

WINTER | 2021

WHERE CURES BEGIN.

InsideSalk



A PERFECT MATCH

**Joan and Irwin Jacobs' transformative
gift to Salk's Campaign for the Future**

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Dear Friends,

When I assumed the role of President of Salk, the Board of Trustees agreed that we should identify strategies to address the critical need for additional research space for our faculty and for acquiring new technologies essential to our pursuit of science. Science is changing rapidly, with powerful new technologies, including cloud computing, artificial intelligence and new approaches to conduct multi-omic sequencing and analysis, creating new ways to approach some of biology’s biggest problems.

What followed was a two-year process that involved a reorganization to maximize space and to relocate administrative offices off the main campus. But when it became apparent that those measures would not be sufficient, a building committee of the Board, co-chaired by Chair Dan Lewis and Trustee and Chair Emeritus Irwin Jacobs, worked with staff to explore options for a new building. From this effort, the parcel of land that is currently used as a parking lot on the east side of the campus, adjacent to North Torrey Pines Road, was identified as the best location and two architecture firms, each with important strengths, were asked to work collaboratively on the design.

Across the world the Salk Institute is revered as a historic architectural masterwork designed by Louis Kahn in collaboration with Jonas Salk. It was their collaboration and innovative ideas for creating flexible, collaborative and open space for research and contemplation that informed the current architects. More than a dozen faculty members, executive leadership and staff, as well as members of the Board of Trustees, contributed thoughtful insights and suggestions for the design of the new building. Salk’s 2008 site Masterplan approved by the California Coastal Commission provided the framework, as did Salk’s 2016 Comprehensive Management Plan created in partnership with the Getty Conservation Institute.

With a location identified and a design concept developed, the next challenge before construction could begin was to identify a broad community of support to help fund the building, recruit the next generation of researchers, and deploy technology to drive discovery. To do so, we launched the Campaign for the Future: Building a More Resilient World in August. Our fall 2021 issue of *Inside Salk* detailed our Campaign priorities.

The first two Salk champions who embraced our fundraising challenge were Irwin and Joan Jacobs. The Jacobs have committed to donating up to \$100 million in matching funds to finance construction of the Joan and Irwin Jacobs Science and Technology Center. Their generous gift will help us leverage triple that amount, with \$1 matched by the Jacobs Challenge for every \$2 leveraged from other donors. With a deadline of June 30, 2022, the Jacobs’ transformative gift will allow construction on the new building to begin in late 2022. Most importantly, their generosity will alleviate our space limitations and advance our scientific activity for decades to come. It is fitting that this issue of *Inside Salk* profiles Irwin and Joan’s long history of support for Salk, as well as their support of many other important organizations in San Diego and beyond.

Salk researchers in the Crick-Jacobs Center for Theoretical and Computational Biology have been at the forefront of computational theory. This issue of *Inside Salk* takes a deeper dive into how computational theory is providing new opportunities to address biology’s more challenging problems. Additionally, Trustee Dan Tierney shares his fascination with how machine learning can advance biology. We also share how Staff Scientist Natalie Luhtala loves to paddle surf in between her experiments to better understand pancreatic cancer metastasis, and we detail how Postdoctoral Fellow Laura Newman is examining how mitochondria could be driving the inflammation observed in diseases such as Alzheimer’s, Parkinson’s, diabetes and obesity.

In the days and weeks ahead, I hope you will consider learning more about Salk’s Campaign for the Future (salk.edu/resilient). Our success is made possible with your support and the passionate community of individuals who believe that science has the power to change our world for the better. Or as Jonas Salk would say, “to turn dreams into reality.”

Sincerely,

Rusty

Fred H. Gage
President

PRESIDENT’S LETTER



“Science is changing rapidly, with powerful new technologies, including cloud computing, artificial intelligence and new approaches to conduct multi-omic sequencing and analysis, creating new ways to approach some of biology’s biggest problems.”



Joan and Irwin Jacobs donate \$100 million, a transformative gift, to Salk's Campaign for the Future

Irwin and Joan Jacobs know a thing or two about perfect matches—they've been married over 65 years and traveled the world together. Along the way, the pair have become two of the most admired and beloved supporters of the arts and sciences in San Diego, and beyond. Through their investment of time, counsel and philanthropic giving, they have enriched the lives of people around the world, most of whom will never know of the Jacobs' good deeds. Their journey began, however, on the other side of the country.

Like Jonas Salk, Irwin Jacobs began his career at a university on the East Coast. In 1959, a few years after Jonas Salk's polio vaccine was declared safe and effective, Jacobs was an assistant professor of electrical engineering at MIT, still decades away from pioneering wireless cell phone technology and founding Qualcomm, a Fortune 500 company that would put space-age computational power in everyone's hands. But his journey towards that destination would soon begin and, like Jonas Salk, it would lead him to San Diego.

It was in 1965 when Joan and Irwin Jacobs first saw the Salk Institute on a visit to San Diego, the newly completed edifice gleaming like a jewel above the Pacific Ocean. Irwin Jacobs recalls being wowed by the sight. The following year, proximity to the stunning Institute and the opportunity for Irwin to teach at the new university across the street—UC San Diego—were deciding factors in the couple's decision to relocate their young family from Boston to La Jolla.

Irwin Jacobs was a professor of computer science and engineering at UCSD until 1972, when he left academia to work in industry. Several years later, in 1985, he invited colleagues to a meeting in the couple's San Diego home where Qualcomm would be born. He would lead Qualcomm as it developed the industry standard for cellular technology, code division

A PERFECT MATCH



Irwin and Joan Jacobs visit the Central Synagogue in Saint Petersburg, Russia, as part of a Salk Summit trip for Board members and Institute leadership in 2017.

The Science and Technology Center will be home to four Centers of Excellence and will provide critical research and administrative space that will advance and expand Salk's scientific efforts for generations to come. (See *Inside Salk*, Fall 2021.)

Today, the Jacobs name is inextricably linked to both UC San Diego and Salk, two of San Diego's pioneering research centers that sit side-by-side, each having established itself as among the top research institutions in the world. The Jacobs' generosity has touched dozens of additional organizations in San Diego and beyond.

"Joan and I long ago began a family tradition of supporting interesting nonprofit institutions with the potential to impact many," says Irwin. "We enjoy working with projects that have well-defined goals and good leadership, and Salk is exemplary in both ways."

The couple's involvement with the Institute goes back much further than the recent gift. It began when Irwin Jacobs joined the Salk International Council (now the Institute Council), a group of professionals dedicated to advocating for Salk science. A 2003 lunch with Salk faculty Francis Crick, Sydney Brenner, Rusty Gage, Charles Stevens and Terrence Sejnowski really piqued his interest.

"I found that neuroscience had connections back to my work in information theory and communications which could be pursued," Irwin Jacobs later told *Inside Salk*.

Those connections were reified in 2004, when the Jacobs helped to establish the Crick-Jacobs Center for Computational and Theoretical Biology, where Salk scientists use computer modeling to study how the brain processes information.

When Irwin Jacobs retired from Qualcomm in 2006, he devoted more time to Salk, becoming Chair of the Board of Trustees, a position he held until 2016.

In his role as Chair, Irwin Jacobs spearheaded Salk's first capital campaign, The Campaign for Salk, which raised \$360 million for the Institute. In 2008, as part of that effort, he and Joan established the Joan Klein and Irwin

Mark Jacobs Senior Scientist Endowed Challenge, encouraging donors to endow 20 chairs for senior Salk scientists. For every \$2 million that a donor contributed toward an endowed chair at the Institute, the Jacobs added \$1 million to achieve the \$3 million required to fully endow a chair for a Salk senior faculty member. This level of support ensured that Salk scientists could continue to pursue the bold, life-changing science the Institute is renowned for. All 20 chairs were endowed.

"It's a testament to Irwin's Board leadership and the respect people have for both Joan and Irwin that Salk's 2008 Campaign was so successful," says Gage. "Joan and Irwin lead by example, and others feel honored to follow."

After the Chair Challenge, the Jacobs launched Salk's Innovation Grants Program, a donor-funded way to support out-of-the-box, potentially trailblazing research ideas that would otherwise not attract traditional funding. Over the years, the program has supported dozens of projects and resulted in paradigm-shifting results reported in high-impact journals such as *Science*, *Cell*, *Nature*, *PNAS* and *Neuron*. (Read about the latest grantees in Spotlight.)

In addition to providing funds for numerous other key programs and initiatives at the Institute, the Jacobs are steadfast supporters of Symphony at Salk, the Institute's annual "concert under the stars," when the San Diego Symphony performs in the iconic Salk Courtyard. For the 25th anniversary of Symphony at



Rendering of the Joan and Irwin Jacobs Science and Technology Center looking through to the iconic Salk Institute Courtyard.

Are You Up for a Challenge?

*Irwin and Joan Jacobs like a good challenge, and they think Salk supporters do, too. That's why they've established a match challenge to help the Institute build the new, state-of-the-art Joan and Irwin Jacobs Science and Technology Center, where the brightest minds will seek solutions to our most difficult health problems. With this challenge, the **Jacobs will match every \$2 donated with \$1**, to fund the cutting-edge new center—and a brighter future for us all. Salk scientists are bold, visionary and committed to making the world a better place. Salk supporters are, too. Together, we can meet any challenge.*

Learn more at: www.salk.edu/resilient

Salk in August, the Jacobs were Zenith sponsors, the highest level of sponsorship.

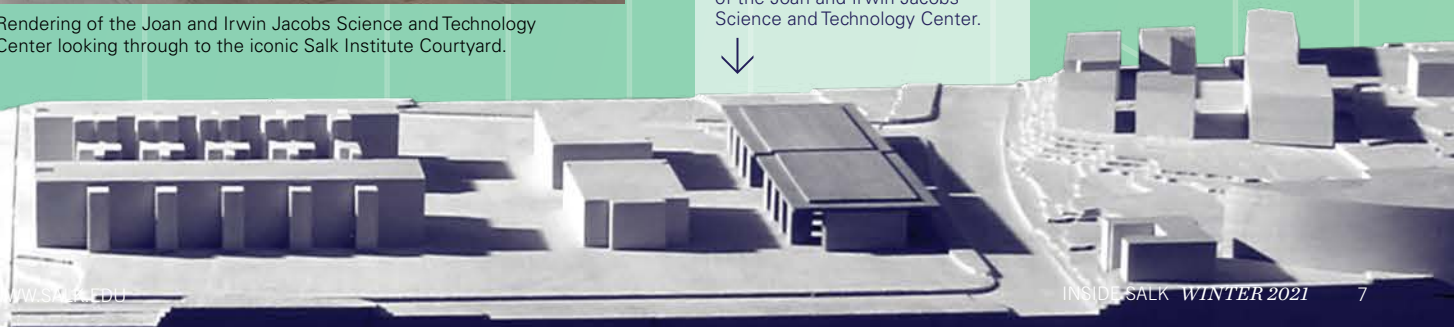
"Joan and Irwin's support of Salk is unwavering," says Rebecca Newman, vice president for External Relations. "They have consistently supported the Institute's highest priorities and now have provided an extraordinary opportunity for us to succeed with the Campaign for the Future."

It seems fitting that the Jacobs, with Irwin Jacobs' background in engineering and computer science and the couple's longtime support of Salk's computational biology, should be providing a key gift to the Campaign for the Future, helping to recruit computer scientists, bioengineers and mathematicians and expanding the Institute's computational biology infrastructure. Dozens of the world's brightest minds will find a welcome home in the Joan and Irwin Jacobs Science and Technology Center at Salk.

Through their generosity, the Jacobs' gift will advance scientific research at Salk for generations to come. Jonas Salk once said that the most important question we could ask ourselves is "how to be good ancestors." In a partnership that has spanned decades, Joan and Irwin Jacobs have shown us all how to answer that question. **S**

BELOW:

Architectural model of the Salk Institute campus with the addition of the Joan and Irwin Jacobs Science and Technology Center.

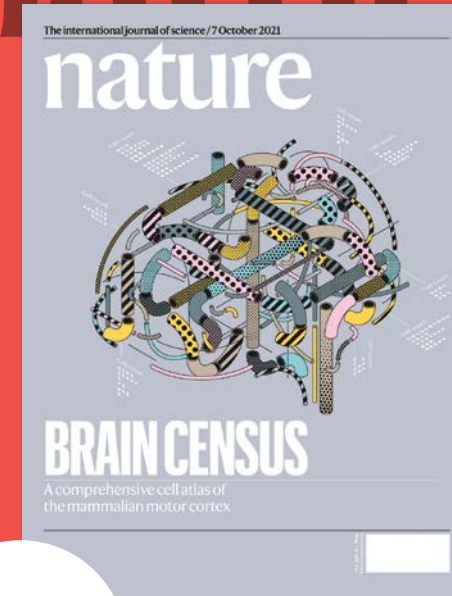


Salk Scientists Advance Groundbreaking Efforts to Prevent and Cure Brain Disorders

It takes billions of cells to make a human brain, and scientists have long struggled to map this complex network of neurons.

Dozens of research teams around the country, led in part by Salk scientists, have made inroads into creating an atlas of the mouse brain as a first step toward an eventual human brain atlas. The researchers, collaborating as part of the National Institute of Health's BRAIN Initiative Cell Census Network (BICCN), report the new data in a special issue of the scientific journal *Nature*. The results describe how different cell types are organized and connected throughout the brain.

nature



NATURE
10 / 2021

The BICCN, one subset of the BRAIN Initiative, specifically focuses on creating brain atlases that describe the full plethora of cells—as characterized by many different techniques—in mammalian brains. Salk is one of three institutions given U19 awards to act as central players in generating data for the BICCN.

The special issue has 17 total BICCN articles, with several co-authored by Salk researchers, that describe approaches to studying brain cells and new characterizations of subtypes of brain cells in mice. Overall, the new data on the mouse brain cells is the first step in creating a complete atlas of the mouse brain—which is critical to future research and brain therapeutics.

“Our first goal is to use the mouse brain as a model to really understand the diversity of cells in the brain and how they’re regulated.”

JOSEPH ECKER — professor and co-director of the BICCN

Measuring chemical markers to determine brain cell type

Salk faculty Joseph Ecker, Margarita Behrens and colleagues analyzed over 100,000 mouse brain cells using a scientific technique that identifies a chemical pattern called methylation, which is one way cells control gene expression. The scientists then applied this technique to thousands of cells from 45 different regions of the mouse brain and identified 161 clusters of cell types, each distinguished by its pattern of methylation. The team also showed that the methylation patterns could be used to predict where in the brain any given cell came from—not just within broad regions but down to specific layers of cells within a region. This means that eventually drugs could be developed that act only on small groups of cells by targeting their unique epigenomics.

“In the long run, to treat brain diseases, we need to be able to hone in on exactly which cell types are having trouble.”

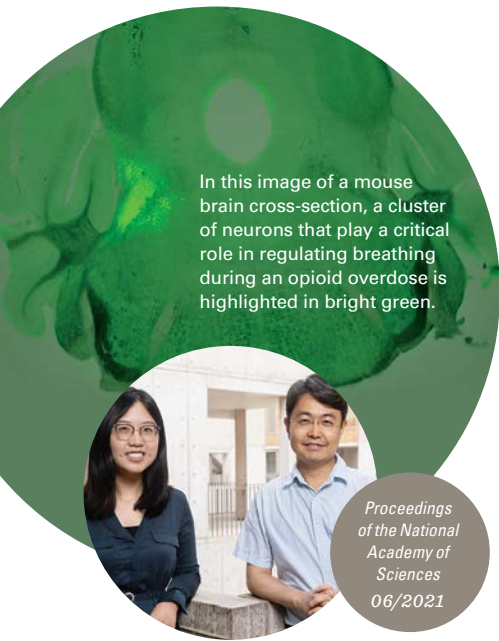
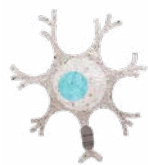
MARGARITA BEHRENS — associate research professor

Charting the brain destinations of neurons

Professors Ecker, Callaway and colleagues studied the association between DNA methylation and neural connections. The team developed a new way of isolating cells that connect regions of the brain and used the approach on over 11,000 individual mouse neurons, all extending outward from the mouse cortex. The patterns of methylation in the cells, they discovered, correlated with cells’ destination patterns.

“In these foundational studies, we’re describing the ‘parts list’ for the brain. Having this parts list is revolutionary, and will open up a whole new set of opportunities for studying the brain.”

EDWARD CALLAWAY — professor



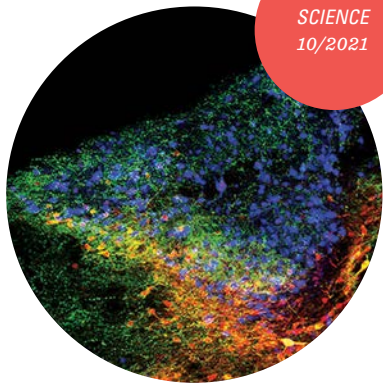
In this image of a mouse brain cross-section, a cluster of neurons that play a critical role in regulating breathing during an opioid overdose is highlighted in bright green.

Proceedings of the National Academy of Sciences
06/2021

RESEARCHERS IDENTIFY NEURONS INVOLVED IN OVERDOSE DEATHS

It’s long been known that opioid overdose deaths are caused by disrupted breathing, but the actual mechanism by which these drugs suppress respiration was not understood. Now, a new study by Assistant Professor Sung Han, first author Shijia Liu and colleagues identified a group of neurons in the brainstem that plays a key role in this process. The findings show how triggering specific receptors in these neurons causes opioid-induced respiratory depression, or OIRD, the disrupted breathing that causes overdose deaths. It also shows how blocking these receptors can cause OIRD to be reversed.

HOW THE BRAIN IGNORES DISTRACTING INFORMATION TO COORDINATE MOVEMENTS



SCIENCE
10/2021

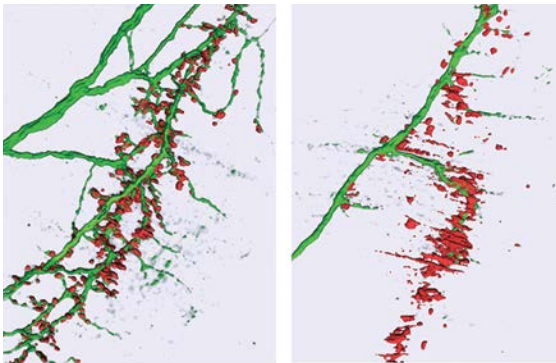
Inhibitory neuron cell bodies (red) in the brainstem with their axonal projections (green) onto the cuneate cells (blue) that transmit touch information. This circuit regulates information conveyed by touch receptors in the hands as it enters the brain.

As you read this article, touch receptors in your skin are sensing your environment. But, unless a stimulus is particularly unexpected or required to help you orient your own movements, your brain ignores many of these inputs. Now, Assistant Professor Eiman Azim, first author and Staff Researcher James Conner and colleagues have discovered how neurons in a small area of the mammalian brain help filter distracting or disruptive signals—specifically from the hands—to coordinate dexterous movements. Their results may hold lessons in how the brain filters other sensory information as well.

SUBTLE GENETIC CHANGES MAY LEAD TO ALS

NEURON
08/2021

Professor Samuel Pfaff, first author Neal Amin and colleagues found that disease-related genes often have different degrees to which they are turned on or off. With only an incremental biological change around a critical threshold, a person can go from having no symptoms to being very sick. Their findings have implications for studying and treating the underlying causes of amyotrophic lateral sclerosis (ALS) and other neurological and psychiatric disorders. The results could also be applicable to a wide range of diseases involving changes in gene expression levels, like cancer.



This computer-aided reconstruction shows how loss of microRNA-218 (right side) causes disrupted neuromuscular synapses and results in paralysis of muscles needed for breathing.

BENEFITS OF TIME-RESTRICTED EATING DEPEND ON AGE AND SEX

CELL REPORTS
08/2021



SATCHIN PANDA



Time-restricted eating (TRE), a dietary regimen that restricts eating to specific hours, has garnered increased attention in weight-loss circles. A new study by Professor Satchin Panda, first author Amandine Chaix and colleagues showed that while age and sex do affect the outcomes of TRE, the eating strategy delivers multiple health benefits for young and old of both males and females, and indicates that TRE may be a valuable intervention for type 2 diabetes, fatty liver disease and liver cancer, and even infectious diseases such as COVID-19, in humans.



SALK SCIENTISTS REVEAL CANCER’S MOST COMMON GENE MUTATIONS

NATURE COMMUNICATIONS
10/2021

Genetic mutations play a fundamental role in the development and growth of cancers. However, while many studies have identified the mutations involved in certain cancers, like breast cancer, no one had ever managed to combine the data in a way that could reveal which mutations are most common in the entire cancer patient population. Now, Assistant Professor Edward Stites and his team of computational scientists have combined gene mutation information with cancer prevalence data to reveal the genetic basis of cancer in patients across the United States. The findings could help guide genetic research to develop more effective treatments than presently available.



Salk study combines data on cancer DNA mutations with rates of cancer development to discover the most commonly mutated genes in all cancers.



EDWARD STITES

Salk partnerships facilitating life-changing discoveries

Since its inception, Salk has been a world leader in biological research. The Institute has produced a number of clinical targets that are now being used to treat a host of diseases, such as cancer, and plant researchers are now tackling the world's biggest problem, climate change. To achieve such success, Salk partners with other research institutions and biotechnology companies to take even more impactful science from the lab into the real world.

NICHOLAS COSFORD

PAMELA MAHER



Salk team launches phase 1 clinical trial for Alzheimer's therapy

In another recent advancement, the investigational Alzheimer's drug CMS121, developed and studied at Salk over the last 15 years, has now moved into a phase 1 clinical trial to evaluate its safety in humans. Salk Research Professor Pamela Maher and Bill Raschke of Virogenics, Inc., received \$4.5 million over two years from the National Institute of Aging to support the trial and expect the first doses to be administered to healthy volunteers in early 2022. In mice, CMS121 reverses signs of aging in the brain and prevents the memory loss associated with Alzheimer's disease.

TODD MICHAEL

NADIA SHAKOOR



Photo credit: Donald Danforth Plant Science Center

REUBEN SHAW

The Salk Institute and Sanford Burnham Prebys license ULK1/2 inhibitors to Endeavor BioMedicines for treatment of cancer

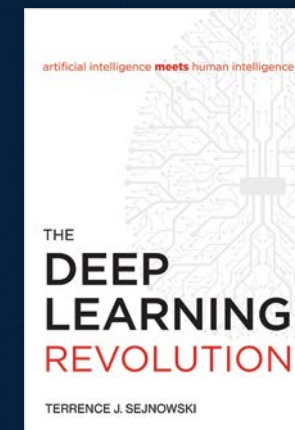
In 2015, Salk Professor Reuben Shaw and Professor Nicholas Cosford at Sanford Burnham Prebys (SBP) demonstrated that by chemically blocking the ULK1/2 protein, they could shut down the cellular recycling pathway known as autophagy that some cancer cells use to stay alive. The researchers found small molecule compounds that effectively blocked ULK1/2 and killed cancer cells, including human and mouse lung cancer cells and human pancreatic cancer cells. Now, Salk, along with SBP, has signed an exclusive licensing agreement with Endeavor BioMedicines for an intellectual property portfolio relating to cancer therapeutics and diagnostics that target ULK1/2. Endeavor plans to complete studies and advance the program into the clinic, initially in colorectal and lung cancers, in the next 18 months.

Salk plant researchers launch collaboration to breed carbon-capturing sorghum

Salk's Harnessing Plants Initiative (HPI) aims to address climate change by optimizing the ability of crop plants to remove carbon from the atmosphere and store it deeply in the ground for long periods. Now, HPI researchers, led by Salk Research Professor Todd Michael, have established a five-year, \$6.2 million collaboration with Senior Research Scientist Nadia Shakoor at the Donald Danforth Plant Science Center to identify and develop sorghum plants that can better capture and store atmospheric carbon. Sorghum, one of the top five cereal crops in the world, is known as an environmentally friendly, drought-resistant plant, making it an ideal crop to optimize for carbon capture.

HOW COMPUTATIONAL BIOLOGY IS MAKING US SMARTER

The Salk Institute is embracing the artificial intelligence revolution and inventing new ways to investigate life.



AI techniques like deep learning are changing everything.

Salk Professor Terrence Sejnowski wrote the book on artificial intelligence—literally. The author of The Deep Learning Revolution, Sejnowski could not be more excited about how AI will revolutionize research and usher in a new scientific revolution.

“We’re seeing these advances everywhere,” says Sejnowski, who heads the Computational Neurobiology Lab, directs the Crick-Jacobs Center for Theoretical and Computational Biology and holds the Francis Crick Chair. “It wasn’t long ago that people had great difficulty talking to machines, but now cell phones can actually understand our speech.

The changes are even more profound in biology. It’s just unprecedented.”

Machine learning, deep learning and other AI techniques (See Sidebar, page 16) are being used to probe massive data sets, identify useful information and make accurate predictions. “Unprecedented” may be selling the technology short—machine learning is accomplishing the impossible.

Consider the protein folding problem. A protein’s 3D shape dictates its function, but the molecules are far too small to see clearly, even with electron microscopes. Scientists use crystallography and other sophisticated imaging methods to infer protein shapes, but that can take years.

Theoretically, computers should be able to calculate a protein’s 3D shape based on its amino acid sequence, but the computational demands are enormous.

“Everyone said the problem was so difficult, we might never solve it,” says Sejnowski. “If you calculated the required computing, it would take the lifetime of the universe.”

Yet in late 2020, Google sibling company DeepMind solved the problem—for thousands of proteins. In 2021, DeepMind published the structures for every protein in the human body. These accomplishments, once thought unreachable, are only the beginning.”

The Salk Institute has long been at the forefront of computational biology and is doubling down to harness information theory and help solve some of biology’s most challenging problems. Through Salk’s Campaign for the Future (see Fall 2021 feature), the Institute is recruiting computer scientists and mathematicians, expanding its computational biology infrastructure and building a 100,000-square-foot Science and Technology Center to catalyze interdisciplinary collaboration.

“In the past, we didn’t have the instrumentation to generate all the data we needed,” says Salk President Rusty Gage, Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease. “That’s not a problem anymore; scientists generate enormous amounts of data. The problem now is analysis and theory building. How do we reduce the enormous data sets to manageable chunks of information that can then be put together in meaningful ways, so we can formulate a new way to look at life? That’s why information theory is so critical.”



The Lifetime of the Universe

Protein configurations are only one challenging data set machine learning is unraveling. Neuron interactions may be even more complex. Sejnowski is working with Uri Manor, assistant research professor and director of Salk's Waite Advanced Biophotonics Core, and others to generate a global picture of how neurons function in large groups.

The team wants to investigate how synapses on the same dendrite (treelike neuronal structures that receive signals) interact with each other and contribute to larger neural circuits.

Sejnowski calls it "anatomy on steroids." Traditionally, researchers would trace the connections from a single cell, which could take weeks—and there are a hundred billion neurons in the brain. To complicate matters, the data often comes from extremely thin tissue slices imaged on electron microscopes. Researchers want to connect those slices to see the larger picture, but traditional methods won't cut it.

"That's all changed," says Sejnowski. "Over the last five years, deep learning has made it possible to automatically trace these neurons in a stack of electron microscope sections."

Researchers have gone from understanding single neurons to reconstructing every neuron in a cubic millimeter of tissue: a hundred thousand neurons with a billion synapses. Now, scientists can start to see how cells are interconnected and model the ways information flows between neurons in different parts of the brain.

"That's what this revolution is all about," says Sejnowski. "We're living in a new world and have to completely reassess both how we do things and what we are even capable of doing."

"We're living in a new world and have to completely reassess both how we do things and what we are even capable of doing."

TERRENCE SEJNOWSKI



Information about Information

The sense of smell is one of our first defenses against digesting spoiled food. For animals, it also plays an important role in identifying predators and members of their own species.

From an evolutionary perspective, smell is one of the oldest senses, but it's the one we know the least about.

Tatyana Sharpee, professor in the Computational Neurobiology Laboratory and holder of the Edwin K. Hunter Chair, is working to understand how smell and other senses are processed in the brain. Sharpee's lab uses mathematical models, algorithms and a variety of laboratory methods to determine how sensory information moves through the brain and influences decision-making.

This two-way process—information comes in, decisions go out—creates a comprehensive rubric to study vision, hearing, touch and smell. She is particularly interested in how the body "invests" in particular senses in proportion to their survival relevance.

As a postdoctoral fellow at the University of California San Francisco, Sharpee developed an approach called "maximally informative dimensions," which helps neuroscientists identify neural mechanisms that optimize how organisms assess information.

"We are using information theory to understand how the nervous system identifies good solutions," says Sharpee.

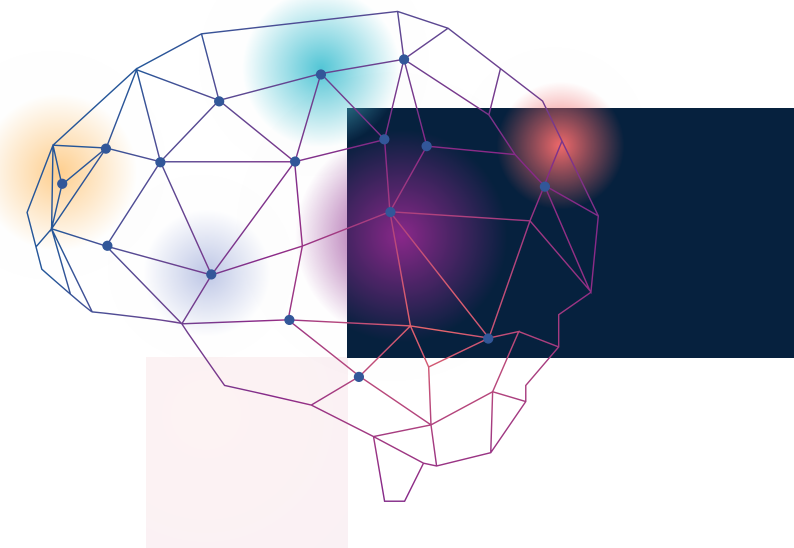
In recent work, the lab redefined how inhibitory neurons improve information processing. Much like stoplights on a busy road, these cells restrain traffic (information)—but in a good way. By modulating signals, inhibitory neurons literally prevent sensory overload.

But Sharpee found their role goes beyond that. When signals from other parts of the brain are delivered to local circuits through inhibitory neurons, this optimizes information flow. This research focused on retinal pathways but could be applied to other sensory inputs.

"By targeting only the most sparsely responding neurons, inhibitory neurons make it possible for the whole circuit to function well," says Sharpee.

In real life, this mechanism helps organisms focus on important signals and events. In other words, inhibition helps the brain prioritize the most immediately relevant signals.

Assessing information is key to survival for humans, microbes



"We are using information theory to understand how the nervous system identifies good solutions."

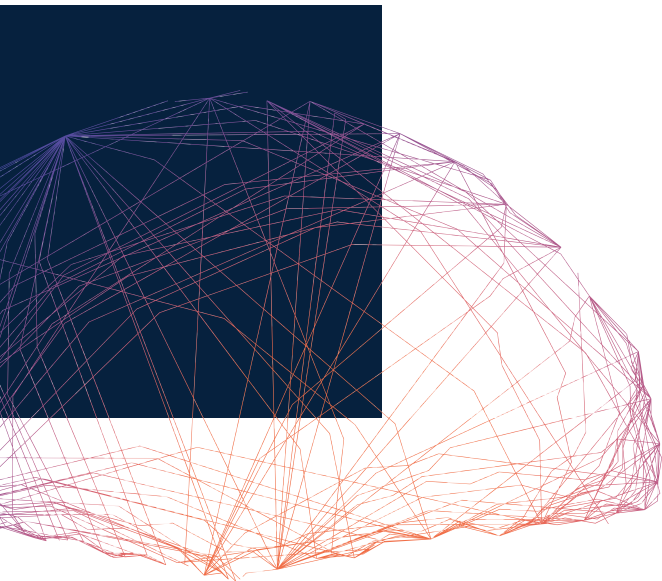
TATYANA SHARPEE



and everything in between. Tiny *C. elegans* worms maximize foraging information by searching small areas before shifting to larger regions. This approach appears random, but Sharpee's lab devised an algorithm that made strategic sense of these worm norms.

This feeds into a larger understanding of information, specifically its costs and rewards. *C. elegans* pay a metabolic price to gain information about food distribution, but the data ultimately improves their ability to find more fuel.

"The data guide their behavior by trying to maximize information, not the direct payout in terms of the molecules they seek," says Sharpee. "They are more guided by the information about the distribution."



Big-Picture Brain Studies

Joseph Ecker, professor and director of the Genomic Analysis Laboratory and Howard Hughes Medical Institute investigator, along with Associate Research Professor Margarita Behrens, is taking a more macro view of brain architecture.

They are collaborating with the Chan Zuckerberg Initiative to expand the Human Cell Atlas, which is a map of every cell type in the body, and have a major NIH grant to build a genomic/epigenomic reference map for the human brain.

“You have two ends of the spectrum here,” says Ecker, who holds the Salk International Council Chair in Genetics. “The Chan Zuckerberg Initiative is looking at how much variation there is between people of different ages and genders. The NIH grant supports mapping the brain in such detail that we have a reference for future work.”

These projects are the latest efforts by Ecker and Behrens to help comprehend the brain’s complexity. The genomics part is relatively easy: All cells have pretty much the same DNA. But epigenomics, the regulatory layer that helps determine which genes get expressed (go to work) and which ones remain silent, is a different story.

These elements can shift based on cell type, function, brain location, age and other factors. Tallying a person’s gene complement is a start, but to truly understand brain function, we need to know which ones are on the job.



MARGARITA BEHRENS AND JOSEPH ECKER

The Chan Zuckerberg Initiative work dovetails with Salk’s efforts to improve life span health. The team will focus on human brain diversity: How does neural gene expression differ between men and women; for people between 25 and 80; and even in different regions of one person’s brain?

“This is a little like the early days after the Human Genome Project,” says Behrens. “We had a genome from one person, but we didn’t know much about the variability between people. Here, we’re taking a deep look at gene expression and comparing it across individuals. We want to understand the ground truth for certain types of neurons.”

Ecker, Behrens and colleagues have been awarded over \$35 million to study how genes are controlled in different parts of mouse and human brains. This pilot project could expand geometrically, as the NIH has requested proposals for the Brain Initiative Cell Atlas Network, which will support a nationwide effort to comprehensively study brain architecture. (See this issue’s Discoveries.)

These will be some of the most complicated investigations humans have ever attempted. Researchers will study brain genetics, epigenetics and spatial and temporal relationships between cells—research that will produce truly epic amounts of information.

“We’re trying to figure out how we’re going to address all that data,” says Ecker. “Not only analyzing, but storing it, moving it around and collaboratively studying it in different locations. Right now, we’re using a supercomputer for mapping, but even that takes several days to complete the epigenetic profile of a single neuronal cell type.”

Ecker and Behrens are confident machine learning and other computational approaches will help solve this data deluge. New algorithms are already emerging that could accelerate analysis four-fold. Other methods will be needed to scale from 80-million neuron studies to 80-billion. Ecker notes this is already happening, as research groups worldwide are developing methods that accelerate supercomputers, assess complex images and automate many necessary tasks.

“We will know the composition of the human brain in enormous detail,” says Behrens. “The payoff will be the brain feels less like a black box. We won’t know everything, but we will know much more about each neuronal type. Perhaps, in the long run, we’ll learn how to target specific types to help people with neurological diseases.”

“We make these incredibly detailed spatial maps, and now the real challenge is to make sense of what they mean.”

PALLAV KOSURI



“The whole time I was using it, I kept thinking, why did we build this huge machine to see a single molecule?” says Kosuri. “We should build small machines to see single molecules.”

The solution was an approach called DNA origami, first conceived in the 1980s. Creating synthetic structures from DNA relies on the molecule’s intrinsic base-pairing properties: adenine (A) binds to thymine (T); cytosine (C) binds to guanine (G).

But other combinations of bases, such as A and G or C and T, don’t like to bind. Armed with these simple rules, scientists can now design DNA in precise patterns, forcing the molecules into unique folded shapes (origami). These, in turn, can help visualize individual molecules in motion.

Kosuri uses this technique to add DNA arms to molecules and measure their rotation. Consider the letter “I.” If you look down vertically, at its cap, “I” looks like a dot. Is it spinning? Who can tell? But a “T” adds an arm, making it easier to track motion.

“Now we can study these rotational movements,” says Kosuri, “and there are countless reactions that have never been investigated that we can start to really see and understand.”

These capabilities can help researchers visualize how DNA is unwound when being read by a cell, or how CRISPR gene-editing machinery searches for target sequences in the genome.

Computational methods play an integral role with DNA origami—designing the origami constructs, simulating how they will behave, analyzing measurements and generalizing the findings.

Kosuri’s lab is also developing new ways to study heart failure. Using patient tissue samples, his team is mapping every cell’s molecular profile and location. These studies provide incredible insights into how heart disease affects individual molecules and cells, but not surprisingly, the data can be overwhelming.

“We make these incredibly detailed spatial maps, and now the real challenge is to make sense of what they mean,” says Kosuri. “We’re seeing which genes are turned on and off in each cell, the exact shapes of these cells, their locations in three-dimensional space, which cells are next to each other and which genes are active in those cells, and so on. Now, we’re working with computational biologists to develop new methods to make sense of it all. If we succeed, we might be able to catch earlier signs of heart disease and figure out how to keep heart cells healthy in the face of aging.”

Where Engineering and Computation Meet

You’ve seen the pictures: microscopic cellular components lit up with fluorescent proteins. These images are beautiful and informative, but they miss a critical trait—motion.

“There is not a single biological component that does not move,” says Pallav Kosuri, assistant professor in the Integrative Biology Laboratory. “But the vast majority of that universe of movements has never been seen, much less studied.”

Kosuri began his efforts to capture molecular motion when he was a postdoctoral researcher but was hamstrung by his tools. One example is an atomic force microscope, a large machine that uses a needle, much like a phonograph, to scan the surfaces of cells and molecules.



People in Motion

Eiman Azim is trying to figure out how people move, a surprisingly complex problem. As assistant professor in the Molecular Neurobiology Laboratory and William Scandling Developmental Chair, Azim is studying brain outputs, the corresponding feedback, and how the nervous system makes adjustments. Even understanding how the brain determines a limb's positioning—a multisensory activity called proprioception—requires tremendous scientific bandwidth.

“We focus on dexterous behaviors because they are some of the least understood, and they’re fundamental to our interactions with the world,” says Azim. “A lot of these movements, like buttoning your shirt or typing a text, are susceptible to disease and injury. If we can understand how these movements are controlled, we’ll be in a better place to repair them when they go wrong.”

The questions come in layers, and those layers have their own layers. For example, what does healthy movement even look like? Azim is combining machine learning, computer vision and engineering to find those answers.

However, training neural networks to recognize different parts of the body in 3D space is complicated. Azim needs training data—observations that teach the neural network. Traditionally, people have supplied this data, but the pace is slow, the data prone to human error and the results hard to generalize.



“We focus on dexterous behaviors because they are some of the least understood, and they’re fundamental to our interactions with the world.”

EIMAN AZIM

“If you train a subset of your data, it works well on the rest of the data acquired in that environment, with the same lighting conditions and camera angles,” says Azim. “But if you change anything—the lighting, the room you’re in—you have to start over.”

To optimize the process, Azim’s lab has been working with engineers at UC San Diego’s Qualcomm Institute (QI), developing an experimental rig, called GlowTrack, which combines fluorescence (to mark body parts), orchestrated strobe lighting and cameras. On a good day, a human researcher might tag a thousand images to train the network. GlowTrack can process millions in the same amount of time.

“By having a much larger training data set, we can dramatically expand how the network generalizes,” says Azim. “Different experimenters can use different setups without doing any new training.”

This refinement did not happen overnight. Azim worked for months with his QI collaborators—designing, testing, redesigning, retesting. That collaboration worked well, but Azim and others believe these capabilities should be in-house at Salk. He and Kenta Asahina, assistant professor in the Molecular Neurobiology Laboratory and holder of the Helen McLoraine Developmental Chair in Neurobiology, are developing an Instrument Design, Engineering and Application (IDEA) Laboratory to make that happen.

“We need engineers on the Salk campus to work with us and develop commercially unavailable solutions to meet our experimental needs,” says Azim. “The IDEA Lab is just a start. Once the Science & Technology Center is built, engineers and biologists will work hand-in-hand, and that will go way beyond building devices to actually pursuing academic bioengineering research with trained engineers.”



Stites and his lab’s mathematical approach discovered that RAS mutations are found in 15 percent of cancer patients, not 33 percent, as previously thought.



EDWARD STITES

“Simple” Math

Edward Stites is an assistant professor in the Integrative Biology Laboratory and Hearst Foundation Developmental Chair. His lab is heavily focused on computational and mathematical methods.

“We really enjoy taking a lot of data where we already understand how things fit together, and then we use mathematics to rigorously investigate the system to get new ideas and new hypotheses,” says Stites.

His team is developing new ways to investigate cancer-causing mutations and their responses to treatment, often studying RAS mutations. RAS has been heavily scrutinized for decades, providing abundant data for computational methods.

Recently, the lab used mathematics to identify RAS mutations that indicate its sensitivity to an available drug. As a result, thousands of colon cancer patients now have a better treatment option.

But something about RAS bothered Stites. Everybody in the field believed RAS mutations were found in 33 percent of cancer patients. That’s been the accepted figure for decades, but is it true? Examining the question from 30,000 feet, the numbers didn’t make sense to Stites. Common tumors, like breast and prostate, hardly ever have RAS mutations.

He envisioned a relatively simple side project and gave it to a lab scientist who came back empty-handed. Stites scratched his head and gave it to another researcher. Same result. There was a problem: two data sets that barely spoke to each other.

Stites and his scientists were forced to dig deeper to find the problem. While the data existed for mutation rates in different cancers, and for the percentages of people who contract those specific cancers, the two data sets could not be readily combined.

“The epidemiologists who provide the data for cancer rates in the US use a detailed, thorough naming system to characterize each cancer,” says Stites. “But cancer genome data are far less granular. A study that measures the mutations that cause breast cancer might include 20 or more subtypes of breast cancer, and not provide the details that would allow it to be mapped back to the epidemiological data. The two types of data were incompatible.”

Slowly, they figured out how to make these different data sets talk to each other—and the accepted numbers weren’t even close.

“RAS isn’t in 33 percent of cancers, it’s more like 15 percent,” says Stites. “It’s less than half as abundant as people thought, which is important because labs spend a lot of money studying RAS, mostly because they think it’s so common.”

These efforts to align data sets could have many other applications, such as reducing biases in population data. White men are disproportionately represented in genomic studies, but the lab’s mathematical approaches could mitigate those misperceptions and provide a truer picture of the actual disease burden across populations.

“I look at computational biology like solving a logic problem,” says Stites. “Like playing Clue. You’re trying to solve the crime with as little information as possible. You can keep playing the game until you stumble upon the right answer, or you can get the answer much quicker by combining the data you have in the right way. The problems we solve are harder and more meaningful than a children’s game, but solving them still provides a fun sense of accomplishment, along with the satisfaction of doing work that makes a difference.”

“The things we can accomplish with machine learning are just amazing. It’s like the first electron microscopes or deciphering the structures of DNA—just an incredible time for discovery.”

MARTIN HETZER



Life Span Health

Professor Martin Hetzer believes information theory will help solve many puzzles. He and others are betting this discipline will unlock the secrets of biological resilience.

“We want to understand the circuits that contribute to good health,” says Hetzer, who is Salk’s senior vice president/ chief science officer and holds the Jesse and Caryl Philips Foundation Chair. “If we can figure out how they work, we can take measures to modulate them and hopefully better control disease.”


Hetzer and colleagues have been working on the problem for years. Their collaborative 2018 study identified molecular signatures in skin cells that could accurately predict a person’s age. Those findings are continuing to spawn new inquiries.

Discovering age markers was a first step towards intervening and improving health. Cancer, heart disease and dementia are all associated with aging. Perhaps adjusting these age-indicating molecular signatures could reduce a person’s disease risk.

“The study provides a foundation for quantitatively addressing unresolved questions in human aging, such as the rate of aging during times of stress,” says Hetzer, who was co-senior author on the paper.

Machine learning was a critical part of this study, and many more that followed, creating a predictive algorithm that was far more accurate than previous methods. “The things we can accomplish with machine learning are just amazing,” says Hetzer. “It’s like the first electron microscopes or deciphering the structure of DNA—just an incredible time for discovery.”

Incorporating sophisticated computational approaches will continue to accelerate Salk’s ability to answer some of the most challenging scientific questions and analyze massive amounts of raw data from cell and molecular biologists, neuroscientists, plant scientists and many others.

“We have this incredible computational toolset that did not even exist just a few years ago,” says Hetzer. “That’s why we’re reimagining the Salk Institute: recruiting mathematicians, computer scientists and engineers; adding emerging technologies; and building a Science and Technology Center to foster even more collaboration. Our goal is nothing less than revolutionizing science.” 

AI DEFINITIONS

Algorithm

Instructions computers use to transform raw data into knowledge.

Artificial Intelligence (AI)

Computer systems that can perform tasks normally reserved for people.

Computational Biology

Adapting data methods, mathematical modeling and simulations to biology.

Information Theory

The science of analyzing, storing and transferring enormous amounts of data.

Machine & Deep Learning

Machine learning systems can “think” beyond their initial programming, learning from large data sets to make accurate predictions. Deep learning is a form of machine learning that uses artificial neural networks—which seek to replicate brain architecture in silicon.

OBSERVATIONS

Biology MEETS Technology

Dan Tierney is no stranger to big data. When Tierney founded a financial technology firm in the late 1990s, long before he joined the Salk Institute’s Board of Trustees, he was fascinated by emerging computational approaches that could crunch data and reveal hidden truths.

“I’ve had this thesis, for a long time now, that biology and technology are converging and this is one of the most important trends of our time.”

DAN TIERNEY

“We didn’t use the term big data at the time,” says Tierney. “We didn’t really even know what it was. We just knew financial markets are an area that produce enormous amounts of information, and we wanted to know how best to utilize it.”


Fast forward 20 years and big data permeates virtually every industry, including the life sciences. Seeing the parallels with his own experience, and recognizing Salk’s innate ability to incorporate new technologies, Tierney began exploring how machine learning could advance biology. He wanted to see how the lessons his team learned in financial technology could be applied to cells and molecules.

“I’ve had this thesis, for a long time now, that biology and technology are converging and this is one of the most important trends of our time,” he says.

Tierney was keenly interested in how Salk was adapting, and had the resources to offer support. One of his colleagues, Fred Monroe, is a whiz at applying machine learning to financial markets. At Tierney’s request, he is helping Salk researchers harness machine learning to solve problems, such as how to make ordinary lab microscopes perform like their million-dollar cousins.

Tierney has also been working with scientists at UC San Diego to bring Salk into the Pacific Research Platform, a high-capacity data freeway system that encourages collaboration among multiple institutions.

This is the vision Tierney shares with President Rusty Gage, Senior Chief Science Officer Martin Hetzer and many others at Salk. Machine learning and other advanced computational methods can be the secret sauce that accelerates innovation. It’s not if but when.

“The next challenge is to think through, in a systematic way, how Salk can be at the forefront of these technologies, building up internal machine learning resources and tapping into outside resources remotely so we get the best of both,” he says. 

Shaping pancreatic cancer research to have real world applications

This year, Staff Scientist Natalie Luhtala celebrates her 10-year work anniversary at the Institute. She came to Salk as a postdoctoral fellow in Professor Tony Hunter's lab and now, in her current role, is directing a project examining an elusive signaling pathway to identify new targets for treating pancreatic cancer.

"I continue to learn and grow at Salk, as there are so many scientific leaders and creative minds to work with here," says Luhtala. "I enjoy being able to collaborate on projects, which leads to more interesting data with clinical applications for the early detection and treatment of cancer."

INSIGHTS

Natalie Luhtala

Staff Scientist



INSPIRATION

Luhtala wants to better shape scientific research to have real world applications. When she was an infant, she was diagnosed with hydrocephalus (fluid accumulation in the brain), which can be a sign of brain cancer. Fortunately, when she was 14, doctors discovered that her hydrocephalus was due to a harmless brain cyst and not brain cancer. Years later, she was reminded of the possible cancer diagnosis when a close family member was diagnosed with glioblastoma, an aggressive brain cancer, while she was diving into the field of cancer research in college. As a result, Luhtala devoted the first chapter of her postdoctoral research to glioblastoma. Now, she is investigating a previously uncharacterized signaling pathway in pancreatic cancer, another aggressive type of cancer. Her uncle recently passed away from pancreatic cancer, further solidifying her drive to work in the field.

"Cancer can affect anyone. There is always someone that you could be helping," says Luhtala. "If you're going to dedicate your life's work to something, then it might as well be something that can help give people back time or their lives."

RESEARCH INTERESTS

Luhtala came to Salk studying exosomes, spherical containers that carry and release biomolecules like fats, proteins and even DNA outside the cell. She was interested in seeing if exosomes communicated cell-to-cell using RAS signaling, which is a driver of cancer. She found that RAS signals primarily within the cell, but exosomes can provide information about a tumor's origin and the types of signals (like RAS) that the tumor is using. This knowledge could advance the development of personalized treatments and diagnostics using exosomes found in biological fluids, such as cerebrospinal fluid, blood and urine.

Luhtala now studies histidine phosphorylation, a process through which a phosphate is added to a histidine amino acid. This process is important for sensing and responding to changes in the cellular environment and for cellular functioning, so she developed a novel way to detect histidine phosphorylation in mouse models of pancreatic cancer.

She is now collaborating with Postdoctoral Fellow Shixin Ma, in Susan Kaech's lab, and Postdoctoral Fellow Nikki Lytle, in Geoffrey Wahl's lab, to explore the role of the histidine phosphorylated enzyme ATP citrate lyase (ACLY) in immune cells in pancreatic tumors. Luhtala believes ACLY may aid certain immune cells in transforming into another type of immune cell, so she is investigating how ACLY behaves during cancer metastasis.

PATH TO SALK

Luhtala was studying RNA binding proteins' contributions to cancer in the final year of her PhD in cancer biology at the University of Arizona when she saw Hunter speak at a seminar. "Tony is the king of cell signaling, and he has a strong interest in cancer," says Luhtala. "After all, his discovery of tyrosine phosphorylation led to the leukemia therapy Gleevec! I knew I wanted to work with him right away."

LEISURE TIME

Surfing and stand-up paddle boarding weren't enough for Luhtala, so she took up stand-up paddle surfing. Now she enjoys scanning the ocean for sea turtles, leopard sharks and dolphins amongst the waves at La Jolla Shores. She's also an avid mountain biker, and her favorite spot to ride is the Cannell Plunge in Kernville, California.

FUN FACTS

Luhtala is originally from Chicago, although her father is French, and she lived in Germany for a brief period of her childhood. She enjoys keeping up her French by conversing with the French researchers in the Hunter lab. She also has a soft spot for Boston terriers and has rescued many over the years. "I just love Bostons as they all have their own way of communicating," says Luhtala. "Some snort while others whine—they're just hilarious."

LONG VIEW

Most patients diagnosed with pancreatic tumors eventually develop tumors in other parts of the body. Luhtala hopes her work on histidine phosphorylation and ACLY will lead to a better understanding of cancer metastasis as well as new therapeutic targets that will improve outcomes for patients with pancreatic cancer. **S**

LAURA NEWMAN

From
mitochondria
to craft beer
and back

Flipping through a biology textbook in middle school, Laura Newman paused at a detailed picture of the cell. Specialized structures inside the cell, called organelles, captured her imagination as she thought about how these delicate, yet complicated, structures came to be.

In particular, she was fascinated by mitochondria, often dubbed the powerhouses of the cell. In evolutionary history, scientists believe that mitochondria began as bacteria with their own DNA before being enveloped by the cell. “Every cell essentially has this ancient bacterium living inside of it,” says Newman. “I thought that was so cool.”

But as she started college at Indiana University, Newman didn’t know that studying the fundamentals of biology was a career option. Instead, she pursued a double major in biotechnology and neuroscience in preparation for medical school. During her junior year, Newman was encouraged to work in a science lab. When she conducted her first experiments, she immediately knew her life would be forever changed.

“I fell in love with science in the lab. The process of conducting an experiment was rational and elegant,” says Newman. “Science is an amazing way to understand the world around you.”

So instead of medical school, Newman pursued graduate school in biochemistry, cell and developmental biology at Emory University. There, she explored the role of mitochondria during cellular stress before seeking a postdoctoral fellowship in a lab where she could further study the relationship between mitochondria, stress and the immune system.

“Salk Professor Gerald Shadel is a leader in how mitochondria activate the immune system. And members of the Shadel lab study everything about mitochondria,” says Newman. “Additionally, Salk is such a unique place to work because people are always excited to share ideas and resources, which makes collaboration so easy.”

At Salk, Newman’s main focus is on how cells can recognize when they’re sick or damaged in order to activate the immune system for cell survival. Collaborating with Assistant Research Professor Uri Manor, director of the Waitt Advanced Biophotonics Core, has allowed her to use cutting-edge microscopy techniques to generate some key revelations in her research. As a result of her and the lab’s research, she believes that mitochondria could be the organelles that signal to the cell that there is a viral infection or, possibly, drive inflammation. And inflammation underlies a lot of diseases, such as Alzheimer’s, Parkinson’s, diabetes and obesity.


Newman was a co-author of a paper about mitochondrial DNA stress signals that was published in *Nature Metabolism* in 2019, and she recently received an NIH-funded MOSAIC Postdoctoral Career Transition Award to Promote Diversity (K99/R00), which will fund her for the next five years as she finishes at Salk and starts to develop her own research program.

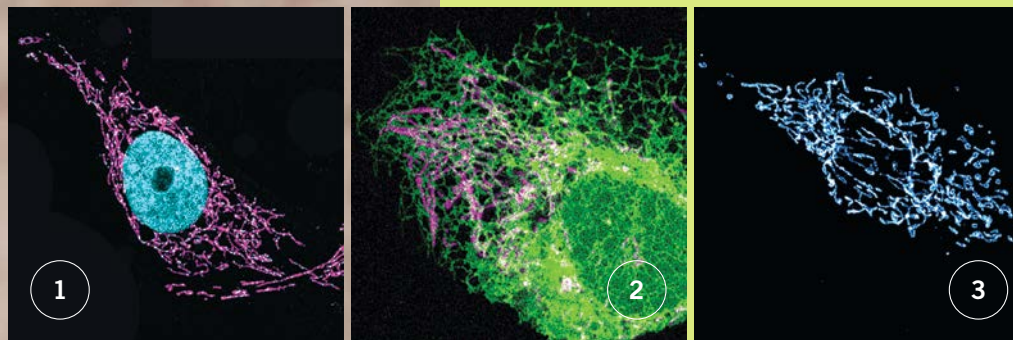
“I’ve always wanted to have my own lab, and this award will help open a lot of doors to allow me to achieve my goal,” says Newman. “When the coronavirus pandemic hit, I took that time away from the lab to work on the grant. I can’t tell you how excited I am that I actually got it.”

One of her interests is to better understand how mitochondria react to viral infections such as influenza, herpes and COVID-19. For example, mitochondrial DNA may get released during a severe COVID-19 infection, so Newman wants to examine the warfare between mitochondria and viruses in infected cells, with a focus on the inflammatory response.

Beyond the bench, Newman takes her expertise in biology home with her where she brews beer and kombucha. She enjoys experimenting with exotic flavors, including jalapeño and Hatch green chili. “I love being able to use my experimental knowledge of microbiology to brew different concoctions,” says Newman. “It’s a fun way to share science with my friends and family.”

Newman is also passionate about cultivating a positive lab environment and promoting mental health. She is a member of Salk’s Society of Research Fellows, the Committee for Trainee Affairs, and the Engagement & Wellbeing Initiative, where she helps foster a welcoming atmosphere.

“I’ve suffered from mental illness, and I am fortunate that at every stage of my scientific career, I felt supported, which helped me thrive despite my struggles,” says Newman. “Research is challenging, as failed experiments and rejection of grants and manuscripts can make it hard to keep going. Underrepresented minorities and women deal with additional challenges on top of that. Community support increases resilience and helps everyone to be successful.” 



- 1: Mitochondria in magenta and DNA in cyan.
- 2: Mitochondria in magenta and the endoplasmic reticulum in green.
- 3: Mitochondria in varying shades of cyan.

SALK APPOINTS NEUROSCIENTIST PAMELA MAHER AS RESEARCH PROFESSOR

The Salk Institute has appointed neuroscientist Pamela Maher to the position of research professor to reflect her achievements conducting groundbreaking research on Alzheimer’s disease.

“Salk is fortunate to have such a talented and dedicated scientist as Pam, and we are thrilled to appoint her as research professor.”

RUSTY GAGE
Salk President

Maher, who has been a senior staff scientist at Salk since 2004, will continue her work screening for compounds that could slow or stop the progression of neurodegenerative diseases. Two of her compounds are currently undergoing clinical trials for the treatment of Alzheimer’s (see this issue’s Discoveries for details).

“Salk is fortunate to have such a talented and dedicated scientist as Pam, and we are thrilled to appoint her as research professor,” says Salk President Rusty Gage.

Maher, who is also the head of Salk’s Cellular Neurobiology Laboratory, uses compounds derived from natural products, such as strawberries, turmeric and cannabis, in order to treat the cellular aging and memory loss observed in Alzheimer’s. Her team has taken multiple drug candidates from conception in the laboratory into clinical trials. Currently, two of these compounds, CMS121 and J147, are in clinical trials for the treatment of Alzheimer’s. In mice, these compounds protected neurons and prevented the molecular changes that are associated with aging.

Maher was previously awarded the Edward N. & Della L. Thome Memorial Foundation Award in Alzheimer’s Disease Drug Discovery and the Michael J. Fox Award for Novel Approaches to Drug Discovery for Parkinson’s Disease. She currently has five NIH-funded grants to examine the relationship between aging, inflammation and Alzheimer’s disease.



JANELLE AYRES

JANELLE AYRES NAMED INAUGURAL RECIPIENT OF THE SALK INSTITUTE LEGACY CHAIR

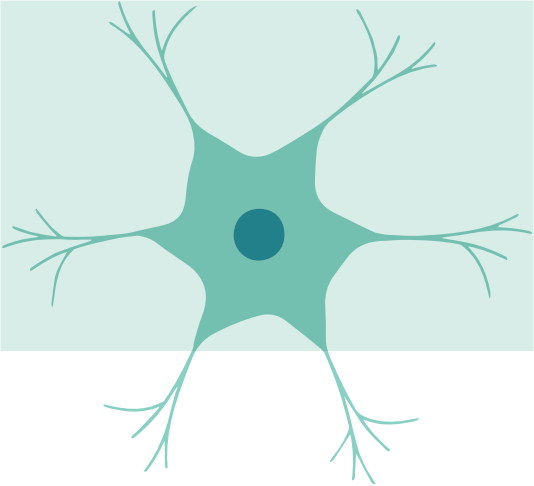
Professor Janelle Ayres, head of the Molecular and Systems Physiology Laboratory and a member of both the Gene Expression Laboratory and the NOMIS Center for Immunobiology and Microbial Pathogenesis, was recognized for her contributions to advancing science through research by being named the inaugural recipient of the Salk Institute Legacy Chair. Through her pioneering work on host-pathogen interactions, Ayres has demonstrated that health is an active process, involving evolved physiological defense mechanisms, creating a new paradigm and field that she calls “the biology of health.” Elizabeth Keadle, a Salk alumna and member of the Board of Trustees, recently donated \$1.5 million in matching funds to establish the endowed chair at the Institute.



AXEL NIMMERJAHN

AXEL NIMMERJAHN LEADS TEAM AWARDED \$11 MILLION BY THE U19 TEAM-RESEARCH BRAIN CIRCUIT PROGRAM

A research team led by Associate Professor Axel Nimmerjahn was awarded \$11.2 million by the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, an effort that aims to investigate overarching principles of brain circuit function, including sensation, perception, decision-making and motor control. Nimmerjahn will lead an interdisciplinary five-year project investigating how astrocytes, star-shaped cells in the brain, process and modulate signals from neurons to better understand overall brain function.



PAMELA MAHER

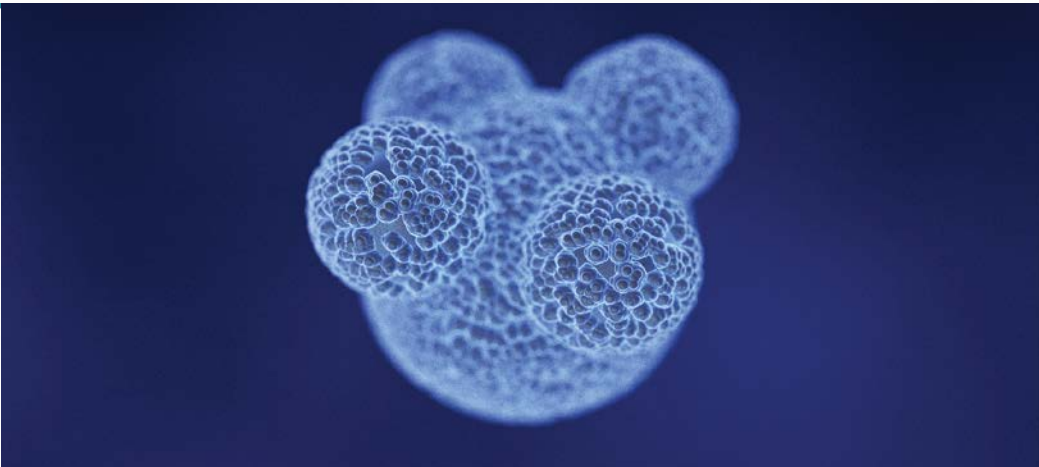


TATYANA SHARPEE

**TATYANA SHARPEE
WINS DELANO AWARD
FOR COMPUTATIONAL
BIOSCIENCES**



Professor Tatyana Sharpee, who holds the Edwin K. Hunter Chair, was awarded the DeLano Award for Computational Biosciences from the American Society for Biochemistry and Molecular Biology. The award recognizes the innovative development or application of computer technology to enhance research in the life sciences at the molecular level. Sharpee's lab studies how the brain and other biological systems work and uses information theory to quantify the activity of neurons.

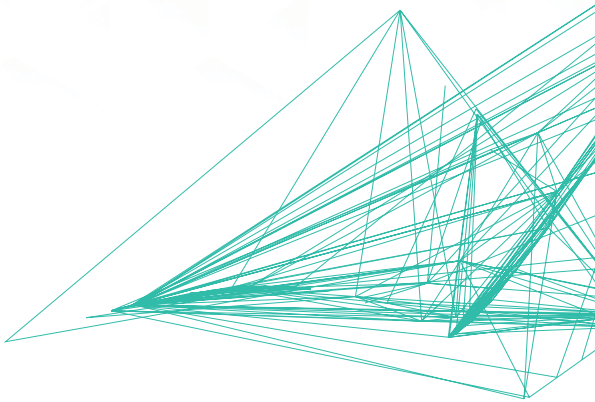


CHRISTINA TOWERS

**CHRISTINA TOWERS RECOGNIZED
AS ONE OF 2021'S WOMEN OF
INFLUENCE IN LIFE SCIENCES**



Assistant Professor Christina Towers was recognized as one of 2021's Women of Influence in the Life Sciences by the *San Diego Business Journal*. Towers focuses on uncovering how cancer cells recycle both their own nutrients and the power-generating structures called mitochondria in order to survive. Her research could lead to decreased cancer recurrence and improved cancer patient outcomes.



KAY TYE

**KAY TYE SELECTED AS
HOWARD HUGHES MEDICAL
INSTITUTE INVESTIGATOR**



Professor Kay Tye was selected as a Howard Hughes Medical Institute (HHMI) investigator, joining a prestigious group of more than 250 HHMI investigators across the United States who are tackling important scientific questions. Tye, who is a member of the Systems Neurobiology Laboratory and holds the Wylie Vale Chair, is known for her seminal work on the neural-circuit basis of emotion that leads to motivated behaviors, such as social interaction, reward-seeking and avoidance.

Funding Unique, Promising Ideas:

The 2021 Salk Innovation Grants

Thanks to the forward-thinking minds of longtime Salk supporters Irwin and Joan Jacobs, every year since 2009 Salk’s Innovation Grants Program has rewarded out-of-the-box ideas that hold significant promise but may not yet have the track record to attract funding from more traditional sources.

With awards given semiannually by peer review, Salk’s Innovation Grants Program is critical for catalyzing emerging science with the power to redefine the future. Since its inception, the program has prompted a host of discoveries. The most recent class of recipients are evidence of the continued impact Innovation Grants awards have on Salk research.

Congratulations to all the 2021 winners!

2021 Innovation Grants



SREEKANTH CHALASANI

The Chalasani lab is seeking to understand how animals make decisions. Associate Professor Sreekanth Chalasani and graduate student Jess Haley will use a novel microscopy system to record the activity of most, if not all, neurons in the *C. elegans* “brain” as it learns, remembers and makes decisions. They will discover neuronal changes associated with each of these three phenomena (learning, memory and decision-making), providing a framework for analyzing more complex brains.



TONY HUNTER

RNA Polymerase III (Pol III) mutations cause hypomyelinating leukodystrophy (HMLD), a fatal neurodegenerative disease caused by defective CNS nerve myelination. In yeast, conserved Pol III HMLD disease mutations cause growth defects, which are rescued by inhibiting the sumoylation pathway. Professor Tony Hunter’s lab will investigate if Pol III mutant-derived neurodegenerative phenotypes are recapitulated in human neural cells and in animal models, and, if so, how the sumoylation pathway contributes to such phenotypes. This could implicate sumoylation as a target for rescue of Pol III-related neurodegenerative diseases.



GEOFFREY WAHL

Intercellular interactions activate signaling pathways and cause phenotypic changes. The Wahl lab suspects such interactions contribute to cancer metastasis, a deadly killer of cancer patients, yet there are no methods to track the constellation of cells that a cancer cell interacts with in the metastatic niche. Professor Geoffrey Wahl, Postdoctoral Fellow Nikki Lytle and Project Scientist Leo Li will develop Contact Tracing, an innovative tool to indelibly label interacting cells for subsequent identification, isolation and analysis. This may reveal cellular relationships that drive metastatic progression.

2021 Collaboration Grants

The Collaborative Grants provide critical seed funding to large, bold ideas involving three or more Salk investigators.

SUSAN KAECH
DIANA HARGREAVES
YE ZHENG
JESSE DIXON

Aging is associated with dysfunctional immune responses, but no one knows the initiating events behind these processes. Professor Susan Kaech, Associate Professors Diana Hargreaves and Ye Zheng and Assistant Professor Jesse Dixon believe epigenetic influences are particularly vulnerable to age and that many of the age-related changes in immune function and inflammation stem from epigenetic dysfunction. The scientists will determine the effects of age on these factors during a viral infection, identify key features in aging-associated decline in immunity, and facilitate efforts to improve immune response in older patients.



SAMUEL PFAFF
AXEL NIMMERJAHN
NICOLA ALLEN
EIMAN AZIM

ALS is hallmarked with delayed adult onsets at unpredictable sites followed by devastating and progressive spread. Professor Samuel Pfaff, Associate Professors Axel Nimmerjahn and Nicola Allen, and Assistant Professor Eiman Azim believe that disease onset is accelerated or triggered by secondary environmental insults. An understanding of these environmental interactions could lead to avenues that would delay ALS onset, so the scientists are investigating how genetic models of ALS react to these environmental insults, which will begin to define how genetic predisposition and secondary environmental events converge to trigger ALS.





CONQUERING CANCER SUMMIT

On September 1, Salk supporters gathered in-person and virtually to attend the Institute's Conquering Cancer Summit and learn how Salk researchers are working to cut cancer's fuel lines to attack deadly tumors. The event highlighted Salk's collaborative effort to exploit the connection between cancer and metabolism and uncover new therapeutic strategies. Salk President Rusty Gage and Salk Cancer Center Director Reuben Shaw emceed the evening along with Cancer Center Advisory Committee Chair, Tim Schoen.

▶ WATCH | www.salk.edu/cancersummit2021



From left: Reuben Shaw, Susan Kaech, Christian Metallo, Satchin Panda, Christina Towers and Daniel Hollern.



From left: Tim Schoen, Rusty Gage and Reuben Shaw.



Cori Bargmann

"It's an incredible honor to be recognized by Salk for this award. As Jonas Salk demonstrated with the polio vaccine, basic science that is aimed at the right questions can make a major impact."

CORI BARGMANN

▶ WATCH | www.salk.edu/medal2021



From left: Rusty Gage, Cori Bargmann and Tony Hunter.



SALK AWARDS MEDAL OF RESEARCH EXCELLENCE TO CORI BARGMANN



On November 11, the Institute awarded neurobiologist and geneticist Cori Bargmann its prestigious Medal for Research Excellence, which recognizes a scientist who has made significant contributions in the area of basic scientific research. Bargmann leads the science program at the Chan Zuckerberg Initiative and is the Torsten N. Wiesel Professor at The Rockefeller University.

"Cori Bargmann has made seminal discoveries into the relationships between genes, motivational states and behavior," says Salk President Rusty Gage. "We are delighted to honor her with Salk's Medal for Research Excellence in recognition of her pioneering work."

Bargmann began her career as a graduate student in the lab of Robert A. Weinberg, a professor at MIT who was awarded the Salk Medal for Research Excellence in 2016 for his excellence in cancer research. While in his lab, Bargmann explored the mechanisms of a cancer gene called the NEU oncogene, which turned out to be relevant in human breast cancer. Targeted tumor therapies, such as Herceptin, were later developed to treat HER2-positive breast cancer, based on her research.

"As a neuroscientist, I believe that studying the brain will lead to exciting discoveries, and to great benefits in human health," says Bargmann. "It's an incredible honor to be recognized by Salk for this award. As Jonas Salk demonstrated with the polio vaccine, basic science that is aimed at the right questions can make a major impact."

A reception and dinner to honor Professor Bargmann was held at Salk and included a medal presentation by Salk President Rusty Gage and Professor Tony Hunter. In accepting the award, Professor Bargmann praised Salk and remarked on the legacy of Jonas Salk and noted the important contributions made by Salk scientists in various fields including computational theory and plant biology.

The Salk Institute medal was designed for the Institute by French fashion designer and businesswoman Paloma Picasso. Known for her dramatic jewelry creations, she is the daughter of Pablo Picasso and painter and writer Françoise Gilot, who later married Jonas Salk.

CLIVE GREENSMITH

Cello

“...a musician of that rare caliber that transports audiences from the ordinary to the sublime.”

PALM BEACH DAILY NEWS



BENJAMIN BEILMAN

Violin

“Poised and monstrously talented.”

PHILADELPHIA INQUIRER



2022 SEASON

FEBRUARY 13 — SEAN CHEN, piano

MARCH 20 — CLIVE GREENSMITH, cello / KAREN JOY DAVIS, piano

APRIL 24 — BENJAMIN BEILMAN, violin

MAY 15 — ZLATA CHOCHIEVA, piano



KAREN JOY DAVIS

Piano

“Ms. Davis’ performance... displayed sparkling brilliance and technical accuracy.”

THE TIMES OF LONDON



SEAN CHEN

Piano

“Chen has the ability to combine poetic sensibilities and dazzling technical prowess.”

LOS ANGELES MUSICAL EXAMINER



ZLATA CHOCHIEVA

Piano

“Zlata Chochieva is the real discovery... an extraordinary pianistic personality.”

THE GUARDIAN

music.salk.edu

SALK RECEIVES NUMEROUS COMMUNICATIONS AWARDS

Inside Salk (both print and online), the *Where Cures Begin* podcast and other Institute collateral garnered numerous accolades across a variety of awards during 2021. The Folio awards are among the most prestigious in the publishing industry, and the San Diego Press Club awards showcase San Diego’s best communicators in media.

DOT COMM AWARDS 2021

- Gold: Website/Nonprofit Salk.edu
- Platinum: Website/Nonprofit Inside.salk.edu

FOLIO AWARDS 2021

- Co-winner: Full Issue/Nonprofit *Inside Salk*, Winter 2020
- Website Design Salk.edu

SD PRESS CLUB AWARDS 2021

First Place

- Drawing/Illustration *Inside Salk*, Summer 2020 “A close look at the novel coronavirus”
- Science/Tech/Biotech *Inside Salk*, Winter 2020 “Leading science into the future”
- Photography *Inside Salk*, Summer 2020 Observations, Eiman Azim “Decoding dexterity”
- Annual Report *Inside Salk*, Winter 2020 Donor Honor Roll
- Newsletter *Inside Salk*, Spring 2021

- Podcast *Where Cures Begin*, Season 3
- TV/Online Video: Video Editing Harnessing Plants Initiative
- Website: Overall Use of Design Salk.edu

Second Place

- Feature/Layout *Inside Salk*, Winter 2020 “Leading science into the future”
- Association/Member Publication *Inside Salk*, Spring 2021
- Radio/Podcast: Audio Editing *Where Cures Begin*, Tom Albright
- PR Writing: Serious Subject “How targeting killer T cells in the lungs could lead to immunity against respiratory viruses”

Third Place

- Special Interest or One-time Publications Planned Giving Brochure

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Visit the Salk Institute at www.salk.edu.

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SCIENCE AND TECHNOLOGY

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Salk Institute has received the highest rating 10 consecutive times from Charity Navigator, the nation's foremost charity evaluator.



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