WINTER I 2019 WHERE CURES BEGIN.

insideSalk

The Promise & Perils of Big Data

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PRESIDENT'S LETTER

Dear Friends,

One of the most enjoyable parts of my work at Salk is the opportunity to meet and talk with our supporters about the research under way at the Institute. Their passion about and understanding of the importance of the work done at Salk are infectious, and I leave those meetings with a renewed energy for the work before me.

Between the pages of this issue of *Inside Salk* you will find the 2019 Salk Donor Honor Roll, our annual acknowledgment and appreciation of those who have supported our work in the last fiscal year. Along with a summary report of the Institute's fiscal health, you will find more than 1,200 names of individuals, families, organizations and businesses who have helped make the 2019 fiscal year (July 1, 2018, through June 30, 2019) so successful. To each of you who have been our partners, I extend my deepest appreciation on behalf of the Salk community and thank you for helping us achieve one of the most successful fundraising years in our history.

Your impact on scientific discovery at Salk has been tremendous.

Over the last year, your support has resulted in dozens of discoveries made in labs across the Institute that have advanced our knowledge of cancer, aging, plant biology, immunology, neuroscience, computational biology and genetics, among others. Donor support has enabled progress on our strategic initiatives to conquer five of the most deadly cancers, develop plants capable of absorbing an increasing share of carbon from the atmosphere, and explore the role cells in the brain play in aging and age-related diseases such as Alzheimer's—all discoveries that will have an impact on our future.

New technologies have helped advance scientific research yielding vast amounts of data while providing new opportunities for discovery. We explore the growing role of "big data" in this issue of *Inside Salk* and dig deeper into the benefits as well as potential pitfalls. We also follow Professor Joseph Noel into the wetlands of the San Dieguito Lagoon and learn how the son of a coal miner emerged as a passionate champion of using science—and plants—in the fight against climate change. His story is one of several you will read in the pages of this edition, along with reports on the latest discoveries from Salk labs.

While this time of year is often characterized by reflection and contemplation, it is also a time of anticipation and excitement for what lies ahead. This is particularly true for all of us at the Institute as we make plans to celebrate our 60th anniversary over the next twelve months. What started as a vision in our founder's mind has emerged as a world-renowned basic scientific research institute making discoveries that seek to understand who we are as human beings, developing therapies for devastating diseases and specifically aiming to change the world for the better. Within the labs, studies and courtyard of this architectural masterwork, Salk scientists continue the pursuit of answers to some of our most challenging problems.

As we continue to pave the way toward new knowledge, I want to thank all of you for your support, interest and dedication. May the new year bring you good health and happiness.

Sincerely,

Fred H. Gage President



"New technologies have helped advance scientific research yielding vast amounts of data while providing new opportunities for discovery."

SALK NEUROSCIENTISTS GARNER MAJOR AWARDS TO INVESTIGATE THE BRAIN AND SPINAL CORD

MAPPING CIRCUITRY FOR MOVEMENT

A team of Salk scientists led by Professor Martyn Goulding has been awarded **\$14.3 million** over five years by the National Institutes of Health (NIH) to create a high-resolution atlas of how the mouse brain generates and controls skilled forelimb movements, such as reaching and grasping. This effort will provide a better understanding of not only how the brain controls movement, but also how it is affected by neurological diseases and spinal cord injuries that compromise arm, wrist and hand function.

Injuries and disorders affecting spinal cord function impact everyday life. Yet, in order to develop new treatments, scientists must understand the fundamental biology of how the spinal cord works. To address these questions, Goulding will lead a spinal cord circuit team, which will include Professor Samuel Pfaff, Professor Tatyana Sharpee, Associate Professor Axel Nimmerjahn, and Assistant Professor Eiman Azim, all from Salk, along with Professor David Golomb of Ben-Gurion University of the Negev, in Israel, to tackle the underlying biology that controls arm movement.

Within the neck lies a region of the spinal cord called the cervical spine. Brain circuits within the cervical spine control skilled arm, wrist and hand actions, such as throwing a dart or playing a guitar. Very little is known about the composition and structure of these circuits. With support from this grant, the team will create a high-resolution database with information about how the neurons communicate with one another and how each neuron contributes to skilled movement. The database will also include information about the neurons' molecular and electrophysiological properties, which will provide a better understanding of the makeup of each cell. Lastly, the researchers will develop testable predictive models of each neural loop to explore the network of interactions that occur to move a limb.

UNDERSTANDING SENSATIONS OF TOUCH, ITCH AND PAIN

Professor Martyn Goulding has received the National Institute of Neurological Disorders and Stroke Outstanding Investigator Award, which will grant him \$9.5 million dollars over the next eight years to further his pioneering studies on sensorimotor circuits in the spinal cord that are important for touch, itch and pain. Goulding, who holds the Frederick W. and Joanna J. Mitchell Chair, will be able to leverage these findings to develop a better understanding of how the spinal cord operates at a cellular level. More importantly, this award will enable his lab to take a high risk-high, highreward approach to address some of the fundamental challenges in the field that require a long-term investment and allow for the discovery of mechanisms that can then be used to develop novel therapeutic approaches for chronic disorders, such as itch, pain and spinal cord injury.



From left: Axel Nimmerjahn, Samuel Pfaff, Martyn Goulding, Tatyana Sharpee and Eiman Azim

RUSTY GAGE

Professor and President of the Salk Institute "We are inspired by the NIH funding of all of these exciting projects, which will lead to critical new insights into the mechanisms for how the brain and spinal cord control behavioral movement in our complex environment. These efforts will allow us to apply the most up-to-date methodologies to answer some of the complex questions in biology and may assist in the development of novel therapies for patients who have movement disorders, chronic pain, nerve damage or other afflictions."

STUDYING THE BRAIN'S DEVELOPMENT, EPIGENOME AND SKILLED MOVEMENT CIRCUITRY

Three NIH BRAIN Initiative grants will support four Salk scientists in their efforts to make new discoveries in neuroscience:

Nicola Allen, an associate professor and holder of the Hearst Foundation Developmental Chair, and Joseph Ecker, a Howard Hughes Medical Institute investigator, professor and director of Salk's Genomic Analysis Laboratory, were awarded a three-year, **\$4.6 million** grant to identify what factors regulate the development and regional specialization of support cells in the brain, called glial cells, and generate new tools to target these cells. Glial cell dysfunction is implicated in a multitude of diseases, including Alzheimer's disease.

Eiman Azim, an assistant professor and the William Scandling Development Chair, was awarded a fiveyear, **\$2.9 million** grant to identify neural circuits that establish the speed and precision of skilled limb movements, such as reaching and grasping. The project aims to shed light on more effective diagnosis and treatment of motor system disease and injury.

Joseph Ecker and Margarita Behrens, a research professor and member of Salk's Computational Neurobiology Laboratory, were together awarded a three-year, **\$5.4 million** grant to study the epigenomes of cell types and gene control elements in different regions of the human brain. **§**

WWW.SALK.EDU

DISCOVEB

Tackling a range of cancers

CANCER DISCOVERY 07/2019

SCIENCE ADVANCES 07/2019 Unlocking therapies for hard-to-treat lung cancers

In two recent papers, Salk scientists revealed insights into the most common– and deadliest—type of lung cancer: non-small-cell lung carcinoma (NSCLC). Some patients with this cancer can be treated with targeted genetic therapies, and some benefit from immunotherapies, but the vast majority of NSCLC patients have no treatment options beyond chemotherapy. In *Science Advances*, Professor Marc Montminy, Professor Reuben Shaw, first author Laura Rodón and colleagues showed that NSCLC tumors can be targeted by drugs that keep a cellular "switch" called CREB from triggering tumor growth.

Additionally, as detailed in *Cancer Discovery*, Shaw, first author Pablo Hollstein and colleagues discovered precisely why an inactivated gene commonly mutated in NSCLC, called LKB1, can result in cancer development. The surprising finding highlights how LKB1 communicates with two enzymes that suppress inflammation in addition to cell growth and could lead to new therapies for NSCLC.

WATCH www.salk.edu/shaw201912



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

SCIENCE 06/2019

SCIENCE SIGNALING 09/2019

Discovery of how colorectal cancer drug works may help patients

Colorectal cancer is a common lethal disease, and treatment decisions are increasingly influenced by which genes are mutated within each patient. Some patients benefit from a chemotherapy drug called cetuximab, but the mechanism was unknown, making doctors hesitant to prescribe it. Assistant Professor Edward Stites, first author Thomas McFall and colleagues have discovered the mechanism behind why some patients respond to cetuximab, which will help doctors identify more effective, targeted treatment plans for people diagnosed with colorectal cancer. The findings demonstrate the power of blending computational and experimental approaches, as well as how foundational scientific research can translate into an immediate impact for patients.

Sugars that coat proteins are a possible drug target for pancreatitis

Patients who suffer from hereditary pancreatitis (inflammation of the pancreas) have a 40 to 50 percent lifetime risk of developing pancreatic cancer. Assistant Professor Dannielle Engle and her team have provided the first evidence that a potentially powerful biomarker, CA19-9, causes the disease it has been correlated with, and they suggest that blocking this complex sugar could be used therapeutically to prevent the progression from pancreatitis to pancreatic cancer.

WATCH www.salk.edu/engle201912



Mapping normal breast development to better understand cancer

Breast cancer is one of the most prevalent cancers, and some forms rank among the most difficult to treat. Professor Geoffrey Wahl, co-first authors Christopher Dravis and Zhibo Ma and colleagues have used state-of-the-art technology to profile cells during normal breast development in order to understand what goes wrong in cancer. The team's findings, shared in a free online resource, lay the groundwork for understanding normal breast development and may lead to new strategies for tackling tumors.

DISCOVERIES



IMMUNE SYSTEM BIOLOGY

nune affect

"Autoimmune diseases affect around 1 in 30 people. This research opens the door to treating these patients without triggering harmful side effects."

Interleukin 17 is a molecule known to be at the root of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and psoriasis.

RONALD EVANS

NEW TARGET FOR AUTOIMMUNE DISEASE COULD ENABLE THERAPIES WITH FEWER SIDE EFFECTS

PNAS 08/2019

Researchers—including Professor Ronald Evans, Associate Professor Ye Zheng, first author Christina Chang and colleagues—have discovered a way to stop certain immune system cells from mistakenly attacking the body. Their findings suggest a new way to target Th17 helper T cells, a type of immune cell that produces interleukin-17, a molecule known to be at the root of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and psoriasis.



GENETICS



A NOVEL TECHNOLOGY FOR GENOME-EDITING A BROAD RANGE OF MUTATIONS IN LIVE ORGANISMS

CELL RESEARCH 08/2019 Professor Juan Carlos Izpisua Belmonte, co-first authors Keiichiro Suzuki, Mako Yamamoto, Reyna Hernandez-Benitez and colleagues, have developed a tool to edit the mouse genome, enabling the team to target a broad range of mutations and cell types. The new genome-editing technology, dubbed SATI, could be expanded for use in a broad range of conditions that arise from gene mutations, such as Huntington's disease and the premature aging syndrome progeria.



Human chromosomes imaged during the metaphase stage of cell division.

COMPUTATIONAL TOOL LETS RESEARCHERS IDENTIFY CELLS BASED ON THEIR CHROMOSOME SHAPE

In the nucleus of every living cell, long strands of DNA are tightly folded into compact chromosomes. Now, thanks to a computational approach developed by Professor Joseph Ecker, first author Jingtian Zhou and colleagues, researchers can use the architecture of these chromosome folds to differentiate cell types. The information about each cell's chromosome structure will give scientists a better understanding of how interactions between different regions of DNA play a role in health and disease.

DISCOVERIES



NEUROSCIENCE



From left: Xin Jin, Sho Aoki and Hao Li.

HOW EMOTION AFFECTS ACTION

eLIFE

Top: A cluster of basal ganglia output neurons (green) that convey emotion information to the movement circuit to control action. Dopaminergic neurons (red) are also present in the image. During high-stress situations, such as making a goal in soccer, some athletes experience a rapid decline in performance, known as "choking." Associate Professor Xin Jin and first authors Sho Aoki, Jared Smith and Hao Li have uncovered what might be behind the phenomenon: one-way signals from the brain's emotion circuit to the movement circuit. The study could lead to new strategies for treating disorders involving disrupted movement, such as depression, along with aiding in improving spinal cord injuries or physical performance under pressure.



From left: Peichao Li, Edward Callaway and Anupam Garg.

DECIPHERING HOW THE BRAIN ENCODES COLOR AND SHAPE



Humans can visually distinguish hundreds of thousands of distinct colors and shapes, but how does the brain process all of this information? Scientists previously believed that the visual system initially encoded shape and color with different sets of neurons and then combined them much later. But a study led by Professor Edward Callaway, along with co-first authors Anupam Garg and Peichao Li, has shown that there are neurons that respond selectively to particular combinations of color and shape, findings that provide valuable insight into how visual circuits are connected and organized in the brain.



NEUROSCIENCE

SCRATCHING THE SURFACE

OF HOW YOUR BRAIN
SENSES AN ITCHLight touch plays a critical role in
everyday tasks, such as picking up a
glass or playing a musical instrument.
In addition, it is part of the detection

glass or playing a musical instrument. In addition, it is part of the detection system that has evolved to protect us from biting insects, such as those that cause malaria and Lyme disease, by eliciting a feeling of an itch when an insect lands on our skin. Professor Martyn Goulding, first author David Acton and colleagues have discovered how neurons in the spinal cord help transmit such itch signals to the brain. Their findings have contributed to a better understanding of itch and could lead to new drugs to treat chronic itch, which occurs in such conditions as eczema, diabetes and even some cancers.



A cross-section from a dorsal root ganglion showing sensory neurons that transmit light-touch information from the skin to Y1 neurons within the spinal cord.

GLIA 07/2019 BRAIN'S ASTROCYTES PLAY STARRING ROLE IN LONG-TERM

Astrocytes tagged

antibody

with green fluorescent

MEMORY

Professor Terrence Sejnowski, first author António Pinto-Duarte and colleagues have discovered that starshaped cells called astrocytes help the brain establish long-lasting memories. The new work adds to a growing body of evidence that astrocytes, long considered merely supportive cells, may have more of a leading role in the brain and could inform therapies for disorders in which long-term memory is impaired, such as traumatic brain injury or dementia.

SALK SCIENTISTS DEVELOP TECHNIQUE TO REVEAL EPIGENETIC FEATURES OF CELLS IN THE BRAIN

Professor Joseph Ecker, Helmsley-Salk Fellow Jesse Dixon, and cofirst authors Dong-Sung Lee, Chongyuan Luo and Jingtian Zhou have developed a method to simultaneously analyze how chromosomes, along with their epigenetic features (such as the chemical tags on DNA), are compacted inside of single human brain cells. The work paves the way for a new understanding of how some cells become dysregulated, causing disease.

DISCOVERIES



NEUROSCIENCE



HOW MAMMALS' BRAINS EVOLVED TO DISTINGUISH ODORS IS NOTHING TO SNIFF AT

The world is filled with millions upon millions of distinct smells, but how mammals' brains evolved to tell those smells apart is something of a mystery. Now, Salk Distinguished Professor Emeritus Charles Stevens and Shyam Srinivasan from UC San Diego have discovered that at least six types of mammals, including mice and cats, can distinguish odors in roughly the same way, using circuitry in the brain that's evolutionarily preserved across species. This and future insights on odor coding and the mechanisms for distinguishing odors could be applied to the development of better machine learning or AI systems.

FINDING A CAUSE OF NEURODEVELOPMENTAL DISORDERS

Neurodevelopmental disorders arising from rare genetic mutations can cause atypical cognitive function, intellectual disability and developmental delays, yet it is unclear why and how this happens. Now, Assistant Professor Diana Hargreaves, first author Fangjian Gao and colleagues have identified the molecular mechanism linking a mutation in a complex of proteins to abnormal nervous system development. The team's findings bring researchers one step closer to understanding neurodevelopmental disorders such as Nicolaides-Baraitser syndrome.

WATCH www.salk.edu/hargreaves201912

"For the first time, we have been able to characterize the mechanism of a known gene mutation implicated in neurodevelopmental disorders."

DIANA HARGREAVES



From left: Diana Hargreaves, Nicholas Elliott and Fangjian Gao. PLANT BIOLOGY

GETTING TO THE ROOT OF HOW PLANTS TOLERATE TOO MUCH IRON



Plants with the GSNOR gene (left) grow better with high iron levels than plants without (right).

Iron is essential for plant growth, but with heavy rainfall and poor aeration, many acidic soils become toxic with excess iron. This can affect the availability of staple foods, such as rice. Associate Professor Wolfgang Busch, first author Baohai Li and collaborators have found a major genetic regulator of iron tolerance, a gene called GSNOR. The findings could lead to the development of crop species that produce higher yields in soils with excess iron.

WATCH www.salk.edu/busch201912

PLANT ENZYME COULD GUIDE DEVELOPMENT OF MEDICINES AND OTHER PRODUCTS

ACS CATALYSIS 09/2019

Plants can manufacture a stunning array of compounds that help them repel pests, attract pollinators and cure infections. Professor Joseph Noel, first author Jason Burke and collaborators uncovered how an enzyme called chalcone isomerase evolved to enable plants to make products vital to their own survival. The knowledge may inform the manufacture of products that are beneficial to humans, including medications and improved crops.

GENE IDENTIFIED THAT WILL HELP DEVELOP PLANTS TO FIGHT CLIMATE CHANGE



From left: Takehiko Ogura and Wolfgang Busch.

Similar to a worm searching for food, hidden underground networks of plant roots snake through the earth, foraging for nutrients and water. Yet the genetic and molecular mechanisms that govern which parts of the soil roots explore remain largely unknown. Associate Professor Wolfgang Busch, first author Takehiko Ogura and colleagues have discovered a gene that determines whether roots grow deep or shallow in the soil. In addition, the findings will also allow researchers to develop plants that can help combat climate change as part of Salk's Harnessing Plants Initiative, which aims to grow plants with roots that can store increased amounts of carbon underground for longer periods, reducing CO₂ in the atmosphere.

WATCH www.salk.edu/busch201912a

the promise and period period

BIG DATA

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"Big data," says Salk Research Professor Margarita Behrens, "is like looking at the night sky and seeing a beautiful, bright star, and then looking through a telescope and having that star get lost against the backdrop of so many others. Initially you can lose your bearings."

The concept of "big data" refers to the idea that vast quantities of data too unwieldy for human calculation can be manipulated and analyzed for meaningful patterns using computational algorithms. The idea has been around for decades, but only recently has a sufficient amount of data generation coincided with enough computing power to truly begin to realize the potential and the challenges—of big data.

It would take the human mind 190,000 YEARS

to read the data from just one 48-hour DNA-sequencing run from a high-throughput sequencer

^{BILLIONS OF BASES OF DNA, AND BEYOND}

In 2013, Behrens, along with Salk professors Joseph Ecker and Terrence Sejnowski, published a groundbreaking paper in the journal *Science* and, as she jokes, "opened Pandora's box."

The paper, for which Behrens and Ecker were the senior authors, provided the first comprehensive maps of epigenomic changes in the brain, known as DNA methylation. These chemical tags on a cell's DNA act as an extra layer of information, overlying the genome and controlling when genes are turned on or off. Behrens refers to the study results as Pandora's box because the "data was so rich."

The researchers set out with what initially seemed like a fairly straightforward goal: cataloging methylation patterns in mouse and human brain samples at different stages of brain development. But, to everyone's surprise, the data revealed a previously unknown level of complexity: the methylation patterns turned out to be specific to whether brain cells were neurons or glia (neurological support cells), which underwent extensive reconfigurations during different developmental stages. The discovery that methylation could be this specific to subtypes of cells opened up a whole new field of identifying and characterizing brain cells based on an ever-expanding set of cellular features including DNA sequence, DNA packaging, RNA sequence and others.

The work was surprising not only for what it revealed about the complexity and dynamism of brain circuitry, but also for what it showed about the power of big data to open up entire new universes of discovery.

Ecker, who directs Salk's Genomic Analysis Laboratory, is keenly aware of how much data scientists can now compute, not just for the epigenome but also to better understand new facets of the genome. Outside Ecker's office is a humming instrument called the NovaSeq 6,000, which is busily sequencing DNA. In 48 hours, it categorizes six terabases of DNA (that is 6 followed by 12 zeros—6,000,000,000,000). That's 6 trillion bases (letters), an amount that is far too vast for the human



mind to comprehend. If it took you one second to read each letter, it would take 190,000 years to read all the letters from just one 48-hour DNA-sequencing run.

And this is 6,000 times greater than the first nextgeneration sequencer that Ecker had purchased only about a dozen years ago, in 2007. So, large computing power is essential for "reading" all of this information.

"We are now to the point where we're looking at the DNA sequences of individual cells from millions of cells in the brain," says Ecker, who is also a Howard Hughes Medical Institute investigator.

Ecker and collaborators, both at Salk and elsewhere, are trying to capture different kinds of genetic data what the genes are, how they're being regulated, how the chromosomes are folding and how the genes are being expressed—all from the same cell, to develop a comprehensive understanding of individual brain cells. By developing such detailed blueprints of healthy cells, scientists will be better able to pinpoint what goes wrong in a variety of diseases, such as cancer and developmental or neurological disorders.

Ecker, Salk-Helmsley Fellow Jesse Dixon and collaborators recently published a pair of papers

"We are now to the point where we're looking at the DNA sequences of individual cells from millions of cells in the brain." JOSEPH ECKER

describing big data computation tools and techniques they have developed, making headway in this area. The first paper, published in *Proceedings of the* National Academy of Sciences, details an algorithm that lets researchers identify cells based on the shape of their chromosomes. The second paper, published in Nature Methods, shows how the team combined two different analysis techniques into one method, enabling the team to identify gene regulatory elements in distinct cell types. Because the majority of the human genome is made up of regulatory DNA-stretches of DNA that don't themselves encode proteins but that help control whether, and when, genes are expressed in any given cell—insights into the regulatory aspects of the genetic code have the potential to greatly further our understanding of health and disease. (See this issue's "Discoveries" for details.)

THIS IS YOUR BRAIN ON BIG DATA

Big data is a direct result of progress in computing and artificial intelligence (AI), the effort to have machines mimic the intelligence of the human brain. Advances in the field of neuroscience, therefore, have greatly informed AI. Sejnowski, head of the Computational Neurobiology Laboratory and holder of the Francis Crick Chair, has been at the leading edge of the AI movement since the 1980s.

"The brain has been in the big data business for a lot longer than we have," Sejnowski says. Indeed, the brain has been the epitome of big data crunching somehow it is able to process and make sense of enormous amounts of data. This data deluge can also overwhelm a brain, which must decide what data to save and what data to ignore. Thus, brains have become an inspiration for new ways to develop AI and other tools. As Sejnowski writes in his 2018 book, *The Deep Learning Revolution: Artificial Intelligence Meets Human Intelligence*, "The recent progress in artificial intelligence was made by reverse engineering brains. Learning algorithms in deep learning networks are inspired by the way that neurons communicate with one another and are modified by experience."

In 2018, as described in the journal *Nature*, Sejnowski and collaborators at UC San Diego trained robotic gliders to soar like birds using an AI approach called reinforcement learning, inspired by how animals learn to adjust their behavior based on the outcome of their actions to achieve goals. The researchers designed field experiments in which the gliders learned on their own how to soar upwards in thermals like birds, results that could help improve the efficiency of unmanned aerial vehicles.

Apart from his expertise on various types of artificial intelligence, Sejnowski has used advanced microscopy and computational algorithms to make profound discoveries about memory, including finding that the brain's memory capacity is 10 times greater than had been thought, and that following stimulation, the sizes of synapses—the junctions between neurons



Computational analysis indicated that the brain's memory capacity is 10 times greater than had been thought.

where memories are stored—can expand and contract as needed, increasing the range of sizes like an expandable file folder. These findings were detailed in *eLife* in 2016 and in *Proceedings of the National Academy of Sciences* in 2018, respectively.

And breakthroughs related to data are only speeding up. As Sejnowski writes in his book, "Data are the new oil. Learning algorithms are refineries that extract information from raw data; information can be used to To process how the brain's neurons exchange information on sights, sounds and smells, vast amounts of data are applied to statistics and probability models.

create knowledge; knowledge leads to understanding; and understanding leads to wisdom."

Professor Tatyana Sharpee, like Sejnowski, is a member of the Computational Neurobiology Laboratory, where she focuses on understanding how the brain's billions of neurons exchange information to process sensory information, such as sights, sounds and smells. To decipher vast amounts of experimental data, she applies mathematical strategies, including statistics and probability models.

In one example, Sharpee's lab yielded a statistical way to understand odor data, which the team was then able to map to discover regions of odor combinations humans find most pleasurable—work that could open new avenues for food scientists, allowing them to engineer smells and tastes. In another discovery, Her lab also used a statistical method to discover that neurons in a region of the brain called V2, which is part of the visual system, were responding to combinations of edges in scenes from nature, such as the outlines of leaves and the texture of bark. The work might improve object-recognition algorithms for self-driving cars or other robotic devices.

"It seems that every time we add elements of computation that are found in the brain to computervision algorithms, their performance improves," Sharpee says. "The challenge is to have the courage to follow the directions where data and experiments lead us rather than settling on approaches that yield immediate results."

The promise of big data, then, is that meaningful patterns are waiting to be discovered within sets of signals; the challenge is that not all patterns will be meaningful. And in the worst cases, results from machine learning may amplify the biases brought by human interpretation and judgement.

USING COMPUTATION TO INFORM CANCER RESEARCH

Cancer biologist Edward Stites is particularly sensitive to both the benefits and the detriments inherent in big data approaches. In his field, time spent chasing down false leads can mean delaying the pursuit of promising ones.

"As a physician who previously trained in mathematics, I completely appreciate the importance of bringing more mathematics, more computation and more data analysis to problems of medical importance," says Stites, an assistant professor in the Integrative Biology Laboratory. "But as someone who has trained in both of these areas, I also think it is critical that these efforts take careful consideration of both the underlying mathematics of utilized methods and the biology that is being studied."

Stites works on problems in cancer biology—a field where the multifaceted nature of the disease complicates progress by traditional methods. However, his lab is using mathematical and computational methods to extrapolate from available data to generate completely new ideas for solutions to those problems. In a paper published in *Science Signaling* in September 2019, Stites and first author Thomas McFall, a Salk postdoctoral fellow, describe how, using a combination of computational and experimental methods, they discovered the mechanism for how the colorectal cancer drug cetuximab works. (See this issue's "Discoveries" section for details.) Knowing how a drug works helps doctors feel more confident in prescribing it, which could benefit upwards of 10,000 colorectal cancer patients per year, according to the researchers.

Stites' team first used computational models to simulate complex reactions and tease out differences between healthy genes and mutant colorectal cancer genes based purely on biochemical information, yet with the ability to explain what was seen in a clinical trial. Their mathematics told them where to look in their laboratory tests to identify the molecular mechanism by which colorectal cancer patients with a specific gene mutation (KRAS G13D) responded to cetuximab. The researchers then replicated their findings across three genetically distinct cell lines to demonstrate the reliability of the results.

The work is an example of how, in the best cases, big data is a tool that enhances researchers' approaches. Computers may find patterns, but you need humans to understand their meaning.

Knowing how a drug works helps doctors feel more confident in prescribing it, which could benefit upwards of 10,000 colorectal cancer patients per year.

Right: Dividing colon cancer cells (green).



SEPARATING THE SIGNAL FROM THE NOISE

Assistant Professor Dmitry Lyumkis says that in his field of extremely highresolution microscopy known as cryo-EM, there's a well-known cautionary example called "Einstein from noise." Just as static on the radio can make it hard to hear music clearly, scientific "noise" refers to an unwanted signal that interferes with information of interest. So, in the cryo-EM example, researchers trained an algorithm using images of Albert Einstein. When they then ran 1,000 images of pure white noise through the algorithm, the pattern it found was . . . Einstein's face. The pattern was not really there, but the algorithm found it based on how it had been trained.

"It was a case of garbage in, garbage out," says Lyumkis, echoing Stites' notion that researchers need to pay careful attention to what their training algorithms are learning, because if the algorithms are not gleaning the right lessons, any results they offer could at best be useless and at worst lead research astray.

As a structural biologist, Lyumkis uses cryo-EM to directly visualize large molecular assemblies isolated from cells under near-native conditions. Because molecular structure is so intimately tied to function in biology, by better understanding the architecture and atomic-level details of large molecular assemblies, scientists may gain clarity on various types of dysfunction that lead to disease, such as HIV. In 2017, in work published in *Science*, Lyumkis' lab solved the atomic structure of a key protein machine called an "intasome," which allows HIV to integrate into human host DNA and replicate in the body. HIV intasome structures have eluded researchers for decades. The findings yield atomic-level clues that are now informing the development of new drugs.

Lyumkis' field has particularly benefited from advances in computing power. Cryo-EM data sets can comprise hundreds of thousands of individual images that have to be computationally analyzed in order to create an accurate three-dimensional reconstruction of a biological sample.

Lyumkis says that at the turn of the millennium, the field was struggling to resolve molecular assemblies to better than 1 nanometer resolution (one nanometer is 100,000 times smaller than the diameter of a hair). By 2008, cryo-EM researchers were able to achieve three times better resolution.

"One way to think about it is that, between the years of 2000 and 2010, microscopes and samples didn't change very much," Lyumkis says. "But what changed is the computing power and algorithms and how much data we can crunch. Improvements in computing power and our ability to make sense of increasingly more complex datasets at higher resolution are continuing to extend the boundaries of the types of questions we can ask."

> "Einstein from noise" is a cautionary example from cryo-EM.

An algorithm trained using images of Albert Einstein along with 1,000 images of pure white noise resulted in a pattern of Einstein's face.

THE BIG PICTURE

Salk Vice President, Chief Science Officer and Professor Martin Hetzer is keen to harness the power of big data by incorporating computational approaches that enhance the experimental approaches of bench science for which the Institute is renowned.

In December 2018, Hetzer and a collaborative team at Salk published a paper in *Genome Biology* describing how they used machine learning to analyze skin cells from the very young to the very old to find molecular signatures that can be predictive of age. Using custom algorithms to sort the data, the team found certain biomarkers indicating aging, and were able to predict a person's age with less than four years of error on average.

"The next big trend in science is about understanding massive amounts of data and will take new kinds of collaborations to do so," Hetzer says.

The process is still ramping up, and scientists need to make sure plenty of checks and balances exist to verify the data and results along the way. But, in the end, Behrens' Greek myth analogy of big data may be apt, because after problems flew out of Pandora's box, what was left was hope. And although scientists are often generating more data than they and computers can analyze, they are optimistic that the analysis will eventually catch up, and big data will help lead to answers for some of biology's most urgent questions.

OBSERVATION

Learning from Lagoons

Professor Joseph Noel, director of Salk's Jack H. Skirball Center for Chemical Biology and Proteomics, is in his element as he guides *Inside Salk* on a tour of the San Dieguito Lagoon.

His eyes light up as he picks up the pace to point out the extensive underwater meadows of verdant eel grass that are thriving in this intertidal zone. He describes how the beds provide shelter for crabs and mollusks and serve as a breeding ground for small fish. Local wetlands, like this one, are vital for maintaining healthy ecosystems. They act like sponges to hold water during heavy rains, which prevents flooding, and they can filter polluted water. A wetland is also a carbonstorage powerhouse, capable of stockpiling significantly more carbon than dry land.

Noel, who holds the Arthur and Julie Woodrow Chair, is fascinated by how lagoon ecosystems evolved to sequester so much carbon. His goal is to learn from nature in order to help crop plants store more carbon in their roots. Doing so will decrease atmospheric carbon dioxide to mitigate the effects of global warming.

Inside Salk sat down with Noel to learn about his path to becoming a scientist and about his current work researching coastal wetlands to help combat climate change.



Your work spans many disciplines, from chemistry to structural biology to the metabolism of plants. What field of science do you consider yourself a part of?

JN: That is actually a really hard question. I grew up loving nature, and when I received more formal schooling, I became very interested in both biology and chemistry. Yet, those interests evolved when I went to graduate school. There, I became focused on structural biology, where I could examine things on a molecular or atomic level.

More than any place I have ever been, the Salk Institute really encourages you to follow your interests rather than pigeonholing yourself into a particular discipline. I feel grateful to be involved and supported in so many areas.

Speaking of your interests, how did you become involved in studying plants in the first place?

JN: I was kind of an unusual kid; I took an interest in plants at a very young age.

My grandmother and great-grandmother are the ones that sparked my curiosity in plants. They lived through the Great Depression and World War II, where citizens were encouraged to try to grow as much of their own food as possible so that they had enough to share with the soldiers. These "victory gardens" were still around when I was growing up, and I loved helping with all of the gardening. Then it just, pardon the pun, blossomed from there.

What was your favorite part of gardening?

JN: I was very interested in composting. I became fascinated by the biology of the soil, and in composting and nurturing plants to get the best yield and the best taste. I would collect grass clippings from all of the neighbors, gather the fallen leaves and frequent the local farms for manure to add to my compost.

When I was a bit older, I worked at the local town park. One summer weekend, a circus came to perform at the park. They had all sorts of exotic animals, including elephants, camels and some giraffes. The Monday after the circus left, I went around and scooped up all the manure from the animals for my compost. I scattered some of the elephant poop on my tomatoes, and I had the best tomatoes in town after that!

When did you start focusing your academic research on plants?

JN: I started scientifically working on plant systems when I arrived at the Salk Institute. Fortuitously, some of my plant colleagues are some of the best plant scientists in the world. For example, Professor Joanne Chory, who is the executive director of the Harnessing Plants Initiative at Salk, renewed my interest in plants. Collaborating with Joanne has been a great opportunity for me to study the systems in plants that give rise to all the chemical diversity that we see in nature.

What is the current focus of your lab at Salk?

JN: My lab began by looking at secondary metabolites, which are molecules that allow plants to survive and prosper in a variety of different ecosystems. We use a fancy microscope to peer down and look at the individual atoms, as well as at proteins called enzymes. These enzymes stitch together all the small atoms that build these really complex chemicals. I want to understand their mechanisms of action and how evolution is reshaping them.

Building on this idea, I want to know if we can reshape these mechanisms for beneficial purposes, such as creating a medicine or fighting global climate change. It is this basic, fundamental research that fascinates me and keeps me awake at night.

Do you think that plants could help humans with the global climate crisis?

JN: For a number of years, we at Salk have thought about how plant biology, plant biochemistry and genetics can help reshape crops, such as corn and rice, so that they can survive in the face of changing climates and growing zones and still produce sufficient amounts of food.

Plants do this miraculous thing of using the energy of the sun and atmospheric carbon dioxide to build molecules that essentially store carbon in their roots. We want to harness this natural process to allow plants to store even more carbon for longer periods of time.

What is the Harnessing Plants Initiative?

JN: The Harnessing Plants Initiative is an ambitious effort we're undertaking to try to mitigate climate change using an unexpected source: cork. When I had my own garden as a kid, I tried to compost the corks from wine bottles. It did not work very well. This is when I first discovered that cork, which is made of a substance called suberin, resists decomposition. It is also made out of quite a bit of carbon that comes solely from carbon dioxide, a greenhouse gas.

Specifically, the Harnessing Plants Initiative aims to use the power of plants to pull large quantities of carbon dioxide out of the atmosphere; convert its carbon atoms into molecules that resist decomposition, such as suberin; and store it in their root systems. We want to coax the plant to make a little bit more suberin so that each plant that you would grow, particularly if it is a crop, could actually leave behind more carbon in the soil than it rereleases when it decomposes.

We are very fortunate at Salk because we have a great plant team here that specializes in roots, genetics and plant processes. We're optimistic we can find natural varieties of plants that have the most extensive, deepest root systems to store the most carbon.

Why do you want to implement this technology in crop plants?

JN: Crop plants essentially grow over the entire terrestrial globe, so the infrastructure already exists. In theory, if we can coax plants into pulling more carbon dioxide out of the air and converting some of it into forms that will stay behind in the soils, then we can draw down some of the carbon dioxide in the atmosphere. Suberin also helps plants to resist drought as well as flooding and diseases. If we succeed in doing this, we might be able to make a dent in this impending crisis of climate change.

Do you think you have enough time to succeed?

JN: We do not have much time, and that is why we are using these modern methods in biology and genetics. We need to speed up the process so that crops can become not only the food we eat, but also a way of mitigating the harms associated with too much carbon dioxide in the atmosphere. The Harnessing Plants Initiative has gained traction beyond just the walls of Salk, not only with the public but also other scientists. I am actually very optimistic that we can do this.

There's a second arm of the Harnessing Plants Initiative that involves coastal plants. Can you tell us about that?

JN: The Initiative began by thinking about what substances in plants resist decomposition. So I started doing research about plants that grow in environments where their roots are wet, such as a lagoon. When you flood a plant, the oxygen that the roots need to breathe is restricted. One way that plants adapt to this is that they make more suberin—more cork—in their roots.

Wetlands globally, whether freshwater or marine or in-between brackish conditions, can trap up to 100 times more carbon perunit area than terrestrial earth. They are astonishing carbonsequestration ecosystems. Surprisingly, these natural ecosystems have not previously been examined on a molecular level.

At Salk, we are examining coastal plants to figure out how they were able to evolve to thrive in these flooded ecosystems. So, rather than reinvent the wheel, we are going to examine the genomes of plants that have already evolved to have more suberin in their roots, to see how these genomes developed over the last 40, 50, 60 million years. Then we can use this information to select the best crop varieties that also can produce the most suberin to store more carbon.

What do you think the future holds for plants on earth?

JN: I think the future for plants is fantastic. However, if we do not solve this climate crisis, the future for humans and other warm-blooded animals is not looking good.

Plants were here first. Photosynthesis first emerged on the earth around 3 billion years ago, in oceans and in inland seas. Plants have experienced atmospheres that have gone from 250 ppm of carbon dioxide, which is around what it was in the 1850s, before the industrial revolution, all the way up to 2,000 ppm, far above where we are even headed now. They thrived in both of these conditions. So plants will figure out a way; they are probably one of the most adaptable living things on the planet. Plants will likely be here long after humans and other animals have gone extinct.

Any last thoughts?

JN: The ironic thing about all of this research is that I am originally from a small coal-mining town in western Pennsylvania. The men in my family were all coal miners, including my father. I am the first generation to get out of the coal mines, and here I am, trying to fight global climate change that has been caused by humanity's dependence on fossil fuels, such as coal. Hopefully, I can help make a positive change. S

RESOLUTION

The root tip of the model plant *Arabidopsis thaliana* senses the environment and adjusts root growth in response. Labeled in red are three layers of cells on the root's surface to the depth of 20 micrometers. Green indicates gene activity associated with lengthening the root. This image, from the lab of Wolfgang Busch, and others like it allow researchers to observe plants under extreme environmental conditions, with the aim of growing plants that can withstand climate change-induced stress.

Credit: Matthieu Platre, Busch Lab



"Our greatest responsibility is to be good ancestors."

JONAS SALK

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Uncovering the mysteries of depression

At some point in their life, one in six people in the United States will experience depression, according to the American Psychiatric Association. Major depressive disorder is one of the most prevalent psychiatric conditions, and a substantial public health problem. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medication for depression, yet they are ineffective in almost one-third of patients. Staff Scientist Krishna Vadodaria wants to know why.

Vadodaria is using novel laboratory techniques to search inside human neurons to discover the biological basis for psychiatric disorders and why some depressed patients do not respond to SSRIs. "As a staff scientist, I am able to stay focused on the science, and I have the freedom to pursue project ideas that interest me most," Vadodaria says. She hopes her research will eventually lead to improved treatment strategies and better outcomes for patients with depression and other psychiatric disorders.

INSIGHTS

Krishna Vadodaria

Staff Scientist

DAY-TO-DAY

As a staff scientist in the Gage lab, Vadodaria contributes to new ways of studying psychiatric disorders by using patient-derived neural cells. She uses stem-cell reprogramming techniques to turn patient skin-cell samples into induced pluripotent stem cells (iPSCs) and then into neurons. This relatively new technology, called iPSC-based neural modeling, allows Vadodaria to directly observe the neural differences between depressed patients that respond to SSRIs and those who do not.

Specifically, Vadodaria examines how SSRIs increase the levels of the neurotransmitter serotonin at synapses (the locations where neurons communicate) and how patient neurons respond. Recently, she found that the neurons of patients with SSRI-resistant depression are shaped differently than the neurons of patients who respond to SSRIs and are more active in response to serotonin. Thus, the neurons of patients with SSRI-resistant depression may be making inappropriate connections with other neurons and may have a different response pattern than they are supposed to have. Vadodaria's results have led to two first-author publications this year, both in the journal Molecular Psychiatry. The findings also have implications for other psychiatric conditions that involve abnormalities in the serotonergic system, such as bipolar disorder and schizophrenia.

INSPIRATION

Vadodaria recently welcomed her first child, a baby boy named Arjun. "Having a child has been a humbling learning experience, as I am witnessing firsthand how biological states can affect mental states," says Vadodaria. "Experiencing the sheer power of biology reaffirms my desire to continue studying the neurobiology of psychiatric conditions."

SUPPORT SYSTEM

Today, Vadodaria's parents live in India, but they visit San Diego. "I have been blessed to have parents that have selflessly encouraged me to pursue my interests and strive for excellence. They never discourage me from taking the harder route, even when that means living halfway around the world from them," she says.

FUN FACT

Vadodaria holds a second-degree black belt in a style of karate called Shōtōkan. For years, she taught students of all ages the strong basic stances (kihon), the patterns of powerful movements (kata) and the dynamic sparring techniques (kumite). The selfdiscipline she learned from Shōtōkan has become a part of her life, and she credits this skill with helping her to be a determined and diligent scientist today.

PATH TO SALK

Vadodaria is originally from India but spent her teenage years near the city of Winston-Salem, in northwestern North Carolina; her father was an IT consultant whose job brought the family to the United States for his longer projects. After living in North Carolina, her family returned to India. She earned a bachelor's degree at the University of Mumbai, where a supportive professor in the microbiology department inspired her to study biology through experimental science.

Vadodaria's passion for discovery only grew from there. While earning her master's degree at the Tata Institute of Fundamental Research, in Mumbai, she was exposed to the captivating world of the neurobiology of mood and behavior. She examined early-life stressors in animal models of depression, and looked at how maternal separation affected the neural pathways related to the stress response later in life. After completing her master's degree, she pursued her PhD at the Swiss Federal Institute of Technology in Zurich, studying adult neurogenesis, a form of neural plasticity thought to be dysregulated in depressive disorders.

Once she graduated, Vadodaria sought postdoctoral fellowships where she could continue to study the neurological basis of psychiatric disorders. Having lived on three continents, she believed that the United States offered a great chance to conduct cutting-edge research. "I was elated to have an opportunity to do my postdoctoral training at the Salk Institute, where I could continue to grow as a scientist under the guidance of such a renowned and respected neuroscientist as Professor Gage."

LONG VIEW

"I am inspired to continue working in this field because I believe that new discoveries and knowledge gained from experimental research can make an impact on how we understand and treat psychiatric disorders," says Vadodaria. "Psychiatric disorders, such as depression, pose an interesting research challenge because they are diverse in their symptomology, not easy to model using animals, and stem from multiple genes. The long-term goal of my research is to use patient-derived neural cells to better characterize the cellular neurobiology of psychiatric diseases. Science is my happy place, and I hope I can make a positive impact through my research."

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Corina Antal

From tagging sharks to tackling tumors

"There are so many scientists who climb. I'll be climbing my route and all of a sudden I hear someone talking about CRISPR or DNA sequencing."

Corina Antal is not your typical researcher. From wrangling bull sharks to climbing mountains to seeking a cure for pancreatic cancer, Antal follows her passions, and she is redefining what it means to be a scientist.

Antal grew up in Chicago, with a keen interest in marine biology; she frequented the nearby world-renowned Shedd Aquarium because the underwater world captivated her imagination. After graduating from high school, Antal moved to Florida to pursue a degree in marine biology at the University of Miami.

In Miami, Antal wanted to understand the population dynamics, diet and genetic differences of sharks in order to aid in global conservation efforts to maintain healthy oceans. Antal would take a boat into Biscayne Bay, hop into the water and then attempt to hold a shark while another student tagged it and took a biopsy.

Although her research was invigorating, Antal wondered what it would be like to conduct research that had a more direct impact on humans. The summer of her junior year, she stumbled across an opportunity to study a chronic bladder condition called interstitial cystitis.

"I wanted to have a bigger impact on human health and disease," says Antal. That desire led her to pursue a PhD in biomedical sciences at UC San Diego. There she examined the role of protein kinase C (PKC) in tumors by trying to identify how cancer-associated mutations affected this enzyme at the molecular level.

"We expected that the PKC mutations would cause tumors. Surprisingly, we found the opposite," says Antal. "PKC was acting as a tumor suppressor, so our research suggested a shift in therapeutic strategies targeting PKC."

Antal's graduate work became nationally recognized for its potential to point to new treatments; she made the 2016 Forbes "30 Under 30" list in the science category for her discovery. "While I was in graduate school, my mother was diagnosed with triple-negative breast cancer, an aggressive and difficult-to-treat cancer," says Antal. "This inspired another change in my career trajectory as I decided that I wanted to tackle the deadliest cancers."

Upon graduating, she joined the lab of Ronald Evans at Salk, where Antal chose to focus on pancreatic cancer, which is difficult to treat and has a poor prognosis. Research in the Evans lab focuses on foundational and translational discoveries, such as figuring out that a chemically modified form of vitamin D can break down the barrier that protects pancreatic tumors, allowing for better drug delivery and immune cell support.

During one of her recent research projects at Salk, Antal identified RNA-binding proteins that seem to play a role in pancreatic cancer. Serendipitously, one of the country's leading experts in RNA-binding proteins was located across the street, at UC San Diego, and he happens to be Antal's husband. As it turns out, Professor Gene Yeo was in the process of writing a paper about the exact protein Antal was interested in. They are now starting an academic collaboration to examine how these RNA-binding proteins affect pancreatic cancer development.

Despite the fact that their work happens to overlap, Antal did not meet Yeo through academic pursuits. They met while training for the Coeur d'Alene Ironman Triathlon (a 2.4-mile swim and a 112-mile bike ride, followed by a 26.2-mile marathon) when she was in graduate school. These days, Antal and Yeo have less time for Ironman training, but they still manage to dash outside to go rock climbing. Two of their favorite spots are Red Rock Canyon and Holcomb Valley Pinnacles.

"There are so many scientists who climb. I'll be climbing my route, and all of a sudden I hear someone talking about CRISPR or DNA sequencing. It's a great community," says Antal.

She also recently became involved with the Pancreatic Cancer Action Network and started a Salk team to participate in the PurpleStride Walk and Run event. Through these experiences, she has met a lot of pancreatic cancer patients, and these relationships drive her to keep searching for a cure.

"I feel like my career has been a series of haphazard opportunities," says Antal with a laugh. "But I'm very happy where I ended up."



THE KAVLI FOUNDATION GIFTS SALK \$3 MILLION FOR CUTTING-EDGE NEUROSCIENCE RESEARCH

In August, The Kavli Foundation committed \$3 million to support ongoing neuroscience research at the Salk Institute as part of the joint UCSD-Salk Kavli Institute for Brain and Mind (KIBM). The gift—matched by an additional \$3 million from Salk—brings \$6 million to the KIBM endowment to enable faculty in neuroscience to work on questions whose answers will have the most impact in the field.

The Kavli Institute for Brain and Mind was established through a \$15.5 million endowment commitment from The Kavli Foundation, shared between Salk and UC San Diego. KIBM's mission aims to support research that furthers an understanding of the origins, evolution and mechanisms of human cognition, from the brain's physical and biochemical machinery to the experiences and behaviors called the mind.

The Salk Institute is home to many of the world's leaders within the field of neuroscience, which includes computational neuroscience, spinal circuitry, pain, movement, learning, vision, psychiatric and developmental disorders, and agerelated decline. The Kavli Foundation also generously gifted \$300,000 to Salk Professor and new KIBM member Kay Tye, holder of the Wylie Vale Chair. Tye's lab seeks to understand the neural-circuit basis of emotion that leads to motivated behaviors such as social interaction, reward-seeking and avoidance. Her lab employs a multidisciplinary approach to find mechanistic explanations for how these emotional and motivational states influence behavior in health and disease.

"The Kavli Institute for Brain and Mind is a nexus for neuroscience research, helping to facilitate collaborations across two world-renowned institutes—Salk and UC San Diego—as well as other neuroscience research centers around the world," says Stephanie Albin, science program officer at The Kavli Foundation.

In recognition of the \$3 million matching gift, Salk has named Institute laboratory space the Kavli Institute for Brain and Mind Laboratories for Neurobiology. The lab space is for research conducted by the following up-and-coming neuroscientists: Nicola Allen, associate professor and the Hearst Foundation Developmental Chair; Kenta Asahina, assistant professor and holder of the Helen McLoraine Developmental Chair in Neurobiology; Eiman Azim, assistant professor and the William Scandling Developmental Chair; and Xin Jin, associate professor.

SALK SCIENTISTS MARGARITA BEHRENS AND JOSEPH ECKER AWARDED \$1.6 MILLION TO EXPAND HUMAN CELL ATLAS

Joseph Ecker, professor and director of Salk's Genomic Analysis Laboratory, and Margarita Behrens, a research professor in Salk's Computational Neurobiology Laboratory, will receive more than \$1.6 million over three years as part of a Seed Networks grant from the Chan Zuckerberg Initiative (CZI). The award will support their work to incorporate data representing human brain diversity into the Human Cell Atlas, a comprehensive database that covers all of the cell types in the human body. Their cutting-edge research will enable a better understanding of the human brain in health and disease.



Margarita Behrens and Joseph Ecker



NEW RANKINGS PLACE SALK SCIENTISTS AMONG MOST HIGHLY CITED IN WORLD In August 2019, a new, comprehensive study published in the journal *PLOS Biology* ranked Salk professors Ronald Evans, Rusty Gage and Tony Hunter in the top 0.01 percent of the top 105,000 scientists worldwide, based on citations. The faculty are world-leading experts in the fields of metabolism, neuroscience and cancer.

SPOTLIGHT



On the Leading Edge

Awarded semi-annually by peer review, Salk's Innovation Grants Program is critical to sustaining emerging science.

The program, launched in 2006 by then-Board chair Irwin Jacobs and his wife, Joan, embodies the vision and spirit of the Institute that bears Jonas Salk's name. The Innovation Grants Program, now supported by a number of forwardthinking donors, is designed to fund out-of-thebox ideas that hold significant promise but may not yet have the track record to attract attention from more traditional funding sources.

Innovation grant awards have enabled many Salk researchers to garner additional investments from prominent grant-makers to continue to pursue potentially life-changing discoveries. Below are the awards announced in the past year (winter of 2018—summer of 2019).

THE 2019-2020 ROSE HILLS FOUNDATION INNOVATOR GRANT PROGRAM

Assistant Professor Kenta Asahina was named The Rose Hills Foundation's 2019-2020 Innovator Grant Program awardee, in coordination with Salk's Innovation Grants Program. The award provides \$100,000 for Asahina to explore a novel approach to studying aging. Asahina, who is holder of the Helen McLoraine Developmental Chair in Neurobiology, will study how the nervous system can contribute to lifespan difference between sexes. Females in many animal species, including humans, live longer than males. Asahina's work aims to provide a novel paradigm for studying aging, with a potential to understand the biological mechanisms that specify human lifespan.

INNOVATION COLLABORATIVE GRANTS

JULY 2019

Directors and Professors Ronald Evans and Susan Kaech and Associate Professor Ye Zheng will lead a team in exploring if a healthy diet and exercise reduces levels of inflammation and renders tumor cells more sensitive to the immune system, with the goal of expanding the efficacy of immunotherapies.

Professors Alan Saghatelian, Joseph Noel and Jan Karlseder will undertake a multipronged approach to develop small-molecule inhibitors of the DNA repair regulator CYREN, with the goal of specifically sensitizing tumor cells to genotoxic therapy.

INNOVATION GRANTS

DECEMBER 2018

Professor Juan Carlos Izpisua Belmonte seeks to determine whether epigenetic inheritance can take place in mammals across generations. If possible, this would mean that the experiences that have shaped the genetic expression of parents (e.g., adaptations to environmental challenges) could be passed to children—a significant question in evolutionary biology, which remains unanswered.

Associate Professor Sreekanth Chalasani, Postdoctoral Fellow Chen-min Yeh and Staff Scientist Gerald Pao seek to answer the question of whether or not brain activity can be used to control a robot. They will leverage advanced live microscopy techniques, in addition to supercomputer technology, to see whether or not the brain activity of zebrafish larvae can control a fish robot.

Professor and Laboratory Head David Schubert and Staff Scientist Antonio Currais are identifying new drug candidates for Alzheimer's disease using screens for mitochondrial dysfunction. Specifically, they will look at a large library of plant extracts that have pharmacological value to see whether any have protective traits that are able to preserve mitochondrial function—one of the earliest clinical challenges in Alzheimer's.

Director and Professor Joseph Ecker is working to develop a method that allows researchers to record the transcriptional activity within a cell into the genetic code so that they can analyze the cascade of transcriptional events that occurs during an organism's development as well as cell reprogramming.

Professor Edward Callaway is undertaking a project that will develop innovative methods for flexible, high-throughput analysis of specific brain-cell types across any species, including humans, that can identify the genetic enhancers that restrict expression of genes that have been passed from one cell (or whole organism) to another.

SPOTLIGHT



Salk's Pedal the Cause team

PEDAL THE CAUSE MAKES LARGEST CONTRIBUTION **TO FUNDING CANCER** RESEARCH



Nearly \$3 million was raised by last year's Padres Pedal the Cause cycling event, providing crucial funding for novel cancer research in San Diego, including Salk faculty.

Salk Institute scientists Professor Tony Hunter, Assistant Professor Graham McVicker, Professor Joseph Ecker and Helmsley-Salk Fellow Jesse Dixon were among the collaborative teams of researchers and medical professionals to receive funding to study pediatric and brain cancers.

The 2019 Salk Cancer Center team included 54 riders. walkers, runners and volunteers who joined together with more than 3,000 others in an effort to support cutting-edge research to accelerate cures for cancer. The event took place on November 16, and highlights included riding over the Coronado Bridge, through Coronado and on the Silver Strand. All cycling routes, which ranged from 25 miles to 100 miles, ended on center field at Petco Park in downtown San Diego.

Padres Pedal the Cause provides research grants to crossinstitutional teams of scientists and physicians from four of San Diego's top cancer organizations: Salk Institute, Moores Cancer Center at UC San Diego Health, Rady Children's Hospital and Sanford Burnham Prebys Medical Discovery Institute. The annual cycling event has raised over \$10 million since its inception in 2013, funding 59 projects on all types of cancers.

SALK TEAM RAISES FUNDS FOR PANCREATIC **CANCER RESEARCH**

Team Salk Cancer Center raised nearly \$5,000 in PurpleStride 2019, a walk to end pancreatic cancer held Cancer Action Network.



Ron Evans and Tony Hunter

Salk's PurpleStride team, captained by Corina Antal (first row, second from left), who is featured in this issue's "Next Gen."

Groundbreaking Salk discoveries on the go!





- NOW AVAILABLE -

Where Cures Begin is the official podcast of the Salk Institute for Biological Studies. In each episode, co-hosts Allie Akmal and Brittany Fair interview Salk researchers about their bold research efforts and learn about the scientists' lives outside of the lab. The first season shares conversations with President and Professor Rusty Gage, Professor Joanne Chory and Assistant Professor Danielle Engle, to name a few. Join us to hear how Salk researchers are making advances in neuroscience, using plants to fight climate change, developing cures for cancer, mastering our circadian clock and more.

The podcast is available on **iTunes**, **Google Play** and anywhere you listen to podcasts.

To learn more, visit Salk.edu/podcast.



SEASON 1:

Associate Professor Nicola Allen on the mysteries of astro<u>cytes</u>

Assistant Professor Eiman Azim on the neuroscience of movement

Professor Joanne Chory on using plants to fight climate change

Staff Scientist Ken Diffenderfer and the technology of stem cells Assistant Professor Dannielle Engle on fighting pancreatic cancer

President and Professor Rusty Gage on the advances of science

Professor Tony Hunter on decades of cancer research

Postdoctoral Fellow Emily Manoogian on circadian clocks

EVENTS

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AN EVENING TO REMEMBER -SYMPHONY AT SALK

The San Diego Symphony, led by conductor Michael Krajewski, and special guest artist Laura Benanti, a Tony award-winner and five-time Tony award nominee, put on a spirited show that delighted 600 guests and 100 volunteers at the 24th annual Symphony at Salk on August 24, 2019.

The concert under the stars also featured spectacular lighting cast on the iconic study towers in the courtyard, which highlighted Salk's microscopy and the paintings of Françoise Gilot.

Symphony at Salk was made possible by many generous supporters who this year included Zenith sponsors Joan and Irwin Jacobs and Karen and Don Cohn; Golden Sun sponsor Tina Simner; and Supernova sponsors Martina and Dan Lewis, Tori and Terry Rosen, and Debra Turner and the Audrey Geisel/Dr. Seuss Fund.

This year's Symphony at Salk raised more than \$1 million for the Institute's unrestricted fund, which provides funding for the Education Outreach program and the innovation grants, as well as other needs such as support for Salk's graduate students and postdocs.



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KARLSEDER BREAKS DOWN THE BASICS OF CANCER DEVELOPMENT

On September 20, 2019, Professor Jan Karlseder shared his research on how cancer cells overcome proliferative boundaries and described strategies that may prevent cancer from happening in the first place. The Back to Basics lecture series provides the public two opportunities each year to learn about the Institute's contributions to science.







HIGH SCHOOL SCHOLARS SOAK UP SALK

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Thanks to Education Outreach's Heithoff-Brody Scholars Program, a group of high school students spent eight weeks this summer working side-by-side with scientists at the Salk Institute. The students learned how to formulate and test hypotheses, prepare experiments and draw conclusions from those experiments. At the end of the eight-week program, the scholars presented their research projects to their mentors, lab members and families.

WOMEN & SCIENCE PROGRAM DIVES INTO THE BRAIN

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Salk's Women & Science program hosted an event on July 24, 2019, emceed by Salk Professor Susan Kaech and featuring Professor Kay Tye, who gave a riveting presentation about the neuroscience of <u>seeking pl</u>easure and avoiding pain.

S U P P O R T I N G T H E A D V A N C E M E N T O F WOMEN IN SCIENCE

salk

WOMEN & SCIENCE PROGRAM HOSTS PANEL DISCUSSION ON THE FUTURE OF CANCER

On October 23, 2019, the Women & Science Program hosted "Breast Cancer: New insights in research, prevention, survivorship and health care delivery," a presentation given by Barbara Parker, MD, medical director of Oncology at Moores Cancer Center at UC San Diego. Salk Professor Geoffrey Wahl emceed a panel discussion that followed on the topic of advancements of breast cancer research and treatments and featured Nikki Lytle, a postdoctoral fellow in the Wahl's Gene Expression Laboratory, Carol Gallagher, Partner with NEA, and Catherine Rivier, Salk Professor Emerita, herself a survivor.

Susan Kaech

Held simultaneously, Pamela Cosman, scientist and author, led a fun, interactive workshop for children ages 8 to 14 as a special Women & Science: Girls in STEAM (science, technology, engineering, art and mathematics) event. The kids explored the world of coding and error correction, and received a signed copy of Cosman's book, *The Secret Code Menace*.



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SALKEXCELLERATORS LEARN OF PLAN TO CONQUER PANCREATIC CANCER

On October 30, 2019, Salk Assistant Professor Danielle Engle shared with the Salkexcellerators group how she creates models of pancreatitis and pancreatic cancer in order to develop more effective diagnostic tools and treatments for these diseases. Salkexcellerators are the next generation of community members who support scientific discoveries at Salk and engage with scientists through an annual calendar of special events.













WIKIPEDIA EDIT-A-THON

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On Saturday, September 7, 2019, Salk hosted a Wikipedia Edit-a-thon event, underwritten by the Salk Office of Equity and Inclusion. A total of 60 people from Salk, UC San Diego, Scripps Research and the San Diego community worked together to elevate the profiles of women in STEM (science, technology, engineering and math) on Wikipedia. The volunteers wrote 15 new articles and updated 41 existing articles.

Every cure begins with you.

Education Outreach

For nearly half a century, Salk has offered programs to inspire and launch—the next generation of scientists. Salk's Education Outreach program includes a Mobile Science Lab, Heithoff-Brody high school scholars curriculum and SciChats@Salk.

Salk Women & Science

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

Salkexcellerators

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

Partners in Research

Invest in the future of cancer, aging, Alzheimer's disease and diabetes research by incorporating philanthropic support for Salk into your estate plans. Salk giving programs offer a range of ways to get involved. Learn about Salk science and support vital research.

> DISCOVER SALK

President's Club

Fuel Salk's ability to recruit top-tier scientists, acquire cutting-edge technology and embark on innovative research initiatives by joining the *President's Club.*

Chairman's Circle

Visionary donors in the *Chairman's Circle* provide the vital resources Salk researchers need to pursue breakthrough science.

Architecture

Conservation Program Ensuring the modernist buildings envisioned by Jonas Salk and brought to life by Louis Kahn are preserved for generations to come.

Cancer Center Director's Fund

Dedicated to spearheading the ambitious new research directions Salk cancer researchers are pursuing in their continued quest for novel avenues into cancer therapies.

Alumni/Faculty Fellowship Fund

Training the next generation of scientists is central to Salk's mission. Contributions to the Salk Alumni program support the hundreds of research associates at the Institute.

Get involved.

Learn more about the many options for joining the Salk community by visiting **www.salk.edu/support** or calling **(858) 453-4100 x1201.**



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CALENDAR

JANUARY

12 Salk Science & Music Series featuring Alessio Bax and Lucille Chung

MARCH

- 08 Salk Science & Music Series featuring Per Nyström & Karen Joy Davis
- 18 Salk Women & Science Spring Event

APRIL

- 01 Back to Basics
- 04 Explore Salk

MAY

03 Salk Science & Music Series featuring Anderson & Roe

THERE ARE MANY WAYS TO SUPPORT SALK.

For detailed information on opportunities, please email giving@salk.edu or call (858) 453-4100 x1201 or visit www.salk.edu/support

VISIT US ONLINE AT: inside.salk.edu

Salk Institute has received the highest rating 9 consecutive times from Charity Navigator, the nation's foremost charity evaluator.

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