

# Where Cures Begin.®

## Salk Institute Science Guide



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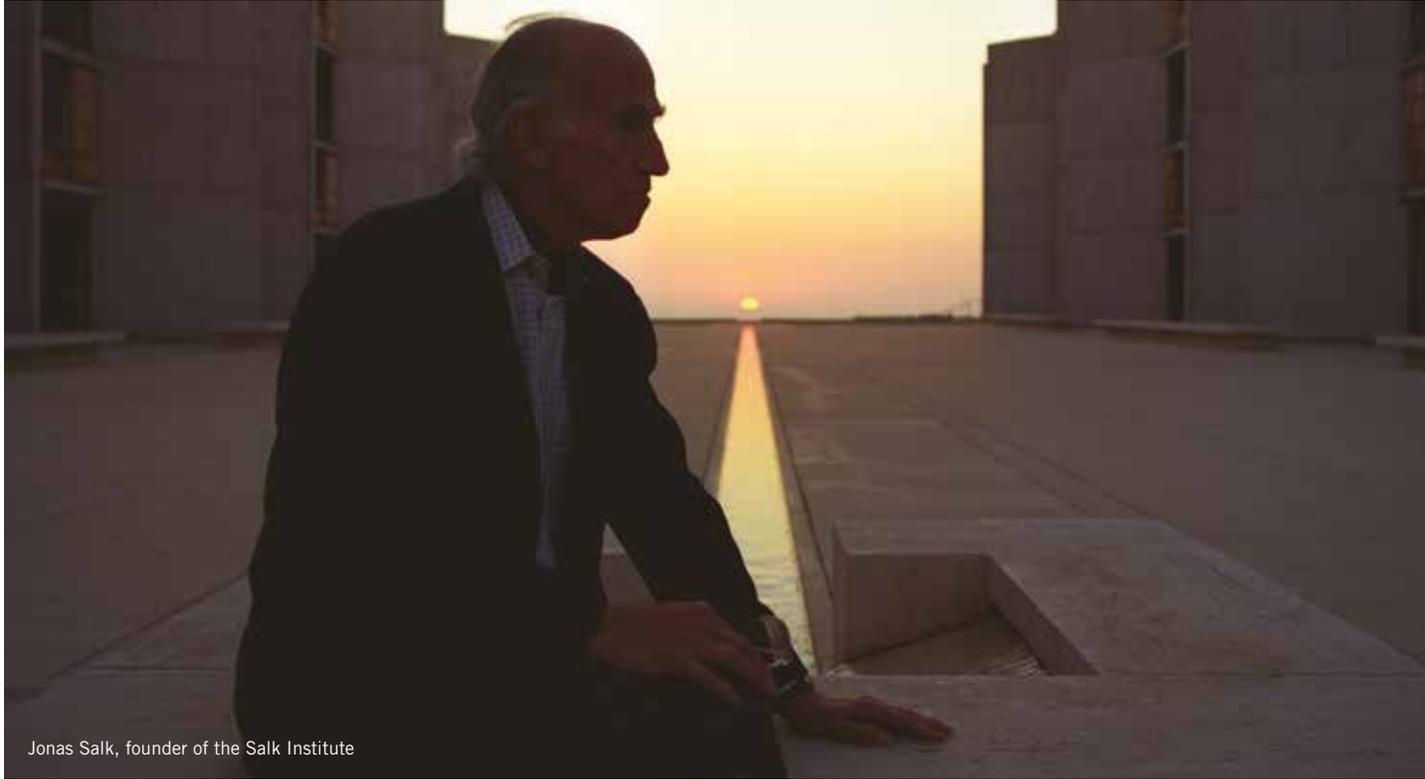
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# Introduction



Jonas Salk, founder of the Salk Institute

## President's Message

The Salk Institute has recently celebrated a number of historic anniversaries. We honored the centenary of Jonas Salk's birth. We recognized the 60th anniversary of his discovery of the world's first effective polio vaccine. And we celebrated the founding of the Salk Institute—Dr. Salk's remarkable "second act."

A half century after Dr. Salk launched his eponymous institute seeking to turn "dreams into reality," I'm confident he would be gratified by our progress. The impressive scientists, research centers and technology core facilities presented here in our *Science Guide* are a testament to his enduring vision of bringing brilliant minds together in an inspiring place.

The excellence of Salk's faculty has been recognized through countless national and international awards and honors. The Institute has been home to five Nobel laureates, including current faculty members Sydney Brenner and Roger Guillemin. Salk professors have received the Albert Lasker Award, the Gairdner Foundation International Award and the National Medal of Science. Present faculty include 14 members of the National

Academy of Sciences, 7 members of the National Academy of Medicine, 2 members of the National Academy of Engineering and 3 fellows of the Royal Society.

In this *Science Guide*, you will discover how Salk scientists are tackling some of the most challenging problems facing humanity. They are developing powerful new technologies and pioneering scientific approaches to make advances in cancer, neuroscience, immunology, diabetes, plant science and more. Their innovations and discoveries, powered by the Institute's cutting-edge research facilities and interdisciplinary research centers, are changing the world by explaining the very foundations of life.

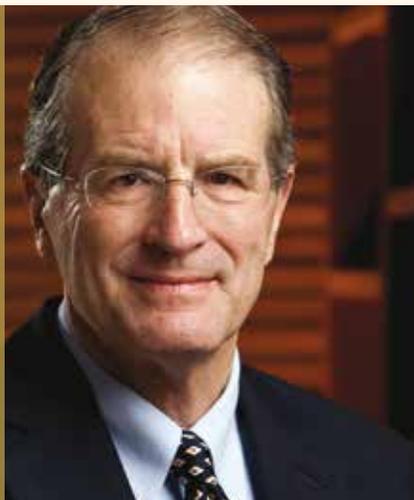
A handwritten signature in cursive script that reads "William R. Brody".

William R. Brody, MD, PhD  
President

# William R. Brody

President

Irwin M. Jacobs Presidential Chair



An acclaimed physician-scientist, entrepreneur and university leader, William R. Brody joined the Salk Institute for Biological Studies on March 2, 2009, after 12 years as president of Johns Hopkins University.

A native of Stockton, California, Brody received his bachelor's and master's degrees in electrical engineering from the Massachusetts Institute of Technology. He earned his doctorate (also in electrical engineering) and his medical degree (MD) from Stanford University. He continued his postgraduate training in cardiovascular surgery and radiology at Stanford, the National Institutes of Health and the University of California, San Francisco.

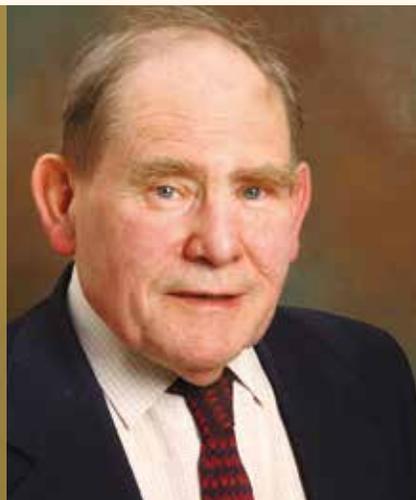
Between 1977 and 1986, he held appointments at the Stanford University School of Medicine, including professor of radiology and electrical engineering; director of the Advanced Imaging Techniques Laboratory; and director of Research Laboratories, Division of Diagnostic Radiology. In 1987, he moved to the Johns Hopkins University School of Medicine where he held several appointments, including the Martin W. Donner Professor of Radiology; professor of electrical and computer engineering; professor of biomedical engineering; and radiologist-in-chief of The Johns Hopkins Hospital. After a two-year stint as provost of the Academic Health Center at the University of Minnesota, he was named president of Johns Hopkins University in 1996.

Renowned for his achievements in biomedical engineering and the field of medical instrumentation, Brody is a member of the National Academy of Engineering and the National Academy of Medicine. He has authored more than 100 articles in U.S. medical journals, holds two U.S. patents in medical imaging and is the co-founder of three medical device companies. He has made significant contributions to the fields of medical acoustics, computed tomography, digital radiography and magnetic resonance imaging. He was an established investigator of the American Heart Association and received the Gold Medal from the Radiological Society of North America.

Brody is a trustee of the Keck Foundation. He has been a national figure in efforts to encourage innovation and strengthen the U.S. economy through investments in research and education. Most recently, he has written and spoken extensively around the country to promote a fuller discussion of health care reform.

# Sydney Brenner

Senior Distinguished Fellow of the Crick-Jacobs Center  
Nobel Prize in Physiology or Medicine, 2002



One of the world's pioneers in genetics and molecular biology, Sydney Brenner has devoted his career to conducting groundbreaking basic research and promoting science around the world.

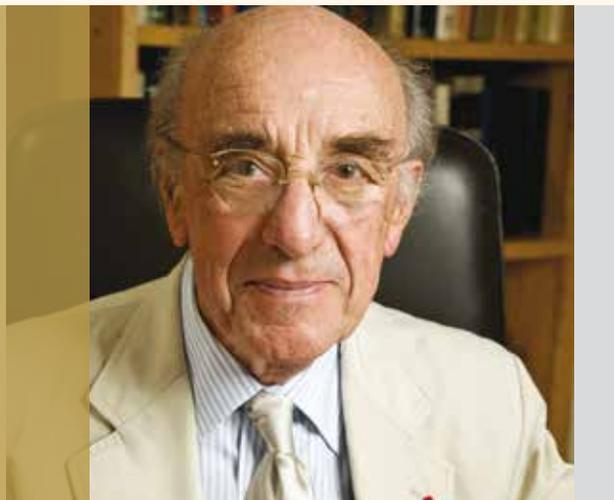
Born in Germiston, South Africa, Brenner earned degrees in medicine and science in 1947 from Johannesburg's University of Witwatersrand before moving to England, where he received a doctorate in chemistry from Oxford University in 1954 and began taking part in leading-edge research into DNA, molecular biology and developmental genetics. By 1956, he was sharing an office in Cambridge with Francis Crick, an alliance that lasted 20 years. Along with Crick, Brenner proposed that a single amino acid was coded by three nucleotides, a triplet, of RNA. He further demonstrated that the triplet combination of uracil, adenine and guanine—the “nonsense” or “stop” codon (a term he coined)—signifies the end of a translation process.

In the early 1960s, Brenner co-discovered the existence of messenger RNA and demonstrated that the nucleotide sequence of mRNA determines the order of amino acids in proteins. This work led to his first Lasker Award in Basic Medical Research; he later received a second Lasker Award in honor of his outstanding lifetime achievements. It was Brenner's pioneering research with *Caenorhabditis elegans*, however, that led to his Nobel Prize. Beginning in 1965, he began to lay the groundwork to make *C. elegans*, a small, transparent nematode, into a major model organism for genetics, neurobiology and developmental biology research. As a direct result of his original vision, this tiny worm became the first animal for which the complete cell lineage and entire neuronal wiring were known. Today, more than 1,000 investigators are studying *C. elegans*, and Brenner's work was further honored when a closely related nematode was named *Caenorhabditis brenneri*.

Beyond his own research, Brenner has been a driving force in advancing scientific research worldwide. He was instrumental in guiding Singapore toward biomedical research and founded the Molecular Sciences Institute in Berkeley, California, in 1996, serving as its president and director of science. He is also founding president of the Okinawa Institute of Science and Technology. Brenner, who previously had served as a scholar-in-residence at The Scripps Research Institute, has been a member of the Salk Institute faculty since 2000.

# Roger Guillemin

Distinguished Professor  
Nobel Prize in Physiology or Medicine, 1977



Considered the founder of the field of neuroendocrinology, Roger Guillemin, MD, PhD, is a scientific pioneer whose research into brain hormones has led to treatments for disorders ranging from infertility to pituitary tumors.

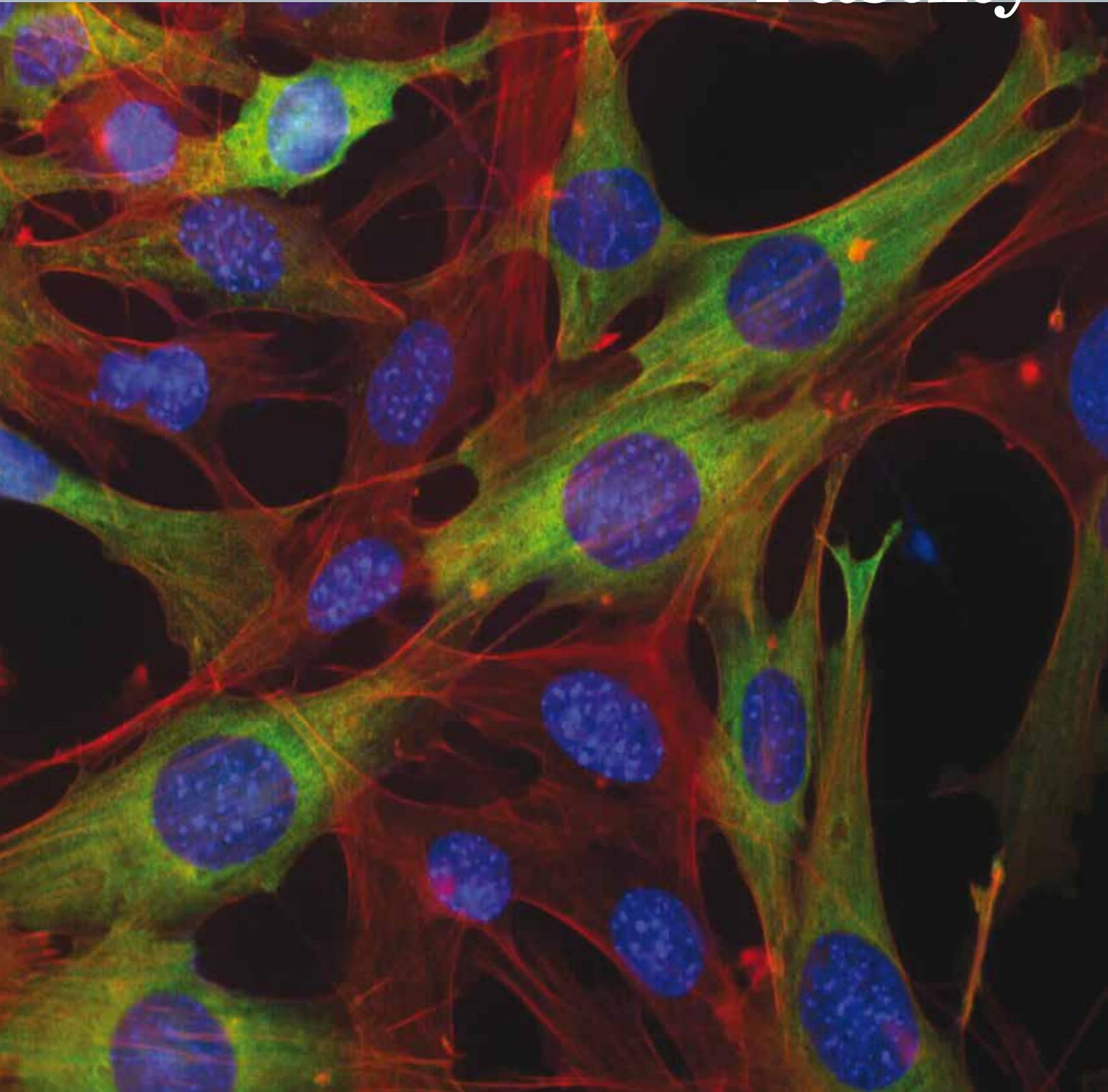
A native of Dijon, France, Guillemin graduated from the University of Lyon's medical school in 1949, then pursued an interest in endocrinology at the University of Montreal's Institute of Experimental Medicine and Surgery, receiving his PhD in 1953 and subsequently accepting an assistant professorship at Baylor College of Medicine in Houston, Texas. In 1969, Guillemin made his first groundbreaking discovery. Although researchers had long suspected that the brain controls the function of endocrine glands, they did not know how these interactions occurred throughout the body. They believed the brain's hypothalamus released a substance that activated these glands, but no one could find evidence for it.

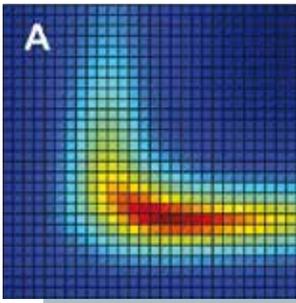
After manipulating 1.5 million sheep brains, Guillemin's group eventually isolated a molecule called TRH (thyrotropin-releasing hormone), which ultimately controls all the functions of the thyroid gland. In the following years, he and his colleagues isolated other molecules from the hypothalamus that control all functions of the pituitary gland—for instance, GnRH (gonadotropin-releasing hormone), a hypothalamic hormone that causes the pituitary to release gonadotropins, which in turn trigger the release of hormones from the testicles or ovaries. This discovery led to advancements in the medical treatment of infertility and is also used to treat prostate cancer.

In 1970, Guillemin joined the Salk Institute to head the newly established Laboratories for Neuroendocrinology, where he and his group discovered somatostatin, which regulates the activities of the pituitary gland and the pancreas and is used clinically to treat pituitary tumors. He was among the first to isolate endorphins, brain molecules that act as natural opiates, and his work with cellular growth factors (FGFs) led to the recognition of multiple physiological functions and developmental mechanisms, including molecules such as inhibins and activins.

The recipient of numerous honors, Guillemin was awarded the 1977 Nobel Prize for Physiology or Medicine for his work with hypothalamic hormones. He is also a member of the National Academy of Sciences and the American Academy of Arts and Sciences and has received the Lasker Award in Basic Sciences and the National Medal of Science, among many others. He was selected for the Hall of Honor at the National Institute of Child Health and Human Development (NICHD) for exceptional contributions to advancing knowledge and improving maternal and child health, and is listed as one of the most "highly cited" scientists from 1981–99 by the Institute for Scientific Information. As interim president of the Institute from 2007–09, he was instrumental in bringing art exhibits to the Salk Institute, fulfilling Jonas Salk's vision of a facility that blends science and art.

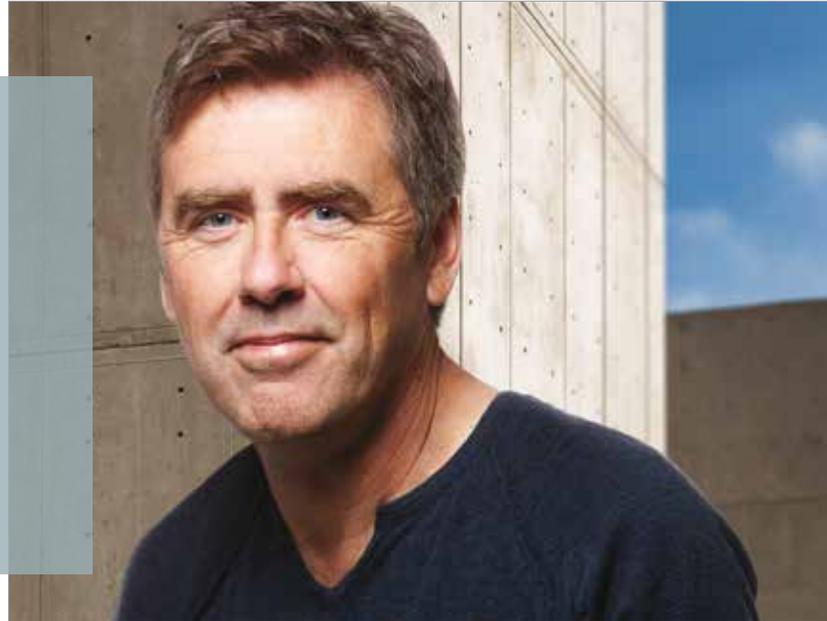
# Faculty





# Thomas Albright

Professor and Director  
Vision Center Laboratory  
Conrad T. Prebys Chair in Vision Research



## The Problem

When you're walking down a busy city street, passing crowds of people and colorful storefronts, not every detail of your surroundings is going to catch your attention. But throw something novel into the mix—say, a kangaroo—and you'll surely notice it. How does your brain know what visual details to pay attention to and which to ignore? Why do some details catch one person's eye, but are ignored by others? And how does your brain remember these images? That's the question scientists are asking to better understand vision and brain, but also to understand what goes wrong in psychiatric diseases that affect visual attention, like schizophrenia.

## The Approach

By combining physiological, neurological and computational studies, Thomas Albright is revealing how the brain enables humans to perceive and behave in a world of varying sensory demands. For example, he studies what happens to the brain's ability to choose attention-worthy details when the environment changes (paying more attention to a kangaroo on a city street than in the Australian outback, for example). The visual system, he's found, has a filter that determines which stimuli—from a kangaroo to a tree—reach the brain's visual processing area in the first place. He's also pinpointed how sets of neurons in the visual cortex are more or less sensitive than others in different

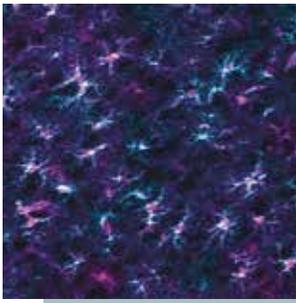
environments to allow for this shift in attention. Aside from better understanding disease, Albright's work can inform how the memory of visual information can be distorted, as well as how to build environments and architecture that encourage learning, productivity and healing.

## The Innovations and Discoveries

- Albright determined how the brain allocates resources to the vast amount of visual data that the eyes receive by using an initial filter to determine which details are given attention at all. On a city street, the information that gets past this filter will be different than information presented on a quiet mountain trail.
- By using brain scans instead of behavioral tests, Albright was able to uncover hallmark signs of problems with attention span in schizophrenic patients. The work could help companies screen for drugs that improve attention in patients with a variety of physiological disorders.
- He co-chaired a National Academy of Sciences committee that published a report sharing cautions and best-practice recommendations regarding eyewitness accounts.

For more information, please visit:  
<http://www.salk.edu/faculty/albright.html>

# Vision, Neurobiology, Autism, Schizophrenia, Neurological Disease



# Nicola Allen

Assistant Professor  
Molecular Neurobiology Laboratory  
Hearst Foundation Developmental Chair



## The Problem

To understand the basis of thought, most neuroscience has focused on the superstars of the brain, neurons. A growing body of research, however, is finding that astrocytes, abundant brain cells thought to merely provide scaffolding for neurons, actually play critical roles in regulating brain function. These prolific cells, which make up about half of the brain, could be the missing piece to understanding—and treating—neurodevelopmental and degenerative diseases.

## The Approach

Nicola Allen studies how astrocytes control the formation and function of neuronal connections, and aims to use this knowledge to develop ways to repair damaged connections to improve cognition and memory. Allen is also investigating whether these properties of astrocytes may regulate the brain's ability to learn new tasks.

Identifying the factors that astrocytes release in the brain is the first step to unraveling astrocytes' potential therapeutic ability. Allen uses biochemical and molecular techniques to identify astrocyte factors, as well as to analyze the neuronal receptors and signaling pathways that these factors regulate. These findings will help researchers understand how astrocytes control neuronal development and function and

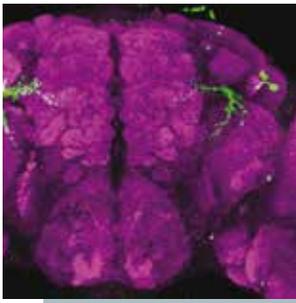
provide new insight into diseases like autism, epilepsy and Alzheimer's disease.

## The Innovations and Discoveries

- Allen discovered a class of proteins secreted from astrocytes that changes the ability of neurons to communicate in the developing brain. This class of proteins modulates connections between neurons, helping to facilitate the signaling that is the basis of our thoughts.
- Allen is searching for ways to treat neurodevelopmental disorders, such as autism, that are caused by defects in neuronal connections. Future and ongoing work explores whether findings from the developing brain can be used to treat diseases (like stroke) by promoting the repair of neuronal connections following injury.
- Allen is seeking additional classes of proteins astrocytes secrete that have different effects on neurons, such as strengthening neuronal connections in the adult brain or inhibiting the formation of new connections between neurons, to get a fuller picture of the complex effects astrocytes can have on neuronal function.

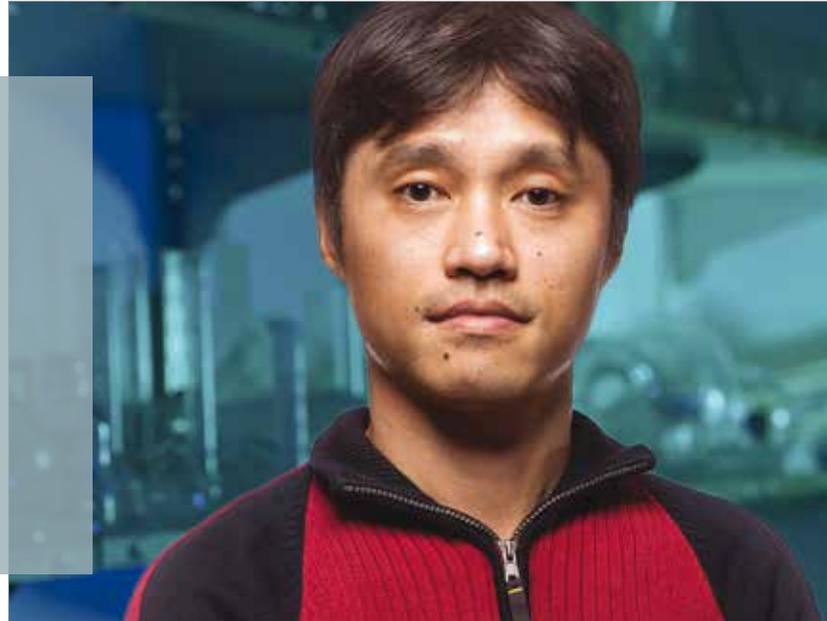
For more information, please visit:  
<http://www.salk.edu/faculty/allen.html>

## Alzheimer's Disease, Autism, Neurobiology, Neurological Disease, Developmental Disease



# Kenta Asahina

Assistant Professor  
Molecular Neurobiology Laboratory



## The Problem

Whether you're a human or an insect, behavior is ultimately supported by functions of molecules. Genetic circuitry and molecular interactions give rise to an animal's choice on how to react to its environment. However, behavior is not always predictable—it can vary dramatically depending on an animal's internal states, experience and reactions from other individuals. Understanding what goes haywire in brains of the socially impaired (such as in autism or attention-deficit disorders) is the first step in developing effective and specific treatments for such neurological disease. It can be difficult, however, to study the basis for behaviors and pathologies in humans, in part because our nervous systems are so complex.

## The Approach

To begin to unravel complex social reactions, Kenta Asahina is studying behavior at the most fundamental level. Asahina is currently using the vinegar fly *Drosophila melanogaster* as a model organism to understand the simple genetic and neural circuits that cause responses like aggression and escape. It's not just about a single "aggression gene" however—genes and neurons are just the beginning. By tracing how the molecular underpinnings of behaviors give rise to more complicated brain activity, he aims to eventually understand social interactions in humans.

To unravel the fundamentals of behavior, he is using multidisciplinary approaches, including advanced genome editing, gene expression control, optogenetic techniques for controlling neurons with light, functional neuronal imaging and computational behavioral analysis. His lab is also interested in expanding the research scope to comparative genomics, evolutionary ethology and social behaviors.

## The Innovations and Discoveries

- Asahina discovered a neuropeptide and several neurons crucial for aggression in vinegar flies. The neuropeptide has been linked to aggressive behavior in several mammals.
- He is expanding on understanding how behavior circuits interact with each other and what makes an animal choose one behavior over another (eating instead of mating, for example).
- He has begun to find "common motifs" between genes that spur behavior for both vinegar flies and mammals and aims to translate his findings into more precise pharmaceutical targets for people displaying aberrant behavior, such as in the case of mental illness.

For more information, please visit:

<http://www.salk.edu/faculty/asahina.html>

# Autism, Dementia, Genetics, Memory, Neurobiology, Neurological Disease



# Janelle Ayres

Assistant Professor  
Nomis Foundation Laboratories for Immunobiology  
and Microbial Pathogenesis



## The Problem

Our main tool for fighting infections is antimicrobials, such as vaccines, antivirals and antibiotics. But there are limitations to this approach: besides not working for all diseases, antibiotics also kill good bacteria that inhabit our bodies and contribute to multi-drug resistant, harmful bacteria (“super bugs”). An additional limitation to this method is that killing an infection does not ultimately determine if a patient will survive. Fixing the physiological impairment (such as tissue and metabolic damage) that occurs during infections is critical to an organism’s health as well.

## The Approach

In a new approach to therapeutics, Janelle Ayres studies how the body controls and repairs the collateral damage generated during interactions with bad microbes. She is taking an innovative approach grounded in mathematical and evolutionary predictions that uses the beneficial microbes that inhabit our digestive system for damage-control therapeutics. In pivotal work, Ayres showed that those damage-control mechanisms are just as important as an animal’s immune system in surviving infection. Her revelation of an entirely new set of defense mechanisms will likely lead to novel therapies that bacteria won’t be able to evolve resistance to. And because pathologies that arise during infection are similar to those created by non-infectious diseases, therapies that manipulate damage-control mechanisms could also have broader

applications than antibiotics. Ultimately, by leveraging those damage-control mechanisms, Ayres aims to develop treatments for infectious and non-infectious diseases (such as pathologies associated with cancer and aging) without the need for antibiotics.

## The Innovations and Discoveries

- Ayres provided the first evidence that an animal’s ability to survive an infection is not solely dependent on the ability of the immune system to kill bacteria. Rather, she determined that damage-control mechanisms are just as important in the animal’s recovery.
- Ayres gave fruit flies a dose of *Listeria* bacteria and tested what variables—from diet to genetics—allowed the flies to survive the infection. She found that distinct sets of genes in the flies encode mechanisms to prevent, limit and repair damage that occurs during infection.
- Ayres showed that when mice consume a strong antibiotic, they’re more prone to developing a lethal, body-wide *E. coli* infection. The reaction, Ayres demonstrated, was dependent on the inflammasome, a particular complex of immune system proteins that becomes activated when the bacterial environment in the intestines shifts.

For more information, please visit:  
<http://www.salk.edu/faculty/ayres.html>

Digestive Disorders, Immunology, Infectious  
Disease, Inflammation, Metabolism, Microbiology



# Ursula Bellugi

Professor and Director  
Laboratory for Cognitive Neuroscience  
Salk Founders' Chair



## The Problem

Humans are wired to be social, communicative creatures, but sometimes this circuitry goes awry. Researchers are striving to pinpoint the links between genes, brain activity and behavior to better understand psychological behaviors and mental disorders, such as autism. Understanding the basis for sign language or the cause of anxiety, for example, can help provide fundamental insights into the genetic mechanisms and neural circuits responsible for human social behavior.

## The Approach

Ursula Bellugi pioneered the study of the biological foundation of language. She is regarded as the founder of the neurobiology of American Sign Language (ASL), because her work was the first to show it as a true language as processed by the brain, revealing more about how the brain learns, interprets and forgets language. Constantly seeking new avenues for illuminating the ties between neural and cognitive functions, Bellugi uses her expertise in neurobiological, genetic and behavioral studies to better understand Williams syndrome—a puzzling genetic disorder that results in low IQ and strong desire for social interactions—and autism. While patients with autism usually shy away from social interactions and eye contact, Williams syndrome patients do exactly the opposite, seeking out interactions with people. Bellugi is using imaging technologies to visualize how related gene deletions alter brain activity, mapping the affected neural

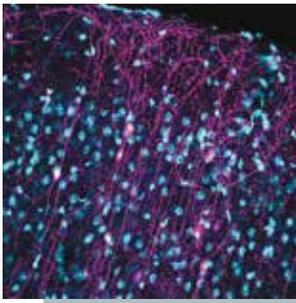
circuits, and developing stem cell reprogramming techniques to unveil the underlying biological basis for these drastically different disorders. Together, her studies on Williams syndrome, autism and sign language help paint a picture of the biology we use to interact with those around us.

## The Innovations and Discoveries

- Bellugi discovered that ASL is processed by the same areas of the brain that interpret the grammar and syntax of spoken language. This was one of the first pieces of neurobiological evidence that ASL is treated as a true language by the brain.
- She found that people with Williams syndrome have boosted levels of oxytocin, the so-called “trust hormone,” explaining why they seek social interaction despite having other learning and cognitive disabilities. The finding helps researchers understand the normal role of oxytocin in the brain as well as which genes regulate the hormone's production and release.
- She compared the language-processing abilities of patients with Williams syndrome and autism and found a difference in brain patterns. When Williams syndrome patients heard a sentence with an out-of-place word, they showed a spike of activity in one area of the brain; the activity peak was absent in those with autism.

For more information, please visit:  
<http://www.salk.edu/faculty/bellugi.html>

Autism, Genetics, Neurological Disease,  
Neurobiology, Stem Cells, Williams Syndrome



# Edward Callaway

Professor  
Systems Neurobiology Laboratories  
Audrey Geisel Chair in Biomedical Science



## The Problem

The billions of cells that make up the brain are a diverse bunch—some neurons are responsible for decision-making and others for memory, while some process information from the eye and others interpret smells. To understand how the brain organizes all these tasks and information, and what causes diseases like schizophrenia and autism, scientists need to map the connections between neurons. But it isn't easy, as the brain is more like a tangled bowl of spaghetti than a neat matrix of city streets. And techniques to look at the brain have mostly only allowed researchers to get a big-picture view of structure rather than to zoom in on individual cells.

## The Approach

Edward Callaway's lab pioneered a new way to map the connections between single neurons and specific cell types in the brain. The approach lets a modified virus hop from one brain cell only to the cells directly connected to the first cell. Then, the virus is stranded. By detecting where the virus ends up, Callaway's team can figure out all the connections from the starting cells. And by identifying the connections of the various cell types in the brain and adding that to information about the functional properties of the cells, they can then make and test theories about how the circuits work.

The methods developed in Callaway's lab are used by labs all around the world to map connections related to numerous nervous system functions and diseases such as schizophrenia, autism and

Parkinson's and Huntington's diseases. Work in the Callaway lab primarily focuses on circuits in the cerebral cortex and how they process visual information. Because the visual cortex uses the same basic cell types and circuits that are used elsewhere in the cortex, this work could also help us understand how the brain enables other abilities, such as decision-making, hearing and movement.

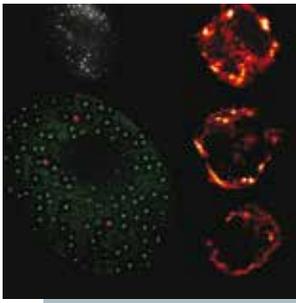
## The Innovations and Discoveries

- Callaway's lab developed a tool that uses a modified rabies virus to trace single connections between neurons, a technique now used across the world.
- During the last year the lab used its novel circuit-tracing methods to obtain a detailed map of connections to specific cell types in the basal ganglia, an area of the brain linked to both movement and decision-making and implicated in Parkinson's and Huntington's diseases. These studies provide insight into how different cell types in the basal ganglia structure contribute to motor control and decision-making.
- Callaway mapped the connections between cells in the retina of the eye and the brain and discovered that there's a unique highway of connections that has the sole purpose of letting the eye and brain work together to sense up-and-down or side-to-side movement.

For more information, please visit:

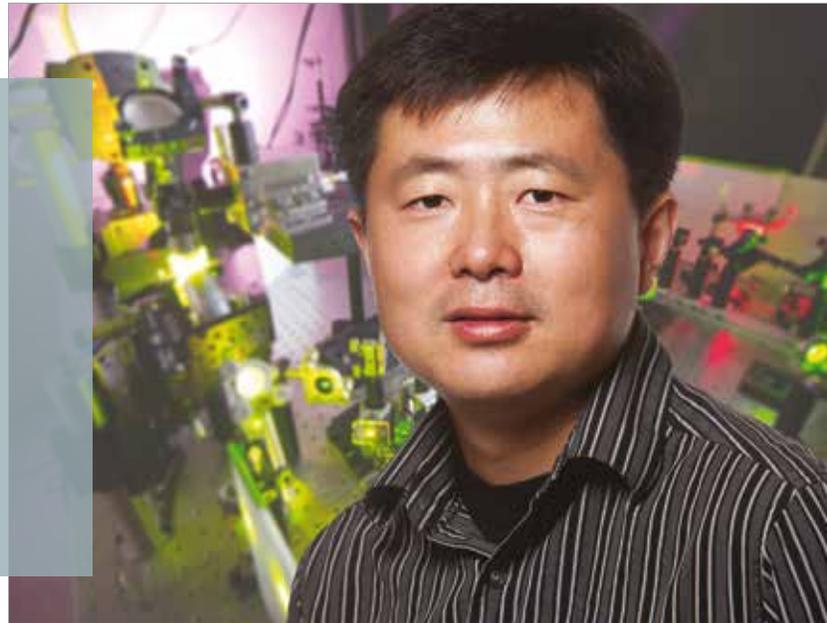
<http://www.salk.edu/faculty/callaway.html>

# Neurobiology, Neurological Disorders, Systems Biology, Vision



# Hu Cang

Assistant Professor  
Waitt Advanced Biophotonics Center  
Frederick B. Rentschler Developmental Chair



## The Problem

Researchers in all realms of biology rely on microscopes to see the organisms, cells and even molecules that they study. But microscopes can only zoom in so far—the resolution of modern microscopes is about a quarter of a micrometer. This means that scientists can see cells and even some parts of cells but individual molecules—like the building blocks of proteins or DNA—are too small to distinguish from one another. Moreover, the dye molecules that can be attached to other molecules to light them up under the microscope wear out quickly, allowing only brief snapshots of their position. So, scientists face obstacles in seeing the tiniest details of molecules and in watching long-term processes inside cells.

## The Approach

Hu Cang wants to improve the resolution of microscopes by designing lenses in a new way. Historically, lenses can only magnify objects that are at least as large as a wavelength of light—this is what has limited the resolution of microscopes. But Cang is developing a “super lens” that sees things smaller than a wavelength of light by assembling a lens from multiple parts. Cang’s group has already made a microscope that can focus light down to a point smaller than ever before, enabling researchers to track individual proteins on the surface of a cell. Cang is also working on solving the second problem limiting today’s microscopy: dyes that quickly fade when exposed to the bright light of a microscope. He is using chemical tricks

to alter the structure and environment of these dyes to extend their lifespan.

With his expertise in cutting-edge microscopy, Cang collaborates with biologists who are trying to see the smallest moving parts of cells. He is particularly interested in using his new “super lens” approach to study the structure of genetic material, which is notoriously hard to visualize. Being able to see how strands of DNA fold and loop when they’re packed within the nucleus of a cell might reveal more on how genes are turned on and off in both healthy and diseased cells.

## The Innovations and Discoveries

- Cang showed how Amazon Cloud, an online data application, can be used to process the immense amount of data generated by super-resolution microscopes. The new approach could process an image that previously took 24 hours in only 72 minutes.
- He teamed up with Salk colleagues to study how proteins fold and bind to one another and develop new, stronger types of bonds. Cang’s imaging approaches let scientists see details of these processes not previously visible.
- He also discovered a new way to stop dyes from fading under the microscope. By changing the environment of a dye, he enabled the dye to give off a thousand times more light before it wears out.

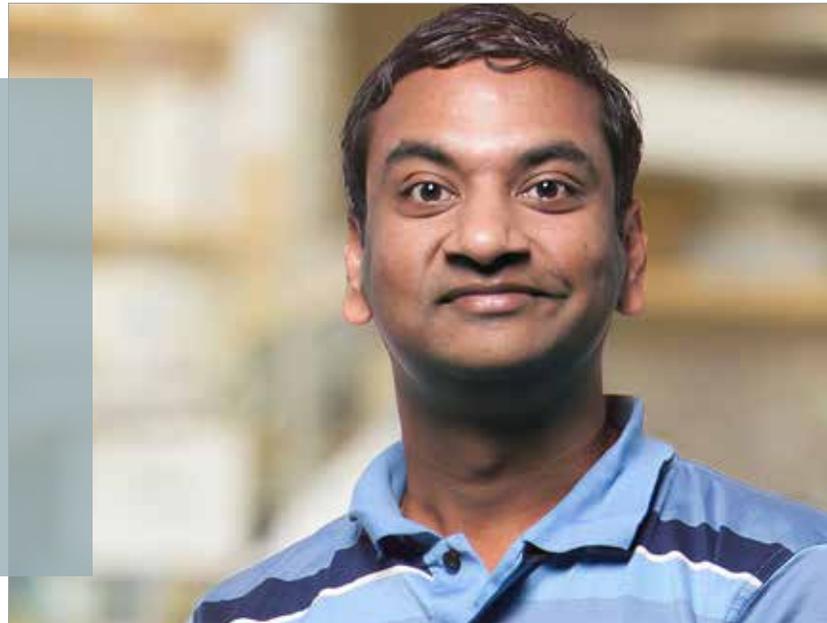
For more information, please visit:  
<http://www.salk.edu/faculty/cang.html>

# Aging, Biophotonics, Cancer, Epigenetics



# Sreekanth Chalasanani

Assistant Professor  
Molecular Neurobiology Laboratory



## The Problem

Every behavior a person carries out—from speaking a sentence to swatting a fly—is dictated by the brain, working at lightning speed to analyze the world and respond to sights, smells and sounds. How does the brain accomplish this? How does it combine all these pieces of information? Researchers want to know how a healthy brain works so they can better understand what's different in the brains of people with diseases, from autism to depression. But it's a daunting question: the human brain contains more than 86 billion neurons and studies of patients have failed to turn up obvious changes to these cells that could lead to disease.

## The Approach

Sreekanth Chalasanani uses an organism with a much simpler nervous system than humans to answer questions about neuroscience: the roundworm *Caenorhabditis elegans*. This animal has only 302 neurons and a few thousand connections between these cells. Each neuron is mapped and named, making it easier to study the effect of environment or gene changes at the resolution of individual cells. But despite its simplicity, the *C. elegans* nervous system has commonalities with a human brain: if you give a worm a dose of the antidepressant Prozac, for example, it becomes less fearful of predators; and if you mutate a gene linked to autism in humans, the worm shows less interest in other worms.

Among other studies, Chalasanani's lab is asking how the roundworm nervous system, one of the simplest in nature, gives rise to such behaviors as fear and aggression. He is exploring what these tiny creatures can tell us about human aggressions and fears, emotions and behaviors often necessary for our survival, but which are also sources of great suffering. The worm's simple nervous system makes it useful for studying human diseases—and testing drugs—in a well-understood model.

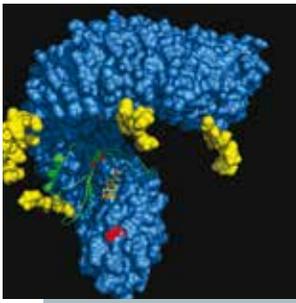
## The Innovations and Discoveries

- Chalasanani used salt-sniffing roundworms to help explain how the nervous system processes sensory information, discovering that insulin plays a role in mediating worms' perceptions and behaviors.
- He also discovered that there was more than one type of neuron involved in processing sensory cues that researchers had previously thought were only sensed by single neurons.
- He is currently studying the relationship between the *C. elegans* roundworm and a predator worm, *P. pacificus*, to explore how the nervous system gives rise to behaviors such as anxiety and aggression.

For more information, please visit:

<http://www.salk.edu/faculty/chalasanani.html>

# Anxiety, Autism, Locomotion, Neurobiology, Neurological Disease



# Joanne Chory

Professor and Director  
Plant Molecular and Cellular Biology Laboratory  
Howard Hughes Medical Institute Investigator  
Howard H. and Maryam R. Newman Chair in Plant Biology



## The Problem

Plant science is needed more today than ever before to help meet the demands of a rapidly growing human population and the disruptions of climate change. The global population recently topped 7 billion and is expected to reach 12 billion by the end of the century. More people means greater demand for food, feed, fiber and fuel, placing tremendous strains on ecosystems around the world. This growing demand, combined with extreme drought and temperature fluctuations, has resulted in widespread environmental damage, economic hardship and malnutrition. It is estimated that one in seven people currently do not have enough to eat, and complications from malnutrition are the greatest killer of children under five.

## The Approach

Joanne Chory has spent more than 25 years using *Arabidopsis thaliana*, a small flowering mustard plant, as a model for plant growth. She has pioneered the use of molecular genetics to study how plants respond to their environment and has made major discoveries surrounding how plants sense light and make growth hormones. The basis of Chory's approach involves mutating *Arabidopsis* genes and then observing the effects on a plant—does it grow faster or taller? Does it stop sending new shoots out in the direction of the sun? Does it need less water? In this way, her team has been able to describe the function of multiple pathways that control plant growth.

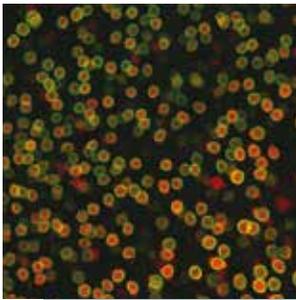
Chory and her team run a vertically integrated program, using genetics, genomics, cell biology, x-ray crystallography, biochemistry and ecological approaches. This has allowed them to determine one of the most complex signaling networks that control growth and development in response to environmental change.

## The Innovations and Discoveries

- Chory and her colleagues discovered that plants make and respond to a steroid hormone to control their final size. In a tour de force genetic study, researchers mapped the entire plant hormone signaling system, defining a new paradigm for steroid perception that is distinct from humans.
- Her team found that greater than 90 percent of the approximately 30,000 *Arabidopsis* genes have a peak of expression at a particular time of day, and moreover, the timing changes with the seasons. Farmers, working with scientists, should be able to use this information to predict the consequences of global climate change on agricultural yield.
- They determined the mechanism by which a shaded plant can outgrow its neighbor. Since dense planting by farmers leads to a major loss of yield, knowledge of this pathway is already being put to good use.

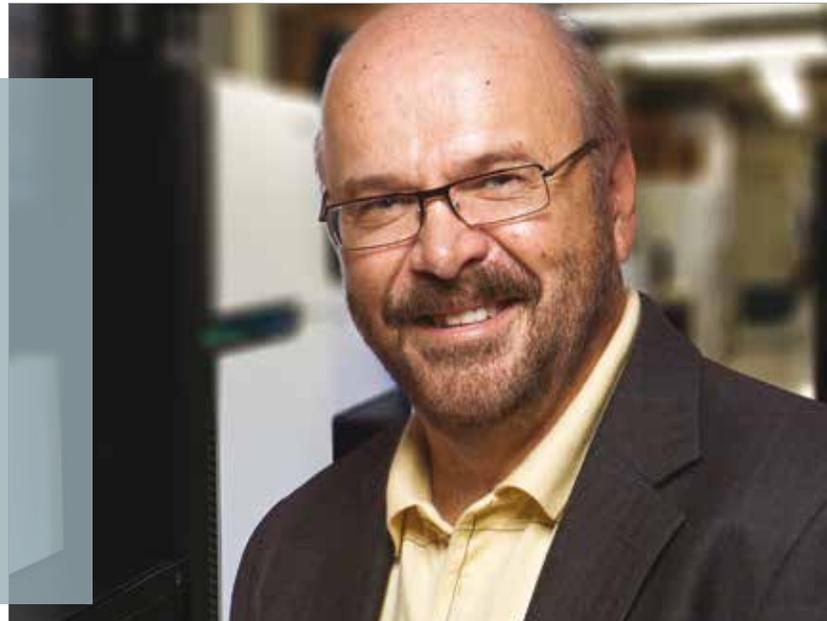
For more information, please visit:  
<http://www.salk.edu/faculty/chory.html>

## Cellular Biology, Circadian Rhythms, Genetics, Plant Biology and Agriculture



# Joseph Ecker

Professor  
Plant Molecular and Cellular Biology Laboratory  
Director, Genomic Analysis Laboratory  
Howard Hughes Medical Institute and  
Gordon and Betty Moore Foundation Investigator  
Salk International Council Chair in Genetics



## The Problem

It was long believed the sequence of genes in a genome was all that was needed to understand that organism's biology. Recently, scientists have realized there's another level of control: the epigenome. The epigenome is made up of chemicals that dot the DNA, dictating when, where and at what levels genes are expressed. But how these epigenomic tags affect biology, health and disease is still poorly understood. To decrypt the information they contain, researchers still need to answer basic questions about this extra genetic code.

## The Approach

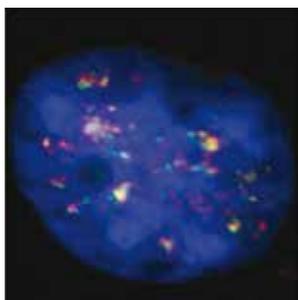
Ecker first became entranced by the epigenome while he was studying *Arabidopsis thaliana*, a small flowering plant used for basic plant biology research. He and his colleagues wanted to know how many *Arabidopsis* genes were controlled by DNA methylation—one form of chemical markers that stud genes to affect how genes are expressed. In the process of the research, Ecker realized there was no good way to get a snapshot of all the methylation marks in a cell, so he created a method called MethylC-Seq to map epigenetic tags in any organism. Ecker has now applied MethylC-Seq to questions about epigenetics that span many fields, in particular, the human brain. He was the first to show that the epigenome is highly dynamic in brain cells during the transition from birth to adulthood. Now, he is charting the epigenetic differences between brain cell types to better understand disorders such as schizophrenia and Alzheimer's disease.

## The Innovations and Discoveries

- In plant research, Ecker co-directed (and his laboratory participated in) an international project that sequenced the first plant genome. The reference plant *Arabidopsis thaliana* is now the most studied plant in the world. His group created the "Salk T-DNA collection" of insertion mutations for nearly all of the genes in the *Arabidopsis* genome, allowing investigators worldwide access to a database of any gene mutation of interest through the click of a button. Additionally, his group discovered most of the genes that allow plants to respond to ethylene, a gaseous plant hormone that regulates growth, resists disease and causes fruit to ripen.
- Ecker was also the first to map the entire human epigenome, creating a starting place for understanding the differences between different people's epigenomes and how these variances could contribute to disease risk.
- With collaborators, Ecker compared the epigenetic marks on different lines of stem cells to determine which methods of stem cell creation led to cells most similar to the "gold standard" embryonic stem cells. Cells created by moving genetic material into empty egg cells, he found, are closest to this gold standard.

For more information, please visit:  
<http://www.salk.edu/faculty/ecker.html>

Epigenetics, Genetics, Neurobiology, Molecular  
Biology, Plant Biology and Agriculture, Stem Cells



# Beverly Emerson

Professor  
Regulatory Biology Laboratory  
Edwin K. Hunter Chair



## The Problem

Just as adults might not stay healthy if they only ate liquid baby formula, new tumors have a different set of requirements than more mature, established cancers to thrive and spread. So when researchers discover a new gene that—when mutated or turned on—seems to drive the growth of cancer, their findings might not hold true in all the stages of a tumor's growth. To develop new drugs and determine what treatments are most appropriate for different tumor stages, scientists need to work out what changes occur at a molecular and genetic level as a tumor progresses.

## The Approach

Beverly Emerson studies how different genes are turned on and off through the course of a cancer—from the time cells become precancerous until the time they develop into a mature cancer and spread to new organs. Many researchers look for genes that are mutated in tumors, as these mistakes in the DNA code can lead to cancer. But Emerson's lab looks at other ways genes can be turned on and off to allow a tumor to grow. She's found that the physical arrangement of DNA inside a cell's nucleus can affect cancer genes: for example, if a gene gets stuck in a folded-up piece of DNA, proteins that normally turn it on can no longer access it.

Her lab also studies how different proteins (and their mutations) interact in cancer cells. Looking at cancer genetics in

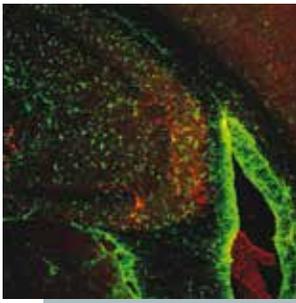
this broader way is helping Emerson to discover new drug targets that may be used to prevent or treat cancers.

## The Innovations and Discoveries

- Emerson and her team uncovered details about how cancer is able to become drug resistant over time. They showed how variations in breast cancer cells' RNA, the molecule that decodes genes and produces proteins, helps the cancer to evolve more quickly than previously thought. The findings may point to a "switch" to turn off this diversity—and thereby drug resistance—in cancer cells.
- Emerson discovered how the gene COX-2, involved in inflammation, is turned on in the early stages of a cancer to help it grow and then off again in a more mature tumor to protect it from immune responses. Developing a way to turn COX-2 back on in advanced colon, breast, and pancreatic cancers might help the immune system shrink tumors.
- She pieced together how two proteins, p53 and TGF- $\beta$ , interact as a tumor matures. While scientists previously thought that a drug targeting TGF- $\beta$  would only be useful in advanced cancers, she discovered that the same drug may help prevent precancerous cells from turning into cancer.

For more information, please visit:  
<http://www.salk.edu/faculty/emerson.html>

# Cancer, Epigenetics, Genetics, Therapeutics



# Ronald Evans

Professor and Director  
Gene Expression Laboratory  
Howard Hughes Medical Institute Investigator  
March of Dimes Chair in Molecular and  
Developmental Biology



## The Problem

Humans are built to hunger for fat but when deluged by foods rich in fat and sugar coupled with a sedentary lifestyle, the modern waistline often far exceeds the need to store energy for lean times. The result has been an epidemic of diabetes, heart disease and other obesity-related problems, including cancer. Although exercise and calorie restriction are known to be effective at preventing and treating diabetes, the obesity epidemic continues to grow and new drugs to treat the problem are desperately needed.

## The Approach

Ronald Evans is an authority on hormones, both their normal activities and their roles in disease. A major achievement in Evans' lab was the discovery of a large family of molecules, called nuclear hormone receptors, which respond to various steroid hormones, vitamin A and thyroid hormones. These hormones help control sugar, salt, calcium and fat metabolism, affecting our daily health as well as treatment of disease. The receptors Evans discovered are primary targets in the treatment of breast cancer, prostate cancer, pancreatic cancer and leukemia, as well as osteoporosis and asthma.

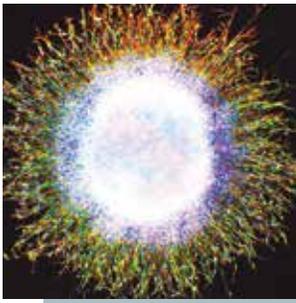
In addition, Evans' studies led to a new class of drugs called exercise mimetics, which promote the benefits of fitness without the need to train. Exercise mimetics represent one of the newest and most important advances in addressing problems arising from excess weight and obesity, such as frailty, muscular dystrophy and the potential treatment of adult onset diabetes (type 2 diabetes).

## The Innovations and Discoveries

- Evans' team developed two innovative approaches for potentially treating diabetes. The group identified the missing link in the regulation of the activity of insulin—a protein known as fibroblast growth factor 1 (FGF1), which reboots glucose metabolism. Evans also developed a new type of diet pill that tricks the body into thinking it has consumed calories, causing it to burn fat. The compound effectively stopped weight gain, lowered cholesterol, controlled blood sugar and minimized inflammation in mice.
- Two receptors found on the nuclei of mouse and human cells, known as REV-ERB- $\alpha$  and REV-ERB- $\beta$ , are essential for synchronizing normal sleep and metabolic cycles. Evans' findings describe a powerful link between circadian rhythms and metabolism and suggest a new direction for treating disorders of both systems, including jet lag, sleep dysfunction, obesity and diabetes.
- Evans' lab discovered that a chemically modified form of vitamin D might offer a new approach to the treatment of pancreatic cancer. The vitamin D derivative makes tumor cells vulnerable to chemotherapy and more sensitive to the body's immune system. With clinicians at the University of Pennsylvania, Evans' team launched a clinical trial to test this drug in cancer patients.

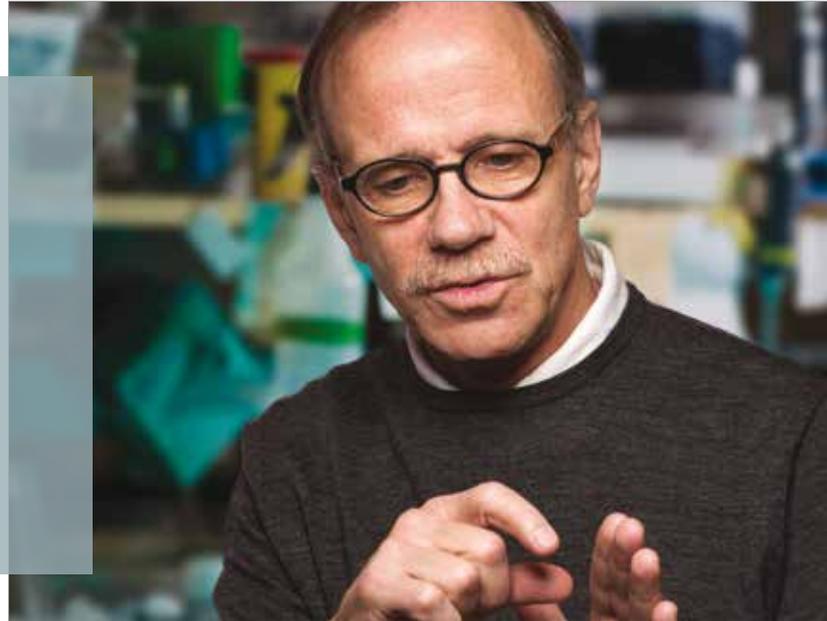
For more information, please visit:  
<http://www.salk.edu/faculty/evans.html>

**Cancer, Circadian Rhythms, Diabetes, Genetics,  
Inflammation, Metabolism, Pancreatic Cancer, Therapeutics**



# Rusty Gage

Professor  
Laboratory of Genetics  
Vi and John Adler Chair for Research on Age-Related  
Neurodegenerative Disease



## The Problem

Variations in the genes we inherit from our parents ensure that each brain is uniquely wired, leading to differences in how we think, learn and behave, and in our propensity for mental illness. Understanding how genes and environment come together to guide these processes is crucial to developing better ways to prevent and treat diseases of the brain. But studying the human nervous system at the molecular level has always been challenging due to the complexity of the brain, as well as the difficulty of obtaining live human neurons for study in the laboratory.

## The Approach

Fred “Rusty” Gage concentrates on the unexpected plasticity (ability to change) and adaptability to the environment that mammals have throughout life. His lab showed that human beings are capable of growing new nerve cells throughout life, in a process called neurogenesis. Gage’s team explores how these cells can be prompted to become mature, functioning nerve cells in the adult brain and spinal cord. He also showed that environmental enrichment and physical exercise can enhance the growth of new brain cells. The team continues to study the underlying cellular and molecular mechanisms of neurogenesis to find possible avenues to repair damaged or aging brains.

Gage’s lab also models diseases in the laboratory using human stem cells. By reprogramming human skin cells and other cells from patients with neurologic and psychiatric diseases into

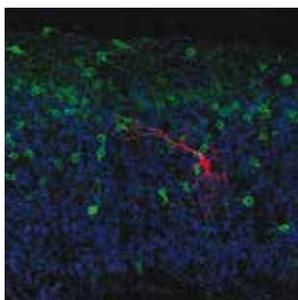
induced pluripotent stem cells (iPSCs) and induced neurons (iN), his work seeks to decipher the progression and mechanisms that lead to brain cell dysfunction. Finally, Gage also revealed that mobile sequences of DNA called “jumping genes” are active in neural stem cells contributing to genomic mosaicism. Specifically, he is interested in how this mosaicism (different sets of genes within a single organism) may lead to differences in brain function between individuals.

## The Innovations and Discoveries

- Gage and his colleagues discovered that the human brain can give rise to new neurons throughout life. He also found that exercise and cognitive enrichment can increase the brain’s ability to generate more neurons.
- Using new stem cell technologies, his team has shown that neurons generated from the skin cells of people with schizophrenia are dysfunctional in early developmental stages, providing a hint as to ways to detect and potentially treat the disease early.
- By sequencing the genomes of single cells, Gage and collaborators showed that the genomic structures of individual neurons differ from each other even more than expected. This may help explain differences between closely related individuals.

For more information, please visit  
<http://www.salk.edu/faculty/gage.html>

# Aging, Autism, Evolution, Genetics, Neurobiology, Schizophrenia, Stem Cells



# Martyn Goulding

Professor  
Molecular Neurobiology Laboratory  
Frederick W. and Joanna J. Mitchell Chair



## The Problem

Organisms from ants to horses to humans all get around the same way—walking. But what happens when a spinal cord injury or disease like Parkinson's damages nerve cells leading to the limbs and makes walking difficult or impossible? And what causes mysterious pain in the limbs, such as those experienced in fibromyalgia or phantom limb pain? Scientists want to create ways to repair or regenerate these nerve cells and restore walking ability or prevent patients from losing coordinated walking as a disease progresses. And they hope to develop better therapies for chronic pain that involves the neural circuitry of the spinal cord and limbs. But there's a big hurdle: they don't have a good understanding of how the nerve cells that allow walking and pain sensation develop in the first place, or even all the cells involved.

## The Approach

Martyn Goulding developed a specialized experimental setup that let him pinpoint in mice the subset of neurons required for locomotion. Neurons called V0 neurons, he discovered, mediate the alternating left-right pattern of walking, while V1 neurons set pace and a third set of neurons controls muscle activity.

Armed with this technique and the new knowledge of important neuron types, Goulding has been able to delve into the genetics and development of these walking neurons. He can introduce genetic mutations into mice and observe the effect on their walking ability, uncovering which genes are important for locomotion. In other experiments, Goulding also studies how

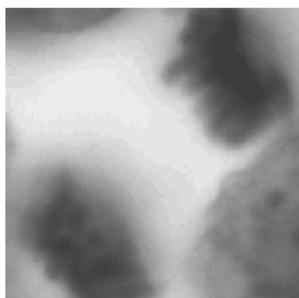
neuron cells implicated in walking grow, develop and connect muscles to the right spots in the brain in fetal mice. The knowledge of what neurons are needed for smooth walking might help scientists develop drugs or techniques that prevent diseases like Parkinson's from affecting walking, or restore walking ability in people with spinal cord injuries. Goulding has also leveraged his expertise in spinal neural circuitry to explore the causes of mysterious chronic pain.

## The Innovations and Discoveries

- Goulding's lab identified an important neural mechanism in the spinal cord that appears capable of sending erroneous pain signals to the brain. By charting the spinal circuits that process and transmit pain signals in mice, the study lays the groundwork for identifying ways to treat pain disorders that have no clear physical cause.
- Goulding's team mapped the neural circuitry of the spinal cord that processes the sense of light touch. A better understanding of these circuits should eventually aid in developing therapies for spinal cord injury and diseases that affect motor skills and balance, as well as the means to prevent falls for the elderly.
- Goulding discovered the role of V3 neurons in walking—the neurons, he showed, help coordinate movement between the two sides of the body.

For more information, please  
visit: <http://www.salk.edu/faculty/goulding.html>

Genetics, Neurological Disease, Locomotion,  
Neurobiology, Parkinson's Disease, Chronic Pain



# Diana Hargreaves

Assistant Professor  
Molecular and Cell Biology Laboratory



## The Problem

Our bodies are comprised of several hundred different cell types, yet each cell possesses the same genetic material. This diversity arises from selectively activating genes that are particular to each cell type, whether it is skin, liver or brain. This activation is achieved by proteins called epigenetic regulators, which work to make specific regions of our genome more or less accessible to transcription. Unlike our fixed genome, epigenetic regulation is dynamic and reversible, allowing cells to respond to developmental and environmental cues. In the past few years, researchers have found that these regulators are often mutated in cancer, suggesting the exciting possibility that the features driving such cancers can be reversed.

## The Approach

Diana Hargreaves studies a particular epigenetic regulator, the SWI/SNF complex, which uses energy to unpack and unwind DNA from structural proteins to alter DNA accessibility and in turn, gene transcription. The SWI/SNF complex is polymorphic, meaning that the complex can assume different forms through various combinations of individual subunits. These particular complex assemblies have been shown to be essential in stem cells and development.

Hargreaves brings her knowledge of biochemistry and epigenetic regulation to investigate a subunit of the SWI/SNF complex called ARID1A, which is mutated in many solid tumors,

such as in ovarian, bladder and colorectal cancers. In the absence of ARID1A, the essential activity of the SWI/SNF complex is provided by a similar protein, ARID1B. Hargreaves is exploring the different activities of these complexes in normal and cancer settings, with an eye toward targeting the essential activities of the SWI/SNF complex in ARID1A mutant cancers.

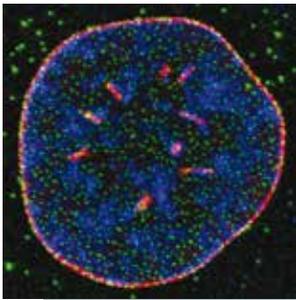
## The Innovations and Discoveries

- Hargreaves has demonstrated that ARID1A is indeed frequently mutated at rates comparable to other known tumor suppressors, the findings of which could have a translational impact for ovarian and other cancers. She has also shown that ARID1A mutations often co-occur with oncogenic mutations in the PI3K signaling pathway, suggesting a connection between these mutations.
- Hargreaves has uncovered an interaction between SWI/SNF and topoisomerase II alpha, a protein involved in DNA maintenance during replication, which underlies the essential activity of the complex in stem cells.
- By examining cells that lack ARID1A, Hargreaves is beginning to pinpoint changes in packaged DNA to better explain the role of ARID1A and ARID1B in driving cancer.

For more information, please visit:

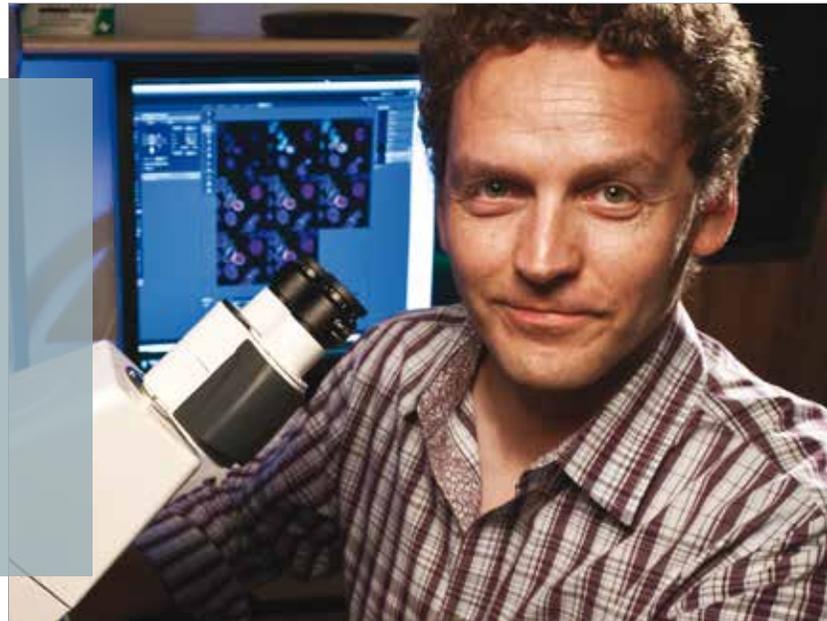
<http://www.salk.edu/faculty/hargreaves.html>

Cancer, Developmental Disease, Epigenetics,  
Genetics, Neuroscience, Neurologic Disease



# Martin Hetzer

Professor  
Molecular and Cell Biology Laboratory  
Jesse and Caryl Philips Foundation Chair



## The Problem

The nucleus of a cell has a tight security system, composed of membranes dotted with channels and gates called nuclear pore complexes that only let some molecules through. If the wrong molecules get into the nucleus, they can incorrectly turn genes on or off or botch normal cellular programs. But sometimes the security system of the nucleus malfunctions: cancer cells have been shown to have lapses in their nuclei, as have brain cells associated with neurodegenerative diseases like Parkinson's. To understand how these leaky nuclei might cause disease—and how to boost these security systems again—scientists first need to understand the normal functioning of nucleoporins, proteins that make up nuclear pore complexes.

## The Approach

Martin Hetzer applies molecular biology techniques to pose questions about how nucleoporins mediate what happens inside a cell's nucleus and why nuclear pore complexes can weaken as a cell ages. Researchers had assumed that irregular nucleoporins associated with some cancers let the wrong molecules in and out of the nucleus, and it's those molecules that alter genes. But Hetzer was among the first to show that the nucleoporins sometimes have an even more direct role in changing gene expression—fragments of some nucleoporin proteins bind directly to genes. He's now investigating how common this phenomenon is among nucleoporins and how it drives cancers.

He also studies what allows nuclear pore complexes to stay relatively intact throughout a cell's entire lifespan. In most

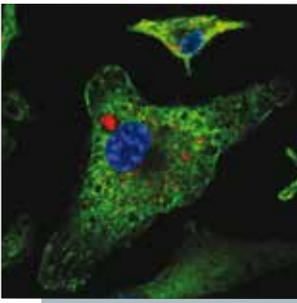
individuals, these channels continue to do their jobs even as cells divide many times over. But in some people with neurodegenerative diseases, it appears that the nuclear pores in older cells start letting large filaments into brain cells. Understanding why this happens is the first step to potentially preventing and treating diseases like Parkinson's.

## The Innovations and Discoveries

- Hetzer showed that one of the ways nuclear pores manage to stay relatively stable for a cell's long life is by occasionally exchanging just one part of the channel complex at a time for a newer part. Since nucleoporin levels drop as a cell ages, however, Hetzer thinks this maintenance is limited.
- He also looked more broadly at the phenomenon of long-lived proteins (LLPs) in the rat nervous system. Most proteins in the body are replaced when they accumulate damage or begin to degrade. But LLPs—which include proteins that make up nuclear pores—last for a lifetime, Hetzer found.
- Hetzer's group recently developed a way to visualize and track micronuclei—small fragments of a cell nucleus. Some types of lung cancer cells, they showed, have especially high numbers of micronuclei, which are formed during mistakes in cell division. The new method will let them further probe how the formation and collapse of micronuclei is linked to cancer progression.

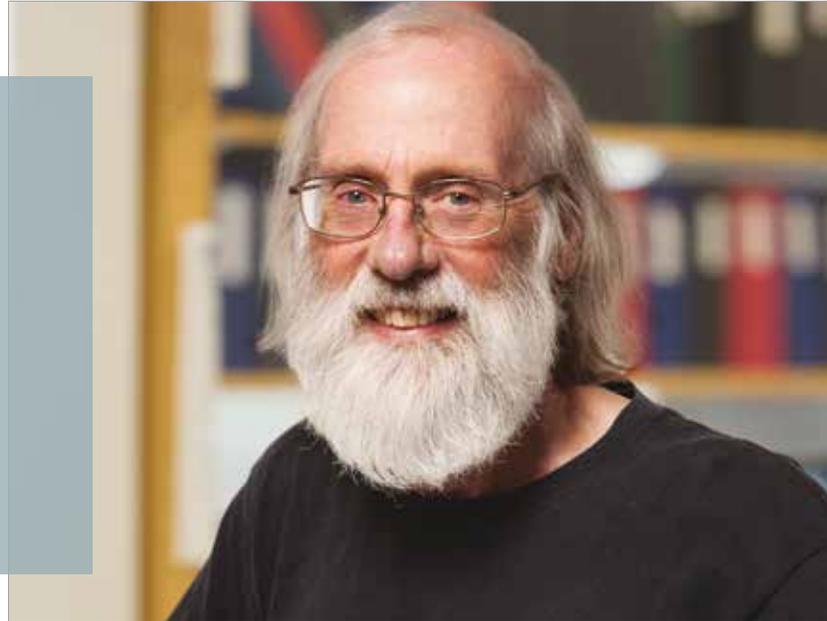
For more information, please visit:  
<http://www.salk.edu/faculty/hetzer.html>

## Aging, Cancer, Neurobiology, Neurological Disorders, Parkinson's Disease



# Tony Hunter

Professor  
Molecular and Cell Biology Laboratory  
American Cancer Society Professor  
Renato Dulbecco Chair



## The Problem

Cells are like creatures of habit—they follow the same cellular cycle over and over, coordinating the timing of gene and protein activation with growth and division. If this cycle is broken, things start to fall apart: cells begin copying the wrong genes, turning on proteins at the wrong times or dividing too fast or too slowly. All of these disruptions can lead to cancer. Understanding how a healthy cell controls its growth cycle can help researchers get a better grasp on what goes wrong in tumor cells when their growth spirals out of control—and how to fix it. But it's hard to pinpoint which individual genes and proteins are most important.

## The Approach

Tony Hunter made the seminal discovery, more than three decades ago, that the addition and subtraction of phosphate molecules to proteins on tyrosine, one of the 20 amino acids, allows cells to control when key proteins are on standby and when they are active. In cancers, he went on to show that growth was switched into an always-on mode by the malfunctions of these phosphates. Since then, his lab has led the field in understanding how chemical additions to proteins control the cell cycle and growth. Hunter uses cutting-edge molecular, genetic and cell biology techniques to probe how these programs interact with each other, what effect they have on cells and how cancers disrupt them to encourage uninhibited growth.

Already, cancer drugs—such as the leukemia therapy Gleevec—have been designed based on Hunter's discoveries. Gleevec turns off an enzyme that normally adds phosphates to proteins, preventing cancers from growing. As Hunter continues to discover other ways in which cells use chemical additions to proteins to control their growth, he aims to find potential therapeutic targets for cancers.

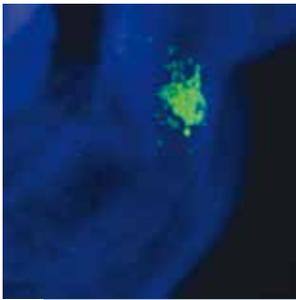
## The Innovations and Discoveries

- Hunter demonstrated that a mechanism called tyrosine phosphorylation (the addition of phosphate molecules to an amino acid) acts as a master on/off switch for a number of key proteins. This discovery has led to new, successful cancer therapies.
- Hunter helped to explain precisely how cells mobilize their repair crews to fix damaged DNA, an important mechanism for preventing cells from turning cancerous.
- He showed how some cancers find a loophole in the cellular security system that should destroy them, which helps them to recover and resume dividing after treatment with DNA-damaging cancer drugs.

For more information, please visit:

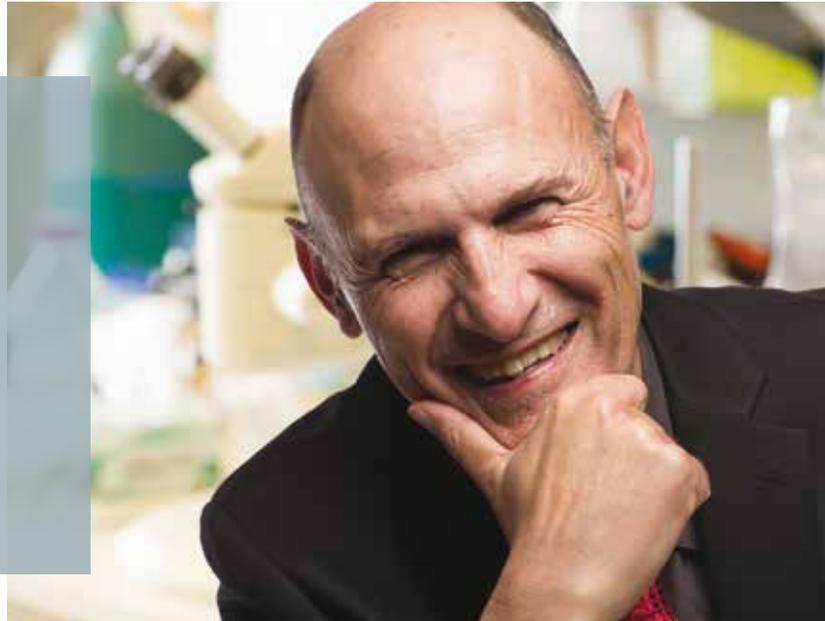
<http://www.salk.edu/faculty/hunter.html>

**Aging, Cancer, Genetics, Epigenetics, Therapeutics**



# Juan Carlos Izpisua Belmonte

Professor  
Gene Expression Laboratory  
Roger Guillemin Chair



## The Problem

Pluripotent stem cells—which can be turned into any cell type in the body—hold promise for treating diseases ranging from cancer to heart disease to blindness. But to develop stem cell-based therapeutics, researchers first need stem cells. Some researchers harvest pluripotent stem cells from embryos, while others follow a reprogramming protocol developed in 2006 that turns adult cells back to their embryonic state. Both approaches have weaknesses—one requires embryos and the other requires tedious genetic manipulations that might compromise the quality of the generated cells and therefore, rapid clinical application.

## The Approach

Juan Carlos Izpisua Belmonte rolls back cells' development to a pluripotent state by improving the methodologies originally described in 2006. In addition, he follows new, more flexible strategies with the goal of providing safer and higher quality products for regenerative medicine. Izpisua Belmonte has spearheaded the development of new techniques to switch cells from one type—such as skin cells—to another type, from blood to brain to kidney, all the while eliminating the need for pluripotent cells. Most notably, Izpisua Belmonte has translated reprogramming technologies to encourage regeneration in living animals in order to, for example, heal infarcted hearts without cell transplantation. All these methods pave the way for stem cell therapies for a plethora of conditions.

Izpisua Belmonte has also created new ways to alter the genes inside stem cells, potentially allowing researchers to create personalized, “corrected” cells that can be transplanted into a patient to cure inherited disease. He showed the approach works with several diseases, including premature aging syndromes, blood disorders and Parkinson's. The platforms generated by Izpisua Belmonte could be used to correct countless other mutations in stem cell lines and treat other genetic disorders.

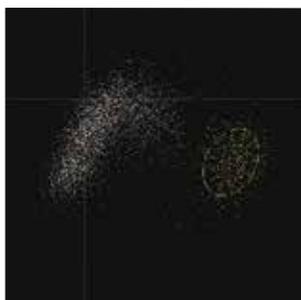
## The Innovations and Discoveries

- Izpisua Belmonte's team discovered a new type of stem cell that allowed them to develop the first reliable method for integrating human stem cells into an animal embryo. This could help them overcome a major hurdle toward growing replacement organs for humans.
- Izpisua Belmonte also tied the aging process to the deterioration of tightly packaged bundles of cellular DNA known as heterochromatin, a discovery that could lead to methods of preventing and treating age-related diseases such as cancer, diabetes and Alzheimer's.
- His team developed a technique in mice to eliminate mitochondrial mutations from eggs or early embryos. If extended to humans, this technique has the potential to prevent babies from inheriting mitochondrial diseases and could lead to therapies for many diseases involving mitochondrial dysfunction.

For more information, please visit:

<http://www.salk.edu/faculty/belmonte.html>

# Aging, Developmental Disease, Genetics, Gene Therapy, Stem Cells, Therapeutics



# Xin Jin

Assistant Professor  
Molecular Neurobiology Laboratory  
Pioneer Fund Developmental Chair



## The Problem

The nervous system works somewhat like a battleship's chain of command. Imagine, for instance, that you decide to tie your shoe. The cortex, acting as captain, makes the big-picture decision to take action ("tie shoes") and that order is conveyed to basal ganglia, the engineering department that manages the sequence of maneuvers: bending down, grabbing the laces, tying the knot. Neurodegenerative diseases such as Parkinson's and Huntington's damage the basal ganglia and undermine this line of communications, disrupting a person's ability to move and function normally. To really understand what's going on in these diseases and others, we first need to know the roles of different kinds of neurons and circuits in the brain.

## The Approach

Xin Jin's team charts the fundamental principles of how the brain learns and generates actions to develop cures for a wide range of related neurological and psychiatric diseases. He uses a variety of tools to uncover the neural circuits and molecular mechanisms underlying action learning and selection. For instance, his lab created a mouse model in which neurons in the striatum (an area of the brain that talks to the basal ganglia) could be controlled with light. The scientists can then turn different neurons in the striatum on and off to see how this alters the animal's behavior, revealing more about which cells do what in the brain.

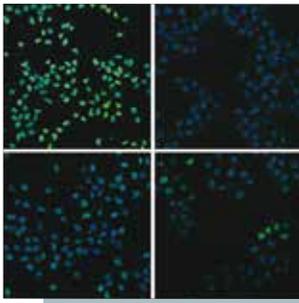
In addition to explaining how different diseases affect the brain, Jin's research might point the way for new therapies for these disorders. If a disease damages one portion of a motor pathway, for example, it might be possible to stimulate neurons further down the circuit, closer to the spinal cord, to initiate sequences of action.

## The Innovations and Discoveries

- Jin found that types of neurons damaged in Parkinson's disease and Huntington's disease can broadcast the signals for starting or stopping newly learned action sequences. The finding provides important insights into the problems with starting and stopping actions observed in patients with those diseases.
- His research demonstrated that learning cognitive actions, such as playing chess or doing math, could involve the same neural circuitry and molecular mechanisms involved in learning motor actions. This introduces the possibility of studying how genetics influence action learning and dysfunction.
- Jin's lab is characterizing basic rules of how the brain executes actions from multiple levels of analysis and providing insights into action-related neurological and psychiatric diseases.

For more information, please visit:  
<http://www.salk.edu/faculty/jin.html>

## Memory, Neurobiology, Parkinson's Disease



# Katherine Jones

Professor  
Regulatory Biology Laboratory



## The Problem

In human biology, our proteins are the key players in managing normal cell and tissue growth and development. When certain proteins—particularly ones that focus on cell replication and the synthesis of other proteins—malfunction or otherwise don't do their duties, their irregularities can have implications for diseases ranging from cancer to HIV. Identifying and understanding these key proteins, and what happens when they glitch, could help point the way to new treatments in diseases.

## The Approach

Katherine Jones' work focuses on a process called transcription elongation, which controls the expression of HIV and cancer genes. Her lab uses proteomics to identify new players in this step, and molecular biology and genetic approaches to understand how these proteins coordinate their unique molecular activities to regulate genes.

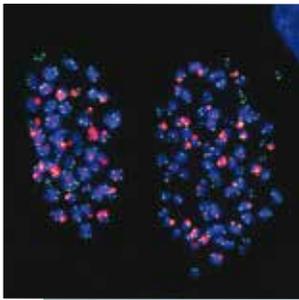
The Jones lab has identified a class of proteins, called elongation factors, which play a pivotal role in the expression of cellular and viral genes. These proteins potentially induce HIV in activated T (immune system) cells, determine whether embryonic stem cells will differentiate to specialized cell types, and are mutated in leukemia and other cancers. Understanding how these proteins function will help suggest new approaches to intervene in many human diseases.

## The Innovations and Discoveries

- Jones discovered two critical proteins required for HIV gene expression, CycT1 and Ssu72. Her team detailed how the HIV Tat protein (created by HIV and essential for its survival) binds and controls the activity of these proteins. Identifying small molecule inhibitors of these enzymes could lead to new therapeutic targets for HIV infections.
- Jones and her team found that the APC protein, which is mutated in colon cancers, regulates the expression of important growth control genes. She showed that the mutant APC protein expressed in colon cancer cells fails to turn off these growth control genes because it is unable to bind to a specific protein that prevents metastasis. As a result, the mutant APC protein in colon cancer increases the stable expression of cancer-causing proteins and prevents the normal shut-off of genes that induce cell growth.
- The lab has recently shown that the transcription elongation factors are also important for differentiation of human embryonic stem cells to specialized cell types. The response of these stem cells to differentiating signals from the environment mobilizes these elongation factors and pushes these cells toward cardiac, liver and pancreatic precursors, suggesting a possible role for these proteins in future stem cell therapies.

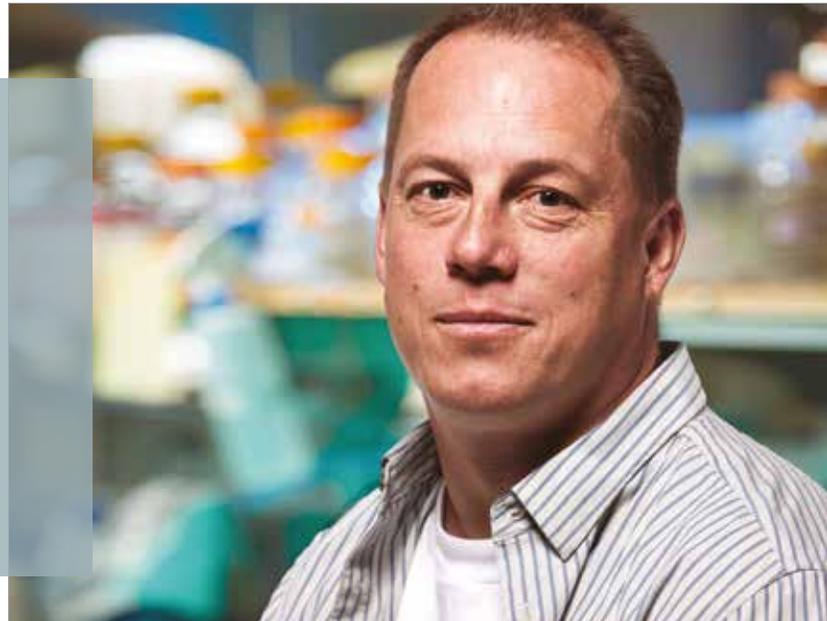
For more information, please visit:  
<http://www.salk.edu/faculty/kjones.html>

## Cancer, Genetics, HIV/AIDS, Stem Cells



# Jan Karlseder

Professor  
Molecular and Cell Biology Laboratory  
Donald and Darlene Shiley Chair



## The Problem

Just as every photocopy of a copy becomes a little less crisp than the last version, each time a cell copies its genetic material, it loses some details from the ends of each chromosome. These ends, called telomeres, eventually erode and expose vital genes to wear and tear, causing a cell to die. But in many cancer cells, the telomeres are constantly rebuilt, thereby endowing a cell with immortality. If scientists can determine how to stop this telomere extension, they may be able to make cancer cells die or render them more susceptible to drugs. On the flip side, learning how to make telomeres grow could treat premature aging syndromes. But first, researchers need to understand the complex ins and outs of normal telomere function and regulation.

## The Approach

Jan Karlseder studies the role of telomeres throughout a cell's life cycle—from the time the cell starts copying its genetic material to the time it divides into two new cells. While other researchers rely on static snapshots of telomeres' placement and characteristics throughout this cycle, Karlseder used time-lapsed, live-cell microscopy to follow telomeres for up to 20 hours at a time. The new details have allowed him to get a fuller understanding of how telomeres move and change, how they shorten over time in normal cells, and how telomere dynamics affect the aging process and prevent cancer development.

He has also spearheaded studies showing that cancer cells are able to keep their telomeres from eroding, even after many cell divisions, by using two pathways to constantly extend the

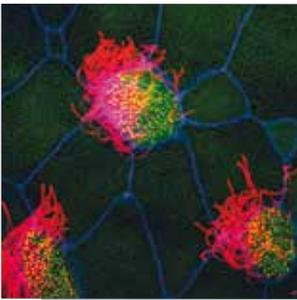
telomeres. Experiments focusing on the genetics and cell biology of tumors have led Karlseder to reveal how genetic mutations in cancer cells lead to longer telomeres. One class of existing cancer drugs, Karlseder's lab discovered, works by blocking the protective function of telomeres. Additional studies on how this works may allow Karlseder's lab to reveal new ways of weakening or killing cancer cells by deprotecting their telomeres.

## The Innovations and Discoveries

- Karlseder showed how disabling telomere protection during cell division prompts cell death. This unexpected finding indicates that telomeres may be central to preventing tumors, a function that could potentially be exploited to improve cancer therapies.
- Karlseder and his team identified why disruption of a vital pathway in the cell cycle control leads to the proliferation of cancer cells. Their findings suggest a potential target for preventive measures against cancer, aging and other diseases.
- His lab discovered that telomeres move to the outer edge of the cell's nucleus after they have been duplicated. The findings may reveal how our genes are regulated and how gene expression programs are altered during cell division, an important step in understanding aging and diseases that stem from genetic mutations, such as cancer.

For more information, please visit:  
<http://www.salk.edu/faculty/karlseder.html>

**Aging, Cancer, Cellular Biology, Epigenetics, Genetics**



# Christopher Kintner

Professor  
Molecular Neurobiology Laboratory  
Rita and Richard Atkinson Chair



## The Problem

Throughout the body, tiny hairs called cilia help keep things moving in tubes and vessels. Cilia move eggs down the Fallopian tubes, push fluid through the brain and sweep dirt out of the lungs and ears. When cilia break down, everything from asthma to infertility to chronic ear infections can result. Being able to restore the function of damaged cilia could treat these diseases, but researchers don't know how cilia develop in the first place or how they coordinate their sweeping movements.

## The Approach

Christopher Kintner uses cutting-edge genetic, biochemistry and microscopy techniques to study how cilia develop in an embryo and function in an adult. For much of his research, he relies on the African clawed frog, *Xenopus laevis*, because the frog's skin is coated with cilia and it's easy to watch the development of the cilia on the outside of the embryo's body. Through testing what mutations affect skin cilia, Kintner has discovered genes and proteins that are key to cilia development and function.

Kintner's findings have implications for patients with primary ciliary dyskinesia, a disorder resulting from an inherited genetic mutation that causes defects in the movement of cilia. The syndrome can cause infertility, due to the sluggish movement of

eggs and sperm without the help of cilia, or respiratory symptoms, resulting from mucus and dirt accumulation in the airways. Being able to guide stem cells to develop cilia could help Kintner find ways to treat these symptoms.

## The Innovations and Discoveries

- Kintner's group revealed the role of the gene FoxJ1 in the development of cilia. The team showed that the gene helps determine where motile cilia—those that have a sweeping motion—form, but doesn't have an effect on sensory cilia, used to aid the sense of touch.
- Kintner identified a second gene, called multicilin, that instructs specific cells when to develop many cilia. This discovery led to recent work showing that patients who lack ciliated cells in the lungs have mutations in multicilin. Multicilin could now be one factor used to coax stem cells to form new cilia to treat diseases.
- He also discovered a two-step mechanism that ensures that nearby cilia all beat in unison. To coordinate their movements, he found, cilia sense the direction of flow and align their movements accordingly.

For more information, please visit:  
[www.salk.edu/faculty/kintner.html](http://www.salk.edu/faculty/kintner.html)

# Birth Defects, Developmental Biology, Genetics, Neurobiology



# Julie Law

Assistant Professor  
Plant Molecular and Cellular Biology Laboratory  
Hearst Foundation Development Chair

## The Problem

In any one organism, every cell has nearly identical genetic information, yet not all cells look or act the same. One cause of this amazing diversity is the presence of chemical tags, called epigenetic modifications, which decorate both the DNA and packaging proteins that organize the DNA within the nucleus. The patterns of these chemical tags differ in each cell type and help instruct the function of cells by indicating which genes should be turned on and which should be ignored. Knowing the effect of these epigenetic changes on a cell's behavior can help us to understand health and disease, but manipulating epigenetics in mammalian cells is often lethal, making these changes hard to study. Fortunately, similar manipulations are viable in a plant model, making this an excellent system to understand the roles of epigenetic modifications.

## The Approach

Rather than using animal cells to study epigenetic modifications, Julie Law is turning to the small flowering plant *Arabidopsis thaliana*. Unlike mammals, *Arabidopsis* plants are more tolerant of changes to their epigenome, making it easier to study the effects of altering these chemical tags. Using this plant, Law is studying how epigenetic modifications are recognized and translated into the desired response by the cell. In particular, she focuses on characterizing several newly identified families of proteins involved with DNA packaging and gene expression, called chromatin binding proteins. By employing genetic, biochemical and genomics approaches, Law aims to not only determine the epigenetic marks recognized by these protein families, but also to

identify their interacting partners and their effects on gene expression. Although Law's research utilizes a plant model, her findings will also hold lessons for human biology as many of the genes involved in adding or removing epigenetic marks are the same in plants as in mammals. Ultimately, her research paves the way for understanding the role of the epigenome in both agriculture and human health.

## The Innovations and Discoveries

- With colleagues, Law provided mechanistic insights into the targeting of two specialized RNA polymerases (Pol-IV and Pol-V) in the *Arabidopsis* genome. These findings provide insight into how epigenetic modifications might be targeted to specific genes for crop improvements or therapeutic benefits to human health.
- Taking a biochemical approach, Law used proteins with known roles in a process called DNA methylation to identify a handful of additional proteins never before linked to epigenetic modifications. Knowledge of the new proteins enhances our understanding of the processes influencing a cell's epigenome.
- Law and her colleagues also revealed, at the level of individual atoms, the precise regions of several proteins that are critical in recognizing specific epigenetic modifications. These studies provide a detailed view of how these proteins function and could reveal how their mutation can lead to epigenetic changes that manifest as developmental defects or the progression of diseases, such as cancer.

For more information, please visit:  
<http://www.salk.edu/faculty/law.html>

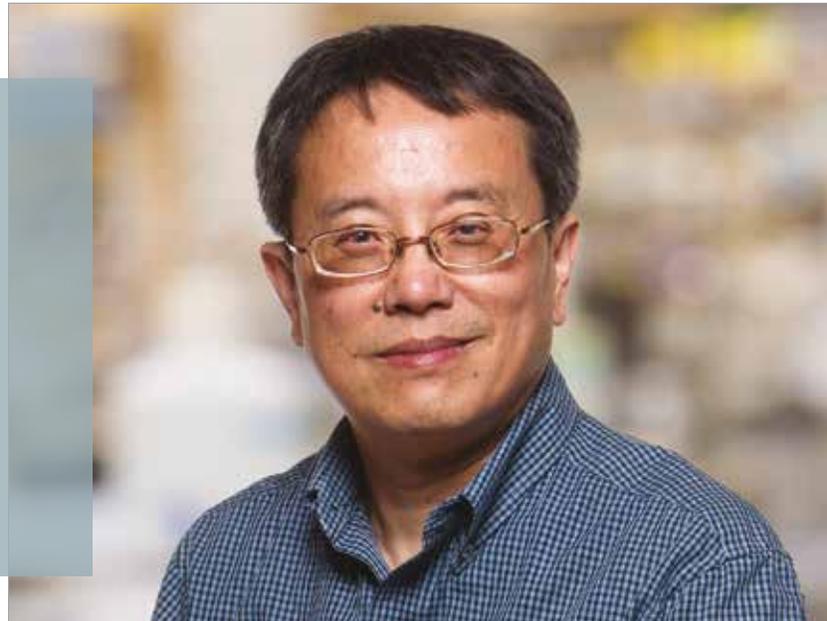
# Cancer, Epigenetics, Genetics, Plant Biology and Agriculture



# Kuo-Fen Lee

Professor

Clayton Foundation Laboratories for Peptide Biology  
Helen McLoraine Chair in Molecular Neurobiology



## The Problem

Frogs, whales and even lab mice have a skill that humans are lacking: the ability to regrow injured nerves. Learning how to replicate this capability in humans could revolutionize the treatment of spinal cord injuries, paralysis or ALS. But people and other primates have a different set of molecules controlling nerve development than many animals—this is why they can't regrow nerves in the first place. So scientists struggle with how to use findings in mice to develop treatments that will work in humans.

## The Approach

Kuo-Fen Lee uses modern genetics to study nerve regrowth in mice with spinal cord injuries. He details how normal mice can naturally heal some nerve injuries and pinpoints which genes and proteins are involved in the process. Then, he studies which of these players can be used in human tissues to change how people's nerves behave after an injury.

Lee has uncovered a handful of genes in mice that are vital to the animal's ability to recover from nerve damage. Some are important because they stop the cell death that can occur when a nerve senses it has been injured. Others are more directly involved

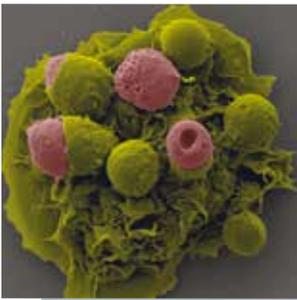
in nerve regrowth, and another set helps ensure that new nerves aren't created just any old place, but in the proper spots of the body.

## The Innovations and Discoveries

- Lee discovered that the protein p45 is responsible for the ability of mice to regrow nerves in the spinal cord after an injury. He reported that p45 blocks proteins that encourage nerve cell death and activates healing pathways instead.
- He went on to show that human nerve cells don't have p45, but instead have a protein called p75 that stops the growth of damaged neurons. But when he added p45 to human cells, Lee found it could break up p75. This suggests that p45—or a similar, synthetic compound—may be able to encourage nerve regrowth in people some day.
- Lee's group has also illuminated the role of a stem cell protein, called nestin, in mediating the link between nerves and muscle cells. Understanding the role of nestin could help researchers ensure that proper neural connections are established after they determine how to initiate nerve regrowth.

For more information, please visit:  
<http://www.salk.edu/faculty/lee.html>

# Cancer, Dementia, Developmental Disease, Neurological Disease, Neurobiology



# Greg Lemke

Professor  
Molecular Neurobiology Laboratory  
Françoise Gilot-Salk Chair



## The Problem

To keep the body healthy, immune cells rely on receptors that sense compounds and signal the cells to take specific actions, for example, attacking a pathogen or clearing away dead cells. Interruptions in a class of these cell receptors, known as receptor tyrosine kinases, can lead to inflammation, cancer growth and autoimmune diseases (such as lupus, rheumatoid arthritis and multiple sclerosis). In order to understand what goes wrong in cell receptor signaling—and how to fix it—researchers must understand how receptors are established and controlled, for example, during brain development or an immune response.

## The Approach

Greg Lemke discovered a family of three receptor tyrosine kinases, called TAM receptors, which play a crucial role in telling immune cells how to handle infection from bacteria, viruses and other pathogens, as well as normal cellular debris. His lab showed how problems with the TAM receptors (called Axl, Mer and Tyro3) or their pathways are associated with increased levels of drug-resistant cancer as well as inflammation and autoimmune disease. Understanding how to separate the roles of each receptor could lead to new classes of drugs to fight viruses and bacteria. Aside from immune function, TAM receptors are involved in the healthy development of the nervous system.

Lemke also focuses on another major family of receptor tyrosine kinases, called Eph receptors. These are one of the

earliest to show up in the developing brain of a fetus and help to guide neuronal connections. Eph receptors help neurons—like those that link the eyes to the brain—know where to go as they grow.

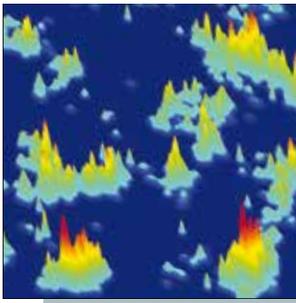
## The Innovations and Discoveries

- Lemke's lab unveiled critical differences between the Axl and Mer receptors, and found that they activate immune cells in an inflamed setting and normal setting, respectively. This distinction points the way to more targeted therapies for autoimmune and cancer treatments.
- Lemke discovered a powerful mechanism by which viruses such as influenza, West Nile and dengue fever evade the body's immune response and infect humans. A substance called phosphatidyserine, located on the surfaces of these notorious "enveloped" viruses, directly activates TAM receptors to prevent the immune system from launching a response. The finding could lead to new antiviral drugs that block the interaction.
- In the area of vision, he revealed how retinal cells missing the TAM receptor Mer results in blindness. He also showed how proteins Vax2, Vax1 and Pax6 interact to create a functioning vision system (optic nerve and eyes).

For more information, please visit:

<http://www.salk.edu/faculty/lemke.html>

Autoimmune Disease, Cancer, Developmental Biology, Infectious Disease, Inflammation, Immunology, Neurobiology, Vision



# Björn Lillemeier

Assistant Professor  
Nomis Foundation Laboratories for  
Immunobiology and Microbial Pathogenesis  
Waitt Advanced Biophotonics Center



## The Problem

When the immune system senses invading bacteria, viruses or cancer cells, it has to act quickly to fend off the threat. Proteins begin to bind or modify each other to activate immune cells. During this activation, many proteins are reorganized: this includes protein movements on a molecular scale or from one part of the cell to another. Understanding how the spatial arrangements of proteins affect the immune response will help scientists to develop new ways to control and modulate the immune system to fight infections, autoimmune diseases or cancers. However, tracking changes in molecular arrangements is difficult, as molecule and cluster sizes are below the resolution of traditional light or fluorescence microscopy.

## The Approach

Björn Lillemeier has developed and adapted cutting-edge microscopy techniques for imaging proteins embedded in the outer membranes of cells. His super-resolution imaging approaches have allowed him to see the exact placement of these proteins in the membranes of immune cells, specifically T cells. He has shown that T cells have distinct clusters of crucial proteins in different areas of their membranes. When the cells are activated—in response to an infected or diseased cell—these clusters dramatically rearrange. Clusters of proteins move to different locations in the plasma membrane, break apart or combine to form distinct molecular niches that are essential for appropriate T cell activation.

Lillemeier's observations of the spatial arrangements of proteins in immune cells, and how they change during an

immune response, are the most detailed descriptions yet. And he's continuing to improve his imaging techniques so he can watch multiple proteins move in real time. His findings could lead to a better understanding of how protein arrangements are misregulated during immune system disorders and how scientists might be able to control their physiological functions.

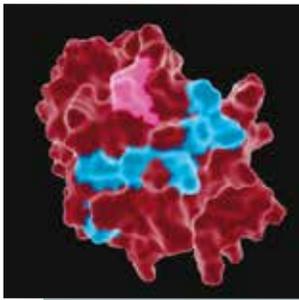
## The Innovations and Discoveries

- Lillemeier and his colleagues described techniques for arranging flat sheets of plasma membranes on grids that can be visualized under an electron microscope. This allows researchers to see the arrangement of proteins on the membrane, and how that arrangement changes under different conditions.
- Using super-resolution microscopy, he also discovered that T cell proteins, which allow the immune system to recognize infected or cancerous cells, are arranged in specific patterns. This organization allows different protein types to coordinate their interaction and to maximize the immune system's response against a pathogen.
- He continues to work on understanding how the spatial and temporal arrangement of proteins in immune cells mediates their function. The research has implications for treating autoimmune diseases, infections and cancer by changing immune responses.

For more information, please visit:

<http://www.salk.edu/faculty/lillemeier.html>

## Autoimmune Diseases, Biophotonics, Cancer, Infectious Diseases, Immunology



# Vicki Lundblad

Professor  
Molecular and Cell Biology Laboratory  
Ralph S. and Becky O'Connor Chair



## The Problem

The presence or absence of just a few letters of DNA on the end of a chromosome can mean the difference between a young cell and a cell at the end of its lifespan. The length of these telomeres—the physical ends of chromosomes—is controlled by an intricate balancing act: a protein complex called telomerase elongates these ends, but other proteins nibble away at them. If telomeres are too eroded, particularly in stem cells that replenish tissues later in life, this contributes to age-related diseases; but in cells where telomerase prevails, cancer can result. If they could control this balancing act, researchers might be able to treat conditions on both ends of the spectrum. But scientists don't yet fully understand these molecular processes and how cells maintain a healthy equilibrium.

## The Approach

Vicki Lundblad employs a single-cell genetic system to study the interplay between the activities that lengthen and shorten telomeres. Her group tweaks specific genes in baker's yeast (the same organism used to make bread and wine), and observes how chromosome ends respond. Using this strategy, her laboratory pioneered the discovery of the protein subunits of telomerase and uncovered mechanisms that control telomere shortening. Lundblad's group also developed a high-resolution assay that detects very small changes at each telomere as a cell divides. Using this assay, her group has identified a protein complex that

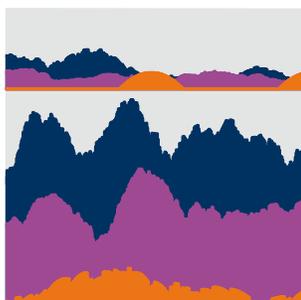
inhibits telomere shortening while it promotes telomerase action. Since these telomere-related proteins are present in mammals, her research also holds lessons about human telomere length control.

## The Innovations and Discoveries

- Lundblad has shown that telomerase is switched on just as a cell has finished copying its genetic material, and then rapidly switched off, through assembly and disassembly of its protein subunits. Learning how to control these switches could allow researchers to turn telomerase activity up in aging cells or down in cancer cells.
- Her lab also discovered a hidden regulatory landscape on the surfaces of cellular proteins, which act as traffic cops for telomerase. For example, one such surface on a protein ensures that telomerase can find its way to the physical ends of chromosomes.
- Lundblad's group has engineered yeast cells that lack telomerase, to study how cells respond to eroding telomeres when telomerase is not present to counter-balance. By watching progressive cell divisions, they have identified new mechanisms that can either accelerate or slow down the process by which cells age.

For more information, please visit:  
<http://www.salk.edu/faculty/lundblad.html>

## Aging, Cancer, Genetics



# Graham McVicker

Assistant Professor  
Integrative Biology Laboratory  
Laboratory of Genetics



## The Problem

Differences in our genome sequences, or genetic variants, have a profound influence on many human traits such as height, blood pressure and disease risk. Yet there are millions of genetic differences between individuals and it is difficult to determine which of them are important. Recently, geneticists have made tremendous progress in this area by sequencing the genomes of thousands of individuals. Many genetic variants are now associated with human traits, however, in most cases we still do not understand how these variants function. Unraveling how genetic variants affect molecular processes within human cells will give us a new understanding of health and disease.

## The Approach

Graham McVicker is developing innovative computational and statistical techniques to unscramble the molecular function of human genetic variation. McVicker is specifically interested in understanding how genetic variants affect chromatin in the immune system. Chromatin is the molecular packaging that organizes DNA within the nucleus of the cell and controls which

genes are turned on in specific cells. By gaining a mechanistic understanding of these variants and linking them to disease risk, he will illuminate why some individuals are more susceptible to autoimmune and infectious diseases.

## The Innovations and Discoveries

- McVicker previously discovered human genetic variants that affect chemical modifications of an important type of protein of chromatin, called histones. He showed that many of these variants disrupt the binding of specific proteins to the DNA sequence and also affect the expression of nearby genes.
- He identified factors that are important for positioning nucleosomes—the fundamental units of chromatin—on the human genome sequence.
- He demonstrated that natural selection has influenced patterns of genetic variation across the human genome.

For more information, please visit:

<http://www.salk.edu/faculty/mcvicker.html>

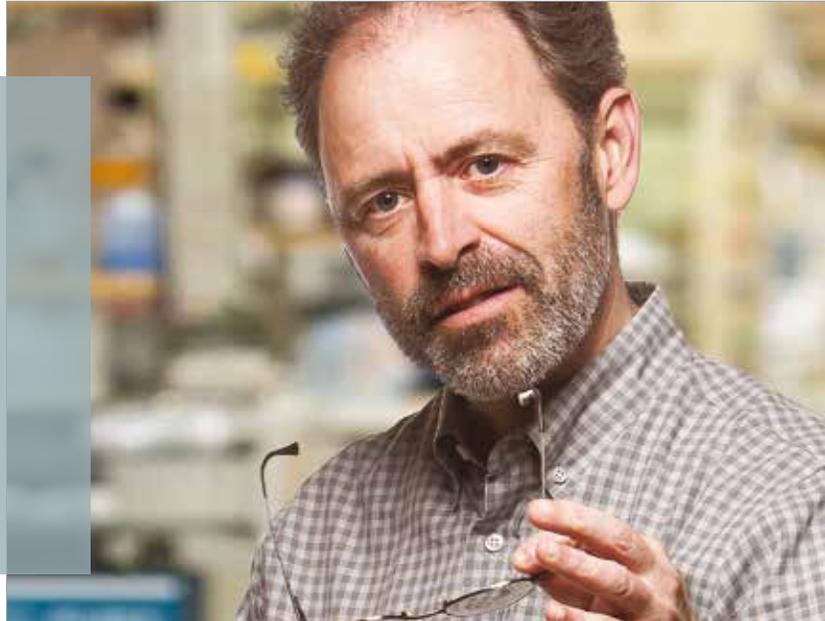
Autoimmune Disease, Computational Biology, Epigenetics,  
Genetics, Immunology, Infectious Disease, Systems Biology



# Marc Montminy

Professor

Clayton Foundation Laboratories for Peptide Biology  
J.W. Kieckhefer Foundation Chair



## The Problem

More than nine percent of the total population of the United States has been diagnosed with some form of diabetes, leading to countless deaths and complications, and costing hundreds of billions of dollars in healthcare spending. Drugs currently on the market to treat the disease work for some patients, but can lose their effectiveness over time and cause numerous unwanted side effects. To develop new classes of treatments, researchers need to better understand the roles of the many dozens of molecules that work together to regulate human metabolism, blood sugar, weight gain and fat storage.

## The Approach

Marc Montminy focuses his research on understanding signaling molecules that help keep all the cells in the body on the same page when it comes to metabolism. Immediately after a meal, these molecules encourage cells to absorb, process and store the sugars and fats that are newly circulating in the bloodstream. During a fast, the signals switch their message, telling cells to release sugars to give the body a constant energy source. But in diabetics, these signaling molecules are no longer regulated or responded to in the right ways, causing blood sugar levels to stay too high all the time.

Montminy discovered one of these key signaling molecules, called CREB, and has described many of its functions. His lab also deciphered the role of another genetic switch, CRT2. In healthy individuals, both are responsible for maintaining the right cycle of sugar storage and release throughout the day. Understanding

how the signals—as well as many other molecules that interact directly with CREB and CRT2—are regulated incorrectly in diabetics could reveal new targets for drugs. Montminy works to reveal these connections and mechanisms by identifying the role of different genes, studying which genes are turned up or down during different metabolic states, and testing how signaling molecules interact within isolated muscle or liver cells.

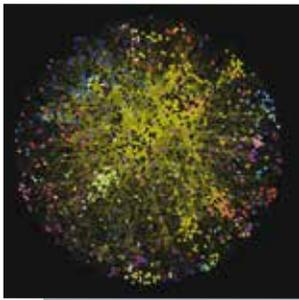
## The Innovations and Discoveries

- Montminy recently discovered a pair of molecules that regulates the liver's production of glucose—the simple sugar that is the source of energy in human cells and the central player in diabetes.
- His lab discovered how a hormone turns on a series of molecular switches inside the pancreas that increases production of insulin. The finding raises the possibility that new designer drugs might be able to turn on key molecules in this pathway to help people with type 2 diabetes or pre-diabetic insulin resistance.
- He has also described how the existing diabetes drug exenatide (Byetta) works by flipping many molecular switches that boost the production of insulin. Understanding all these switches can help scientists develop even more effective and long-lasting ways of controlling their function.

For more information, please visit:

<http://www.salk.edu/faculty/montminy.html>

# Circadian Rhythms, Diabetes, Genetics, Metabolism, Therapeutics



# Saket Navlakha

Assistant Professor  
Integrative Biology Laboratory



## The Problem

Biological systems, from protein interactions to neural networks, are highly complex, and we still have only a basic understanding of how they work. With current and newly emerging technologies, biologists are producing massive amounts of data that could unveil the rules that govern complex biological processes and how these processes are disrupted by diseases. But new algorithmic and computational methods are needed to decipher this data to help inform future experiments and gain a better understanding of biology.

## The Approach

Saket Navlakha develops new algorithms to understand the interactions, dynamics and evolution of large, noisy and complex biological networks. By mining massive amounts of data in new ways, he aims to reveal how molecular and cellular networks are organized and have evolved. Navlakha also studies “algorithms in nature”—for example, how groups of distributed molecules and cells communicate and process information to collectively solve computational problems. Discovering such shared principles can lead to the design of improved computing algorithms and can provide a way to understand, quantify and predict the behavior of large, distributed biological systems. To accomplish this,

Navlakha is bridging theoretical computer science and systems biology and developing collaborations with experimentalists to learn from biological data.

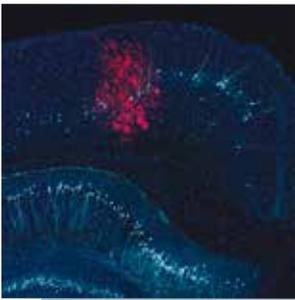
## The Innovations and Discoveries

- Navlakha is uncovering new principles of neural circuit development in the brain to improve the design of communication networks and to understand why too many or too few synapses during critical periods may lead to neurodevelopmental disorders, such as autism and Rett syndrome.
- He is comparing strategies of how biological and engineered networks attempt to overcome environmental noise, failures and disturbances and is making predictions of how the networks perform in different conditions.
- Navlakha’s lab is developing new algorithms to: model ancestral molecular interactions in the cell to understand how networks evolved; extract critical modules embedded within networks to predict protein function and disease-causing genes; and identify missing edges in signaling pathways.

For more information, please visit:

<http://www.salk.edu/faculty/navlakha.html>

Computational Biology, Immunology, Neurobiology,  
Plant Biology and Agriculture, Systems Biology



# Axel Nimmerjahn

Assistant Professor  
Waitt Advanced Biophotonics Center



## The Problem

The human central nervous system (CNS), which includes the brain and spinal cord, consists of an incredibly diverse set of cells, and each cell type carries out highly specialized functions in cellular networks of dazzling complexity. While much research has focused on understanding the circuits formed by neurons, brain cells called glia are equally pervasive and account for roughly an equal number of cells in the human brain. Glial cells were long believed to play a merely passive, supportive role in the CNS. However, it is becoming increasingly clear that glia make crucial contributions to CNS formation, operation and adaptation. Additionally, glial cells are involved in practically all CNS injuries and diseases, including viral and bacterial infections, Alzheimer's and Parkinson's diseases, cancer and stroke. This makes glia promising targets for future therapeutic interventions.

## The Approach

Axel Nimmerjahn has spearheaded the development of new microscopy techniques to visualize the dynamics of glial cells and their functional cellular interactions in the living brain. Additionally, he has created new tools for cell type-specific staining and genetic manipulation and for analysis of large-scale imaging data. This has allowed him to address long-standing questions regarding the role of glial cells in the intact healthy or diseased brain. Resolving these fundamental questions has broad implications for our understanding of brain function and the treatment of neuroinflammation and neurological

disorders. Nimmerjahn has recently expanded his studies to the spinal cord and related maladies.

He continues to push the boundaries of microscopy. In collaboration with other engineering experts, he has worked to shrink the size of microscopes to make them wearable. His tiny microscopes are less than 0.2 cubic inch in size, weigh less than two grams and have allowed him to reveal how cellular brain activity relates to animal behavior.

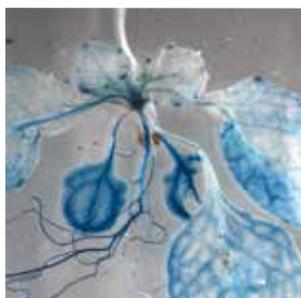
## The Innovations and Discoveries

- Nimmerjahn discovered that microglia, the brain's resident immune cells, continuously survey the cellular environment with their fine branches. He showed that through this behavior, microglia provide the first line of defense against tissue injury and infection.
- Nimmerjahn's lab used cutting-edge microscopy approaches to visualize the blood-brain barrier (BBB) breakdown after stroke. His team found that stepwise impairment of different cellular mechanisms accounts for the BBB deficits in stroke. The findings could lead to new ways to treat the disease.
- Nimmerjahn uncovered that astroglia, a major regulatory cell type in the brain, show large-scale activity that potentially initiates macroscopic changes in brain dynamics. He also showed how general anesthesia disrupts this waking state activity.

For more information, please visit:

<http://www.salk.edu/faculty/nimmerjahn.html>

## Biophotonics, Cancer, Neurobiology, Neurological Disease, Stroke



# Joseph Noel

Professor and Director  
Jack H. Skirball Center for Chemical Biology and Proteomics  
Howard Hughes Medical Institute Investigator  
Arthur and Julie Woodrow Chair



## The Problem

Plants use a remarkable diversity of capabilities to respond to their environment—they can sense light, water, chemicals and even wind flows, and in turn, speak with other plants and organisms in their environment using the language of chemistry. Over millions of years, plants evolved to harness the energy of the sun, survive in a myriad of challenging environments, absorb carbon dioxide that most other organisms find toxic and gather nutrients from decaying life in the soil, all while firmly planted in the ground. But farmers want to further improve how plants grow, fight off pests, generate natural medicines and produce healthy food crops. To improve plants' health and yield in globally sustainable ways, scientists first need to understand how plants have already optimized their biology through the process of evolution over nearly 500 million years.

## The Approach

Joseph Noel studies the structure and chemistry of compounds produced by plants as well as how plants have evolved unique ways to make their own specialized products adapted to nearly every ecosystem on Earth. He uses biological assays to test how a plant's behavior is altered by genetic changes. He also employs chemistry techniques to replicate a plant's production pathways in the lab. The knowledge he uncovers holds clues as to how to improve plants' chemical reactions or even apply them to animal cells. For example, Noel has pieced together each step required for a plant cell to produce fatty acids. These fatty acids make up the membranes of plant cells, provide plant seeds with oils, satisfy humans with healthy fats and even offer a green and sustainable

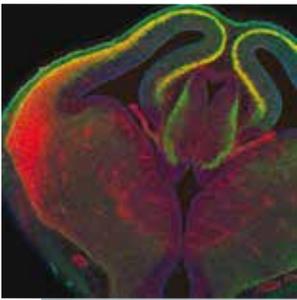
energy source. Learning how plants produce them—and how to improve these chemical reactions—could give manufacturers a new source of natural oil.

## The Innovations and Discoveries

- Using tricks he learned from plant biology and biochemistry, Noel engineered the enzyme plants use to make the anti-aging compound resveratrol, commonly found in red wine. He produced it in many other plants to arm them in their constant battle against environmental pathogens while offering potential benefits to humans as well.
- Noel was part of a group of scientists that explained how karrakins—chemicals released by plants when they are burned up—stimulate the growth of long-buried seeds to regenerate forests. The finding helps researchers understand the cycle of regrowth and renewal that happens after forest fires.
- His lab also was instrumental in the discovery of a protein, called VAS1, which coordinates different metabolic pathways in plants to make sure their parts grow at the appropriate time when light levels change. The work has paved the way to intelligently engineer a new generation of plants using completely natural genetic and biochemical programs for the benefit of humans. The findings also reveal how other organisms—including humans—coordinate all of the thousands of chemical reactions needed to survive and prosper.

For more information, please visit:  
<http://www.salk.edu/faculty/noel.html>

# Biophotonics, Cancer, Neurobiology, Neurological Disease, Stroke



# Dennis O'Leary

Professor  
Molecular Neurobiology Laboratory  
Vincent J. Coates Chair in Molecular Neurobiology



## The Problem

When studying diseases ranging from cancer to dementia, researchers have found that, in some cases, a surprising number of genes are involved which originally help the brain develop in an embryo. If these genes are incorrectly regulated or turned back on in an adult, it turns out, they can boost cell division (leading to cancer) or mistakenly kill brain cells (one cause of dementia). To understand how developmental genes can relate to adult diseases, researchers need to first uncover their normal role early on. Answering this question could not only lead to treatments for cancer and dementia but for developmental disorders including autism and paraplegia.

## The Approach

Dennis O'Leary tackles questions about brain development in order to better understand the genes and molecules which not only help neurons form and find their place in a developing brain, but also play key roles in neural function and health throughout life. He focuses on genes that aid neurons in a growing brain to connect from one place to another, following chemical cues to find their target. He also strives to understand how other genes are involved in pruning back neurons later in development, removing unneeded connections from the brain. This same process, scientists suspect, may also play a role in the later disappearance of certain adult neurons whose absence may be tied to dementia.

O'Leary has also integrated stem cell research into his laboratory in order to develop related therapies tied to the genes

he studies. In this arena, he's identified molecules that help determine what type of neuron stem cells develop into.

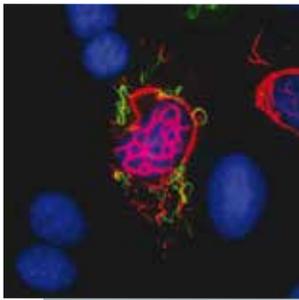
## The Innovations and Discoveries

- O'Leary probed how the brain maps its sensory areas, with distinct brain sections for specific body parts. Changing this map in the brain, he's found, alters how an animal can sense its environment.
- O'Leary collaborated with Salk researchers Inder Verma and Rusty Gage to discover that a gene most commonly linked to breast and ovarian cancer, called BRCA1, also plays a crucial role in brain development. When brain stem cells in mice were missing BRCA1, the brains formed in a disorganized and incomplete fashion. The newly found role of BRCA1 in the brain helps explain why some patients with breast cancer also get seizures.
- His lab showed that for the cortex of the brain—a region associated with thought and consciousness—to develop properly, it must receive input from the brain's thalamus. Blocking the connections between these areas led to improper cortex development in mice. The finding could have implications for understanding autism, which has been correlated with unusual cortex size.

For more information, please visit:

<http://www.salk.edu/faculty/oleary.html>

**Brain Cancer, Dementia, Developmental Disease, Neurological Disease, Genetics, Neurobiology, Stem Cells, Therapeutics**



# Clodagh O'Shea

Associate Professor  
Molecular and Cell Biology Laboratory  
William Scandling Developmental Chair



## The Problem

Cancer is a leading cause of death in the United States. Most cancer patients are treated with nonspecific poisons, but a holy grail of treatment is therapeutic agents that are as sophisticated as the disease itself, able to precisely target the cancer. To develop better cancer therapies, scientists must first decipher what goes wrong with cellular mechanisms that normally regulate cell growth and survival. But finding these targets to create truly game-changing treatments requires rethinking how we approach cancer research and cancer medicine.

## The Approach

Clodagh O'Shea exploits the common cold virus, adenovirus, as a powerful agent to both understand and treat cancer. Viruses are nature's nanomachines: their outer coats enable them to enter specific tissues in our body where they express a small number of proteins that hijack the cell's replication machinery to reproduce. The very same cellular replication machinery controls are targeted by the mutations that give rise to cancer.

One way O'Shea's team is exploiting this overlap is by creating synthetic viruses that act like guided missiles, infecting and replicating only in tumor cells. These helpful, hijacked

viruses burst apart cancer cells and release thousands of virus progeny that can seek out and destroy distant metastases. Such intelligent viral therapies have enormous potential in improving the treatment of patients suffering from cancer.

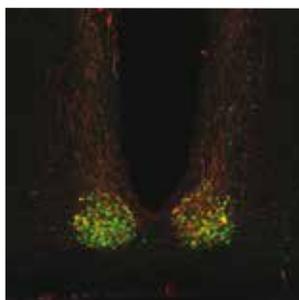
## The Innovations and Discoveries

- O'Shea identified how adenovirus uses a protein polymer to hijack a cell's molecular machinery, including large cellular machines involved in growth, replication and cancer suppression. She is testing new cancer therapies that mimic the strategies employed by the viruses.
- Her team discovered a mechanism used by adenovirus to sidestep the cell's suicide program. This could help explain how tumor suppressor genes are silenced in tumor cells, and could pave the way for a new type of targeted cancer therapy.
- O'Shea is working on new methods to visualize DNA and its surrounding proteins in a living cell to better understand what goes wrong in those interactions that can lead to disease.

For more information, please visit:

<http://www.salk.edu/faculty/oshea.html>

Cancer, Cellular Biology, Therapeutics, Virology



# Satchidananda Panda

Associate Professor  
Regulatory Biology Laboratory



## The Problem

Like most people, you probably wake up, get hungry for meals and doze off in bed at about the same time every day. If you've ever experienced jet lag or pulled an all-nighter, you know that this schedule can easily be thrown off kilter. But for some people, that imbalance—difficulty sleeping at night, hunger at odd times, or sudden fatigue at noon—is a constant. Scientists are starting to uncover the links between our circadian clocks (the internal program that mediates daily rhythms) and health.

## The Approach

Satchidananda Panda explores the genes, molecules and cells that keep the whole body on the same circadian clock. A section of the hypothalamus called the suprachiasmatic nucleus (SCN) lies at the center of the body's master clock and gets input directly from light sensors in the eyes, keeping the rest of the body on schedule. Panda discovered how these light sensors work, as well as how cellular timekeepers in other parts of the body function. He also uncovered a novel blue light sensor in the retina that measures ambient light level and sets the time to go to sleep and wake up every day.

In the process of exploring how the liver's daily cycles work, Panda found that mice which eat within a set amount of time (12 hours) resulted in slimmer, healthier mice than those who ate the same number of calories in a larger window of time, showing that *when* one eats may be as important as *what* one eats. If the benefits

of this "12-hour diet" hold true in humans, it could have profound impacts on treating overeating disorders, diabetes and obesity.

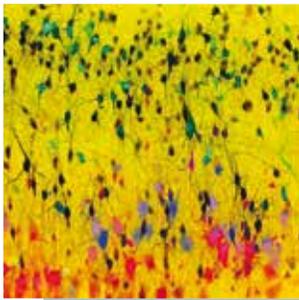
The circadian clock, he found, even mediates the immune system. Mice with a crucial circadian molecule missing had higher levels of inflammation in their bodies than other mice, suggesting that genes and molecules involved in the circadian clock could be drug targets for conditions linked to inflammation, such as infections or cancer.

## The Innovations and Discoveries

- Panda's lab discovered that confining caloric consumption to an 8- to 12-hour period—as people did just a century ago—might stave off high cholesterol, diabetes and obesity. He is exploring whether the benefits of time-restricted eating apply to humans as well as mice.
- Panda's team discovered a single gene that can simultaneously reset all the cells in the SCN. Mice with the lowest levels of the gene recovered the fastest from a simulated time zone change. The finding suggests a new target for treating jet lag or sleep disorders.
- He identified a pair of genes that help keep eating schedules in sync with daily sleep cycles, making you feel hungry for meals at the same time every day. Mutations in these genes could explain night eating syndrome.

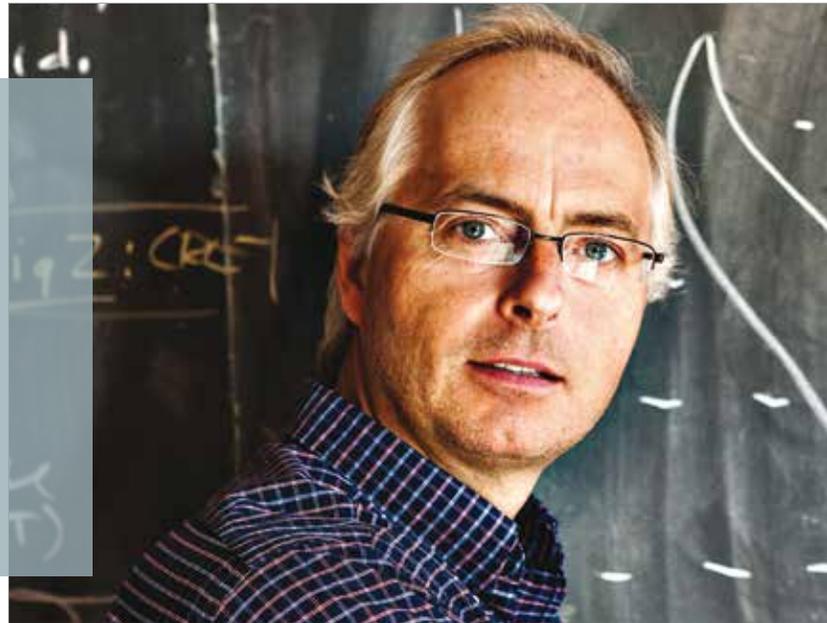
For more information, please visit:  
<http://www.salk.edu/faculty/panda.html>

Aging, Cell Biology, Circadian Rhythms,  
Depression, Genetics, Metabolism



# Samuel Pfaff

Professor  
Gene Expression Laboratory  
Howard Hughes Medical Institute Investigator  
Benjamin H. Lewis Chair



## The Problem

The brain has exquisite control over the body's 650 muscles, allowing us to perform tasks with ease that are difficult for even sophisticated robots. We often take the precision of our movements for granted until we have a personal experience with stroke, spinal cord injury or neurodegenerative disease such as Parkinson's, ALS or spinal muscular atrophy. Each of these affects the nervous system differently, nevertheless, they illustrate how a number of sites within the brain and spinal cord are involved in controlling movement. Neuroscientists study motor control to understand how our brains develop and perform calculations, and to find solutions that can be used to repair injuries and diseases. The complexity of motor circuitry creates many challenges to finding new therapies. These include finding methods to visualize active neurons in living animals, defining the cellular and molecular pathways involved in building the motor system and identifying the cellular and molecular systems affected by injuries and diseases.

## The Approach

Samuel Pfaff uses a combination of genetics, biochemistry and microscopy with cutting-edge optogenetics tools. The Pfaff laboratory is a leader in the study of motor neurons. This group is

widely recognized for identification of the genetic pathways that allow motor neurons to develop and grow axons to muscles. His team's recent work has exploited its unique knowledge of motor neuron genetics to develop novel labeling tools that help reveal more about both motor circuitry and disease processes.

## The Innovations and Discoveries

- Pfaff's lab used genome sequencing to identify molecular pathways involved in gene regulation and spinal cord development. Using this knowledge, they successfully created functional spinal motor circuitry from embryonic stem cells.
- His team discovered neurons within the spinal cord that form a critical regulatory node for controlling motor activity and developed mouse lines that permit spinal neuron activity to be visualized during walking.
- The lab created an in vitro model of spinal muscular atrophy to define the fundamental underpinnings of the genetic pathways that go awry in this disease. The group also worked with a team of San Diego scientists to develop an ALS therapy for humans.

For more information, please visit:  
<http://www.salk.edu/faculty/pfaff.html>

Birth Defects, Developmental Disease, Locomotion, Neurobiology,  
Neurological Disease, Post-Polio Syndrome, Stem Cells



# John Reynolds

Professor  
Systems Neurobiology Laboratory  
Fiona and Sanjay Jha Chair in Neuroscience



## The Problem

Scientists have identified approximately 600 diseases of the nervous system so far, but we still lack a full understanding of how the brain normally works and how it fails in disease. As a consequence, researchers do not have a well-defined, long-term strategy for developing new and effective treatments for mental disorders. At this stage, there is little to assist with the treatment and prevention of these diseases, although the cost of neurological diseases to society is enormous. Dementias alone, for example, cost more than heart disease and cancer, exceeding \$160 billion in the United States, equivalent to \$500 per citizen per year. Likewise, treatments for schizophrenia and autism are also stalled. Aside from cost, the toll in human suffering is also steep in these disorders, both to the patients and to their families. And as the aging population grows, these problems will continue.

## The Approach

John Reynolds' team is working to decipher the neural mechanisms that enable us to perceive, understand and interact with the world around us, capacities that are impaired in brain disease. The long-range goal of his laboratory is twofold: to understand the fundamental nature of the computations that are carried out by the brain and to relate these to perception and conscious awareness.

Reynolds and his team tackle these questions by studying how the mammalian brain sifts through and makes sense of the

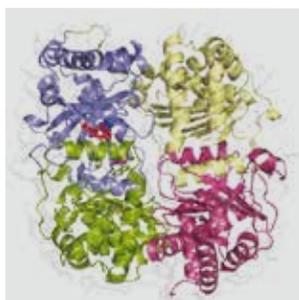
immense amount of sensory information that we receive from our environment at any given moment. To study this question, they deploy a range of experimental techniques, including neurophysiology, neuroanatomy, computational modeling, visual psychophysics, two-photon microscopy and cutting-edge optogenetic techniques, which entail the use of viruses to change the DNA of neurons so that they become sensitive to light. Reynolds' team then uses lasers to control neuronal activity in order to understand brain computations.

## The Innovations and Discoveries

- Reynolds identified competitive brain circuits that enable us to attend to task-relevant objects while withdrawing attention from task-irrelevant objects.
- Based on this discovery, Reynolds developed the leading computational model of attention, providing a unified, quantitative framework for understanding attentional selection in healthy brains, and how this selection fails in brain disease.
- His group discovered that neuronal activity fluctuations are reduced when attention is directed to a stimulus, resulting in improved perception of that stimulus. This phenomenon accounts for the majority of the beneficial effects of attention.

For more information, please visit:  
<http://www.salk.edu/faculty/reynolds.html>

Alzheimer's Disease, Autism, Dementia, Memory,  
Neurological Disease, Neurobiology, Vision



# Alan Saghatelian

Professor  
Clayton Foundation Laboratories for Peptide Biology  
Dr. Frederik Paulsen Chair



## The Problem

Peptides and metabolites are two important classes of biological molecules, referred to as small molecules. Changes in the levels of these small molecules are known to cause prevalent diseases. For example, lower levels of the peptide insulin lead to diabetes, while higher levels of the metabolite cholesterol cause heart disease. There are thousands of small molecules in our bodies, so how do we find these disease-causing peptides and metabolites? Thanks to advances in a technology called mass spectrometry, scientists can now measure peptides and metabolites in a biological sample (cell, tissue or organism). By analyzing disease samples, researchers can identify those molecules that are changing during a disease. Just as the identification of insulin led to a new treatment of diabetes, these discoveries of disease-associated peptides and metabolites will likely pave the way for a new generation of therapeutics to improve human health.

## The Approach

Alan Saghatelian's work touches on virtually all areas of human biology. He has developed and applied new mass spectrometry strategies that measure changes in small molecules overlooked by traditional biological methods, which typically focus on DNA, RNA and proteins. In particular, Saghatelian focuses on metabolites and peptides, which have been understudied because of technical challenges in their detection. Exploring this uncharted territory has enabled Saghatelian to make important discoveries, including the recent finding of a novel human lipid that reduces inflammation

and reverses the symptoms of diabetes. Saghatelian hopes to use the knowledge gained from his lab's work to accelerate the development of new medicines in the area of diabetes. He is also collaborating with many laboratories at Salk to understand the roles of peptides and metabolites in cancer, neurodegenerative and immunologic disorders.

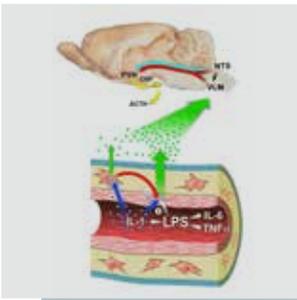
## The Innovations and Discoveries

- By discovering how a gene associated with type 2 diabetes controls insulin levels, Saghatelian and colleagues developed a drug-like compound called 6bK—which improves blood glucose in mice—as a potentially new anti-diabetic therapeutic.
- With collaborators, Saghatelian analyzed changes in metabolite levels in mice that are resistant to diabetes, which led to the discovery of a lipid, called FAHFA. FAHFAs are also found in humans. Administration of these lipids to mice reduces inflammation and improves the symptoms associated with diabetes, making these interesting therapeutic candidates and revealing a new disease-associated metabolite.
- Saghatelian also identified a previously unknown cluster of human genes that produce peptides that control fundamental cellular processes, such as DNA repair, highlighting their potential importance in cancer.

For more information, please visit:

<http://www.salk.edu/faculty/saghatelian.html>

# Cancer, Diabetes, Immunology, Metabolism, Neurological Disease



# Paul Sawchenko

Professor and Laboratory Head  
Laboratory of Neuronal Structure and Function  
Wylie Vale Chair



## The Problem

When the human body senses a threat, be it real or perceived, our physiology shifts to a defensive mode orchestrated by the brain—the immune system and appetite ramp down, metabolism is altered to liberate fuels, and blood flow is redirected to deliver these fuels to muscles that need them. In the short term, these changes help prepare the body for coping with the emergency at hand. But if this defensive mode is sustained, these same stress-related adaptations can contribute to a wide range of disease states, including pathologies of the central nervous system, such as dementia and multiple sclerosis. To find new ways of keeping stress from worsening disease, researchers need to understand how the stress response machinery works in the first place.

## The Approach

Paul Sawchenko uses cell biological and genetic approaches in rodent models to study how stress-responsive systems are organized at a molecular level within the body and particularly within the brain. His work seeks to identify how different kinds of stressful information reach the brain and to unravel the pathways and molecules involved in conveying this information to brain centers. Knowledge of this basic wiring diagram, and particularly of the molecules that govern the flow of information within it, helps identify drug targets that could combat the wide range of stress-related neurological diseases in a more effective and informed manner.

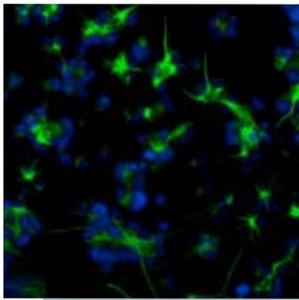
## The Innovations and Discoveries

- Sawchenko showed that a receptor for the stress hormone, corticotropin-releasing factor (CRF), is directly involved in modifying certain brain proteins in such a way as to contribute to the development of plaques and tangles, the two defining neuropathological hallmarks of Alzheimer's disease. Drugs that block signaling through this CRF receptor reduce brain damage and deficits in learning and memory in a mouse model of Alzheimer's, suggesting a new potential treatment for this devastating disease.
- Sawchenko and colleagues discovered a novel anti-inflammatory signaling mechanism within the brain's blood vessels. The lab is working to harness this mechanism to improve the clinical outcome in animal models of the many neurodegenerative disorders that have an inflammatory component, including ALS, Alzheimer's and Parkinson's diseases.
- Sawchenko's lab also aims to unravel brain circuitry related to past experience, emotion and stress in the hopes of better understanding a range of psychiatric disorders, including depression and post-traumatic stress disorder (PTSD).

For more information, please visit:

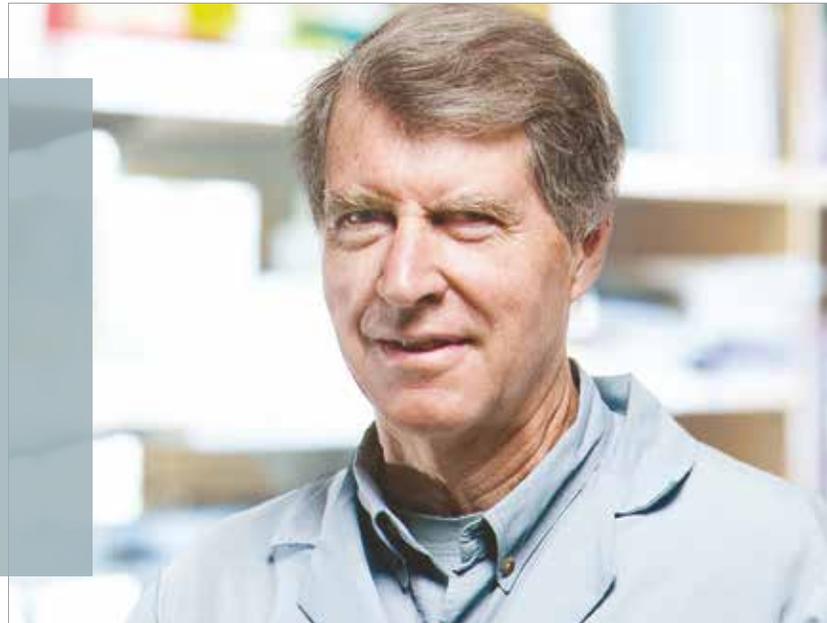
<http://www.salk.edu/faculty/sawchenko.html>

Aging, Dementia, Autoimmune Disease, Neurological Disease, Inflammation, Immunology, Neurobiology, Therapeutics



# Dave Schubert

Professor and Laboratory Head  
Cellular Neurobiology Laboratory



## The Problem

Although Alzheimer's disease has been described for more than a century, there is currently no effective treatment. There are also no drugs to prevent the progression of Parkinson's disease, Huntington's disease or ALS. The causes and symptoms of neurodegenerative diseases, particularly those associated with old age, are extremely complex and not well understood, making finding drug candidates especially challenging.

## The Approach

Dave Schubert is taking a different approach to finding drugs for neurodegenerative disorders. Many labs and companies focus on the molecules that cause the diseases and then develop targeted drugs that turn on or off these molecules. Schubert, however, has created a way to screen many chemical compounds for their ability to prevent nerve cell death. With his assays, he can sift through thousands of potential drugs and pick out those that show potential to protect or help recover brain cells without having to pick a specific, predetermined drug target.

Schubert can then home in on what these potential drugs do, how they help or protect neurons, and, in some cases, make them even more therapeutic by tweaking their structure or chemical properties. By screening molecules derived from plants, Schubert's lab has uncovered a handful of drug candidates that were modified through medicinal chemistry to improve their pharmacological properties and make them more potent. Several of these synthetic drug candidates are now being studied for their

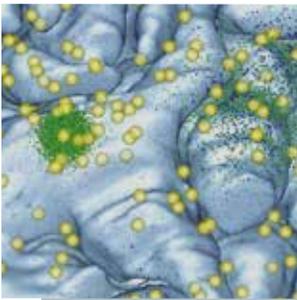
potential benefit to humans, and one is making its way through the FDA clinical trial process for Alzheimer's. He's also creating additional screening techniques to look for drugs useful in other areas, as well as refining the approaches his lab uses to optimize drugs after identifying candidate molecules.

## The Innovations and Discoveries

- Schubert uses his novel screening approach to discover and optimize the compound J147 for use in preventing the nerve cell damage and cognitive decline associated with Alzheimer's disease. The drug, his team found, has a broad ability to protect nerve cells from degeneration, making it potentially useful for stroke as well.
- Schubert's team, in conjunction with senior staff scientist Pamela Maher's lab, discovered that the natural plant compound fisetin—found in strawberries and other fruits and vegetables—prevents cognitive and kidney damage associated with rodent models of diabetes, and also memory and learning deficits in mouse models of Parkinson's and Alzheimer's diseases. The team will also test fisetin in a new autism model.
- Schubert and his colleagues have shown that a simple synthetic derivative of the curry spice turmeric improves many of the symptoms associated with stroke and traumatic brain injuries. This compound directly helps neurons in the brain survive by inhibiting a molecular pathway that leads to inflammation.

For more information, please visit:  
<http://www.salk.edu/faculty/schubert.html>

**Aging, Autism, Dementia, Neurological Disease,  
Neurobiology, Parkinson's Disease, Therapeutics**



# Terrence Sejnowski

Professor and Laboratory Head  
Computational Neurobiology Laboratory  
Howard Hughes Medical Institute Investigator  
Francis Crick Chair



## The Problem

Every time you look at the world around you, pay attention to something new, anticipate the future or recall a memory, a unique set of electrical signals sweeps through your brain. How do these pulses contain all the information necessary to form a thought or memory? The sheer quantity of the billions of cells—and exponentially more routes that a signal can take as it zips through the brain—makes it hard to answer this question. But doing so could illuminate how diseases that affect thought and memory—ranging from schizophrenia to multiple sclerosis—arise as well as point to ways to treat them.

## The Approach

Terrence Sejnowski has turned to computer modeling techniques to try to encapsulate what we know about the brain as well as to test hypotheses on how brain cells process, sort and store information. While other scientists have focused on mapping the physical arrangement of neurons (tracing which cells connect to which), Sejnowski is interested in a more functional map of the brain, one that looks at how sets of cells are involved in processes—from filtering what we see to recalling memories.

To collect data on brain function, Sejnowski records the electrical activity of select sets of cells, as well as analyzes thin slices of autopsied brains. He uses that information to create and refine computational models on how the brain stores information for different activities. Through these models, he gets a better understanding of what information different cell types encode,

what molecules are needed and how signals move throughout the brain. At the same time, he learns how diseases such as schizophrenia or Parkinson's might alter these patterns.

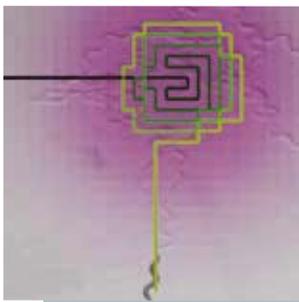
## The Innovations and Discoveries

- Sejnowski discovered the role of astrocytes, a type of brain cell, in producing unique brain waves that let mice recognize an object as new. When he blocked astrocyte function, mice treated everything in their cage the same rather than giving more attention to newly added objects.
- His lab developed a new model for how memories are consolidated—or stored in the brain—during sleep. During sleep, researchers hypothesized, some memories are strengthened while others, deemed less important, are lost. Revealing more about how the brain stores memories could help researchers understand how memory is affected in disorders such as Alzheimer's disease.
- Sejnowski built upon a computer model of how neurons transmit electrical impulses and found an unexpected link between a cellular channel and a potassium current—the ratio of densities between the two determines whether neurons can fire properly, providing new knowledge for symptoms of multiple sclerosis.

For more information, please visit:

<http://www.salk.edu/faculty/sejnowski.html>

Alzheimer's Disease, Computational Biology, Neurological Disease, Memory, Neurobiology, Parkinson's Disease, Schizophrenia, Systems Biology



# Tatyana Sharpee

Associate Professor  
Computational Neurobiology Laboratory  
Helen McLoraine Developmental Chair



## The Problem

Vision and hearing are essential to our wellbeing. Although we often take these senses for granted, the ability to parse the environment around us into objects has largely defied our efforts to replicate it outside of the brain, for example, in computers and robots. Yet, understanding how these processes are carried out in the brain is essential not only for creating efficient computer and robotic systems but also for ameliorating the effects due to stroke and neurodegenerative disorders that, in some cases, can prevent someone from recognizing his or her own face in the mirror.

## The Approach

Some of the most enigmatic parts of the human brain respond only to representations of natural stimuli. Researchers want to analyze reactions to these stimuli in order to find out how individual neurons represent such complex scenes and sounds. Tatyana Sharpee and her group are developing new statistical methods that make such analyses possible, as well as carrying out long-term observations of neural responses to natural stimuli. Sharpee's research is helping guide the development of new models that explain how the brain focuses on details or carries out a visual search. These findings have implications for not

only how we see, but also how we respond to other senses, such as smell, sound and touch.

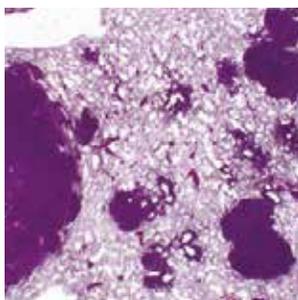
## The Innovations and Discoveries

- Sharpee recently showed how even simple organisms can implement maximally efficient strategies when searching for food. This theory offers clues into the basic mechanisms of decision-making: how we decide whether to continue with a project or start a new one, for example.
- Sharpee and collaborators have recently developed a theory that explains when it becomes advantageous for an organism to use new types of neurons. This theory could help catalogue and determine the number of separate neuronal types in the brain.
- She also discovered that, when the brain is trying to pick a shape out of a background, there's a trade-off between the complexity of the shape and the possible positions it can be in and still be recognized—a shape that's not very complex can still be picked out of the background by the brain even if it's upside down or sideways, for example.

For more information, please visit:

<http://www.salk.edu/faculty/sharpee.html>

Computational Biology, Memory, Neurobiology,  
Neurological Disease, Systems Biology, Vision



# Reuben Shaw

Professor  
Molecular and Cell Biology Laboratory  
Howard Hughes Medical Institute Early Career Scientist



## The Problem

Diabetes and lung cancer are two leading causes of death in the United States. It turns out they have something else in common: both diseases involve a mishap in how cells use energy. In tumors, mutated cells usurp energy to grow aggressively. In diabetes, cells can no longer properly process a key source of energy, sugar. Now, scientists are seeing that medicine for diabetes may help treat drug-resistant lung (and other) cancers and vice versa, indicating that cancer and diabetes are linked by mechanisms that control how cells use energy. Increasingly, researchers are exploring this new field of cancer metabolism to find more efficient therapies.

## The Approach

Ever since discovering a decade ago that a gene altered in lung cancer regulated an enzyme used in diabetes medicine, Reuben Shaw wondered if drugs originally designed to treat metabolic diseases could also work against cancer. This tantalizing connection between cancer and metabolism opens up a host of new possible therapeutics for both diseases and is quickly moving to the forefront of cancer research.

This link is the AMPK pathway, which Shaw discovered stalls cell growth and changes metabolism when nutrients are scarce. He found that the pathway halts tumor cells' aberrant revved-up metabolism, as well as restores normal function to the liver and other tissues in diabetics. His lab identified a number of new molecular components of the AMPK pathway, which connects nutrition and exercise to the suppression of both cancer and diabetes. In the past several years at Salk,

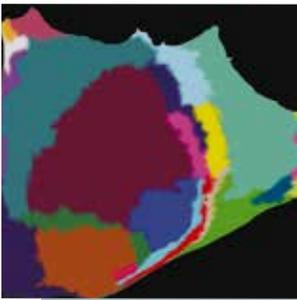
the lab's studies have led to the discovery of new therapies for both cancer and type 2 diabetes.

## The Innovations and Discoveries

- While investigating one of the most commonly mutated genes in lung cancer, LKB1, Shaw discovered that it directly activates the metabolic master switch AMPK. This direct connection of LKB1 to AMPK provided a stronger molecular link between cancer and diabetes than was ever known previously. Additionally, he found that a diabetes drug called phenformin, which targets the mitochondria, is especially effective in treating lung cancers lacking the LKB1 gene. This discovery has led to clinical trials focusing on cancer patients with LKB1 gene mutations.
- Shaw identified a gene, called DIXDC1, responsible for stopping the spread of cancer from the lungs to other parts of the body, indicating a new way to fight one of the world's deadliest cancers. By identifying the cause of this metastasis—which often results in a bleak survival rate—he explained why some tumors are more prone to spreading than others.
- Shaw's lab discovered that proteins tied to cancer, called histone deacetylases (HDACs), are regulated by AMPK and play a vital role in directing glucose production in the liver. This finding suggests that HDAC-inhibitor drugs in clinical trials for cancer may also be useful in the treatment of diabetes.

For more information, please visit:  
<http://www.salk.edu/faculty/shaw.html>

Cancer, Developmental Disease, Diabetes, Genetics,  
Lung Cancer, Metabolism, Therapeutics



# Charles Stevens

Professor  
Molecular Neurobiology Laboratory



## The Problem

In many ways, the brain is like a computer: it stores information for future access, compresses memories and pulls up those files when needed. Virtually all of the neural pathways in the brain are able to increase their computational power by simply growing in size while conforming to a single basic design. Understanding this evolution and how brains are able to vary in size without any major changes in organization could not only answer questions about brain development and function, but also help computer engineers build better computers that mimic the human brain.

## The Approach

Charles Stevens is one of the only researchers in the world trying to formulate a complete list of the principles that govern organization in brains both large and small. His research encompasses an area called scalable architecture—the idea that something can gain more properties simply by making it bigger. Stevens wants to know how scalable architecture is enforced in the brain and if there are always constant ratios between the size of cells and structures.

To answer these basic questions, Stevens has begun to pinpoint these scaling laws that dictate how brains grow and develop. He observes how organisms develop from an embryo to an adult and, in particular, has started with the goldfish as a model organism. Unlike mammals, goldfish have brains that continue to grow throughout their adult lives. Stevens has

already unearthed some design rules of the goldfish brain, such as set relationships between certain brain areas and laws on how neurons leading from the eyes to the brain are organized. He continues to chart how those rules are enforced during development and growth.

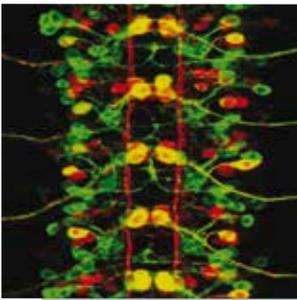
## The Innovations and Discoveries

- Stevens recreated classic experiments—using modern techniques—to verify that the number of neurons found in one square millimeter of the brain's cortex is a constant number. Like the older experiments had shown, Stevens found that the neuron density is the same across species and throughout the whole cortex.
- Stevens showed that the ratio of neurons in the cortex that produce the neurotransmitter GABA—now called GABAergic neurons—remains the same throughout development. The observation hints at how the balance of different neuron types is established in an embryo.
- He examined goldfish eyes to determine how eyes improve as they grow. He found that the fish gain more photosensitive cells as well as bigger cells. The fundamental principle of how size mediates eye structure likely holds true for other organisms, including humans.

For more information, please visit:

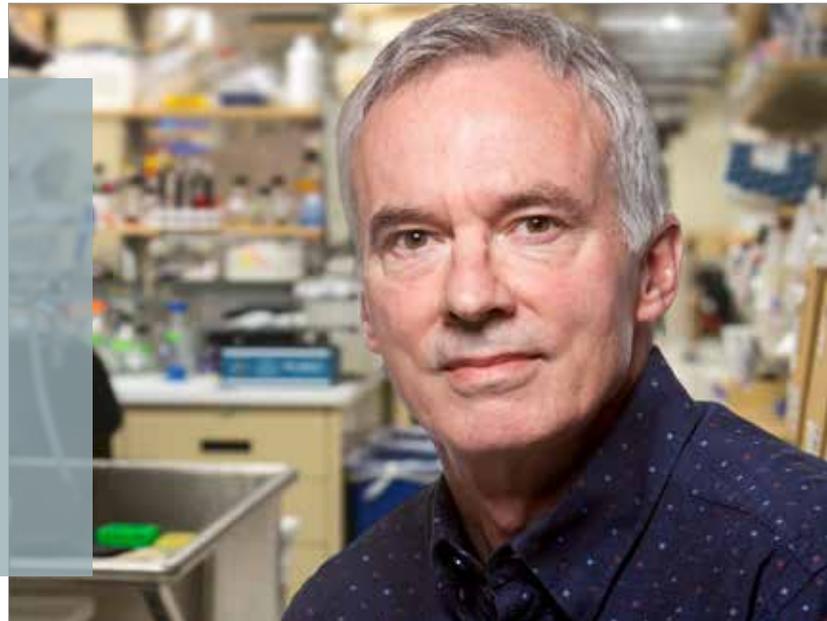
<http://www.salk.edu/faculty/stevens.html>

Cellular Biology, Evolution, Neurological  
Disease, Neurobiology, Systems Biology, Vision



# John Thomas

Professor  
Molecular Neurobiology Laboratory



## The Problem

Glioblastomas, one of the most common types of brain tumors, are aggressive and incurable. Not only are the tumors hidden inside the skull, but they also contain many aberrant pathways acting as cohorts to drive the cancer's growth. Turning off just one of these pathways with a drug might not stop the cancer. With a better understanding of how all these pathways activate each other—like falling dominoes—researchers may be able to figure out how to reverse the cancer once and for all.

## The Approach

John Thomas studies the molecules that help the brain grow in a developing embryo and which are later reactivated in many aggressive cancers of the nervous system. In both an embryo and a cancer, these molecules act in pathways that encourage the growth of brain cells; in the case of the embryo, that's a good thing, while in cancer, it's not. By studying both brain development and the molecular details of brain tumors, Thomas can determine where the two overlap—and where the pathways have weaknesses that will allow them to be turned off with drugs, stopping cancer growth.

Thomas developed a *Drosophila* (vinegar fly) model of brain tumors—using flies with particular genetic mutations

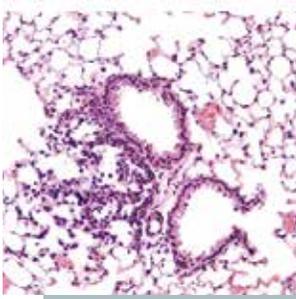
allows him to probe the domino effect of these pathways as well as test potential treatments.

## The Innovations and Discoveries

- Thomas showed how mutations in two genes, EGFR and PI3K, set off a cascade of events that caused the growth of glioblastomas in flies. He demonstrated how one step in this cascade—the activation of a set of proteins—could be blocked with drugs to weaken the cancer. Further research will be needed to determine whether targeting the same pathway in human patients shrinks glioblastomas.
- He discovered some of the chemical road signs that guide growing neurons on their paths through the brain in a developing embryo. The tracks that these neurons take ultimately shape organisms' thoughts and behaviors for the rest of their lives.
- Thomas has also turned his attention to how vinegar flies regulate their metabolism. Thomas is employing many of the same genetic approaches he previously used in order to study how molecular pathways in the brain are involved in metabolism, with the aim of better understanding diabetes and obesity.

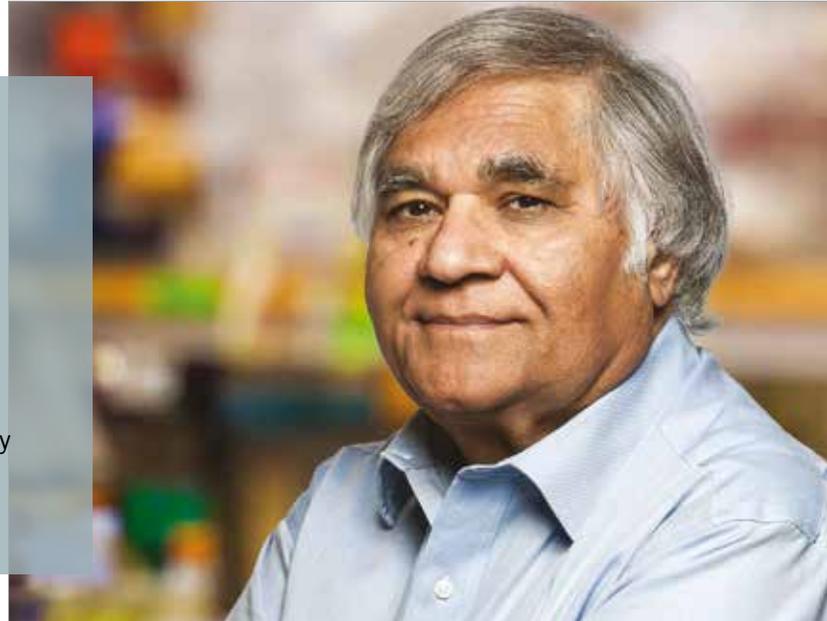
For more information, please visit:  
<http://www.salk.edu/faculty/thomas.html>

Cellular Biology, Developmental Biology, Developmental Disease,  
Genetics, Metabolism, Neurobiology, Neurological Disease



# Inder Verma

Professor  
Laboratory of Genetics  
American Cancer Society Professor of Molecular Biology  
Irwin and Joan Jacobs Chair in Exemplary Life Science



## The Problem

Our DNA masterminds the operation of the cells that make up our bodies. Cancer—now the second leading cause of death in the United States after heart disease—manifests when certain genes are missing or mutated. The laboratory-based study of animals and cells (known as disease models) can be a powerful method for understanding illness. However, it is difficult to accurately model human cancers in traditional animal or cellular systems. Developing new genetic-based models will help overcome these challenges and lead to more effective therapies. Furthermore, the same technologies used to create genetic models of cancer show promise as gene therapies capable of repairing mutations that lead to a range of diseases.

## The Approach

Inder Verma is one of the world's leading authorities on gene therapy and cancer. Verma developed innovations in two tools—viral vectors and gene editing—to study pathways that underlie cancer, metabolism and other diseases. Verma was the first scientist to genetically engineer HIV-based tools to insert new genes into cells. These cells can then be returned to the body, where they produce proteins whose absence causes disease. This retroviral vector technique is now a tool routinely used in molecular biology labs and clinical trials.

In the case of gene editing, Verma is creating induced pluripotent stem cells (iPSCs) from patients by taking, for example, skin cells of patients, coaxing them back into an early stem cell state, and then providing conditions to make those

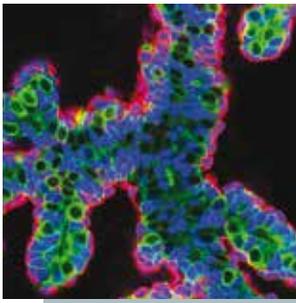
cells develop into more complex brain, lung, prostate and breast tissues. This lets his lab trace how genetic abnormalities that arise during development lead to cancer. With these tools, Verma is revealing how the aberrant expression of normal cellular genes can cause tumors. In particular, he is interested in explaining how inflammation in the body alters cellular pathways, resulting in cancers and other diseases.

## The Innovations and Discoveries

- Using a lentiviral vector, Verma demonstrated that the deadliest type of brain tumors (glioblastoma multiforme) could originate from several types of nervous system cells, contrary to conventional belief. The work points to new targets for treating this devastating disease.
- Verma's lab developed an iPSC technique to grow, for the first time, fully functional cells that line airways leading to the lungs. The lab-grown airway tissue can be used to study lung diseases—from rare disorders to common afflictions like asthma—and test new drugs.
- He also discovered, with Salk collaborators, that the gene BRCA1, found to be mutated in breast cancer, also regulates gene activity in the brain. Aside from better understanding neurological damage that occurs in a percentage of people susceptible to breast cancers, the new work also helps to better understand the evolution of the brain.

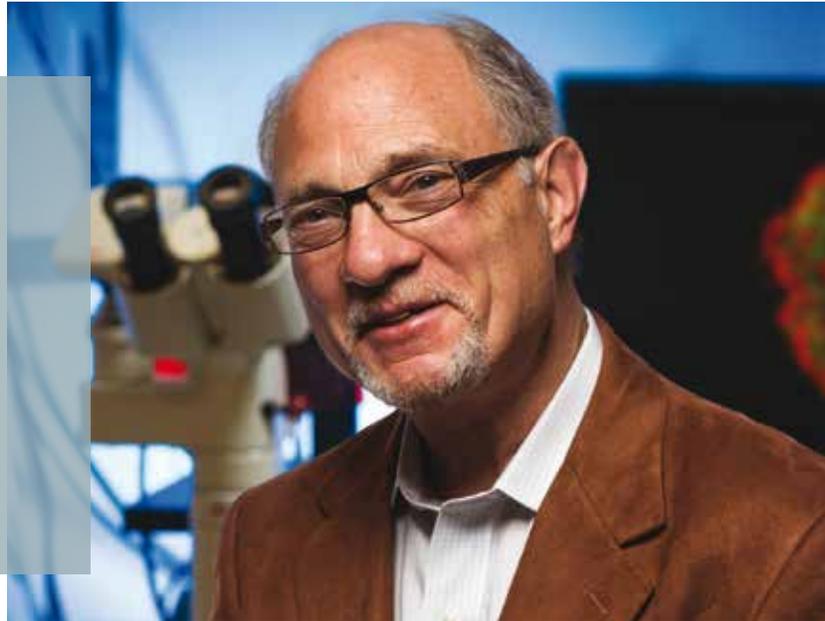
For more information, please visit:  
<http://www.salk.edu/faculty/verma.html>

Cancer, Gene Therapy, Genetics, Inflammation,  
Lung Cancer, Stem Cells, Therapeutics



# Geoffrey Wahl

Professor  
Gene Expression Laboratory  
Daniel and Martina Lewis Chair



## The Problem

Scientific research has taught us that cancer is a disease of aging and not actually one disease, but many. Knowing the molecular defects that produce a particular cancer subtype can indicate which drugs should be used to treat it most effectively. Yet, we must overcome major challenges to better treat cancer patients. For example, we only have molecular targets for a handful of cancers. Additionally, the cells within a single cancer often have differing molecular defects that we must target individually. Clearly, we need innovative strategies to chart the molecular interactions and genetic underpinnings of cancers. Such knowledge will generate the new therapies that will enable us to live with, rather than die from, these diseases.

## The Approach

Geoffrey Wahl's team is pursuing a three-pronged approach to better understand cancers and develop efficient therapies. First, his lab is studying whether the most aggressive forms of breast cancer are fueled by deranged versions of the stem cells that generate the mammary gland. Important differences between these and normal cells may enable the cancer-causing cells to be targeted selectively by new drugs to which they are especially vulnerable.

Secondly, some cancers, like pancreatic, are encased in a protective covering of cells that both prevents drugs from reaching the tumor cells and provides substances that fuel the growth of the cancer. Wahl's lab is developing a strategy to weaken this armor plating, thereby disrupting this important

element of the tumor's "control center" to make it more sensitive to therapeutic intervention.

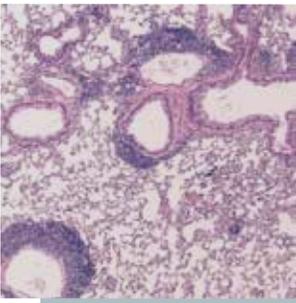
Finally, most of the functions of cells are carried out by groups of proteins that act together like "nano-machines." In cancer, abnormal nano-machines form and fail to respond to the cues that would normally turn them off. Wahl's team has developed a powerful new way to study when these abnormal nano-machines are formed. This technology is enabling the team to identify drugs that can interfere with those most relevant to several forms of cancer.

## The Innovations and Discoveries

- Wahl's lab discovered striking similarities between genetic signatures found in certain types of human breast cancer and those of stem cells in breast tissue in mouse embryos. The findings may lead to new ways to predict and personalize the diagnosis and treatment of some of the most aggressive forms of breast cancer.
- He discovered how to keep mammary stem cells alive and functioning in the lab, a breakthrough that allows him to study both breast development and the formation of breast cancers.
- Wahl's team developed a rapid and versatile method for observing subtle and previously hidden interactions between proteins in living cells. The technology promises to dramatically accelerate the identification of many potential new drug targets and drug candidates.

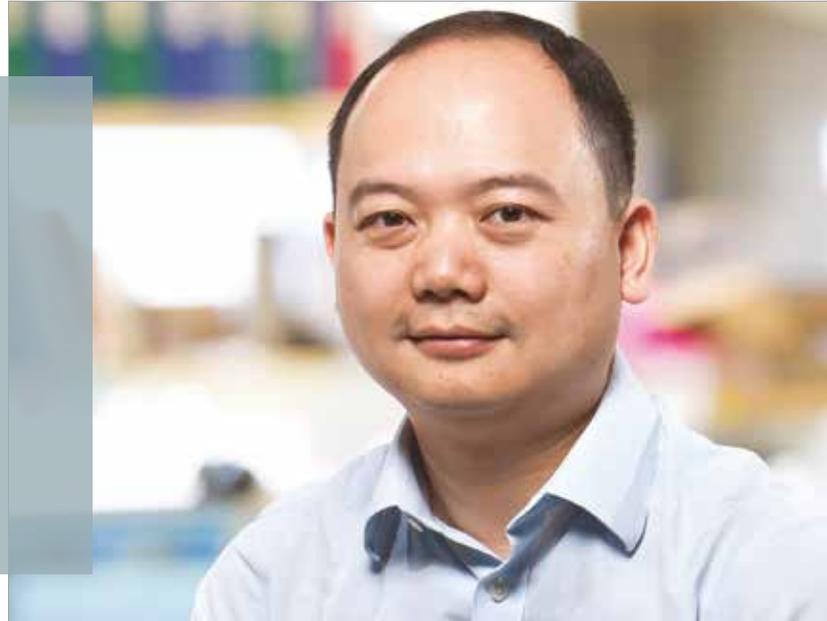
For more information, visit:  
<http://www.salk.edu/faculty/wahl.html>

# Breast Cancer, Pancreatic Cancer, Genetics, Stem Cells, Therapeutics



# Ye Zheng

Assistant Professor  
Nomis Foundation Laboratories for Immunobiology  
and Microbial Pathogenesis



## The Problem

The immune system is a powerful, double-edged sword. On one hand, it is armed to fight a wide range of invading foreign pathogens. On the other hand, if left unchecked, it can also attack an organism's own tissues and cause inflammation and autoimmune disorders such as allergies, asthma, rheumatoid arthritis, multiple sclerosis and type 1 diabetes. There are multiple safeguards built into our cells to prevent an autoimmune reaction, but these can go haywire. What's more, some types of cancer can also evade or co-opt the immune system's detection, allowing tumor cells to proliferate.

## The Approach

To learn how to strengthen or correct the immune system, Ye Zheng focuses on a specialized set of immune cells called regulatory T (Treg) cells. Tregs control the immune response, telling the more aggressive immune system cells when to stop their frenzied attack. Abnormal Treg function has been linked to multiple autoimmune diseases and tumors. In particular, a key molecular component of these cells, a protein called Foxp3, is often responsible for deficient Tregs.

Zheng is making advances in understanding the genes that control Foxp3—as well as genes that Foxp3 controls—to ultimately

lead to ways to manage Treg function. Since manipulations of Tregs can either weaken or strengthen the immune response, his findings can potentially open new avenues in the treatment of autoimmune diseases, improve organ transplant survival and uncover new cancer targets.

## The Innovations and Discoveries

- Zheng has mapped hundreds of genes directly related to Tregs' Foxp3 protein to get a fuller picture of how these cellular peacekeepers develop and function.
- Zheng's lab discovered that a particular genetic sequence in Foxp3 (called CNS2) is responsible for the stability of a Treg. If they removed CNS2, Tregs became unstable and often morphed into killer T cells—the type of cell they are supposed to be controlling—resulting in autoimmune disease in animals.
- His team identified a group of proteins directly regulated by Foxp3 that drive Treg function. These proteins can be targeted to boost Treg function for treatment of autoimmune diseases such as type 1 diabetes, allergy and asthma.

For more information, please visit:

<http://www.salk.edu/faculty/zheng.html>

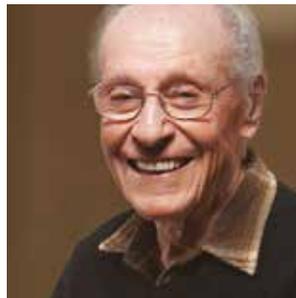
# Autoimmune Disease, Cancer, Diabetes, Immunology, Inflammation, Metabolism

# Emeritus Faculty



Suzanne Bourgeois

Suzanne Bourgeois conducted pioneering work on the regulation of gene expression using the bacterial lactose (*lac*) operon as a model system. In the 1960s, when the nature of the regulatory molecule was still unknown, she demonstrated that the *lac* “repressor” was a protein. She used that system to carry out the first characterization of the interaction of a regulatory protein with DNA. She later studied the regulation of genes in animal cells and eventually identified compounds that could be useful to reverse multidrug resistance in cancer. More recently, Bourgeois has turned her attention to the history of science—specifically, the early history of the Salk Institute. She is the author of the book, *Genesis of the Salk Institute: The Epic of its Founders*.



Melvin Cohn

Melvin Cohn, a founding and resident fellow of the Salk Institute, studied the body’s immune response, which protects vertebrates from the lethal effects of pathogens. Though the immune system cannot predict which of the diverse array of pathogens it will encounter, it nevertheless must respond promptly to defend the host organism from that invader. His investigations were theoretical and dealt with the evolutionary selection pressures that shape the immune system. A major thrust of his work has been the creation of a computer simulation of immune responses using the principles of nested cellular automata and adapting them to programs that can be run on typical desktop computers or on a remote Internet server.



Walter Eckhart

Walter Eckhart served as director of the Salk Institute Cancer Center and head of the Molecular and Cell Biology Laboratory for more than 30 years. He studied regulation of cell growth, including the effects of cancer-causing genes (oncogenes), growth factors, and communication between adjacent cells (gap junctional intercellular communication). The viral genes he studied stimulate cellular growth signaling pathways, allowing the cells to divide continuously. Identification of growth signaling pathways has led to the development of drugs that inhibit the growth of cancer cells.

# Emeritus Faculty



Catherine Rivier

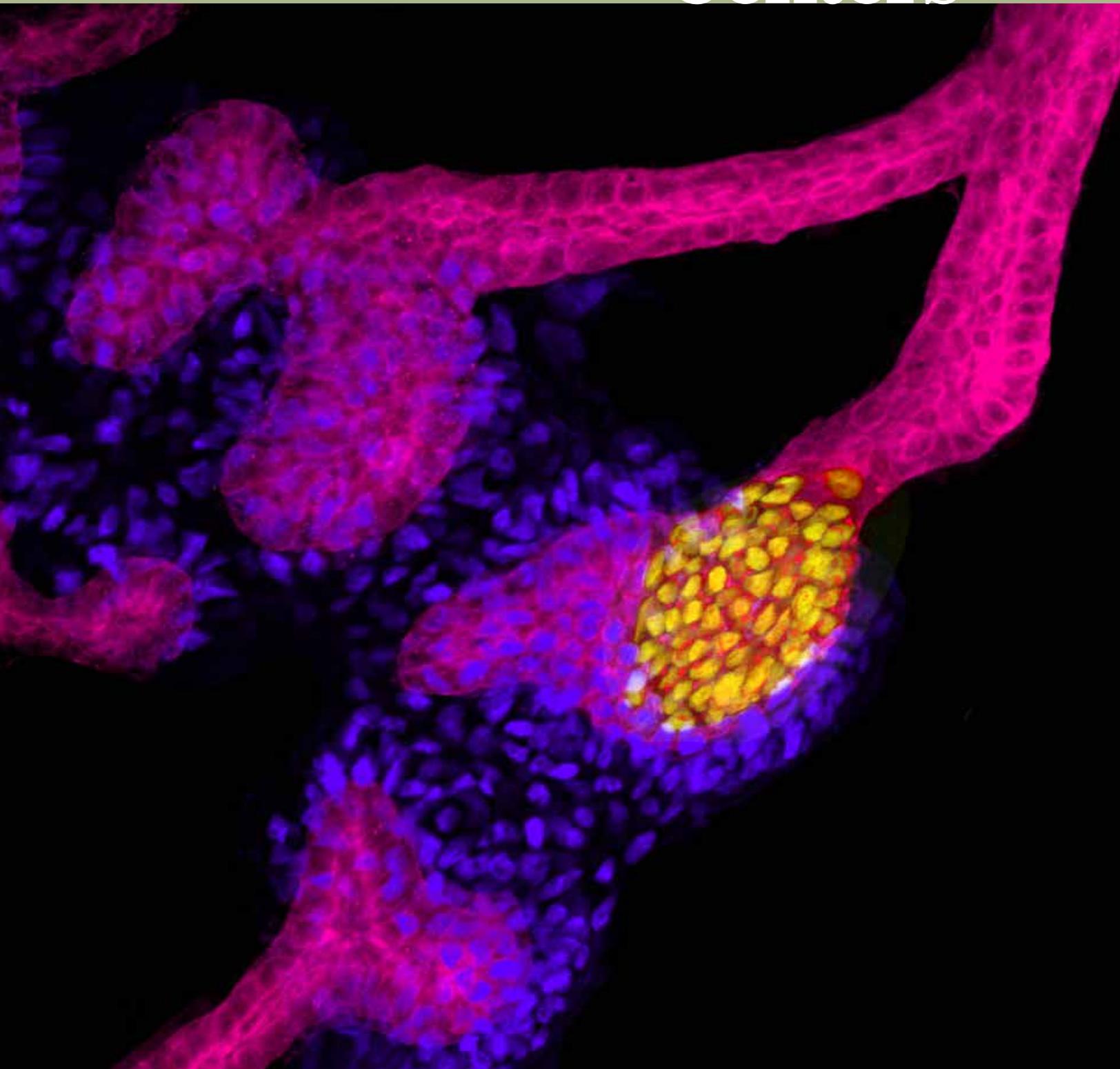
Catherine Rivier studied hormones that shuttle messages between the periphery and the brain. Specifically, she investigated how the brain perceives and responds to external stressors, such as infection, exposure to psychological threats, or alcohol. Her laboratory identified mechanisms through which the occurrence of stressors is conveyed to specialized areas of the brain. Rivier's team showed that rodents exposed to alcohol during embryonic development released excessive levels of a brain hormone associated with stress and showed elevated adrenal responses to stressors when they reached adulthood. She also showed that exposure to alcohol during adolescence also causes permanent changes in areas of the brain associated with the development of drug abuse in adulthood. Finally, her team identified a new pathway through which the brain controls the activity of the testes, a discovery that offered insights into puzzling cases of low testosterone secretion connected to stressors or diseases.



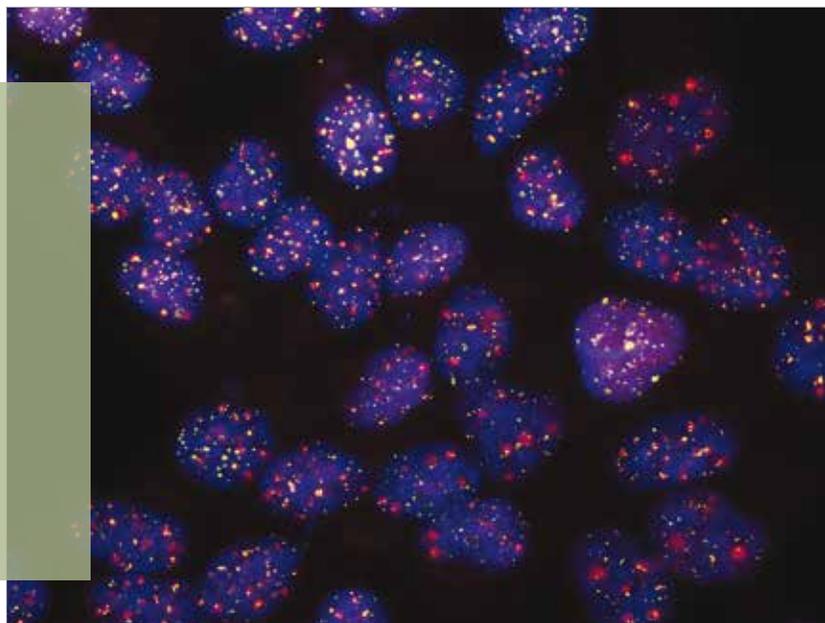
Jean Rivier

Jean Rivier spent his career as a Salk professor studying a class of stress hormones called corticotropin-releasing factors (CRFs). He showed that CRFs are responsible for many of the body's reactions to stress, including disabling the immune system in irritable bowel syndrome (IBS). In an attempt to develop treatments for these conditions, he designed peptide molecules that block CRF receptors. He recently founded a company called Sentia Medical Sciences Inc. and obtained exclusive rights to CRF-targeted molecules from the Salk Institute. Aside from his contributions to understanding stress, his work has resulted in eight drugs used to diagnose and treat neuroendocrine tumors, prostate cancer, hypogonadism, pituitary dwarfism and intractable pain.

# Research Centers



# NCI Cancer Center



The Cancer Center, a National Cancer Institute–designated basic research center, was established in 1970 by Jonas Salk. Today, under the leadership of Director Tony Hunter and Deputy Director Reuben Shaw, researchers in the Cancer Center probe the fundamental aspects of cancer biology, with the ultimate goal of reducing incidence, morbidity and mortality.

In addition to excellence in research, the Cancer Center provides a supportive environment in which trainees and faculty members are encouraged to develop as independent investigators. Some of these scientists remain at the Salk Institute, while others move on to productive careers at other institutions.

Stemming from a philosophy that basic research has the power to illuminate underlying causes of cancer, often in unexpected ways, the center's research is divided into three programs: Metabolism and Cancer, Mouse Models and Cancer Stem Cells, and Growth Control and Genomic Stability.

**Director**

Tony Hunter

**Deputy Director**

Reuben Shaw

**Metabolism and Cancer**

Janelle Ayres  
Ronald Evans  
Tony Hunter  
Marc Montminy  
Joseph Noel  
Satchidananda Panda  
Alan Saghatelian  
Reuben Shaw  
Ye Zheng

**Mouse Models and Cancer Stem Cells**

Joseph Ecker  
Rusty Gage  
Juan Carlos Izpisua Belmonte  
Christopher Kintner  
Julie Law

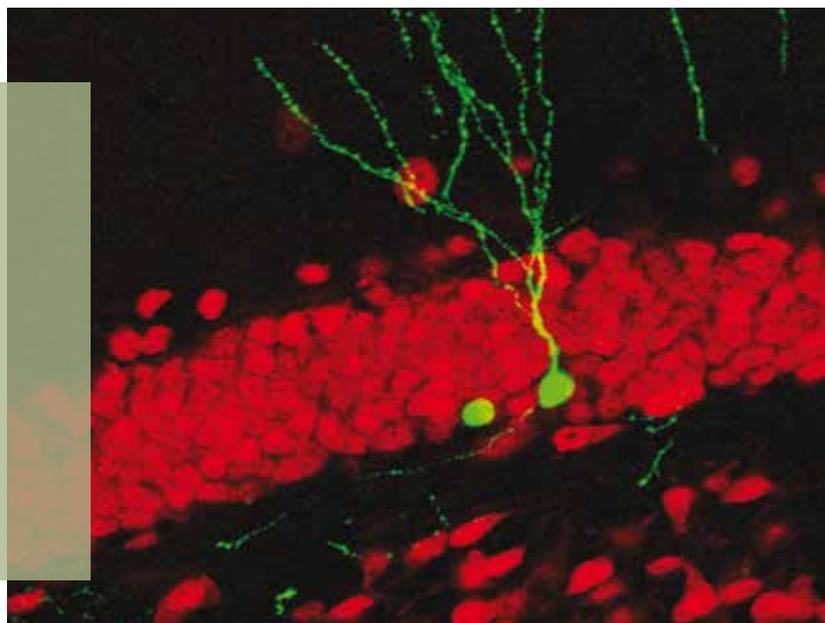
Kuo-Fen Lee  
Greg Lemke  
Axel Nimmerjahn  
Samuel Pfaff  
John Thomas  
Inder Verma

**Growth Control and Genomic Stability**

Beverly Emerson  
Diana Hargreaves  
Martin Hetzer  
Katherine Jones  
Jan Karlseder  
Björn Lillemeier  
Vicki Lundblad  
Clodagh O'Shea  
Geoffrey Wahl

For more information please visit:  
[http://www.salk.edu/faculty/cancer\\_center](http://www.salk.edu/faculty/cancer_center)

# Crick-Jacobs Center for Theoretical and Computational Biology



The Crick-Jacobs Center is an interdisciplinary neuroscience research unit named in honor of the late Nobel laureate Francis Crick and Irwin Jacobs, chairman of the Salk Board of Trustees.

The overall goal of the center is to integrate experimental and theoretical approaches to understand the organization of signaling systems and the functional anatomy of the brain, from the molecular to the systems levels, as well as how behavior arises from the interactions between the brain's many components.

Under the leadership of Terrence Sejnowski, the scientists who work at the Crick-Jacobs Center combine approaches from biology, physics, chemistry, mathematics, computer science and engineering and exploit techniques that include computer simulations, imaging, viral vectors and molecular genetics.

**Director**

Terrence Sejnowski  
*Salk Institute*

**Senior Fellows**

William Bialek  
*Princeton University*

Sydney Brenner  
*Salk Institute*

Edward Callaway  
*Salk Institute*

Sean Eddy  
*Janelia Farm*

David Kleinfeld  
*University of California,  
San Diego*

Christof Koch  
*California Institute of  
Technology*

Mel Simon  
*California Institute of  
Technology*

Larry Smarr  
*University of California,  
San Diego*

Charles Stevens  
*Salk Institute*

Susumu Tonegawa  
*Massachusetts Institute of  
Technology*

**Fellows**

Nicola Allen  
*Salk Institute*

Sreekanth Chalasani  
*Salk Institute*

Xin Jin  
*Salk Institute*

Saket Navlakha  
*Salk Institute*

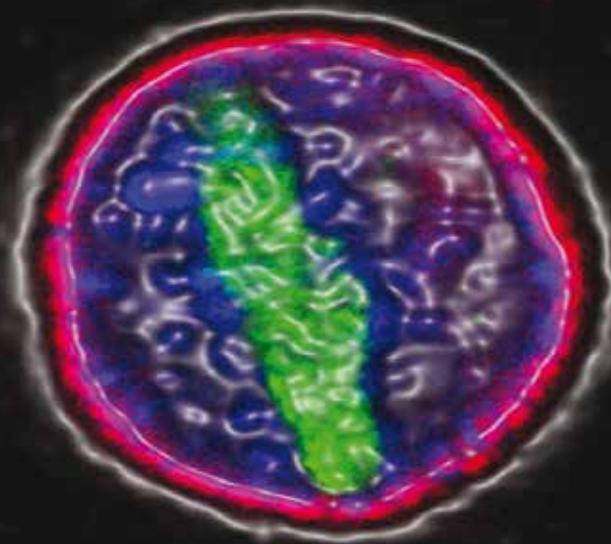
Tatyana Sharpee  
*Salk Institute*

**Junior Fellow**

Krishnan Padmanabhan  
*Salk Institute*

**For more information, please visit:**  
<http://www.salk.edu/faculty/crick-jacobs-center>

## Glenn Center for Aging Research



The Glenn Center for Aging Research was established in January 2009 with a \$5 million gift from the Glenn Foundation for Medical Research. The Glenn Foundation continued its generous support with a \$3 million gift in 2014. The Glenn Center focuses on a three-level approach: whole systems biology, organ biology and cellular aging biology. Expertise at all these levels is required to understand aging, age-related disease and the differences between healthy and pathological aging.

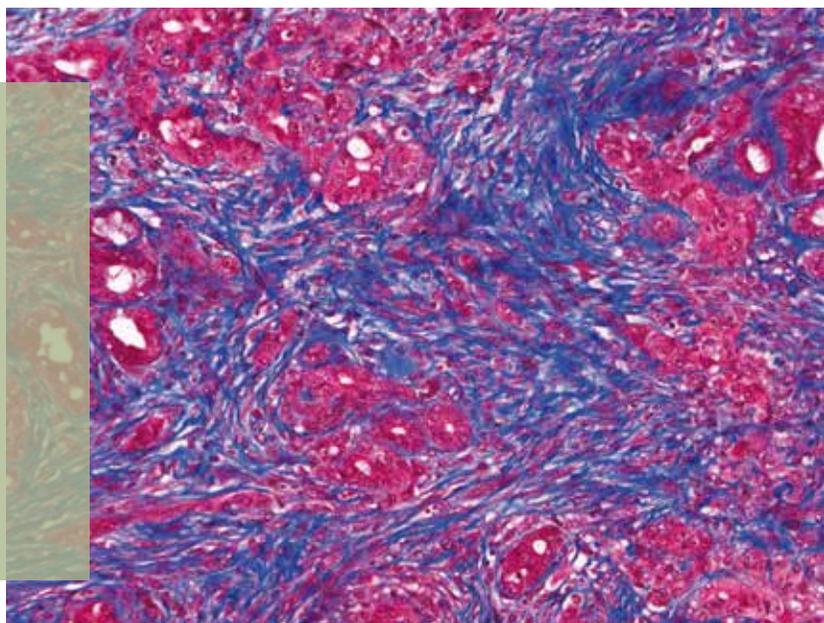
The Salk Institute is uniquely suited to such an interdependent model, as its small size facilitates a highly collaborative approach toward projects, allowing researchers to tackle questions that are too complex for any one scientist. As a group, Salk researchers have deep expertise in metabolism, organ and tissue regeneration, stem cell biology, neurobiology and neurodegenerative diseases, inflammation, telomere biology, senescence, genome stability, cancer biology, nuclear structure, genome organization and cell signaling. The free exchange of information across disciplines allows scientists to rapidly move between cells, organs and systems, enormously accelerating the rate of discovery.

### Glenn Center Members

Jan Karlseder (Director)  
Martin Hetzer (Co-Director)  
Sreekanth Chalasani  
Ronald Evans  
Rusty Gage  
Juan Carlos Izpisua Belmonte  
Julie Law  
Vicki Lundblad  
Marc Montminy  
Satchidananda Panda  
Reuben Shaw  
Inder Verma

For more information, please visit:  
<http://www.salk.edu/glenn>

# Helmsley Center for Genomic Medicine



The genomic revolution is upon us, transforming basic biological research and the entire field of health care. The Helmsley Center for Genomic Medicine (HCGM) at the Salk Institute for Biological Studies was established through a historic \$42 million gift from The Leona M. and Harry B. Helmsley Charitable Trust to further our understanding of the deep genetic connections shared by chronic diseases. The center is led jointly by Salk professors Ronald Evans, Rusty Gage and Inder Verma. The center focuses on three primary areas of research.

Although chronic illnesses manifest themselves in very different ways, they share similar genetic properties, suggesting closely related underlying biological processes. If we can understand the similarities between chronic illnesses at the genomic level, we can fundamentally transform the ways we study and treat these diseases. Knowledge of these key common activators will provide the framework for the development of novel therapies and regenerative tools to treat disease at the molecular level.

## **Cancer**

The goal is to determine the roles of genetic alterations, metabolic dysregulation, inflammation and tumor heterogeneity in the initiation and progression of human cancers, including glioblastoma, colorectal, lung, pancreatic and prostate cancers.

## **Diabetes and Metabolism**

Metabolism is arguably not only the most fundamental of biological processes but also the most complex. The center uses genomic, metabolic, proteomic and pharmacologic approaches to understand how metabolic homeostasis is achieved and the impact of its dysregulation in chronic diseases.

## **Stem Cells**

The overall goal is to discover new therapeutic treatments for chronic human diseases involving cell transplantation and/or the identification and development of compounds with therapeutic activities. The center's research is aiding the progression of stem cell and regenerative therapies to the clinic.

## **Directors**

Ronald Evans  
Rusty Gage  
Inder Verma

## **Principle Investigators**

Juan Carlos Izpisua Belmonte  
Marc Montminy  
Reuben Shaw

## **Associates**

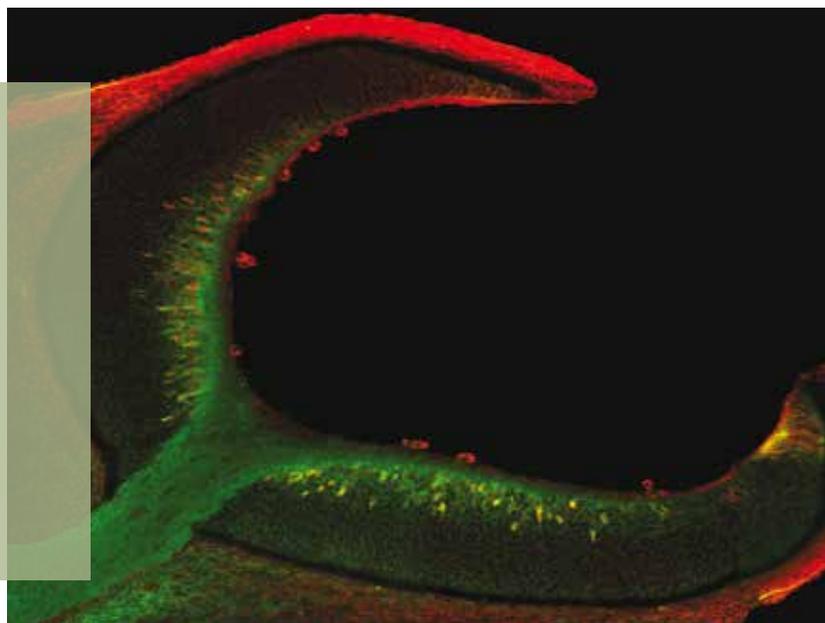
Tony Hunter  
Greg Lemke  
Clodagh O'Shea  
Satchidananda Panda  
Alan Saghatelian  
Paul Sawchenko  
Geoffrey Wahl

## **Helmsley-Salk Fellows**

Dmitry Lyumkis

**For more information, please visit:**  
<http://www.salk.edu/hcgm>

# NEI Center for the Neurobiology of Vision



The Center for the Neurobiology of Vision was designated as a basic research center by the National Eye Institute in 2009. Directed by Thomas Albright, the center comprises 15 independent investigators, whose research programs span nearly the full range of visual processing stages, from the retina through object recognition and visual-motor control. The development and plasticity of these processing stages is addressed at multiple levels of experimental analysis, ranging from theoretical and molecular genetic investigations through studies of individual cells and their interactions, small neuronal circuits, larger neuronal systems and behavior. Emphasis is also placed on clinical disorders of visual perception and visually guided behavior, such as Williams syndrome and autism.

#### **Director**

Thomas Albright

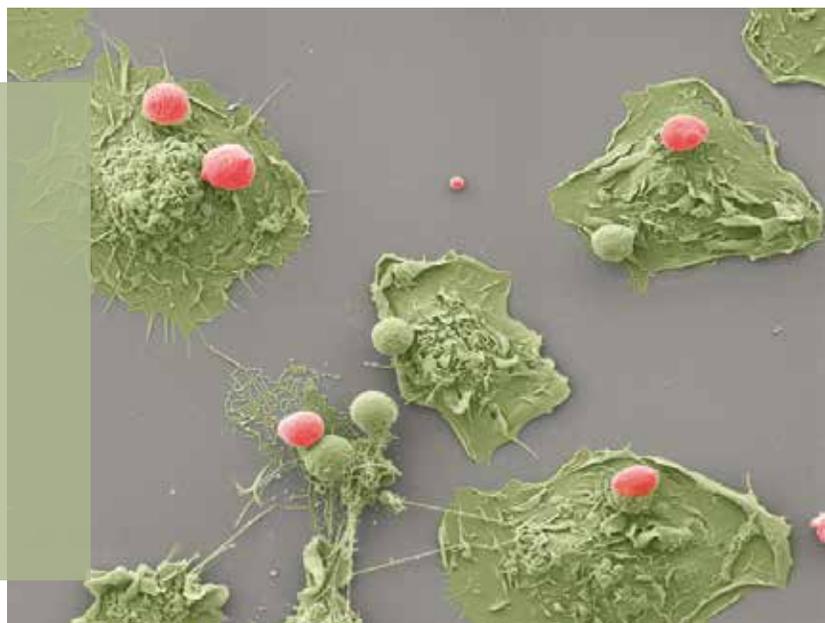
#### **Members**

Ursula Bellugi  
Edward Callaway  
Sergei Gepshtein  
Greg Lemke  
Dennis O'Leary  
Satchidananda Panda  
John Reynolds  
Terrence Sejnowski  
Tatyana Sharpee  
Charles Stevens  
Gene Stoner

**For more information, please visit:**

<http://www.salk.edu/cnv>

# Nomis Center for Immunobiology and Microbial Pathogenesis



The Nomis Center for Immunobiology and Microbial Pathogenesis was launched in 2008 with gifts totaling \$18 million from the Nomis Foundation, a European foundation established by Salk trustee G.H. “Heini” Thyssen.

The center aims to shed light on the molecular mechanisms that cause infectious diseases, define key molecules involved in the body’s response to injury and infection, elucidate the rules of engagement between the body’s microbiome and immune system, and understand why inflammatory processes spin out of control under some circumstances.

It is increasingly appreciated that chronic inflammation is the culprit behind the most common illnesses of middle and old age. It is capable of bursting plaques in coronary arteries, leading to heart attacks and damaging nerve cells in Alzheimer’s patients. It drives autoimmune disorders and is intricately linked with the early stage development of cancer, diabetes and autoimmune diseases.

#### **Director**

Greg Lemke

#### **Members**

Janelle Ayres

Melvin Cohn

Ronald Evans

Tony Hunter

Björn Lillemeier

Clodagh O’Shea

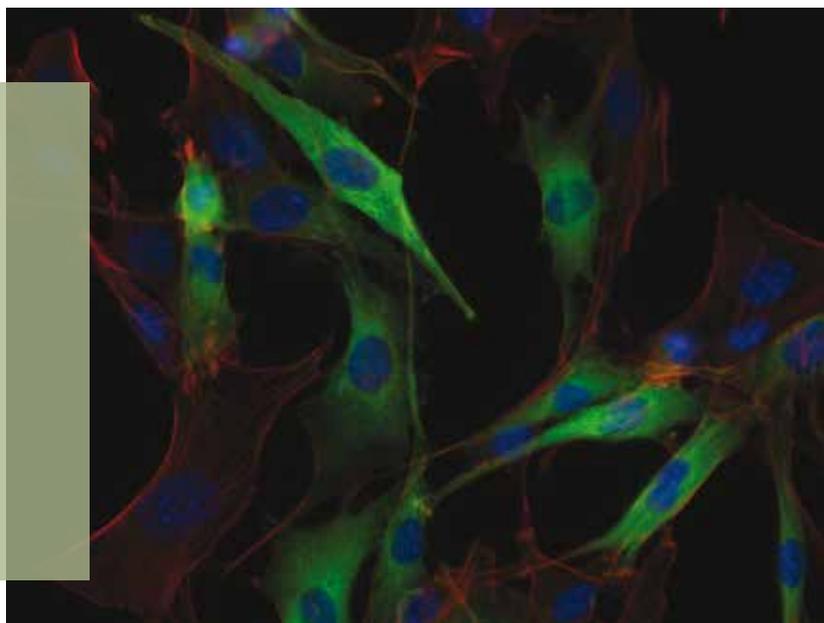
Inder Verma

Ye Zheng

**For more information, please visit:**

**[www.salk.edu/faculty/nomis-center](http://www.salk.edu/faculty/nomis-center)**

# Center for Nutritional Genomics



Founded in 2009 with a \$5.5 million grant from the Leona M. and Harry B. Helmsley Charitable Trust, the Salk Center for Nutritional Genomics employs a molecular approach to nutrition and its impact on the role of metabolism in diabetes, obesity, cancer, exercise physiology and lifespan, thereby increasing the understanding of how nutrients affect health. It includes a metabolic core facility and an interdisciplinary fellows program.

The center approaches fundamental aspects of medical physiology and endocrinology from the perspective of the genome. Members look at metabolic control as a product of the regulated activity of metabolic genes, which undergo dramatic shifts, not only in response to fasting or feeding, but also in aging and disease.

These metabolic shifts provide a critical underpinning in many disease processes. Loss of control of these metabolic shifts underlies the development of both type 2 diabetes and obesity, as well as other insulin-resistant conditions such as polycystic ovary

syndrome. In addition, deregulated glucose metabolism is a long-known hallmark of tumor cells, and recent links have connected the pathways controlling glucose and lipid metabolism in tissues such as liver and muscle to the processes deregulated in many human cancers.

#### **Directors**

Ronald Evans  
Marc Montminy  
Reuben Shaw

#### **Helmsley Fellows**

Weiwei Fan—Evans Lab  
Narayana Yeddula—Verma Lab  
Erin Quan Toyama—Shaw Lab

**For more information, please visit:**

**<http://www.salk.edu/cng>**

# Sloan-Swartz Center for Theoretical Neurobiology



The principal objective of the Sloan-Swartz Center for Theoretical Neurobiology, which was established in 1994 with major financial support from the Alfred P. Sloan Foundation and continuing funding from the Swartz Foundation, is to develop a firm theoretical infrastructure for modern experimental neurobiology. To accomplish this goal, its members promote the application of theoretical concepts and techniques, drawn from the physical sciences, to a wide range of problems in neurobiology.

Their areas of study span a wide range of critical levels of analysis, including molecular characterization of ion channels, synaptic transmission and plasticity, developmental events in circuit formation, characterization of the properties of cortical neurons, and the relationship of the latter to sensory, perceptual and cognitive experience.

The center also seeks to educate conventionally trained neurobiologists about modern theoretical tools.

## **Members**

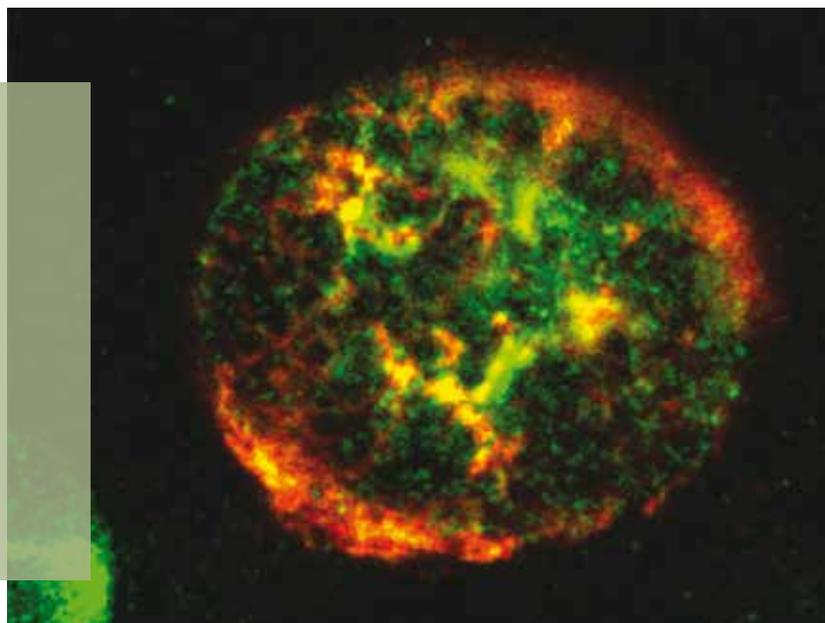
Thomas Albright  
Nicola Allen  
Ursula Bellugi  
Edward Callaway  
Sreekanth Chalasani  
Martyn Goulding  
Xin Jin  
Christopher Kintner  
Greg Lemke  
Dennis O'Leary  
John Reynolds  
Terrence Sejnowski  
Charles Stevens  
John Thomas

## **Sloan-Swartz Fellows**

Sergei Gepshtein  
Jude Mitchell  
Samat Moldakarimov

**For more information, please visit:**  
[www.sloan-swartz.salk.edu](http://www.sloan-swartz.salk.edu)

# Waitt Advanced Biophotonics Center



The Waitt Advanced Biophotonics Center was founded in 2008 with a \$20 million challenge grant from the Waitt Foundation, which was established by Ted Waitt, a member of Salk's Board of Trustees. The eponymous center develops and applies highly sophisticated imaging technologies and methods. Ultimately, these new tools will allow scientists to understand how single molecules function inside our cells in real time, to shed light onto the molecular organization of complex cellular structures and to investigate how cells connect with one another in organs such as the brain in healthy and diseased states.

The center is led by Martin Hetzer, a professor in the Molecular and Cell Biology Laboratory, whose research uses advanced imaging methods to investigate normal and pathological cell organization and genome function and their role in cancer and age-related degenerative diseases. The center is also home to three outstanding junior faculty members, Hu Cang, Björn Lillemeier and Axel Nimmerjahn. The Cang laboratory focuses on developing novel super-resolution microscopes to visualize single molecules in cells and tissues. The Lillemeier laboratory is developing a combination of super-resolution imaging and correlation spectroscopy to study membrane-associated signal transduction pathways in the immune system. The Nimmerjahn laboratory is developing the next generation of imaging tools that will enable unprecedented insights into the function and activity of brain cells in animals.

The core facility is a state-of-the-art microscopy center equipped with the latest commercial imaging and data analysis technologies. Both the biophotonics faculty and the core staff work together in a closely collaborative relationship to further advances in imaging technology and apply and integrate those new methods into the biological research community at Salk.

#### **Director**

Martin Hetzer

#### **Members**

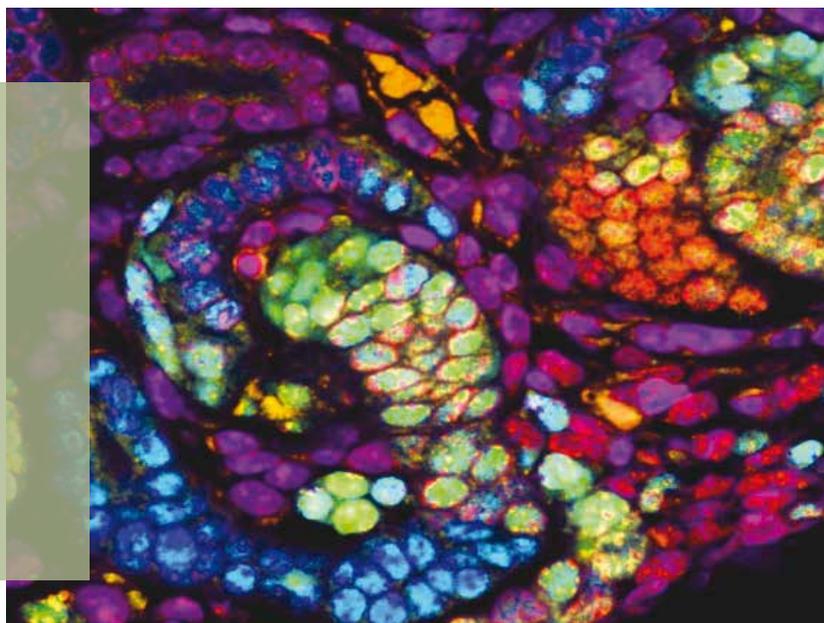
Hu Cang  
Björn Lillemeier  
Axel Nimmerjahn

#### **Core Staff**

Travis Berggren (Interim Director)  
Michael Adams  
Sarah Dunn  
Andrew Loftus

**For more information, please visit:**  
<http://www.salk.edu/biophotonics>

# Center of Excellence in Stem Cell Genomics



The Center of Excellence in Stem Cell Genomics was established in 2014 through a \$40 million award by California's stem cell agency, the California Institute for Regenerative Medicine. The center, jointly led by Joseph Ecker of the Salk Institute and Michael Snyder of Stanford University, brings together experts and investigators from seven major institutions in the state to focus on bridging the fields of genomics—the study of the complete genetic make-up of a cell or organism—with cutting-edge stem cell research.

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

The center provides a platform for collaboration, allowing California's stem cell scientists and genomics researchers to bridge these two fields and generate critical genomics data that will be shared with scientists throughout California and the rest of the world.

In addition to outside collaborations, the center will pursue some fundamental questions and goals of its own, including

collecting and characterizing induced pluripotent stem cell lines from patients with familial cardiomyopathy, applying single-cell genomic techniques to better understand cellular subpopulations within diseased and healthy brain and pancreatic tissues, and developing novel computational tools to analyze networks underlying stem cell genome function.

The University of California, San Diego, Ludwig Institute for Cancer Research, The Scripps Research Institute and the J. Craig Venter Institute, all in San Diego, collaborate on the project, in addition to the University of California, Santa Cruz, which runs the data coordination and management component.

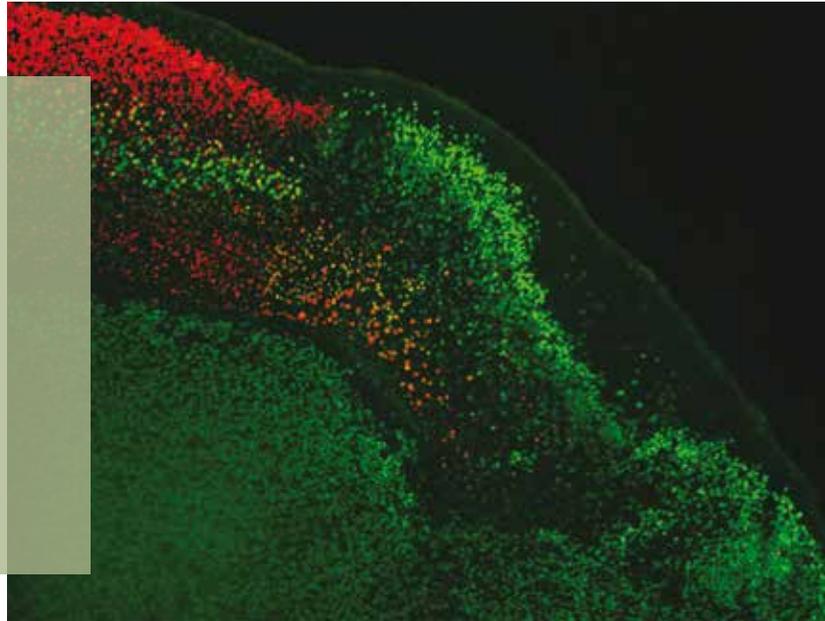
#### **Directors**

Joseph Ecker  
*Salk Institute*

Michael Snyder  
*Stanford University*

**For more information, please visit:**  
<http://www.salk.edu/cescg>

# NINDS Neuroscience Core Center



The Salk Neuroscience Core Center was established in 2012 with \$4.5 million of funding over five years from the National Institute of Neurological Disorders and Stroke (NINDS). The center provides critical infrastructure to support research efforts in the neurosciences consistent with the NINDS mission. The goal of the center is to support these research activities to develop a better understanding of congenital brain defects and neurological diseases and help in the design of more effective treatments for them. By centralizing and expanding these core services, the Neuroscience Core Center provides neuroscientists with access to new research technologies or technologies not practical to maintain at the level of individual labs and that are a significant resource multiplier for Salk investigators.

Directed by Dennis O'Leary, the Salk Neuroscience Core Center has established core facilities in three areas that are particularly important for neuroscience: genome manipulation, imaging and behavioral studies. Brain researchers are increasingly focused on the links between genes and behavior, exploring how genetics plays a role in brain development, structure and organization, as well as disease, which is ultimately manifested in a person's ability to function. The three cores are designed with these critical links in mind. The genome manipulation core, directed by Kuo-Fen Lee, helps scientists develop genetically modified mice as model organisms to study human neurological diseases and genetic disorders, such as autism, schizophrenia and Alzheimer's. The

animal behavior core, directed by Rusty Gage, provides a broad range of behavioral testing of these and other mouse models of neurological diseases and disorders. The imaging core, directed by Paul Sawchenko, focuses on electron microscopy and integrating structural analysis across imaging technologies to help scientists visualize the cellular and molecular mechanisms at work in the normal, diseased and genetically defective nervous system.

More than half the Salk faculty is engaged in neuroscience research, many of whom have direct grant support from NINDS and benefit from the Salk Neuroscience Core Center. An external advisory board, which includes Gerald Fischbach (Simons Foundation), Carla Shatz (Stanford University), and Thomas Jessell (Columbia University), advises the internal steering committee overseeing the Salk Neuroscience Core Center.

#### **Director**

Dennis O'Leary

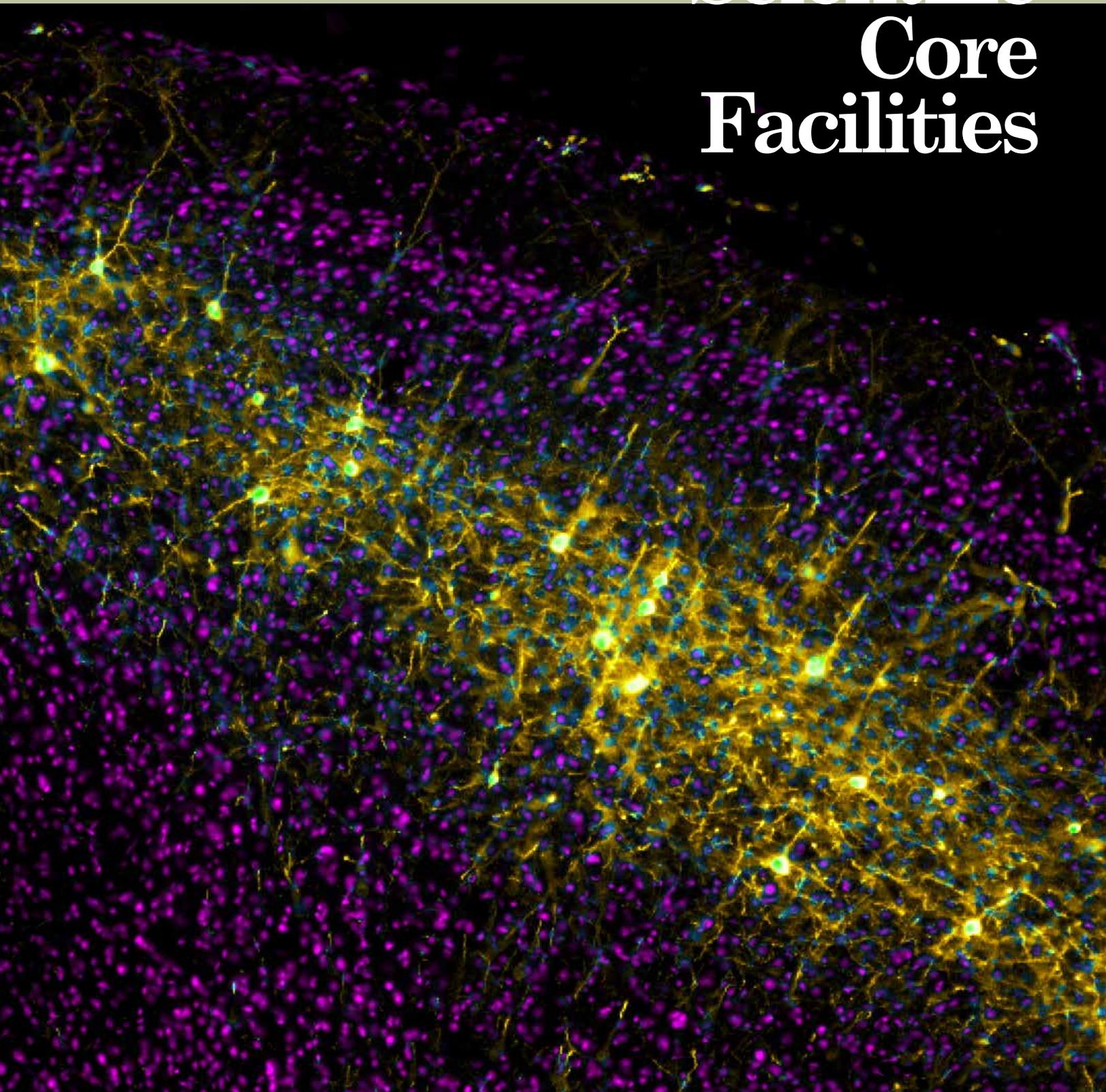
#### **Core Directors**

Rusty Gage

Kuo-Fen Lee

Paul Sawchenko

# Scientific Core Facilities





## Scientific Core Facilities Senior Director's Office

W. Travis Berggren, Senior Director



The Salk Institute's unique scientific core facilities provide faculty, researchers and students with an array of specialized equipment, technologies and services to support the Institute's innovative research. Thirteen cores operate under the senior director of scientific core facilities as shared resources, offering a wide variety of services, instruments and technologies critical for advancing the pace of discovery in biological research. Each core typically offers unique or high-end instrumentation and equipment that is most effectively shared by users from multiple labs.

The senior director's office provides general management and oversight for administrative, scientific, budgetary and personnel matters for all the scientific core research facilities at the Salk Institute. The senior director focuses on long-term strategic planning and initiating new core facilities when needed, and merging or decommissioning core resources when necessary. This office is a key liaison with the faculty to assure that core resources meet current needs and evolve with the rapid pace of scientific discovery at the Institute.

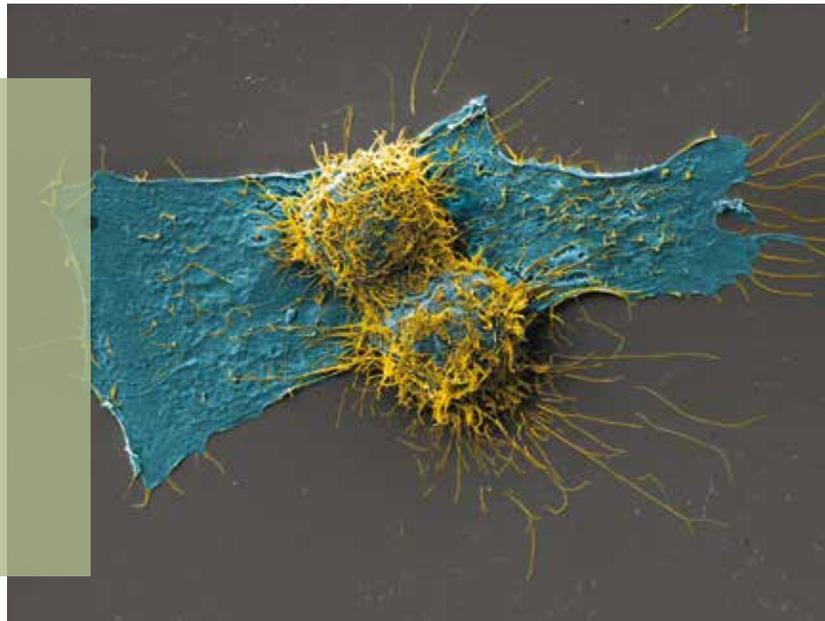
Each core has its own director, assistant director or manager who serves as the technical lead for planning, implementation and maintenance of their core resources. Directors oversee staff and day-to-day operations within their cores. They provide scientific consultations and engage in teaching, training and outreach to scientific and lay audiences with a focus on promoting their technologies and services to the benefit of Salk researchers. All of the core facilities operate on a recharge or fee-for-service basis, but they all offer highly subsidized rates as a result of federal, state and private philanthropic grant and gift support. The Salk Institute has made major commitments to advancing these facilities, and their continued success is critical to maintaining the highest quality of biological research.

**For more information, please visit:**  
<http://www.salk.edu/cores>



# Waitt Advanced Biophotonics Center Core

W. Travis Berggren, Interim Director  
Martin Hetzer, Faculty Advisor



The Waitt Advanced Biophotonics Center Core promotes the integration of state-of-the-art imaging technologies into the biological research programs at the Salk Institute. The facility allows scientists to visualize biological phenomena at multiple length and time scales, from the movements of single molecules to the development of whole organisms.

The core director and staff currently provide access and technical support to nearly all Salk faculty labs and have served more than 450 postdoctoral and graduate student trainees. Examples of tools available for use are fluorescence microscopy, confocal microscopy, live cell microscopy, TIRF microscopy, two-photon microscopy, super-resolution microscopy, slide scanning microscopy, laser capture microdissection, transmission electron microscopy, cryo-transmission electron microscopy, scanning electron microscopy and serial block face-scanning electron microscopy. The core operates a BSL-2-capable tissue culture facility to enable Salk researchers to conduct long-term, live-cell imaging projects as well as a fully equipped sample preparation suite for electron microscopy sample generation.

Recognizing that large amounts of data are collected during imaging experiments, the core provides advanced data analysis and storage services. The facility operates a data analysis suite that allows researchers to perform sophisticated three-dimensional modeling using imaging data. The core provides access to data storage for all Salk researchers. Current distribution is around 900 terabytes. In addition, the core operates a computational cluster for large-scale data analysis applications.

The facility is convenient for all Salk researchers to undertake a variety of multi-scale imaging experiments in close proximity to their own research space. The core operates on a recharge basis that is subsidized by support from the Waitt Foundation, the National Cancer Institute and the National Institute for Neurological Disorders and Stroke.

**For more information, please visit:**  
[bpho.salk.edu](http://bpho.salk.edu)



# Behavior Testing Core

Catherine Borna Farrokhi, Director  
Rusty Gage, Faculty Advisor



Standardized behavioral testing in medical research significantly improves the translation of animal models to human conditions and better predicts treatment outcome. Mice have become the fundamental tool in drug discovery and the study of human disease due to their availability and remarkable biological similarity to humans. The Behavior Testing Core provides a centralized resource for investigators who have isolated genetic or potential therapeutic targets, transposed them into a rodent model and require neurobehavioral testing to support the viability of their target.

The Behavior Testing Core integrates standardized procedures and innovative technology to assess mouse sensory, motor, cognitive and complex behaviors. **Sensory** function is characterized by targeting specific sensory modalities such as vision and somatosensation. **Motor** function is characterized by assessing movement and coordination using tests that target gait and kinematics. **Cognitive** tests utilize measures that target representations of learning and memory formed through sensory (i.e., sight, sound, smell), spatial or emotion-based associations. **Complex** behavioral responses to pleasure, social interest and fear exist in all mammalian species and are used in screening therapeutic targets to treat depression, anxiety and addiction, as well as understanding developmental disorders such as autism.

Monitoring changes in these behaviors is a fundamental tool in modeling human neuropsychiatric conditions, neurodegenerative disease, congenital defects or injuries to the spine, brain or peripheral nervous system. The core provides broad range behavioral phenotyping for characterizing novel transgenic and knockout mouse lines and helps determine efficacy of targeted gene, immune, vaccine, stem cell and drug therapies. Neurobehavioral test results can also be used to satisfy FDA requirements for moving from preclinical testing to filing an Investigational New Drug application. Since opening in 2012, the Behavior Testing Core has provided neurobehavioral testing for dozens of studies including autism, Alzheimer's, Parkinson's and ALS models.

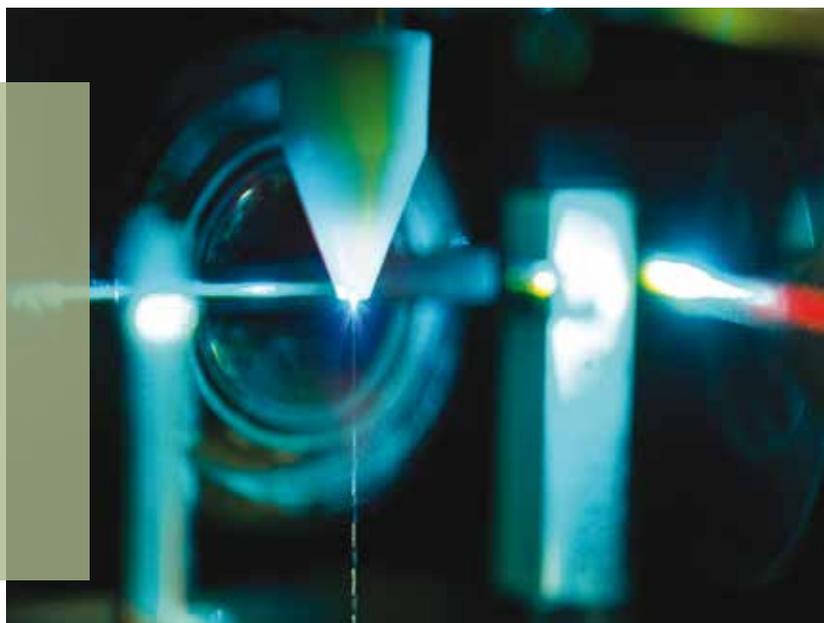
Testing is conducted by core staff, or training is offered for independent use of facility resources. The Behavior Testing Core is part of the Salk Institute Neuroscience Core Center supported by the National Institute of Neurological Disorders and Stroke. It is open to all investigators within the Salk community on a nominal recharge basis.

**For more information, please visit:**  
[btc.salk.edu](http://btc.salk.edu)



# Flow Cytometry Core

Carolyn O'Connor, Assistant Director  
Ye Zheng, Faculty Advisor



Flow cytometry may be used to analyze large numbers of cells or particles in a short time with the further option of isolating populations of interest. The arsenal of available fluorescent probes—such as dyes, labeled antibodies and fluorescent reporter proteins—allows researchers to interrogate a diverse variety of biological processes, including cell cycle, apoptosis, proliferation and expression of surface and intracellular proteins.

The facility offers training and services on three analytical flow cytometers including: LSRII (5 lasers and 15 fluorescence detectors); Canto II (3 lasers and 8 fluorescence detectors); and FACScan (1 laser and 3 fluorescence detectors).

The Flow Cytometry Core facility is also equipped with two instruments and expert staff to perform cell sorting on live or fixed cells using the following: Influx (5 lasers and 11 fluorescence detectors); and FACS Vantage SE DiVA (3 lasers and 8 fluorescence detectors).

Cells retrieved from a heterogeneous sample may be used for subsequent analyses or may be further expanded in culture. Up to six distinct populations can be isolated simultaneously from a sample into separate tubes or target populations may be deposited into a variety of multi-well plate formats.

This core operates on a recharge basis and with support from the National Cancer Institute.

**For more information, please visit:**  
[fccf.salk.edu](http://fccf.salk.edu)



# Functional Genomics Core

Ling Ouyang, Manager  
Satchidananda Panda, Faculty Advisor



The overall objective of the Functional Genomics Core is to provide Salk researchers access to high-quality gene expression analysis services and expertise in a timely, affordable manner. The services offered include the following:

## Gene expression analysis

The Functional Genomics Core provides instrumentation and expertise for RNA transcript profiling. DNA microarrays provide a highly parallel means of measuring the abundance of RNA for targeted genes in a biological sample. The facility supports oligonucleotide arrays synthesized by Affymetrix, Inc.

## SNP genotyping

The core offers single-nucleotide polymorphism (SNP) genotyping service using Affymetrix Genechip technology and Applied Biosystems real-time polymerase chain reaction (PCR) instruments.

## Qualitative and quantitative analysis of DNA, protein, and RNA samples

The core utilizes the Agilent 2100 Bioanalyzer, which is a microfluidics-based platform to support the use of the quantitative

and qualitative analysis of DNA, RNA and proteins. The results are shown in gel-like images, electropherograms and tabular formats.

## Quantitative PCR

The core relies on the ABI PRISM® 7900HT Sequence Detection System to offer reliable real-time detection of PCR. It uses fluorescent primers and probes (Taqman) or Sybr green to quantify the accumulation of nucleic acid sequences.

In addition, the Functional Genomics Core offers an automated mini-prep service for rapid handling of DNA samples—a cost-effective and convenient way for laboratories to analyze large numbers of samples.

This core is in the process of merging with the Next Generation Sequencing Core to provide enhanced functional genomic services to the Salk research community. This core operates on a recharge basis and with support from the National Cancer Institute.

**For more information, please visit:**  
[fgl.salk.edu](http://fgl.salk.edu)



# Genome Manipulation Core

Tsung-Chang Sung, Staff Researcher  
Kuo-Fen Lee, Faculty Advisor



Neuroscientists and other Salk researchers are increasingly focused on the links between genes and behavior, exploring how genetics play a role in brain development, structure and function, which ultimately manifest in traits of behavior. The Genome Manipulation Core helps scientists develop genetically modified mice and mouse cells to perform studies that will provide insight into human neurologic diseases such as autism, Parkinson's and Alzheimer's, among others.

The Genome Manipulation Core provides services to generate homologous, recombination-based gene targeted mouse embryonic stem (mES) cell lines for making genetically altered mouse models. The core's personnel consult with Salk researchers to design and construct targeting vectors for generating conventional and conditional knockout mouse models and conduct gene targeting in mES cells. The core also generates multiple-drug resistant mouse embryonic fibroblast (mEF) cells for mES cell culture, provides genomic DNA for screening targeted mES cell

clones, provides mES cell culture reagents, expands mES cell lines for investigators and establishes new mES cell lines from wild-type and mutant mouse lines.

The Institute ensures that all employees dealing with the animals understand their individual and collective duty and embrace their ethical obligation to provide the highest level of care, conforming to all relevant regulations and rules concerning laboratory animal husbandry. The use of mice by the Genome Manipulation Core is overseen by the Institutional Animal Care and Use Committee (IACUC).

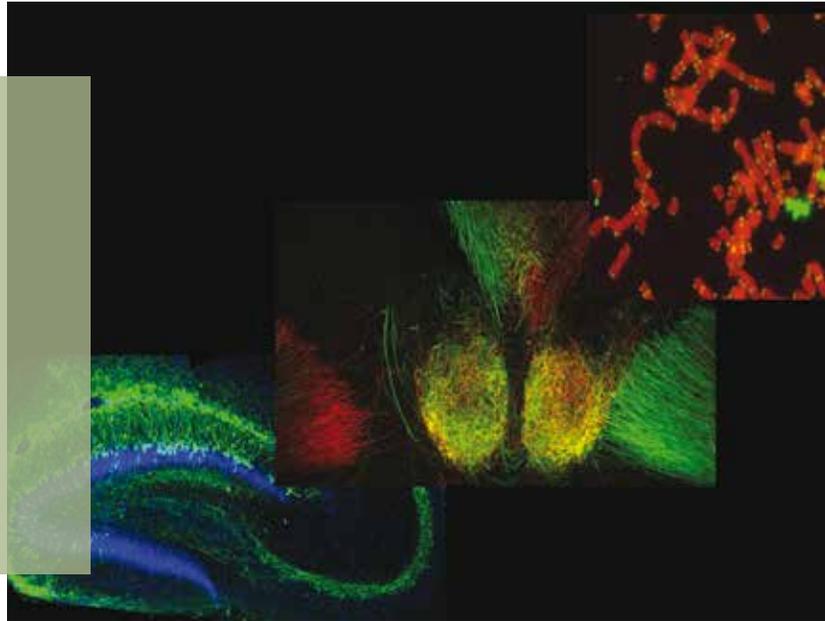
The Genome Manipulation Core operates on a recharge basis and with support from the National Institute of Neurological Disorders and Stroke.

**For more information, please visit:**  
[gm-core.salk.edu](http://gm-core.salk.edu)



# Gene Transfer, Targeting and Therapeutics Core

Leszek Lisowski, Director  
Edward Callaway, Faculty Advisor



Recombinant viral vectors are now the method of choice for targeted, rapid and regulated gene delivery in many experimental systems. This technology allows scientists to control genetic activity in cells and in animals to better understand fundamental cellular functions and the molecular underpinnings of disease. The Gene Transfer, Targeting and Therapeutics Core (GT3) was established at the Salk Institute in 2008 with National Institutes of Health funding to provide researchers at Salk and other institutions with a resource for developing and producing viral vectors and other gene transfer systems. The facility specializes in the design, development and production of high-quality *in vitro* and *in vivo* grade recombinant viral and nonviral mini-intronic plasmid vectors. The GT3 core offers convenient, ready-to-use stocks, as well as custom vector preparations including lentiviral, retroviral, adeno-viral, adeno-associated viral, vesicular stomatitis viral and rabies vaccine-based vectors. In addition, GT3 has initiated a DNA Clone Bank, which is available at no cost to Salk investigators as a resource for ready-to-package viral vector constructs and/or plasmids for cloning purposes.

The GT3 core is housed in the cross-institutional Sanford Consortium for Regenerative Medicine building and acts as a central resource for gene transfer technology. Core staff work closely with investigators to provide expert guidance, consultation and hands-on training in the use of viral vectors, from initial consultation and experimental design to the production and development of new viral constructs, as well as the production and validation of stock and custom viral vectors. In conjunction with the Salk Stem Cell Core, GT3 also produces and distributes functionally validated, off-the-shelf induced pluripotent stem cell (iPSC) reprogramming vectors based on retroviral and lentiviral systems, and customized vectors for *in vivo* and *in vitro* genome editing.

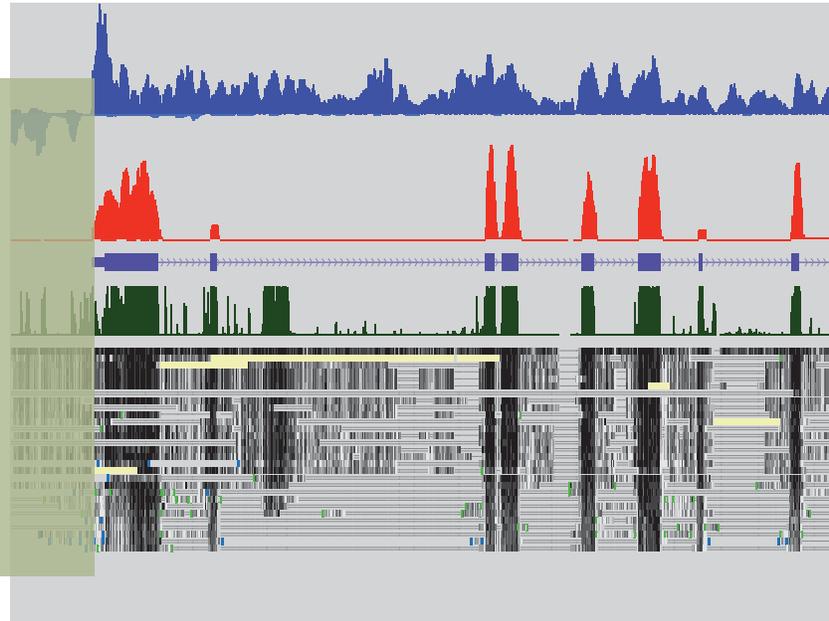
This core operates on a recharge basis and with support from the National Cancer Institute, National Eye Institute and National Institute on Aging.

**For more information, please visit:**  
[vectorcore.salk.edu](http://vectorcore.salk.edu)



# Integrative Genomics and Bioinformatics Core

Chris Benner, Founding Director  
Ronald Evans, Faculty Advisor



The Integrative Genomics and Bioinformatics Core supports genomics research efforts at Salk. New technologies are shifting the scope of biological research from single genes to whole genomes. Most notably, next-generation sequencing has enabled a variety of new genome-scale assays, allowing researchers to map inheritable chemical changes to DNA, known as the epigenome, discover genetic variants driving disease, and even measure RNA profiles from single cells. The core provides expertise in the design and analysis of these types of experiments and assists Salk laboratories in leveraging the data generated by these assays.

The mission of the Integrative Genomics and Bioinformatics Core is three-fold. First, the core provides assistance and resources for the primary analysis of next-generation sequencing data. This includes the use of supercomputers to analyze and store terabytes of sequence data. Raw data is processed and normalized to provide biologically meaningful measurements depending on the type of experiment, such as gene expression levels or binding sites for proteins that regulate DNA transcription.

The core's second purpose is to drive the development of cutting-edge analysis techniques. The core develops novel algorithms and software programs to help groups analyze their data. This work encompasses the integration of different types of genomics data, such as linking genetic mutations to the molecular pathways and epigenetic changes involved in disease.

Finally, the core educates Salk researchers about genomics analysis through workshops and individualized training. The field of genomics is rapidly expanding, touching every area of research from plant biology to personalized medicine. By better educating Salk scientists, these technologies can be leveraged for the greatest possible impact.

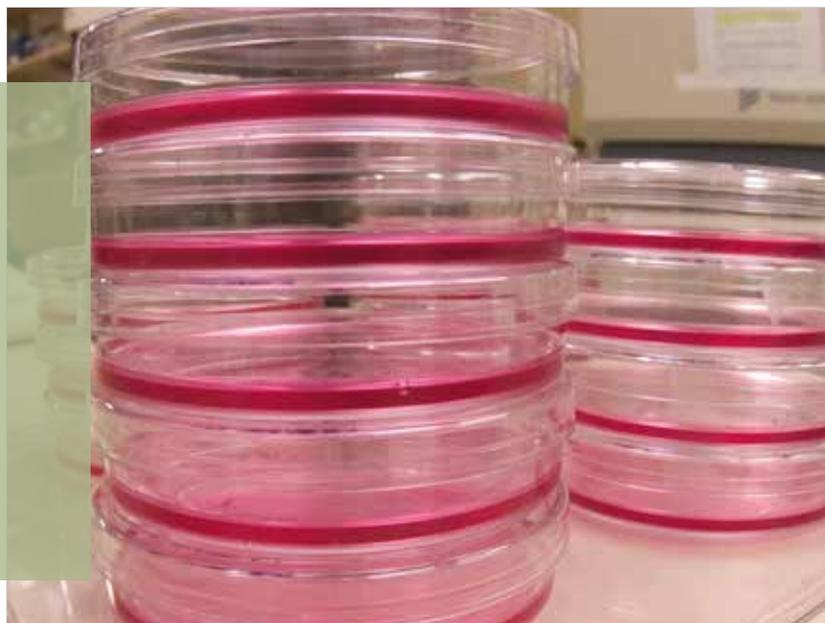
The Integrative Genomics and Bioinformatics Core is part of the Salk Institute's Integrative Genomics Center. It operates on a recharge basis and with support from the Leona M. and Harry B. Helmsley Charitable Trust and the National Cancer Institute.

**For more information, please visit:**  
[igc.salk.edu](http://igc.salk.edu)



# Media Preparation Core

Rebecca Bassett, Core Manager



The Media Preparation Core Facility was formed to support Salk scientists with media, plates and commonly used buffers for molecular biology applications and for culturing mammalian cells, *C. elegans*, yeast and bacteria. In addition to maintaining a “grab and go” supply center for common reagents, the Media Preparation Core excels at producing specialized media and reagents.

This core is set up to produce large volumes of commonly used agar plates, liquid broth and media, and tissue culture buffers. Orders up to 40 liters of liquid media may be processed at one time, while three automatic plate pourers supported by two programmable media kettles are capable of producing up to nine liters of agar or nutrient media per run under gentle and

reproducible conditions. All media are checked for sterility before, during and after preparation to ensure that laboratories receive reliable products. Meeting the individual needs of each user is considered essential.

The Media Preparation Core is conveniently located in the East Building on the Salk campus and is available to all investigators within the Salk community. The core operates on a recharge basis.

**For more information, please visit:**  
**[mediaprep.salk.edu](http://mediaprep.salk.edu)**



# Peptide Synthesis Core

Jill Meisenhelder, Manager  
Tony Hunter, Faculty Advisor



The current peptide synthesizer, a Tribute model with real-time UV monitoring from Protein Technologies, was purchased in June 2013 and is operated by core manager Jill Meisenhelder, whose role has expanded to include providing advice on the design of peptides and protocols in which they will be used. She arranges for the purification of the crude peptides and their analysis by mass spectrometry in the proteomics facility, and evaluates the results to gauge the fidelity of the synthesis.

Peptides synthesized by the facility are frequently utilized for developing antibodies that can be used for immunoprecipitation or immunoblotting. Synthetic peptides are also used to identify regions of protein-protein interactions by testing whether peptides representing defined regions of a protein can either interact with other cellular proteins or block the interaction between two full-length proteins. In addition, they are used in biological assays to

stimulate cells or receptors on the cell surface or, by adding a short sequence of positively charged amino acids to the sequence of interest, can be delivered directly into cells. Hydrophobic peptides that readily form aggregates, such as those found in the brains of Alzheimer's patients, have been used for structural studies.

During a typical year, more than 80 peptides are synthesized, including phosphopeptides, peptides with chemical modifications such as acetylation or biotinylation, and peptides incorporating specially derivatized amino acids to control peptide folding.

This core operates on a recharge basis and with support from the National Cancer Institute.

**For more information, please visit:**  
**[peptide.salk.edu](http://peptide.salk.edu)**



# Mass Spectrometry Core for Proteomics and Metabolomics

James Moresco, Director  
Jolene Diedrich, Associate Director

Alan Saghatelian, Faculty Advisor  
John Yates III, Adjunct Faculty Advisor



The role of the Mass Spectrometry Core is to provide access and services involving state-of-the-art instrumentation and techniques for analyzing targeted and complex mixtures of proteins and small molecules (metabolites). Within a cell, tissue or organism, it is the proteins and small molecules that are the building blocks, workhorses and functional molecules that carry out the instructions from the genome. In healthy cells and tissues, it is these proteins and metabolites that keep biological processes functioning properly. In disease states, proteomic and metabolomics studies can give new and meaningful insight into the mechanisms of what went wrong.

The Mass Spectrometry Core was renovated in 2015 to add new instrumentation and personnel in order to offer the latest in proteomics analysis by mass spectrometry to Salk

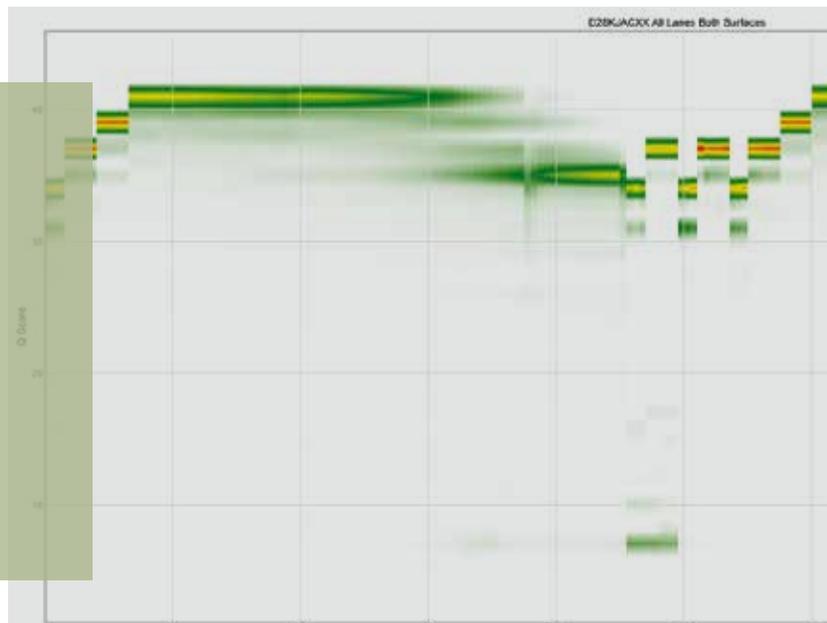
researchers. A fully equipped new Orbitrap Fusion™ Tribrid™ Mass Spectrometer has been added, along with a state-of-the-art Q-Exactive benchtop Orbitrap-MS. The core also houses a Thermo LTQ-Orbitrap XL to provide additional analytical capacities. The core is adding additional experienced personnel to offer the latest expertise in qualitative and quantitative mass spectrometry-based proteomics. The core is also looking to expand the offering of metabolomics analysis services via the new LC-Triple Quad MS (TSQ). The core operates on a recharge basis and with support from the Leona M. and Harry B. Helmsley Charitable Trust and the National Cancer Institute.

**For more information, please visit:**  
[massspec.salk.edu](http://massspec.salk.edu)



# Next Generation Sequencing Core

Manching (MC) Ku, Director  
Inder Verma, Faculty Advisor



Next Generation Sequencing (NGS) is a revolutionary tool that allows studies of unprecedented breadth and depth and enables a wide variety of innovative approaches in all branches of biology and medicine. These range from sequencing an individual's genome and identifying genomic regions associated with disease to studying how the genome functions in a single cell and novel high-throughput drug screens.

The NGS Core was created to meet Salk researchers' needs for high-throughput sequencing. With an Illumina HiSeq 2500 and an Illumina NextSeq 500, the core is equipped for high-volume and rapid turnaround experiments. The core offers low-cost, high-quality library preparation services for standard assays including whole genome and RNA sequencing (RNA-Seq), exome capture and chromatin immunoprecipitation sequencing (ChIP-Seq). In addition, the core provides access to cutting-edge equipment required for sequencing-based assays.

To help Salk scientists best take advantage of sequencing in their research, the NGS Core staff provides training, technical support and scientific consultation on sequencing-based methodology. This includes advice on assay choice, experimental design,

participation in grant writing, and collaboration on establishing and developing sequencing-based methods. To this end, the NGS Core team brings years of experience in epigenomics, genome biology and method development to Salk and serves as a knowledge platform for NGS applications within the Institute.

High-throughput sequencing experiments generate massive amounts of data, shifting much of the scientific work from the experiment to data analysis and interpretation. To help tackle this bottleneck, the NGS Core works closely with Salk's Integrative Genomics and Bioinformatics Core to offer seamless integration of sequencing, data analysis and interpretation to Salk scientists.

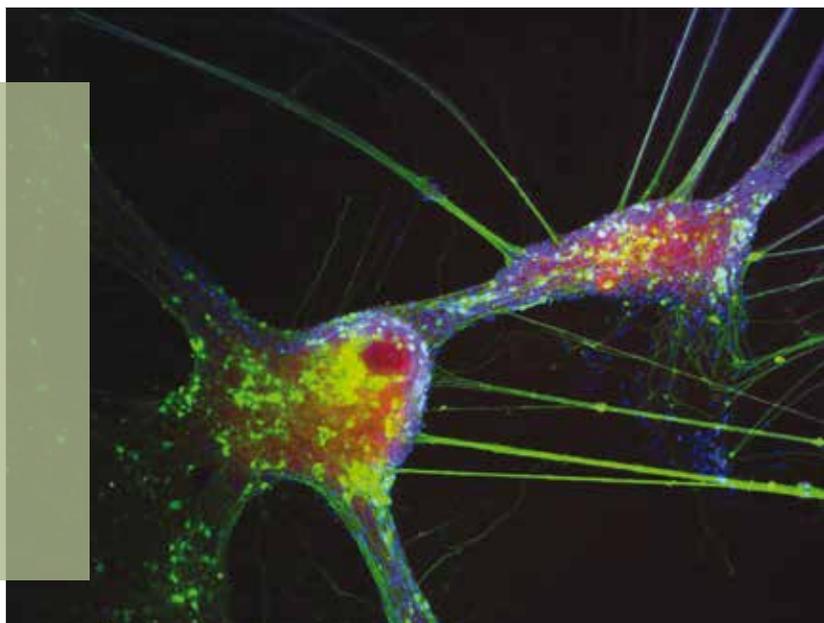
The NGS Core was founded in 2013 with grants from the Leona M. and Harry B. Helmsley Charitable Trust and the H.A. and Mary K. Chapman Charitable Foundations. It operates on a recharge basis that is supplemented by support from the Leona M. and Harry B. Helmsley Charitable Trust.

**For more information, please visit:**  
[ngs.salk.edu](http://ngs.salk.edu)



## Stem Cell Core

Leah Boyer, Director  
Inder Verma, Faculty Advisor



The Stem Cell Core is a multi-user shared research facility dedicated to supporting work involving human stem cells at the Salk Institute. The core is tailored for Salk scientists to perform studies involving existing human pluripotent stem cell lines and to support the derivation of newly reprogrammed ones. The core characterizes, banks and distributes pluripotent stem cells, including human embryonic and induced pluripotent stem (iPS) cells.

The facility is located on the Salk campus, making it convenient for researchers to drop in while staying within easy reach of their laboratories. This core was designed to enhance most effective stem cell culture practices—including the segregation of tissue culture spaces into separate suites—to allow for flexibility for new research projects and cell lines while protecting the existing ones from external contamination. The core has all the requisite equipment and resources for successful stem cell culture, including three cell culture rooms, benchtop research space, a microscopy suite and cryo-preservation equipment.

Salk scientists use the core's reprogramming resources for biomedical studies that involve turning a patient's skin, blood

or fat cells into iPS cells. These reprogrammed stem cells now have the potential to be coaxed into mature cells including, most importantly, those involved in diseases being studied. This methodology is so powerful because the cells retain the same genetic information that may have led to disease, allowing researchers to generate models of human diseases in a laboratory dish.

In addition to providing all the cells, reagents and equipment necessary for human stem cell research, the core staff provides individualized training in proven techniques for successfully culturing these cells. Since its creation in 2008, the core has trained over 200 Salk researchers in pluripotent cell culture. Staff is also available for consultation on experimental design and collaboration with execution. The core's goal is to accelerate the pace of human stem cell research at the Salk Institute.

The Stem Cell Core operates on a recharge basis and with support from the Leona M. and Harry B. Helmsley Charitable Trust.

**For more information, please visit:**  
**[stem.salk.edu](http://stem.salk.edu)**



# Transgenic Core

Yelena Dayn, Director  
Kuo-Fen Lee, Faculty Advisor



Transgenic and knockout mouse models have become an integral part of the research programs at the Salk Institute. The Transgenic Core is dedicated to providing access to cutting-edge technologies to create these models. Core services include microinjection of DNA constructs into one-cell stage embryos, microinjection of gene targeted mouse embryonic stem cells into blastocysts, CRISPR gene editing, lentiviral transductions, in vitro fertilization (IVF), cryopreservation and rederivation of mouse lines.

The Transgenic Core develops and implements new techniques and applications, provides immediate access to individuals with knowledge of dealing with transgenic mice, and offers the potential for research collaborations. More than 100 publications have been based on genetically altered mouse lines created by the Transgenic Core since its inception in 1994.

This core is located within a pathogen-free barrier facility in which only animals from select vendor sources are allowed. It maintains a mouse colony in four holding rooms adjacent to six procedure rooms. The Institute ensures that all employees dealing with the animals understand their individual and collective duty and embrace their ethical obligation to provide the highest level of care, conforming to all relevant regulations and rules concerning laboratory animal husbandry. The activities of the Transgenic Core are overseen by the Institutional Animal Care and Use Committee (IACUC).

The Transgenic Core operates on a recharge basis and with support from the National Cancer Institute.

**For more information, please visit:**  
[tg-core.salk.edu](http://tg-core.salk.edu)



# Faculty and Staff Scientists 2015/2016

## **ACADEMIC COUNCIL**

Beverly Emerson, PhD  
Chair  
Professor  
Regulatory Biology Laboratory  
Edwin K. Hunter Chair

Edward Callaway, PhD  
Chair-Elect  
Professor  
Systems Neurobiology Laboratories  
Audrey Geisel Chair in Biomedical  
Science

Greg Lemke, PhD  
Past-Chair  
Professor  
Molecular Neurobiology Laboratory  
Françoise Gilot-Salk Chair

Sreekanth Chalasani, PhD  
Joseph Ecker, PhD  
Julie Law, PhD  
Samuel Pfaff, PhD  
John Reynolds, PhD  
Alan Saghatelian, PhD  
Tatyana Sharpee, PhD

## **FACULTY**

### **President**

William Brody, MD, PhD

### **Distinguished Professors**

Sydney Brenner, PhD  
Roger Guillemin, MD, PhD

### **Professor Emeritus**

Suzanne Bourgeois, PhD  
Melvin Cohn, PhD  
Walter Eckhart, PhD  
Catherine Rivier, PhD  
Jean Rivier, PhD

## **Professors**

Thomas Albright, PhD  
Ursula Bellugi, PhD  
Edward Callaway, PhD  
Joanne Chory, PhD  
Joseph Ecker, PhD  
Beverly Emerson, PhD  
Ronald Evans, PhD  
Rusty Gage, PhD  
Martyn Goulding, PhD  
Martin Hetzer, PhD  
Tony Hunter, PhD  
Juan Carlos Izpisua Belmonte, PhD  
Katherine Jones, PhD  
Jan Karlseder, PhD  
Christopher Kintner, PhD  
Kuo-Fen Lee, PhD  
Greg Lemke, PhD  
Vicki Lundblad, PhD  
Marc Montminy, MD, PhD  
Joseph Noel, PhD  
Dennis O'Leary, PhD  
Samuel Pfaff, PhD  
John Reynolds, PhD  
Alan Saghatelian, PhD  
Paul Sawchenko, PhD  
David Schubert, PhD  
Terrence Sejnowski, PhD  
Reuben Shaw, PhD  
Charles Stevens, PhD  
John Thomas, PhD  
Inder Verma, PhD  
Geoffrey Wahl, PhD

## **Associate Professors**

Clodagh O'Shea, PhD  
Satchidananda Panda, PhD  
Tatyana Sharpee, PhD

## **Assistant Professors**

Nicola Allen, PhD  
Kenta Asahina, PhD  
Janelle Ayres, PhD  
Hu Cang, PhD

Sreekanth Chalasani, PhD  
Diana Hargreaves, PhD  
Xin Jin, PhD  
Julie Law, PhD  
Björn Lillemeier, PhD  
Graham McVicker, PhD  
Saket Navlakha, PhD  
Axel Nimmerjahn, PhD  
Ye Zheng, PhD

## **SENIOR STAFF SCIENTISTS**

W. Travis Berggren, PhD  
Michael Downes, PhD  
Wolfgang Fischer, PhD  
Pamela Maher, PhD  
Carol Marchetto, PhD  
Jon Reuter, PhD  
Gene Stoner, PhD

## **STAFF SCIENTISTS**

Ge Bai, PhD  
Margarita Behrens, PhD  
Christopher Benner, PhD  
Louise Bilezikjian, PhD  
Catherine Farrokhi, PhD  
Sergei Gepshtein, PhD  
Peter Gray, PhD  
Manoj Hariharan, PhD  
Sven Heinz, PhD  
Manching Ku, PhD  
Mathias Leblanc, PhD  
Soon Lee, PhD  
Leszek Lisowski, PhD  
Fernando Lopez-Diaz, PhD  
Inigo Narvaiza, PhD  
Mike Nunn, PhD  
Gerald Pao, PhD  
Marilyn Perrin, PhD  
Benjamin Spike, PhD  
Huaiyu Sun, PhD  
Jesse Woodson, PhD  
Shingo Yoshikawa, PhD  
Quan Zhu, PhD

# Salk Non-Resident Fellows

Non-resident fellows partner with the research faculty to shape Institute research policy, although their primary responsibilities are at research institutions throughout the world.

**David Baltimore, PhD**

Nobel Laureate, 1975  
President Emeritus  
California Institute of Technology

**Elizabeth Blackburn, PhD**

Nobel Laureate, 2009  
Professor, Department of Biochemistry and Biophysics  
University of California, San Francisco

**Caroline Dean, PhD**

Professor and Project Leader, Department of Cell & Developmental Biology  
John Innes Centre

**Jack Dixon, PhD**

Associate Vice Chancellor, Scientific Affairs  
University of California, San Diego

**Thomas Jessell, PhD**

Howard Hughes Medical Institute  
Professor, Departments of Neuroscience, Biochemistry and Molecular Biophysics  
Columbia University Medical Center

**Eric Lander, PhD**

President and Director, Broad Institute of Harvard and MIT  
Professor of Biology, MIT  
Professor of Systems Biology, Harvard Medical School

**Jennifer Lippincott-Schwartz, PhD**

Bethesda, Maryland

**Anthony Movshon, PhD**

University Professor, Silver Professor, and Director, Center for Neural Science  
New York University

**Carla Shatz, PhD**

Professor of Biology and Neurobiology Director, BioX at the James Clark Center  
Stanford University

**Irving Weissman, MD**

Director, Institute of Stem Cell Biology and Regenerative Medicine Stanford University School of Medicine



# Honors

Elections to the National Academies of Sciences, Medicine or Engineering are considered one of the highest honors accorded a U.S. scientist.

## **National Academy of Sciences**

Thomas Albright  
2008

Ursula Bellugi  
2007

Sydney Brenner  
1977

Joanne Chory  
1999

Joseph Ecker  
2006

Ronald Evans  
1989

Rusty Gage  
2003

Roger Guillemin  
1974

Vicki Lundblad  
2015

Tony Hunter  
1998

Marc Montminy  
2009

Terrence Sejnowski  
2010

Charles Stevens  
1982

Inder Verma  
1997

## **National Academy of Medicine**

Sydney Brenner  
2010

William Brody  
1992

Ronald Evans  
2003

Rusty Gage  
2001

Tony Hunter  
2004

Terrence Sejnowski  
2008

Inder Verma  
1999

## **National Academy of Engineering**

William Brody  
2007

Terrence Sejnowski  
2011

**Rebecca Newman**

Vice President,  
External Relations

**Anna-Marie Rooney**

Chief Communications Officer

**Christopher Emery**

Director of Scientific Communications  
and Media Relations

**Kristina Grifantini**

Science Writer

**Liz Hincks**

Director of Electronic and Graphics  
Communications

**John McDonagh**

Web Developer

**Joe Belcovson**

Photographer

**Máximo Escobedo**

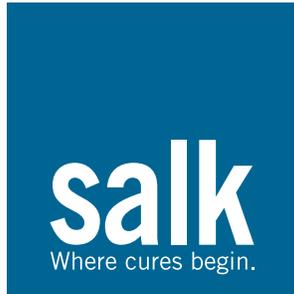
Senior Designer

**Sara Jacobsen**

Graphic Communications Specialist

**Care Dipping**

Communications Coordinator



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