

InsideSalk

Where cures begin.
Salk Institute 04 | 14

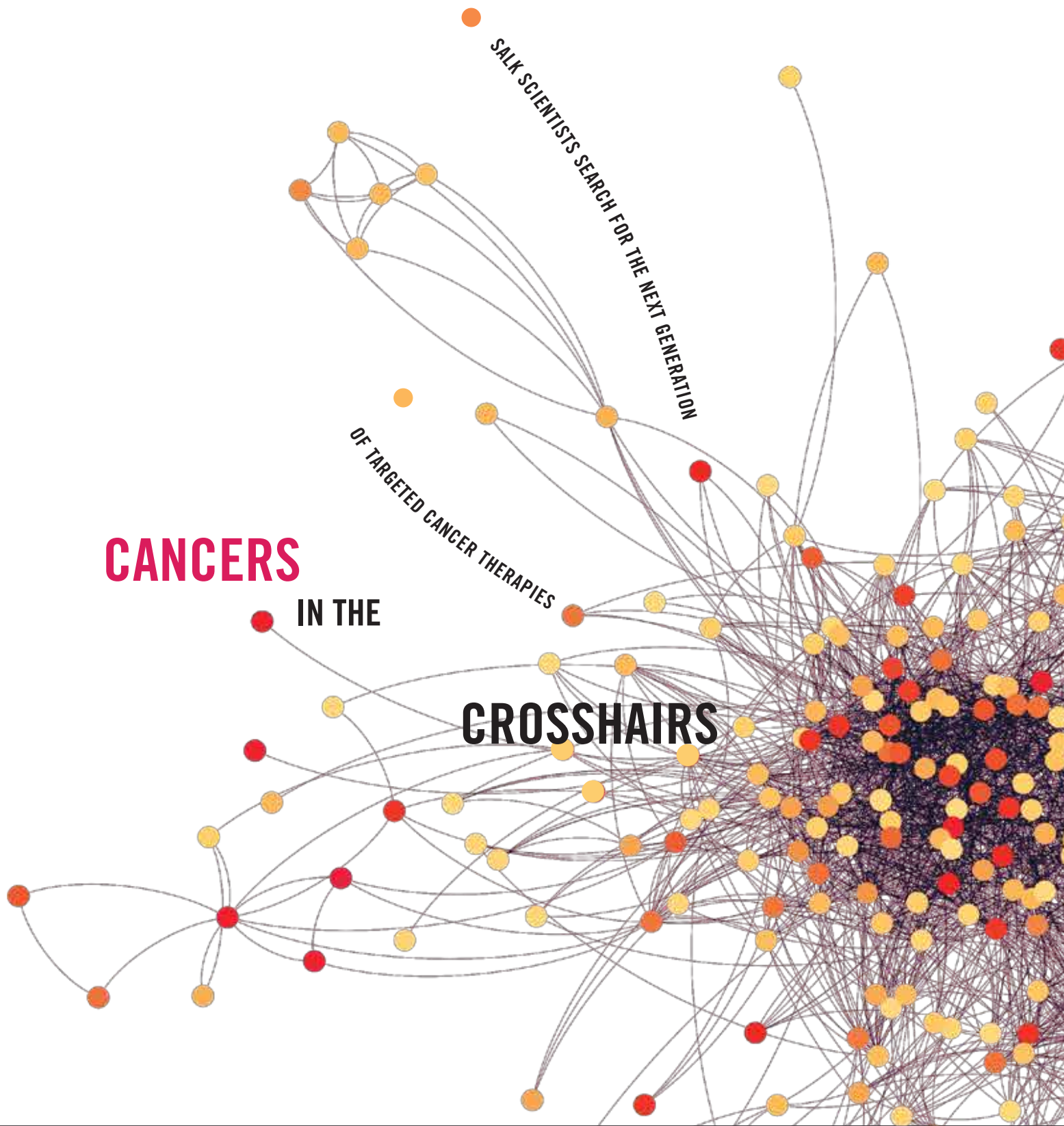
SALK SCIENTISTS SEARCH FOR THE NEXT GENERATION

OF TARGETED CANCER THERAPIES

CANCERS

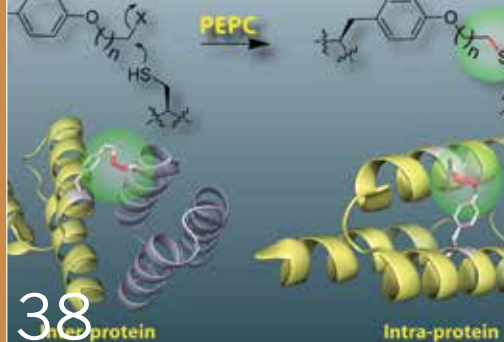
IN THE

CROSSHAIRS



April 2014

Inside Salk



Engineering super-powered proteins for disease therapy



Next generation: Ignacio Sancho-Martinez



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

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

Rebecca Newman
Vice President,
External Relations

Anna-Marie Rooney
Chief Communications Officer

Christopher Emery
Director of Scientific Communications
and Media Relations

Kristina Grifantini
Science Writer

Sarah Lifton
Staff Writer

Liz Hincks
Web Editor

John McDonagh
Web Designer

Joe Belcovson
Photographer

Jon Labes
Video Manager

Melanie Norton
Media Relations Manager

Máximo Escobedo
Senior Designer

Melissa Figueroa
Graphic Designer

Visit the Salk Institute at www.salk.edu

3 EXECUTIVE MESSAGE

LEAD STORY

4 Cancers in the Crosshairs

INSTITUTE NEWS

12 One on one with...Geoff Wahl

16 The Howard Hughes impact

22 The Art and Science of Cuisine: Inaugural wellness event serves up fine food and research

24 90 years of creativity: Salk fetes Roger Guillemin

26 President's Club continues a holiday tradition

Small molecules, big opportunities

27 Science and Music Series hits the right notes

28 Teachers seize rare opportunity to tour Salk labs

Save the date for Symphony at Salk 2014!

29 Talk, tour and lunch mark annual Partners in Research event

A fond farewell to a master interpreter of Salk's architecture

AWARDS-ACCOLADES

30 Salk Scientist Fred Gage named to National Academy of Inventors

31 Salk Institute and Stanford University to lead new \$40 million stem cell genomics center

32 Three Salk discoveries land on 2013 "best of the year" lists

DISCOVERY ROUNDUP

33 Induced pluripotent stem cells reveal differences between humans and great apes

34 Salk scientists identify factors that trigger ALT-ernative cancer cell growth

35 Missing molecule in chemical production line discovered

36 Connecting the dots between genes and human behavior

37 Generating "mini-kidney" structures from human stem cells may lead to much-needed therapies for kidney disease

38 Engineering super-powered proteins for disease therapy

NEXT GENERATION

40 Sound instincts: Ignacio Sancho-Martinez specializes in crossing boundaries

PHILANTHROPY NEWS

44 Foundation Visits

45 Defeating cancer, one gift at a time

46 Salk science leads to discoveries

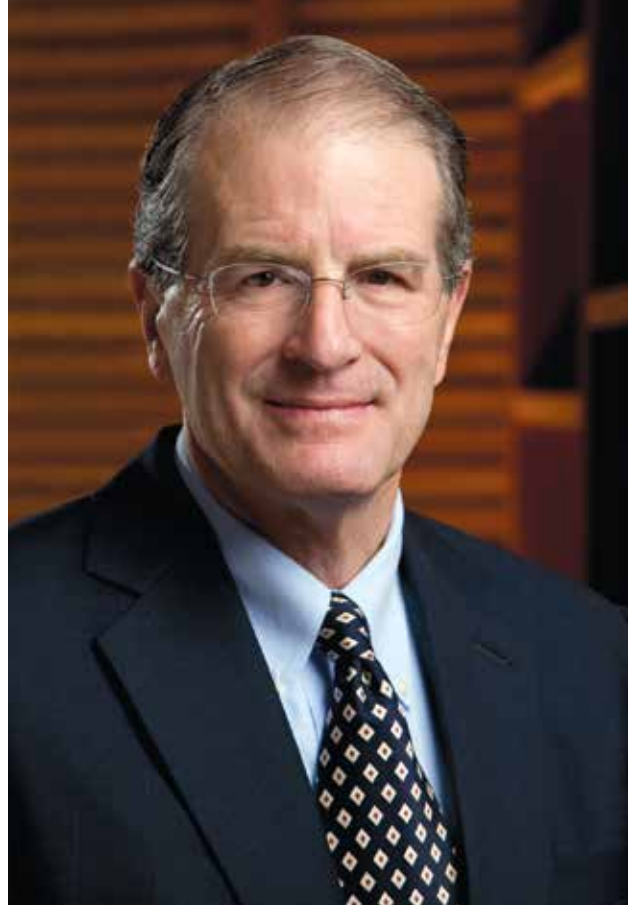
47 Insider's View

CALENDAR

Back Cover

InsideSalk is printed on recycled paper.

InsideSalk is published by the Salk Institute for Biological Studies. We welcome your input. Please send comments to communications@salk.edu or contact the communications department at 858.453.4100 x1226.



William R. Brody


Dear Friends,

AS MEDICAL AND SCIENTIFIC CHALLENGES GO, THERE CAN BE little question that cancer remains among the most enigmatic, confounding and vexing. But every day at the Salk Institute, investigators are learning more and more about the mechanisms behind the 100+ diseases called cancer, offering hope that someday incremental advances from their labs will coalesce into significant discoveries that lead to new, more effective treatments. From where I stand, that's a tremendously exciting prospect.

This issue of *Inside Salk* celebrates the important discoveries that our scientists have made (and will continue to make) in the quest for new understanding of cancer and new therapeutic alternatives. Our cover story introduces the diverse, yet complementary, work of some of our leading cancer researchers, while our One on One feature reveals a different side of **Geoff Wahl**, a professor in the Gene Expression Laboratory, who has devoted his life to studying the disease, with a special focus on breast cancer. Our Next Generation article shines a spotlight on postdoc **Ignacio Sancho-Martinez**, whose wide-ranging interests freely cross boundaries, including possible connections between the way the body regenerates damaged organs and ways to approach cancer cells using reprogramming techniques.

These advances reflect the Institute's extraordinary strength in cancer research, and it's one of the reasons why cancer is a key scientific initiative of the Campaign for Salk. Few institutions are as well equipped to tackle the riddles of the condition, and by generating the resources to bolster support for cancer studies at the Institute, the initiative promises to accelerate the pace of discovery and bring us closer to the day when cancer is outwitted by the therapies employed against it.

Complementing the stories on cancer research is a feature on the Howard Hughes Medical Institute and how its support of Salk scientists has transformed their work and an article on **Lei Wang's** fascinating breakthroughs with artificial amino acids.

I hope you'll enjoy reading about the latest science and related goings-on here at Salk. I firmly believe that our successes are your successes because nothing we do would be possible without the support of friends like you. All of us at the Institute are most grateful for your friendship. 

William R. Brody

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



ON THE COVER

Network representation of genes directly and indirectly involved in lymphoma. Each circle is a specific gene and the connections indicate various kinds of biological interactions. Darker colors indicate a stronger association with disease.



SALK RESEARCHERS USE POWERFUL NEW TECHNOLOGIES

CANCERS

IN THE

TO TARGET SOME OF THE

CROSSHAIRS

Nothing stopped Dan Lewis—until that day in 2006.

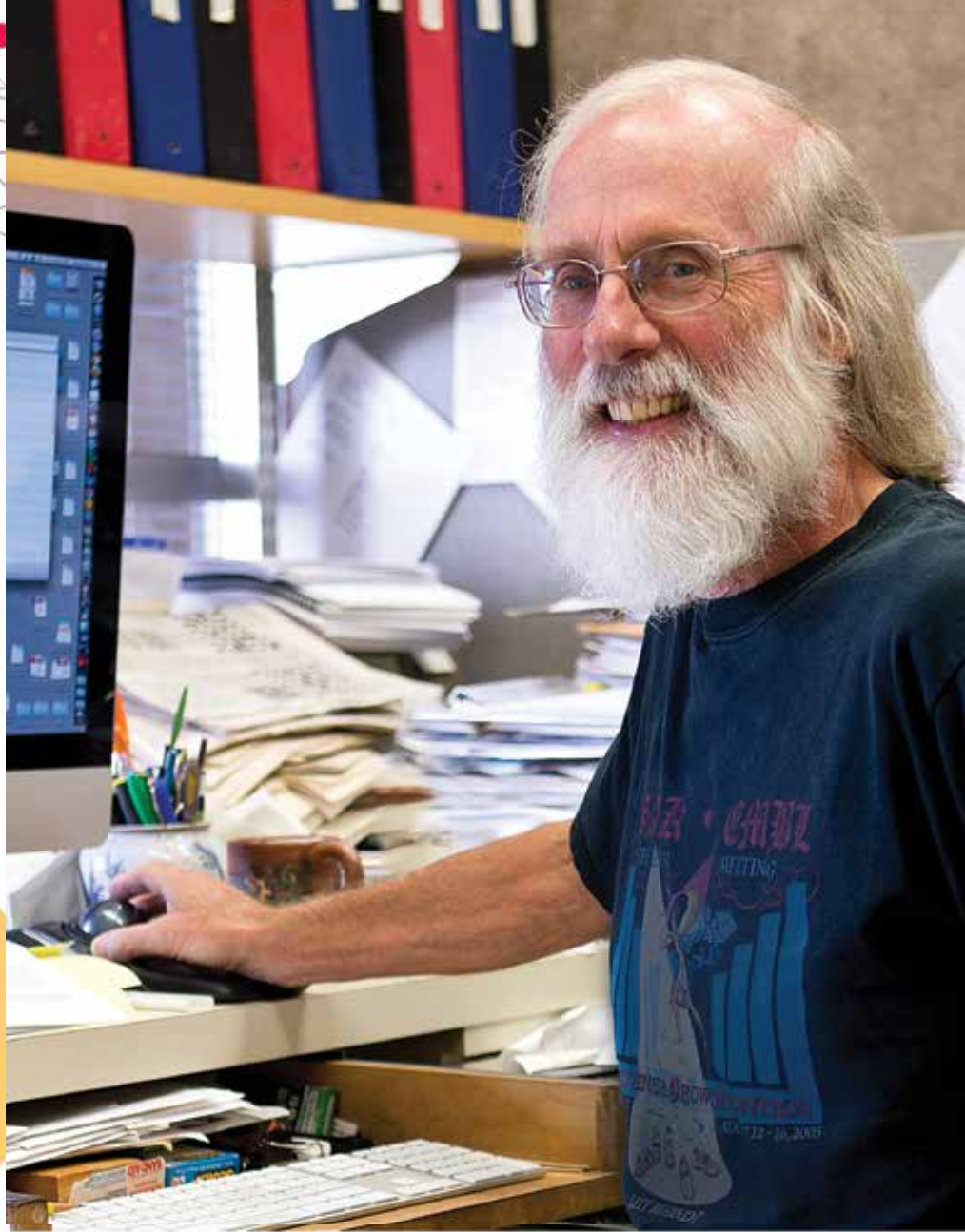
The hardworking president of a global management and strategy consulting firm, as well as a commercial aviation industry consultant, Lewis was always on the go. But that day, in a New York doctor's office after a busy weekend in Chicago, he was brought up short.

"I'll bet you think you're going somewhere tomorrow on business," the doctor told him. "But you're not going anywhere. Not until I tell you to."

As president of Booz Allen Hamilton Global Management Consulting, Lewis was required to get frequent checkups, which included blood tests. A test he'd taken before his Chicago trip had sounded an alarm. The doctor explained that Lewis had chronic myelogenous leukemia, or CML, a cancer of the white blood cells that starts in the bone marrow and causes uncontrolled growth of white blood cells called myeloid cells. Left untreated, the diseased cells overrun the bone marrow and circulatory system, leading inevitably to death.

But there was also good news. Had he contracted the disease a decade earlier, his prognosis would have been bleak: the average survival time with standard chemotherapy back then was just three to five years. By 2006, when he received his diagnosis, an entirely new kind of drug, a targeted cancer therapy called Gleevec, was rewriting the rules for how doctors treated CML—and by extension other forms of cancer. For most patients, Gleevec had transformed

DEADLIEST CANCERS



Tony Hunter

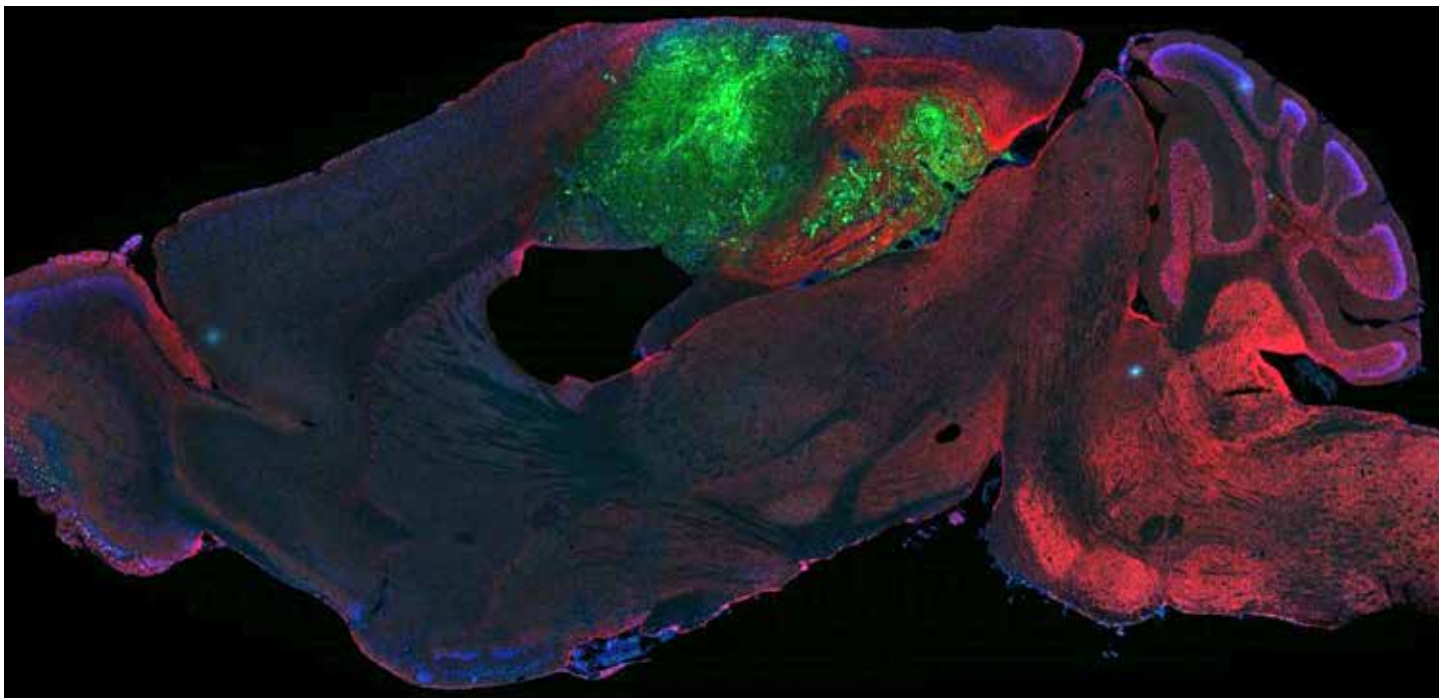
CML from a fatal disease into a chronic disease—with nearly 90 percent of patients surviving at least five years, many with no symptoms.

Lewis later learned that the breakthrough that made Gleevec possible, a discovery by a scientist named **Tony Hunter** of a form of protein regulation in cells, had taken place at the Salk Institute, where Lewis happened to be a member of a far-flung group of supporters known as the International Council. “I’ve been on Gleevec for six or seven years now, which is a testament to the importance of Dr. Hunter’s discovery,” says Lewis, who has since joined Salk’s Board of Trustees. “Before, people were thinking about trying to kill cancers with chemotherapy, but Tony’s work helped launch a whole new paradigm.”

Indeed, that new paradigm, the development of precisely targeted cancer therapies, owes much to discoveries made by Salk scientists. Just a few decades ago, cancer was a black box. Little was known about the biological processes underlying its development and progression, and finding diagnostics and treatments for cancers was very much a hit-or-miss process. Scientists of the Salk Cancer Center, which was established in 1970 and designated in 1973 by the National Cancer Institute (NCI) as the first of seven basic cancer research centers in the United States, have played a central role in prying open that black box. Salk researchers were well ahead of the curve, for instance, in approaching cancer as a disease of normal cells gone rogue due to genetic mutations—a discovery for which the late Salk scientist **Renato Dulbecco** received the Nobel Prize.

And Salk isn’t resting on its laurels. Using new technologies, including powerful imaging techniques, stem cell-based studies and genome sequencing, the Institute’s scientists are speeding their exploration of the molecular mechanisms underlying cancers. Even as they continue to aggressively root out the molecular bad actors, they are building on their expertise in cellular mechanics to identify and test promising therapies against tumors. By bridging the gap between basic biological research and clinical trials, Salk researchers are ensuring that laboratory discoveries become medical breakthroughs.

“These are complex diseases at the molecular level, which means sophisticated science is needed to develop the tools for diagnosing and treating them,” says Hunter, who directs the Salk Cancer



This high-resolution mosaic image of a tumor (green) induced by injection of lentivirus containing tumor-suppressor genes shows the aggressive nature of glioblastomas.

Center and holds the Renato Dulbecco Chair in Cancer Research. “Thanks to Gleevec and other targeted therapies, the prognosis for patients with certain cancers has improved dramatically. We think that can be true for all cancers, that the mutations leading to cancer can be tamed.”

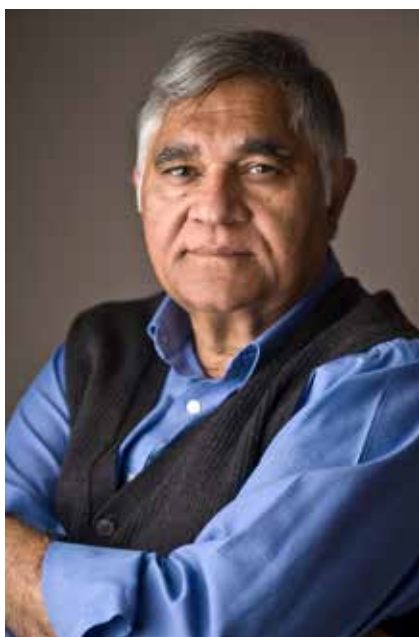
AN UNLIKELY ALLY

Odd as it seems, viruses have proven one of the most valuable tools for Salk’s cancer researchers. Much maligned for their pathological tendencies, viruses are whizzes at infiltrating other organisms’ cells and altering their DNA, an ability that scientists have appropriated for studying cancer. In fact, it was studies of a tumor virus that led to Hunter’s discovery of the new type of enzyme that is targeted by Gleevec. And researchers in the laboratory of Salk professor **Inder Verma** have made great progress using de-fanged viruses to study a particularly aggressive form of brain cancer, glioblastoma multiforme (GBM).

Every year more than 14,000 Americans succumb to malignant brain tumors, and the average life expectancy after the disease is detected is just over a year. Verma’s team developed a mouse model to study the pathophysiology of these tumors. To do this, they harnessed the power of modified viruses, of a viral type called lentiviruses, to disable tumor suppressor genes that regulate the growth of cells and inhibit the development of tumors.

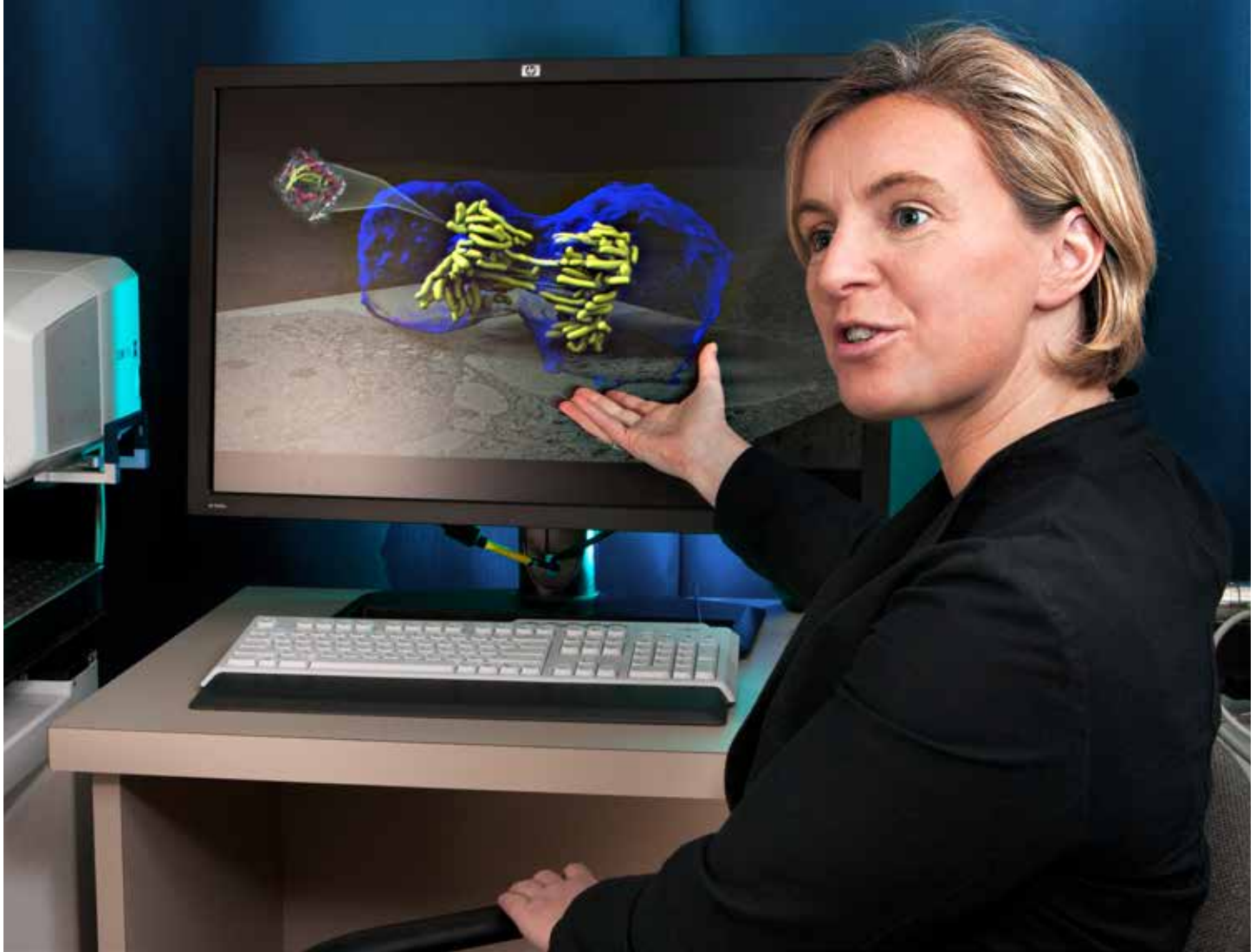
Scientists had long believed that GBM begins in glial cells that make up supportive tissue in the brain or in neural stem cells. But through studies of their mouse model, Verma’s team found that the tumors can originate from other types of differentiated cells in the nervous system, including cortical neurons. Their findings, reported recently in *Science*, also offer an explanation for the recurrence of GBM following treatment and suggest potential new targets to treat these deadly brain tumors.

“One of the reasons for the lack of clinical advances in GBMs has been the insufficient understanding of the underlying mechanisms by which these tumors originate and progress,” says Verma, holder of the Irwin and Joan Jacobs Chair in Exemplary Life Science. “The cancer-causing insults to neurons or glial



“WHAT WE’RE WORKING ON NOW IS DEVELOPING DIFFERENT MODELS FOR OTHER CANCERS, WHICH IS IMPORTANT BECAUSE DIFFERENT CANCERS OPERATE IN DIFFERENT WAYS.”

— Inder Verma



Clodagh O'Shea

cells reprogram them into stem cells which can continue to proliferate and induce tumor formation, thereby perpetuating the cycle of continuous cell replication to form malignant gliomas.”

Verma has also used his viral vector technique to create a mouse model for non-small cell lung cancer, a type that accounts for as much as 80 percent of all lung cancer cases in humans. In one study with these mice, Verma's team found that blocking the activity of the enzyme IKK2, which helps activate the body's inflammation response, slowed the growth of tumors in mice with lung cancer and increased their lifespan. The findings suggested that drugs targeting this inflammation pathway may present a new avenue for treating certain lung cancers.

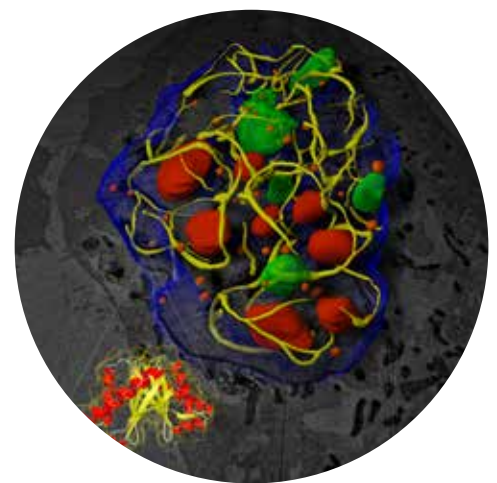
“These models offer us a way to study cancer in a living organism that faithfully follows the pathology, physiology and molecular signatures of human cancers,” says Verma. “It not only lets us explore the mechanics behind the various forms of cancer, but also provides us with a platform for testing therapeutics against tumors. What we're

working on now is developing models for other cancers, which is important because different cancers operate in different ways.”

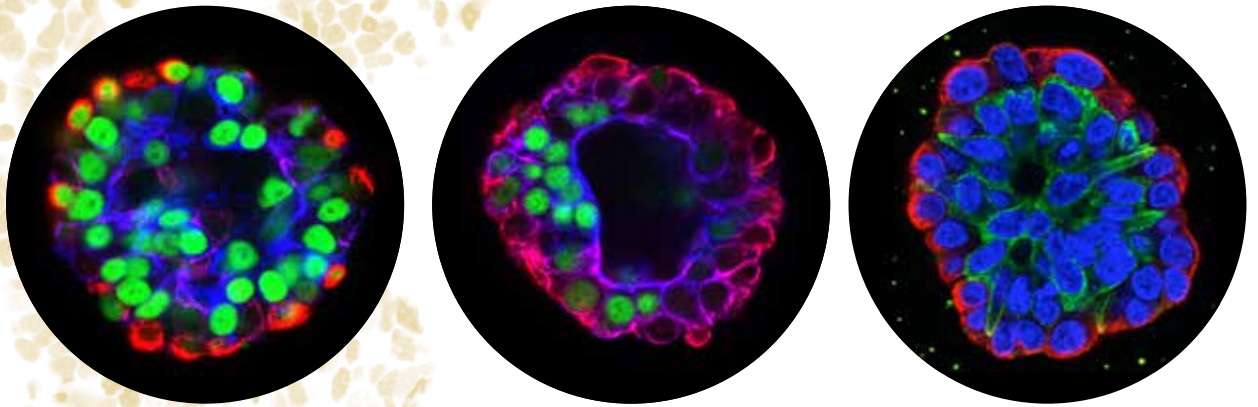
Clodagh O'Shea, an associate professor at Salk, is exploring another highly promising avenue for using viruses in the development of cancer therapeutics, based on modified adenovirus, a type of cold virus. Adenovirus has developed molecular tools that allow it to hijack a cell's operations, including large cellular machines involved in growth, replication and cancer suppression.

O'Shea studies E4-ORF3, a cancer-causing protein encoded by adenovirus, which prevents the p53 tumor suppressor protein from binding to its target genes. Normally, p53 suppresses tumors by causing cells with DNA damage—a hallmark of cancer—to self-destruct. This tumor suppressor pathway is inactivated in almost every human cancer, allowing cancer cells to escape normal growth controls and acquire new cancer-causing mutations. Similarly, by inactivating p53, the E4-ORF3 protein enables adenovirus replication in infected human cells to go unchecked.

O'Shea's team revealed the ultrastructure of the remarkable polymer that E4-ORF3 assembles in the nucleus—something that previously had proven difficult since the polymer is effectively invisible using conventional electron microscopy. “What you see is the E4-ORF3 polymer bending



A nuclear matrix that traps tumor suppressors, featured on the cover of *Cell*.



Normal mammary gland cells are marked in blue and red, while the fraction of cells that stay in a stem cell-like state are genetically labeled with a green fluorescent protein (left two panels).

and weaving and twisting its way through the nucleus,” she says. “It does appear to have a single repeating pattern and creates a matrix that captures several different tumor suppressors and silences p53 target genes.”

O’Shea’s findings may help scientists develop drugs capable of destroying tumors by binding and disrupting large and complex cellular components that allow cancer cells to grow and spread. Understanding how viruses overcome healthy cells may also help scientists engineer tumor-busting viruses. Such modified viruses would destroy only cancer cells because they could only replicate in cells in which the p53 tumor suppressor has been deactivated. When a cancer cell is destroyed, it would release additional copies of the engineered viruses, which in turn would seek out and kill remaining cancer cells that have spread throughout the body.

GAME-CHANGING TECHNOLOGIES

The evolution of cancer research has always relied on the progression of technology, and now, more than ever, Salk scientists benefit from a critical mass of cutting-edge research technologies. Verma’s virus-based gene delivery systems and mouse models are just one example.

Stem cell techniques provide another powerful method of charting important growth and development pathways involved in cancers. Salk’s Waitt Advanced Biophotonics Center allows Salk researchers to visualize the inner workings of cancers in stunning visual detail. And new high-throughput sequencing devices provide a tool for intercellular cartography, letting scientists map out the entire genetic code of a patient or a tumor. In combination, these technologies prove particularly valuable, helping researchers tackle longstanding questions that were difficult or impossible to answer in the past. In one case, they’ve even allowed a Salk lab to breathe new life into a theory that was first proposed 150 years ago but was never fully explored due to technological limitations.

While reading the writings of two 19th-century scientists, Francesco Durante and Julius Cohnheim, Salk professor **Geoff Wahl** realized that their theories about where cancers originate might still have merit for modern science. In the 1870s, Durante and Cohnheim proposed that cancers come from cells in adults that persist in an immature, embryonic-like state.

“What Durante and Cohnheim were saying makes a lot of sense,” says Wahl, who holds Salk’s Daniel and Martina Lewis Chair. “Tumors and embryonic cells share many similarities. They divide



Geoff Wahl

rapidly, can generate different cell types, have similar metabolism that enables them to grow in limited oxygen, and in some tissues must develop the capacity to move and burrow into adjacent tissues. Given these similarities, we wondered whether the genomic programs active in developing embryos might be reactivated in certain types of cancers, but to the detriment, not benefit, of the individual.”

Thanks to advances in stem cell research and genomic sequencing, Wahl’s team was able to explore this question with tools unavailable until very recently. Using sophisticated methods of stem cell and developmental biology, genetic manipulation of mice, microscopy and microfluidics, the Salk researchers were able to isolate stem cells found in the developing mammary glands of mice. Using genomic sequencing techniques, they compared the genetic activity of these mammary stem cells with stem-like cells found in breast cancers.

They found that the genetic signatures of the mouse cells were remarkably similar to the stem-like cells found in aggressive breast cancers. This was true for a significant fraction of virulent cancers labeled “triple-negative,” a

name that indicates the tumors do not express the genes for estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2).

When a patient’s tumor tests positive for HER2 or one of these other markers, the doctor’s treatment approach is more precise and typically far more effective. By blocking the activation of the receptor, the drug Herceptin stops the growth of breast cancers. Because triple-negative tumors lack the HER2 receptor, however, there are fewer good options for treatment, so the outcomes are usually worse—something Wahl aims to change.

His team’s findings suggest that triple-negative cancers rely on signaling through pathways

similar to those that drive fetal breast stem cell growth. They also found that the fetal breast stem cells are sensitive to a class of targeted therapies that already exists, so these therapies might also work in the considerable subset of triple-negative breast cancers that resemble the fetal breast stem cells. Laboratory studies and clinical trials are currently underway to test this possibility.

“We’ve now got the tools to find the weaknesses of these cancers, to give them molecular names that reflect what they are, not what they aren’t,” says Wahl. “I don’t want to call a tumor triple-negative. I want it to have a name that tells a doctor how to stop it from growing.”

“WE’VE NOW GOT THE TOOLS TO FIND THE WEAKNESS OF THESE CANCERS, TO GIVE THEM MOLECULAR NAMES THAT REFLECT WHAT THEY ARE, NOT WHAT THEY AREN’T.” — GEOFF WAHL



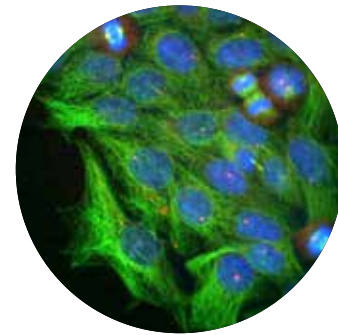
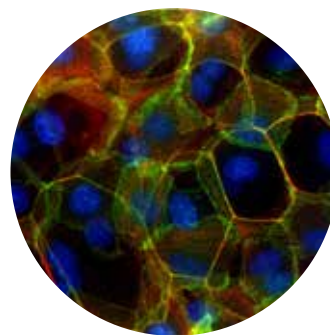
DISCOVERIES INTO CURES

Like Wahl, Salk professor **Ron Evans** sees translational research—the bridging of basic and clinical science—as the natural evolution of his foundational research on the physiology of cells.

An authority on hormones, both their normal activities and their roles in disease, Evans discovered a large family of molecules named nuclear receptors, which respond to various steroid hormones, vitamin A and thyroid hormones. In addition to impacting our daily health by controlling sugar, salt, calcium and fat metabolism, the receptors are primary targets in the treatment of breast cancer, prostate cancer and leukemia. Evans's discoveries have led to a remarkable number of clinically relevant discoveries, so much so that *Nature Biotechnology* named him the top translational researcher in the world in 2012, based on the number of patents resulting from his studies (114).

One of Evans's discoveries resulted in Entinostat, a new breast cancer drug that targets certain enzymes found in cancers that have become resistant to chemotherapy. Entinostat has proven so effective in early clinical trials that the U.S. Food and Drug Administration designated it a “Breakthrough Therapy,” which will speed the drug's progress toward clinical use.

More recently, Evans's lab has studied the role of hormone receptors in pancreatic cancer, where the lifespan after diagnosis is typically counted



in mere months. Inflammation of the pancreas, or pancreatitis, is a serious pathologic state associated with both acute and chronic inflammation that is linked to the development of pancreatic cancer. Stromal cells, supporting cells found in connective tissues of the pancreas, are known to release substances that stimulate tumor growth, tumor invasion and tumor resistance to therapy.

“These cells are a promising target for stopping pancreatic inflammation, pancreatitis and cancer,” says Evans, a Howard Hughes Medical Institute investigator and holder of the March of Dimes Chair in Molecular and Developmental Biology. “We know the key molecular players in these signaling pathways, so we may be able to control their activity. Tackling inflammation may represent an entirely new therapeutic approach to controlling the disease process.”

His team's preliminary studies identified the vitamin D receptor (VDR), a known potent anti-inflammatory regulator, in inactivated stromal cells. They hypothesize that drugs that modify VDR signaling may prove effective at suppressing the genomic events that lead to cancer development. The lab is currently collaborating on a human clinical trial that explores whether VDR activators, alone or in combination with the anticancer drug gemcitabine, can stop inflammation and the development of pancreatic cancer.

Ron Evans





Reuben Shaw

Like Evans, Salk professor **Reuben Shaw** has also discovered links between metabolism, inflammation and cancer. Shaw, a Howard Hughes Medical Institute early career scientist, studies a tumor suppressor gene called LKB1, which is lost in 30 percent of lung cancers. The gene's normal action is to turn on a metabolic enzyme called AMPK when energy levels run low in cells, suppressing their growth and proliferation. But in certain lung cancer tumors lacking the normal LKB1 gene, cells cannot sense their own energy levels, resulting in out-of-control growth. This led Shaw to speculate that drugs that lower cellular energy levels and slow cellular metabolism may kill lung tumors with defective LKB1.

Interestingly, the best-known drugs to lower cellular energy levels are used in diabetes treatment. This past year, Shaw and his team demonstrated that phenformin, a derivative of the widely-used type 2 diabetes drug metformin, decreased the size of lung tumors in mice and increased the animals' survival.

Like the Gleevec and other targeted medicines, the treatment is most effective in lung tumors carrying the specific genetic mutation that sensitizes them to this therapeutic option, in this case, the LKB1 gene.

The next step is to determine how phenformin would perform in combination with other existing standard-of-care lung cancer drugs. In addition, Shaw's team is further studying other ways to alter cellular metabolism and target this large proportion of lung cancer patients.

"Increasingly, this is where Salk's cancer research is headed," says Shaw. "Cancer is complicated, which is part of the reason clinical progress has been slow compared to other diseases. But we now have the technologies to marry laboratory science and clinical studies—and that's going to give doctors the targeted therapies they need to turn these deadly acute diseases into manageable chronic conditions." 🏢

🔗 **WE NOW HAVE THE TECHNOLOGIES TO MARRY LABORATORY SCIENCE AND CLINICAL STUDIES—AND THAT'S GOING TO GIVE DOCTORS THE TARGETED THERAPIES THEY NEED TO TURN THESE DEADLY ACUTE DISEASES INTO MANAGEABLE CHRONIC CONDITIONS.** 🔗

— REUBEN SHAW



One on one with... Geoff Wahl

A professor in Salk's Gene Expression Laboratory and holder of the Daniel and Martina Lewis Chair, Geoff Wahl has been involved in various aspects of cancer research for his entire 40-year career. At the Salk, he and his team are studying the genetic basis of the origin and progression of cancer and developing new strategies to tailor-make drugs based on the genetic signature of a patient's tumor.

Recently, they discovered striking similarities between genetic signatures found in certain types of human breast cancer and those of stem cells in breast tissue in mouse embryos. These findings suggest that cancer cells subvert key genetic programs that guide immature cells to build organs during normal growth. Their work may provide new ways to predict and personalize the diagnosis and treatment of cancer.

In a recent conversation, Wahl noted fundamental connections between his chosen career and his pastimes.

One key: taking his time.



Geoff Wahl

Geoff Wahl, 2014

How long have you been a photography enthusiast?

Since the '70s. I used to develop my own film, and I earned part of the money I needed for graduate school by taking pictures at plays. I was dating a girl at Wellesley who was in Shakespeare performances there, and I took photos of her and other student actors because the parents couldn't always be present. It was all ambient light, no flash. I'd develop them in the darkroom of the biology/chemistry department at Harvard because, of course, I couldn't afford that kind of equipment. The most disconcerting thing I remember was watching a huge cockroach crawling across the developing stand one evening. Coming from California, I'd never seen a cockroach before. It was something between a rat and an insect. They're big!

Did you ever consider becoming a professional photographer?

Well, I sort of masqueraded as one for a while. After getting my Ph.D., I took some time to travel around the country with my camera. It was 1976, and I made my way to Plains, Georgia, because I sensed something was going to happen there, whether or not Jimmy Carter won the election. So I was hanging out with some other photographers one day, and they asked me which paper I worked for. I told them I was an "independent." They asked if I was going to Billy's house later to watch the election returns. I didn't know who Billy was, but I said yes, only I've lost the directions. Just hang out with us, they said. So that's how I ended up watching the election returns in the home of the president's brother.

You like to cook, too, and it's been said that cooks make good scientists. Do you agree?

I can see how cooks would make good scientists—they're both mixing things together. The best chefs, you know, are the ones who understand the principles of cooking, then take those principles and apply them in an unusual way. That's similar to scientists. The best scientists not only read a protocol—the recipe—they understand why things are being done in that protocol. That way, if something goes wrong with the experiment, they can recover from it. That's important because an experiment can often take many months. If you can find your mistake early and proceed from there, then the project's not totally wasted. The most important thing about being a good cook and a good scientist is being able to adapt. You do the recipe once as given, then you modify it and do it again, always making sure you can generate results that are meaningful, reproducible and insightful.

“One of the addictive parts of science is being able to see or conceptualize something for the first time. It is a feeling like no other.”

— GEOFFREY WAHL



Wahl with his family Matthew, Allison and Barbara Parker at the Galápagos Islands.



What about photographers—do they make good scientists?

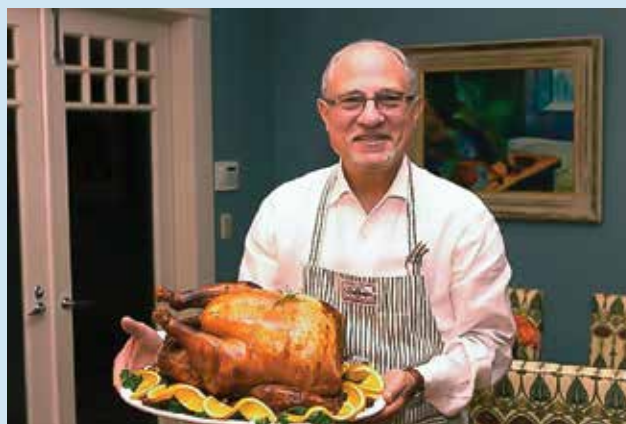
I think there are some similarities between science and photography as well, certainly in the old days when you were mixing chemicals and doing your own developing. Often we refer to scientific results as “beautiful,” especially when something strikes you viscerally. As humans, we like to see things; we like to visualize what we’ve made. You know, the connection between the eye and the brain is the strongest computer available. And it seems that if someone can present something in a visually appealing way—simple yet elegant—then they must really know what they’re doing. A good photograph, like a good experiment, should transport you to a different place of understanding.

So is that the key to successful science: transporting you to a different place of understanding?

There are three keys: the power and importance of observation; interaction and listening to others; and spending the time to observe. One of the problems with science today is trying to get things done very rapidly. Funding is so scarce; there’s competition for limited resources. But sometimes working fast makes you blind to the jewels that are right in front of you, the jewels that nature is hiding. We need to take time, be more attentive.

At the recent Art and Science of Cuisine event, where you were a panelist, Deborah Szekely talked about spending time with your food, looking at it, tasting it and appreciating it. That applies to photography, too, right?

It does. You have to see, and you have to wait. A lot of people think the best light is at sunset, but they’re wrong. The best light is after sunset; you have to be patient because something usually happens after sunset





From left: Karissa Huang, Rose Rodewald, Benjamin Spike, Annabelle Kraus, Claire Johns, Geoff Wahl, Maya Ridinger, Bianca Lundien Kennedy, Chris Dravis and Christy Trejo

that you can use to your benefit to represent a certain mood. Most of my pictures I've not been happy with because they don't elicit the feeling I had at the moment I took the image. A photograph is not successful if it doesn't give you new insight into something you may have seen many times before or a sense of wonder and excitement about something you are seeing for the very first time. One of the addictive parts of science is being able to see or conceptualize something for the first time. It is a feeling like no other.

We think of science as being cutting edge, but doesn't history play a role?

It does, absolutely. We build on the observations of others. Back in the 1800s, you know, scientists had only rudimentary microscopes. They were very limited in what they could view. But they could see cells; they could see the shapes of cells. And they had plenty of time to observe things.

Obviously, they knew about cancer, but they didn't know where it came from. It was Rudolph Virchow who enunciated the theory that "all cells come from cells." And it followed that if all cells come from cells, then cancer had to have come from the cells that preceded the cancer. Francesco Durante posited that maybe cancers come from this embryonic form that stays around and is later activated by whatever "humours" are in the body. You could read that to say, "Maybe there's a latent state of

cancer that is activated by inflammation." He just didn't have the vocabulary to accurately describe what we now know. There are so many parallels between what these early scientists observed and what we're discovering to be true; so yes, history plays an incredibly important role in making us both appreciative of what our scientific ancestors generated and, in sort of a natural evolution of things, where we need to go next.

The science of the Salk Institute is often referred to as "basic" research, but you've said before that it's really an inadequate term. Why is that?


I think paying attention to the foundations of science puts it better because we all stand on the shoulders of giants. "Foundational science," we should call it. Basic trivializes the work that we do. We're investigating the very principles by which life works—when consciousness arises, the brain conceptualizes, the eyes see. How we relate to each other, how fundamental malfunctions arise: obesity, diabetes, cancer. Are these basic? No, these go much deeper. These are foundational issues. We must take the necessary time to examine the foundational issues of human biology; our future health depends on it. And that is why we have to solve the funding problem that is currently so threatening to the research enterprise in the United States. 



Photo courtesy of HHMI.

The Howard Hughes impact

FOR ALMOST TWO DECADES, JOSEPH ECKER STUDIED THE GENETICS OF *Arabidopsis thaliana*, a small flowering plant with a rapid life cycle that's become a staple model organism in plant biology labs. He helped spearhead the international effort to sequence the *Arabidopsis* genome and worked out how the plant turns its genes on and off. Ecker became one of the top *Arabidopsis* researchers in the world. But in the process, he realized that the underlying questions he was asking and methods he was developing to study gene regulation weren't just relevant to plants. He started wondering what his approach could allow him to discover about animal cells and human health.

For a plant biology lab to shift its focus to animal cells or human cultures requires extensive resources, new equipment and new support staff. For Ecker, though, help came at just the right time in the form of a five-year appointment from the Howard Hughes Medical Institute (HHMI) and the Gordon and Betty Moore Foundation (GBMF), awarded to him in 2011.

With the award, Ecker became the seventh scientist at the Salk Institute to join the current ranks of HHMI-funded scientists. While most federal grants offer researchers money for a specific project, HHMI works differently. Through sporadic competitions, scientists are chosen based not on a specific project but on the merit of their entire research portfolio. As HHMI investigators, researchers then receive research support and their full salary and benefits from HHMI, although their labs remain at their home institutions. The appointment lasts for five years and can then be renewed in five-year increments. In Ecker's case, a collaboration between GBMF and HHMI provided additional research support.



"Having this kind of funding gives scientists the freedom to actually do experiments rather than spend time writing grants," says Ecker. "It's already had a big impact on my ability to follow my nose." Recently, he says, a colleague who studies vision in macaque monkeys approached him about collaborating on a project to study how genes involved in vision are regulated. Rather than worry about how to fund the project, Ecker moved right into brainstorming what the collaboration could accomplish.

His story is more than just a testament to the power of being well funded. It highlights all the



From left: Joe Noel, Joe Ecker, Reuben Shaw, Ron Evans, Terry Sejnowski, Sam Pfaff, Joanne Chory

reasons that the HHMI model of science works so well, particularly at Salk: both institutions emphasize collaboration and the idea that the best science takes place when talented researchers have the time and resources to pursue whatever ideas come their way. For the seven Salk scientists currently working under the auspices of HHMI—six as HHMI investigators and one as part of HHMI's early career scientist program—the benefits of Howard Hughes support are clear and have helped push all to be more creative, productive, accomplished researchers.

“ We look for people with innovative ideas—big thinkers—and give them freedom to follow their instincts. ”

– ERIN O'SHEA, HHMI VICE PRESIDENT AND CHIEF SCIENTIFIC OFFICER



Howard Hughes founded the Howard Hughes Medical Institute in 1953.

Legacy of an Aviator

In the late 1940s, businessman, film producer and aviator Howard Robard Hughes, Jr., then one of the richest people in the world, was looking for new ways to invest his money. Funding basic scientific research had been a lifelong dream of his, and he began making it a reality with the help of a group of like-minded advisors. In 1951, he granted money to six scientists, and two years later he officially chartered the Howard Hughes Medical Institute.

Since Hughes's death in 1976, the institute has grown, and its mission has crystallized on supporting biomedical researchers through flexible, long-term support.

"We like to say that we focus on 'people, not projects,' and that is reflected in our unique funding structure," says Erin O'Shea, HHMI's vice president and chief scientific officer. "We look for people with innovative ideas—big thinkers—and give them freedom to follow their instincts."

Today, HHMI has more than \$16 billion in assets and is the nation's largest private supporter of academic biomedical research. In 2012, it granted \$78 million toward science education and \$695 million in support of basic research. Three hundred scientists at 70 institutions are HHMI investigators, and among their ranks are 17 Nobel laureates. HHMI has been one of the largest funders of

Salk researchers, providing more than \$75 million in support—a fact that is celebrated on the list of donors posted at the entrance to the Institute.

For scientists—at Salk and elsewhere—an appointment as an HHMI investigator not only means financial support but opportunities for collaboration with other HHMI researchers, idea sharing at annual HHMI conferences and a recognition that they are at the top of their field.

A Second Home

When **Ron Evans**, director of Salk's Gene Expression Laboratory, was appointed an HHMI investigator in 1985, he didn't fully appreciate the effect the grant would have on his career.

"I knew very little about Hughes—the institution didn't circulate much information back then and was much more private than it is now," he says. "But in retrospect, it was really catalytic in its impact on my research. It was basically like adding jet fuel to a race car."

In the same year as his HHMI appointment, Evans discovered a new class of proteins, nuclear proteins known as receptors that mediate the action of steroid hormones such as cortisol, estrogen and testosterone. The discovery opened up a deluge of questions and follow-up experiments for Evans. How many of these nuclear receptors existed? Does the discovery of new receptors imply the existence of new hormones? If so, what other physiological processes might be controlled by these new hormone-sensing receptors?

HHMI Faculty at Salk



Joanne Chory

Plant Molecular and Cellular Biology Laboratory, HHMI Investigator
1997–present

Joanne Chory, holder of the Howard H. and Maryam R. Newman Chair in Plant Biology, studies how plants respond to patterns of sunlight, shade, temperature and moisture to alter their growth and maturation and strive to survive. Her research has implications within agriculture for learning how to optimize the production of crops. It also has broader lessons about how organisms coordinate the growth of different tissues and respond to factors in their environments.

“Hughes has a great model for thinking about how to best do science through collaboration, creativity and risk taking, and Salk is the place where this all comes together.” —RON EVANS

“We were a relatively small, young lab all of a sudden facing this huge biological problem,” says Evans. “So it was the perfect timing to be brought into this Hughes system that was really geared toward risk-oriented, cutting-edge research.”

In the decades since, Evans has defined about 50 receptors known as the steroid receptor superfamily and realigned his focus on new hormone signaling pathways that are intertwined with issues of metabolic disease, insulin resistance, obesity and muscle growth. He’s elucidated how two receptors, dubbed PPAR gamma and PPAR delta, control whether fat is broken down for energy or stored in the body, providing a potential drug target to help treat metabolic disease. And his lab showed that by activating PPAR delta in mice with a newly designed drug, the animals not only lost weight but gained greatly improved running endurance. His “exercise in a pill” drugs were rapidly (and illegally) adopted as a new class of performance enhancers. For his findings, Evans has won some of the preeminent prizes in biology—the Wolfe Prize in Medicine, the Albert Lasker Award and the Albany Medical Center Prize, among others.

Throughout it all, Evans has been inspired, pushed and supported both by his colleagues at Salk and his fellow HHMI investigators.

“A critical part of being in the HHMI organization is that we have the benefit of having two intellectual communities,” says Evans. “For 30 years, I’ve had a home at Salk and I’ve had a second home with HHMI. And getting the benefit of having two home bases for research has really been a game changer.”

The two institutions, he says, fit particularly well together because of their similar approaches to science. Both encourage researchers to pursue questions that they’re passionate about, whatever they may be.

“Hughes has a great model for thinking about how to best do science through collaboration, creativity and risk taking, and Salk is the place where this all comes together,” Evans says.

Allowing Cutting-Edge Science

The freedom to be creative as a scientist and pursue your interests is certainly key to being successful, but also important in a research lab is the ability to have the latest technology and the best-trained staff possible. For **Samuel Pfaff**, a professor in Salk’s Gene Expression Laboratory and an HHMI investigator since 2008, access to such resources, possible only through his HHMI funding, has been integral to advancing his research program.

Pfaff studies how nerve cells are formed and correctly wired in a developing brain. His research has implications for developmental brain diseases and neurological disorders such as amyotrophic lateral sclerosis (ALS). But understanding brain development requires looking at neurons from every angle—studying how patterns of gene expression vary between neurons, testing how genetic mutations in mice change the development of the animals’ brains, and using cutting-edge microscopy to see how neurons are arranged and what areas are active when.

“Looking at this whole landscape of the brain requires some pretty costly equipment,” says Pfaff, “and also relies on the ability of a lab to recruit people who know how to use the equipment.” Since becoming an HHMI investigator, he says, both these things have become easier.

Last year, Pfaff took advantage of the latest microscopy technologies in his lab to reveal which molecules on the end of a growing nerve cell and in its surroundings are responsible for guiding the direction of the cell’s growth. He’s also expanded his lab to have the capabilities to do experiments on embryonic stem cells, letting his team discover how genes cycle on and off in stem cells, controlling their ability to differentiate into new cell types. The work required access to RNA sequencing technologies, which allowed him to analyze which genes were being expressed when.

Joseph Ecker

Plant Molecular and Cellular Biology Laboratory, HHMI Investigator
2011–present

Joe Ecker, holder of the Salk International Council Chair in Genetics, is an expert in the model organism *Arabidopsis thaliana*, having spent decades studying its genetics and how its gene expression is regulated. Recently, he’s begun applying these lessons to other organisms and cell types, looking at the epigenetics of stem cells, brain development and the human liver, among other systems.



Ronald Evans

Gene Expression Laboratory, HHMI Investigator
1985–present

In the 1980s, Ron Evans, holder of the March of Dimes Chair in Molecular and Developmental Biology, discovered a new family of proteins known as receptors that are sensors for hormones and dietary nutrients such as fat. Since then, he’s discovered a superfamily of 48 members and focused in on the fat-sensing receptors that control obesity, metabolism, muscle growth and cardiovascular endurance. His ideas have changed how scientists think about weight gain, diets and exercise.





Howard Hughes Medical Institute headquarters in Chevy Chase, Maryland. Photo courtesy of HHMI.



Pfaff's lab group has also become one of only a few in the country with the capability to screen mice with random genetic mutations for any defects in neural system development. Such so-called random mutagenesis screens are usually reserved for use with model organisms that are cheaper and have faster generation times, like flies and worms. The method is now giving Pfaff the chance to find brand-new genetic pathways involved in brain and spinal cord development.

"Both here at Salk and within the HHMI community, scientists are striving for a much higher standard than elsewhere," Pfaff says. "We want to be the best at what we do and not just add noise and modest contributions to the field."

In the current economic climate, funding for basic research is hard to come by, and Pfaff says that researchers should consider doing science to be a privilege. It's through the joint support of Salk and HHMI, he says, that he enjoys the privilege of being a scientist.

Sharing the Wealth

In Salk's Plant Molecular and Cellular Biology Laboratory, director **Joanne Chory** says that her appointment as an HHMI investigator isn't just a boon to her work; it has had an impact on the entire plant science community. Chory's appointments at Salk and HHMI helped to introduce these two biomedically oriented institutions to the wonders of plant genetics, variation and adaptation to new environments.

Together with Gerry Fink, a former non-resident fellow of Salk and member of the Medical Advisory Board of HHMI, she introduced a select group of plant biologists to HHMI's scientific leadership during a 2009 workshop at HHMI headquarters in Maryland. This led to the appointment of 15 new HHMI and Gordon and Betty Moore investigators in 2011.

HHMI's commitment to this new program sent an important message about the importance

of plants to human health and the long-term sustainability of our planet. Despite its central role in feeding and clothing humans, plant biology is one of the most poorly funded areas within the life and biomedical sciences.

"This is because the discipline of plant biology does not have a strong advocate in Washington," says Chory. "Funding for plant biology labs has traditionally come from agencies that have other things on their minds. Having to distribute food stamps and manage farm subsidies, the USDA has not had the time to develop strategies for supporting long-term basic research. Likewise, the National Science Foundation's mission is to help create a scientifically literate public."

With the funding she's received from HHMI, NIH and other federal funding agencies, Chory has made a number of seminal discoveries about the mechanisms of plant growth, including the finding that plants, like animals, use



Joseph Noel

Jack H. Skirball Center for Chemical Biology and Proteomics, HHMI Investigator 2005–present

Joe Noel, holder of the Arthur and Julie Woodrow Chair, is interested in how the enzymes and metabolic products made by plants have changed over evolutionary history and what these changes mean about the coevolution of plants and animals. His research is not only vital to shedding light on the past but also for understanding how plants produce defenses and signaling molecules, which could help optimize agriculture.



Samuel Pfaff

Gene Expression Laboratory, HHMI Investigator 2008–present

Sam Pfaff, holder of the Benjamin H. Lewis Chair, studies how neurons are formed and correctly wired in a developing brain and how nerve cells connect the spinal cord to muscles in the body. His research has implications in developmental brain diseases and neurological disorders such as amyotrophic lateral sclerosis (ALS) and Alzheimer's disease.

steroid hormones to control growth, development and sexual reproduction. However, unlike the nuclear receptors studied in the Evans lab, Chory showed that plants use a unique class of cell surface receptors, called LRR receptor kinases, to bind plant steroids and thus control plant growth.

Over the past 15 years, she and **Joe Noel**, a fellow Salk professor and HHMI investigator, have discovered how the plant hormone auxin is synthesized and how its levels are regulated to control plant growth and development. Understanding where and when plants alter the levels or sensitivity to these two hormones explains how plants outcompete their neighbors for light. More recently, she has identified how chloroplasts signal to the nucleus and, together with Noel, how smoke from forest fires spurs dormant seeds to begin growing.

"Having long-term funding from HHMI has allowed us to integrate our research," says Chory. "Over the past 25 years, we have amassed a unique toolkit, which, along with collaboration with colleagues, has enabled my lab members to go from a genetic screen to gene discovery to cell biology to crystal structure and back to ecological response."

Straddling Disciplines

Ecker, the newest HHMI investigator at Salk, already notices parallels between HHMI and Salk and sees why Salk researchers fit so well with the HHMI system. Both institutions, he says, encourage scientists to collaborate and learn from colleagues not only working on similar projects, but those in drastically different fields.

At HHMI's annual meetings, researchers from all areas—from neuroscience to cancer and structural biology to plant science—present their latest work for each other. Similarly, at Salk, weekly seminars and regular faculty meetings bring together all scientists from across the Institution.

"It's great to be forced to go to meetings that really expand your horizons," says Ecker, "because you really never know where your next idea is going to come from."

For Ecker, learning about fields outside *Arabidopsis* has paid off. With the help of Salk and HHMI, his lab has successfully expanded and collaborated to study stem cells, soybeans and even mice. Most recently,


he collaborated with **Terrence Sejnowski** of Salk's Computational Neurobiology Lab, who is also an HHMI investigator. Together, the team used the methods that Ecker had developed in plants to study the chemical marks on genes inside neurons in the brains of mice. Their results—which show that the types of chemical marks change as neurons mature—is paradigm-changing for the fields of epigenetics and brain development. Tom Insel, director of the National Institute of Mental Health, named the discovery one of the ten most important of 2013.

Carl Rhodes, a senior scientific officer at HHMI, says the unlikely pairing of a computational neurobiologist and a plant scientist-cum-epigenomics guru is precisely the kind of creative science HHMI seeks to foster. "For us, it's a great story," he says, "because you've got two HHMI investigators from very different areas of expertise coming together to tackle a problem from a totally new angle."

The study, Ecker says, wouldn't have progressed as fast or efficiently if the team hadn't been able to turn to its HHMI funding to support the project.

"A lot of the science that becomes most informative is science that's on the edge of disciplines," he says. "But the flexibility to work across disciplines is very difficult because of the way our federal grant system works."

At both Salk and HHMI, however, such cross-disciplinary studies and collaborations are encouraged. By putting top-notch researchers in proximity to each other, letting them share ideas and giving them the space and resources to follow up on their ideas, both institutions help foster the kind of science that changes the way people think about the world. Whether a discovery revolves around how the brain works, how plants grow or how genes are regulated, the HHMI-supported researchers at Salk are changing the way we think.

"HHMI and Salk have a shared culture and a shared concept as to what the goal is, which is great science and great truths in advancing different tiers of knowledge for the benefit of mankind," says Pfaff. "Salk aggregates the people within the actual structure itself; Hughes creates a structure that distributes the people in different environments. So it's actually very nice to get the benefit of both. It's a very special thing for those of us who are here and who are embedded in the HHMI system." 

Terrence Sejnowski

Computational Neurobiology Laboratory, HHMI Investigator
1991–present

Using cutting-edge microscopy and electrochemical methods, Terry Sejnowski, holder of the Francis Crick Chair, studies how the brain changes at a molecular level after something new is learned. His experiments, revealing the complexity of how the brain stores information, help researchers better understand disorders in which memory and learning are affected, such as Alzheimer's disease.



Reuben Shaw

Molecular and Cell Biology Laboratory, HHMI Early Career Scientist
2009–present

Reuben Shaw's group focuses on a molecule called LKB1 in human cells. LKB1, an enzyme, adds phosphates to other proteins and affects the metabolism of cells. Shaw has found links between the enzyme and both cancer and diabetes. He is funded by HHMI through the early career scientist program, which aims to jump-start the careers of promising young scientists.





Deborah Szekely, Honorary Chair



Attendees enjoy the healthy fare at Salk's Art and Science of Cuisine event.

The Art and Science of Cuisine:

Inaugural wellness event serves up fine food and research

The idea that we are what we eat was put into sharp focus at the inaugural Art and Science of Cuisine, presented by the Salk Institute on January 22. Talented chefs and scientists pooled their experience to inform and entertain a sold-out crowd of over 300 people eager to pursue healthier lifestyles in 2014.

ASSISTANT PROFESSOR JANELLE AYRES INTRODUCED FIVE CHEFS and three scientists—**Ronald Evans**, **Geoffrey Wahl** and **Reuben Shaw**—for a panel discussion about the significant links between diet, nutrition, health and disease. Honorary chair Deborah Szekely, cookbook author and cofounder of world-renowned spas Rancho La Puerta and Golden Door, initiated a lively conversation about food in America. One cause of rising obesity, agreed the chefs, is the all-too-easy availability of prepared foods. All panel members emphasized that fresh vegetables and fruits should be at the core of a proper diet but acknowledged that people often sate their cravings with junk food. That led Wahl to explain the difference between true hunger and craving. “Hunger is physiological,” he said. “But craving is different; craving takes experience because you have to have tasted it to crave it. Carbs and fats activate the opiate receptors in our brains. It’s interesting to note that cravings often come from stress or boredom—and both can be relieved through exercise!”

Following the panel, the crowd descended upon individual food stations to put the talk to the taste test. Chefs and their teams plated generous portions of tapas, tostadas, wraps and rolls. The Trustees Room,

transformed into a “dessert lounge,” featured abundant organic treats.

Satisfied guests departed well equipped to keep their health-related new year’s resolutions. The Art and Science of Cuisine proved that science isn’t just for the lab; the discoveries being made at the Institute impact our everyday lives, informing the choices we make. As Shaw concluded, “It’s an exciting time to bridge these worlds of nutrition and diet and science.”

The Salk Institute thanks participating chefs Nathan Coulon, Isabel Cruz, Joy Houston, Michelle Lerach, Denise Roa and Su-Mei Yu as well as event partners Bee Green, Bird Rock Coffee Roasters, Cups Organic, Deanna’s Gluten Free, Delicious Revolution, Great News! Cooking School, Isabel Cruz Restaurants, La Cocina Que Canta, Rancho La Puerta, Saffron, *San Diego Magazine*, Snake Oil Cocktail Company, Suzie’s Farm and True Food Kitchen. 🍴

» [For additional information, recipes, photos and videos, visit
www.salk.edu/cuisine/](http://www.salk.edu/cuisine/)



Left to right: Reuben Shaw, Nathan Coulon, Janelle Ayres, Ron Evans, Deborah Szekely, Joy Houston, Michelle Lerach, Geoff Wahl, Denise Roa, Isabel Cruz



“Hunger is physiological...But craving is different; craving takes experience because you have to have tasted it to crave it.” — GEOFFREY WAHL



Roger Guillemin

SCIENTIST, ARTIST, NOBEL LAUREATE
Celebrating Ninety Years of Creativity



Roger Guillemin receives the Nobel Prize in 1977.

EARLY IN HIS CAREER, WHEN ROGER GUILLEMIN WAS ATTEMPTING TO isolate a mystery substance suspected to control the function of the pituitary gland—and seeing more than a decade pass by—he must have wondered if his efforts would ever amount to anything. Would all the work prove worthwhile?

As scientists around the world know, it certainly did. Guillemin's findings brought to light a new class of substances important in regulating growth, development, reproduction and responses to stress, earning him a Nobel Prize in 1977. Today he is widely considered one of the founders of the field of neuroendocrinology. To mark his 90th birthday in January, the Salk Institute hosted a celebratory dinner and symposium that drew guests from as far away as Europe.

The festivities began on January 12 (the day after Guillemin's birthday) with a gathering of 175 friends and family in the specially decorated Salk foyer. Guillemin and his wife, Lucienne, were present, along with all six of their children and a number of grandchildren and great-grandchildren. At his request, and underscoring the fact that any success is a team effort, the guest list included associates who had worked alongside him in his lab or neighboring labs over the years, as well as Salk administrators who had supported him during his interim presidency at the Institute from 2007 to 2009. Among the speakers was **Catherine Rivier**, professor emerita in the Clayton Foundation Laboratories for Peptide Biology and a driving force behind the event; Salk president **William R. Brody**; and Guillemin's daughter, Claire, who led the crowd in singing "Happy Birthday" to her father. A standing ovation greeted the honoree when he made his way to the podium.



“In science there is such a thing as the law of gravity, the laws of DNA replication, and so on, whereas in art, there are no laws.”

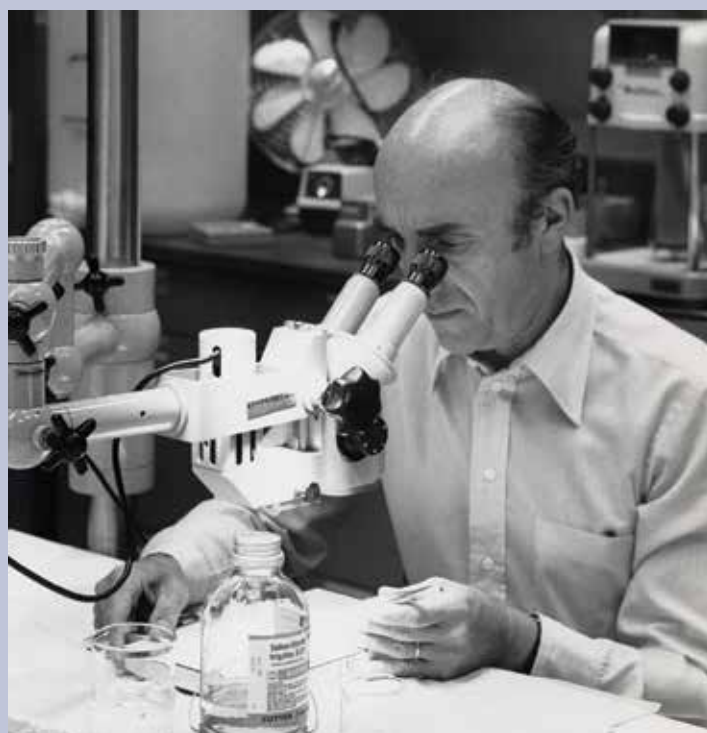
– ROGER GUILLEMIN



The following day, over 200 people arrived on the Salk campus to take part in a symposium titled “Hypothalamic factors: A trove for novel therapeutic and diagnostic applications.” The speakers discussed successful new therapies based on Guillemin’s original discovery of hypothalamic peptides, many of which are the only currently available treatments for sex steroid-dependent diseases and those involving skeletal growth. The speakers also highlighted recent developments in peptide study that have led to unique diagnostic tools for specific cancers—a development not foreseen when Guillemin made his original discoveries.

Although Guillemin retired from the active pursuit of science in 1989, he has never stopped seeking out new worlds to explore, one of which is art. Using his computer, he now creates striking images that have been described as ranging from “molecular art structures [and] impressionistic landscapes to pure abstractions.” One brilliantly colored example, “Grotte de Fingal #1aaa/blue skies,” was featured on the cover of the event program. Additional framed works were hung in the Salk foyer for guests to enjoy. Guillemin has exhibited in galleries around the world and in 2012, took particular pleasure in mounting a joint exhibition with his son François, a sculptor, at the Athenaeum Music and Arts Library in La Jolla.

For the doctor, the scientist, the artist and the man, the future remains boundless. “In science,” he has said, “there is such a thing as the law of gravity, the laws of DNA replication, and so on, whereas in art, there are no laws.” 📊



Roger Guillemin



President's Club continues a holiday tradition

SOME OF SALK'S MOST DEDICATED SUPPORTERS GATHERED AT the Institute December 5 for the annual President's Club holiday luncheon. The President's Club consists of donors who contribute \$2,500 or more each year to the Salk Annual Fund—a diverse group that includes friends, volunteers, faculty and staff. At the luncheon, Salk president **William R. Brody** spoke about the Healthy Aging initiative of the Campaign for Salk, an effort that supports research into chronic diseases associated with aging. **Martin Hetzer**, a professor in the Molecular and Cell Biology Lab, gave a presentation titled "The Brain's Achilles Heel: Old Proteins." Hetzer studies developmental and pathological changes in the organization and functions of the cell nucleus as they relate to aging. The consensus of the crowd, which numbered nearly 70 people, was that it was an outstanding event, and they're very much looking forward to the 2014 holiday luncheon. To learn more about the President's Club, please visit www.salk.edu/presidentsclub/ or call (858) 453-4100 x 1405. 📺

» To view video and photos from the event visit:
www.salk.edu/presidentsclub2013/

Small molecules, big opportunities

New faculty appointment to bring novel technology to Salk

ON JULY 1, WHEN SALK'S NEWEST FACULTY member, **Alan Saghatelian**, officially joins the Clayton Foundation Laboratories for Peptide Biology, the Institute will not only gain considerable expertise in metabolite and peptide profiling; it will also gain access to his innovative technique for analyzing these small molecules. The result will almost certainly be numerous cross-disciplinary collaborations that promise to advance our knowledge of metabolism and help identify potential therapeutic targets for a host of diseases.

Saghatelian, currently an associate professor of chemistry at Harvard, was first bit by the research bug two decades ago, while studying chemistry at UCLA. After working in an organic chemistry professor's lab for a few years, however, he was ready for something new following graduation. Intrigued by the intersection of chemistry and biology, he entered the graduate program at The Scripps Research Institute, where he concentrated on the synthesis of peptides capable of carrying out chemical reactions.

"It was a really important decision, even though I didn't realize how important," he says. "One of the things I liked about TSRI was that it was different from traditional chemistry departments. People were trying risky things, and I felt it would be a great opportunity to learn. And although my graduate research focused on biochemistry, I realized that I found problems in biology more interesting."

After earning his Ph.D. in 2002, Saghatelian remained at TSRI four more years as a post-doc, developing a novel technology to identify

metabolites. "Being an organic chemist, I was very interested in small molecules," he explains. "Metabolites are a group of molecules that aren't usually analyzed. We know a lot about proteins in many diseases, but we don't know if metabolites are involved at all or if so, which ones."

Metabolites and peptides have vital roles in human physiology and disease. The peptide hormone insulin, for example, controls physiological levels of the metabolite glucose, and the aberrant signaling of either leads to diabetes. But to understand their function and regulation, it is necessary to detect and quantify these molecules under different biological conditions, such as identifying changes in them during disease. Unfortunately, a dearth of available experimental tools has made it difficult to study them.

Part of the problem, Saghatelian says, is that the tools that are normally used to measure gene and protein levels completely miss metabolites. So for his own work, he turned instead to mass spectrometry, leveraging its capabilities to glean the information he needed. "If you're looking at lots of small molecules, it's the best way to tell what's going on," he says.

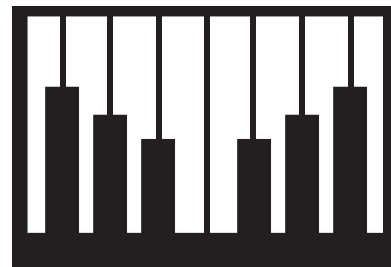
At Harvard, Saghatelian continued his research and expanded his focus to include bioactive peptides, such as hormones, to understand their regulation. Among the breakthroughs his technique produced was the discovery of a new metabolite that may have an impact on diabetes.

Despite this progress, in recent years, he had begun to feel the need for collaborations with biologists to take his research to the next level. "If I detect that a molecule is changing, I have



some ideas of what is important and what to do with it," he says. "But it's also really helpful to talk with somebody who has done this before and who can tell me which model to look at or refer me to people who can get me the best samples to analyze and tell me what I should be looking for."

Because his interests are much more in line with those of Salk scientists, and because Salk is structured without departments and silos, when the opportunity to move his lab to the Institute came up, Saghatelian jumped at the chance. "Salk offers a unique opportunity for me to integrate with some of the world's best biologists," he says. "I think it will push me to be a better biologist and push the research forward by showing the full scope of its power to make discoveries that can impact medicine." 📺



SALK & MUSIC SERIES

Science and Music Series hits the right notes

MUSIC-LOVING MEMBERS OF THE SALK COMMUNITY HAVE discovered a uniquely satisfying way to cap a weekend. Approximately one Sunday afternoon a month, they have been gathering in the Institute's de Hoffmann auditorium to enjoy musical masterpieces performed by emerging artists and learn about Salk discoveries straight from the stellar scientists responsible for them.

Since last October, the Science and Music Series has boasted sold-out performances ranging from classical to jazz, featuring winners of such prestigious international musical contests as the Arthur Rubenstein, Van Cliburn, Paganini and Fulbright Concerto competitions. Sharing the billing with these extraordinary musicians has been a Steinway concert grand piano, a generous gift from Conrad Prebys, and distinguished Salk scientists **Fred Gage**, **Ron Evans**, **Greg Lemke**, **Tom Albright** and **Marc Montminy**, who have spoken about their cutting-edge research. Most recently, on March 16, Karen Joy Davis joined award-winning violinist

Sean Lee in a program of works by Beethoven, Dvořák, Falla and Wieniawski. In addition to her musical talents, Davis is the executive producer of the Science and Music Series.

By all accounts, the unusual pairing is a big success. "The auditorium is so cozy that you feel as if you're getting a private performance," says Edward Shamieh, a retired engineer and frequent attendee. "Plus you get to learn a little about what's going on at the Salk Institute. It's a beautiful combination: music for the spirit and science for the mind."

The six-concert series concludes May 18, with Fei-Fei Dong, 2013 Cliburn Competition finalist. **Clodagh O'Shea**, associate professor in the Molecular and Cell Biology Laboratory, will discuss her work engineering novel virus-based cancer therapies.

For more information on the Salk Science and Music Series or to purchase tickets, visit the website www.salk.edu/music/ or phone 858.453.4100 x 2098. 📺

Yoonie Han

Joe Locke and Geoffrey Keezer






Teachers seize rare opportunity to tour Salk labs


FOR 32 TEACHERS WHO HAD TRAVELED to San Diego in January to attend the Murdock Trust Partners in Science conference, an invitation from Salk's Education Outreach department to tour several labs at the Institute was too good an opportunity to resist. After visiting the Next-Generation Sequencing Core, Stem Cell Core and

Plant Biology Laboratory, the group's consensus was that the tour was both informative and inspirational. In a follow-up letter, one teacher wrote, "I was left in awe after the visit. The ease with which [the researchers] conveyed the purpose and function of their respective areas of study in an understandable manner for novices

was exceptional." Introducing cutting-edge science to the community is the ongoing mission of the Education Outreach department. Supported by donor contributions, its programs play a key role in kindling a passion for scientific research. 



Save the date for SYMPHONY_{at} SALK 2014!

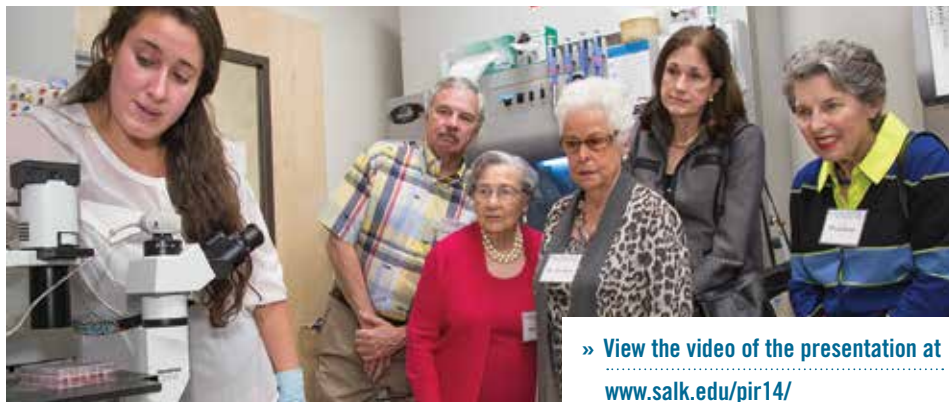
ON SATURDAY, AUGUST 23, THE INSTITUTE'S CENTRAL COURTYARD WILL ONCE AGAIN BE TRANSFORMED into an extraordinary open-air concert venue for the 19th annual Symphony at Salk. Beyond the spectacular setting, amid the Institute's landmark buildings and against a backdrop of the Pacific; beyond the glorious music featuring the renowned San Diego Symphony and a special guest artist; and beyond the gourmet meal catered by a celebrated chef, Symphony at Salk is truly greater than the sum of its parts. This one-of-a-kind event, which provides critical resources to support Salk's education outreach program and scientific research, sells out each year, so mark your calendar now so you don't miss out. And watch for updates in the next issue of *Inside Salk* and online at www.salk.edu/symphony/. 



© Françoise Gilot, 2013
Alchemy
36 1/4 x 28 3/4 inches
From the collection of F. Gilot


Talk, tour and lunch mark annual Partners in Research event

THE TOPIC WAS STEM CELLS—AND THE promise they hold—at the annual gathering of Salk's Partners in Research. **Cheryl Dean**, senior director of planned giving, welcomed the 42 guests to the Institute on February 13 and introduced them to **Leah Boyer**, associate director of Salk's Stem Cell Core facility. After explaining the differences between adult, embryonic and induced pluripotent stem cells, Boyer spoke about the facility's role in supporting research by Salk scientists. Boyer herself is currently supporting the development of a novel stem cell-based therapy for Parkinson's disease. Following the talk, the group toured the Stem



Cell Core facility, then enjoyed lunch hosted by the Institute.

Participation in exclusive behind-the-scenes tours is just one of the opportunities afforded Partners in Research. Other activities include special receptions, lectures and invitation-only

events that keep members abreast of the latest Salk discoveries. If you are interested in joining Partners in Research by including the Salk Institute in your estate planning, please contact Cheryl H. Dean, Esq. at 858.500.4884 or cdean@salk.edu. 

» [View the video of the presentation at www.salk.edu/pir14/](http://www.salk.edu/pir14/)

A fond farewell to a master interpreter of Salk's architecture

LOOKING BACK, IT WAS PERHAPS INEVITABLE THAT KENDALL MOWER would find his way to the Salk Institute. A retired architect who had traveled much of his life, Mower not only was a longtime fan of Louis Kahn, the architect of Salk's famed buildings, but often found himself retracing the steps, after a fashion, of various Salk luminaries. Whether he was designing buildings for the Baylor College of Medicine in Houston, where **Roger Guillemin** worked before coming to the Salk or, later on, creating pen and ink drawings for the La Jolla Historical Society, which helped support **Suzanne Bourgeois's** history of the Institute, his connections to Salk kept surfacing at various times in his life.

In 1997, when Mower retired, he and his wife, Kathryn, moved to La Jolla, setting the stage for over a decade of direct involvement. He began devoting significant time to volunteer work, and in 1998, after taking a tour of the Salk, he decided to become a tour guide there. With his architecture background and voluminous knowledge of Louis Kahn's contributions, Mower quickly became one of the Institute's most active and accomplished guides.

"I think I understood Jonas Salk's idea that the discoveries at Salk belong to humanity," he says. "And in much the same way, I believe that the buildings belong to humanity, and it's my job to educate and promote these fantastic buildings to the public."

Over the years, Mower introduced countless people to the Institute and its stunning architecture. Among the most memorable was Sue Kahn, Louis Kahn's daughter, who was especially interested in the details of the Salk buildings because at the time she was working on the Franklin D. Roosevelt Four Freedoms Park in New York's East River, which her father had designed. Another time, Michael Kimmelman, the *New York Times* architecture critic, requested a tour, and Mower led him and his son around the Institute on a Saturday.

Other noteworthy tour groups included the board of the Nestlé Corporation, when it held its annual meeting at Salk, and the members of the Brazilian legislature, who were interested in exploring the Institute to help inform the design of a medical research building the country was planning. Most recently, he took the artist Christo and an entourage of European visitors on a tour.



Kendall Mower


Mower is perhaps proudest of the role he played in connection with Salk's 50th anniversary celebration in 2010, leading the first and last tours.

"I felt very good that I was consulted about it," he says. "We had 5,000 people in a two-week period, and I helped suggest how to do it."

His affection for the Salk has also been manifest in his commitment to its library. Early on, he was very interested in raising money for the Salk library and donated many books related to the Institute's architecture. "They have almost every Kahn book in the library now," he says with pride.

After 16 productive and influential years at Salk, however, the world traveler is now moving on. Aware of the challenges accompanying advancing age, Mower and Kathryn are moving to Orange County to be closer to their daughters. Although he plans to stay in touch with his friends at Salk, he will no longer be within easy commuting distance and is reluctantly hanging up his docent's badge.

"I'll miss the extraordinary sense of place of the Institute, and learning about scientific discovery news because you are right in the middle of it," he says. "I'll miss the sheer beauty of Louis Kahn's design, and I'll also miss the people."

While it goes without saying that the Institute will miss Mower deeply as well, his legacy will endure in the passionate insights he shared with thousands of visitors about Jonas Salk, Louis Kahn and one of the world's architectural masterpieces. 

Salk Scientist Fred Gage named to National Academy of Inventors



FRED H. GAGE, PROFESSOR IN THE SALK INSTITUTE'S Laboratory of Genetics and holder of the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease, has been elected a Fellow of the National Academy of Inventors (NAI).


NAI Fellows, who must be nominated by their peers, are honored for having demonstrated “a prolific spirit of innovation in creating or facilitating outstanding inventions and innovations that have made a tangible impact on quality of life, economic development, and the welfare of society.” Fellows must be a named inventor on at least one patent issued by the United States Patent and Trademark Office and must be affiliated with a university, nonprofit research institute or other academic entity.

Gage’s research focuses on modeling diseases in the laboratory using human stem cells. Through reprogramming of human somatic cells from patients with neurologic and psychiatric disease, his work seeks to understand the progression and mechanisms that lead to neuronal and glial dysfunction. His lab also studies the genomic mosaicism that exists in the brain as a result of mobile elements that are active during neurogenesis. Specifically, Dr. Gage is interested in differences between individuals and how somatic-induced genomic mosaicism may lead to functional diversity.

Gage joins a number of accomplished innovators in the 2013 class who collectively hold more than 5,600 U.S. patents. Included are 26 presidents and senior leadership of research universities and non-profit research institutes, 69 members of the National Academies, five inductees

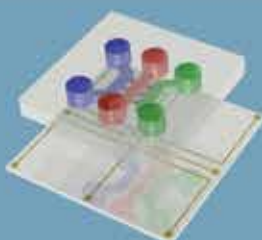
of the National Inventors Hall of Fame, six recipients of the U.S. National Medal of Technology and Innovation, two recipients of the U.S. National Medal of Science and nine Nobel laureates.

Gage will be inducted into the NAI by the deputy U.S. commissioner for patents during the Academy’s annual conference in Alexandria, Virginia, next March.

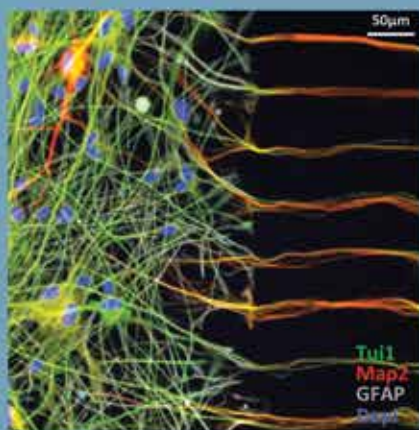
The National Academy of Inventors is a non-profit organization comprised of over 3,000 members spanning more than 200 institutions. It was founded in 2010 to recognize and encourage inventors holding patents issued by the U.S. Patent and Trademark Office, as well as to enhance the visibility of academic technology and innovation, encourage the disclosure of intellectual property, educate and mentor innovative students, and translate the inventions of its members to benefit society. The NAI edits the multidisciplinary journal *Technology and Innovation—Proceedings of the National Academy of Inventors*. 



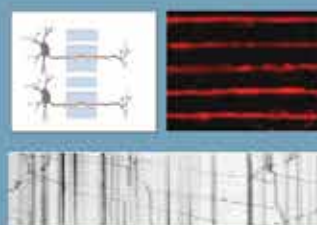
Microfluidic compartmentalized platform



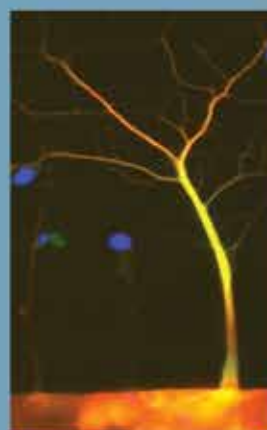
Microfluidic device embedded with MEA



H9 NPCs derived neurons
(8 months differentiation)



Mitochondrial dynamics



Adult hippocampal progenitors
(Dendrite arborization)

Salk Institute and Stanford University to lead new \$40 million stem cell genomics center

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES WILL JOIN STANFORD

University in leading a new Center of Excellence in Stem Cell Genomics, created through a \$40 million award by California's stem cell agency, the California Institute for Regenerative Medicine.

The Center will bring together experts and investigators from seven different major California institutions to focus on bridging the fields of genomics – the study of the complete genetic make-up of a cell or organism – with cutting-edge stem cell research.

The goal is to use these tools to gain a deeper understanding of the disease processes in cancer, diabetes, endocrine disorders, heart disease and mental health, and ultimately to find safer and more effective ways of using stem cells in medical research and therapy.

"The Center will provide a platform for collaboration, allowing California's stem cell scientists and genomics researchers to bridge these two fields," says **Joseph Ecker**, a Salk professor and Howard Hughes Medical Institute and Gordon and Betty Moore Foundation investigator. "The Center will generate critical genomics data that will be shared with scientists throughout California and the rest of the world."

Ecker, holder of the Salk International Council Chair in Genetics, is co-director of the new Center along with Michael Snyder, a professor and chair of genetics at Stanford.

The Center of Excellence consists of Stanford University and the Salk Institute for Biological studies as the joint principal investigators. U.C. San Diego, the Scripps Research Institute, the J. Craig Venter Institute and Illumina Inc., all in San Diego, and Howard Hughes Medical Institute will also collaborate on the project. U.C. Santa Cruz will run the Data Coordination and Management component.

"This Center of Excellence in Stem Cell Genomics shows why we are considered one of the global leaders in stem cell research," says Alan Trounson, president of the stem cell agency. "Bringing together this team, to do this kind of work means we will be better able to understand how stem cells change as they grow and become different kinds of cells. That deeper knowledge, that you can only get through a genomic analysis of the cells, will help us develop better ways of using these cells to come up with new treatments for deadly diseases."

In addition to outside collaborations, the Center will pursue some fundamental questions and goals of its own, including collecting and characterizing induced pluripotent stem cell lines from patients with familial cardiomyopathy; applying single-cell genomic techniques to better understand cellular subpopulations within diseased and healthy brain and pancreatic tissues; and developing novel computational tools to analyze networks underlying stem cell genome function.

The award includes \$19 million for the Center team to carry out independent and collaborative projects including investigating disease




Joseph Ecker

“The Center will provide a platform for collaboration, allowing California’s stem cell scientists and genomic researchers to bridge these two fields.”

– JOSEPH ECKER

mechanisms and the development of new technologies for this kind of work. The Data Coordination and Management program will enable the research to be shared with other investigators around California and the world.

In addition to the Center of Excellence, the stem cell agency's governing Board, the Independent Citizens Oversight Committee (ICOC), also approved more than \$27 million in funding for the Basic Biology V awards. These go to researchers trying to advance the field by tackling significant, unresolved issues in human stem cell biology.

Salk Professor **Ron Evans**, holder of Salk's March of Dimes Chair in Molecular and Developmental Biology and a Howard Hughes Medical Institute investigator, was among the recipients. He was awarded \$1,491,900 to investigate the role nuclear hormone receptors play in the generation of stem cells, with implications for understanding the growth of cells in cancer and the regeneration of tissues. 



Three Salk discoveries land on 2013 “best of the year” lists

As 2013 came to a close, three Salk Institute discoveries won national recognition by being named to prestigious scientific “best of the year” lists. *Science* magazine lauded the groundbreaking work manipulating stem cells in **Juan Carlos Izpisua Belmonte**’s lab, naming it a runner-up for 2013 Breakthrough of the Year. And team findings on the complexity of the human brain, research led by **Fred “Rusty” Gage** and **Joe Ecker**, earned the number four spot on a year-end list compiled by Tom Insel, director of the National Institute of Mental Health.

On a “ten best” list that included gene-editing, brain-imaging and sleep studies, the editors of *Science* praised researchers’ success in getting pluripotent stem cells to grow into tiny “organoids” in the lab. “It’s still a challenge to coax stem cells to grow into specific tissues, let alone into organized structures,” the magazine’s editors wrote. “This year, researchers did just that, in spectacular style, growing a variety of ‘organoids’ in the lab: liver buds, mini-kidneys, and, most remarkably, rudimentary human brains.”

At the Salk Institute, Izpisua Belmonte and his team were able to grow the “mini-kidneys,” an accomplishment reported earlier in *Nature Cell Biology*. Building on research that had indicated stem cells could be used to create precursors of kidney cells, the Salk team became the first to coax human stem cells into forming actual three-dimensional cellular structures similar to those found in human kidneys.

“Attempts to differentiate human stem cells into renal cells have had limited success,” said Izpisua Belmonte, a professor in Salk’s Gene Expression Laboratory and holder of the Roger Guillemin Chair. “We have developed a simple and efficient method that allows for the differentiation of human stem cells into well-organized 3D structures of the ureteric bud, which later develops into the collecting duct system.”

In an initial testing of their protocol, Izpisua Belmonte’s team used induced pluripotent stem cells (iPSCs) collected from a patient with a genetic disorder known as polycystic kidney disease (PKD) and found that they were able to produce kidney structures from the patient-derived iPSCs. The team’s accomplishment holds great promise for treating kidney disease, since these organs rarely recover function once they are damaged.

For the year-end list compiled by NIH’s Tom Insel, Salk scientists Fred Gage and Joe Ecker were lauded for their work revealing new complexities in the human brain in two separate papers published in *Science*.

“2013 will be the year when we begin to realize how much the brain differs from other organs,” Insel wrote. “We already knew that cells in the brain express (translate into protein) more of the genome and use more energy than any other organ. But two discoveries this year really made the case for the human brain as not only the most mysterious but the most exceptional of organs.”

One discovery came from the lab of Fred Gage, professor in the Laboratory of Genetics and holder of the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease. Using single-cell sequencing, Gage and his colleagues showed that the genomic structures of individual neurons differ from each other even more than expected. The scientists took a high-level view of the entire genome, looking for large deletions and duplications of DNA called copy number variations (CNVs). What they discovered was that as many as 41 percent of the cells in the frontal cortex have at least one mutation, with a million DNA bases either duplicated or deleted.

“These are mutations not seen in blood cells (which are the basis for all psychiatric genetic studies),” Insel wrote, “or in neurons elsewhere in the brain.”

A discovery by Joe Ecker, professor and director of Salk’s Genomic Analysis Laboratory and holder of the Salk International Council Chair in Genetics, added to the unfolding appreciation of the brain’s complexity. When the discovery was first published, NIH director Francis Collins described it as revealing “an entirely new perspective on a fundamental issue in biology or medicine.”

Working with Salk professor **Terry Sejnowski**, holder of Salk’s Francis Crick Chair, Ecker and his team showed that the landscape of DNA methylation, a particular type of epigenomic modification, is highly dynamic in brain cells during the transition from birth to adulthood, helping to understand how information in the genomes of cells in the brain is controlled from fetal development to adulthood.

“The entire DNA strand consists of only four bases: cytosine, guanine, adenine and thymine,” Insel wrote in his year-end roundup. “Whereas in most cells in the body silencing occurs where cytosine and guanine are adjacent, brain cells follow a different set of rules with all the base pairs involved. This means that the mechanisms by which experience influence biology are completely different in brain cells compared to blood cells or liver cells.”

Underscoring the value of the research performed by the two Salk teams, Insel concluded, “The lesson is that we cannot use peripheral cells to know what is happening in the brain.”



From left: Ahmet Denli, Carol Marchetto, Iñigo Narvaiza and Fred Gage

Induced pluripotent stem cells reveal differences between humans and great apes

SCIENTISTS REGULARLY USE INDUCED PLURIPOTENT STEM CELLS (iPSCs) to model diseases using cells that would be otherwise difficult to obtain from a living person or animal. By adding a combination of four key factors, a skin cell can be made into an iPSC, which can then be coaxed into forming liver, lung and brain cells in a culture dish.

It's now also possible to compare iPSCs from humans to those of our closest living relatives—great apes. Recently, scientists working in the lab of **Fred Gage**, who holds the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease, took chimpanzee and bonobo skin cells and for the first time turned them into iPSCs.


“Comparing human, chimpanzee and bonobo cells can give us clues to understand biological processes, such as infection, diseases, brain evolution, adaptation or genetic diversity,” says senior research associate **Iñigo Narvaiza**, who led the study with senior staff scientist **Carol Marchetto** and senior research associate **Ahmet Denli**.

In the study, published in *Nature*, the team found disparities in the regulation of jumping genes, or transposons—DNA elements that can copy and paste themselves into spots throughout the genome—between humans and non-human primate cells. Jumping genes provide a means to

rapidly shuffle DNA and might be shaping the evolution of our genomes, the researchers say.

The group identified genes that are differentially expressed between iPSCs from humans and both chimpanzees and bonobos. To their surprise, two of those genes code for proteins that restrict a jumping gene called L1, which along with a handful of other jumping genes is abundant throughout our genomes. Compared with non-human primate cells, human iPSCs expressed higher levels of these restrictors.

Using L1 tagged with a fluorescent marker, the scientists found, as expected, that an excess of the two proteins dampened the mobility and reduced the appearance of newly inserted DNA in the non-human primate cells. These results suggested that L1 elements insert themselves less often throughout our genomes. Indeed, looking at genomes of humans and chimpanzees that had already been sequenced, they found that the primates had more copies of L1 sequences than did humans.

The new study provides proof of concept that iPSC technology can be used to understand some of the evolutionary differences between humans and non-human primates. 



Salk scientists identify factors that trigger ALT-ernative cancer cell growth

UNREGULATED GROWTH IN CANCER IS DUE IN LARGE PART TO THE fact that tumor cells can rebuild the protective ends of their chromosomes. Normally, cell division halts once these structures, called telomeres, wear down. But cancer cells keep on going by deploying one of two strategies to reconstruct telomeres.

One strategy, which occurs in about 90% of cancers, requires increased production of a telomere-elongating enzyme called telomerase. A less understood strategy, employed by the remaining 10–15% of cancers, is called ALT (for Alternative Lengthening of Telomeres). Biologists knew ALT existed simply because tumor cells could rebuild long, albeit unkempt-looking, telomeres without telomerase, but how they did it remained a mystery.

Recently, scientists in the laboratory of **Jan Karlseder**, holder of the Donald and Darlene Shiley Chair, reported in *Nature Structural and Molecular Biology* the first experimental induction of an ALT telomere-building program in human cells.


“People have been targeting telomerase as a potential cancer therapy for a long time,” Karlseder says. “But mouse studies show that when you suppress telomerase, cells can upregulate ALT. That makes it absolutely critical to develop ways to block ALT.”

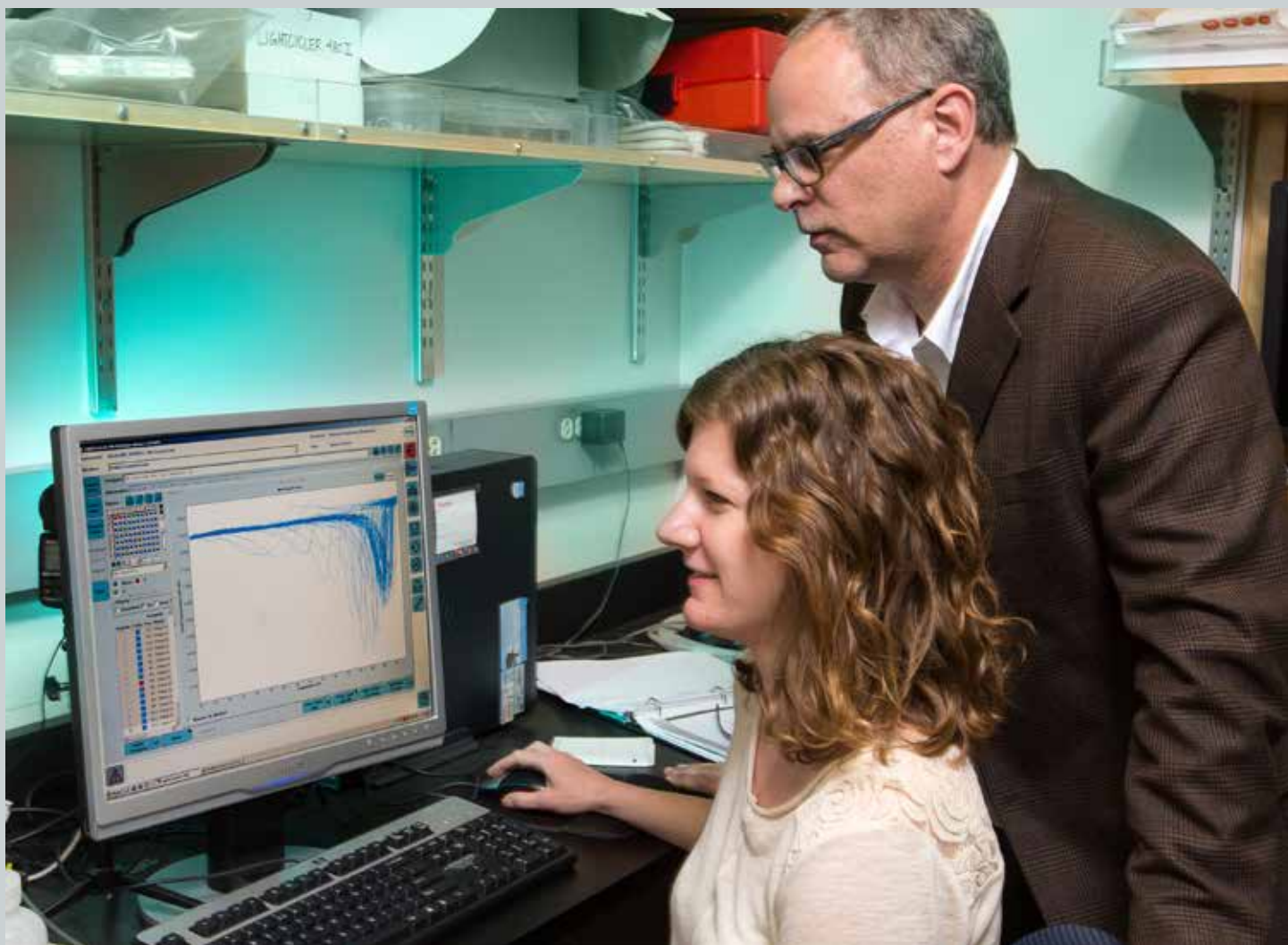
To learn how cells switch on ALT, the group eliminated two proteins, ASF1a and ASF1b, in normal lung cells and in a cancer cell line that relies on telomerase for immortality. They found that ASF1-depleted cancer cells switched off telomerase but continued to thrive, meaning that tumor cells can exploit either strategy for elongating telomeres.

Most significantly, microscopy showed that nuclei of the depleted cells contained aggregates of telomeric DNA, known as PML bodies, which are a hallmark of ALT-dependent cancers.

“Massive PML body formation in normal cells was unexpected,” says **Roddy O’Sullivan**, a postdoctoral fellow in the Karlseder lab. “It was our first clue that ASF1 loss induces ALT.”

The team also found that ASF1 loss initiated an intra-nuclear ping pong game: cells replicated an embedded fluorescent tag, then tossed it back and forth between different chromosomes, building disorganized but serviceable telomeres.

“In mammalian cells we have only been able to study ALT in cells derived from ALT-dependent tumors,” adds Karlseder. “Now that we have a controlled way to induce the pathway, we can test any gene that might act as an inhibitor.” 



Suzanne Thomas and Joseph Noel

Missing molecule in chemical production line discovered

IT TAKES DOZENS OF CHEMICAL REACTIONS for a cell to make isoprenoids, a diverse class of molecules found in every type of living organism. Cholesterol, for example, is a large isoprenoid chemical. So is the molecule that gives oranges their citrusy smell and taste.

Now a team led by **Joseph Noel**, holder of the Arthur and Julie Woodrow Chair, has discovered a missing step in the chain of reactions that some cells use to produce isoprenoids. The findings, published in *eLife*, have immediate implications for how isoprenoids are produced for commercial use.

All larger isoprenoids are derived from a common building block molecule called IPP, which can be made through two chemical pathways. Animal cells use the mevalonate pathway to make IPP; many bacterial cells use a

pathway dubbed DXP; and plant cells use both. But scientists have struggled to understand how some bacteria produce IPP. While many of these organisms lack proteins key to the DXP pathway, they're also missing the proteins that perform two final steps of the mevalonate pathway. Normally, these steps involve first adding phosphate to the intermediate molecule and then removing an atom of carbon.

In 2006, a team of scientists discovered that some bacteria had an enzyme called IPK, which could add phosphate to the precursor molecule only if the carbon had already been removed, suggesting that these two steps of the pathway could be reversed. But a protein that could remove the carbon—called a decarboxylase—hadn't been found.

Noel and his group used bioinformatics to find all organisms with the IPK enzyme, suspecting that these would all also have the decarboxylase they were looking for, and the approach worked. In an unusual type of bacteria that live in hot springs, he and his colleagues pinpointed a decarboxylase that works in conjunction with IPK. First it removes carbon, and then IPK adds a phosphate—the process, reversing the last two steps of the classic mevalonate pathway, still ends in IPP.

For companies that produce isoprenoids—as a source of drugs, scents and flavor molecules—the discovery provides a new potential chemical pathway with which to make their products. 🏭



Ursula Bellugi



Connecting the dots between genes and human behavior


ESTABLISHING LINKS BETWEEN GENES, THE BRAIN AND HUMAN behavior is a central issue in cognitive neuroscience research, but studying how genes influence cognitive abilities and behavior as the brain develops from childhood to adulthood has proven difficult. Recently, by studying individuals with a rare disorder known as Williams syndrome, an international team of scientists made inroads to understanding how genes influence brain structure and cognitive abilities and how neural circuits produce language.

Williams syndrome is caused by the deletion of one of the two usual copies of approximately 25 genes from chromosome 7, resulting in mental impairment; nearly everyone with the condition is missing these same genes. The condition affects approximately 1 in 10,000 people around the world, including an estimated 20,000 to 30,000 in the United States.

Although those with Williams experience developmental delays and learning disabilities, they are exceptionally sociable and possess remarkable verbal and facial recognition abilities. **Ursula Bellugi**, professor and director of Salk's Laboratory for Cognitive Neuroscience, has spent much of her career studying those with Williams syndrome and was integrally involved in the recent project, which was led by Debra Mills of Bangor

University in Wales; **Julie Korenberg**, a University of Utah professor and an adjunct professor at Salk, led the genetics aspects of the study.

Using highly sensitive sensors to measure brain activity, the researchers presented study participants with both visual and auditory stimuli in the form of unfamiliar faces and spoken sentences. They charted the small changes in voltage generated by the areas of the brain responding to these stimuli. While it had previously been believed that in individuals with Williams, the ventral portion of the brain operated normally, the team discovered that this area of the brain also processed information differently than it did in those without the syndrome and did so throughout development, from childhood to adulthood. This suggests that the brain was compensating in order to analyze information, exhibiting plasticity. The team also showed that Williams is due not to a single gene but to distinct subsets of genes, hinting that the syndrome is more complex than originally thought.

The results of this study, which was published in *Developmental Neuropsychology*, not only advance science's understanding of the links between genes, the brain and behavior, but may lead to new insight into such disorders as autism, Down syndrome and schizophrenia. 

Generating “mini-kidney” structures from human stem cells may lead to much-needed therapies for kidney disease

DISEASES AFFECTING THE KIDNEYS

represent a major and unsolved health issue worldwide. The kidneys rarely recover function once they are damaged by disease, highlighting the urgent need for better knowledge of kidney development and physiology.


Researchers led by **Juan Carlos Izpisua Belmonte**, who holds the Roger Guillemin Chair, have now developed a novel platform to study kidney diseases. For the first time, they have generated three-dimensional kidney structures from human stem cells, opening new avenues for studying the development and diseases of the kidneys and for discovering new drugs that target human kidney cells to help restore kidney function. The findings were reported in *Nature Cell Biology*.

Scientists had created precursors of kidney cells using stem cells as recently as last summer, but Izpisua Belmonte's team was the first to coax human stem cells into forming

three-dimensional cellular structures similar to those found in kidneys. Their findings demonstrate for the first time that pluripotent stem cells (PSCs)—cells capable of differentiating into the many cells and tissue types that make up the body—can be made to develop into cells similar to those found in the ureteric bud, an early developmental structure of the kidneys, and then can be further differentiated into three-dimensional structures in organ cultures. The scientists accomplished this with both human embryonic stem cells and induced pluripotent stem cells (iPSCs), human cells from the skin that have been reprogrammed into their pluripotent state.

After generating iPSCs that demonstrated pluripotent properties and were able to differentiate into mesoderm, a germ cell layer from which the kidneys develop, the researchers made use of growth factors known to be essential during the natural development of kidneys to culture both iPSCs and embryonic stem cells.

This was sufficient to commit the cells toward progenitors that exhibited clear characteristics of renal cells in only four days.

Izpisua Belmonte's team also tested their protocol on iPSCs from a patient clinically diagnosed with polycystic kidney disease (PKD), a genetic disorder characterized by multiple, fluid-filled cysts that can lead to decreased kidney function and kidney failure. They found their methodology could produce kidney structures from patient-derived iPSCs. Because of the many clinical manifestations of the disease, neither gene- nor antibody-based therapies are realistic approaches for treating PKD. Izpisua Belmonte's technique might help circumvent this obstacle and provide a reliable platform for pharmaceutical companies and investigators studying drug-based therapeutics for PKD and other kidney conditions. 

Engineering super-powered proteins for disease therapy

ENHANCED PROTEINS EQUIPPED WITH STABLE ARTIFICIAL AMINO acids, recently developed by Salk associate professor **Lei Wang**, are proving to be promising candidates for future therapeutic use, particularly in cancer.

Protein-based therapy could, in theory, directly target a variety of diseases and be less toxic than other drugs. However, attempts to engineer proteins with therapeutic characteristics by genetically integrating artificial amino acids have often failed, until recently.


“We can provide novel insights into mechanisms of some types of cancers and aim to eventually develop a really useful biologically based drug,” says Wang, who is also the Frederick B. Rentschler Developmental Chair. “And we can certainly expand this new platform technology into multiple other areas, such as neurodegenerative diseases, immunology, stroke treatment and more.”

Wang first outlined the breakthrough technology last summer, when he announced the development of an artificial amino acid that was able to genetically assimilate into a protein and provide strong bonds within the protein. The challenge was to develop an amino acid not too chemically active (and thereby likely to destroy the cell), but reactive enough to provide a new ability once in the protein.

The artificial amino acid Wang and his collaborators created—dubbed Ffact—meets this balance by forming an irreversible bond when near the naturally occurring Cys amino acid. This controlled bonding (called “proximity-enabled protein crosslinking,” or PEPC) is like a staple, letting researchers bind and shape proteins that can, for example, target cellular proteins thought to go astray in some cancers. Since Ffact, Wang and his lab have created about a dozen similarly effective amino acids for wielding fine control over the shape of the protein. He is aiming to build a library of about 50 for varied therapeutic tests.

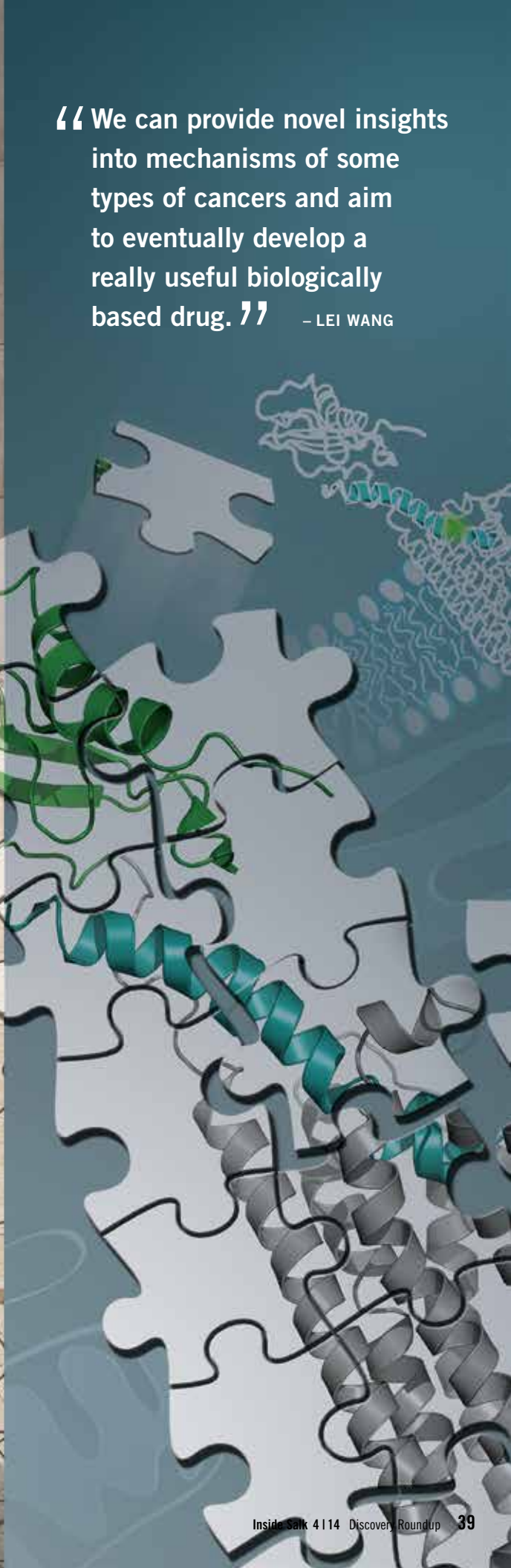
These PEPC-capable amino acids promise to advance protein therapies in two important ways: by providing proteins with the ability to interact with other proteins and by beefing up their stability.

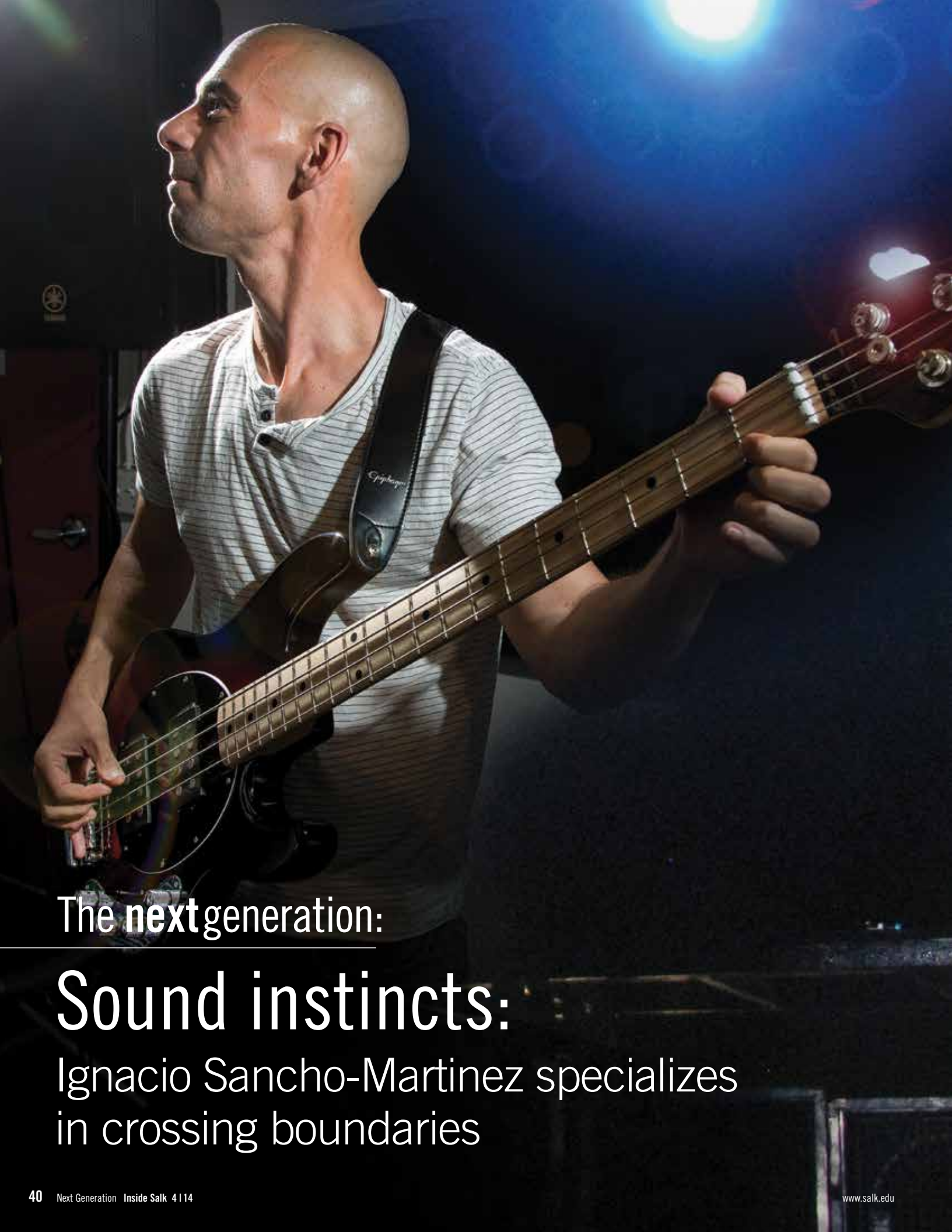
“What we’re doing is totally different from the traditional way of thinking,” says Wang. “Previously, artificial amino acids were used as a probe or handle for tracking proteins. But now we are making the protein interact with native proteins as well as making itself stronger.”

Now armed with the new amino acids, Wang’s lab is configuring proteins to target and interact with pathways involved in cancer—most particularly, pathways that halt the cell’s self-destruct sequence (apoptosis), leading to cancer’s unchecked and deadly proliferation. The lab is currently focusing on types of proteins known to be involved in cancer’s inhibition of apoptosis, such as p53, STAT and caspases. Wang says the results have been very interesting so far, and he looks forward to sharing them in the coming year. 



“We can provide novel insights into mechanisms of some types of cancers and aim to eventually develop a really useful biologically based drug.” – LEI WANG





The **next** generation:

Sound instincts:

Ignacio Sancho-Martinez specializes
in crossing boundaries

THE ACCOMPANYING MUSIC DOESN'T SATISFY. THE drummer's role on the computerized recording is too repetitive. Boring. So **Ignacio Sancho-Martinez** ups the tempo, adding his own fills, changing the rhythm. Now it's more syncopated. Unpredictable. "I follow my instincts," he says. "I play what I feel."

It's that willingness to explore novel paths that's characterized how the Salk postdoctoral researcher has pursued his scientific career. Straddling disciplines and cultures, his ever-curious mind draws connections where none were noticed.

A native of Spain, Sancho-Martinez holds degrees in several fields. He graduated from the University of Oviedo with a bachelor's in biology and a master's in genetics and biotechnology before moving to the German Cancer Research Center in Heidelberg. There he studied the migration of cancer cells, especially glioblastoma, eventually identifying a new signaling pathway of this deadly cancer. His team's findings are currently being used by a biotech company in clinical trials. Eager to expand his sphere of knowledge, he went on to earn a doctorate in mathematics and natural sciences, then moved to the United States and the Salk Institute in 2010.

Having lived and worked in three different countries with three distinct cultures suits Sancho-Martinez just fine; he feels that changing boundaries can change your outlook. "As scientists," he says, "we tend to focus on the research and data within our own fields. But if you look around and explore other fields, you make novel discoveries."

"It was when I was working with glioblastoma in Germany that I decided I needed to go back to the basics," he continues. "If I am really focused on oncology, I told myself, I need to understand how cancer cells work, how stem cells work. That's what led me to the Salk."

Now in the Gene Expression Laboratory, headed by **Juan Carlos Izpisua Belmonte**, he challenges himself with a variety of projects, each equally attractive to his agile mind. "One of my favorites involves the endogenous regenerative response—the way the body regenerates damaged organs—especially as it relates to the mammalian heart."

Without skipping a beat, he adds, "And another project, the one that has probably always been in the back of my mind is utilizing reprogramming approaches to cancer cells, the idea of dedifferentiation, which is the regression of a cell to a more embryonic, non-specialized form. There are so many questions to be answered."

As he ponders the as-yet-unknowns, he grows more animated: "How do you regulate gene expression? How can you do it without iPSCs [induced pluripotent stem cells]? How do you get cells to revert to an intermediate state? The reversibility of cancer cells is very exciting."

Sancho-Martinez credits Izpisua Belmonte with creating a lab atmosphere conducive to this kind of intellectual roaming. "I like to wander around and see what other people are doing," he says. "It's not like that at every facility, you know. The Salk is very collaborative. Do you know how amazing it is that I can walk into a completely different lab and talk to the professor about what he or she is doing? They can tell you things that you never thought about. That takes you out of the box. That opens up possibilities, opens up the mind."



“I like to wander around and see what other people are doing. It's not like that at every facility, you know. The Salk is very collaborative.”

– IGNACIO SANCHO-MARTINEZ





» [View video of Sancho-Martinez discussing his research:](http://www.salk.edu/martinez/)
www.salk.edu/martinez/

Izpisua Belmonte is more than happy to encourage Sancho-Martinez's curiosity. "He is an exceptional scientist and extremely bright," he says. "He consistently brings new and fresh ideas to our team. And he is unmatched in his passion and dedication to science."

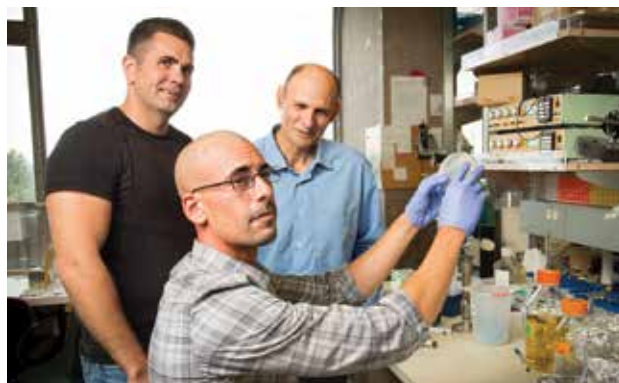
That restless mind keeps him exploring outside the lab, too, continually seeking new areas of study and making new connections. Take music, for instance.

He and some friends started a band in Spain when he was about 17, even though none of them knew how to play. Each simply chose an instrument, and Sancho-Martinez ended up with the bass guitar. Together they began playing hard rock, and while it was a lot of fun, they mostly got paid in beer. When Sancho-Martinez moved to Germany, he decided to get serious about his music and began taking lessons. "I wanted to play classic rock, like Led Zeppelin or AC/DC," he says. "But one day my instructor put on some music that was like nothing I'd ever heard. 'What is that?' I asked. 'It's jazz/fusion,' he said. And that opened up a whole new passion for me. Now I really like jazz, especially from the '50s. John Coltrane is a favorite."

But jazz is just one genre, and the guitar is just one instrument. There are so many other avenues to explore, including his current interest: drums. "This is a completely new world for me because it's basically about a feeling, just going with the music and then adding your own riffs and beats," he says. "I'm teaching myself because there's so much instructional software out there, and then I let myself improvise, just follow the groove."

Electronic drums and headphones allow him to practice without disturbing his neighbors, but the sessions are so stimulating that he won't allow himself to play the drums at night; he saves that for the morning. "I'm a big coffee drinker," he says, "so I brew some espresso, and then I sit down and drum for about 15 minutes. It's really a great way to start the day. Then I shower and head to work."

It's a routine he loves. "I don't see my work as a job. It's good to get paid, of course, but there's a duality to it. You follow your instincts, you go down the path because you're curious. Where is my research going to lead me next? You're just always exploring." 🎧



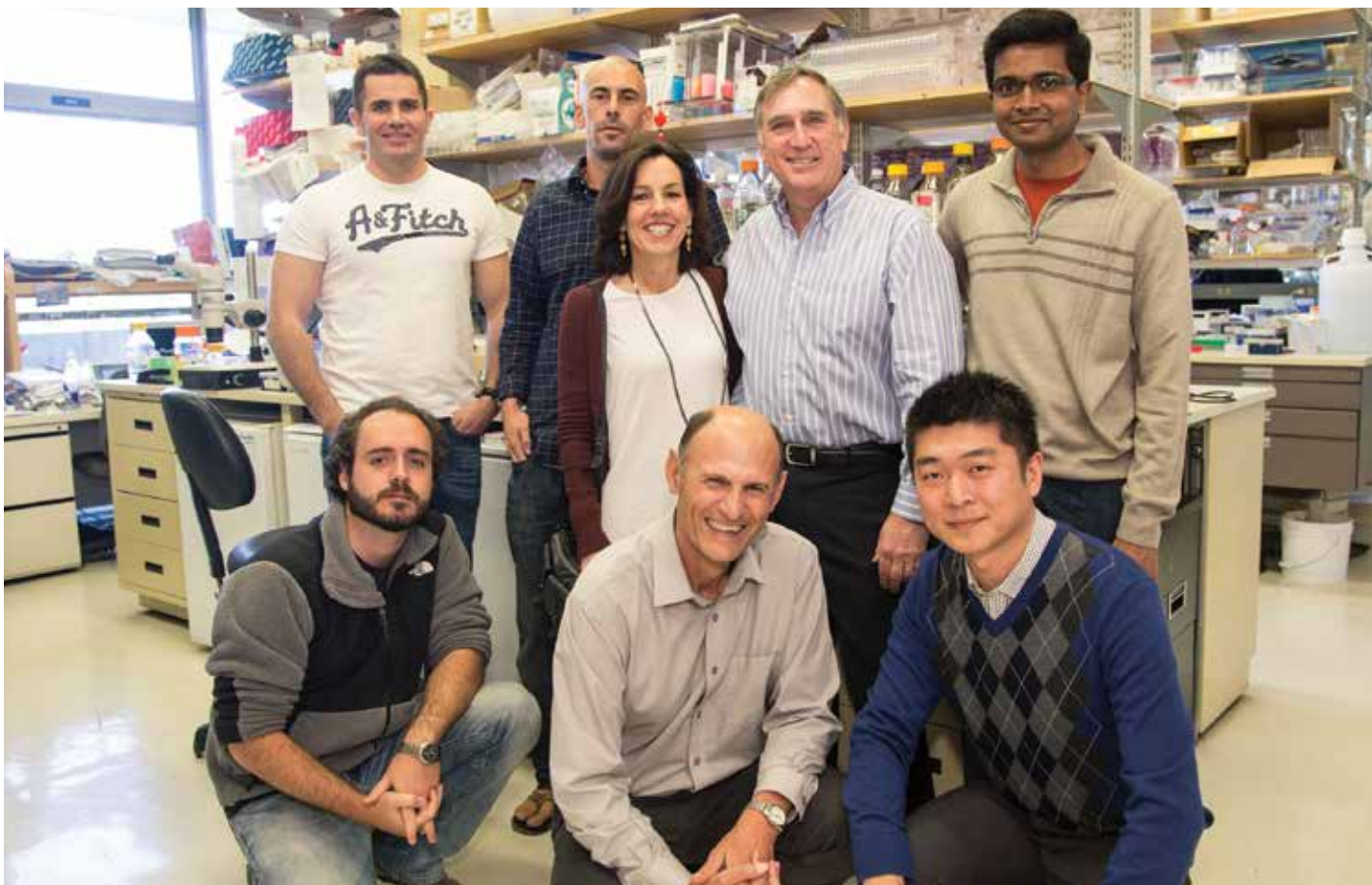
From left: Emmanuel Nivet and Juan Carlos Izpisua Belmonte. Seated: Ignacio Sancho-Martinez

“He consistently brings new and fresh ideas to our team. And he is unmatched in his passion and dedication to science.”

– JUAN CARLOS IZPISUA BELMONTE



Dayle Iverson, CEO of the James B. Pendleton Charitable Trust, visited the Salk Institute in November of last year to get an update on the Institute's HIV/AIDS research and see the MicroTime 200 microscope that the Trust partially funded. Iverson (right) stands with a group of Salk faculty, **Ye Zheng**, **Janelle Ayres**, **Björn Lillemeier** and **John Young** (left to right), in front of the plaque that acknowledges the Trust and the Nomis Foundation for funding the microscopy room.



In January, Rick and Joy Handelman (center), from the G. Harold and Leila Y. Mathers Charitable Foundation, toured the laboratory of Salk Professor **Juan Carlos Izpisua Belmonte** (center front), whose research the foundation supports.



Susan and Jim Blair

DEFEATING CANCER, ONE GIFT AT A TIME

AS A VENTURE CAPITALIST SPECIALIZING IN THE LIFE SCIENCES, Jim Blair has been involved in the creation of more than 40 biotech companies over the past 35 years. So when he and his wife, Susan, began to support the Salk Institute in 2010, it was something of a homecoming. Through his work, Jim was already acquainted with a number of Salk scientists, including **Ron Evans** and **Inder Verma**, and he and Susan knew Salk president **William R. Brody** and his wife, Wendy, socially.

But it was more than friendship and respect for Salk science that inspired the Blairs to start contributing to the Institute: it was the opportunity to help advance pioneering cancer research. The couple have had their share of cancer and cancer scares in the family, so for them, cancer is personal.


"Susan and I want to support things where we can make a real difference in changing the course of the disease," says Jim. "We don't want to act as if there's nothing we can do about it. We can do something about it, and we feel excited when we see progress being made."

As a longtime follower of the biomedical field, Blair is delighted to see that progress unfolding before his eyes.

"What I think is most exciting is the type of science we are able to do today compared to 10 or 12 years ago," he says. "We're learning how cancer starts and evolves and how to treat it much more effectively, in large part because of our understanding at the molecular level. That's the basis of the research going on with people like Ron and others at the Salk, and it's fantastic."

Beyond Salk, the Blairs also support some of the sister institutions on the Torrey Pines Mesa because they feel the scientific contributions are complementary and very important. "It's a responsibility if you live in this community to support these institutions," Jim explains. "We believe it makes a difference, plus federal sources are very interested in the degree to which the community stands behind the institutions as well."

At Salk, the Blairs hope their commitment will help ensure the continuation of the leading-edge research that takes place there.

"Contributions to the Salk work," Jim says. "They're truly making a difference. We're not investing in hope. We're investing in results and in a team that's proven it has the ability to get tangible results." 

Salk Science Leads to Discoveries.

IMPACTING HUMAN HEALTH BEGINS AT THE SALK.

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

Get Involved

FRIENDS OF SALK

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

SALKEXCELLERATORS

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

PRESIDENT'S CLUB

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

CHAIRMAN'S CIRCLE

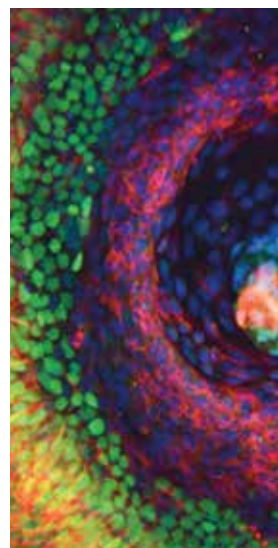
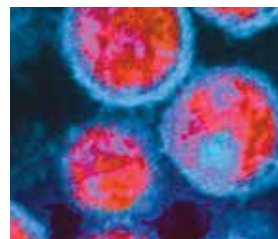
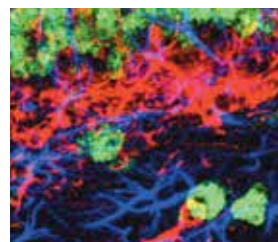
Chairman's Circle visionary donors support the Institute's mission with unrestricted annual gifts of \$25,000 and above. Their generous support fills a vital need for the Institute by providing the world's finest minds in science with the resources to pursue discoveries at the frontier of human knowledge.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

SPECIAL PROJECTS

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

PARTNERS IN RESEARCH

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





Insider's View

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

President, Salk Institute

Irwin M. Jacobs Presidential Chair

The War on Cancer

IN 1971, PRESIDENT NIXON SIGNED THE NATIONAL CANCER Act, a milestone considered the beginning of the “war on cancer” in the United States. One side effect of his declaration of war was making the National Cancer Institute, already well established as one of the institutes in the National Institutes of Health, more independent and providing a burst of funding to accelerate the scientific search for new treatments and cures.

Now, more than 40 years later, when we see cancer deaths rising in the United States and worldwide, people conclude that we are losing the war on cancer. While the added funding and focus on cancer research was a positive outcome of Nixon's declaration, other aspects have created a public relations challenge for people studying cancer and treating cancer patients. In hopes of spreading some light on the diseases we call cancer, I would like to offer the following observations. Of course, in a few paragraphs, I cannot do justice to the discussion, let alone compete with the fabulous book *The Emperor of All Maladies* by Siddhartha Mukherjee, which provides a fascinating overview of cancer that is quite readable by non-specialists.

1. Cancer is many diseases, not one disease. Even breast cancer or lung cancer, two common diseases, actually exist as hundreds, if not thousands, of distinct types of tumors, each with its own unique physical characteristics, genetic mutations, hormonal sensitivity, response to radiation therapy, propensity to spread, lethality and the like. Hence we should not lump the thousands of different tumors into one category called “cancer.”
2. We now have a high success rate against some cancers through early detection and treatment. When I was in medical school, Hodgkin's disease and childhood leukemia were usually fatal diseases. Now a significant fraction of patients with these can-

cers, as well as others, can be successfully treated and regain a normal life. Nearly every week, new insights into the biology of cancer lead to amazing new treatments.

3. Patients speak of being “cancer survivors” with good reason—few diseases, including cancer, are cured by modern medical science, but many diseases can be treated so successfully that life expectancy and quality of life return to near normal.
4. With increased information comes more patient-specific treatments for cancer. A relative of a colleague was recently diagnosed with breast cancer. The biopsy showed a specific type of breast cancer, and further analysis showed that the woman's tumor did not have any of the three known receptors for which selective chemotherapy can be highly effective. The next step is to sequence the genome of the tumor to determine whether there are specific mutations that are responsive to another set of chemotherapy drugs.
5. The old saw “an ounce of prevention is worth a pound of cure” is exemplified by the relatively recent introduction of a vaccine by Merck, Gardasil, that effectively immunizes young women against the human papilloma virus, which was found to cause about 70 percent of cases of cervical cancer. Recent studies using immunotherapy for cancer have had amazing successes as well.

The message of cancer in the 21st century is that continuing discoveries coming out of the labs at places like the Salk Institute are shedding light on what goes awry in tumors and what specific drugs may be effective at destroying or at least stopping the growth of that cancer. Given the genetic map of the tumor and information about other specific “markers,” we are literally developing smart bombs that can selectively target the aberrant cells.



SALK INSTITUTE FOR BIOLOGICAL STUDIES

10010 N Torrey Pines Rd
La Jolla, California 92037-1002

Telephone: 858.453.4100
Fax: 858.552.8285

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

There are many ways to support Salk. For detailed information on opportunities, please email giving@salk.edu or call 858.550.0472

Salk Calendar

APRIL

12 Second Annual Step into Discovery

MAY

14-16 42nd Annual Tax Seminar
for Private Foundations

18 Science & Music Series

21 San Diego Salkexcellerators

JUNE

26 Salk Alumni Mixer

JULY

23 Salk Women & Science

AUGUST

23 Symphony at Salk

© Françoise Gilot, 2013
Alchemy
36 1/4 x 28 3/4 inches
From the collection of F. Gilot



Follow us on:



facebook.com/salkinstitute



twitter.com/salkinstitute

