 100th birthday in inimitable Salk style on November 13 with a global health symposium during the day and a private concert with violin virtuoso Itzhak Perlman at night.

As the host of "Global Health Symposium: Viruses, Vaccines and Pandemics," **Inder Verma**, professor of genetics and one of the world's leading authorities on gene therapy, welcomed prominent immunologists and virologists from the United States and Europe.

In all, there were five guest speakers during the day-long symposium, with topics ranging from poliovirus and Ebola to viral diversity and vaccines. Kicking off the day with a talk on polio was Higgins Professor of Microbiology & Immunology at Columbia University Vincent Racaniello, PhD. Gary Nabel, MD, PhD, chief scientific officer at Sanofi, followed with a presentation titled, "Addressing Viral Diversity: The Challenges of an AIDS Vaccine."

Rino Rappuoli, PhD, global head of vaccines research at Novartis Vaccines and Diagnostics in Siena, Italy, presented his talk, "Vaccines: Science, Health, Longevity

and Wealth." Alfred Sommer, MD, MHS, dean emeritus at the Bloomberg School of Public Health and distinguished service professor at Johns Hopkins University presented, "Global Health: A Personal, Peripatetic Perspective." Finishing off the day was Paul A. Offit, MD, professor of pediatrics in the division of Infectious Diseases and director of the Vaccine Education Center at Children's Hospital of Philadelphia. Offit gave a talk on the Cutter Incident.

In the evening, nearly 300 invited guests were treated to a talk on pandemic prevention by Nathan Wolfe, founder and

CEO of Metabiota, followed by Perlman's recital in remembrance of Jonas Salk. Following the concert, Irwin Jacobs, Salk's board chairman, presented Perlman with the Salk Institute Medal for Public Service, noting all Perlman has done to help eradicate polio around the globe. Perlman is only the fifth person to receive the Salk award that is given to individuals who have contributed to science, medicine, public health or public service.

The scientific Global Health Symposium was underwritten by the ResMed Foundation, the Farrell Family Foundation and Dr. and Mrs. Herbert W. Boyer. 📺



Nathan Wolfe



Paul Offit



Giuseppe Mentuccia

Two performances remaining in the Science & Music Series

ITALIAN PIANIST GIUSEPPE MENTUCCIA PERFORMED AT THE SALK

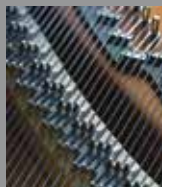
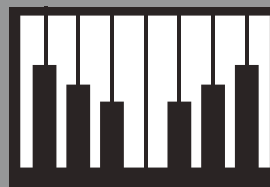
Institute on January 25 as part of the Salk Science & Music Series.

Mentuccia's concert was the third in the six-part series. The event included a scientific talk by Salk President **William Brody**.

The Salk Science & Music series features performances by established and emerging classical and jazz musicians, along with riveting talks on the latest scientific discoveries. There are two concerts remaining before the series concludes in June.

On April 26, 2015, pianist Fei-Fei Dong, a finalist in the 2013 Cliburn Competition, will perform. She will be joined by **Juan Carlos Izpisua Belmonte**, professor in the Gene Expression Laboratory, for a presentation on his latest work. On June 7, the Brubeck Brothers Quartet will perform a tribute to Dave Brubeck. **Satchidananda Panda**, associate professor in the Regulatory Biology Laboratory, will share some of his lab's newest work. 📺

Tickets for future Science & Music Series concerts are available at www.salk.edu/music





Google Doodle honors Salk

ON JONAS SALK'S 100TH BIRTHDAY ANNIVERSARY—OCTOBER 28, 2014—Google celebrated the scientist behind the first effective polio vaccine with a rare honor: a Google Doodle. These artistic reinterpretations of Google's logo commemorate holidays and events throughout the year. Penning the colorful version of the Google logo, artist Mike Dutton depicted children dancing and carrying balloons below a sign that reads "Thank You, Dr. Salk!" As a result of the Doodle, traffic to the Salk website increased 375 percent that day.

The Institute will mark yet another milestone this year with the 60th anniversary of the development of Salk's polio vaccine, which, on April 12, 1955, was officially announced to be safe and effective. Wanting the vaccine to be distributed as widely as possible, Salk did not patent or profit from his discovery. In the two years before the vaccine was widely available, the average number of polio cases in the United States was more than 45,000. By 1962, that number had dropped to 910. 📊



Marion Cotillard and Ronald Evans

FRENCH CONNECTION

THE SALK INSTITUTE'S TRAVERTINE courtyard and zigzag stairwells were the backdrop for a Dior photo shoot in January featuring Academy Award-winning French actress Marion Cotillard, who modeled the fashion giant's 2015 Fall line. The face of Dior for the past six years, Cotillard personally championed having the photo shoot at the Institute. Although she had never visited the Salk before, she became a devotee a decade ago after watching "My Architect," the film Nathaniel Kahn

produced about his father, Salk architect Louis Kahn. In between changes of clothes, Cotillard was given a private tour of the Institute by **Rebecca Newman**, vice president of External Relations, and **Anna-Marie Rooney**, chief communications officer. The tour included a visit to the lab of **Ronald Evans**. After her day at the Salk, Cotillard wrote in an Instagram post: "It was one of my dreams to visit @SalkInstitute. Louis Kahn you are an artist and this place is an oeuvre d'art!" 📊





Alan Saghatelian

Salkexcellerators hear from new Salk faculty member, Alan Saghatelian

A PRIVATE RECEPTION FOR THE SAN DIEGO SALKEXCELLERATORS WAS HELD ON October 22, 2014 at the Salk Institute. The event featured a presentation by one of the Institute's newest faculty members, **Alan Saghatelian**, professor in the Clayton Foundation Laboratories for Peptide Biology. His lab focuses on the biology of metabolites and peptides, two classes of molecules that are extremely important in disease—particularly diabetes, cancer and autoimmune disease.

Saghatelian shared with the group a discovery made by his team and Beth Israel Deaconess Medical Center (BIDMC) in Boston, which was detailed in the journal *Cell* in October. Through their collaboration, the researchers discovered a new class of molecules produced in human and mouse fat that protects against diabetes. Scientists found that giving this new lipid, called fatty acid hydroxy fatty acids (FAHFAs), to mice with the equivalent of type 2 diabetes lowered their elevated blood sugar. FAHFAs were also lower in humans with early stages of diabetes and higher in mice resistant to diabetes.

"These lipids are amazing," says Saghatelian. "Because they can also reduce inflammation, this suggests that we might discover therapeutic opportunities for these molecules in inflammatory diseases, such as Crohn's disease and rheumatoid arthritis, as well as diabetes."

New mass spectrometry techniques developed by Saghatelian enabled him and collaborators to uncover the FAHFAs. Saghatelian plans to integrate these and other mass spectrometry methods through cross-disciplinary collaborations to discover new therapies for many diseases.

For more information on the Salkexcellerators program, visit www.salk.edu/salkexcellerators or contact **Megan Shockro** at mshockro@salk.edu or (858) 453-4100 x1405. 📱



From left: Lorena Monzon and Maggie Curiel



Laura and Brian Tauber



Jelena Ostojić named recipient of 2014 Salkexcellerators Fellowship

RESEARCHER JELENA OSTOJIC, WHO works in Professor **Marc Montminy's** lab in the Clayton Foundation Laboratories for Peptide Biology, has been named the 2014 Salkexcellerators Fellowship recipient.

Montminy's lab is studying communication between a cell's nucleus, where gene expression occurs, and other organelles from the cell, called the mitochondria.

"We will investigate whether this communication between the nucleus and mitochondria can be disrupted early in the onset of disorders such as insulin resistance and diabetes," says Ostojić, whose work aims to understand the cellular factors that trigger type 2 diabetes. The lab's research will focus on finding useful strategies for designing drugs to prevent and cure metabolic disorders.

Salkexcellerators support a restricted fund that provides an annual fellowship for talented Salk postdoctoral scholars. Contributions, in their entirety, provide support for the fellowship recipient's salary, supplies and travel expenses.

To learn more about Salkexcellerators, contact **Megan Shockro** at mshockro@salk.edu or (858) 453-4100 x1405, or visit www.salk.edu/salkexcellerators

» **View video:**
www.salk.edu/insidesalk/apr15/ostojic



Nicola Allen

salk women & science

Where cures begin.

Women & Science presentation gives insight into brain diseases

LOCAL FEMALE BUSINESS AND COMMUNITY members gathered on October 7 to hear a presentation from **Nicola Allen**, assistant professor in Salk's Molecular Neurobiology Laboratory.


Allen studies enigmatic cells in the brain called astrocytes and their impact on neurodevelopment and degenerative diseases like autism, epilepsy, schizophrenia, stroke and Alzheimer's disease.

Prior to Allen's talk, **Rebecca Newman**, vice president of External Relations, welcomed the crowd of 70 saying, "This is the 100th-year anniversary of the birth of Jonas Salk, and for us at the Institute, it is going to be a year of celebration of his vision." Newman spoke of Salk's vision for collaboration among scientists and the potential for innovation across disciplines.

Allen is one such scientist who has embraced innovation in her exploration of astrocytes, the study of which have only recently edged into the field of neurobiology as a viable research area. It

was once thought that the only purpose of astrocytes was to serve as scaffolding for neurons. Yet, in the last decade astrocytes have been shown to be critical in brain function.

Allen's lab explores how these prolific cells influence connections between neurons as the brain develops and ages. One of her major goals is to find out if and how one could use proteins from astrocytes to encourage new connections to form between neurons in damaged or aging brains, potentially restoring brain function.

The Women & Science program is in its third year and continues to gain momentum by engaging the community in biological science and technology. The next Women & Science presentation will take place this summer. Learn more about the program at: www.salk.edu/womenandscience or contact **Betsy Reis**, director of Donor Relations, at (858) 453-4100 x1426 or breis@salk.edu. 

Women & Science Special Awards Initiative reaches \$100,000 goal

THE SALK WOMEN & SCIENCE SPECIAL

Awards Initiative has reached its goal of \$100,000, which will provide critical support to advance the careers of Salk Institute graduate students and postdoctoral trainees. Awards will be granted to up-and-coming scientists who have completed at least three years of training and are pursuing innovative research.

The awards initiative was announced in October and soon after received a kick-start in the form of three lead grants from loyal Women & Science supporters. Elizabeth Keadle, Carol and John Gallagher of the Gallagher Charitable Fund, Lynne Rosenthal and Patti Silver of the Leo S. Guthman Fund all helped establish the awards initiative with their generous contributions.

In February 2015, Lynne Rosenthal and Patti Silver created a \$25,000 challenge grant in memory of renowned scientist Rosalind Franklin. They graciously matched every dollar, up to \$25,000, donated to the initiative.

Breakthroughs by Salk scientists are driving discovery. We hope you will partner with Salk Women & Science by making a gift to the Special Awards Initiative. For more information about the Salk Women & Science program, contact **Betsy Reis**, director of Donor Relations, at (858) 453-4100 x1426 or breis@salk.edu.



From left: Reena Horowitz and Joani Nelson



From left: Nicola Allen, Faye Hunter and Julia Miller



Inder Verma




Jean-Pierre Changeux

Symposium celebrates life and science of **STEPHEN F. HEINEMANN**

MORE THAN 300 COLLEAGUES, FAMILY AND FRIENDS OF SALK neuroscientist **Stephen F. Heinemann** attended his memorial service on January 22, 2015 in the Conrad T. Prebys Auditorium that was part of the 9th Annual Salk Institute, Fondation IPSEN, and Science Symposium on Biological Complexity: Neurodegenerative Diseases. Heinemann, who joined the core faculty of the Salk Institute in 1970 and established the renowned Molecular Neurobiology Laboratory, died August 6, 2014 at 75 after a long illness.

Eulogists included French neuroscientist Jean-Pierre Changeux, Nobel laureate Susumu Tonegawa of Japan and Isabel Pérez-Otaño of the Center for Applied Medical Research at the University of Navarra in Spain. Louis Reichardt and Gerald Fischbach, both of the Simons Foundation Autism Research Initiative, and Salk Professor **Charles Stevens** were among those who delivered personal tributes.

The three-day symposium, hosted by **Inder Verma**, drew more than 200 scientists to the Institute to hear presentations on the current research of neurodegenerative diseases such as ALS and Alzheimer's, Huntington's and Parkinson's diseases. Kicking off the convention was the Sydney Brenner Nobel Lecture delivered by Susan Lindquist of the Whitehead Institute for Biomedical Research, who spoke about powerful discovery platforms that combat neurodegenerative disease. The symposium's closing dinner speaker was Fischbach, who talked about the social, scientific and therapeutic challenges of autism spectrum disorders. 



Stephen Heinemann's son, Danny Heinemann.



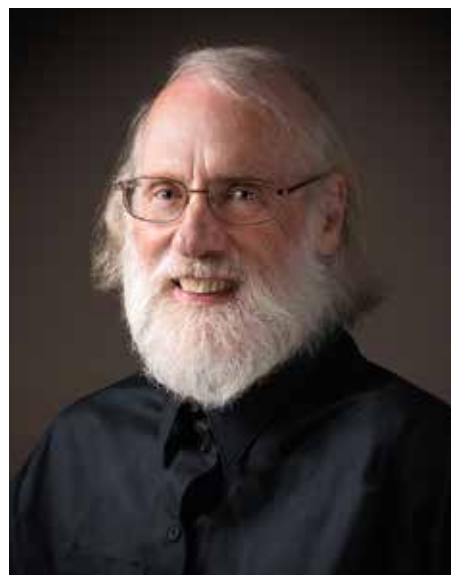
Tony Hunter wins BBVA Foundation Frontiers of Knowledge Award in biomedicine

TONY HUNTER, PROFESSOR AND DIRECTOR OF THE SALK INSTITUTE Cancer Center, has received the BBVA Foundation Frontiers of Knowledge Award in the biomedicine category for “carving out the path that led to the development of a new class of successful cancer drugs.”

Hunter will share the prestigious award with Joseph Schlessinger of the Yale School of Medicine and Charles Sawyers of Memorial Sloan Kettering Cancer Center in New York. The three recipients will split the €400,000 prize, which will be awarded at a ceremony in Madrid, Spain, in June 2015.

The award recognizes “the contributions of three eminent scientists who have taken the field all the way from initial basic discoveries to clinical applications that save lives,” according to the award jury.

The new treatments, all of them approved in the last 10 years, differ from traditional chemotherapy in that they specifically target the mechanisms causing each type of cancer, making them less toxic for the patient. They are, as such, the first dividend of a profound understanding of the biology of cancer rather than scatter-gun molecular test activity. Imatinib, approved in 2001 and the first of this new class of pharmaceuticals, transformed chronic myeloid leukemia from a fatal cancer into one that is nearly always treatable. Now dozens of such “targeted” drugs are in use for lung and breast tumors, melanoma and lymphomas.



The jury remarked that the three laureates have participated independently in a chain of advances running from “the basic discoveries of tyrosine kinase proteins to clinical applications that save lives.”

Hunter launched the field in 1979 with his discovery of tyrosine kinases, a family of proteins instrumental in regulating vital cell processes like proliferation and metabolism. Some time later, Schlessinger identified how these tyrosine kinases were activated. And finally, Sawyers found a way to interfere with their activity in the presence of mutation, “leading to the clinical translation of these basic concepts into the treatment of cancer,” the citation continues.

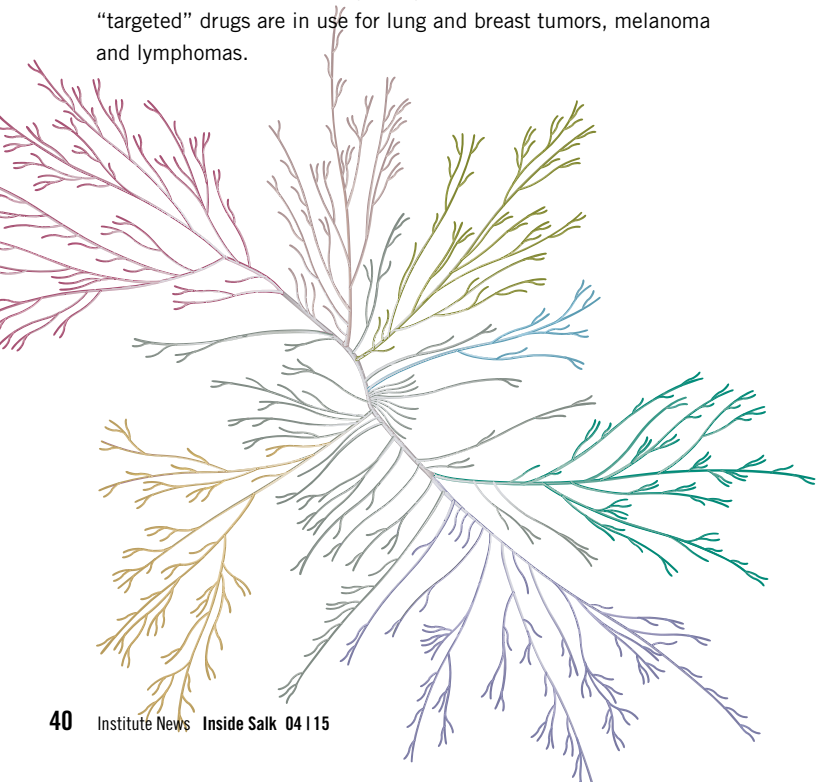
Since many human cancers are driven by mutations increasing tyrosine kinase activity, these proteins and the molecules they interact with have come center stage as therapeutic targets. Today, it is estimated that about a third of pharmaceutical research and development effort goes into targeting tyrosine kinase receptors and their signaling pathways for cancer therapies.

Hunter’s breakthrough, which set the story in motion, was a product of basic research on a chicken RNA tumor virus: the 1979 discovery of the first tyrosine kinase paved the way for our understanding of how cells perceive their environment and respond appropriately to growth signals. External cues act on tyrosine kinase proteins embedded in the cell membrane to induce a cascade of signals with a vital role in regulating cell proliferation. When aberrantly activated by mutation, these signals can cause cancer and are the targets for a new class of personalized cancer drug.

Hunter was born in Ashford, Kent (United Kingdom) in August 1943. He graduated in 1965 from the University of Cambridge, where he also obtained his PhD. In 1975, he joined the Salk Institute, rising to a professorship in 1982. Since 1983, he has also held a professorship at the University of California, San Diego. He has headed the Salk Institute Cancer Center since 2008.

Author of almost 550 publications, he has held editorial posts with 26 journals, including *Cell*, *Proceedings of the National Academy of Sciences* and *eLife*.

Among his multiple distinctions, he is a fellow of the Royal Society of London and member of the United States National Academy of Sciences and the Institute of Medicine of the National Academies.



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 x1405.

Get Involved

FRIENDS OF SALK

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

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.

PRESIDENT'S CLUB

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

CHAIRMAN'S CIRCLE

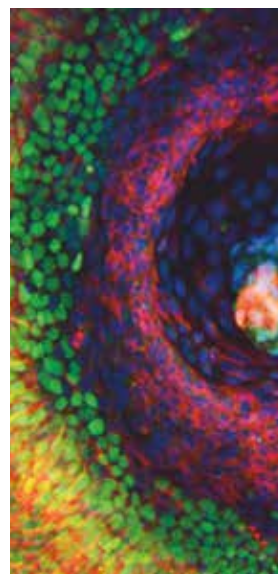
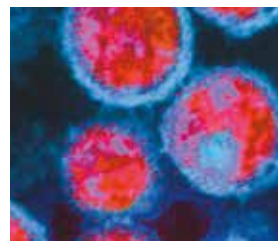
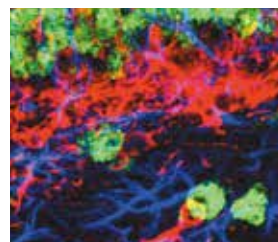
Chairman's Circle visionary donors support the Institute's mission with unrestricted annual gifts of \$25,000 and above. Their generous support fills a vital need for the Institute by providing the world's finest minds in science with the resources to pursue discoveries at the frontier of human knowledge.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

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.

PARTNERS IN RESEARCH

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





Insider's View

William R. Brody, MD, PhD

President, Salk Institute

Irwin M. Jacobs Presidential Chair

THERE IS A SAYING THAT THE “EXPERTS ARE always wrong.” Over the past couple of decades, experts predicted a doomsday scenario known as the “patent cliff” that prompted a great deal of handwringing in the pharmaceutical industry. Many pharmaceutical companies were relying heavily on profits generated by a small number of so-called “blockbuster drugs” that emerged during the early- to mid-1990s. With these cash cows slated to come off patent between 2005 and 2015, there were no replacement blockbusters in the pipeline. The fear was that an influx of generics would cause a sharp drop in prices, resulting in the companies’ revenues falling off the patent cliff.

At the same time, the number of new molecular entities (read “unique drugs”) being approved by the U.S. Food and Drug Administration dropped to a 20-year low, and various groups blamed the FDA for clogging the pipeline. In reality, however, there were very few novel drugs being sent to the FDA for approval. Rather, more prevalent were the “me-too” drugs: already approved drugs that, when combined, could be priced like a new unique drug.

Indeed, the profit fears were justified when looking at individual drugs, as a company can suffer a real shock when a blockbuster comes off patent. The classic example is Pfizer’s cholesterol-lowering drug Lipitor. A highly effective cholesterol lowering statin, Lipitor came on the market in the mid-1990s and by its peak in 2006, generated nearly \$13 billion in sales. After Lipitor came off patent in 2011, a number of companies started selling generic versions, and by 2013, Pfizer’s sales of the drug had dropped to \$2.3 billion, still a

healthy number, but far from the pre-cliff days. Other blockbuster drugs similarly took the plunge. Novartis’ blood-pressure drug Diovan, Bristol-Myers Squibb and Sanofi’s anti-clotting drug Plavex and Merck’s asthma and allergy drug Singulair all lost patent protections in 2012. Each drug sold in the billions at its peak, and in each case, generics flooded the market and revenues of the former patent holder took a dive.

In a fit of panic, various organizations that represent diseases like cancer, diabetes and Parkinson’s, lobbied Congress to set up a completely new research funding organization called “Faster Cures.” Fortunately, the proposal lacked sufficient support to get out of committee, but had it passed, it would have led to major cuts in the NIH budget, just at a time when basic science was making startling discoveries that would lead to groundbreaking new drugs.

The experts were wrong. Pharmaceutical companies combatted the patent cliff in three ways: 1) Developing mergers with other big pharma companies, eliminating thousands of employees and drastically cutting research budgets to raise profitability; 2) Acquiring the rights to develop and market drugs produced by biotech companies; and 3) Retooling their R&D programs by moving from their traditional corporate headquarters to set up labs in Cambridge (England and Massachusetts), Silicon Valley and San Diego. These moves allowed them to take advantage of the developments in molecular biology, genomics and the significant discoveries from universities that identified new targets on which drugs could act.

With these changes, the industry is again thriving, and the drug development pipeline—which doomsayers warned would slow to a trickle—is churning out new drugs faster than ever. Last year, the FDA approved 44 new (NME) drugs, the most since 1996, its

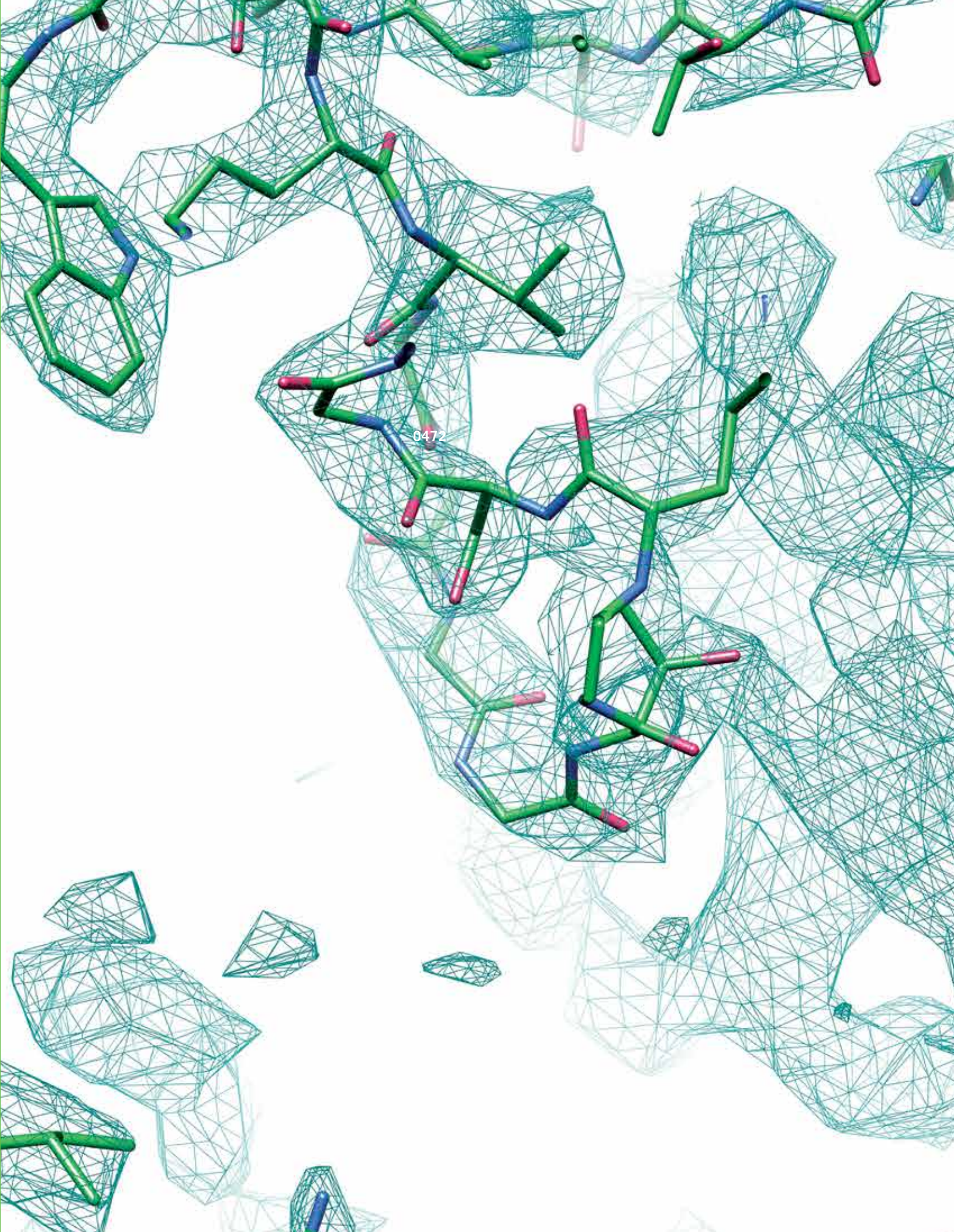
previous high-water mark. These included 12 drugs for treating infectious diseases, 8 new cancer therapies and other drugs for treating everything from gastrointestinal disorders to neurological diseases.

So what happened? Put simply: science happened. In the past, most drugs were developed by a shotgun approach that involved one part savvy and nine parts luck. Drug companies developed hundreds or thousands of different molecules and threw them all at a disease hoping for a therapeutic effect. It was often brute force science that produced drugs, not an understanding of how they worked.

Thanks to decades of discoveries by scientists at Salk and other basic research institutions, we not only have a detailed understanding of many diseases, but, in fact, often have identified a target molecule against which a drug can work to enable or disable the function of that molecule. With this powerful knowledge, researchers are no longer groping blindly through the molecular haystack, but instead are precisely targeting the molecular weaknesses of diseases.

The science of genomics is allowing the segmentation of patient groups who seem to have a common disease (like breast cancer) but are quite disparate based upon genetic mutations in the tumor. Armed with that information, clinical trials can select a subset of patients with a disease who are most likely to respond to a drug. Previously, a drug against breast cancer might affect survival in 10 percent of patients, and was therefore deemed unsuitable for FDA approval. Today, armed with genetic sequencing, we treat only the 10 percent of patients who could have an 80- to 90-percent improvement in survival—a dramatically positive result and an approvable drug.

Thanks to basic science, the patent cliff turned out to be a molehill. *Faster discoveries lead to faster cures.* ■■■





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Salk Calendar

APRIL

- 11 Explore Salk open house
- 26 Salk Science & Music Series featuring Fei-Fei Dong

MAY

- 11-13 43rd Annual Tax Seminar for Private Foundations
- 20 San Diego Salkexcellerators

JUNE

- 7 Salk Science & Music Series featuring the Brubeck Brothers Quartet

AUGUST

- 29 Symphony at Salk



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