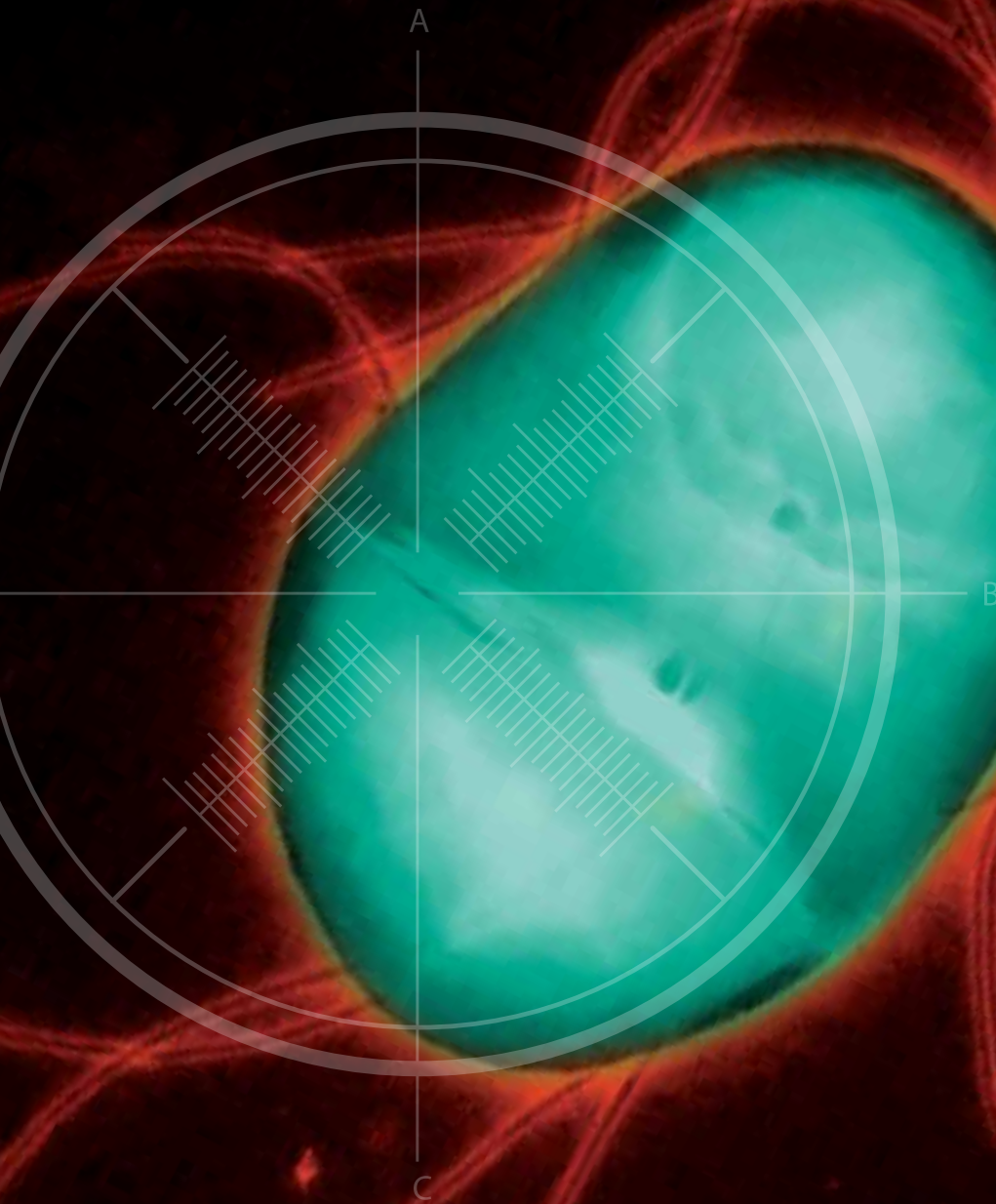


SPRING | 2017

WHERE CURES BEGIN.

insideSalk



SURVIVING SUPERBUGS

ENDING THE ARMS RACE
WITH INFECTIOUS DISEASE

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Janelle Ayres poses a radical strategy for surviving infection: Superbugs.

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The bacteria *Salmonella* Typhimurium interacts with its host in surprising ways that may change how we think about infectious disease.

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An original sketch (circa 1963) of the Salk Institute, designed by famed architect Louis Kahn. It shows a conceptual meeting place (foreground), living place (back right) and laboratories (back left).

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PRESIDENT'S LETTER

Dear Friends,

Thoughts of rejuvenation arrive with spring and in this issue of *Inside Salk* you'll find that much of our current work at the Institute focuses on innovative ways to achieve vibrancy and health.

You'll meet Janelle Ayres, one of our rising star faculty members, who is challenging the traditional use—and sometimes overuse—of antibiotics to fight infectious diseases. As anyone who reads the headlines knows, diseases that have long been controlled by antibiotic medications are staging a worldwide resurgence. According to the Centers for Disease Control, at least 2 million people in the U.S. become infected with antibiotic-resistant diseases each year and around 23,000 die. Janelle proposes a new way of tackling this problem: rather than trying to kill the invading bacteria, she aims to harness the body's own "good" bacteria—its microbiome—to counter the damaging effects of pathogens. Her studies, already proving successful, are redesigning the protocol for how we deal with infectious disease.

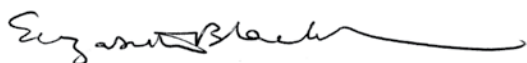
In headlines of another kind, Juan Carlos Izpisua Belmonte, professor in the Gene Expression Laboratory, is being hailed internationally for his work addressing the chronic shortage of donor organs by coaxing human cells to grow inside another species. You'll read about this and many more groundbreaking findings in our Discoveries section.

Here on the Salk campus, we're undergoing rejuvenation of an architectural nature. A months-long project to restore the teak components of our buildings, in partnership with The Getty Conservation Institute, is nearing completion. Filmmaker Nathaniel Kahn, son of famed architect Louis Kahn, who designed the Institute, and Dr. Jonathan Salk, Jonas Salk's son, speak in this issue on the importance of the architectural icon their fathers worked together to create some 50 years ago.

Finally, you'll get a peek inside the inventive mind of Ted Waitt, Salk's new chairman of the Board. Ted, who founded Gateway, Inc., and guided it to a multibillion-dollar corporation, has been immensely successful applying innovative strategies to drive businesses forward. We are working closely with him here at Salk as we begin implementing an ambitious strategic plan to propel Salk forward for the next 50 years. That's just about the time we'll be returning our attention to the teak.

Be well!

Sincerely,



Elizabeth Blackburn
President, Salk Institute
Irwin M. Jacobs Presidential Chair



“Thoughts of rejuvenation arrive with spring and in this issue of *Inside Salk* you'll find that much of our current work at the Institute focuses on innovative ways to achieve vibrancy and health.”

DISCOVERIES



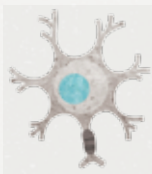
In the last few months, Salk scientists have had groundbreaking work published in top journals and covered in notable media outlets. Read on to learn more.



View the full news reports
and more discoveries online
at www.salk.edu/news

RESEARCH

AT SALK



NEUROSCIENCE

We are entering a new era in neuroscience where our knowledge of the brain is beginning to match the urgent need to prevent and treat diseases of the brain.



METABOLISM

At Salk, we are working to understand human metabolism and what happens when this biological system breaks down. The problem is important as the burden of diabetes on society increases.



PLANT BIOLOGY

To match human population growth, world agricultural production must double over the next quarter century. We study plants so that humans will have the food, clothing, energy and medicines they need now and in the future.



GENETICS

In many ways, we are our genes. At Salk, we explain the role of genes in everything from how tumors form to why certain people are at higher risk for neurological disorders.



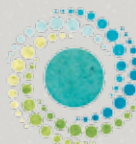
CANCER

We are rapidly demystifying cancers and leading the search for the next generation of targeted cancer therapies. We see a future where every cancer and every patient has a cure.



MICROBIOME

We are not alone: the human body is home to trillions of bacteria. At Salk, we are exploring how this community of bacteria helps us stay healthy, and how we might help it fight disease.



REGENERATIVE MEDICINE

Many disorders and life-threatening diseases could be cured by replacing or fixing dysfunctional cells. We aim to uncover novel ways to provide new tissues and cells to the body while minimizing organ rejection.



AGING

Getting older doesn't have to mean getting sicker. We are committed to discovering the fundamental causes of aging and finding new ways to prevent and treat aging-related diseases.



IMMUNOLOGY

In a world full of dangers, from bacterial infections to cancer, our immune system is our fortress. We study the immune system to boost our ability to fight off numerous diseases.



RESETTING NATURE'S

The science of healing and renewal

NATURE
11/2016

Gene-editing technology partially restores vision in blind animals

Along with Professor Juan Carlos Izpisua Belmonte, first authors Jun Wu, Reyna Hernandez-Benitez, Keiichiro Suzuki and colleagues discovered the ability to, for the first time, insert DNA at a target location into the nondividing cells that make up the majority of adult organs and tissues. The technique, which the team showed was able to partially restore visual responses in blind rodents, will open new avenues for basic research and a variety of treatments, such as for retinal, heart and neurological diseases. Until now, techniques that modify DNA—such as the CRISPR-Cas9 system—have been most effective in dividing cells, such as those in skin or the gut, using the cells' normal copying mechanisms. The new Salk technology, which they named HITI, is 10 times more efficient than other methods at incorporating new DNA into cultures of dividing cells, making it a promising tool for both research and medicine. More importantly, HITI represents the first time scientists have managed to insert a new gene into a precise DNA location in adult cells that no longer divide, offering new possibilities for therapeutic applications in these cells.



WATCH

<http://www.salk.edu/insidesalk/0417/belmonte-1>

CELL
12/2016

Turning back time: Salk scientists reverse signs of aging

Salk Professor Juan Carlos Izpisua Belmonte, along with first authors Alejandro Ocampo, Paloma Martinez-Redondo, Pradeep Reddy and colleagues, found that intermittent expression of genes normally associated with an embryonic state can reverse the hallmarks of old age. Their approach, which not only prompted human skin cells in a dish to look and behave young again, also resulted in the rejuvenation of mice with a premature aging disease, countering signs of aging and increasing the animals' lifespan by 30 percent. The early-stage work provides insight both into the cellular drivers of aging as well as possible therapeutic approaches for improving human health and longevity. The Salk researchers believe that induction of epigenetic changes via chemicals or small molecules may be the most promising approach to achieve rejuvenation in humans.

AS SEEN IN

The New York Times



READ

<http://bit.ly/belmonte-aging>



WATCH

<http://www.salk.edu/insidesalk/0417/belmonte-2>

CLOCK

AGING



NATURE
STRUCTURAL
& MOLECULAR
BIOLOGY
12/2016



See microscopy from
this research on page 44

The Goldilocks effect in aging research

Ever since researchers connected the shortening of telomeres—the protective caps on the ends of chromosomes—to aging and disease, the race has been on to understand the factors that govern telomere length. Salk Professor and holder of the Donald and Darlene Shiley Chair Jan Karlseder, first author Teresa Rivera and colleagues have found that a balance of elongation and trimming in stem cells results in telomeres that are, as Goldilocks would say, not too short and not too long, but just right. The finding deepens our understanding of stem cell biology and could help advance stem cell based therapies, especially related to aging and regenerative medicine.

CELL
01/2017

Findings highlight promise of chimeric organisms for science and medicine

The word “chimera” originally described mythological creatures or deities in polytheistic religions. In science, an interspecies chimera is an organism containing cells from different species. Rapid advances in the ability to grow cells, tissues and organs of one species within an organism of another species (forming “chimeric” organisms) offer an unprecedented opportunity for tackling longstanding scientific mysteries and addressing pressing human health problems, particularly the need for transplantable organs and tissues. The lab of Juan Carlos Izpisua Belmonte combined cutting-edge gene-editing and stem cell technologies to grow a rat pancreas, heart and eyes in a developing mouse, providing proof-of-concept that functional organs from one species can be grown in another. The work marks the first steps toward the generation of transplantable human organs using large animals.

AS SEEN IN

The New York Times



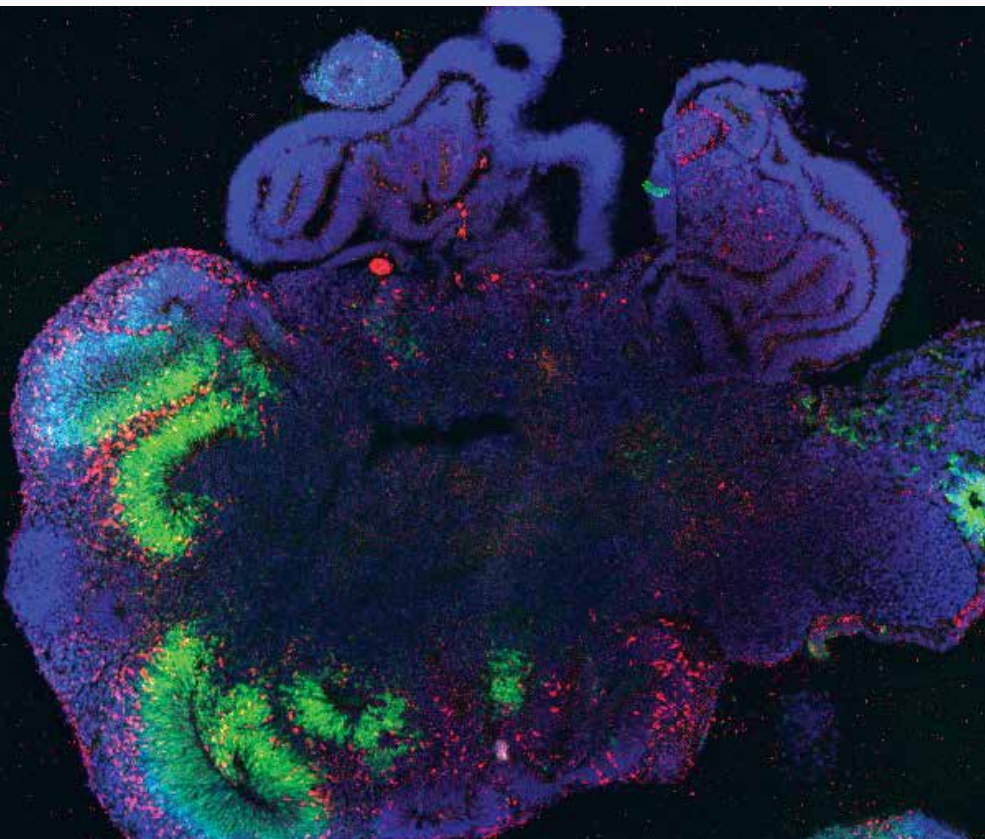
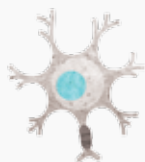
READ

<http://bit.ly/belmonte-stemcells>



WATCH

<http://www.salk.edu/insidesalk/0417/belmonte-3>



Fluorescent cross-section of a cerebral organoid or “mini-brain.”

Credit: Madeline Lancaster/MRC-LMB
(Medical Research Council, Laboratory of Molecular Biology), UK

BUILDING A BETTER BRAIN

When you build models, whether ships or cars, you want them to be as much like the real deal as possible. This quality is even more crucial for building model organs, because disease treatments developed from these models have to be safe and effective for humans. Salk Professor Joseph Ecker, first author Chongyuan Luo and European collaborators have studied a 3D “mini-brain” grown from

human stem cells and found it to be structurally and functionally more similar to real brains than the 2D models in widespread use. The discovery, appearing in the December 20, 2016, issue of *Cell Reports*, indicates that the new model could better help scientists understand brain development as well as neurological diseases like Alzheimer’s or schizophrenia. [S](#)



“PRINCESS LEIA” BRAINWAVES HELP SLEEPING BRAIN STORE MEMORIES


Every night while you sleep, electrical waves of brain activity circle around each side of your brain, tracing a pattern that, were it on the surface of your head, might look like the twin hair buns of Star Wars’ Princess Leia. Salk Professor Terrence Sejnowski, first author Lyle Muller and colleagues, who discovered these circular “Princess Leia” oscillations, think the waves are responsible each night for forming associations between different aspects of the day’s memories. The findings were described in the journal *eLife* on November 15, 2016. [S](#)



WATCH

<http://www.salk.edu/insidesalk/0417/sejnowski>


WORMS HAVE TEENAGE AMBIVALENCE, TOO

Work by Sreekanth Chalasani's lab suggests that, in both roundworms and humans, adolescent brains mature to stable adult brains by changing which brain cells they use to generate behavior. Teen worm brains drive wishy-washy behavior that allows them to stay flexible in an uncertain world, while adult worm brains drive efficient behavior. The discovery, published online in *eNeuro* in January by Chalasani, first author Laura Hale and colleagues, provides insight into the underlying drivers of neurological development that could help better understand the human brain and disease. 



SALK SCIENTISTS ADAPT COMPUTER PROGRAM TO GAUGE EYE SPASM SEVERITY

In an attempt to provide a more objective scale for research and diagnosis, Terrence Sejnowski, first author David Peterson and colleagues have developed a computer program that takes over the job, analyzing videos of patients' faces. The program could eventually be expanded to help

study facial tics and twitches in other contexts, including Tourette syndrome, schizophrenia and Parkinson's disease. The research was described online on October 21, 2016, in *Neurology*, the medical journal of the American Academy of Neurology. 



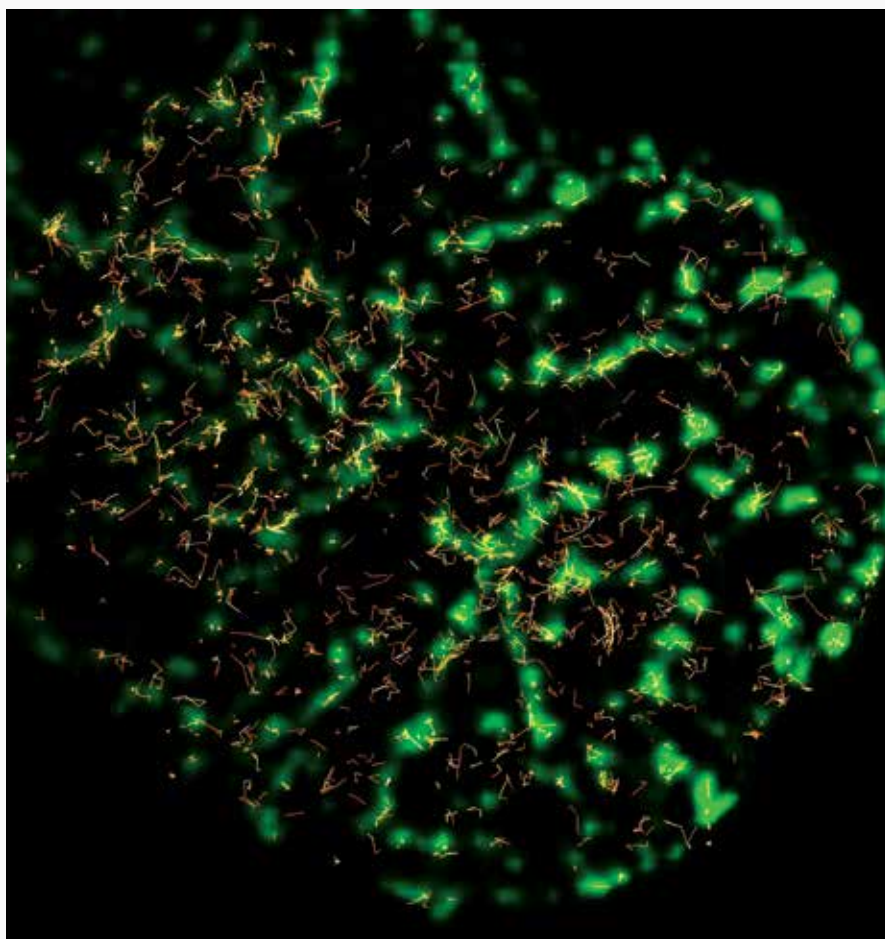
A *C. elegans* roundworm



[http://www.salk.edu/
insidesalk/0417/chalasani](http://www.salk.edu/insidesalk/0417/chalasani)

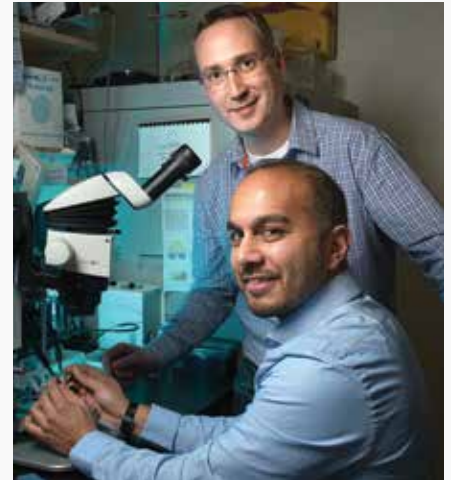
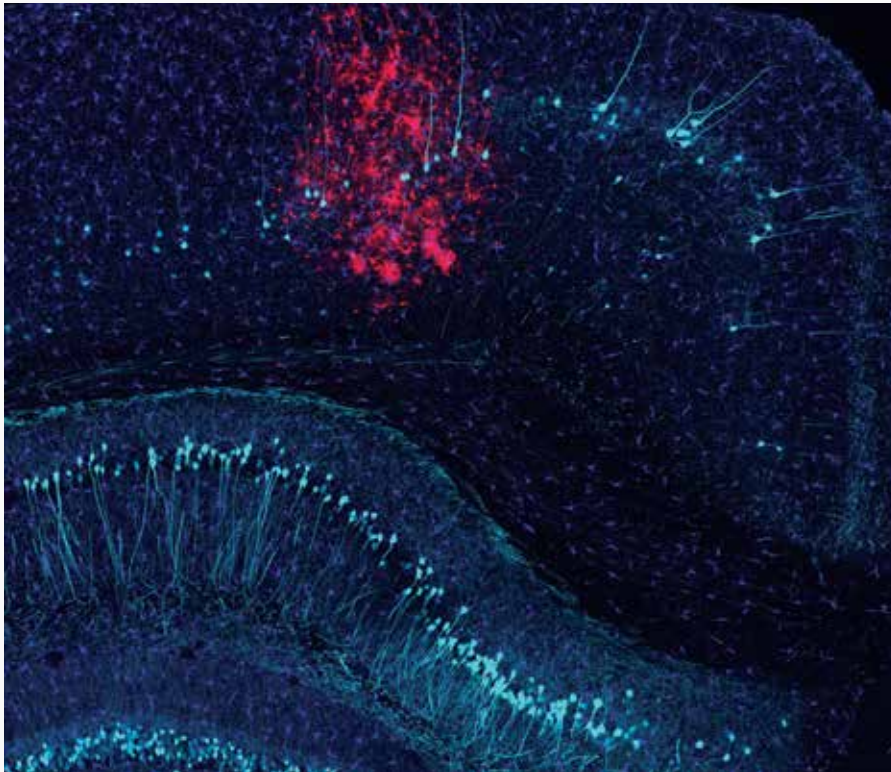


IMMUNE RECEPTORS AMPLIFY “INVADER” SIGNALS BY TURNING INTO MINI-MACHINES



When a receptor on the surface of a T cell—a sentry of the human immune system—senses a single particle from a harmful intruder, it immediately kicks the cell into action, launching a larger immune response. But exactly how the signal from a single receptor, among thousands on each T cell, can be amplified to affect a whole cell has puzzled immunologists for decades. Salk Associate Professor Björn Lillemeier, first author Zachary Katz and colleagues discovered the key to the amplification of an “invader” signal: the T cell receptor that detects the intruder turns into a mini-machine, activating and releasing copy after copy of a protein called ZAP70. The finding, published in *Nature Immunology* on November 21, 2016, could help scientists design better immune-mediated treatments for cancer or autoimmune diseases. [!\[\]\(339a16584d5da0f0a3ca4e9ec17bf6a1_img.jpg\)](#)

Salk Institute scientists discovered how immune receptors use a protein called ZAP70 to amplify “invader” signals and attack a biological intruder. Single molecule tracks of ZAP70 overlaid with T cell receptor microclusters show signal transfer at early moments of T cell activation.



Left: Inhibiting the protein PLSCR1 controls the infected cell's antiviral response and provides long-term protection from immune attack and excessive inflammation. In the cortex of a mouse, adenovirus-transduced cells (red) appear among labeled microglia (dark blue) and subsets of neurons (light blue).

Above: Yusuf Tufail (front) and Axel Nimmerjahn

CURB YOUR IMMUNE ENTHUSIASM

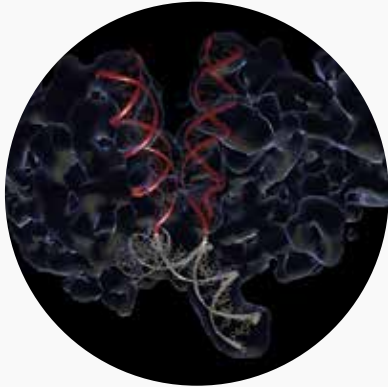
Normally when we think of viruses, from the common cold to HIV, we want to boost people's immunity to fight them. But for scientists who develop therapeutic viruses (to, for example, target cancer cells or correct gene deficiencies) a more important question is: How do we keep people's natural immune responses at bay? In these cases, an overenthusiastic

immune response actually undermines the therapy. Salk Associate Professor Axel Nimmerjahn and first author Yusuf Tufail—along with Associate Professor Clodagh O'Shea, Professor Greg Lemke and colleagues—discovered that inhibiting a protein called phospholipid scramblase 1 (PLSCR1) controls the infected cell's antiviral response and provides long-

term protection from immune attack and excessive inflammation. The results, described in the January 19, 2017, issue of *Neuron*, hold promise both for virally delivered treatments and inflammatory conditions like infections, autoimmune disorders such as lupus, or neurodegenerative diseases such as Alzheimer's. **S**



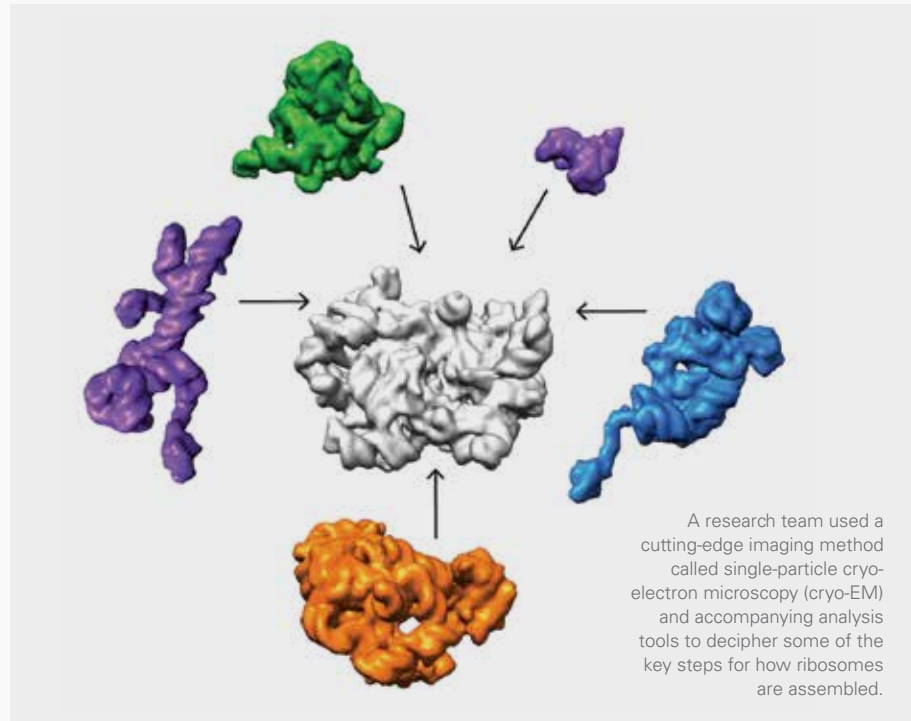
www.salk.edu/insidesalk/0417/nimmerjahn



Salk Institute scientists solved the structure of the HIV intasome, a large molecular complex that inserts viral DNA (red) into the genomes of its host (silver).

SALK SCIENTISTS CRACK THE STRUCTURE OF HIV MACHINERY

Helmsley-Salk Fellow and senior author Dmitry Lyumkis, first author Dario Passos and collaborators have solved the atomic structure of a key piece of machinery that allows HIV to integrate into human host DNA and replicate in the body. The findings about this machinery, known as the “intasome,” appeared January 6, 2017, in *Science* and yield structural clues informing the development of new HIV drugs. **S**



A research team used a cutting-edge imaging method called single-particle cryo-electron microscopy (cryo-EM) and accompanying analysis tools to decipher some of the key steps for how ribosomes are assembled.

COLLABORATION UNCOVERS HOW MOLECULAR MACHINES ASSEMBLE

Ribosomes—macromolecular machines consisting of RNA and proteins that twist, fold and turn—are responsible for making all of the protein within a cell, but because they assemble so speedily, researchers haven’t been able to figure out how they come together. As part of a collaboration between Salk and The Scripps Research Institute, co-senior author Dmitry Lyumkis, a Helmsley-

Salk Fellow, deployed a cutting-edge imaging method called single-particle cryo-electron microscopy (cryo-EM) and accompanying analysis tools to decipher some of the key steps for how ribosomes are assembled, a first step in understanding their roles in health and disease. The results appeared online December 1, 2016, in the journal *Cell*. **S**

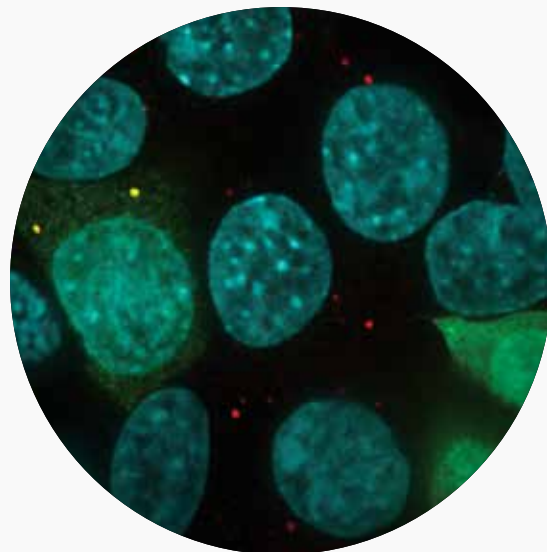


HEART DISEASE, LEUKEMIA LINKED TO DYSFUNCTION IN NUCLEUS

We put things into a container to keep them organized and safe. In cells, the nucleus has a similar role: keeping DNA protected and intact within an enveloping membrane. But a new study by the lab of Martin Hetzer, detailed in the November 2, 2016, issue of *Genes & Development*, reveals that this cellular container acts on its contents to influence gene expression. Using a suite of molecular biology technologies, Hetzer, first author Arkaitz Ibarra and colleagues discovered that two proteins, which sit in the nuclear envelope, together with the membrane-spanning complexes they form, actively associate with stretches of DNA to trigger expression of key genes. Better understanding these higher-level functions could provide insight into diseases that appear to be related to dysfunctional nuclear membrane components, such as leukemia, heart disease and aging disorders. **S**

Human kidney cells stained with a P-body marker (red) and NoBody (green); yellow dots are where P-bodies and NoBody interact. Cell nuclei are shown in blue.

Credit: MIT/Yale University



SMALL BUT MIGHTY: TINY PROTEINS WITH BIG ROLES IN BIOLOGY

We all know how hard it is to find something small like a dropped contact lens that blends into the background. It's similarly tough for biologists to find tiny proteins against the complex background of the cell. But, increasingly, scientists are learning that such microproteins, which are overlooked by traditional detection methods, also have important biological roles to play. Using a new microprotein detection strategy, Salk Professor Alan Saghatelian,

research associate Jiao Ma and collaborators discovered a human microprotein involved in one of the cell's key housekeeping tasks: clearing out genetic material that's no longer needed. The new molecule, dubbed NoBody, could provide a better understanding of how the levels of genes, including disease genes, are controlled in the cell. The paper appears in the December 5, 2016, issue of *Nature Chemical Biology*. **S**



SURVIVING SUPERBUGS

We're losing the war with infectious diseases

Ending the arms race with infectious diseases could mean learning to live with them

Two years ago, Janelle Ayres received a frantic text from her mother 12 hours after her father was discharged from the hospital.

“He can’t walk. I need to call an ambulance. I don’t know what’s wrong with him.”

Ayres’ father, Robert Lamberton, had undergone routine gallbladder surgery and was supposed to be recovering at her parents’ home on the outskirts of Oakland. It was a common surgery and nothing was supposed to go wrong. But something was very wrong. Ayres knew from the symptoms her sister described on the phone that her father had sepsis, a poorly understood condition in which the body’s reaction to an infection is more deadly than the infection itself.

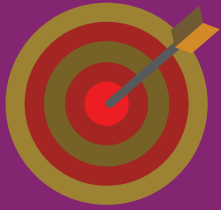
She caught the first flight from San Diego to Oakland and rushed to the hospital where her father had been taken by ambulance. When she entered his room in the intensive care unit, her father smiled and gave her the thumbs up she’d seen a thousand times as a child.

The doctors explained that the gallstones went undetected for too long, resulting in an infection in his gallbladder. The bacteria had spread to his bloodstream and taken hold in his spine. They confirmed he had sepsis. The only treatment option was administration of broad-spectrum antibiotics.

Over the next several days, Ayres stayed in the hospital room with her father, obsessively watching his vital monitors. She was hoping the next blood pressure read would be higher or the next ventilator read would be lower, anything to suggest the antibiotics were working. All the while, her father watched endless reruns of

Janelle Ayres, pictured with her father, Robert Lamberton, and her mother, Frankie Lamberton, at her 2008 commencement at the Stanford School of Medicine.





World's Most Dangerous Superbugs

PRIORITY 1: CRITICAL

- 1 *Acinetobacter baumannii*, carbapenem-resistant
- 2 *Pseudomonas aeruginosa*, carbapenem-resistant
- 3 *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

PRIORITY 2: HIGH

- 4 *Enterococcus faecium*, vancomycin-resistant
- 5 *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- 6 *Helicobacter pylori*, clarithromycin-resistant
- 7 *Campylobacter spp.*, fluoroquinolone-resistant
- 8 *Salmonellae*, fluoroquinolone-resistant
- 9 *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

PRIORITY 3: MEDIUM

- 10 *Streptococcus pneumoniae*, penicillin-non susceptible
- 11 *Haemophilus influenzae*, ampicillin-resistant
- 12 *Shigella spp.*, fluoroquinolone-resistant

Source: World Health Organization (2017)

Blue Bloods, a cop drama that he didn't particularly like, but it was something to do. His numbers never got better, and as the days progressed, his condition worsened. The infection was antibiotic resistant, making the only treatment option available to him useless.

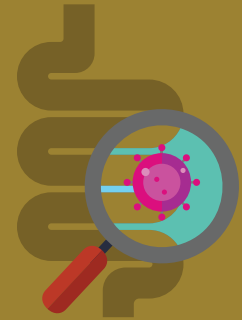
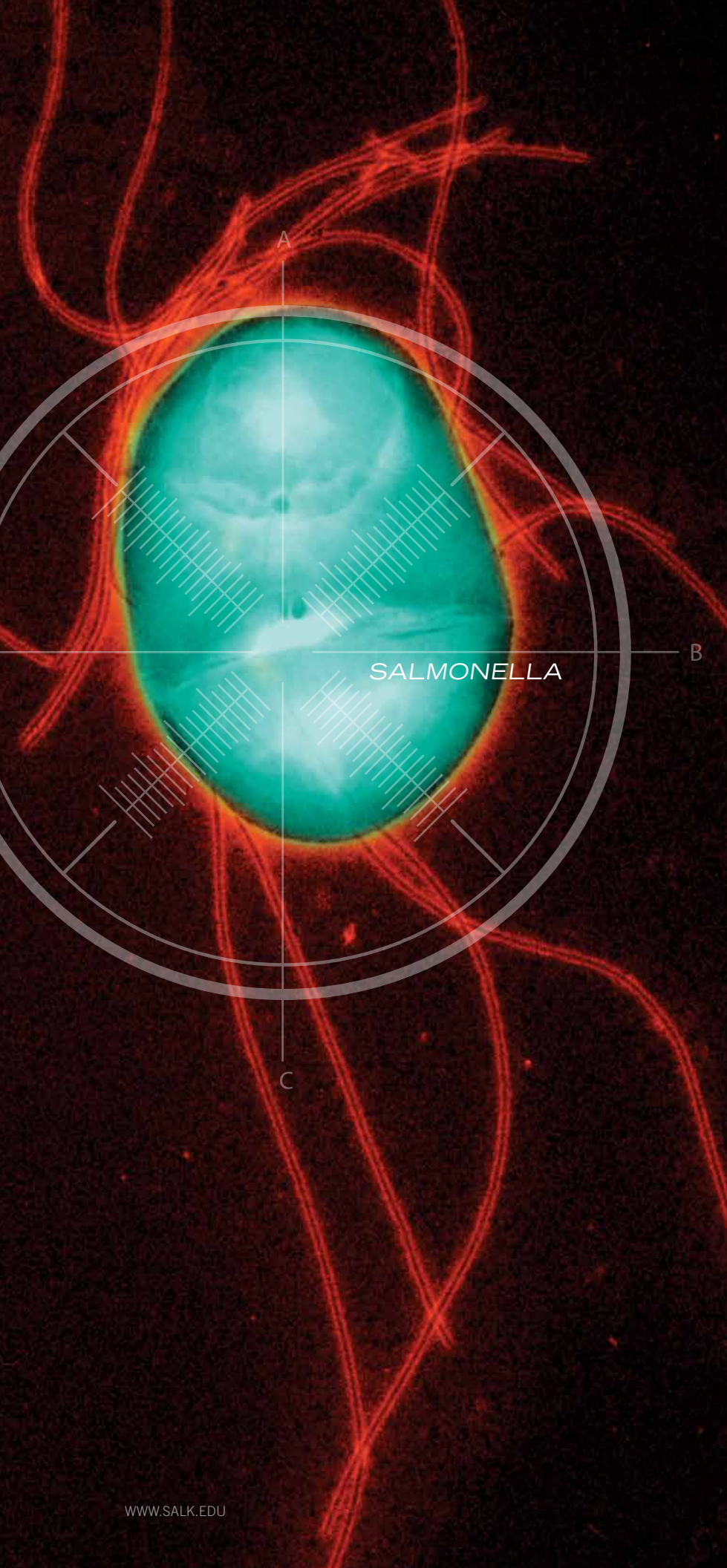
Her father fought for nine days after he was readmitted to the hospital. But in the end, the bacteria won.

From fighting to surviving

Losing a parent is emotionally devastating, but for Ayres the ordeal also was surreal and frustrating. Surreal because Ayres, an associate professor at the Salk Institute and one of the world's foremost experts on bacterial infections, watched a loved one succumb to the kind of infection she studies every day in the laboratory. Frustrating because in her research she had discovered a completely different approach to treating infections—an approach that likely would have saved his life.

Her first breakthrough had come seven years earlier, when she was a graduate student at Stanford University School of Medicine. She earned her admission to graduate school and a prestigious research fellowship to fund her education through hard work—the only kind her father believed in. A German immigrant, after his service in the Navy and Vietnam, Lamberton went to aviation school and became a jet engine mechanic for National Airmotive Corporation and later Rolls Royce, both in Oakland. He had commuted more than two hours each day for his job and for as long as Ayres can remember, he worked seven days a week. He rarely took a sick day, and he raised his three daughters with that same work ethic. He pushed them to set goals and taught them that if they worked hard they could accomplish anything. He insisted that his daughters take after school jobs in high school so that they could learn the value of hard work and accountability. During high school Ayres served ice cream at Baskin-Robbins and worked at a grocery store. During her undergraduate years at the University of California, Berkeley, similar to her father, she commuted over two hours each day and she worked full time in a molecular cytogenetics laboratory at Lawrence Livermore National Laboratory. The schedule was demanding and tiring, but she graduated with her bachelor's degree and a 4.0 grade point average—a goal she had set when she started college.

While at Berkeley, Ayres attended a seminar on infectious diseases that inspired her to devote her career to combating the global health crisis of infectious diseases and drug resistance. To pursue her goal, she entered the microbiology and immunology



Feed a cold, starve a fever? Not so fast, according to Salk research

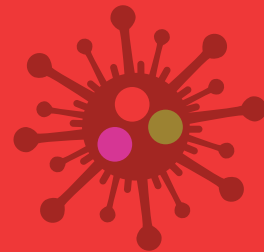
The last time you had a stomach bug, you probably didn't feel much like eating. This loss of appetite is part of your body's normal response to an illness but is not well understood. Sometimes eating less during illness promotes a faster recovery, but other times—such as when cancer patients experience wasting—the loss of appetite can be deadly. Research by Ayres and first author Sheila Rao showed how bacteria block the appetite loss response in their host both to make the host healthier and also promote the bacteria's transmission to other hosts. This surprising discovery, published in the journal *Cell* on January 26, 2017, revealed a link between appetite and infection and could have implications in treating infectious diseases, infection transmission and appetite loss associated with illness, aging, inflammation or medical interventions (like chemotherapy).

▶ WATCH

<http://www.salk.edu/insidesalk/O417/ayres>



BURKHOLDERIA
THAILANDENSIS



Each year*:

700,000

people die from antimicrobial-resistant infections worldwide.

23,000

people die from antibiotic-resistant infections in the United States.

2 million

people are infected by antibiotic-resistant bacteria in the United States.

*Source: CDC and WHO



WATCH

"Ending the arms race with infectious diseases"

<http://www.salk.edu/insidesalk/0417/ayres-tedx>

doctorate program at Stanford University, working with David Schneider, a world-renowned immunologist and infectious disease researcher. As part of her research in Schneider's lab, Ayres studied how fruit flies respond to bacterial infections, searching for clues in the flies' DNA to the biological interactions between a host and pathogen. In a breakthrough experiment, Ayres dosed a group of flies with *Listeria* bacteria, a food-borne microbe that causes a potentially deadly infection in humans known as listeriosis. She found that some of the infected flies were more resilient than others, showing fewer symptoms of disease and better chances of survival. What was surprising was that the flies' chances were unrelated to the level of infection in their bodies. Of two flies with the same degree of infection, one might die while the other survived. It might not sound like a dramatic result, but it challenged one of the pillars of immunology dogma: that survival during an infection depends entirely on how effective the immune system is at killing the offending pathogen. Ayres' experiments showed that flies with similar immune responses had very different outcomes. She realized that something other than the immune system was kicking in during the infections, something that focused not on killing an invading pathogen but on saving the host's life. She gave this phenomenon a name: tolerance defense system. The implications were profound and heretical.

Since the dawn of the field of immunology, the reigning mantra has been that the best defense is a good offense. The predominant metaphor has been war and the goal was the eradication of the pathogen—the enemy. It served humanity well—for a while. The first effective way of dealing with pathogens was soap, a low-tech (and still very effective) tool for killing microbes. Nowadays, we expect doctors and nurses to wash their hands, but the modern concept of medical hygiene didn't really exist until the mid-1800s, when an Austrian obstetrician named Ignaz Semmelweis began advocating for doctors to scrub before delivering babies. As a result, far fewer women died from infections contracted during childbirth. Later, in the early 1900s, the German scientist Paul Ehrlich popularized the idea of a “magic bullet” drug that would target a specific bacterial infection but not harm patients. The first such drug was discovered in 1928 by Scottish scientist Alexander Fleming, who found penicillin in a moldy laboratory dish. Since then, more than a hundred antibiotics have been developed and those drugs have saved hundreds of millions of lives. The early generation antibiotics were so effective that many

health officials declared infectious diseases would soon become a worry of the past.

But the enemy is wily. Over time bacteria evolve resistance to drugs, an ability largely overlooked in the early exuberance for magic bullets. Overuse and misuse of antibiotics have created a global health crisis. Every year in the United States alone, 2 million people are infected by antibiotic-resistant bacteria. Of those, at least 23,000 die from the infections. Worldwide, approximately 700,000 people succumb every year to antimicrobial-resistant infections. As tragic stories and urgent warnings spread, superbugs can seem like fearsome monsters sprung from out of nowhere, but in truth they are of humanity's own making. And fearsome as they are, we keep feeding them. Every year, the problem gets worse, driven by overuse of antibiotics in humans and livestock that puts intense evolutionary pressure on bacteria to develop resistance to the drugs. As a result, the more we use antibiotics, the less useful they are.

Highlighting the urgency of the situation, the World Health Organization (WHO) recently published medicine's equivalent of the FBI's Most Wanted List, naming a dozen superbugs that pose the greatest threat to human health. At the top of the list are microbes that present a particular risk in hospitals, including *Acinetobacter*, *Pseudomonas* and various bacteria that live in the gut, such as *Klebsiella*, *Serratia*, *Proteus* and *E. coli*, the type that took Robert Lambertson's life. The WHO announcement warned of the decline in the development of new antibiotics. Compared to other classes of drugs, antibiotics are far less profitable for drug makers because they are only used for short periods of time—during an infection—and their clinical effectiveness ends when bacteria evolve resistance. Many pharmaceutical companies have moved away from antibiotic research in favor of more profitable drugs used for chronic illnesses, such as antidepressants, targeted cancer therapies, anti-inflammatories and drugs for high blood pressure and cholesterol. Ironically, in many cases, patients suffering from these chronic diseases have weakened immune systems and part of their treatment regimen is antibiotics. In releasing their list, the WHO officials were sounding an alarm that humanity is approaching a dangerous superbug-filled chasm at a time when the pipeline for new antibiotics is running dry. The war cry is clear: We need more weapons!

And yet, from Ayres' perspective, this "arms race" mentality has limits that have been laid bare by history and the superbug epidemic. The current crisis has its roots in the early days of infectious disease medicine and its myopic focus on fighting with microbes. Her research points to another way of thinking about disease—one that focuses less on killing bacteria and more on helping patients survive. It offers the potential to develop drugs that promote survival of patients without driving drug resistance in pathogens.

From Typhoid Mary to tolerance

When Ayres joined the Salk Institute in 2013, she was intent on finding out more about the mysterious survival skills she'd discovered in fruit flies while at Stanford. She built her Salk laboratory to focus on exploring the same phenomena in mice, fellow mammals that offer more insight into human infectious disease biology. Repeating her fruit fly experiments in mice, she found that rodents appear to have a similar tolerance defense system in place. By extension, we humans very likely have such a system at work in our bodies. And, in fact, evidence for this comes from the examination of a variety of human infectious disease cases. Take Mary Mallon, an Irish immigrant to the United States in 1883, known to history by the infamous moniker a prominent medical journal gave her: Typhoid Mary.

Mallon was a cook who worked for several families and public kitchens in New York in the early 1900s. She also was an asymptomatic carrier of *Salmonella* Typhi, the bacterium that causes typhoid fever. She showed no symptoms of the disease, yet was a "super shedder" who left a trail of typhoid outbreaks and deaths as she moved from kitchen to kitchen. Mallon was convinced she was being unfairly persecuted when health officials asked her to stop cooking—she even refused their pleas to at least wash her hands before handling food. Exasperated, authorities arrested and quarantined her for three years, releasing her only after she promised not to work as a cook. She stuck to the bargain for a while, but then changed her name to Mary Brown and went back to concocting her deadly dishes. Eventually, as a public safety measure, she was found and forcibly quarantined on a small island in New York's East River for the remainder of her life. Estimates hold that prior to her incarceration, at least 50 people were infected and

three people died from eating her tainted fare. Like Ayres' infection-tolerant flies, Mallon and other asymptomatic carriers of infections provide evidence that our bodily relationship to microbes is not as simple as kill-or-be-killed. Mallon breezed along with trillions of *S. Typhi* in her body while some of her customers dropped like flies. Another clue that our relationship with bacteria isn't solely adversarial is our microbiome, the community of beneficial bacteria living in and on our bodies, mostly in our intestinal tract. Our bodies contain more than 9 trillion bacteria, about 10 times as many bacteria as human cells, and this community of microbes collectively weighs about 3 pounds—as heavy as our brain. There is much evidence that we have coevolved a symbiotic relationship with our microbial passengers. Among other things, they make enzymes essential for helping us digest food, they generate molecules that help our cells function correctly and they are essential for maturation of our immune system.

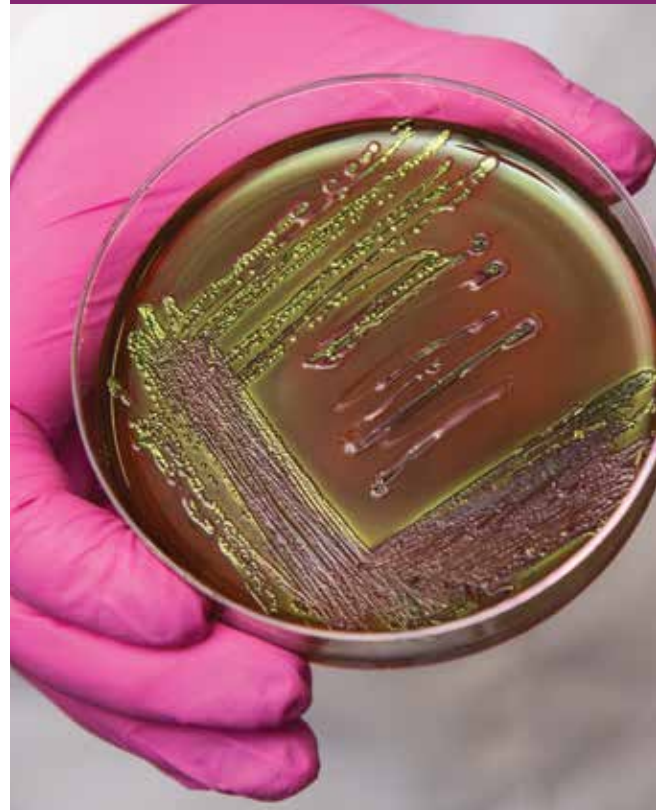
Ayres suspected this relationship goes much further and that our microbiome might play a central role in the tolerance defense system she discovered. If the microbiome was in fact key to infection tolerance, she hypothesized, the composition of a person's microbiome would help determine their ability to tolerate an infection. To test this, she collected mice from labs around the country. The mice were genetically identical, but carried microbiome communities specific to their geographic origins. A mouse from Long Island, New York, had a different array of bacteria, for instance, than one from Northern California. In her Salk laboratory, Ayres and her team studied how mice from different locations responded to intestinal infections of *Salmonella* Typhimurium (a relative of *Salmonella* Typhi) and pneumonia caused by the bacteria *Burkholderia thailandensis*. They discovered that one population of mice showed no signs of muscle wasting, one of the most dangerous symptoms of serious infections. These resilient mice didn't have a genetic advantage—all the populations were genetically identical—nor did they have stronger immune systems. All signs were pointing to a superior tolerance defense system. By comparing the makeup of the intestinal microbiome of the different populations of mice, Ayres' team identified a strain of *E. coli* that was present only in the more resilient mice. But was this strain of *E. coli* really the superhero bug in the story? To test this, they gave mice lacking the strain an oral treatment of the beneficial *E. coli* and observed what happened when they were sick. Sure enough, the mice gained the ability to maintain their muscle and fat mass during infections.

This was the first direct evidence that a specific bacteria from the microbiome could help an organism endure a pathogen by promoting the tolerance defense system. Ayres and her team pushed on in their experiments and found that in response to the infection, the *E. coli* was leaving the gut and moving into the animal's fat deposits. There it was activating metabolic switches that communicated with the muscles, nourishing them to prevent wasting. Not only was a bacterium maneuvering in the body to bolster its defenses, it was activating genetic pathways that might well be part of the tolerance defense system. The implications were profound.

The discovery demonstrated the possibility of entirely new classes of therapies. Superhero bacteria such as Ayres' *E. coli* might be used as therapies to help patients tolerate infections—microbes as medicine. New types of drugs could focus on promoting a patient's health, raising their chances of surviving infections. Unlike antibiotics, such drugs wouldn't target pathogens and so wouldn't drive the evolution of drug resistance. This could spell the end of our arms race with pathogens. Tolerance-enhancing drugs could be used for treating other diseases such as cancers and inflammatory conditions that cause similar pathologies in the body as infectious diseases. Muscle wasting, for example, also occurs in response to tumors and chemotherapy. In that vein, Ayres and her team showed that their tolerance-promoting *E. coli* can block muscle wasting caused by inflammatory bowel disease. They are now testing this approach in preclinical cancer models to determine the spectrum of diseases in which this beneficial microbe can promote tolerance.

Ayres' research offers a ray of hope that is desperately needed. The 20th century, thanks to rapid advances in medical hygiene, vaccinations and antibiotics, was marked by a seemingly inexorable march of progress in the fight against infectious disease. In the 21st century, the battle has tilted against us. Our medical advances have created monsters that grow more lethal the more we fight them.

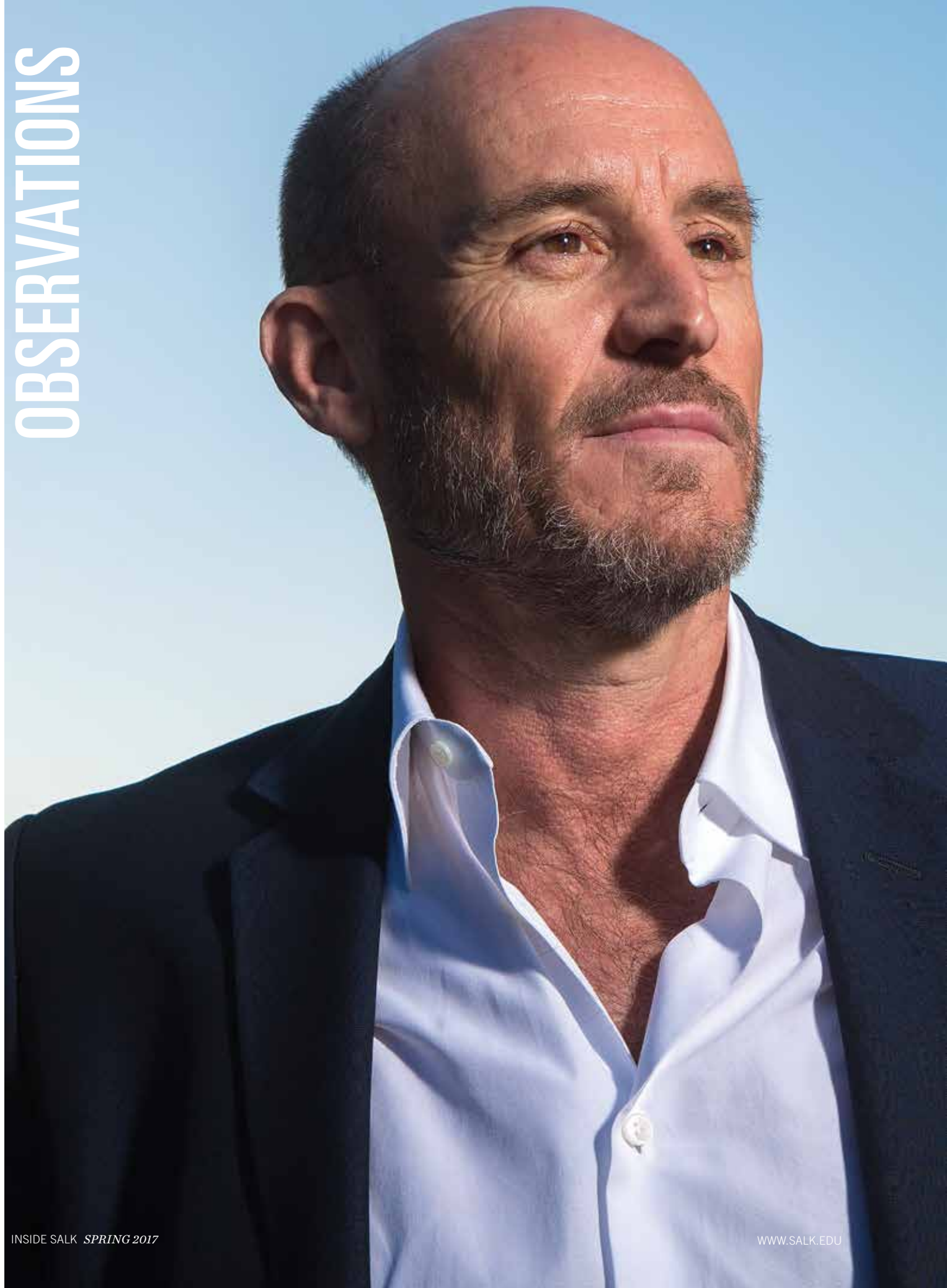
Ayres decided to take on infectious diseases years before her father's death. But now it's personal. "When I talk about infections, my dad is now the patient I am talking about," she says. "I didn't care whether the antibiotics were killing the bacteria, I care that they did nothing to help my father survive. It shouldn't have happened to him and I don't want it to happen to anyone else." **S**



Top: Ayres' team discovered that this strain of *E. coli* bacteria (shown growing in a lab dish) helped mice tolerate dangerous infections.

Bottom: Ayres with her dog, Hans Ferdinand, whom she named after her late father (using his German name).

OBSERVATIONS



Whether it's vital funding, imaginative technology or the perspective of a successful CEO, new Board Chair Ted Waitt says adding a little magic in the right place enables great discoveries.

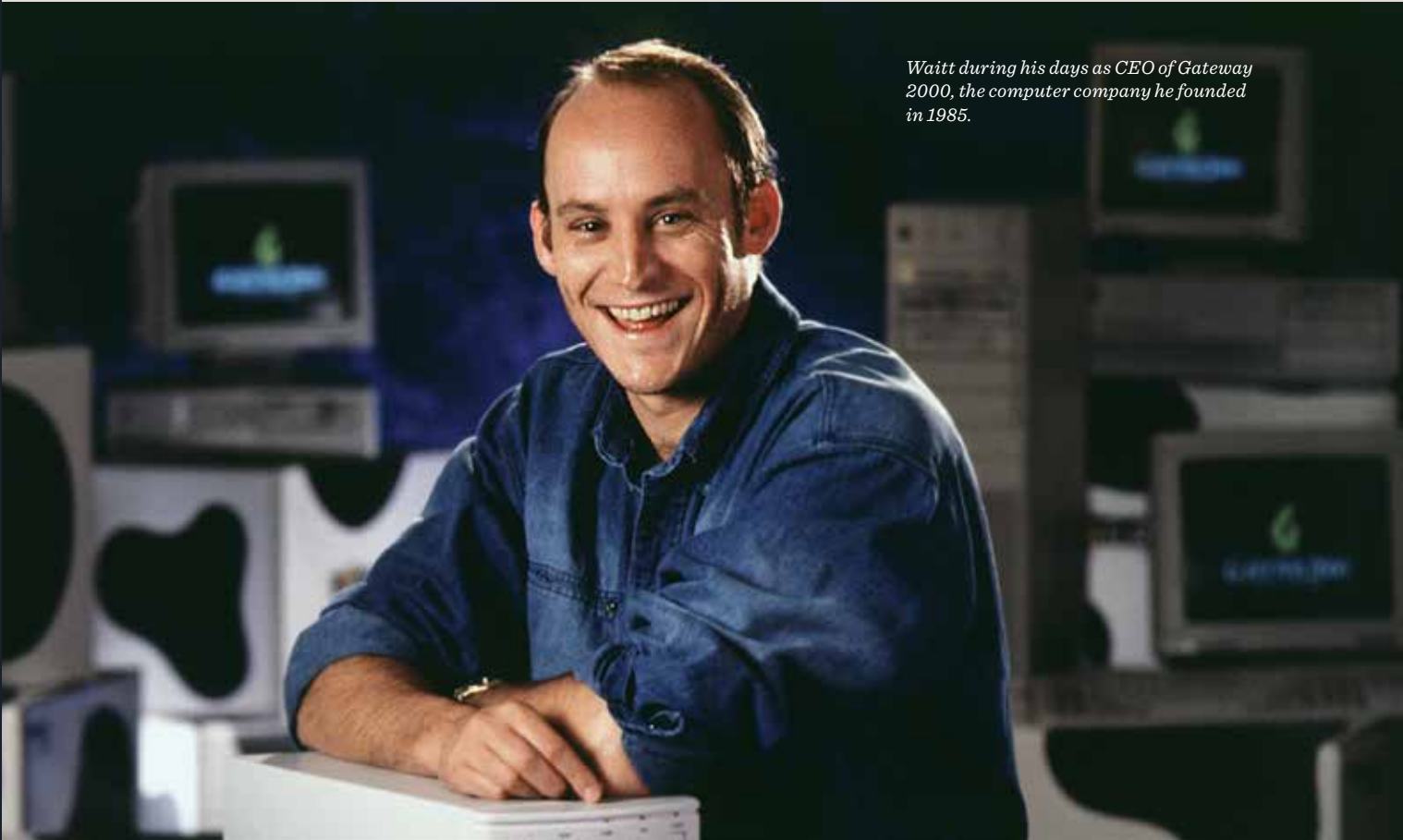


INSIDE THE MIND OF

Ted Waitt

In 2004, Ted Waitt was starting the next chapter in his life. He'd recently retired from Gateway, Inc., the computer company he founded in Sioux City, Iowa, in 1985 and guided to a phenomenal, multibillion-dollar success. He'd worked long and hard for that success, practically missing out on an entire decade by his own admission, because he was so focused. He was ready then to turn that focus toward other ventures. And he wanted to give back. A friend and fellow Iowan, Ted Roth, mentioned the Salk Institute. *Have you seen it?* He hadn't. So from his beach home he ventured along the coast to investigate. He liked what he found and, before long, had joined the Board of Trustees.

Business Week has named Waitt one of America's 50 most generous philanthropists. Many would add that he's also one of the most passionate. He disciplines his pursuits to a narrow focus in order to achieve the best results. Ocean conservation is one; preventing violence is another. And then there's scientific research. Waitt is passionate about developing the sort of cutting-edge technology that furthers scientific discovery. In 2008, his Waitt Foundation donated \$20 million to Salk to fund the creation of the Waitt Advanced Biophotonics Center. This center develops next-generation imaging tools that enable investigators to visualize how living systems function at a level of detail previously not possible. These new insights are rapidly advancing Salk's research into aging, cancer, neuroscience, metabolism, vision, infectious diseases and genetic disorders.



Waitt during his days as CEO of Gateway 2000, the computer company he founded in 1985.

In January, Waitt stepped into the role of chair of Salk's Board of Trustees. As passionate as ever about the power of science to improve the world and its people, he sat down for an interview to share his thoughts.

When you created the Waitt Foundation you were only 30 years old. That's a relatively early age to begin giving back to society. How did you decide what to focus on?

It was an interesting evolution. We started the foundation in Sioux City in 1993 and originally my sister did most of the work because I was still in CEO mode. When I retired from Gateway the first time, in 2000, we did projects helping at-risk communities and we launched some initiatives focusing on domestic violence prevention. But those were really started by my sister. It wasn't until I retired the second time—I went back to Gateway for a stint from 2001 to 2004—that I set out on this period of discovery. I like to call it finalizing my education. And I went on two boards, the National Geographic board and the Salk board.

What sold you on the Salk Institute?

Working with the faculty here and seeing the incredible science that's going on. I'm very fortunate that I've been able to further my education through

the Rusty Gages, the Inder Vermas and their like who can teach me biology. I have the A team. I'm still in awe of what they do and their passion for their work. I have a tremendous amount of respect for them.

What was the conduit to your ocean work?

I was traveling the world, just exploring. As a member of the National Geographic board, I often worked with their scientists. One of the first big projects I got involved in was called the Genographic Project, and involved collecting DNA samples from indigenous peoples around the world. That project was based on *The Journey of Man* by Spencer Wells. It was fascinating. It's highly scientific but it's all about history, not the future, as the science here at Salk is.

My interest in oceans comes from seeing firsthand how badly we've degraded the ocean, and then looking at the science to see if it can come back quickly. The scientists are predicting a total disaster by 2048 in the oceans, but we can do something about it. It's the biggest problem no one knows about. There's still time to fix our oceans. The foundation works to end overfishing, create marine protected areas and raise public awareness about the rapid decline in ocean health. It's all based on science. Everything I do now is founded on strong basic research because that proves what works.

You're known as a hands-on leader, right? You like to get your hands dirty?

Yes, it's just my nature. I come from a long line of entrepreneurs, or "highly unemployable people," as I call them. It's the CEO in me and the entrepreneur in me. I want to contribute where I'm needed. That's also the reason that I don't sit on a bunch of boards; I want to do effective work.

Salk is an entrepreneurial place in terms of science.

Yes, it is. And I definitely gravitate toward scientists and the way they work as opposed to corporations. But Gateway was an unconventional corporation; we were highly entrepreneurial in our advertising, our marketing. We were taking on the big guys, challenging conventions.

As chair, how do you let Salk be Salk? How can it continue to be entrepreneurial but adapt and grow as an organization? What's your vision for the Institute?

I've been working with Liz Blackburn for about a year now and we both want to maintain that entrepreneurial spirit that's born of passion yet still works within a structure. It's a delicate balance but we know from experience there's magic when you collaborate. So our strategy is to find those specific places where you can put in a little magic, add some resources or a connection that can enable great discoveries. At the end of the day, it's all about giving people the tools they need to go do incredible work and then staying out of the way.

Where are we in the history of science?

Advances in technology are fueling amazing breakthroughs in basic science. They're enabling us to see and do things in a different way. As Liz says, we used to take things apart to see how they worked; now we're putting them back together to see how they interrelate. We're learning so much about how the bacteria in our bodies affect the nervous system or how plants work together in a microenvironment.

We're facing some pretty steep challenges—climate change, an aging population, threatened food supplies. Again, I firmly believe that with the power of technology and science—along with education—we'll be able to solve these problems. It's very motivating. When something has the potential to save the world, that drives you. **S**



Waite SCUBA diving in Raja Ampat, Indonesia.

A MASTERFUL DESIGN

A black and white photograph showing two men in conversation. On the left, an older man with light hair, wearing a suit and a dark bow tie, is looking towards the right. On the right, a younger man with dark hair and glasses, wearing a suit and tie, is looking back at the older man. The background is slightly out of focus, showing what appears to be a window with blinds.

"Create a facility worthy of a visit by Picasso."

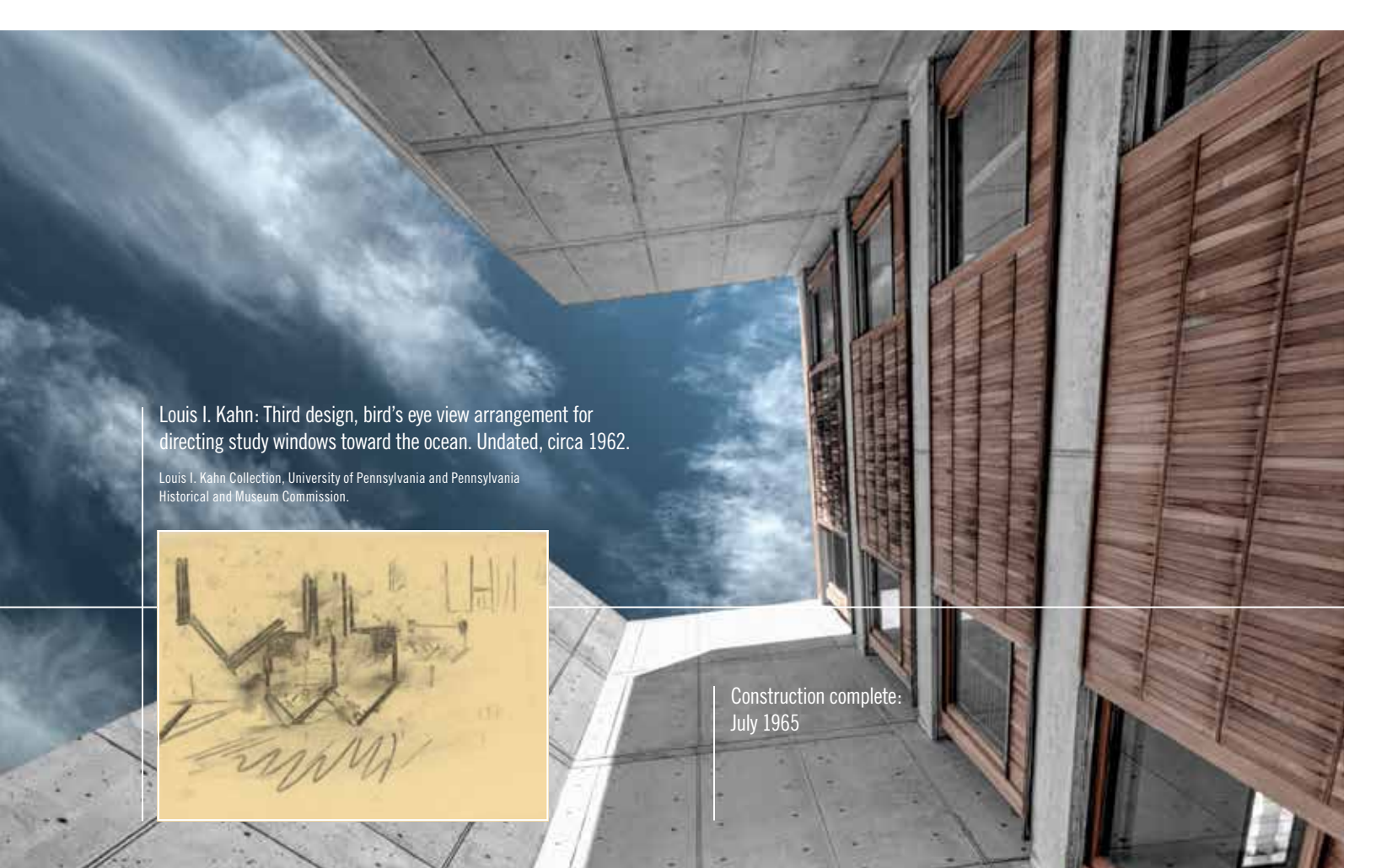
—Jonas Salk to Louis Kahn (left)

Updates to the Salk Institute's iconic architecture ensure that great science and the original vision of the design live on.

Most people don't associate concrete with beauty. But for Jonas Salk, founder of the Salk Institute, and Louis Kahn, famed architect who designed the building, selecting the right concrete for what would become a historical icon deserved special attention.

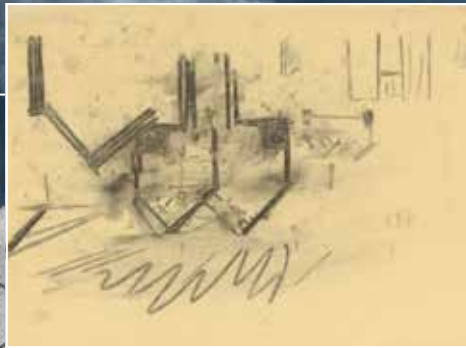
"Concrete is the material of parking garages and overpasses and highways, but in the Salk Institute, the concrete has an enormous warmth to it and changes in beautiful ways as the sun moves around or the fog rolls in," says Nathaniel Kahn, son of Louis Kahn and creator of the Oscar-nominated 2003 documentary *My Architect*. He recalls his father examining the sand that would go into the concrete under a microscope, as he looked for the perfect hue. "It couldn't be too green or too blue, like most concrete. It had to have warmth."

The team mulled over many samples to find the perfect fit. Kahn ended up drawing inspiration from Roman times to select "pozzolanic" concrete, which turns a subtle pink when the sunlight hits. Once the concrete was set in the building, completed in 1965, Kahn allowed no further processing of the finish—no grinding, no filling, and above all, no painting. As a result, the building's exterior today looks much as it did back then. The lack of a finish



Louis I. Kahn: Third design, bird's eye view arrangement for directing study windows toward the ocean. Undated, circa 1962.

Louis I. Kahn Collection, University of Pennsylvania and Pennsylvania Historical and Museum Commission.



Construction complete:
July 1965

is intentional: in some ways the look of the unfinished materials is a reflection of the fundamental, bare-bones biology the scientists within strive to uncover, day in and day out, to better understand disease and development.

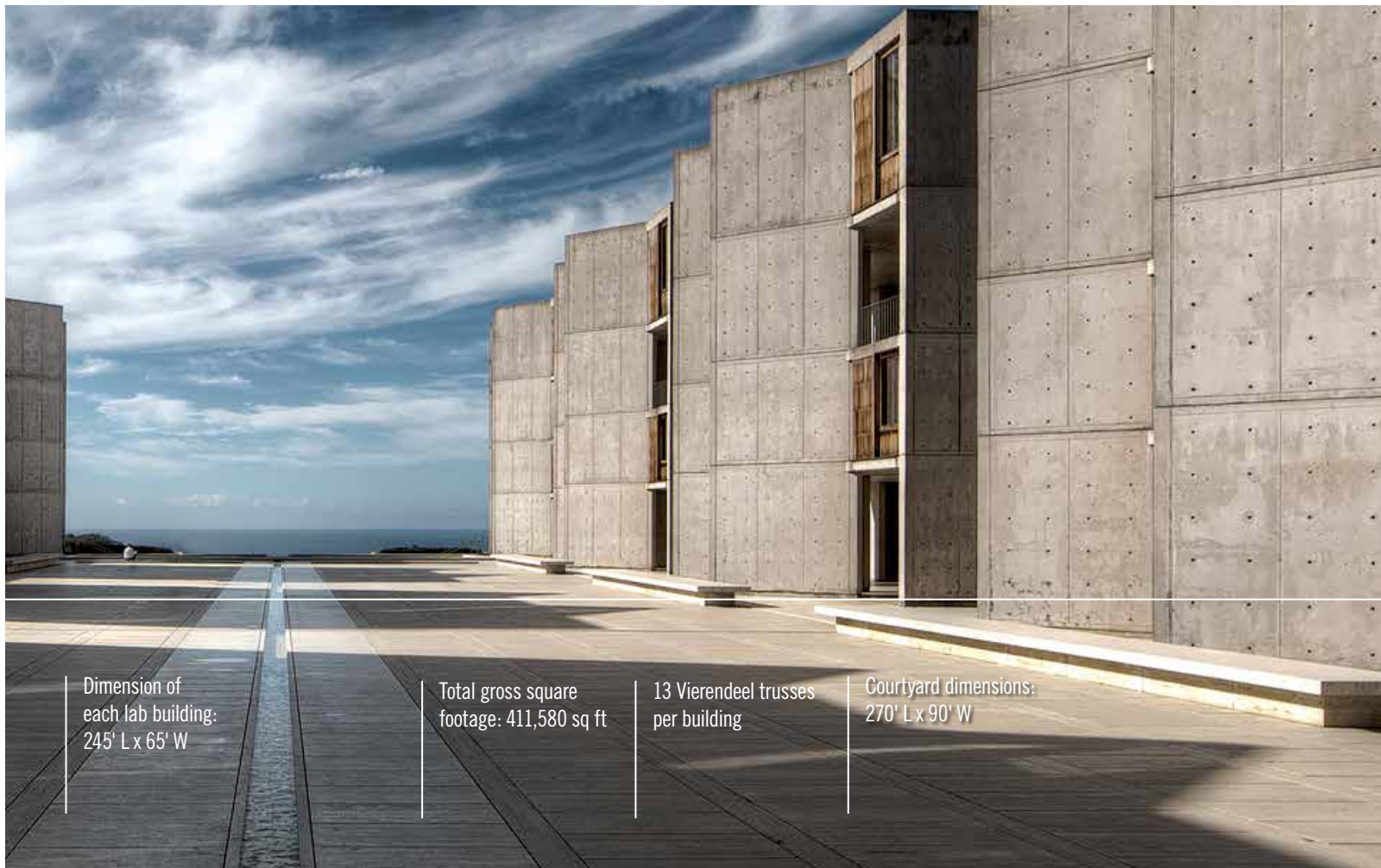
“As a teenager, I saw the building as stark and sterile, but as I grew to adulthood I came to see the spiritual quality of the building and realized what an architectural masterpiece this is,” says Jonathan Salk, youngest of Jonas Salk’s three sons. “My father loved this building. He had a way of walking along and absent-mindedly touching the surface of the concrete to connect with it as if it were a friend or family member.”

When visiting the Salk Institute for the first time, one may not notice the subtle selection of the concrete, like many other careful touches that help make the building the historical structure it is today. Visitors walk past the two east buildings (a later addendum to the design to support the Institute’s growing administrative and technology needs) beneath towering eucalyptus trees, up a few steps bordered by a modest orange grove to finally reach the travertine courtyard, where they pause at the grand view. Flanked on either side by identical buildings, the courtyard overlooks the

wild Southern California bluffs and directs the visitor’s gaze to the infinite expanse beyond the Pacific. A slender murmuring stream dubbed the “River of Life” cuts along the travertine to point to the sea, and lines up directly with the sunset during the spring and fall equinoxes.

“You walk up several steps and suddenly you’re in this courtyard, the sea is beyond, the continent behind you, the sun is shining, maybe a gull is circling. You somehow connect with what it is to be a human being and you feel your own potential,” says Nathaniel Kahn. “Art does that.”

The Institute is still considered one of Louis Kahn’s greatest masterpieces and has been described as a temple to nature and a monument to scientific thought. And, perhaps most astonishingly, the Institute has held up over the decades, its prescient design able to adapt to the rapidly changing technological demands of modern science, ensuring the Institute is a place where world-renowned discoveries continue to happen. Now, thanks to the recent completion of a Getty Institute-guided conservation management plan and teak restoration project, the Salk Institute will continue to enjoy many more years of housing breakthroughs in science.



Dimension of
each lab building:
245' L x 65' W

Total gross square
footage: 411,580 sq ft

13 Vierendeel trusses
per building

Courtyard dimensions:
270' L x 90' W

Built for tomorrow

The level of care and commitment that two of the time's most visionary artistic and scientific minds—Kahn and Salk—put into the building saved it from the obsolescence that many other great buildings suffer and created the sustainable, functional site that is still the Salk Institute today. Clever practical design features complement an ethos of simplicity and inspiration. As Salk famously said, the building “guesses tomorrow.”

“There is no other place like the Salk Institute,” says the Institute’s President, Elizabeth Blackburn. “Here, one has the mental and physical space to think deeply and collaborate to unravel the complexities of biology and achieve great work.”

One stroke of architectural genius that allows for the Institute’s remarkable flexibility was the physical design of the floors. Kahn separated floors that contained lab spaces and offices from ones that contained electricity, ventilation and other utilities. These interstitial spaces allow maintenance and other work to go on without interrupting science. On the alternating three floors that conduct science (lower, ground and upper), massive 245-foot-long

spaces supported by beams at the perimeters permit labs to be even more configurable. Removable walls and windows can be adjusted over time as new scientists and technologies come in.

This open floor plan, aside from being adaptable, also prompts a deliberately collaborative environment. No borders separate individual labs in order to encourage scientists to share equipment and bump into each other, perpetually cross-pollinating ideas from different fields of biological research and occasionally leading to collaborative, world-changing discoveries. Nowadays the concept of a collaborative workspace is all the rage, but in the '60s, not many buildings were designed with open, flowing spaces to prompt the open exchange of ideas. But the Institute has a balance: scientists can also retreat into office spaces or studies when they need solitude or time to reflect.

The single courtyard was also designed with collaboration and unity in mind, to prompt happenstance encounters. Initially, the central plaza—the most memorable feature of the Institute—was conceived as two, but the design didn’t sit well with Salk, who realized it might create a divide and result in two cultures at the Institute rather than one. In a famous moment in architecture,

Museum of Art debuts Kahn collection

Louis Kahn: The Power of Architecture, featured last winter at the San Diego Museum of Art, paid tribute to one of the most influential architects of the 20th century. The retrospective exhibition presented over 200 objects related to his selected buildings and projects in the form of architectural models, plans, original drawings, photographs, films and more.



Luis Barragán
Salk Institute Courtyard
(1965-1966)

Perspective sketch
Image courtesy of the Barragán
Foundation

he and Kahn told the team they had to start again, that it was worth it to get it right. They redesigned it with a single central space, which Kahn debated making into a monastic garden or covering with trees. But when Mexican modern architect Luis Barragán visited, he reportedly told Kahn that the space should be an open plaza, without vegetation so it could function as a civic space, resulting in the dramatic, single travertine plaza that mirrors the openness of the sky today.

Keeping to the sense of staying in touch with nature and science, placement of many of the Institute's studies, stairwells and rest-rooms was designed to require people to step outside, forcing a break from the inside and yielding a quiet moment to appreciate nature, fresh air, sunshine or a sea breeze. The thoughtfulness toward nature continues with sustainability crafted into the building's design. For one, Kahn added light wells—long open spaces—to let light pour into the floors below ground level to reduce the need for manmade illumination. For another, the "River of Life" and fountain at its end capture rain runoff in an underground cistern, which is used to replenish the water feature. Additionally, in the 1990s, an expanse of solar panels was added, generating a half megawatt of power that provides the air conditioning for the entire Institute.

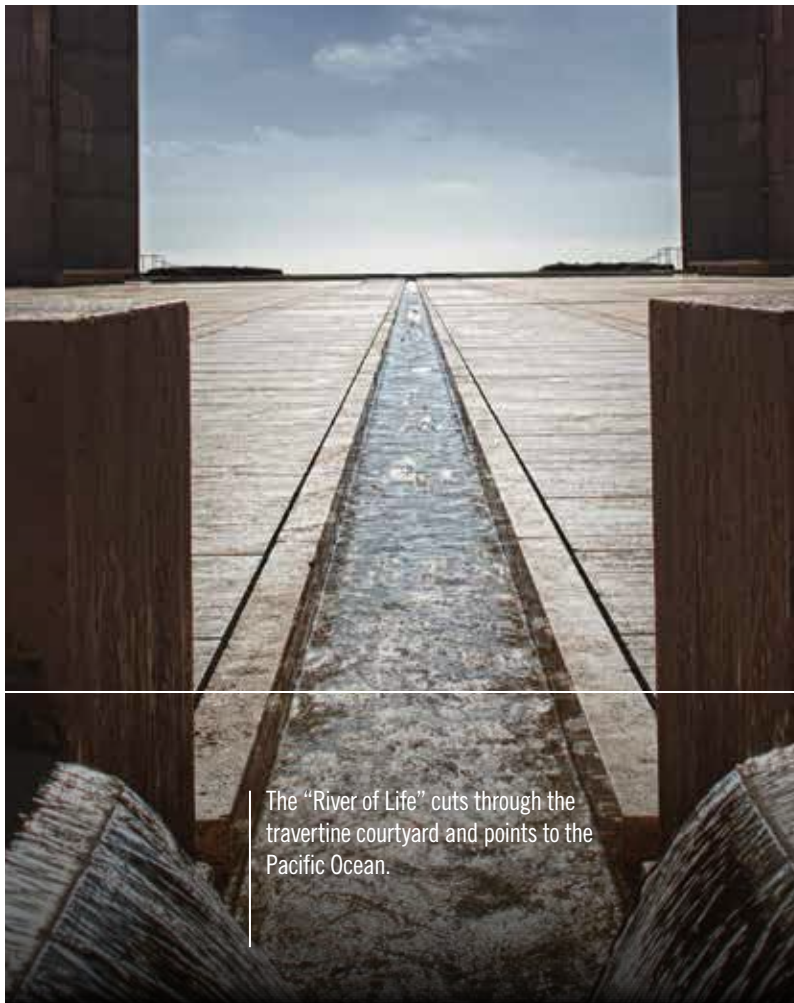
"It's amazing that this building, designed over 50 years ago, still functions as a cutting-edge research institute today," says Thomas Albright, a Salk neuroscientist and head of the Vision Laboratory who studies not only vision but also the connections between the brain and architecture. "Aside from being an inspiring structure, that continued functionality speaks to the design's original intent of paying homage to science and art."

Indeed, the building still provides inspiration today for many architects and artists, and was the subject of a Robert Redford documentary on the "souls" of buildings, called *Cathedrals of Culture*.

Conserving for the future

Even the most well designed buildings experience some wear and tear. The Salk's 50th anniversary in 2015 also marked the age when most Modernist buildings, bare of the facades and finishes that provide other structures some buffer against time, need restoration.

For Kahn's iconic structure, the teak wood covering the window systems and other exterior openings were the first call for



The "River of Life" cuts through the travertine courtyard and points to the Pacific Ocean.

The Getty Conservation Institute developed a preservation strategy to replace and restore damaged teak (background) in the window wall assemblies (restoration, insert).



A family visit

In November 2016, the families of Jonas Salk and Louis Kahn convened at the Salk Institute to take an in-depth architecture tour and learn about the restoration work. Attendees included, from left: Ellen Salk, Peter Salk, Nathaniel Kahn, Hugh Salk, Elizabeth Blackburn, Ben Salk, Sue Ann Kahn, Alex Tyng, Elizabeth Shepherd and Jonathan Salk.



preservation. The warm reddish wood panels mark a professor's study, and are meant to balance out the concrete with organic tones. Kahn had also chosen an unfinished look for the teak surrounding the study towers and west office windows, and he directed that no sealer or stain be applied to the wood. However, Kahn could not have predicted that the Institute's signature panels would weather from exposure to the marine environment as well as to a fungal infection from nearby eucalyptus trees that resulted in a black patina on the lighter wood.

To restore one of the Institute's key features—the teak window wall assemblies—the Salk Institute partnered with The Getty Conservation Institute (GCI) under its Conserving Modern Architecture Initiative to develop a preservation strategy. GCI conducted historical research, on-site condition surveys, physical and laboratory analysis of the teak, surface coatings and fungus, and a series of mock-ups trialing conservation solutions in order to develop a conservation program. A conservation management plan for the long-term care of the overall site was recently completed with support from the Getty Foundation as part of its Keeping It Modern Initiative.



LEARN MORE

www.salk.edu/architecture




According to Getty Conservation Institute project specialist Sara Lardinois, “The GCI sought to address issues on a long-term basis while preserving cultural significance and addressing the needs of those managing the site. Our aim was to help the Salk Institute incorporate a conservation approach into its overall site management at a critical point in the building’s history—the 50-year mark often coincides with the need for a first major repair in modern buildings.”

To be good environmental stewards, GCI and Salk took a scientific, almost surgical approach to the repair and conducted forensics on the wood, according to Tim Ball, Salk’s senior director of Facility Services. A feasibility study helped them understand how to preserve and repair what was already on the building in order to use as much existing wood as possible.

After three years of study and research, GCI provided a guide for restoration, which, under the execution of the architecture firm Wiss, Janney, Elstner Associates, Inc., and construction firm Rudolph and Sletten, began in 2016 and will end in the summer of 2017. Through this careful planning, the effort was

able to reuse over 70 percent of the original teak, a figure that Ball says is a remarkable success.

“We got at least a minimum of 50–70 years more on the old wood thanks to the conservation plan,” says Ball. The treatment included UV protection, resin and biocide on the teak to reject biospores and help the teak age uniformly. They also created a weather barrier system to prolong the life of the teak. The next steps are restoring some of the concrete as well as the travertine courtyard.

“When we talk about preserving a place, it’s not just the physical environment we’re preserving, we’re preserving the idea of a place and the possibilities that will come out of the place,” adds Nathaniel Kahn. “Through preservation efforts such as this, ideas that will transform our civilization and make it great can continue to come from places like the Salk Institute.” 

Read “Louis Kahn’s Salk Institute, the building that guesses tomorrow, is aging—very, very gracefully”

Los Angeles Times <http://lat.ms/2gbNptr>

When many of us look at a plant, we see a collection of stems and leaves. If it's flowering, we might notice the shape or the color of its blossoms. When **Liang Song** looks at plants, she sees millions of years of evolution. And she marvels at all the adaptations that particular plant has had to make through evolutionary history to be growing where she has found it, on a hike or while traveling in a foreign land.



Solidago canadensis

Song, who grew up in China, has always been fascinated by flora. As a young child one of her favorite games was collecting different flowers and presenting them on a plate, like a chef with a signature dish. Later, as an undergraduate, she studied ecology. While surveying the spread of *Solidago canadensis*, an invasive plant from North America, Song was introduced to some techniques from molecular biology. Always interested in learning novel approaches to address fundamental scientific questions in a new way, she decided to get her PhD in that field.

[A S O N G I N B L O O M]

NEXT GEN

Arabidopsis thaliana*Utah columbine (southwest UT)**Monkeypod-tree flower (Big Island, HI)**White clusters of green-onion flowers (San Diego, CA)**Pine cone (Mt. San Jacinto, CA)**Spring wildflowers (Antelope Valley, CA)**Flowering legumes (Mt. Laguna, CA)*

Above are photographs Song has taken on her travels. She says she tries to understand places through their plants and loves photographing them and learning about them from the locals.

Today, as a research associate in Joseph Ecker's lab, Song studies the crosstalk of plant hormones ("phytohormones") in the weed *Arabidopsis thaliana*. Specifically, she employs high-throughput sequencing to examine the myriad transcripts, or protein-making instructions, produced when the phytohormone abscisic acid (ABA) begins cascades of chemical chatter in response to an environmental stressor, such as drought.

In a recent study published in *Science*, Song tracked real-time changes in genetic activity in *Arabidopsis*' response to ABA, and found that, in the face of environmental hardship, plants employ a small group of proteins that act as conductors to manage their complex responses to stress. She discovered new stress-response genes via snapshots of key proteins binding to DNA throughout the genome. The results may help in developing new agricultural technologies to optimize water use in

plants so that they can better adapt to drought and other climate-related stressors.

Snapshots, as it happens, are another passion of Song's. In her spare time she is an avid photographer who particularly enjoys capturing images of flora she encounters when she travels. Every time she goes to a new place, she tries to understand the local plants through photography. One of the most memorable of late was a columbine (pictured above) she came across while hiking in Utah's Bryce Canyon. Amid a tumble of rocks in the arid landscape was a "cute little flower with tiny leaves."

While taking the shot, Song thought about how the smallness of the leaves helps the plant conserve water. She was impressed by the delicacy of the columbine's stem, which somehow managed to support a giant bloom, an act of defiance in the harsh terrain.

For Song, photography and plant biology, travel and science—all are ways to better understand the world—and her place in it. **S**

SPOTLIGHT



PIONEER AWARD

Salk Professor Juan Carlos Izpisua Belmonte has received the coveted National Institutes of Health (NIH) grant of at least \$2.5 million over 5 years to fund his innovations in generating functional primate organs and tissues in a large-animal host using novel stem cell technologies.

NIH DIRECTOR'S EARLY INDEPENDENCE AWARD

Helmsley-Salk Fellow Jesse Dixon is among 16 scientists nationwide to receive the prestigious young career award of \$1.25 million over 5 years from the NIH to explore how the genome folds into 3D configurations and the implications for human disease and health.



BRAIN INITIATIVE AWARD

Salk Associate Professor Sreekanth Chalasani will receive over \$1 million for the first year of NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative award to expand his technology to selectively activate brain, heart, muscle and other cells using ultrasonic waves, which has the potential for applications in neuroscience research and medicine.



V FOUNDATION FOR CANCER RESEARCH

Assistant Professor Diana Hargreaves has received a V Scholar Grant from the V Foundation for Cancer Research, which will provide \$100,000 per year for two years to support her investigation of gene mutations in ovarian cancer with the ultimate goal of finding new strategies to combat the disease.

NATIONAL ACADEMY OF INVENTORS FELLOW

Ronald Evans, Salk professor and director of the Gene Expression Laboratory, is one of 175 leaders in academic invention to become inducted into the National Academy of Inventors (NAI) in 2016 for having demonstrated a "prolific spirit of innovation in creating or facilitating outstanding inventions that have made a tangible impact on quality of life, economic development, and welfare of society."



INAUGURAL MELVIN COHN AWARD

The first Melvin Cohn Award for Best PhD/Postdoc Study was awarded last fall to Hiutung Chu, a postdoctoral researcher from the California Institute of Technology. Named for Cohn, a founding fellow of the Salk Institute and professor emeritus who conducted pioneering studies on the immune system, the award was established to recognize scientific innovation and impact of early career scientists, specifically graduate students and postdoctoral researchers.

Tony Hunter awarded inaugural Sjöberg Prize for cancer breakthrough

Salk Professor Tony Hunter, who holds an American Cancer Society Professorship, has been awarded \$500,000 as part of the \$1 million Royal Swedish Academy of Sciences' inaugural Sjöberg Prize for Cancer Research for "groundbreaking studies of cellular processes that have led to the development of new and effective cancer drugs."

The prize ceremony, which is modeled after the Nobel Prize ceremony, was held in Stockholm during the Academy's annual meeting on March 31, 2017, in the presence of His Majesty the King and Her Majesty the Queen of Sweden.

Hunter studied how normal cells become tumor cells, demonstrating that a special process was necessary: tyrosine phosphorylation of proteins. His discovery led to the development of a new type of cancer pharmaceutical, tyrosine kinase inhibitors. These have revolutionized the treatment of chronic myeloid leukemia and also are of great benefit in several other forms of cancer. Hunter's work has led to a complete catalogue of the 90 human genes that encode tyrosine kinases, over half of which have become targets for the development of drugs to treat cancer and other human diseases. Currently, 26 tyrosine kinase inhibitors are FDA approved for human therapy, with many more in clinical trials.

The annual prize, which includes \$100,000 as a personal award and \$900,000 designated as a grant for future research, is shared equally by the awardees. Hunter shares the honor with immunologist James P. Allison of the University of Texas MD Anderson Cancer Center.



Award-winning faculty join Salk to advance RNA, plant, cancer research



GERALD JOYCE

Gerald Joyce, recognized as a pioneer in the field of in vitro evolution, has joined the Salk Institute as a professor in the Jack H. Skirball Center for Chemical Biology and Proteomics. Joyce uses biochemical techniques to explore the potential of RNA to serve as a catalyst in critical reactions and has devised molecules whose function is to disrupt disease-related pathways. Joyce designed the first and several subsequent examples of DNA enzymes, some of which are now in human clinical trials for the treatment of cancer, asthma and skin diseases.

Previously, Joyce worked at The Scripps Research Institute. He serves as director of the Genomics Institute of the Novartis Research Foundation and is the recipient of numerous scientific awards. Joyce received his bachelor's degree from the University of Chicago, and his MD and PhD in neurosciences from the University of California, San Diego.



WOLFGANG BUSCH

Wolfgang Busch joined the Institute as an associate professor in the Plant Molecular and Cellular Biology Laboratory. Busch uses a systems genetics approach—which combines techniques from genetics, genomics and other science fields—to understand how root growth in given environments is determined by a plant's genes. Discoveries in this area could reveal critical insight into growing plants (and food) that can thrive in more extreme environments prompted by climate change, such as drought.

Busch comes to Salk from the Gregor Mendel Institute of Molecular Plant Biology, and is a recipient of the Society for Experimental Biology President's Medal. He earned his degrees in biology from the University of Tübingen, in Germany.

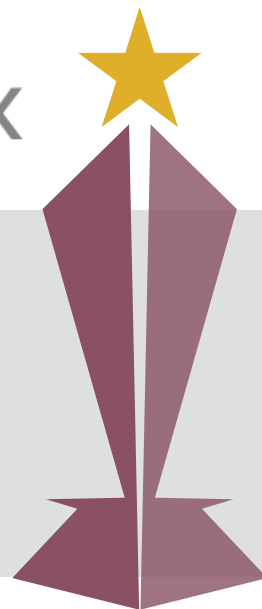


EDWARD STITES

Edward Stites, a physician-scientist who studies key cellular proteins that usher signals into the cell nucleus from outside the cell, joins the Salk Institute as an assistant professor in the Integrative Biology Laboratory. By using both traditional experimental and computational techniques, Stites aims to develop a new generation of precision therapies that can better target cancers.

Prior to joining Salk, Stites was a clinical pathology resident in the Physician Scientist Training Program at Washington University in St. Louis, Missouri. He received both his MD and PhD degrees from the University of Virginia in Charlottesville, obtaining his doctorate in biophysics as part of the Medical Scientist Training Program. His research was recognized with the University of Virginia's Michael J. Peach award.

nature INDEX



*According to a new report by Nature Research, the Salk Institute **ranks second in the world** for high-quality, high-impact scientific collaborations in the life sciences.*

The data, published November 16, 2016, as a supplement to *Nature* in a report called Nature Index 2016 Collaborations, use a series of metrics related to papers published between January 1, 2012, and December 31, 2015, to evaluate over 8,500 scientific institutions across the globe. Salk was ranked second worldwide, behind only Harvard, in a list of the top 50 overall collaborators to the life sciences based on a ratio of collaborations to institution size.

HELMSLEY CHARITABLE TRUST AWARDS \$25 MILLION GRANT


The Salk Institute has received a \$25 million grant—a renewal of the largest research gift in the Institute’s 56-year history—to expand its effort to decipher the role chronic inflammation plays in driving human disease.

Announced in November, the grant from The Leona M. and Harry B. Helmsley Charitable Trust extends the historic \$42 million Helmsley gift made to Salk in 2013. That gift established the Helmsley Center for Genomic Medicine, which enables Salk’s leading scientists to delve into the genetic underpinnings of some of humankind’s most devastating afflictions, and paves the way to new therapies for chronic illnesses, including cancer, diabetes, inflammatory bowel disease and Alzheimer’s disease.

The new grant began January 1, 2017, and underwrites three years of research for Salk scientists from more than a half-dozen disciplines, including cancer, stem cells and metabolism. Led by senior investigators Inder Verma, Ronald Evans and Rusty Gage, scientists who will continue to be funded by Helmsley include Reuben Shaw, Juan Carlos Izpisua Belmonte, Marc Montminy, Clodagh O’Shea, Alan Saghatelian, Tony Hunter, Greg Lemke, Paul Sawchenko, Satchidananda Panda and Geoffrey Wahl. Additional support will also be provided to Jan Karlseder, Martin Hetzer, Ye Zheng, Diana Hargreaves, Janelle Ayres, Dmitry Lyumkis, Patrick Hsu and Jesse Dixon. Grant funding will continue as well to support many core facilities at Salk.

A central theme of this program is that chronic inflammation lies at the root of most of the health problems in the world today. The Helmsley grant is designed to promote collaborative interdisciplinary research that will yield new diagnostic tools, therapeutics and preventive measures for a broad range of disorders. Amazing discoveries in diabetes, neuroscience and cancer have already been made since the original grant three years ago, resulting in two clinical trials.

With support from the historic Helmsley grant, the Salk Institute launched its successful Salk Fellows program in 2014. To date, the program has brought three scientists from broad disciplines to the Institute to trigger innovation and collaboration in single-particle cryo-electron microscopy, three-dimensional genomic organization and the gene editing technology known as CRISPR. The Helmsley-Salk Fellows have each garnered a prestigious Director’s Early Independence Award from the National Institutes of Health.

In 2009, the Helmsley Trust awarded its first grant to Salk, \$5.5 million to establish the Salk Center for Nutritional Genomics to study nutrition at the molecular level and its impact on the role of metabolism in diabetes, obesity, cancer, exercise physiology and lifespan. Helmsley gave additional support with a \$15 million grant in 2010 to create a collaborative stem cell project involving Salk and Columbia University. The success of the first two grants led to the establishment of the Center for Genomic Medicine. 

SPOTLIGHT

EYEWITNESSES AND MICROBIOMES: SALK FACULTY INSPIRE AT TEDXSANDIEGO

Salk faculty Janelle Ayres and Thomas Albright spoke about their research at the seventh annual TEDxSanDiego in October at Copley Symphony Hall. Albright discussed how eyewitness testimony is undermined by uncertainty, bias and overconfidence and Ayres shared her research on the microbiome, the trillions of good bacteria living in our bodies, and how this community of bacteria could help tackle infectious diseases and antibiotic resistance.



WATCH

<http://www.salk.edu/insidesalk/0417/tedx-video>



Tom Albright

SALK PRESIDENT COAUTHORS *NEW YORK TIMES* BESTSELLER ON SLOWING HUMAN AGING



From left: Elissa Epel and Elizabeth Blackburn
Credit: Digital Natives

In their new book for greater health throughout our lives, Salk President and Nobel Laureate Elizabeth Blackburn and health psychologist Elissa Epel explain an important aspect of the aging process in humans at a fundamental level. Based on this science, they share the changes people can make to their daily habits that will keep them vital and disease-free.

Released in early January, *The Telomere Effect: A Revolutionary Approach to Living Younger, Healthier, Longer* made *The New York Times* Best Sellers list three weeks later. Their road map explaining the science of aging and habits to live well ranked #15 in the nonfiction hardcover category and #13 for e-Books nonfiction.

The book outlines how the length and maintenance of one's telomeres provide a biological basis for bettering health, and includes information on how sleep, exercise, diet and even social connections profoundly affect telomeres and how chronic stress can eat away at them. Included are lists of which foods are healthy for telomeres; how aging begins in utero; information about protecting sleep and tips for exercising; and the impact of stress and ways to manage it.

Order the book on [Amazon.com](https://www.amazon.com).

YESTERDAY'S SCHOLARS, TODAY'S SCIENCE SUPERSTARS

A decade ago, Doug Jacobs was much like any other junior at La Costa Canyon High School—thinking about which colleges to apply to and what he wanted to study. Today, the internal medicine resident physician and health policy researcher at Brigham and Women's Hospital in Boston credits his career in part to the Salk Institute's High School Scholars program.

"In many ways, the program jumpstarted my interest in science and medicine," says Jacobs, who landed a spot in Ronald Evans' lab over the summer of 2006 to research proteins related to HDL cholesterol. "I hadn't gotten my hands dirty in the science world yet. It's one of the few programs that gets students into the lab doing work."

For more than 40 years, the intensive eight-week High School Scholars program has given students that rare hands-on bench research experience in a Salk lab under the tutelage of a faculty member. The scholars maintain laboratory notebooks, formulate and test hypotheses and prepare experiments, concluding their summer with a presentation of their findings before mentors, lab colleagues and families.

Sakina Palida, a postdoctoral researcher who currently studies molecular mechanisms of neurodegeneration at Cedars-Sinai Medical Center in Los Angeles, first became interested in scientific research as a career as a 16-year-old High School Scholar in Joanne Chory's lab.

"I not only saw how scientists approach biological questions in the lab, but I actually got to participate in the research and acquire technical and analytical skills that helped me in both my undergraduate studies at UC Berkeley and graduate research in Roger Tsien's lab at UCSD," says Palida. "My experiences through the summer program and the people I interacted with, including Dr. Chory and my postdoc mentors Greg Vert and Jesse Woodson, were altogether invaluable to my development as a scientist."

In 2014, the program was renamed the Heithoff-Brody Scholars Program for Salk supporter Ken Heithoff and former Institute president William Brody. Heithoff was inspired to make a generous




Participants in the 2016 Heithoff-Brody Scholars Program

gift to Salk's Education Outreach program after seeing the mentorship his grandson Cameron received as a scholar for two consecutive summers in the labs of Jan Karlseder and Samuel Pfaff.

"I can't tell you how important mentors were in my own background," says Heithoff, a physician. "In the Salk Institute, I see an opportunity for really strong, scientifically-minded kids to become the next generation of Nobel laureates. Those are the people who change history and that's why I want to give that experience to more kids."

Mentorship is one of the best memories Stephanie See has of her 2006 High School Scholars summer. Now a third year graduate student in the Chemistry and Chemical Biology PhD program at UC San Francisco, See focuses on the molecular mechanisms that control the spread of aggregating proteins in models of neurodegeneration.

"My interest in neuroscience began in Rusty Gage's lab," says See. "I was mentored by postdoctoral fellows who taught me the foundations of the scientific method and instilled the technical rigor and mental perseverance that would become valuable at every step of my scientific journey. I'm so grateful to these mentors and the High School Scholars Program for helping me explore interests that have since grown into a job and career I love." 

EVENTS

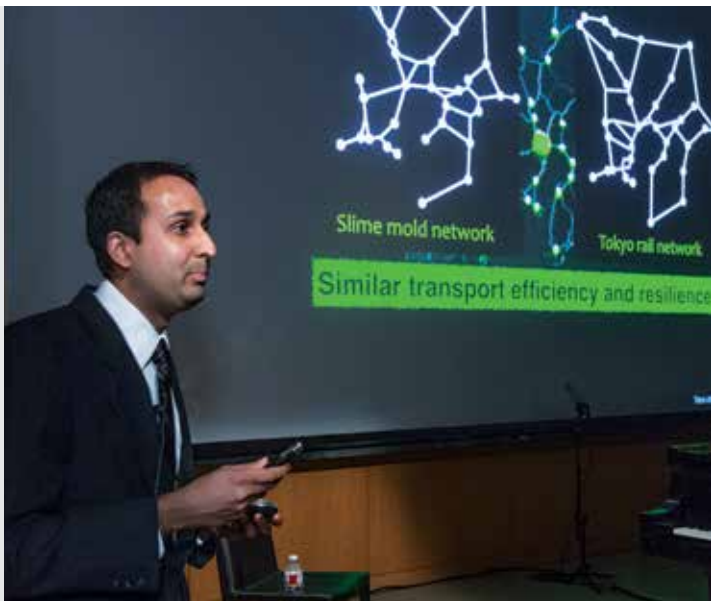


HEADLINING AT THE INSTITUTE

From Brahms to integrative biology, the Salk Science & Music Series has presented classical performances paired with science talks in recent months to enthusiastic audiences. The six-concert fourth season concludes April 30, 2017, with the jazz group the Helen Sung Quartet.

Tickets: <http://www.salk.edu/music> or call (858) 587-0657.

From left: Assistant Professor Saket Navlakha and pianists Sean Chen and Karen Joy Davis



IT PAYS TO PEDAL

The Salk Institute received \$300,000 for cancer research for participating in the Padres Pedal the Cause cycling fundraiser. More than 20 cyclists on Team Salk Cancer Center rode November 12–13 to help raise \$2 million, which was shared with three other local research centers.



Professor Inder Verma dresses up as Elvis Presley to introduce the Rockstar Fund; attendees celebrated Irwin Jacobs' service to the Institute; From left: Irwin Jacobs and Ted Waitt.



SALK'S "ROCKSTAR"

Outgoing Salk Board Chair Irwin Jacobs was feted like rock royalty at the Trustees' dinner in November at the La Jolla home of Michele and Ted Waitt, Salk's new Board chair. In recognition of Jacobs' decade of service and support of Salk science, the creation of a three-year, \$50 million Rockstar Fund for faculty recruitment was announced. Jacobs remains on the Salk Board as chairman emeritus.



SYMPOSIUM NAMED FOR ELLEN POTTER

Nearly 100 science teachers attended the inaugural "Ellen Potter Research Connections for Teachers Symposium" at the Institute this fall in honor of Salk's retiring Education Outreach director. The meeting for middle and high school teachers featured Salk scientists describing the latest trends in biological research on topics including cancer, diabetes and epigenetics. Potter retired in December after 38 years at the Institute, beginning as a research assistant in the Regulatory Biology Lab.

EVENTS



Back to Basics

→ BACK TO BASICS ON GLIA

Salk supporters filled the Conrad Prebys Auditorium for a Back to Basics lecture on November 9 featuring Nicola Allen, assistant professor in the Molecular Neurobiology Laboratory. Allen spoke about her lab's research on glia, a cell proving essential for the brain to work properly. The Back to Basics program offers lay science lectures to the public twice a year.

salk | EXCELLERATORS

→ KEEPING PACE WITH SALKEXCELLERATORS

Michelle Booden, Salk's senior director of licensing and intellectual property, addressed Salkexcellerators' fall forum in November with stories of how commercialized Salk technologies impacted diseases that affect human health. Salkexcellerators are the next generation of community members committed to supporting scientific discovery at the Institute. The 10-year-old program provides social and educational events throughout the year and supports a fellowship fund for the Institute's postdoctoral researchers.

President's Club

→ BLACKBURN ADDRESSES PRESIDENT'S CLUB

President Elizabeth Blackburn spoke about her vision for the future of Salk and its scientific objectives at the annual President's Club luncheon on November 30 at the Institute. Contributions at the President's Club level are allocated to the areas of greatest need and make it possible to recruit and retain top-tier scientists, acquire the latest technology and fuel innovative research initiatives.



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Salk giving programs offer a range of ways to get involved.
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GIVING PROGRAMS

EDUCATION OUTREACH



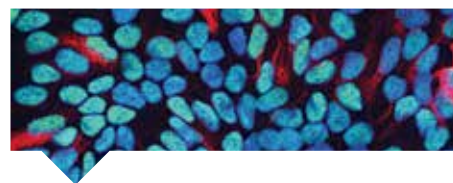
Offering nearly half a century of programs to inspire—and launch—the next generation of scientists, Salk's Education Outreach includes a Mobile Science Lab, High School Scholars curriculum and SciChats@Salk.

SALK WOMEN & SCIENCE



Showcasing the achievements of Salk's women of science, this program welcomes community and business leaders interested in inspiring others to embrace scientific research personally and philanthropically.

SALKEXCELLERATORS



Designed for young business professionals and community members committed to supporting Salk scientific discovery, Salkexcellerators offers a unique opportunity to support cutting-edge research while connecting with like-minded people.

PARTNERS IN RESEARCH



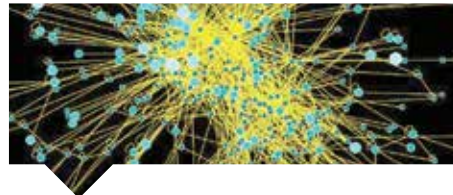
Invest in the future of cancer, aging, Alzheimer's disease and diabetes research by incorporating philanthropic support for Salk into your estate plans.

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Dr. Elizabeth Blackburn Precision interception

PERSPECTIVE

For centuries medical professionals have been trained to react to disease with punishing force. When a bacterium or parasite or cancer manages to invade a patient's body and inflict damage, these professionals wage an all-out war, often prescribing strong doses of broad-spectrum antibiotics or massive amounts of toxic chemicals to banish the invader. There is no doubt that these medical approaches transformed our world into one of longer life and less fear of disease. Their attendant negative side effects, however, can take such a toll on the patient that critics tend to mutter, "The treatment is worse than the disease."

Now, scientific advances—a majority of them arising from foundational biological research—are offering us new perspectives and new strategies for dealing with diseases. Opposite from an all-out bombardment, these strategies employ targeted, customized and very effective treatments. Yet an even more dramatic difference is emerging from the older world of medicine, which was largely to react to a specific disease once it is clinically apparent: to attack the very roots of the disease. I call it "precision interception" and it's opening an entirely new view on human healthcare. It is now possible to contemplate this as a reality, because the processes giving rise to serious and prolonged diseases such as cancers, diabetes and even neurological diseases are becoming better understood. We are now able to see how we can target a specific mechanism of a disease even before it takes hold, thus derailing its potency. Further aided by incredible genetic technologies and access to big data, we can tailor therapies to interface with a patient's unique genetic makeup. We are even beginning to predict what the disease will do next. Truly, we are entering an astounding era for human health and longevity.

Salk science helped lay the groundwork for this new perspective years ago. In 1979, Tony Hunter began studying the Rous sarcoma virus, the first virus known to cause cancers. A surprising result from one experiment in his lab led to a seminal discovery: adding or subtracting phosphate molecules to the proteins, on an amino acid called tyrosine, could regulate cell activity. Controlling this process, Hunter realized, could prevent the sort of unregulated cell growth that often drives cancers. Fast forward a few decades to a remarkable outcome: the development of Gleevec, a groundbreaking drug that has turned chronic myelogenous leukemia from a fatal disease into a chronic, manageable disease. Gleevec led the way for a whole class of such targeted anticancer therapies. Tony's discovery, just one in an illustrious career that has expanded our biological knowledge, has earned him worldwide

recognition. And this past February, the Royal Swedish Academy of Sciences selected him to receive the prestigious Sjöberg Prize for Cancer Research.

By understanding the specific biology of a disease, we can point the way toward targeted—and thus more effective—treatments. Each human is unique, however. And unique genetic profiles comprised of elaborate molecular pathways and idiosyncratic mutations add layer upon layer of complexity to designing successful therapies. That means that a drug that works for one person doesn't necessarily work for another. So scientists are turning to big data to fine-tune their insights.

Here at Salk, Ed Stites studies the complex behaviors of the molecular pathways and signaling networks implicated in cancers through the dual lenses of mathematical and computational models. The big data he produces not only reveals new understanding of how these networks promote cancer but also predicts how the specific cancers will respond to treatment. With this information in hand, doctors can more knowledgeably prescribe the most appropriate drugs for their patients. They can also better identify patients at high risk for certain cancers and suggest early intervention, while continuing to monitor those at a lower risk. Heading off diseases before they become intractable is a hallmark of precision interception.

In yet another twist on how to manage disease, Janelle Ayres is proposing that we shift from our combative strategy of trying to kill all harmful bacteria toward focusing on mitigating the damage they do to our bodies. In other words: learn to tolerate the enemy. Many invading harmful bacteria instruct our bodies to unwittingly unleash collateral damage, ranging from muscle wasting to multiple organ failure. But in precise studies with mice infected with harmful bacteria, Janelle discovered that helpful microbes leave their home in the gut and instruct the animals' muscles to prevent wasting, thus mitigating damage. Her lab is now exploring ways to harness these beneficial microbes, trillions of which live inside our own bodies.

Having also discovered the exact cellular molecules of our bodies that the helpful bacteria instruct, Janelle is paving the way to inventing drugs that act on our own cells. Her investigations suggest that we may soon be able to boost the health-conferring abilities of beneficial microbes or possibly administer them as a "drug."

At Salk, we continue apace to invest in basic, foundational science combined with state-of-the-art technology and big data analysis. I am convinced that this is the path to invaluable impacts on people's lives. I foresee that the next decade or so will bring significant changes in the way we treat diseases, with added emphasis on intercepting and even preventing them. It's a new perspective yet still perfectly aligned with Salk's mission: Where cures begin.

Elizabeth Blackburn | *President, Salk Institute*

Stem cells are unique in their ability to keep dividing to produce new daughter cells that can turn into any cell type in the body—a quality called pluripotency. Stem cells renew our skin as well as the lining of our gut. In order to manage this constant renewal, stem cells must be able to maintain their telomeres, the protective caps on the ends of chromosomes that determine how many times a cell can divide. To better understand telomere maintenance, Jan Karlseder's lab reverted skin cells into stem cells and looked at what length of telomeres was ideal for pluripotency by staining for proteins called TRA-1-60 and Nanog, which are expressed in all embryonic stem cells and their derivative cells (like stem cells induced from skin) but not in non-pluripotent cells.



Image credit: Teresa Rivera Garcia

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