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## WHERE CURES BEGIN.

## insideSalk

## **BEYOND DNA:**

UNLOCKING THE SECRETS OF THE EPIGENOME



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## ON THE COVER:

A layer of regulatory information on top of our genome—called the epigenome is proving to be as important as genes for the health of our bodies and minds.

Courtesy of Scot Nicholls

## **PRESIDENT'S LETTER**

## Dear Friends,

Recently, we honored the 100th anniversary of the birth of the late Francis Crick, who spent the second chapter of his scientific life at the Salk Institute. As you will no doubt recall, Crick, who was born on June 8, 1916, shared the Nobel Prize in Physiology or Medicine with James Watson and Maurice Wilkins for describing the double-helical structure of DNA. Crick later joined the Salk Institute and turned his attention to understanding the brain, another monumental challenge. Their discovery provided access to the operating manual for all living things including our human bodies. Even now, more than 60 years later, the workings of DNA continue to puzzle and surprise scientists.

In this issue of *Inside Salk*, we take a look at the epigenome, a layer of information that coats the genome and modifies its functions, often altering the way cells implement DNA's instructions. Scientists are finding that the epigenome plays critical roles in health and disease and that it can change in surprising ways throughout a person's lifetime; it can even be passed down to the next generation. This is a tantalizing frontier for science.

Another exciting frontier explored in this issue's Observations interview with Salk professor Ye Zheng is immune system research—and the possibility that our immune system might be leveraged to fight a much broader range of diseases than previously thought possible. Zheng and other Salk scientists are at the cutting edge of exploring how to mobilize the immune system to fight cancers, metabolic disorders and even prevent neurodegenerative diseases such as Alzheimer's.

On a somber note, we also honor in this issue the lives of John Codey and Conrad Prebys, visionary supporters of scientific research and great friends to the Salk Institute, both of whom recently passed away. As a trustee of the Helmsley Charitable Trust, Codey, along with his fellow trustees and the staff of the Trust, made extraordinary gifts to support Salk science over the past decade, including \$42 million to launch the Institute's Helmsley Center for Genomic Medicine. Prebys gave \$25 million to Salk's unrestricted endowment, which funds basic research. In honor of that gift, the single largest to the Institute's endowment, the Salk Institute auditorium was named the Conrad T. Prebys Auditorium. Codey's and Prebys' ardent enthusiasm for Salk and the power of science to change lives led to numerous discoveries, some of them currently being tested in clinical trials. They are highlighted here in the Discoveries section.

Sincerely,

Ezamogra

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



"Scientists are finding that the epigenome plays critical roles in health and disease."





## CANCER

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



## GENETICS

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



## MICROBIOME

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



### METABOLISM

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



## NEUROSCIENCE

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



## PLANT BIOLOGY

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



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



METABOLISM

## FINDING THE "SECRET SAUCE"

for personalized, functional insulin-producing cells

Researchers uncover molecular switch to make effective sugarresponsive, insulin-releasing cells in a dish, offering hope for diabetes therapy.

For more than a decade, scientists across the globe strived to replace failing pancreatic beta cells linked to immune destruction in children (type 1 diabetes) or obesity-associated diabetes in adults (type 2 diabetes). Although cells made in a dish were able to produce insulin, they were sluggish or simply unable to respond to glucose.

"We found the missing energy switch needed to produce robust and functional human beta cells, potentially turning this discovery into a viable treatment for human diabetes," says Ronald Evans, co-senior author and director of the Gene Expression Laboratory at Salk. The new work was published in *Cell Metabolism* on April 12, 2016.

The Salk technology begins with induced pluripotent stem cells (iPSCs), a technique where tissue from a patient is reprogrammed into other types of cells, such as from the pancreas. This step yields the pre-beta cells, which produce insulin but are not yet functional. While several research groups reached this juncture, the road forward to functional cells was not clear.

"Pancreatic beta cells must be able to do two things to work effectively: respond to glucose and produce insulin," says Evans. "No one had been able to figure out how to make pancreatic cells from human patients that can do both until now."

Eiji Yoshihara, first author and Salk research associate, together with Evans and Salk colleagues, closely studied the basic biology of a beta cell and uncovered several molecular switches, called transcription factors, that were switched off but might control the transition to a fully functional state. The "secret sauce," the Salk team found, was one particular switch the Evans lab had studied for years for its role in cell signaling. This protein switch, called ERR-gamma, turned out to be crucial to awakening silent beta-like cells that could now respond to glucose and release insulin accordingly. The team found that when the matured beta cells were transplanted into type 1 diabetic mice, the procedure quickly rescued their diabetes.

"This advance will result in a better controlled insulin response than currently available treatments," says Michael Downes, co-senior author and a Salk senior staff scientist. He adds that the team's technique is an easy, fast and inexpensive way to make transplantable human pancreatic beta cells in a dish that genetically match patients. The researchers hope to move to human trials within the next few years. S

To learn more about these discoveries, visit www.salk.edu/news

## **DISCOVERIES**



METABOLISM



A Salk team revealed a link between cellular recycling centers called lysosomes and the development of different layers of cells in an organism. This image shows a well-differentiated structure derived from normal embryonic stem cells, with all nuclei stained blue. Only one layer of cells (endoderm, green) contains high levels of lysosomes (red).

Credit: Anwesh Kamireddy/Salk Institute

## SALK SCIENTISTS UNCOVER HOW A CELL'S "FUEL GAUGE" PROMOTES HEALTHY DEVELOPMENT

Salk Professor Reuben Shaw's lab revealed how a cellular "fuel gauge" responsible for managing energy processes—a protein complex called AMPK—has an unexpected role in development. The work was published March 2016 in *Genes & Development*.

Shaw, first author Nathan Young and colleagues discovered that embryonic stem cells without a functioning AMPK pathway don't execute the development process properly, creating more of one germ layer than another. This lapse turns out to be due to a loss of lysosomes, structures responsible for degrading and reusing cellular components. By turning on lysosomal genes, the team was able to restore normal development in the AMPK-deficient cells.

According to Shaw, the connection between AMPK and lysosomes reveals more about cellular growth and metabolism.

Currently, lysosome inhibitors are in dozens of clinical trials for certain cancers, even though the exact link between lysosomes and tumors is not understood. "We are decoding underlying connections that might indicate when and how cancer drugs might be useful," says Shaw. "This work may help us make better, more specific ways of targeting lysosomes in cancer." §

## POWERING UP THE CIRCADIAN RHYTHM

At noon every day, levels of genes and proteins throughout your body are drastically different than they are at midnight. Disruptions to this 24-hour cycle of physiological activity are why jet lag or a bad night's sleep can alter your appetite and sleep patterns for days—and even contribute to conditions like heart disease and cancers.

Now, scientists led by Ronald Evans have discovered a key player—a protein called REV-ERB—that controls the strength of this circadian rhythm in mammals. The discovery, published May 2016 in *Cell*, is unusual in the field, as most circadian genes and proteins only shift the timing or length of the daily cycle.

The study's first author Xuan Zhao, Evans and colleagues analyzed levels and molecular characteristics of REV-ERB in the livers of mice. After the protein's levels peaked during the day, two other proteins, CDK1 and FBXW7, reduced REV-ERB to a low point by the middle of the night. When the team targeted these proteins to block the degradation of REV-ERB, normal daily fluctuations in gene expression were suppressed, but the timing of the cycles wasn't affected. Altering the strength of the gene expression oscillations profoundly affected metabolism, disrupting the levels of fats and sugars in the blood. What's more, mice that lacked REV-ERB developed fatty liver disease, stressing the importance of regulating the intensity of the cycle. S

From left: John Thomas, Marc Montminy and Janelle Ayres

## DISCOVERY OF "OUTLIER" ENZYMES COULD OFFER NEW DIABETES TREATMENTS

Scientists at the Salk Institute and The Scripps Research Institute (TSRI) discovered two enzymes that could someday be targeted to treat type 2 diabetes and inflammatory disorders, as detailed in *Nature Chemical Biology* on March 28, 2016.

The discovery is unusual because the enzymes do not bear a resemblance in their structures or amino-acid sequences—to any known class of enzymes, according to co-senior authors Alan Saghatelian, Salk professor, and Benjamin Cravatt, chair of TSRI's Department of Chemical Physiology.

These "outlier" enzymes, called AIG1 and ADTRP, appear to break down a class of lipids Saghatelian uncovered in 2014 called fatty acid esters of hydroxy fatty acids (FAHFAs). Saghatelian had found that boosting the levels of one FAHFA lipid normalizes glucose levels in diabetic mice. In principle, inhibitors of AIG1 and ADTRP could be developed into FAHFA-boosting therapies that reduce inflammation as well as improve glucose levels and insulin sensitivity.

The labs are collaborating on further studies of the new enzymes and potential benefits of inhibiting them in mouse models of diabetes, inflammation and autoimmune disease.



## GENETIC SWITCH TURNED ON DURING FASTING HELPS STOP INFLAMMATION

A molecular pathway activated in the brain during fasting halts the spread of intestinal bacteria into the bloodstream, according to work published May 2016 in the *Proceedings of the National Academy of Sciences*.

Salk Professor Marc Montminy, in collaboration with the labs of John Thomas and Janelle Ayres, uncovered this brain-gut signal in fruit flies, which could eventually inform the treatment of inflammatory bowel diseases in people.

To detail this pathway, first author Run Shen and colleagues studied a genetic switch in the brain called Crtc. They found that the guts of fruit flies without Crtc expressed molecules indicating that the immune system was keyed up, suggesting that without Crtc, bacteria leak from the gut into the fly's circulation. The normal role of Crtc is to fortify the barriers of the gut to prevent bacteria from entering the bloodstream and awakening the immune system. Without Crtc, the connections between cells that line the gut tube became disrupted, causing bacteria to leak out, activating the immune response and depleting energy reserves. The team also discovered that without the protein sNPF (found in the fly brain and with a human equivalent), the flies showed signs of gut inflammation similar to those flies missing Crtc. What's more, the normally tight seals along the GI tract were broken down, letting bacteria out. Conversely, flies expressing more than the normal amounts of Crtc or sNPF in their neurons were able to survive longer without food and showed less disruption to the tight junctions that maintain their GI barriers. The team is conducting more experiments to understand how the neuropeptides activate the gut receptors that help protect it from bacterial invasion. S

## **DISCOVERIES**



## TINY MICROSCOPES REVEAL HIDDEN ROLE OF NERVOUS SYSTEM CELLS

The miniaturized technology offers unprecedented insight into nervous system function and could lead to novel pain treatments for spinal cord injuries and neurodegenerative diseases.



Kohei Sekiguchi (left) and Axel Nimmerjahn reveal the world's first imaging data on spinal cellular activity during behavior, enabled by their innovative miniaturized microscopes.

www.salk.edu/insidesalk0816/nimmerjahn

A microscope about the size of a penny is giving scientists a new window into the everyday activity of cells within the spinal cord. The new miniaturized imaging methods, described on April 28, 2016 in *Nature Communications*, reveal more about nervous system function and could lead to pain treatments for spinal cord injuries, chronic itch and diseases such as amyotrophic lateral sclerosis (ALS).

The spinal cord has proven challenging for live observation in part because it is close to pulsating organs, which can hinder stable views of cells within. However, by building upon his miniaturized microscopes and developing new procedural and computational approaches, Salk Assistant Professor Axel Nimmerjahn, together with first author Kohei Sekiguchi and colleagues, were able to capture the action of living cells in real time and during vigorous movements.

By visualizing changes in cellular activity in awake, roaming mice, the team found that distinct stimuli—such as light touch or pressure—activate different subsets of spinal sensory neurons. Certain features, like the intensity or duration of a given stimulus, were also reflected in the activity of the neurons.

Surprisingly, the study revealed that astrocytes—cells in the nervous system traditionally viewed as merely supportive—unexpectedly react to intense sensation. Though the astrocytes cannot send electrical signals like neurons can, they generated their own chemical signals in a coordinated way during intense stimuli.

"Now we can look at disease contexts like spinal cord injury and see how treatments actually affect the cells," says Nimmerjahn. **S** 



In a mouse brain section (thalamus), neurons providing monosynaptic inputs to cortical inhibitory neurons are traced via rabies (blue). Purple counterstaining shows surrounding cellular architecture.

## BRAIN MAPPING TOOL 20 TIMES MORE POWERFUL THAN PREVIOUS VERSION

Edward Callaway's lab has developed a new reagent to map the brain's complex network of connections that is 20 times more efficient than their previous version. This tool, detailed by first author Euiseok Kim in *Cell Reports* in April 2016, improves upon a technique called rabies virus tracing, which was originally developed by Callaway and is commonly used to map neural connections.

This dramatic improvement will help researchers illuminate aspects of brain disorders where connectivity and global processing goes awry, such as in autism, schizophrenia and some motor and neurodevelopmental diseases. §

## TAMPING DOWN NEURONS' ENERGY USE COULD TREAT NEURODEGENERATION

Salk Institute scientists showed how an FDAapproved drug boosts the health of brain cells by limiting their energy use. Like removing unnecessary lighting from a financially strapped household to save on electricity bills, the drug—called rapamycin prolongs the survival of diseased neurons by forcing them to reduce protein production to conserve cellular energy.

Rapamycin has been shown to extend lifespan and reduce symptoms in a broad range of diseases and, at the cellular level, is known to slow down the rate at which proteins are made.

But the new Salk research, led by Salk Professor Tony Hunter and published in the journal *eLife*, suggests that rapamycin could also target the neural damage associated with Leigh syndrome, a rare genetic disease, and potentially other forms of neurodegeneration as well. Previous studies on rapamycin, which blocks an energy sensor in cells, suggested that the drug prevents neurodegeneration by encouraging cells to degrade damaged components. But recent data hinted that rapamycin might also affect mitochondria, organelles that produce energy in the form of adenosine triphosphate (ATP).

Hunter, Salk Professor Rusty Gage, first author Xinde Zheng and colleagues reprogrammed skin cells from patients with Leigh syndrome into brain cells in a dish. The Leigh syndrome neurons decayed and showed clear signs of energy depletion. Meanwhile, Leigh syndrome neurons exposed to rapamycin had more ATP and showed less degeneration. By turning down the dial on protein production, the diseased neurons were able to survive longer.

The teams are continuing to investigate how rapamycin's effect on reducing protein synthesis could be harnessed into a treatment for mitochondriarelated neurodegenerative diseases. §

## **DISCOVERIES**



## ADULT BRAIN PRUNES BRANCHED CONNECTIONS OF NEW NEURONS

Defects in the dendrites of neurons have been linked to numerous brain disorders including Alzheimer's and schizophrenia. Charting how the brain shapes these branches may be the key to understanding mental health.

Over a period of about a month, the Salk team kept track of each new neural branch, called a dendrite, on growing neurons, as well as each dendrite that was pruned away. Here, the branches of one cell are shown—new dendrites are in green, those pruned away are orange, and dendrites that both developed and were pruned away since the last snapshot are in pink. When tweaking its architecture, the adult brain works like a sculptor starting with more than it needs so it can carve away the excess to achieve an ideal design. That's the conclusion of a new study that tracked developing cells in an adult mouse brain in real time.

New brain cells began with a period of overgrowth before the brain pruned back its connections. The observation, described May 2016 in *Nature Neuroscience*, suggests that novel cells in the adult brain have more in common with those in the embryonic brain than scientists previously thought.

While most of the brain's billions of cells are formed before birth, Salk Professor Rusty Gage and others previously showed that in a few select areas of the mammalian brain, stem cells develop into new neurons during adulthood. In this study, his group focused on cells in the dentate gyrus, an area thought to be responsible for the formation of memories.

Gage and first author Tiago Gonçalves followed—on a daily basis—the growth of neurons over several weeks. When mice were housed in environments with lots of stimuli, the new cells grew quickly, sending out dozens of branches called dendrites which receive electrical signals from surrounding neurons. When kept in empty housing, new neurons grew slightly slower and sent out less dendrites. But, in both cases, the new dendrites began to be pruned back.

Defects in the dendrites of neurons have been linked to brain disorders like schizophrenia, Alzheimer's, epilepsy and autism. Charting how the brain shapes these branches—both during embryonic development and in adulthood—may be the key to understanding mental health. §



An accumulation of dead cells (green spots) is seen in the subventricular zone (SVZ) of the brain in a mouse lacking the receptors Mer and Axl. (Blue staining marks all cells.) No green spots are seen in the SVZ from a normal mouse.



## **BRAIN GUARDIANS REMOVE DYING NEURONS**

By adolescence, your brain already contains most of the neurons that you'll have for the rest of your life. But a few regions continue to grow new nerve cells and require the services of cellular sentinels, specialized immune cells that keep the brain safe by getting rid of dead or dysfunctional cells.

Greg Lemke's lab described the surprising extent to which both dying

and dead neurons are cleared away April 2016 in *Nature*.

Previously, Lemke discovered molecules called TAM receptors, two of which (dubbed Mer and Axl) help immune cells that act as garbage collectors to consume billions of dead cells that are generated in a human body every day.

The team wondered if the receptors did the same job in the brain. When the researchers removed Axl and Mer from cells called microglia (responsible for destroying pathogens in the brain) in mice, they found that the absence resulted in a large pile-up of dead cells, but only in regions where the production of new neurons is observed. Together with first authors Paqui G. Través and Lawrence Fourgeaud, Lemke's lab found that many more living nerve cells were able to migrate into the olfactory bulb (smell center) in the absence of the receptors, suggesting that Mer and Axl have another role aside from clearing dead cells: they may also target living, but functionally compromised, cells. This isn't necessarily a bad thing: the brain produces more neurons than it can use and then prunes back the cells that aren't needed. However, in an inflamed or diseased brain, the destruction of living cells may backfire.

The team also looked at the receptors in a mouse model of Parkinson's disease and found that afflicted mice missing Axl and Mer actually lived longer. This may be because in the presence of disease, there are more dysfunctional neurons than normal and Axl and Mer may be prompting the destruction of too many neurons, suggesting potential new targets for treatment. S

www.salk.edu/insidesalk0816/lemke





and

## HELMSLEY

Celebrate A New Partnership

THE CENTER FOR GENOMIC MEDICINE



## John Codey's vision opened the doors to discovery

The Salk Institute lost an ardent and visionary supporter in May with the death of John Codey, a trustee of the Leona M. and Harry B. Helmsley Charitable Trust. He played an integral role in accelerating research in diverse areas of science, including cancer, diabetes, Alzheimer's, stem cell biology and regenerative medicine.

A \$42 million award from the Helmsley Trust in 2013—the largest in the Institute's history—established the Helmsley Center for Genomic Medicine at Salk and enabled the Institute's leading scientists to use genomic data and powerful technologies to understand how certain cellular pathways serve as lynchpins for chronic diseases and to pave the way to effective new therapies.

Through Codey's advocacy and the support of the other trustees and staff, the New York trust reached beyond its base in the Northeast to help Salk build on its long track record for groundbreaking discoveries. The Trust has issued other major gifts to Salk, as well. In 2009, the Trust awarded a \$5.5 million grant to establish the Salk Center for Nutritional Genomics to study nutrition at the molecular level and its impact on the role of metabolism in diabetes, obesity, cancer, exercise physiology and lifespan. In 2010, it awarded an additional \$15 million to create a collaborative stem cell project involving Salk and Columbia University to fast-track the use of induced pluripotent stem cells to gain new insight into disease mechanisms and screen for novel therapeutic drugs.

These centers have made a number of important breakthroughs already, including developing new ways to use stem cells to study psychiatric diseases in the laboratory, advances in understanding the genes underlying cancers and the development of a drug currently being tested as a treatment for obesity and metabolic disease. Those are just a few of the innumerable ways that Codey and the Helmsley Charitable Trust have been making a difference through their generous support of Salk science.

In addition to participating in a number of Salk events in La Jolla and New York every year, Codey was an active member of the Salk International Council and traveled with the group to Spain, France and Venice. A raconteur with a warm personality, Codey will be greatly missed by the entire Salk community. His legacy of stalwart support for Salk science will carry far into the future. S

## 2009 \$5.5 Million Helmslev Charitable Trust gift establishes

the Salk Center for Nutritional Genomics.

## \$15 Million

Gift establishes collaborative stem cell project involving Salk and Columbia University.

## 2013

## \$42 Million

Largest gift in Institute's history establishes the Helmsley Center for Genomic Medicine.

## **GENDONICS** A LAYER OF REGULATORY INFORMATION ON TOP OF DNA IS PROVING TO BE AS IMPORTANT AS GENES

FOR DEVELOPMENT, HEALTH AND SICKNESS.

Why is a queen bee enormous compared to her worker bees? Why does one flower have petals that grow in a star-shape while another genetically identical flower forms petals in a mirror reflection? And how can two mice differ in color and shape even though they have the same DNA? In these cases and others, the two comparisons are genetically identical, possessing the same DNA code. So why does the same genetic code lead to very different outcomes?

Welcome to the epigenome. Many people are now familiar with the genome—a term used to denote the entirety of a person's genetic code—but the epigenome, a lesser known, secondary layer of information that coats the genome, may be just as important in making us who we are.

This layer, made up of proteins and other molecules that bind onto the genes like tags, is proving to play a vital role in development, health and disease. Some have likened the epigenome to a symphony, where the DNA sequence is sheet music that can be expressed in vastly different ways through the direction of epigenomic regulators.

"The notes are identical but musicians can change the tempo or use a variety of instruments for different effects," says Joseph Ecker, director of Salk's Genomic Analysis Laboratory and codirector of California Institute for Regenerative Medicine (CIRM)'s The Center of Excellence for Stem Cell Genomics. "Likewise, these epigenetic factors along with other factors in cells each 'play' a role in how and when cells are to become heart tissue versus a liver, for example."

The genome is constantly assailed by cellular molecules that temporarily turn genes on or off in response to the environment or in preparation for cell division. This is a stark contrast to more permanent changes like a mutation, where the gene itself is irreversibly changed.

The epigenome (whose precise definition can vary depending on who you talk to) can have both temporary and long-term effects on gene expression. It often consists of modifications to the genome that can persist for a time but are still ultimately reversible—able to fall off and leave the genes as they were.

One intriguing aspect of the epigenome is that epigenetic changes can be heritable, passed on from cell to cell as they divide and sometimes from parent to offspring. The epigenome may be affected by diet, activities like exercise or smoking, development and environment, suggesting that your lifestyle—and thus, epigenome—could have implications not just for you but also for your potential children or even grandchildren. Studies in mice, for example, suggest that how attentive a mother is to her pups after birth affects their epigenome, which later dictates levels of hormones and stress they experience as adults. The epigenome may also explain why some humans born in stressful or traumatic environments experience higher levels of sickness later in life, even in a safe and healthy setting.

"So much more research is necessary to determine if there is a causal link between cases where epigenetic variation has been observed and any health, diet or disease associations," says Ecker, whose group participates in the NIH Roadmap Epigenomics Mapping and ENCODE (ENCyclopedia Of DNA Elements) Consortium. Both are efforts to map the epigenome and its intricate workings to understand how it influences the cell in development and how it changes in disease. More and more, scientists are showing that certain epigenomic changes can have a profound impact on everything ranging from cancer to diabetes to mental disorders. Scientists are banking on the idea that learning how to read—and manipulate—the epigenome may help us unlock entirely new suites of treatments.

## MAPPING THE MUSIC

In the early 2000s, the announcement of the completion of the Human Genome Project led to unprecedented insights into how genetics influence health and disease. While fully sequencing the human genome promised to move us closer to personalized medicine that could individualize treatments to better cure disease, it turned out that mapping out the entire sequence of adenine, thymine, cytosine and guanine (A, T, C and G) pairs provides only a piece of the picture. A next step is to chart the epigenome—one component of which is the pattern of chemical tags called methyl groups that stud DNA to influence whether or not genes are activated. (See sidebar, page 16, for ways the genome can be modified.)

What do these methyl tags do exactly? These branched molecules of carbon and hydrogen typically are attached to cytosine (the "C" of DNA base pairs) and tell other proteins to go away—or, in some cases, to gather—turning the attached gene off or on. Acting as on/off switches or stop-and-go signals, millions of methyl tags pepper the genomes of your cells.

Ecker first became intrigued by the epigenome while studying *Arabidopsis thaliana*, a small flowering plant used for basic plant biology research. He and his colleagues wanted to know how many *Arabidopsis* genes were controlled by DNA methylation. But while methylation has been studied for decades, there was no good way to get a snapshot of all the methylation marks in a cell's DNA. So Ecker created one.

His lab designed a method called MethylC-Seq, which entails several chemistry techniques that break DNA into small pieces to process them through highspeed computers and technology such as sequencers built by the San Diego-based company Illumina. The resulting data allows scientists to, for the first time, see and quantify those methyl marks on the 3-billionbase genome. "MethylC-Seq allows us to extract that information from the invisible (methylated cytosine) and make it visible," says Ecker, who is also a Howard Hughes Medical Institute and Gordon and Betty Moore Foundation investigator.

MethylC-Seq displays this methylation in patches of yellow, letting Ecker's team compare different cells in one organism or across organisms to search for links, for instance, between aberrant DNA methylation and disease. Ecker's methods have led to the first maps of the epigenome for plants and also animal cells, including humans, which has shown evidence that methylation increases from birth to adulthood. His major publication in 2015 in *Nature* provided, for the first time, details into the epigenome of a variety of tissues from organ donors of different genders and ages. TO EXPLAIN HOW THE EPIGENOME WORKS, SOME HAVE LIKENED IT TO A SYMPHONY: THE SHEET MUSIC (GENOME) IS THE SAME, BUT CAN BE EXPRESSED IN VASTLY DIFFERENT WAYS DEPENDING ON THE GROUP OF PLAYERS AND THEIR INSTRUMENTS (EPIGENOME).



## What is an epigenome?

The epigenome is a secondary layer of molecular information that sits on top ("epi") of the genome to affect what genes are activated or silenced. The epigenome can change over time during development or in the presence of disease, for example, and may provide new clues to targeting disorders.

## AFFECTING THE GENOME:

MANY MOLECULES ACT ON THE GENOME WITHOUT CHANGING THE GENES THEMSELVES. WHILE DNA METHYLATION IS A COMMON EPIGENETIC CHANGE TO THE GENOME, OTHER FACTORS ARE ABLE TO INFLUENCE GENE EXPRESSION, ULTIMATELY AFFECTING HEALTH AND DISEASE. HERE ARE SOME EXAMPLES:



## **DNA Methylation**

Methyl groups, made of a single carbon and three hydrogens, modify the bases in DNA and act as molecular signage to turn on or off genes. DNA methylation marks can persist for many cell generations and, in some organisms, can even be transmitted across generations.

## Chromatin remodelers

These proteins interact with chromatin, the complex of DNA and proteins that are packed within the cell nucleus, to rearrange its shape, allowing other proteins to physically access the DNA and to turn genes on or off.

## Histone modification

DNA is wound around histone proteins for packaging into chromatin. Modifications to histone proteins can make genes more or less accessible to other proteins and therefore affect which genes are able to be transcribed.

## Non-coding RNA

Some ribonucleic acid sequences interact with enzymes to influence histone modification and DNA methylation.

## **Transcription factors**

These proteins bind to the genome to affect gene expression, but are generally more dynamic and act on a faster scale than epigenetic modifications.

## WHAT'S IN A BRAIN?

In 2013, Ecker and his neuroscience collaborators Margarita Behrens and Terrence Sejnowski published work in the journal Science showing something surprising. They had mapped the pattern of millions of methylation changes in the brain's frontal cortex using human tissue. Methylation usually occurs on the DNA base cytosine ("C") when it is adjacent to guanine ("G"). This epigenomic map of a healthy human brain revealed a type of methylation not normally seen in the body: methyl tags in neuronal cells were binding to DNA in places other than C. His team found that this alternative methylation (called non-CG) starts at birth and increases throughout early adulthood. Ecker and others suspect that abnormal patterns of methylation of this type might be associated with mental disorders like schizophrenia, whose symptoms don't manifest until early adulthood.

"We found a major difference in the epigenome of neurons which is an accumulation of a new kind of methyl mark that we didn't even know existed before in neurons," says Behrens, a Salk senior staff scientist. "This non-CG methylation accumulates from birth through adolescence during a critical period of brain maturation when connections are being made."

When it comes to the brain, other studies have shown that environmental factors—medicine, diet, age, stress and chemical exposure—can change methylation in brain cells. Ecker and others are examining this global epigenomic reconfiguration during brain development to uncover potential ties to mental disorder. In one study, they are examining the effects of viruses and chemical exposure in animal models to see how environment changes this new type of methylation in brains during development. In another, his team has begun to map the epigenome of neurons from those with Alzheimer's. "Even if these epigenetic events are not causative for these disorders, they can provide useful markers of disease progression," Ecker says. "And because methylation and other epigenomic changes are in essence temporary, there may be ways to tweak the epigenomic code to help treat diseases of the brain and the body."

## THE SHAPE OF DNA

Salk Assistant Professor Julie Law focuses on another aspect of the epigenome: the complicated and cryptic realm of chromatin, which is the dynamic combination of proteins, small RNAs and other molecules that surround DNA and which plays key roles in controlling its expression and stability.

"We are trying to understand how you get different outcomes from the same DNA," says Law. "Epigenetic modifications are one way in which you can achieve this diversity to the genome in a manner that doesn't change the underlying DNA sequence. But what we don't understand is how epigenetic modifications target different places in various cells and are recognized and translated into desired responses."

Part of the answer may be found in an epigenome change called chromatin remodeling, where proteins alter how the DNA is stored. Human DNA in a single cell is enormously long—six feet—and folds with proteins into intricate packages (chromatin) to fit within a nucleus. Imagine rolling and storing sweaters and mothballs into sealed vacuum bags to both keep them safe and make room for storage. In a similar way, the packaging of the DNA begins with histone proteins, which act as spools to wind DNA. The histones, DNA and other proteins are then further packaged into larger chromatin. Like sweaters hanging in the front of a closet, genes on the outside of chromatin are more easily accessed and usable than those stored deeply away.

Proteins that sit on top of the chromatin and control its spatial arrangement play an integral role in what genes are used or not and, similar to methyl tags, can have grave effects on health and disease. Adding chemical markers (methyl tags and others) to histone proteins can result in rearranging the chromatin, dictating which genes are ignored and which are turned on.

To understand these epigenetic factors, Law uses the *Arabidopsis* plant that, unlike mammals, is more tolerant of changes to the epigenome. She's turned her attention to several newly identified families of proteins involved with DNA packaging and gene expression, called chromatin-binding proteins. She is striving to determine the epigenetic marks recognized by these protein families as well as identify their interacting partners and their effects on gene expression. Although Law's research utilizes a plant model, her findings will also hold lessons for human biology as many of the genes involved in adding or removing epigenetic marks are the same in plants as in mammals.

Graham McVicker, a Salk assistant professor who studies the human genome and chromatin, says, "It's as if the genome is a big landscape and the cell can plunk down flags-DNA methylation marks or histone modifications-to indicate which parts of the landscape have specific functions." McVicker, who aims to understand how differences in the genome sequence affect our cells at a molecular level, adds that the genomes of unrelated individuals only differ by about one base in every thousand and that most of these differences have no function. "One way to understand which genetic differences are important is to look for the ones that are associated with the expression of genes or changes in histone modifications," he says. "The goal is to understand how genetic differences affect gene expression or epigenetics and ultimately how these differences contribute to human traits and diseases."

## UNTANGLING CANCER

Salk Professor Beverly Emerson drills into the epigenome's mechanistic processes from another angle: cancer.

In the last few decades, researchers have shown that changes in the epigenome are tied to many types of cancer through projects like ENCODE or NIH's Cancer Genome Atlas (TCGA) Network, which compares genomes and epigenomes of normal and cancerous cells. Despite these efforts, it is difficult to untangle causes from correlations when it comes to epigenetics and cancer.

"The cell has a whole constellation of proteins to read and decode its DNA. Epigenetics is an elaborate way to allow the DNA coding sequence to be read in a manner contingent upon physiological signals," says Emerson, holder of Salk's Edwin K. Hunter Chair. "But when a DNA base change or a mutation occurs, epigenetic changes can promote the overgrowth of cancer or suppress the immune system."

The body's cells undergo changes in signaling to their genomes all the time: when you eat, when you get sunburnt, when you feel certain emotions. Emerson's team is trying to distinguish those normal changes of the epigenome versus cancer-causing changes that result from chronic stress to the cell.

"There are so many changes in a cancer cell that often you don't know what the driver was," says Emerson. "Cancerous cells are already massively epigenetically modified, but we want to know how epigenetic changes and alterations in transcriptional programming primes cells to become cancerous."

By studying normal breast tissue samples and observing how those cells respond to prolonged stress, she hopes to understand how cells turn into breast cancer. To do this, she examines how alterations in DNA methylation and the cells' chromatin regulators lead to critical tumor suppressant genes becoming rapidly silenced.

"Our hypothesis is that such abnormal cells accumulate with time and age. They've changed their epigenomic programming and are more vulnerable to becoming cancerous," says Emerson. "A gene can become permanently locked into a repressed state through methylation, which is a problem if the gene happens to be a tumor suppressor or related to immune function."

One way in which a gene can get locked into a repressed state is by mutations to epigenetic modifiers themselves, which is increasingly observed in the sequencing of human cancers. Salk Assistant Professor Diana Hargreaves is examining one such target in cancer, an epigenetic regulator called the SWI/SNF complex, which unpacks and unwinds DNA from chromatin to alter gene accessibility. Many pieces or subunits of the SWI/ SNF complex are mutated in cancer, including ARID1A, which is mutated in ovarian, bladder, lung and colorectal cancers. Hargreaves is exploring the different activities of the SWI/SNF complex in normal and disease settings in order to figure out how to target ARID1A mutant cancers.

## MethylC-Seq Method

This method uses a series of chemistry techniques that break DNA into small pieces to process them through high-speed computers and technology like Illumina's sequencers. The resulting data allows scientists to, for the first time, see and quantify those methyl marks on the 3-billion-base genome. "MethylC-Seq allows us to extract that information from the invisible and make it visible," says Ecker.

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HUMAN DNA IN A SINGLE CELL IS ENORMOUSLY LONG—SIX FEET—AND FOLDS WITH PROTEINS INTO PACKAGES (CHROMATIN) TO FIT WITHIN A NUCLEUS. IF WE CAN BETTER UNDERSTAND PROTEIN COMPLEXES INVOLVED IN CHROMATIN REMODELING AND HOW MISTAKES IN MAKING SPECIFIC REGIONS OF THE GENOME MORE OR LESS ACCESSIBLE LEADS TO CANCER, WE CAN DEVELOP TARGETED TREATMENTS.





From left: Diana Hargreaves, Beverly Emerson, Joseph Ecker and Julie Law

"We now know that mutations in chromatin remodeling proteins, such as ARID1A, can shift the balance of epigenetic modifiers at key tumor suppressor genes, leading to changes in histone modifications and gene accessibility that repress these genes. In the context of growth signals, this can rapidly lead to cancer," says Hargreaves. "If we can better understand how mutations in protein complexes involved in chromatin remodeling prime the cell to become cancerous, we can begin to develop targeted treatments for SWI/SNF mutant and potentially other cancers."

Researchers are already testing and applying drugs that target the epigenome by stripping away methylation

in hopes of removing the tags that have silenced tumor suppressant genes. (One example is the drug temozolomide, used for treating brain tumors called glioblastoma.) However, there are some obstacles: such a treatment would strip away methylation on the rest of the genome, potentially leading to additional issues. Secondly, methylation is only one aspect of the epigenome; proteins that regulate chromatin are also often mutated in cancer. Nevertheless, refining ways to target methyl tags and other epigenetic regulators could be a boon for treatments in part because the epigenome is more reversible and malleable than say, a genetic mutation.

## CHARTING THE EPIGENOME'S REACH

So far, researchers have shown that some types of modifications to histone proteins, cytosine methylation and molecules called small RNAs can be inherited in mice, flies and plants, for example, but it's unclear to what extent epigenetics is inherited in people. "Just as everything—disease, obesity, depression—used to be blamed on the genome, now you will see all sorts of claims about the epigenome and I would not believe most of it," Ecker says. "What I would say is that we're really just at the beginning of understanding the epigenome and heritability but if there is the possibility that your diet or environment could affect your children or grandchildren, that will be important to know and exploring the molecular mechanisms using model systems may help us to understand these phenomena better."

Aside from exploring methods of inheritability, Ecker and others are now making a slew of maps of normal and disease states to generate comprehensive epigenomic references for everything from neurodegenerative and developmental disorders to metabolic diseases like diabetes as well as cancer. In one study, Ecker and Salk Professor Ronald Evans are studying how exercise might affect your epigenome. In another effort recently funded by the NIH, Ecker is researching whether viruses can act on the epigenome during development to cause autism.

"At Salk, we have scientists interested in understanding epigenetics related to cancer, neuroscience, regenerative medicine and other fields, as well as researchers who have the potential to make small molecule drugs to target the epigenome," says Ecker. "We're really at the very beginning and it's the interplay of these areas of specialties that is going to advance the science and help us understand how the epigenome is affected by development, nutrition, disease and aging." §





## Tapping our Immune System's **SUPERPOWER**

We all have a superhero—or supervillian—inside our bodies. It's called our immune system. Every day, a healthy immune system repels a host of adversaries—bacteria, viruses, parasites—you name it! But it can also go berserk, resulting in multiple sclerosis, rheumatoid arthritis and other autoimmune disorders.

Its powers to heal or harm don't stop there. Ye Zheng, associate professor in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis, says that immunology is a rapidly expanding field with a direct impact on people. Scientists are discovering that the immune system is entwined with additional diseases such as autism, cancer and diabetes. If they can decipher the links between the immune system and these diseases, they may have a whole new weapon to maintain human health.

In a conversation with *Inside Salk*, Zheng shares his hopes and his hesitations about tapping our immune system's superpower in ways not even imaginable just a few years ago.

## What do people misunderstand about the immune system?

People make the mistake of thinking that the immune system deals solely with infectious diseases. But it's much more than that. It's always on duty, performing regular cleanup of bodily waste, such as dead cells. A lazy immune system that allows waste build-up leads to chronic inflammation. And inflammation underlies many diseases. In my lab we're asking questions such as: How exactly does the immune system interact with chronic inflammatory diseases? And how can we correct this? It is a less developed segment of immunology. There is still much to learn.

## Did you always want to be an immunologist?

Not really. It sort of happened by accident. I grew up in Beijing, where my parents were electrical engineers, and early on I was good with science and math problems. In fact, when I was in high school, I was chosen to be on China's four-person entry in the International Chemistry Olympiad. We won the gold medal. I earned my PhD in biological sciences at Columbia University and then, with a postdoctoral fellowship, conducted research in the lab of immunologist Alexander Rudensky, first at the University of Washington in Seattle and later at Memorial Sloan Kettering Cancer Center in New York City. I like immunology because it's a very large, very interesting field and also very helpful to people.

## What do you enjoy doing outside the lab?

I love nature—camping and hiking. I especially liked living in Seattle where there is such a variety of terrain: mountains, ocean, islands. A change of environment is very good for stimulating your thinking. My wife, Yang Dai, also loves the outdoors. We have a 16-month-old daughter, Marissa, and we just bought a larger van so that we can go camping together.

## What is the most surprising advancement in immunology?

Through human genetic mapping, we are finding a surprising overlap between genes linked with disease and genes linked with immune system function. Our hope is that, with a better understanding of this relationship, we can find additional ways to intercept and treat diseases.

## Former President Jimmy Carter made headlines last year when immunotherapy was used, apparently successfully, to treat his melanoma. Are you excited about the prospects of using the immune system to fight cancer?

I'm excited but also cautious about making the promise that the immune system can cure cancer. We are not there yet, at least not for the majority of the cancer patients today. I believe the most benefit to cancer patients will come from a combination of immunotherapy and other standard treatments.

The problem is this: While immune cells can be trained to kill cancer cells—you risk them continuing their attack on other parts of the body. It can cause autoimmune disease, and even be lethal. There must be a balance when you turn the power of the immune system loose; there has to be some sort of check.

www.salk.edu/insidesalk0816/zheng



## What would you like to know about the immune system in the next five to ten years?

Two things: one is more about tumor immunology and immunotherapy. The problem right now is that you can have two people with the same type of tumor yet the prescribed therapy only works on one person. What can we do to change that?

The second subject is neurological disorders, such as autism and Alzheimer's, where there aren't really any highly effective drugs. If we can develop more mechanistic insight into how immune cells play a role in these disorders then we can do something about it.

## What is the focus of your lab in the immunology field?

In my lab we focus on immune cells called Tregs. They help regulate the more aggressive immune cells, telling them when to pull back from attack. A protein called Foxp3 plays a key role within Treg cells and we recently discovered a particular genetic sequence in this gene that is responsible for the stability of a Treg. Being able to manipulate Tregs into strengthening or quieting the immune response could lead to ways to treat autoimmune diseases as well as attack cancer cells.

## You're collaborating with Salk Professor Ronald Evans on yet another newly identified role for the immune system: its effect on metabolism. What are you learning?

Yes, this is another emerging field called immunometabolism. We are studying how immune cells interact with fat cells to regulate energy storage and consumption. People think that fat is static but it isn't. Fat has so many immune cells it almost looks like an immune organ. A few months ago Ron and I discovered how immune cells were causing diabetes in aged, lean mice. We're calling it a new disease: type 4 diabetes. This discovery could have real impact for our aging population. §

"Through human genetic mapping, we are finding a surprising overlap between genes linked with disease and genes linked with immune system function. Our hope is that, with a better understanding of this relationship, we can find additional ways to intercept and treat diseases."



## All about town with Pablo Hollstein

Growing up in Quito, Ecuador, Pablo Hollstein was passionate and precise —about science from an early age. While his grammar school classmates were bringing half-dead seedlings for a class project, he was sharing pots of lentils and beans that had flourished so fantastically, no one believed he had nurtured the seeds himself.

That enthusiasm and talent for science carried through his undergraduate and graduate studies at Harvard University and continue at Salk today where, as a research associate in Reuben Shaw's lab, Hollstein studies LKB1, one of the most commonly mutated genes in lung cancer. In its normal state, LKB1 acts as a tumor suppressor that controls a crucial cellular metabolism process in response to nutrient and energy availability. This direct connection of the gene to cellular metabolism, first uncovered by the Shaw lab, points the way to potential new therapies. Hollstein and colleagues are endeavoring to better understand the functions of LKB1 to find out how to counter the loss of this gene in order to help treat lung cancer.

When he's not at the bench, he works as chair of Salk's Society of Research Fellows to enrich the lives of postdoctoral researchers on campus by planning and coordinating Institute seminars and mixers. Off campus, Hollstein likens himself to an urban explorer, driven to discover new cultural experiences, especially of the culinary kind. For one, he has always been an adventurous eater. Aside from supping on haggis (sheep stomach) and sea urchin, he was even game to try a bite of pungent, fermented fish—a Swedish delicacy called surströmming from one of his Salk lab mates. Alas, the substance had liquefied in the can and was beyond sampling.

A passionate mixologist, Hollstein humbly claims to have perfected the Dark N' Stormy (a classic concoction of rum and ginger beer), which goes down quite smoothly after a meal of haggis or sea urchin.

Pablo Hollstein, a research associate in the Molecular and Cell Biology Lab, is an explorer in the lab and out. Here are a few favorite noshes he's discovered since moving to San Diego:



## Fab fish taco

Move over Rubio's. The **Pacific Beach Fish Shop** has got the best fish tacos "hands down" at 1775 Garnet Ave., Pacific Beach.

## Authentic pie

For old-world pizza, look no further than **Buona Forchetta**, 3001 Beech St., South Park.

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The "Hood Burger," adorned with gruyere, blue cheese and caramelized onions, speaks for itself at **Neighborhood**, 777 G St., East Village. Besides its hamburgers, **Neighborhood** (see Best Burger) has a hidden

speakeasy that is easily

one of the city's finest

watering holes.

For ambience and a lively oyster hour, shuck out **Herringbone**, 7837 Herschel Ave., La Jolla.

http://www.salk.edu/insidesalk0816/hollstein



## Protein structure illuminates how viruses take over cells

Using cutting-edge imaging technology, Helmsley-Salk Fellow Dmitry Lyumkis together with Harvard Medical School researchers determined the structure of a protein complex that lets viruses similar to the human immunodeficiency virus (HIV) establish permanent infections within their hosts.

Contrary to previous assumptions, the newly detailed viral protein complex structure, called an intasome, indicates that this type of molecular architecture differs across retroviruses. This information helps reveal how retroviruses insert their genomic information into human cells and may have implications not only for treating diseases like HIV, but also for improving gene therapy methods to deliver new DNA to patients with genetic mutations. The work was published in *Nature* on February 18, 2016.

ANALYSIS

## Viral DNA

The virus uses the intasome complex to grab a DNA copy (blue) and bring it to the nucleosome.

## Intasome

A complex of viral proteins (purple, green, red, yellow) bound to viral DNA that lets viruses like HIV establish permanent infections in their hosts. Colors represent the 8 viral proteins of this multi-component complex.

## Host DNA

Once the intasome brings the viral DNA to host nucleosomes, it uses a biochemical reaction to irreversibly insert DNA into host DNA (gray). This allows the virus to hijack the host's genomic material, permanently infect the cell, and make many copies of itself.

## Host histones and nucleosomes

Proteins called histones (beige) bundle and package host DNA (gray) in nucleosomes, which are the primary targets of viral intasome complexes.



-Hans Christian Andersen

## **CONRAD PREBYS** 1933 - 2016



Ubiquitous throughout the San Diego region, Conrad Prebys' name can be found connected to medical centers, arts programs, even the zoo. He was a particularly bold presence on The Mesa, where he donated millions to institutions such as the Salk Institute.

The Salk Institute proudly counted Prebys as a visionary and supportive friend who followed his passions and gave with joy. His philanthropy to the Institute spanned years, enabling researchers to discover the next generation of breakthrough medical therapies.

Prebys' gift of \$25 million to Salk's unrestricted endowment in 2014 was a philanthropic milestone for the Institute; it was the largest gift yet received to support emerging scientific priorities as they occurred. In honor of that gift, the Salk Institute auditorium was named the Conrad T. Prebys Auditorium. The gift is "a debt I owe," Prebys said at the time, referring to Jonas Salk's development of the first safe and effective polio vaccine. "This is a long time saying 'thank you."

For years, Prebys also generously underwrote the San Diego Symphony for the annual gala Symphony at Salk, and he contributed \$2 million to establish the Conrad T. Prebys Endowed Chair in Vision Research for Professor Thomas Albright. He further supported and helped shape Salk as a member of the Board of Trustees from 2009 to 2014.

On behalf of Salk Board Chairman Irwin M. Jacobs, President Elizabeth Blackburn, the Board of Trustees and the entire Salk community, our deepest sympathies go to Prebys' life partner, Debra Turner.



## SALK SCIENCE & MUSIC SERIES 2016-2017 SEASON

PRODUCED FOR THE SALK INSTITUTE BY KAREN JOY DAVIS

### SUNDAY, OCTOBER 2, 2016

**SA CHEN, piano** One of China's most celebrated artists will make her San Diego debut at the Salk Institute

SUNDAY, NOVEMBER 20, 2016 ASI MATATHIAS, violin with piano

SUNDAY, JANUARY 22, 2017 AMIT PELED, cello with NOREEN POLERA, piano SUNDAY, FEBRUARY 12, 2017 SEAN CHEN & KAREN JOY DAVIS Duo piano concert

SUNDAY, MARCH 12, 2017 ZLATA CHOCHIEVA, piano

Renowned Russian pianist makes her West Coast debut at the Salk Institute

SUNDAY, APRIL 30, 2017 HELEN SUNG QUARTET Jazz

CONCERTS BEGIN AT 4:00 P.M.

## PREPARE TO BE AMAZED AND INSPIRED

The ever-popular Salk Science & Music Series returns this fall for a fourth season of classical and jazz performances paired with riveting talks on the latest discoveries by the Institute's world-renowned scientists.



TICKETS & INFORMATION: www.salk.edu/music (858) 597-0657

# SPOTLIGHT





## SATCHIDANANDA PANDA



**SREEKANTH CHALASANI** 



**BJÖRN LILLEMEIER** 



YE ZHENG

Satchidananda Panda, a scientist in Salk's Regulatory Biology Lab, was promoted this spring to the rank of full professor. Also honored with promotion, from assistant professor to associate professor, were Sreekanth Chalasani in the Molecular Neurobiology Lab, and Björn Lillemeier and Ye Zheng, both in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis.

## To read more about their work, visit:

http://www.salk.edu/insidesalk0816/fourfaculty.

## SALK MEDAL RECIPIENTS HONORED



From left: Elizabeth Blackburn, Solomon Snyder, Robert Weinberg and Tony Hunter

For the first time, the Salk Institute bestowed its Medal for Research Excellence on not one, but two, distinguished scientists. Both recipients delivered lectures on their work to a full auditorium before receiving the awards during the April Board of Trustees dinner at the Institute.

Robert Weinberg, a founding member of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, was chosen by Salk's faculty medal committee for his internationally recognized, lifelong work on the genetics of human cancer. Solomon Snyder, Distinguished Service Professor of Neuroscience, Pharmacology and Psychiatry at Johns Hopkins University, was selected for his transformative research on neuropharmacology.

The medal was created to award individuals who make significant contributions in basic science research with particular impact on science policy, humanities, the Institute, or human health.

http://www.salk.edu/insidesalk0816/salkmedal

## AWARD-WINNING NEUROBIOLOGIST RECRUITED

Eiman Azim, recognized for his research on neural circuits that control skilled movement and an Eppendorf & *Science* Prize winner, has joined the Salk Institute as an assistant professor in the Molecular Neurobiology Laboratory. A postdoctoral research fellow at Columbia University Medical Center, Azim received undergraduate degrees in biology and philosophy from Stanford University and his PhD from Harvard University. He joined the Institute in May and will continue his investigation of neural circuits in the spinal cord and brain to determine how skilled movements work to potentially help generate new treatments for neural and spinal cord dysfunction.



Eiman Azim

### HHMI RESEARCH ASSOCIATE JOINS SALK

Sung Han, a postdoctoral fellow studying behavioral neuroscience and psychiatric disorders at the Howard Hughes Medical Institute/University of Washington School of Medicine, joins the Salk Institute as an assistant professor. Previously, Han worked in the university's Department of Pharmacology and at LG Life Sciences and LG Chem. He received his bachelor's degree in genetic engineering from Kyungpook National University, a master's degree in neuroscience from Pohang University of Science and Technology and his PhD in neuroscience from the University of Washington School of Medicine. In the Peptide Biology Lab, Han will continue his research into the neural circuitry of neurons that contain specific neuropeptides to provide fundamental insight for developing therapies for anxiety, panic and autism spectrum disorders, schizophrenia and metabolic syndromes such as obesity and hypertension.



Sung Han

## SPOTLIGHT



## GAGE ELECTED TO NAS COUNCIL

Rusty Gage began his three-year term on the governing council of the National Academy of Sciences (NAS), an institution that advises the nation on science and technology issues. Gage, a professor in the Laboratory of Genetics and holder of the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease, is the first Salk scientist to be elected to the 17–member NAS council. He and 14 Salk colleagues are among the more than 2,700 members and 450 foreign associates of the NAS, which was established in 1863 by an act of Congress, signed by President Abraham Lincoln.





From left: Elizabeth Blackburn, Anne Marberger and Reuben Shaw



## SALK PREPS FOR PEDAL '16

Team SCC, Salk's Cancer Center cycling group, shifted into high gear this summer to train for the fourth annual Pedal the Cause fundraising ride for cancer research. Rebranded this year as Padres Pedal the Cause, the November 12-13 event will feature courses of varying lengths and challenges beginning and ending at Petco Park. This spring, Salk joined Moores Cancer Center at UC San Diego Health, Sanford Burnham Prebys Medical Discovery Institute and Rady Children's Hospital in receiving \$1.3 million in grant funding from the 2015 ride.

To learn more about Padres Pedal the Cause, or to find out how to join Salk's road warriors, visit http://sandiego.pedalthecause.org or contact Jamie Simon at jsimon@salk.edu.

# EVENTS



## A BEAUTIFUL DAY IN THE NEIGHBORHOOD

The fourth annual Explore Salk open house welcomed nearly 2,000 people to the Institute on April 16 for an up-close examination of Salk science through lab tours and interactive activities from pipetting to planting.

Highlights included Professor Satchidananda Panda's talk on circadian rhythms and the community debut of new Salk President Elizabeth Blackburn, who spoke to a packed auditorium about her career in telomere and telomerase research.







# EVENTS

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## SUPPORTING RISING STARS

Early career scientists Nausica Arnoult, Amandine Chaix, Wei-Mien (Mendy) Hsu, Liang Song and Mako Yamamoto were honored at the second annual Salk Women & Science Special Awards Initiative ceremony, where they received funds from \$165,000 specifically raised to help support female researchers conducting high-risk research projects. Salk Trustee Haeyong Kong Tang hosted the March 30 program, which began with a conversation with President Elizabeth Blackburn moderated by Senior Vice President/CFO Kim Witmer.

From left: Mako Yamamoto, Nausica Arnoult, Amandine Chaix, Ursula Bellugi, Elizabeth Blackburn, Wei-Mien (Mendy) Hsu and Liang Song





Joseph Ecker, right, talks with attendees about the epigenome.

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## EXPLORING THE EPIGENOME

The long-held belief that the sequence of genes was all that was needed to understand an organism's biology was put under the microscope at the Back to Basics lecture delivered last spring by Salk Professor Joseph Ecker. Before a full audience in the Conrad Prebys Auditorium, Ecker described recent research in the field of epigenetics and how the findings are influencing our understanding of human health.



## SALK HOSTS FIRST PHILANTHROPY SUMMIT

Curing cancer, funding STEM education and forging frontiers in neuroscience were among the lofty themes explored during the inaugural Breakthrough Biomedical Philanthropy held May 12-13 at the Salk Institute. Drawing science and philanthropy thought leaders from across the country, the summit, a revitalized program of the former Tax Seminar, included keynote addresses by Salk's President Elizabeth Blackburn and Trustee Ted Waitt.

From left: Salk Professor Satchidananda Panda and attendee Diana Kalman





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## RE-IMAGINED INSTITUTE COUNCIL MARKS SECOND YEAR

More than 40 members of the Salk Institute Council (formerly the International Council) convened for the second annual meeting May 11 to discuss Salk science and ways to advance the Institute's mission. With faculty liaison Reuben Shaw and co-chairs Salkexcellerator Laing Rikkers and Trustee Rich Heyman, the council toured labs, joined faculty roundtable talks and posed for posterity on the travertine courtyard.



## 1916–2004 HAPPY 100, FRANCIS CRICK

"It's true that by blundering about we stumbled on gold, but the fact remains that we were looking for gold."



So said the eminently quotable Francis Crick about his 1953 discovery with James Watson of the structure of the DNA molecule. Crick joined the Salk Institute faculty in 1976 and for the next 27 years focused on neuroscience, championing research to discover the neural underpinnings of consciousness. This year, on June 8, Salk commemorated the centenary of his birth.



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

## SALK WOMEN & SCIENCE



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

## SALKEXCELLERATORS



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

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*Inside Salk* is published by the Salk Institute for Biological Studies. Please send comments to communications@salk.edu or contact the Communications Department at (858) 453-4100 x1371.



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## CALENDAR

## AUGUST

20 Symphony at Salk

## OCTOBER

- 2 Salk Science & Music Series featuring Sa Chen
- 5 Salk Women & Science Lecture

## NOVEMBER

- 2 Salkexcellerators Lecture
- 9 Back to Basics Lecture
- 20 Salk Science & Music Series featuring Asi Matathias



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