Cover: A microscope image of a mammary bud in a mouse at about 15 days of embryogenesis. Image courtesy of Dannielle Ergle and Geoff M. Wahl.
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Jonas Salk changed the world. Inspired to rid civilization of polio, he used basic science to solve its mysteries and in the process helped alter the course of the 20th century along with the future of science, medicine and human health. Untold millions have benefited from his work.

It’s the same inspiration that drives us today at the Salk Institute. Created to attract the best scientific minds in the world, we’ve built on his vision to become a leading center for independent research into the most serious biological questions of our time.

It’s this “critical mass of intellect,” embracing the most modern technologies and prizing discovery over credit, which distinguishes Salk. This results in some of the world’s most breathtaking discoveries, which advance our understanding of diseases and lead the way to successful preventions, therapeutics and cures.

As we celebrate the accomplishments of our current scientists, we are laying the groundwork for a bright future by appointing five new faculty: Nicola Allen and Xin Jin, in the Molecular Neurobiology Laboratory; Hu Cang, in the Waitt Advanced Biophotonics Center; Janelle Ayres, in the Nomis Foundation Laboratories for Immunobiology and Microbial Pathogenesis; and Julie Law, in the Plant Biology Laboratory.

These promising young scientists and the other remarkable Salk faculty highlighted in the following pages are using advances in genomics, stem cells, imaging tools, bioinformatics and disease modeling to integrate their research and delve more deeply than ever into the extraordinary complexity of living organisms.

The Institute is embarking on its first-ever capital campaign to support them in revolutionizing biomedical research, providing them with powerful technologies, exemplary new colleagues and support for creative research projects. The campaign will focus on four major scientific initiatives—Cancer, Dynamic Brain, Genomic Medicine and Healthy Aging—areas where investment promises to produce tremendous results in conquering disease.

Through our visionary supporters, who understand the importance of basic research to developing cures, the campaign will build on Jonas Salk’s legacy, creating a healthier future with the bold science for which the Salk Institute is known.

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

Marsha Chandler, Ph.D.  
Executive Vice President
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 The 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 (M.D.) from Stanford University. He continued his post-graduate 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, 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 Donner Professor and director of the department 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 The 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 Institute 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 member of the policy-making Scientific Management Review Board of the National Institutes of Health and 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 (C. 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 working on 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, CA, 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.
Considered the founder of the field of neuroendocrinology, Roger Guillemin, M.D., Ph.D., 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 medical school in 1949, then pursued an interest in endocrinology at the University of Montreal's Institute of Experimental Medicine and Surgery, receiving his Ph.D. 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 Medicine or Physiology 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.
“Light reflected from objects in the environment projects onto the retinal surface, resulting in intricate and dynamic patterns of brightness and color. Human observers interpret these images, nearly instantaneously and generally without awareness, to yield unequivocal and behaviorally informative percepts. Our goal has been to understand the neuronal structures and events that underlie visual perceptual experience and its contributions to knowledge, behavior and consciousness.”

We live in a dynamic environment. Optimal encoding of sensory information requires that sensory systems be continuously tuned to the prevailing environment, much like fine-tuning your car for the current driving conditions. Yet while it is important that sensory information be represented with high fidelity, the brain has only limited resources available. Albright and his team are interested in how neural systems reconcile these conflicting demands in the visual system.

Using their working hypothesis that sensory systems resolve the dilemma by way of compromise, the scientists examined the effects of sensory resource reallocation—a phenomenon commonly known as sensory adaptation—on the perception of visual motion. The initial theoretical work led to predictions about the patterns of perceptual and neuronal change expected in a system that reallocates its resources to dynamically optimize perception in a changing environment. Behavioral studies put these predictions to the test by revealing the perceptual changes induced by adaptation. Physiological studies uncover the neuronal mechanisms of sensory reallocation.

The results reveal that sensory systems enhance the neuronal representation of those aspects of the environment that are frequently encountered and are significant for successful behavior. The enhancement comes at the cost of reduced sensitivity to those stimuli that are less commonly encountered. Specifically, the observed perceptual recalibration is mediated by changes in motion-selective neurons in the visual cortex. Some of the neurons change their sensitivity to particular stimuli and others shift their sensitivity to other stimuli. These findings indicate that the neuronal mechanisms of perception can only be understood by studying how sensitivity is dynamically distributed across neurons tuned to the entire range of visible stimuli.

Taken together, the observations of Albright and his colleagues reveal that sensory processing is markedly adaptable. This adaptability enables us to optimize perception and behavior in a world that presents us with varying sensory demands, caused by changes in the environment, behavioral goals and age-related decline in sensory function.

For more information, please visit www.salk.edu/faculty/albright
Neurons in the brain are connected by billions of synapses, the points of communication between nerve cells. I want to know what controls when and where these synapses are formed, and how synaptic connections are modified to allow memories to be stored.

Allen’s lab investigates the molecular pathways that lead to connections between neurons, known as synapses, in the developing brain. Her group focuses on signaling interactions between neurons and astrocytes, a class of star-shaped glial cells. Astrocytes constitute half of the cells in the brain, and astrocyte processes, the “arms” that project outward from the cells, surround the majority of neuronal synapses. This places them in an ideal location to be actively involved in synapse formation and maintenance and in the modulation of communication between neurons. In fact, in the absence of astrocytes, few functional connections form between developing neurons, while their presence profoundly increases the number of functional synapses.

Previous studies began to identify the molecular signals between neurons and astrocytes and showed that thrombospondins and glypican family proteins secreted from developing astrocytes affect synapse formation. The hypothesis is that astrocytes play a crucial role in dictating synapse formation and function via the release of specific proteins that determine the type of synapse that will form, and the strength of that connection.

The current goal of the lab is to further investigate how these two protein families promote synapse formation, by identifying the neuronal receptors and cellular signaling pathways involved, and to understand how they interact to determine what type of synapse is formed. In addition, they will continue to use biochemical and molecular techniques to identify other ways that astrocytes influence distinct aspects of synapse formation and maturation and how they control the types of connections that develop.

The pathways they identify will be investigated for roles in neurodevelopmental disorders, such as autism, that are caused by defects in synapse formation and function. In future studies, they will explore whether these developmental findings can be used to address diseases such as stroke by promoting the repair of neural connections following injury.

For more information, please visit www.salk.edu/faculty/allen
“A major goal of my laboratory is to understand the defense strategies that enable a host to survive and even thrive when interacting with microbes. Knowledge of these defense mechanisms should lead to new treatments for infectious and inflammatory disease.”

When faced with a microbial threat, such as infectious bacteria or viruses, hosts can utilize two defense strategies to protect their health: resistance and tolerance. Resistance mechanisms allow the host to directly attack microbes to eliminate the infection. Tolerance mechanisms minimize the harm caused by microbes, for example, by neutralizing toxins generated by the pathogen. Ayres provided some of the first evidence that tolerance is crucial for defense against infections in animals. Using fruit flies infected with lethal bacteria, she identified genes and environmental factors, such as diet, that are important for tolerance and, ultimately, survival of infections. Furthermore, she demonstrated that a single gene could influence both resistance and tolerance so that conditions that enhance tolerance against one type of infection also can influence resistance against a different pathogen.

Recently, to identify mechanisms involved in tolerance of bacteria, Ayres turned to the mammalian intestine. Humans and other mammals tolerate the colonization of trillions of bacteria in their intestines, and these communities perform important functions for host physiologies. Within this microbial community live pathobionts, microbial species that can cause disease when homeostasis is disrupted, such as when antibiotics disrupt this complex community. Pathobionts have been implicated in triggering a number of diseases, including Crohn’s, rheumatoid arthritis and sepsis, an inflammatory response to infection that can lead to shock, organ failure and even death.

In studies in mice, Ayres found that antibiotics caused overgrowth of a multi-antibiotic-resistant E. coli pathobiont in the intestine, which spread to the lung and liver following intestinal injury. This triggered hypothermia and multi-organ damage—hallmarks of sepsis. She discovered that infection with this E. coli pathobiont leads to an overly exuberant inflammatory response and sepsis due to inappropriate stimulation of the inflammasome, a component of the body’s innate immune system. Ayres suggests that the inflammasome may be a useful therapeutic target in patients harboring antibiotic-resistant pathobionts.

In the future, Ayres will expand her studies to determine the mechanisms that facilitate tolerance of pathobiont colonization in the intestine under homeostatic conditions. She will also determine how members of the intestinal microbial community influence tolerance of pathogenic infections. Her work will provide a better understanding of host defense against microbes and suggest new therapeutic approaches for treating infectious and inflammatory diseases.

For more information, please visit [www.salk.edu/faculty/ayres](http://www.salk.edu/faculty/ayres)
Ursula Bellugi
Professor and Director
Laboratory for Cognitive Neuroscience

“Williams syndrome is a perfect example of a genetic predisposition interacting with the environment to sculpt the brain in unique ways. It provides an exceptional window for understanding how a few missing genes and the resulting changes in brain structure and function ultimately shape behavior.”

To children with Williams syndrome, people are much more comprehensible than inanimate objects. Despite myriad health problems, generally low IQs and high levels of anxiety, they are extremely gregarious and irresistibly drawn to strangers, and they insist on making eye contact. This strange mix of mental peaks and valleys allows Ursula Bellugi and her collaborators to untangle the connections between genes, brain function and prosocial behavior.

In 2011, Bellugi and her collaborators, including Salk professors Fred Gage and Terrence Sejnowski and Salk adjunct professor Julie Korenberg, were awarded a renewal of an NIH program project grant to link the unusual prosocial behavior typified by the condition to its underlying neurobiological and molecular genetic basis. The researchers work in such disparate fields as social cognition, molecular genetics, stem cell biology, neuronal architecture and neuroimaging and are tackling the disorder from several directions.

Williams syndrome is caused by the absence of a tiny set of genes on one copy of chromosome 7, presenting a strong relationship between genes and altered behaviors. Virtually everyone with Williams syndrome is missing the same genes, but some rare individuals retain one or more genes that most people with the condition have lost, providing clues to the function of those genes and gene networks.

Bellugi and her colleagues are charting how these genetic aberrations may lead to the unusual cognitive and social behaviors characteristic of Williams syndrome. This includes using imaging technologies to visualize how the gene deletions alter brain activity, mapping the neural circuits affected by the disorder, and using stem cell reprogramming techniques to study the cellular aspects of the syndrome in the laboratory with neurons derived from patients’ skin cells. Recently, her team reported that the system that regulates two hormones associated with emotions, oxytocin and vasopressin, appears to be altered in people with Williams syndrome. This link between genes, hormones and behavior is an unprecedented opportunity to study how genes influence social behaviors and their role in Williams and other mental disorders, such as autism and anxiety. Understanding Williams syndrome also may provide fundamental insights into the genetic mechanisms and neural circuits responsible for human social behavior.

For more information, please visit www.salk.edu/faculty/bellugi

From left to right: Yvonne Searcy, Dop Nguyen, Davide Crivelli, Ben Dering, Patricia Fillet, Philip Lai, Lucia Chen, Ursula Bellugi, Wenny Wong, Cindy O’Grady, Minh Nguyen, Michelle Dewitt, Connor Batch, Andy Arnold
“Today we take the Salk Institute and its success for granted. It is edifying—and makes a good story—to explore what it took to get us here and to be what we are: the idea, the people, the circumstances, the location, the building.”

Suzanne Bourgeois
Professor Emeritus and Founding Director
Regulatory Biology Laboratory

After a scientific career researching bacterial cell regulation and gene expression in cancer cells, Bourgeois has turned her attention to the history of science—specifically, the early history of the Salk Institute. Because she was a witness to the Institute’s history since before its inception, Bourgeois is uniquely qualified to bring that story alive. She also had the privilege, while working in New York and Paris in the 1950s and 1960s, of knowing many of the pioneers of molecular biology, several of whom helped establish the Salk Institute. She therefore is completing work on a book-length history of the Salk Institute, which will be a well-documented personal chronicle that is based on extensive research encompassing archival material, interviews and her own diaries.

Jonas Salk’s original concept for an institute evolved under many influences, including those of the physicists Robert Oppenheimer and Leo Szilard. In the late 1950s and early 1960s, Salk contacted the scientists who were to become the Institute’s founders: Melvin Cohn, Francis Crick, Renato Dulbecco, Edwin Lennox and Jacques Monod. At the same time a mathematician and humanist, Jacob Bronowski, joined the group, and another mathematician and remarkable man became the first chairman of the Board of Trustees: Warren Weaver, who coined the term “molecular biology.” The success of the polio vaccine earned Jonas Salk the respect and friendship of Basil O’Connor, the first president of the March of Dimes, whose support ultimately made the Salk Institute a reality.

The Institute’s founders belonged to the generation of World War II and the Manhattan Project and, afterward, the Cold War. The original faculty and several of the early presidents and trustees had actively participated in those events, which shaped what they wanted to do, how they operated and how they saw the future. Most importantly, that background distinguished them as members of an impressive network of outstanding achievers. That legacy of accomplishment remains the foundation of the Salk Institute to this day.

For more information, please visit www.salk.edu/faculty/bourneis
Our brain performs millions of complex computations every second. We are studying the neural circuits in the visual cortex to better understand how specific neural components contribute to the computations that give rise to visual perception and to elucidate the basic neural mechanisms that underlie cortical function.

Neuroscientists have identified dozens of types of neurons in the brain that work together in distinct networks. But the circuits are intermingled, and even neighboring neurons of the same type differ in connectivity and function. Without access to a “wiring diagram”—a map of the neuronal connections—attempting to grasp how the brain lets us understand language, recognize faces and schedule our day is akin to trying to discern how a computer works simply by looking at it.

Recently, Callaway and his team have jumped a major hurdle to preparing that diagram: mapping single connections between neurons. They successfully modified the rabies virus so that it crosses from an infected nerve cell to another neuron just once, allowing scientists to identify all the neurons to which the infected neuron connects. Viruses that naturally spread between neurons have previously been used to trace the flow of nerve cell communication, but without a way to stop them in their tracks, over time, they will light up the whole brain.

Callaway’s team deleted a gene required by the virus to spread between neurons, marooning the virus inside a cell. Supplying the missing gene in that same cell, however, allowed the virus to slip into all the cells that were directly connected to it but to spread no further. To restrict the viral infection to a certain cell type or even to single cells, they covered these neurons with avian surface molecules and equipped the rabies virus with a homing device specifically for neurons “disguised” as bird cells.

While the first experiments were conducted using slices of brain, more recent studies are using genetically modified mice to target a specific class of neurons. With these tools, the wiring map can then be constructed step by step as subsequent populations of cells are visualized. Callaway’s lab then takes advantage of this information about each cell type’s connections to match it with the functional visual responses of the same types of neurons under different conditions. This leads to ideas about how each cell type contributes to brain function that can be tested by selectively activating or inactivating cell types and observing the consequences.

For more information, please visit www.salk.edu/faculty/callaway.
“The resolution of a lens is limited to about a quarter of a micrometer, which is a hundred times larger than the size of most biomolecules. The goal of our research is to develop new technologies to break this limit and build a microscope that can visualize biological processes at the single-molecule level.”

Advances in optical engineering now routinely provide researchers with an unprecedented ability to control, manipulate and detect light. Simultaneously, modern manufacturing and fabrication technologies allow access to the world at the nanoscale level.

The Cang lab in the Waitt Advanced Biophotonics Center focuses on using these advances to further enhance the ability to manipulate light to explore the molecular basis of life.

The wavelength of light is determined by its interactions with the surrounding medium, and the stronger the interaction, the shorter the wavelength. A microscope that uses short wavelengths can be used to visualize smaller objects. Noble metals, such as gold and silver, exhibit one of the strongest interactions with light, making it possible to use these metals to build super-resolution microscopes.

Cang and his collaborators were the first team to focus light down to a point about the size of a single protein, using aluminum and silver nanodevices. In another study, they revealed that certain nanostructures can shield molecules from photodamage, enabling researchers to extract up to three orders of magnitude more light photons out of dye molecules of the sort used to visualize cellular processes under a microscope.

Cang’s group also may have found a way to overcome longstanding limitations on designing microscope lenses. Since the 17th century, lenses have been designed using a “ray tracing” method based on calculating the path of light through a medium. However, the method could not be used for lenses capable of magnifying an object smaller than the wavelength of light. Cang’s group showed that it may be possible to circumvent this problem by dividing the design into many parts that could later be reconstructed into a single lens.

The goal of this theoretical work is to design a new lens system whose optical resolution will no longer be limited by the wavelength of light. In principle, this “super lens” will enable an optical microscope to reach the same resolution levels as that of an electron microscope, allowing researchers to zoom in on single molecules in living cells to investigate their biological functions.

For more information, please visit www.salk.edu/faculty/cang
Our brain contains roughly 100 billion cells, each connected through thousands of contact points, adding up to at least a quarter of a million miles of wiring—enough to reach from here to the moon. This marvel of evolutionary engineering allows us to navigate an ever-changing environment, to learn and to remember, but its stunning complexity makes it difficult to trace how information travels from one neuron to another. The Chalasani lab uses the nematode Caenorhabditis elegans (C. elegans), as a model to understand how neural circuits transform sensory input into behaviors. Despite its simplicity, C. elegans displays a number of sophisticated behaviors, making it an ideal model to explore how a simple, well-defined nervous system is able to integrate information from multiple sensory neurons and remember it for long periods of time.

The worms spend about 15 minutes searching for food when they are moved from a plate with food to a food-free plate. The duration of this search time is a function of the quality of the food and the amount of time they have spent feeding on it before being moved. The worms are able to learn the size of a food patch they were growing on and remember it for at least one hour. Chalasani and his team have localized the spatial memory to a pair of interneurons and identified a crucial role for dopamine signaling in executing this behavior.

C. elegans neural circuits integrate multiple sensory inputs to generate complex behaviors. Chalasani has identified that sensory neurons use neuropeptides (small signaling molecules) to communicate information about the identity and strength of the sensory stimuli to the rest of the nervous system. Neuropeptide signaling represents a new approach for coding sensory information in the brain.

He and his group have also observed an interesting predator-prey relationship between C. elegans and a larger worm called Pristionchus pacificus. They found that C. elegans uses three previously undefined sensory neurons to detect and avoid predators and their secretions. Surprisingly, pre-treating the worm with human anti-anxiety drugs attenuates its response to the predator.

In the future, Chalasani plans to extend his lab’s studies to zebrafish larvae to test whether vertebrate and invertebrate circuits use similar mechanisms to process information, hoping to gain new insight into how the human brain functions.

For more information, please visit www.salk.edu/faculty/chalasani
“Visual information is transmitted from the eye to the brain in just 1.25 million optic nerve fibers—about as many fibers as there are pixels in a cheap digital camera. Somehow we exploit this information to perform all sorts of critical tasks all the time, such as recognizing objects and navigating busy freeways, that even the most advanced robots are only starting to do. I want to understand how the retina, the neural tissue lining the back of the eye, encodes visual information so the brain can use it to produce visual experience.”

Visual processing begins when photons entering the eye strike a layer of light-sensitive nerve cells in the retina, known as rods and cones. These cells convert light into electrical signals and send them to an intermediate layer, which in turn relays signals to a collection of 1.25 million neurons known as retinal ganglion cells. These cells carry visual signals from the eye to the brain.

To understand how this neural circuitry in the retina produces high-resolution vision, Chichilnisky’s lab uses a state-of-the-art 512-electrode recording system, developed in collaboration with an international group of high-energy physicists. This system is capable of recording simultaneously the tiny electrical signals generated by hundreds of retinal ganglion cells that transmit information about the outside visual world to the brain. These recordings are made at high density and with fine spatial detail, sufficient to detect complete populations of the tiny and densely spaced output cells known as “midget” retinal ganglion cells.

This has allowed the researchers to map the full cone mosaic found in a region of the retina and to trace for the first time the neuronal circuitry that connects individual photoreceptors to retinal ganglion cells. It also has shed light on the neural code used by the retina to relay color information to the brain.

Based on this research, Chichilnisky’s team is designing approaches to making artificial retinas to restore vision in people who are blinded by retinal degenerative diseases, such as macular degeneration or retinitis pigmentosa. In principle, retinal implants could bypass the damaged retina with the help of tiny electrode arrays that mimic the electrical signals sent to the brain in response to light. In order to engineer these prosthetics, however, scientists need to understand how neurons in the retina function as a network to produce an image, and how to electrically stimulate the retina in a manner that can reproduce important aspects of normal vision.

For more information, please visit www.salk.edu/faculty/chichilnisky
The premise that “form follows function” became a mantra for numerous leading architects and industrial designers during a good part of the last century. In biology, evolution operates according to a similar premise because forms with better functionality are likelier to be selected. Trying to understand the relationship between a molecule’s fine structure and the functions it carries out, Choe and his colleagues use x-ray crystallography and NMR spectroscopy to zoom in on ion channels and receptors in the cell membrane to visualize how they interact with messenger proteins. Recent work focused on analyzing the three-dimensional structure of a whole protein complex to illustrate how TGF-beta, a messenger molecule that plays a role in cancer, the immune system and heart disease, binds to its receptor molecules on specific target cells to instruct them to do its bidding. An extension of this work explores the possibility of designing new messages to instruct cells to carry out non-natural processes such as coaxing differentiated cells back into an immature, pluripotent state. These types of newly created messages will have tremendous clinical potential as guiding molecules.

Human integral membrane proteins (hIMPs) are attached to the membrane surrounding each cell, serving as gateways for absorbing nutrients, hormones and drugs; removing waste products; and allowing cells to communicate with their environment. Many diseases, including Alzheimer’s, heart disease and cancer, have been linked to malfunctioning hIMPs, and many drugs, ranging from aspirin to schizophrenia medications, target these proteins. These receptors and ion channels are extremely hard to produce and hence notoriously difficult to study, but Choe’s group recently developed a new technique for rapidly determining their structure. Knowing the exact three-dimensional shape of hIMPs allows drug developers to understand the precise biochemical mechanisms by which current drugs work and to develop new drugs that target the proteins.

For more information, please visit www.salk.edu/faculty/choe

“Biological messages are written and delivered between cells by messenger molecules in the body. The two messenger systems we are focusing on are called ion channels (for e-mails) and protein hormone receptors (for snail mail). By visualizing these messengers to better understand how such messages are coded for specific delivery, we can create brand-new messages of our own.”
“Our lab is interested in identifying the mechanisms that plants use to respond to changes in their environment, particularly light. Our hope is that by discovering the molecular triggers that determine whether a plant matures into a spindly or robust specimen, we can contribute to efforts to increase crop yield and alleviate hunger.”

Stuck where the seed germinates, plants have to make the best of their real estate. They rely on an arsenal of light-sensitive photoreceptors to decide when to germinate and flower to ensure the next generation of seeds. The Chory laboratory studies the signaling pathways plants use to detect changes in the sunlight that hits their leaves, not only when seasons change, but also when they grow in shady, crowded conditions. She and her group have assigned specific functions to a number of photoreceptors that regulate plant growth, identified components of the light signaling pathways, and shown that photoreceptors link hormone biosynthesis and signaling pathways within the plant to the local light environment.

Chory’s laboratory has made significant contributions to the studies of three major plant hormones. Her team identified the steroid receptor and signaling pathway utilized by all flowering plants. They determined the structure of the receptor for a class of small hormones called cytokinins, which are utilized as herbicides. And they solved the long-running mystery of how plants produce auxins, which play essential roles in plant growth and development. Recently, Chory’s laboratory showed that the major plant auxin is synthesized by a simple pathway from the amino acid, tryptophan.

Chory is also investigating how genetic variation in light-sensitive pathways in thale cress plants ensures that plants in northern latitudes are more sensitive to light than those in the sun-drenched Mediterranean. Using a reference strain of the plant, her team is assessing the contribution of almost every gene to light sensing and signaling in a variety of light environments. Knowing the full spectrum of genes that can be altered in the laboratory to affect an adaptive trait—and how this compares with the genes that affect plants’ appearance in the wild—will advance understanding of how genes evolve together to make an efficient, coordinated network. This work is important not only to evolutionary biologists and plant breeders, but also to human biology, where similar experiments cannot be carried out. Chory’s research may eventually enable researchers to develop plants that are particularly well-adapted to challenging environments, boosting the yields of agricultural crops.

For more information, please visit www.salk.edu/faculty/chory
Melvin Cohn
Professor Emeritus
Conceptual Immunology Group

“The immune system is a complex of organs—highly specialized cells and even a circulatory system separate from blood vessels—all of which work together to protect the body from invading pathogens. Unlike most immunologists, who wield pipettes and petri dishes, I use my brain to bring order to what might well be one of biology’s most complex fields.”

Unable to predict which of the diverse array of pathogens it will encounter, the immune system must nevertheless respond promptly to defend the host organism from that invader. Complicating matters, pathogens evolve at a rate that is vastly more rapid than that of their hosts. Cohn’s solution was to establish a set of basic immunologic rules based on the immune system’s evolutionary origins.

Invertebrates invented a number of biodestructive and ridding mechanisms to deal with pathogens, but their limited flexibility was not enough to keep up with the rapidly changing landscape of disease-causing agents. This created a selective pressure to invent a mechanism expressed in vertebrates that generated a large and random repertoire of molecules able to recognize foreign invaders, which in turn required two new regulatory mechanisms: 1) a somatic decision mechanism to sort the repertoire into anti-self (the portion that needs to be inactivated to avoid autoimmune diseases) and anti-nonself (the activated portion that is now available to recognize invading pathogens and protect the host) and 2) a germline-selected decision mechanism to control the kind and magnitude of the immune response.

The rules Cohn developed cover most of immune behavior: the Combinatorial Theory of the nature of the repertoire; the Associative Recognition Theory of the self-nonself discrimination; Trauma Theory for the determination of the magnitude and effector class of the response; the B-Protecton Theory of humoral responsiveness and the T-Protecton Theory of cell-mediated responsiveness. These theories are linked together by a computer program based on cellular automata principles called the Synthetic Immune System. Available online, the Synthetic Immune System allows Cohn and others to test their assumptions about how the real immune system works, facilitating understanding and predictability.

While understanding how the immune system functions is Cohn’s primary goal, being able to predict the consequence of any given antigenic input would be an invaluable guide for the development of new vaccines, the treatment of autoimmune and allergic disorders, as well as the enhancement of the body’s response to infectious disease.

For more information, please visit www.salk.edu/faculty/cohn
Motor learning is an intricate process whose outcome—a smoothly executed backhand, let’s say—is easy to spot. The underlying cell biological changes, however, are much harder to identify, not least because the neuronal circuitry for almost all behaviors is poorly understood. Trying to understand the molecular and cellular changes that underpin behavioral learning, du Lac and her team focus on a simple type of learning: How does the brain learn to stabilize an image on the retina and use eye movement to compensate for a moving head? This so-called vestibulo-ocular reflex, or VOR, needs to be fast. For clear vision, head movements must be compensated for almost immediately; otherwise, our vision would resemble an undecipherable blur. To achieve the necessary speed, the connection involves only three types of neurons: sensory neurons, which detect head movement; motor neurons directing eye muscles to relax or contract; and neurons in the brainstem that link the two.

To glean meaningful information from in vitro physiological measurements taken from individual neurons, scientists need to know where they fit into the in vivo circuitry. However, unlike the clearly defined layers of the cortex—the brain’s powerful central processing unit responsible for higher functions—the brainstem, which controls automatic functions such as breathing and swallowing, resembles a uniform jumble of neurons, making it difficult to even distinguish between different cell types. To overcome that limitation, du Lac developed a battery of techniques and tools that allows her to manipulate molecular and genetic components of specific neurons within the VOR circuitry. Recently, she and her team identified two classes of neurons within the VOR circuitry: superfast neurons that rely on glutamate or glycine to transmit signals between cells and can sustain firing rates of up to 600 spikes per second, and GABAergic neurons, which are much slower but still faster than any neuron in the cortex. Their findings demonstrate that these microcircuits are tuned for speed, while the whole system is tuned for resilience. Gaining a better understanding of the neurobiological and molecular mechanisms underlying learning might lead to the development of preventive and therapeutic approaches for strokes, learning and movement disorders, as well as balance problems.
Although the human genome sequence lists almost every single DNA base of the roughly 3 billion bases that make up a human genome, it doesn’t tell biologists much about how its function is regulated. That job belongs to the epigenome, the layer of genetic control beyond the regulation inherent in the sequence of the genes themselves. Being able to study the epigenome in its entirety promises a better understanding of how genome function is regulated in health and disease, as well as how gene expression is influenced by diet and the environment.

One of the ways epigenetic signals can tinker with genetic information is through DNA methylation, a chemical modification of one letter, C (cytosine), of the four letters (A, G, C, and T) that comprise our DNA. In the last couple of years, Ecker’s laboratory started to zero in on genomic methylation patterns, which are essential for normal development and associated with a number of key cellular processes, including carcinogenesis.

To ascertain how the epigenome of a differentiated cell differs from the epigenome of a pluripotent stem cell, his team used an ultra-high-throughput methodology to determine precisely whether or not each C in the genome is methylated and to layer the resulting epigenomic map upon the exact genome it regulates. The study revealed a highly dynamic, yet tightly controlled, landscape of chemical signposts known as methyl groups and resulted in the first detailed map of the human epigenome, comparing the epigenomes of human embryonic stem cells and differentiated connective cells from the lung called fibroblasts. The head-to-head comparison brought to light a novel DNA methylation pattern unique to stem cells, which may explain how stem cells establish and maintain their pluripotent state.

Now that they are able to create high-resolution maps of the human epigenome, Ecker’s group will begin to examine how it changes during normal development as well as in a variety of disease states.

“Nature vs. nurture, genes vs. environment—what is more important? My group is interested in understanding the roles of genetic and ‘epigenetic’ processes in cell growth and development. By understanding how the genome and epigenome talk to one another, we hope to untangle the complexity of gene regulatory processes that underlie development and disease in plants and humans.”
“The overall interest of my laboratory has been the regulation of cell growth, including the action of cancer-causing genes, communication between cells and the effects of growth factors on the development of breast cancer.”

The growth of cells is tightly controlled, but cancer cells turn a deaf ear to signals that cause normal cells to stop dividing. Eckhart identified and characterized genes in tumor viruses—so-called viral oncogenes—that override normal cell cycle controls. 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.

Cancer cells also lose the ability to communicate with each other through the exchange of materials through channels called gap junctions. This communication is important for coordinating the activities of cells in tissues, including normal regulation of cell growth. The proteins that form the channels are called connexins. Eckhart found that some cancer-causing genes modify connexins, thereby shutting off communication between adjacent cells and disrupting normal growth. Restoration of communication allows the cells to grow normally again, suggesting that agents that regulate cellular communication might help in reversing cancer. Eckhart also studied the effects of a growth factor, insulin-like growth factor-1 (IGF-1), on human mammary epithelial cells growing in a three-dimensional culture system that mimics the environment of the body. Abnormal signaling by IGF-1 stimulated changes in the growth properties of the cells, similar to changes that happen during early tumor development. Studies like these are helping to define how changes in genes and growth signaling can lead to breast cancer.

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 phased out his laboratory research program and became professor emeritus in 2010. He presently serves on advisory committees for cancer centers, the National Institutes of Health and voluntary health agencies.

For more information, please visit www.salk.edu/faculty/eckhart
"The transcription machinery is proposed to be a pivotal stress sensor that influences cell fate decisions by gauging the severity of damage. Hopefully, the mechanistic information that we generate will provide insight into the influence of promoter structure in directing appropriate responses to stress and facilitate the development of more specific transcription-based therapies."

Most people had been looking for clues within the immediate vicinity of the gene but came up empty-handed. When Michael Witcher, a researcher in Emerson’s lab, extended his search further upstream, however, he discovered a binding site for a protein known as CTCF. This protein forms the centerpiece of the molecular fence posts that separate heterochromatin from the rest of the genome. A closer look revealed that CTCF is lost from several binding sites in numerous types of cancer cells, leading to the collapse of the molecular boundary. Once the boundary was gone, the adjacent heterochromatin encroached and silenced the nearest gene.

For a long time scientists have been trying to understand how tumor suppressor genes get silenced in cancer. Understanding one of the key molecular events that leads to their inactivation might allow them to exploit this mechanism to develop novel therapies.

For more information, please visit www.salk.edu/faculty/emerson
“Because humans are good at storing fat during times of plenty, we are also excellent at surviving times of famine. The fat tissues of our body are like batteries, providing us with a steady source of energy when food is scarce. Understanding the storage and burning of fat, literally the ebb and flow of energy throughout our body, is crucial to normal physiology and ultimately the treatment of metabolic diseases such as obesity and diabetes.”

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.

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.

Against this backdrop, Evans’s team identified the missing link in the regulation of metabolism. This linchpin is a protein known as fibroblast growth factor 1 (FGF1), which may open new avenues in the treatment of diabetes. The lab found that FGF1 activity is triggered by a high-fat diet and that mice lacking the protein swiftly develop diabetes. This suggests that FGF1 is crucial to maintaining the body’s sensitivity to insulin and normal levels of sugar in the blood.

The scientists also found that the antidiabetic drug Actos, which is used to increase the body’s sensitivity to insulin, regulates FGF1. But Actos and related drugs, though helpful, have side effects that limit their use. Thus, Evans plans to explore whether FGF1 itself might point to a new way to control diabetes by avoiding the drawbacks of Actos and providing a more natural means of increasing insulin sensitivity.

In addition to dietary regulation, mammalian metabolism is highly circadian, with major hormonal circuits corresponding to our sleep-wake cycles. Sleeping is a fasting period, while the remainder of the day involves periodic eating. Synchronizing rhythms of behavior and metabolic processes is important for cardiovascular health and for preventing metabolic disease. Two receptors found on the nuclei of mouse and human cells, known as REV-ERB-α and REV-ERB-β, are essential for synchronizing normal sleep and metabolic cycles. Evans’s 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 disorders, obesity and diabetes.

For more information please visit www.salk.edu/faculty/evans
"Differences arise at every level of the brain’s astonishingly intricate architecture, leading to variances in how we think, learn and behave and in our propensity for mental illness. Jumping genes may explain how some of these differences arise, even in identical twins."

Variations in the genes we inherit from our parents ensure that each of our brains is wired differently. But even identical twins, who inherit the same set of genes, can differ markedly in their mental functioning, behavioral traits and risk of mental illness or neurodegenerative disease. From where do these differences arise?

Gage’s laboratory has identified a likely suspect in the hunt for an explanation for this mysterious variability in brain function: jumping genes. Such genes (also known as “retrotransposons”) can insert copies of themselves into other parts of the genetic code, making one neuron function very differently than its neighbor. Many such insertions may create a mosaic of cells possessing varying genetic operating instructions, which in turn could influence cognitive abilities, personality traits and susceptibility to neurological problems.

To better understand how jumping genes play a role in brain function, Gage and his colleagues have investigated the genetic underpinnings of Rett syndrome, a rare neurodevelopmental disease that affects mostly girls and is considered one of the autism spectrum disorders. Typical features of the disorder include loss of speech, stereotypic movements, mental retardation and social-behavioral problems. Although almost all cases are caused by a mutation in the MeCP2 gene, how severely people are affected by the symptoms of Rett syndrome varies widely.

Gage’s team found that a mutation in the MeCP2 gene mobilizes the L1 retrotransposons in brain cells of Rett syndrome patients, reshuffling their genomes. Their research showed that the mutation in the brains of mice with Rett syndrome resulted in a significant increase in numbers of L1 insertions in their neurons, suggesting that the jumping genes might account for some of the effects of the MeCP2 mutation. Using stem cell reprogramming techniques, the researchers generated neurons from skin cells of Rett syndrome patients, which they could then study in the laboratory. Similar to the findings in mice, these human neurons possessed high numbers of L1 copies, which might explain the variability in symptoms seen in people with the disorder.

Gage’s findings may not only explain how a single mutation can cause the baffling variability of symptoms typical of Rett syndrome but also shed new light on the complexity of molecular events that underlie other psychiatric disorders, such as autism and schizophrenia.

For more information, please visit www.salk.edu/faculty/gage
“Studies in my lab are directed at understanding how different types of spinal cord ‘interneurons’—neurons that bridge communications between sensory and motor neurons—control how we move and how we respond to touch and pain. Knowing more about how these cells develop and function is a critical step in devising new therapies to regenerate and activate circuits in the spinal cord following injury.”

Investigating how movement is controlled lies at the center of our quest for understanding how our nervous system works. We now know that a hierarchy of “motor” networks in the nervous system controls movements. Among these are specialized networks of interneurons in the spinal cord—commonly referred to as central pattern generators (CPGs)—that direct the rhythmic muscle movements that underlie locomotion. These spinal CPGs are engaged and controlled by the brain to produce the coordinated muscle movements that allow us to walk, talk and play an instrument.

Although scientists have known about the locomotor CPG for nearly 100 years, the identity of the neurons that make up the circuitry had remained a mystery. Goulding’s lab, in pioneering efforts to break the molecular code that generates these different interneuron cell types, has begun unraveling the wiring of the spinal cord. Previously, Goulding and his team discovered that a subset of interneurons, called V0 neurons, governs the left-right alternating pattern of activity that is needed for stepping, as opposed to hopping, movements. They have also analyzed the function of other neurons, including V1 neurons that set the pace at which animals walk.

However, identifying the cells that control our ability to flex and extend our limbs has proven more difficult. These have an essential role in movement, as without them we would not be able to bend and stretch our arms and legs. In a recent series of experiments, Goulding’s team identified a second class of inhibitory neuron that cooperates with the V1 neurons to control muscle activity that is needed to move the limbs and walk. Strikingly, they found that the same neurons are present in the spinal cords of swimming vertebrates, leading Goulding to propose that the “walking” CPG is an evolutionary adaptation of the “swimming” CPG circuit. More recently, efforts in the lab have turned to understanding how the spinal CPG is activated both by touch and pain pathways that are important for protective reflexes, and by descending pathways from the brain—knowledge that is essential for developing new treatments for spinal cord injury.

For more information, please visit www.salk.edu/faculty/goulding
For close to a decade, pharmaceutical researchers have been pursuing compounds to activate a key nicotine receptor that plays a role in cognitive processes. Triggering it, they hope, might prevent or even reverse the devastation wrought by Alzheimer’s disease. Researchers in Heinemann’s lab, however, whose group first identified the brain receptors that respond to nicotine, have discovered that when the receptor, alpha-7, encounters beta amyloid, the toxic protein found in the disease’s hallmark plaques, the two may actually go rogue. In combination, alpha-7 and beta amyloid appear to exacerbate Alzheimer’s symptoms, while eliminating alpha-7 seems to nullify beta amyloid’s harmful effects.

Alpha-7 is expressed all over the brain, in all mammals, which means that it is probably essential, but investigators have not yet discovered for what. Intrigued by earlier studies showing that beta amyloid seemed particularly drawn to the alpha-7 nicotinic receptors, Heinemann and his team hypothesized that the receptors mediate beta amyloid effects in Alzheimer’s disease. To test their theory, they crossed mice engineered to lack the gene for alpha-7 with a mouse model for Alzheimer’s disease, which had been genetically engineered to overexpress amyloid precursor protein (APP), an antecedent to beta amyloid. They then put the offspring through a series of memory tests. Surprisingly, those with both mutations—too much APP and no gene for alpha-7—performed as well as normal mice. The Alzheimer’s mice, however, which had the alpha-7 gene and also overexpressed APP, did poorly on the tests. Pathology studies revealed the presence of comparable amounts of plaque in the brains of both types of mice, but in those lacking the alpha-7 gene, they appeared to have no effect. Similar disparities were evident in measurements of the synaptic function underlying learning and memory.

These findings, which suggest a completely different target for potential Alzheimer’s drugs than those that have been tried, could have important implications for researchers seeking to combat the disease.

For more information, please visit www.salk.edu/faculty/heinemann
Ordinarily, the proteins known as nucleoporins are among the 30 gene products serving as the bricks and mortar of nuclear pore complexes, the communication channels that regulate the passage of molecules to and from a cell’s nucleus. But recent research in Hetzer’s laboratory suggests that some also have a second job of regulating specific genes during development, and that they sometimes stray from the straight and narrow to play a role in cancer as well.

For more than a decade, scientists have known that when the nucleoporin NUP98, which should be turned off during cell differentiation, abnormally fuses with certain proteins that regulate gene expression, the marriage causes leukemia. Moreover, in many cancers, the nucleoporins NUP214 and NUP88 are misregulated and in particular are associated with very aggressive forms of lung cancer.

Investigators have long questioned why these components of the cell’s transport channel are implicated in cancer and have theorized that the connection relates to a problem in the conveyance of molecules in and out of the nucleus. But Hetzer offers a different explanation. He and his team believe these proteins also function as a new class of gene transcription regulators, which turn specific genes on and off during cell differentiation or tissue development. They found that nuclear pore proteins are not only part of the transport channels but also play a role in the organization of the genome and a very direct role in gene expression.

In another line of research, the Hetzer laboratory used metabolic pulse-chase labeling of whole animals in combination with quantitative mass spectrometry to identify and characterize extremely long-lived proteins (ELLPs) that reside in the nucleus. These proteins exhibit little to no protein turnover in the adult rat brain and thus escape the central mechanism that allows cells to maintain a functional proteome. This raises important questions about the biochemical properties of these proteins and whether the failure to maintain proper levels and functional integrity of ELLPs could be a major contributor to age-related changes in the function of post-mitotic tissues such as those of the brain and heart.

For more information, please visit www.salk.edu/faculty/hetzer
The goal of our group is to elucidate signal transduction mechanisms utilizing protein phosphorylation/dephosphorylation, ubiquitylation, and sumoylation and to investigate how these processes regulate cell proliferation, growth control and the cell cycle. Ultimately, we want to use this information to uncover how dysregulation of such post-translational modifications is involved in cancer.

Protein kinases are key cellular enzymes; they attach phosphates to other proteins in the cell and thereby regulate their activities. This process, which is known as phosphorylation, is reversed by a second type of enzyme that removes the phosphate. Phosphorylation therefore acts as a molecular on/off switch. The human genome encodes nearly 540 different protein kinases, making them among the most abundant and important types of gene products.

One major function of protein phosphorylation is to control cell proliferation in response to external signals. A hallmark of cancer cells is that they continue to proliferate even in the absence of external signals to grow. In many cases, this is due to genetic changes that result in a protein kinase being continuously active instead of being toggled on and off in response to signals. Kinases that add phosphate to the amino acid tyrosine in proteins are particularly important cancer-causing "oncoproteins," and a number of new cancer drugs are designed to block these rogue enzymes. However, kinases that add phosphates to the amino acids serine or threonine in proteins also play roles in cancer. Recent efforts to sequence entire tumor genomes have revealed that many types of protein kinases sustain mutations in cancer, including numerous ones that were not previously known to be involved.

Hunter and his team have analyzed the consequences of mutations in some of these cancer mutant kinases in the hope that they might identify new cancer drug targets. For one kinase that phosphorylates serine and threonine, known as death-associated protein kinase 3 or DAPK3, they found that the cancer mutations actually cause a decrease in the ability of the kinase to add phosphate to proteins. This unexpected discovery suggests a new model in which DAPK3 normally acts to rein in the growth of cells, whereas in cancer cells this "suppressor" activity has been lost through inactivating mutations. Thus, DAPK3 would not be a target for inhibitor drugs. Nevertheless, other mutant kinases emerging from sequencing studies may prove to be good targets, and Hunter’s group is continuing to study cancer mutant kinases in the hope that unlocking their secrets will lead to better cancer therapies.

For more information, please visit www.salk.edu/faculty/hunter

Back row, left to right: Mike French, Justin Zimmermann

Front row, left to right: Brandon Lamarche, Huiyu Sun, Andrea Carrano, Megan Lambert, Yu Shi, Jill Meisenhelder, Lorena Puto, Tony Hunter, Natalie Luhtala, Suzy Simon, Xinde Zheng, Aaron Aslanian, Zheng Wang, Hui Ma
“Our ultimate goal is to try to understand the molecular and cellular basis of organ and tissue regeneration.”

Juan Carlos Izpisua Belmonte
Professor, Gene Expression Laboratory
Roger Guillemin Chair

Ever since the first adult cells were converted into induced pluripotent stem cells (iPSCs), they have generated excitement as an alternative to embryonic stem cells and a potential source for patient-specific stem cells. Unfortunately, reprogramming adult cells into iPSCs is a slow, inefficient and costly process and carries the risk of cancer, limiting the cells’ therapeutic value. Two recent studies in Izpisua Belmonte’s lab, however, offer the prospect of safer, faster and more efficient approaches to coaxing cells back in time.

The most widely used technology involves the forced expression of four transcription factors in fully committed adult cells: Oct4, Sox2, Klf4 and c-Myc. Because only a tiny fraction of cells transmogrify into iPSCs that look and act like embryonic stem cells, Izpisua Belmonte wondered whether the process used to reprogram the cells was inducing a response that stopped them from growing. Izpisua Belmonte and his team showed that adding Klf4 and c-Myc, which are oncogenes, activated the pathway for the tumor suppressor p53. In cells genetically engineered to lack p53, reprogramming efficiency increased at least tenfold, clearly demonstrating the important role that p53 played in reining in cells trying to revert back into a stem-like state. Because iPSCs generated with the full complement of reprogramming factors can turn malignant, Belmonte and his team also tried reprogramming mouse cells lacking p53 using only Oct4 and Sox2. The cells readily converted into iPSCs and gave rise to healthy, full-term mice that were able to reproduce, passing the ultimate test for pluripotent embryonic stem cells.

In related work, Izpisua Belmonte’s group set out to transform immunologically immature hematopoietic stem cells isolated from umbilical cord blood into iPSCs. They not only successfully converted them using only Oct4 and Sox2, but did so in less time than any previously published methodology. The resulting iPSCs were indistinguishable from human embryonic stem cells and passed all standard tests for pluripotency, establishing the possibility of a comprehensive bank of tissue-matched, cord blood–derived stem cells.

For more information, please visit www.salk.edu/faculty/belmonte
“Action is the basic way we interact with the world. My lab is interested in understanding how the brain learns, selects and executes actions. By dissecting the neural circuits and molecular mechanisms underlying the brain’s generation of adaptive behavior, we hope to contribute to the development of more effective therapeutic interventions for neurological diseases, such as Parkinson’s disease and obsessive-compulsive disorder.”

We all explore the world by acting, and learn to repeat actions that lead to happy outcomes and avoid those that lead to unpleasant results. We all balance the cost and the outcome of different possible actions and pick the ones that best match our expectation. How does our brain accomplish such amazing tasks, evaluate situations and direct our behavior according to the ever-changing environment? And why are those extraordinary abilities compromised in different neurological diseases? Studying a series of complex behavioral tasks in mice, Jin’s lab is working to understand how the neurons and molecules in the brain interact to implement the computation, memory and selection of actions.

Numerous motor and mental diseases, including Parkinson’s, Huntington’s, obsessive-compulsive disorder, schizophrenia and depression, have been linked to the dysfunction of circuits composed of basal ganglia, a group of interconnected structures deep in the brain. Jin found that nigral dopaminergic neurons, whose degeneration is responsible for Parkinson’s disease, and the neurons in the striatum, which degenerates in Huntington’s disease, can broadcast the signals selectively for starting or stopping the newly learned action sequences. The finding provides important insights into the action initiation and termination deficits observed in those diseases. His research further demonstrated that learning cognitive actions, such as playing chess or doing math, could involve the same neural circuitry involved in learning motor actions, and that they may share similar molecular mechanisms. This introduces the possibility of studying cognitive action learning and dysfunction in genetic models.

The lab plans to continue exploring the molecular and circuit mechanisms underlying action learning and selection, employing a vast array of cutting-edge genetic, physiological and optical techniques in freely behaving mice. Ultimately, Jin hopes to characterize the fundamental principles of how the brain generates actions from multiple levels of analysis and to develop cures for a wide range of action-related neurological and psychiatric diseases.

For more information, please visit www.salk.edu/faculty/jin
The search for unified theories is not limited to those who study physics or the cosmos. A ‘unified theory’ of gene expression is required to explain how transcription—the complex, multistep process that generates messenger RNA copies from protein-encoding genes—is coordinated within the cell.”

If stretched out, the DNA of a single human cell would form a thin thread about six feet in length. To fit inside the cell nucleus, the DNA is threaded around histone proteins and coiled up in a condensed structure called chromatin. When genes are actively transcribed, the tightly folded chromatin must open up just enough to give the transcriptional complex access to the DNA.

Recently, Jones and her team discovered that Spt6, a histone “chaperone” protein that functions to move nucleosomal histones out of the path of the oncoming transcription complex, interacts directly with RNA polymerase II (RNAPII), the central catalytic enzyme responsible for copying genes to RNA. Surprisingly, the complex assembled by Spt6 on RNAPII does not include factors required for transcription, but instead includes enzymes that work with Spt6 to modify the histones during transcription, as well as other proteins that transfer onto the newly made RNA to negotiate its export from the nucleus. They are currently identifying new proteins in this complex that integrate transcription with chromatin organization and downstream steps in gene expression.

The lab has also discovered that transcription elongation and histone methylation of highly induced genes is controlled by RNA-binding proteins that mediate alternative splicing of RNAs. Interestingly, these positive elongation factors become inactivated in cells that are subjected to various kinds of stress, resulting in the rapid shut-off of many cellular genes. However, within the HIV-1 genome and at a handful of cellular genes, transcription is induced by environmental or genotoxic stress, suggesting that stress might also destroy negative regulators of transcription.

Jones’ lab recently discovered that a central human RNA-binding protein plays a hitherto unsuspected role in the repression of stress-regulated genes. This transcriptional inhibitor protein is removed from the nucleus upon stress, releasing transcription at HIV-1 and other responsive genes. Transcription elongation requires either the inactivation of this negative elongation factor by stress or, in normal cells, its release from the promoter via positive-acting elongation factors. Therefore under stress, transcription elongation may be uncoupled from the Spt6-RNAPII complex.

For more information, please visit www.salk.edu/faculty/kjones

From left to right: Lirong Zhang, Yupeng Chen, Brian Page, Katherine Shanks, Kathy Jones, Seung Hyuk Choi, Ranveer Jayani, Allene Chang, Janika Schulze
Safeguarding the ends of linear chromosomes, known as telomeres, is essential for survival. We are trying to understand how cells keep tabs on their telomeres, how they control cellular proliferation and lifespan and how they regulate the interrelationship of aging and cancer.

Telomeres, the protective ends of chromosomes, become shorter each time cells divide. Often described as the genomic equivalent of the plastic caps that keep shoelaces from fraying, telomeres mask those ends from vigilant repair proteins, which might mistake exposed chromosome ends for broken DNA. When telomeres become critically short and fail to protect the chromosomes, cells cease to grow, or die. On one hand, this process controls cellular and organismal aging by limiting the number of times cells can divide. On the other hand, this limitation on cellular proliferation ensures that cells do not become immortal and therefore represents a powerful tumor suppressive pathway, illustrating the intricate relationship between aging, proliferation and cancer formation.

Karlseder and his group have recently discovered that the relationship between telomeres and cancer extends much further than previously assumed. The group discovered that if cells take too long to undergo cell division, the telomeres send out a molecular SOS signal. These findings have dual implications for cancer therapy. First, they show how a class of anti-cancer drugs that slows cell division—known as mitotic inhibitors—kills cells. This class includes the commonly used chemotherapy drugs vinblastine, Taxol and Velcade. While these drugs have been in use for decades, it was unclear why they actually killed cancer cells. Research from the Karlseder lab has now demonstrated that exposure to mitotic inhibitors causes telomeres to lose their protective function, and the cells respond with stress signals that eventually lead to the death of cancer cells.

Second, these findings suggest ways to make therapies with mitotic inhibitors more potent; novel strategies could be used in combinatorial cancer chemotherapy regimes, which rely on the synergy between two or more drugs. The theory is that a multi-pronged approach might pack more of a wallop than a sledgehammer alone. By providing the link between mitotic inhibition, telomere deprotection and cell death, Karlseder’s lab continues to unravel the intricate links between chromosome ends, aging and cancer.

For more information, please visit www.salk.edu/faculty/karlseder

From left to right: Liana Goodwin, Daniel Lackner, Makoto Hayashi, Laure Crabbe, Candy Haggblom, Jan Karlseder, Nausica Arnoult, Tony Cesare, Teresa Rivera Garcia, Roddy O’Sullivan
We are studying the genetic and developmental mechanisms that guide the formation of ciliated cells, with the goal of using this information to better diagnose and treat ciliopathies, which can cause respiratory problems, middle ear infection and infertility.

Tiny hairlike structures called motile cilia sweep mucus and dirt out of our lungs, propel the egg from the ovary through the Fallopian tube into the uterus, and move fluid through the brain’s ventricles. A lot is known about the structural details of cilia: an array of microtubules arranged in nine doublets around a central pair is anchored through the so-called basal body inside the cell. But how cilia form in epithelial cells and how they coordinate the direction of their stroke along a common polar plane is far from clear.

The Kintner lab has identified the gene FoxJ1 as a key factor required for motile cilia, but on its own FoxJ1 can only induce the formation of a single cilium. By searching for genes that are only expressed in cells that make hundreds of motile cilia, Kintner and his team identified a novel gene, called multicilin. When expressed in nonciliated cells, it both activates FoxJ1 and a program required to form hundreds of basal bodies, resulting in multiciliated cells that are indistinguishable from those found in the lung. Ongoing studies are elucidating the genetic mechanisms that allow multicilin to convert epithelial cells into multiciliated cells.

In a separate study, Kintner’s group tracked the orientation of hundreds of cilia in Xenopus frog larvae, whose skin is covered with multiciliated cells. They found that during early embryonic development, cilia point more or less in the general direction of the body’s back end and start creating a weak flow. During the following refinement phase, all cilia get in line and trim their sails to the prevailing winds. When they analyzed the planar cell polarity (PCP) pathway, which is widely used as a mechanism to orient structures within cells and tissues, they found that the PCP pathway has several functions in ciliated cells: It not only orients cilia in a specific planar direction through cell–cell interactions, but also positions basal bodies within cells so that cilia can form.

Identifying the components involved in cilia-specific functions and in the molecular mechanisms underlying the various ciliopathies is likely to facilitate the development of novel therapeutic strategies.

For more information, please visit www.salk.edu/faculty/kintner
“The expression of genetic information within each cell must be precisely regulated for normal development, as is evident by the numerous diseases and developmental defects associated with aberrant gene expression. One layer of gene regulation involves the addition of chemical groups, or ‘epigenetic modifications,’ to chromatin, a combination of DNA and proteins in a cell’s nucleus. I am interested in understanding how these chemical instructions are recognized and translated into stable gene expression patterns.”

In plants, mammals and other eukaryotic organisms, the addition of epigenetic modifications to both DNA and histones (proteins that package and order DNA) are known to influence the expression of the underlying genes and to play critical roles in diverse biological processes, including cellular differentiation, development and the maintenance of genome integrity. However, compared to the amount of data generated over the last few decades regarding the proteins and pathways responsible for establishing, maintaining and removing epigenetic modifications, relatively little is known about how epigenetic modifications actually lead to changes in gene expression and chromatin structure.

The plant *Arabidopsis thaliana* provides an ideal system to study epigenetic processes. It is genetically malleable, highly amenable to whole genome analyses and, unlike mammals, is highly tolerant of dramatic changes to its epigenetic code. In addition, plants and mammals share many of the key proteins and pathways involved in establishing and maintaining epigenetic modifications, so findings in plants may be applicable to animals and humans. To gain a better understanding of the cascade of events that lead from the addition or removal of a particular epigenetic modification into a change in gene expression, Law focuses on the characterization of several newly identified families of chromatin binding proteins. By employing genetic, biochemical and genomic approaches, she aims to determine the epigenetic modifications recognized by these protein families, identify their interacting partners and determine their effects on gene expression and higher order chromatin structure. This will provide a holistic view of how epigenetic modifications control gene expression.

Such studies will begin filling a gap in our current understanding of epigenetic gene regulation and will greatly enhance our ability to understand and control the expression of existing and newly introduced genes, which has broad implications in both agriculture and gene therapy.

For more information, please visit www.salk.edu/faculty/law
“Communication happens at many different levels and in many different ways, but all instances have one thing in common: They need underlying hardware to convey the information. I am interested in how the nervous system wires up the body during embryonic development so the brain can send and receive signals.”

Proteins, like people, are often judged by the company they keep. A protein known as p75, for instance, belongs to the same family as tumor necrosis factor, a protein that can induce cell death. Thus, in addition to regulating neuronal growth, survival and degeneration and guiding nerve fibers in growing embryos to their final destinations, p75 was widely thought to mediate cell death in some context.

Various in vitro studies have examined p75 in combination with beta amyloid, seeking evidence that it helps induce nerve cell death in Alzheimer’s disease. A team of scientists in Lee’s laboratory, however, found that p75 instead has a neuroprotective effect on the sympathetic nervous system.

Scientific interest in the peripheral nervous system has been growing as investigators studying neurodegenerative diseases seek new insights into disease progression. To gather evidence about p75 and the sympathetic nervous system, Lee’s group crossed a mouse model for Alzheimer’s disease with a line of mice genetically modified to lack the gene for p75. Without p75, they theorized, the neurotoxic effects of beta amyloid would be reduced, and the mice would show fewer Alzheimer’s symptoms.

Along with profound motor problems, the p75-deficient mice exhibited severe defects in the wiring of nerves to multiple organs, and the majority died within just three weeks. (Mice normally live up to two years.) But when the researchers scaled down the production of toxic beta amyloid by deleting one copy of BACE1, which encodes the molecular shears that make the first cut in the production of beta amyloid fragments, the nerves in the sympathetic nervous system of p75-deficient mice were substantially restored.

This was the first time the interplay between p75 and beta amyloid in the peripheral sympathetic system has been demonstrated. Lee’s findings not only challenge the prevailing view of p75’s harmful role in Alzheimer’s, but could lead to new insights and, ultimately, new protocols for managing the secondary deficits that accompany the condition’s hallmark dementia and memory loss.

For more information, please visit www.salk.edu/faculty/lee

From left to right: Evan Booker, David Vierra, Akhila Alapati, Peter Gray, Ariela Haimovich, Soheil Karbassi, Kuo-Fen Lee, Jiqing Xu, Bertha Dominguez, Thomas Gould, Debbie Doan, Zhijiang Chen
In biology, the ability to turn something on is always coupled with a mechanism to turn it off. In the absence of this regulation, a biological system is akin to the ‘Sorcerer’s Apprentice,’ who set in motion a chain of events over which he had no control. TAM receptors play this role in the immune system: They regulate the innate immune responses to bacteria, viruses and other pathogens, ensuring that it is strong enough to defeat these threats, but not so strong that it endangers the host.

Antigen-presenting cells or APCs, which provide the body’s first line of defense against disease-causing bacteria and viruses, are constantly on the prowl in search of pathogens. When they encounter foreign invaders, they unleash a “cytokine storm”—a wave of chemical messengers that jumpstart the T and B cell response. When the invaders have been successfully vanquished, the APCs need to shut down; otherwise, chronic inflammation ensues, overwhelming the regulatory mechanisms that normally distinguish “self” from “non-self,” leading to autoimmune diseases such as lupus and rheumatoid arthritis.

Lemke and his team explored how the so-called TAM receptors (Tyro3, Axl, Mer) in mice stop the immune system from mounting an out-of-control, destructive inflammatory response against invading pathogens. When receptors studded on the surface of patrolling APCs encounter a pathogen, the cells release an initial burst of cytokines, which is then amplified in a second stage through cytokine receptors. But this same activation pathway trips the fuse that is designed to prevent the inflammatory response from spiraling out of control.

The researchers found that a stimulator of inflammation—the type 1 interferon receptor (IFNAR)—turns on the expression of Axl, a TAM receptor. Axl and IFNAR then physically bind together and activate SOCS genes, whose products are potent inhibitors of pro-inflammatory signaling pathways. Without TAM receptors, they discovered, the APCs never shut down after their initial activation, but remain in a state of red alert.

Knowing how important TAM receptors are to the control of inflammation in mice will not only aid our understanding of human immune system disorders but might enable researchers to manipulate the switch in ways that could be clinically beneficial. For example, a drug that inhibited TAMs in the short term could be given along with a therapeutic vaccine in order to help the body mount a better immune response. Conversely, it may be possible to engage the TAMs early in an immune reaction to treat chronic autoimmune diseases such as lupus.

For more information, please visit www.salk.edu/faculty/lemke.
“While signal transduction is traditionally seen as a sequence of protein interactions and modifications, it has become clear that these events are also spatially controlled through plasma membrane compartmentalization. To further understand this, my lab studies the architecture of the plasma membrane in general, as well as its contribution to signal transduction in T cells.”

In eukaryotes, the plasma membrane—a double layer of lipid molecules that encloses all cells—not only segregates the cell from its environment, but also serves as the principal interface for communication between cells. Not surprisingly, the plasma membrane’s structure and properties impact many biological processes. T cells, whose main job is to fight infection, for example, utilize and reorganize their plasma membrane constantly during activation and effector functions. This is most dramatically seen in the establishment of signaling microclusters and the formation of the immunological synapse between T cells and antigen-presenting cells upon activation of the former by the latter.

He discovered that all membrane-associated proteins in the cells that he examined are clustered into what he refers to as “protein islands,” which led him to postulate a novel concept for the general architecture of plasma membranes. Lillemeier also found that the T cell receptor signaling cascade is spatially and temporally controlled through the segregation and association of distinct membrane microdomains (protein islands) that contain specific subsets of T cell signaling molecules. He believes that this type of signal control may be a general feature of membrane-associated signaling and is probably used in a variety of signaling processes.

Lillemeier will expand his research to understand how this higher order in the plasma membrane is achieved and what molecular mechanisms are in place to utilize it during signal transduction. His studies will help to expand knowledge of spatio-temporal signaling control, which will suggest new approaches in manipulating the response of the immune system to pathogens and diseases.

For more information, please visit www.salk.edu/faculty/lillemeier

From left to right: Christian Klammt, Supriyo Ray, Björn Lillemeier, Amy Blount, Tom Li
“I am fascinated by the complex DNA transactions that chromosomes undergo—particularly the types of events that occur at telomeres, the very tips of chromosomes. When these telomere-associated DNA processes start to run out of steam or, conversely, become overly active, this can lead to either premature aging or cancer predisposition.”

Whether cells have a finite or infinite ability to proliferate is determined by the ends of the chromosomes, called telomeres, which are tended to by a dedicated enzyme called telomerase. In cells where telomerase is inactive, telomeres shorten with each cell division until they become so whittled away that they signal the cell to stop dividing; cells that retain telomerase are able to continue dividing indefinitely.

Although our knowledge of how telomerase is regulated in human cells remains incomplete, researchers do know that there is a telomerase complex, which was first identified in simple single-celled organisms. Lundblad’s group discovered the key protein subunit of telomerase in budding yeast, providing the tools to identify its human counterpart. In budding yeast, telomerase consists of three proteins, called Est (for “ever shorter telomeres”). The Est2 protein, together with a telomerase-dedicated RNA, does the heavy lifting in terms of telomere reconstruction, while Est1 and Est3 help orchestrate the process.

Lundblad’s lab is now looking for the proteins that tell telomerase when and how to act, again using budding yeast as the starting point. Earlier, her group found a clue when they showed that a small area on the surface of Est1 acted like molecular Velcro, by attaching Est1 (and thus the rest of the telomerase complex) to a telomere-bound protein, thereby ensuring that yeast cells continuously divide. Simply changing a single amino acid on this site prevented telomerase from reaching the ends of chromosomes, and the telomeres shortened.

Lundblad’s group postulates that there must be multiple docking points on the surfaces of the three Est proteins, each performing a distinct regulatory activity. To test this, they are surveying the entire surface of the telomerase complex. So far, her group has identified two additional molecular tethering points, on Est1 and Est3, and they are hot on the trail of the proteins that interact with these two sites.

For more information, please visit www.salk.edu/faculty/lundblad
In order to develop new and effective treatments for diabetes, researchers need to understand the complex and delicate biology behind human metabolism as well as the disorders that develop when this finely tuned system is out of balance.

When a person’s blood sugar level is high even when the person hasn’t recently eaten—known as an “elevated fasting glucose level”—it provides a first clue that he or she is at risk of developing type 2 diabetes.

Finding ways to lower blood glucose offers great promise for diabetes treatment because doing so reduces the risk of the many diabetes complications that substantially affect the quality of life. The need for new drugs is accelerating as almost 26 million Americans have type 2 diabetes, and an estimated 79 million people are at risk of developing the condition.

During the day, when we feed, we use high-octane glucose from the food we take in to get around. And at night, when we fast, our body shifts to burning the fat from adipose stores, which provide a lower-power but longer-lasting source of energy.

Although most organs in the body can use glucose or fat as a source of energy, the brain requires glucose during both night and day. The liver assumes this task during fasting, when it becomes a glucose-producing organ. Obese individuals with insulin resistance produce too much glucose, leading to elevated glucose levels in the bloodstream that contribute to the development of type 2 diabetes.

The Montminy lab identified the function of a genetic switch, called CRTC2, which controls the production of glucose by the liver during fasting and in diabetes. The researchers found that the CRTC2 switch is turned on in liver cells during fasting in response to a hormone called glucagon. Glucagon flips the CRTC2 switch on in liver cells by causing a chemical change in CRTC2 known as de-phosphorylation. The group showed that inactivating the CRTC2 switch blocked the hormone’s ability to stimulate glucose production by the liver during fasting.

In recent studies, the Montminy lab has determined that the CRTC2 switch controls glucose production through an enzyme that associates with the switch. Inactivating this enzyme with a small molecule inhibitor was sufficient to lower blood glucose levels in obese, insulin-resistant mice. These findings may offer new targets for drug development and provide effective therapies for the treatment of type 2 diabetic individuals.

For more information, please visit www.salk.edu/faculty/montminy
Axel Nimmerjahn
Assistant Professor
Waitt Advanced Biophotonics Center
Richard Allan Barry Developmental Chair in Biophotonics

“My lab studies an enigmatic set of cells called glia, which are involved in many nervous system injuries and diseases. Most treatment efforts have focused on neurons, but determining how glial cells function normally and become dysfunctional in disease is critical for development of new and improved treatments for such disorders.”

The human brain consists of an incredibly diverse set of cells, and each cell type fulfills highly specialized functions in cellular networks of dazzling complexity. While much research has focused on understanding the circuits formed by neurons, glial cells account for up to 90 percent of cells in the human brain and around half of its volume. These cells were long believed to play a merely passive, supportive role. However, over the past few years it has become clear that glia make crucial contributions to the formation, operation and adaptation of the nervous system. Additionally, glial cells are involved in many injuries and diseases, including cancer, Alexander’s disease and amyotrophic lateral sclerosis.

Work in Nimmerjahn’s laboratory centers on developing microscopic tools that enable the study of glial cells and their interaction with other cells in the normal and diseased brain. He and his team have developed tools for staining and genetically manipulating specific cell types, imaging cellular dynamics in the brain and automating analysis of large-scale imaging data. Using these tools, they showed, for example, that “resting” microglia—the resident immune cells within our brain—have highly mobile branches that provide extensive and continuous surveillance of intercellular spaces, and that upon local disruption of the blood-brain barrier, microglia rapidly shield the site of injury and clear cellular debris. Using custom miniature fluorescence microscopes, Nimmerjahn’s team provided the first optical measurement of neuronal and glial activity during behavior. This allowed them to reveal unknown forms of neuronal and astroglial excitation and to determine how these dynamic patterns are altered by behavior and anesthesia.

Nimmerjahn’s laboratory currently focuses on the development of new, integrated tools for study of glia–neuron and glia–vascular interactions in superficial and deep regions of the healthy and diseased brain. This work promises to yield better understanding of glial cells’ role in information processing, regulation of vascular dynamics, and brain disorders that either result from, or are exacerbated by, defective or disordered glial function, such as migraine, stroke or cancer.

For more information, please visit www.salk.edu/faculty/nimmerjahn

From left to right: Yusuf Tufail, Pavel Shekhtmeyster, Christopher Aprea, Axel Nimmerjahn, Charles Clark, Da Meng
“Nature has been perfecting enzymes for at least three billion years because they carry out the hundreds of thousands of chemical reactions in all organisms, and these reactions are needed by us all to survive and prosper. We could learn a lot by understanding that three-billion-year-old experiment.”

Noel’s laboratory explores how specialized enzymes and metabolic pathways allowed plants to adapt and spread across the planet and what these mechanisms can tell us about improving modern-day agriculture. His team discovered a family of plant proteins that plays a role in the production of seed oils, substances important for animal and human nutrition, biorenewable chemicals and biofuels.

Plant oils are composed primarily of triglycerides, formed by linking together three fatty acid molecules, and are stored mostly in seeds, where they are used for energy during germination. Seeds are crucial sources of oils for nutrition, flavoring and industrial applications, such as the production of soap, cosmetics and biofuels. With growing concerns about global climate change and petroleum security, producing biofuels for use in transportation and energy generation is a burgeoning industry.

Scoring a rare scientific hat trick, Noel’s lab identified three related proteins in thale cress plants (Arabidopsis thaliana) that regulate the metabolism of fatty acids, chemical components of all cell membranes and vegetable oils. They dubbed these fatty-acid–binding proteins FAP1, FAP2 and FAP3. They found that the proteins bind fatty acids, including the major plant omega-3 fatty acid, an important nutritional component found in certain seeds.

This work has major implications for modulating the fatty acid profiles of plants, which is important to sustainable production of food, biorenewable chemicals and fuels. Because very high-energy molecules such as fatty acids are created in the plant by solar energy, these types of molecules may ultimately provide the most efficient sources for biorenewable products.

The findings of Noel’s lab may lead to the development of improved crops yielding higher qualities and quantities of oils, helping to address growing demands for food and fuel and the consequent environmental pressures on the world’s ecosystems. The discovery may also help bioengineers focused on creating new enzymes for industrial uses by revealing how nature evolves proteins into chemical machines known as enzymes.

For more information, please visit www.salk.edu/faculty/noel

Back row, left to right: Mingli Ye, Jing-Ke Weng, Hyun Jo Koo, Helena Sun, Yongxia Guo, Charles Stewart, Ryan Philippe

Front row, left to right: Gordon Louie, Marianne Bowman, June Brennan, Joe Noel, Charisse Crenshaw, Justin Pacheco, Kate Woods
“Identifying mechanisms that regulate brain development is requisite for understanding the basis of most neurological disorders and disease and is essential both for prevention and for developing repair strategies.”

Dennis O’Leary, together with his research group, studies critical genetic and molecular mechanisms that regulate brain development, using the mouse as a primary model system. His work focuses on two important questions: how the brain assembles itself during development, including its wiring, and how different parts of the cerebral cortex, the largest and most complex part of the brain, become uniquely specialized to perceive vision and touch, as well as generate movements. O’Leary’s goal is to understand the mechanisms used by the brain to accomplish these crucial tasks, providing the knowledge required to prevent genetic disorders and disease or to repair defects.

O’Leary’s previous work demonstrated that specific wiring between parts of the brain or from the eye to the brain arises from initially exuberant connections between neurons, followed by a selective pruning, occurring by the degeneration of many of the early connections to retain only the correct ones. These connections are formed by axons, the outgoing “wires” on each cell that convey electrochemical impulses between neurons. Among O’Leary’s current work, he is studying the molecular mechanisms that decide which axons die or live, and once this selection is made, how those axons fated for death are actually eliminated. This work has important implications for the mechanisms that underlie most, if not all, neurodegenerative diseases, including Alzheimer’s and Parkinson’s.

In a distinct set of projects, O’Leary has recently identified specific transcription factors (proteins that regulate large sets of genes to specify the properties of cells and tissues) that specify progenitors, or natural stem cells, in the developing brain to make parts of the cerebral cortex that are specialized to process vision or touch. By manipulating these genes in mice, he can, for example, make the visual or touch processing parts of the cerebral cortex larger or smaller, which initiates a cascade of changes in other parts of the brain outside the cerebral cortex and has a significant influence on behavior. This work has implications for many neurological disorders, including autism and other genetic-based brain disorders that have prominent behavioral components.

A common link among the studies performed by O’Leary and his research team is the identification of genes that control important developmental functions and the molecular mechanisms by which they operate, thereby providing a framework for potential treatments in the future.

For more information, please visit www.salk.edu/faculty/o’leary
“One of the burning questions in contemporary cancer research is, ‘What are the critical therapeutic targets that uncouple aberrant growth and survival?’ I am employing viruses to pin down key cellular processes that are dysfunctional in cancer cells and to develop novel, virus-based cancer therapies.”

If a cell suffers non-repairable injury to its genetic material, or cell growth starts to go astray, the tumor suppressor protein p53 pulls the emergency brake, a built-in “auto-destruct” mechanism that eliminates abnormal cells from the body before they can cause disease, including cancer. To sidestep the cell’s suicide program—a process called apoptosis—tumor cells need to inactivate p53, which turns on genes that mediate cell cycle arrest and apoptosis.

Similarly, adenovirus, which causes upper-respiratory infections, needs to get p53 out of the way to multiply successfully; therefore it brings along a viral protein, E1B-55K, which binds and degrades p53 in infected cells. Without E1B-55K to inactivate p53, adenovirus should only be able to replicate in p53-deficient tumor cells, making it the perfect candidate for oncolytic cancer therapy. Oncolytic viruses offer a novel and potentially self-perpetuating cancer therapy: Each time a virus infects a cancer cell and successfully multiplies, the virus ultimately kills the cancer cell by bursting it open to release thousands of viral progeny. The next generation seeks out remaining tumor cells and distant micro-metastases but leaves normal cells unharmed.

Clinical trials found such viruses to be safe and promising. Contrary to all expectations, however, patient responses did not correlate with the p53 status of their tumors. When O’Shea followed up on this unexpected finding, she discovered that the inability of the E1B-55K-mutant virus to replicate in normal cells was not because the virus failed to degrade p53. Instead, adenovirus brings along another protein, E4-ORF3, which neutralizes the p53 checkpoint through a completely different mechanism. It prevents p53 from binding to its target genes in the genome by modifying histone proteins, the “spools” around which DNA winds. With its access denied, p53 is powerless to pull the trigger on apoptosis. O’Shea and her team are now exploiting this new viral protein as a powerful tool to both pinpoint and connect critical new targets in the cellular p53 tumor suppressor network and to develop the next generation of oncolytic viruses.

For more information, please visit www.salk.edu/faculty/o’shea

Standing, left to right: Shigeki Miyake-Stoner, Kristen Espanman, Colin Powers, Zohreh Akhavan Aghdam, Horng Ou, Carine Bossard, Govind Shah

Seated, left to right: Jason DeHart, Clodagh O’Shea, Jennifer Higginbotham
“Just as the biological clock in the brain wakes us in the morning and puts us to sleep at night, clocks in every other organ tune physiology and metabolism to appropriate times of the day. When these timing mechanisms don’t work well, it can lead to sleep problems, depression, metabolic diseases, cancer and accelerated aging.”

Panda’s team explores how our biological clocks control our metabolism and physiology, as a means for coming up with new strategies to treat or prevent chronic diseases. His lab discovered that a light receptor, called melanopsin, senses blue light in our environment and tells our brain when to sleep and when to stay alert. The discovery has inspired architects and designers to redesign lighting at workplaces, homes and hospitals to improve the quality of life. His team is also actively pursuing a novel idea for finding drugs that can mimic light or dark so that diseases like depression and sleep disorders can be effectively treated.

Panda’s work on clocks outside the brain revealed that eating times synchronize clocks in other organs, including the liver, muscles and fat tissues. These clocks, in turn, orchestrate when and for how long our body breaks down sugar, fat and cholesterol.

His team may have found another option for preventing obesity by preserving natural feeding rhythms without altering dietary intake. They discovered that mice who ate fatty food frequently throughout the day gained weight and developed high cholesterol, high blood glucose, liver damage and diminished motor control, while the mice restricted to eating for only eight hours per day weighed 28 percent less and showed no adverse health effects, despite consuming the same amount of calories from the same fatty food. When given an exercise test, the time-restricted mice also outperformed the ad lib eaters and control animals fed a normal diet. The findings suggest that the control of energy metabolism is a finely tuned process that involves an intricate network of signaling and genetic pathways, including nutrient-sensing mechanisms and the circadian system. Time-restricted feeding acts on these interwoven networks and moves their state toward that of a normal feeding rhythm.

Although the findings have not yet been duplicated in humans, most successful human lifestyle interventions were first tested in mice, so Panda and his team are hopeful their findings will follow suit, providing a simple and effective lifestyle intervention to contain the obesity epidemic.

For more information, please visit www.salk.edu/faculty/panda
“Our brains are composed of neuronal circuits with an estimated 100 trillion connections. My lab is interested in unmasking the strategies that nature has devised to generate this immense diversity of cells and complexity of connections by focusing on the way that the spinal cord is assembled during fetal development. We expect this information to provide novel insight into how we can harness ‘embryonic pathways’ to repair or augment the central nervous system to treat birth defects, injuries, diseases and aging.”

The neuromuscular circuitry that controls bodily movements relies on constant sensory feedback to fine-tune its commands to hundreds of muscles. Muscle fibers are each controlled by one motor neuron in the spinal cord that relays signals from the brain. Sensory receptors send information from the periphery back to the central nervous system. These nerves are not unlike a roadway, with orderly traffic moving in both directions.

The traditional view has been that during embryonic development, sensory and motor neurons are able to incorporate into tightly coordinated pathways without getting mixed up because growth cones—structures that guide growing axons to their destination—are studded with Eph proteins that constantly search their environments for other proteins called ephrins, which nudge them in the right direction. (Axons are long projections that conduct electrical impulses away from the nerve cell body.) Researchers in Pfaff’s laboratory, however, found that neurons not only carry both types of proteins, but that the role of Ephs and ephrins can change, raising the question of what happens when adjacent neurons bump into one another.

To find the answer, Pfaff’s team studied sensory and motor neurons, which extend their axons along the same pathway to the periphery. They found that with ephrin/Eph signaling intact, the axons sorted into separate fascicles containing either sensory or motor axons, but never both. When they deleted EphA3 and EphA4 in motor neurons, however, sorting between the fascicles of the motor and sensory axons broke down; instead of reaching for muscles, some motor neurons made a U-turn, joined the sensory lane and headed back toward the spinal cord.

Ephrins and Ephs appear to control where the axons grow, as well as maintain the normal arrangement between the motor and sensory pathways. They also play a major role in preventing spinal cord neurons from regenerating after injuries. As scientists in the spinal cord field work to overcome the block preventing axonal growth within the central nervous system, Pfaff’s findings demonstrate that this research needs to be approached cautiously, lest it promote indiscriminate motor axon growth and cause severe problems.

For more information, please visit www.salk.edu/faculty/pfaff
The long-range goal of our laboratory is twofold—to understand the fundamental nature of the computations that are carried out by the neocortex and to understand how and why these computations fail in brain disease.”

Evolution has endowed our brains with a system of neural mechanisms whose function is to choose which information will be selected to guide our behavioral decisions. When this system fails, as in disorders such as schizophrenia, Alzheimer’s disease and attention deficit hyperactivity disorder (ADHD), the effects on the quality of life can be devastating. Reynolds’s team is working to decipher the neural mechanisms of attention, which are key to understanding and treating brain diseases in which the attention system fails.

At any point in time, our brains are able to process only a small fraction of the totality of information available in the sensory environment. Even if we wanted to pay attention to many things at once, there are limits on how many stimuli we can juggle simultaneously. What’s more, only a small fraction of available sensory information is needed to make effective behavioral decisions, and the information that is needed changes from moment to moment, depending on our needs and the risks and possibilities presented by our ever-changing environment. The attentional system thus plays the critical role of “perceptual gatekeeper,” selecting task-relevant information for processing while keeping distracting information from entering conscious awareness.

Reynolds’s team has found that when attention is directed toward a stimulus, attentional control centers of the brain send signals that tell the perceptual systems to favor certain circuits over others. As a result, neurons that convey information about an attended stimulus are more active, while neurons that would otherwise convey distracting information are suppressed. They have also recently discovered that attention reduces the variability or “noise” in neuronal signals, improving the quality of information about the visual stimuli to which we attend.

They are now conducting experiments to understand the neural mechanisms underlying these attention-dependent changes in neural signaling. To do this, they use a range of techniques, including neurophysiology, neuroanatomy, computational modeling, visual psychophysics and cutting-edge optogenetic techniques that enable the use of viruses to change the DNA of neurons so that they create proteins that act as light sensors. This enables them to use light to alter the activity of specific types of neurons and understand their role in perception, attention and behavior.

For more information, please visit www.salk.edu/faculty/reynolds

From left to right: Jude Mitchell, Emily Anderson, John Curtis, Hendrikje Nienborg, Anita Disney, Catherine Williams, Jonathon Nassi, John Reynolds
"Our research focuses on hormones, the chemical messengers that mediate interactions between the brain, the immune system and the neuroendocrine systems. Specifically, we investigate how the brain perceives and responds to stressors, such as drugs and alcohol, and how that plays out all the way down to the level of neuroendocrine responses."

The health of mammals depends on their ability to maintain the internal environment of their bodies within narrow and clearly defined limits in the face of physiological or psychological threats. Challenges to the body’s homeostasis—whether perceived or real—are handled by the hypothalamic-pituitary-adrenal (HPA) axis, which involves the interaction of the brain structure known as the hypothalamus, the pituitary gland (just below the hypothalamus) and the adrenal glands (at the top of the kidneys). Together, these three organs control reactions to stress and regulate many body processes, including digestion, the immune system, mood and emotions, sexuality, as well as energy storage and expenditure.

Alcohol is one of the stimuli that activate the HPA axis in rodents, but the mechanisms responsible for it are not yet fully understood. Rivier’s laboratory had shown earlier that the peptide corticotropin-releasing factor (CRF), which is produced in the hypothalamus, was essential for an appropriate HPA axis response to acute alcohol. While the ultimate effect of alcohol is the binding of CRF to specific receptors on pituitary cells, and the ensuing release of ACTH and adrenal steroids, recent experiments by Rivier and her team revealed a more complex picture of alcohol’s action on the brain. They found that alcohol increases the activity of dopamine b-hydroxylase, the enzyme directly responsible for the synthesis of norepinephrine. The latter contributes to the HPA axis’s response to alcohol, and this knowledge may help the development of specific therapies that counteract some of the deleterious effects of this drug.

Stress is thought to play a role in the ability of addicted individuals to maintain abstinence. Thus, a better understanding of the function of the HPA axis during the development of alcohol dependence, and how the activity of this axis differs between dependent and non-dependent animals, will be helpful in pursuing novel therapies for the treatment of alcohol addiction.

For more information, please visit www.salk.edu/faculty/crivier
"Remissions leading to a full recovery or relapses progressing to recurrences are characteristic of a significant number of pathological conditions. We are concentrating our efforts toward understanding how the temporal restoration of the body's homeostasis may induce remission and ideally lead to recovery."

Like a central command center, a brain area known as the hypothalamus sends out "master" brain hormones, which regulate basic bodily functions. Many of these hypothalamic hormones, including the "stress hormones" corticotropin releasing factor (CRF) and the urocortins (Ucn), as well as their two receptors (CRFR1 and CRFR2), were characterized at the Salk Institute. Because of their broad distribution, CRFs and CRFRs mediate numerous complementarily stress-related endocrine, autonomic, metabolic, immune, cardiovascular, gastrointestinal and cutaneous pathologies.

To test whether molecules that block CRF's functions may induce remissions, Rivier, in collaboration with Salk colleagues Wylie Vale and Catherine Rivier, developed a series of very effective CRF antagonists. Working with Lixin Wang, Mulugeta Million and Yvette Taché at UCLA, Rivier and his team then tested the effects of a potent and long-acting version in mice that overexpress CRF. Without treatment, these mice develop symptoms that are typical of Cushing's syndrome, such as thinning of the skin, loss of fur and fat accumulation at the midsection of the body as they get older. When treated with a CRF antagonist, however, their fur immediately started to regrow.

Under stressful conditions, the body responds initially by mounting a multipronged counterattack that normally deals successfully with acute challenges but more likely than not will fail in the face of chronic challenges. When unsuccessful, the body's defense mechanisms such as the immune system become compromised, triggering a recurrence of the disease. If the chronic stress response is mitigated either psychologically or pharmaceutically, Rivier believes that those systems recover their ability to deal with the insult, thus triggering a remission—the first step toward full recovery. He is now testing this hypothesis in animal models, including prematurely weaned pigs, which suffer from stress-induced diarrhea. Initial promising results indicate that CRF antagonists could play an important role in treating irritable bowel syndrome and, hypothetically, most other conditions initiated by or relapsing as a result of stress.

For more information, please visit www.salk.edu/faculty/rivier
“Our ability to respond to stress is a double-edged sword. In the short term, stress responses facilitate our ability to cope with real or perceived threats to our well-being. If stress exposure is repeated or sustained, however, these responses can precipitate or worsen any number of pathological states, including neurodegenerative diseases.”

The typical signs of an infection—fever, listlessness, lack of appetite—are orchestrated by the brain in response to inflammatory cytokines, which are the immune system’s signaling molecules. Cytokines are generated at the site of infection, then circulate in the blood and communicate with neurons in the brain to engage the hypothalamic-pituitary-adrenal (HPA) axis, an integral part of the brain’s stress response machinery.

But cytokines are big molecules, and how their reach extends beyond the almost impenetrable blood-brain barrier has been the topic of much dispute. Earlier research by Sawchenko and others suggested a vascular route whereby cytokines interact with vessel walls to generate secondary messengers, which then engage the relevant circuitry in the brain. Tightly packed endothelial cells, which line narrow capillaries throughout the brain, are perfectly positioned to record circulating immune signals, but they require a very strong signal to become activated. Perivascular macrophages, on the other hand—specialized white blood cells that digest cellular debris and pathogens and are lined up along the blood-brain barrier—are more sensitive but lack direct access to the bloodstream.

To determine the role of these two cell types, Sawchenko’s group recently injected liposomes containing clodronate, a drug that can cause cell death, into the lateral cerebral ventricle of rodents. The liposomes were taken up by the macrophages, which were killed off. Without perivascular macrophages, the animals were unable to respond to blood-borne interleukin-1, which is a cytokine, and initiate the brain’s so-called acute phase responses, which help the body tackle the challenge at hand but also cause the feeling of “being sick.” To their surprise, however, Sawchenko’s team found that the same cells suppressed the pro-inflammatory activities of endothelial cells, which are only stirred to action when they encounter lipopolysaccharide, a key component of the cell walls of certain bacteria.

The identification of a potent anti-inflammatory mechanism in the brain may pave the way for new therapies for chronic neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson’s, Alzheimer’s and prion diseases, in which central inflammatory mechanisms play an important role.

For more information, please visit www.salk.edu/faculty/sawchenko
“Our research group is using a novel drug discovery paradigm developed in our laboratories to make drugs for Alzheimer’s and Parkinson’s diseases, stroke and diabetic complications. The goal is to get these new drugs through the initial stages of development and into the clinic as rapidly as possible.”

There are currently no effective treatments for any age-associated neurological disease, including Alzheimer’s, Parkinson’s or the neurological complications of diabetes. There are many reasons for this deficiency. One is the innate disease complexity, for in most cases the nerve cells die from multiple stresses and toxins. Therefore, drugs to treat these conditions must block the different pathways that together kill cells, not just a single target.

Plants synthesize drug-like molecules to defend themselves against pathogens and predators. Most of these molecules have numerous biological activities, but they have not yet been exploited for the treatment of neurodegenerative diseases. Scientists in the Schubert laboratory are using a series of innovative biological assays to identify plant products that are broadly neuroprotective. They then use medicinal chemistry to improve their drug-like properties. To date, they have identified two lead compounds that meet the above criteria and have synthesized a series of much more potent derivatives that maintain the multiple biological activities of the parents.

The first is fisetin, which is found in strawberries and is orally active in animal models of Alzheimer’s, Huntington’s and Parkinson’s. It is also very active in rodent models of stroke. Fisetin has a unique ability to protect from the vascular inflammation that is associated with all neurodegenerative conditions. Schubert’s team also has made potent synthetic derivatives of curcumin, the major component of the Indian spice turmeric, that work extremely well in animal models of Alzheimer’s and ischemic stroke. Some members of both groups of compounds are ready to start the FDA drug approval process, pending funding.

This work is being extended in three areas: refinement of the chemical structures to improve their pharmacological properties, characterization of the multiple molecular pathways that are responsible for the exceptionally neuroprotective properties, and testing in additional animal disease models. The ultimate goal is to get these compounds to the clinic to treat diseases for which there are currently no cures.

For more information, please visit www.salk.edu/faculty/schubert

From left to right: Chandramouli Chiruta, Antonio Jose Martins Currais, Pamela Maher, David Schubert, Marguerite Prior, Richard Dargusch, Jennifer Ehren
“My goal is to discover the principles linking brain mechanisms and behavior. My laboratory uses both experimental and modeling techniques to study the biophysical properties of neurons and synapses, the sites at which neurons connect with each other, as well as the population dynamics of large networks of neurons.”

Multiple sclerosis affects an estimated 400,000 Americans and more than 2.5 million people worldwide. A chronic, often disabling disease that attacks the central nervous system, it is characterized by a baffling range of neurological symptoms, including numbness, tingling, motor weakness, paralysis and vision loss. It is thought to result when the immune system attacks the myelin sheath that insulates axons, the nerve fibers that conduct electrical impulses to and from the brain and between neurons within the brain. Ordinarily, the myelin speeds up the signals the axons transmit, but when axons lose their insulation, either signal conduction fails because the demyelinated axons are unable to generate an impulse, or the axons become hyperexcitable and overcompensate by firing even in the absence of an input.

The first computer model of axonal transmission, developed in the 1950s for the giant axon of the squid, which lacks myelin, tracked positively charged sodium and potassium ions, whose movements across the neuronal membrane generate the necessary electrical signals. Building on that model, Sejnowski and his team included myelin in their own model, then demyelinated one of the sections and incorporated all the changes known to take place as a result. Most prior studies had focused on the sodium channel because it is responsible for initiating the electrical signal. But to everyone’s surprise, Sejnowski’s group found that it was the ratio of densities between the sodium channel and a previously ignored but ubiquitous voltage-insensitive potassium current, called the leak current, that determines whether neurons can fire properly.

If the sodium level drops, an accompanying drop in the leak current will maintain the signal, whereas if the sodium drops but the leak current doesn’t, signal transmission may fail. Conversely, if the sodium level is too high and the leak current doesn’t increase, a patient may experience twitching. Sejnowski’s model not only offers an explanation for many of the bizarre symptoms that multiple sclerosis patients experience but could also provide a new target for drugs that increase or decrease the potassium leak current to maintain a constant ratio and offer relief.

For more information, please visit www.salk.edu/faculty/sejnowski
“Neurobiologists are on a perennial quest to understand how the brain codes stimuli in the environment. In the past, scientists had to rely on simplified objects on a computer screen. I try to take it a step further and analyze how brain cells respond to stimuli typical of our natural environment.”

Sharpee’s lab works on theoretical principles of how the brain processes information and explores how sensory processing in the brain is shaped by our need to create representations of events in the outside world. Researchers used to rely on simplified objects on a computer screen or random stimuli to garner information on how the brain processes visual information. But our brains are meant to operate in a remarkably complex and fast-changing world, so these methods offered limited insight into the brain’s workings. In contrast, natural stimuli, such as a short video clip or sound recorded during a stroll on a forest trail, are often much better for probing neural responses. This is particularly true when studying intermediate and high-level neurons in the brain that translate sensory stimuli from the environment into meaningful information. These neurons rarely respond to simple patterns that are devoid of recognizable real-world objects, but they will respond to the rich ensemble of object combinations found in our environment.

Sharpee and her colleagues are developing methods to identify which features of natural stimuli cause a response in high-level neurons and how the brain prioritizes and makes sense of this information. A key obstacle to understanding how our brain functions is that neurons respond in highly nonlinear ways to complex stimuli, meaning that signals are amplified and suppressed in unexpected ways. As a result, stimulus-response relationships are extremely difficult to discern.

To address this, Sharpee’s team has worked out rigorous statistical methods for modeling how visual and auditory stimuli are coded and decoded through nonlinear transformations in different brain centers. These studies are beginning to uncover the common principles of hierarchical information processing in the brain and will help us better understand how neurological disorders and injuries interrupt these crucial processes. Knowing how information moves through our sensory systems may offer new strategies for helping people with impairments, such as improving the performance of retinal implants that could help restore vision in the blind.

For more information, please visit www.salk.edu/faculty/sharpee
“We investigate the mechanisms connecting cell metabolism to growth control by studying an ancient signaling pathway that goes awry in both cancer and type 2 diabetes. By understanding the connection between these diseases, we pave the way to better therapies for both.”

While investigating one of the most commonly mutated genes in lung cancer, LKB1, Shaw’s lab discovered that the gene directly activates a metabolic master switch known as AMPK. This direct connection of LKB1 to AMPK provided a stronger molecular link between cancer and diabetes than was ever known previously. The lab went on to molecularly decode a number of new components of this biochemical pathway that connects nutrition to both cancer and diabetes. In the past two years, their studies have led to the discovery of new therapies for both cancer and type 2 diabetes.

Recently, Shaw’s group found that AMPK initiates a cellular recycling process known as autophagy, which allows cells to dispose of toxins, by activating an enzyme known as ULK1. To test the effects on autophagy of deregulating these enzymes, the group focused on large intracellular structures called mitochondria, whose role is to generate energy. Mitochondria are easily damaged in detoxifying tissues like liver, and defective mitochondria are turned over through a special form of autophagy called mitophagy. The researchers found that the ability to recycle their defective mitochondria allowed cells to survive starvation better. This work suggests that drugs regulating ULK1 itself may be useful for treating certain forms of cancer or metabolic disease.

The Shaw lab also discovered another new set of AMPK targets, but in this case focused on targets that may be key for diabetes, knowing that AMPK is one of the critical enzymes controlled by the widely used diabetes drug metformin. They discovered that proteins known as histone deacetylases (HDACs) are regulated by AMPK and play a vital role in directing glucose production in the liver. Normally, in response to fasting, hormonal cues tell the liver to produce its own glucose from scratch to keep the body alive, and these HDACs are required in liver cells for the hormone to transmit that signal. This new finding—that HDACs play a critical role in diabetes—further connects metabolic disease with cancer. Prior to this, a number of HDAC inhibitor drugs were being evaluated in clinical trials as potential treatments for cancer, some of which now may find utility in the treatment of diabetes.

For more information, please visit www.salk.edu/faculty/shaw
Drugs of abuse can produce long-term changes in the electrical activity of neurons in the brain. Recently, we have been researching a new role for GIRK potassium channels—proteins that control the movement of potassium ions in the brain—in drug addiction. Our studies may provide new insights into the cellular mechanisms of drug addiction as well as some mental disorders, such as depression and attention deficit hyperactivity disorder (ADHD).

Dopamine is a primary neurotransmitter used in the brain’s reward pathway. The activity of dopamine neurons in the reward pathway increases in response to rewards, such as sex, food and drugs. Psychostimulants, such as methamphetamine and cocaine, co-opt this pathway and alter the brain’s response to dopamine. Understanding the neuroadaptations that occur in the reward pathway in response to consumption of abused drugs is a critical step in the development of treatments for drug addiction.

Previous research has shown that use of cocaine and methamphetamine in mice enhances excitatory connections to dopamine neurons. Slesinger and his colleagues have been examining the function of neurons that inhibit dopamine transmission, namely GABA neurons. Slesinger and collaborators recently found that psychostimulants profoundly change the function of these inhibitory GABA neurons. With a single injection of cocaine or methamphetamine, these GABA neurons become unable to control their firing and release more than the usual amount of inhibitory GABA neurotransmitter. This profound change in inhibitory neuron function persists for up to seven days after the injection, suggesting that the psychostimulant creates a cellular memory trace of the drug exposure.

Slesinger’s team investigated the biochemical underpinnings of this memory trace and discovered that there is an increase in the activity of a protein phosphatase, which regulates the levels of a GABA\(\beta\) receptor and a potassium channel known to be important for controlling the electrical activity of the inhibitory neurons. A decrease in signaling through the GABA\(\beta\) receptor and potassium channel results in an increase in excitability of the inhibitory neurons, indicating a possible compensatory mechanism that could be protective during exposure to drugs. The Slesinger lab is currently examining how chronic use of psychostimulants alters this inhibitory signaling pathway and how these changes lead to the acquisition of drug addiction in humans.

For more information, please visit www.salk.edu/faculty/slesinger
“The goal of my laboratory is to learn what classes of mathematical computations are carried out by neural circuits and what design principles govern the construction of these circuits. This research starts with various types of experimental data—relating to brain structure, function and development—and uses techniques employed by theoretical physics to discover general biological principles that apply to the brain.”

Virtually all of the neural circuits in the vertebrate brain possess what computer scientists call a scalable architecture, allowing them to increase their computational power by simply growing in size while conforming to a single basic design. The vast majority of computers currently in use have what is known as a von Neumann architecture, which is not scalable. For evolution to work, however, brains need to be able to adapt to increased demands without the need for significant reconfiguration. Research in Stevens’s laboratory is aimed at learning the design principles that endow vertebrate neural circuits with a scalable architecture.

How can the scalability of neural circuits be studied? Most vertebrate brains—for example, the human brain—are nearly the same size for a given species, so that circuits of very different sizes are not available for comparison. Brains across a series of evolutionarily related species, such as primates, have a range of sizes that can be studied, but these brains are not necessarily comparable because of adaptive specializations of specific species. Stevens is interested in discovering principles that govern all vertebrate brains, so he started by comparing the brains of a single species, goldfish, which come in a variety of sizes but are strictly comparable. Fish, unlike mammals, continue to grow throughout their lives and add new nerve cells to their neural circuits as they grow older and larger. Of course, any principles discovered in fish must be confirmed by studies in mammals.

Scalability implies that quantitative aspects of brain structure and function follow what are called scaling laws—orderly relationships that, for example, dictate for all brains how the number of neurons in one brain area is related to the number of neurons in a second area that receives information from the first one. These scaling relations embody general design principles, so the job of a theorist is to figure out the computational significance of the scaling laws and learn how the brain grows in a way that conforms to the scaling law during the organism’s development.

For more information, please visit www.salk.edu/faculty/stevens
Nervous systems generate behaviors through the coordinated activity of specific neural circuits. During development, these circuits are formed by growing nerve cells extending long projections called axons, which hook up with other nerve cells or with muscles to control locomotion. At the tip of each growing axon is the growth cone, which steers the axon to its target cells by responding to cues in the extracellular environment. Capitalizing on our advanced knowledge on the genetics of the fruit fly *Drosophila*, Thomas’s lab has identified key molecules in the axon’s navigation system that govern basic events common to all nervous systems, such as axons growing from one side of the brain to the other or projecting out of the nervous system to connect with muscles.

Crosstalk between the two sides of the nervous system is essential for many behaviors, from simple coordinated locomotion to the integration of higher cognitive functions. Its importance is underscored by the large number of nerve cells that project their axons across the midline to the opposite side. Thomas has identified a number of axon guidance molecules, including receptors on the growth cone that bind to specific ligands in the extracellular environment, guiding axons along specific routes across the midline. These receptors and ligands belong to larger families of related molecules that have also been found to guide axons in mammals. This means these guidance molecules are deeply rooted in who we are, whether we are a fly on the wall or a human being wielding a flyswatter.

Once the neural circuits are formed during development using the axon guidance molecules, how do they generate behaviors? The Thomas lab activates and inactivates specific nerve cells to understand the circuit that generates locomotion. Just like the axon guidance molecules, the principles of how circuits generate locomotion in flies will be important to understanding the neural basis of locomotion in higher vertebrates, including humans.

For more information, please visit www.salk.edu/faculty/thomas
“One of the major interests in our laboratory is understanding the molecular mechanisms of cancer and the role of inflammation, which is the underlying cause of many diseases.”

The mouse has long provided researchers with valuable insights about cancer. But the most commonly used technique for producing a cancer mouse model—transplanting human tumor tissue or cancer cell lines in immunocompromised mice—ignores the role of the immune system in cancer. Other animal models either express oncogenes in a tissue-specific manner or shut down the expression of tumor suppressor genes in the whole tissue. But tumors generally develop from a single cell or a small number of cells of a specific cell type, which is one of the major determinants of the characteristics of tumor cells.

To create a better mouse model, researchers in Verma’s laboratory turned to gene therapy techniques, using modified viruses to infect cells and ferry activated cancer genes (oncogenes) into a small number of cells in adult, fully immunocompetent mice. After initial experiments confirmed that the approach was working, his team injected viruses carrying two well-known oncogenes into three brain regions of mice lacking one copy of the gene encoding the tumor suppressor p53. They specifically targeted astrocytes, star-shaped support cells that are suspected of being the source of glioblastoma, the most common and deadly human brain cancer. Within a few months, massive tumors that displayed all the histological characteristics of glioblastoma developed in two of the regions.

To test whether the induced glioblastomas contained cancer stem cells, the investigators isolated and cultured individual tumor cells in the lab, which looked and behaved just like neural stem cells. Less than 100 and as few as ten cells were enough to initiate a tumor when injected into immunodeficient mice. These findings show that this cancer model will not only allow scientists to gain new insights into the biology of glioblastoma but will also help them answer many questions surrounding cancer stem cells. Verma and his team are currently using this methodology to investigate lung and prostate cancers.

Verma’s lab is also exploiting the technologies developed for gene therapy to generate induced pluripotent stem cells (iPCs) from patients and converting them into hematopoietic stem cells, hepatocytes and lung cells.

For more information, please visit www.salk.edu/faculty/verma
Geoffrey M. Wahl
Professor
Gene Expression Laboratory
Daniel and Martina Lewis Chair

“We are studying the genetic basis of the origin and progression of cancer and developing new strategies to tailor-make drugs based on the genetic signature of a patient’s tumor.”

Significant advances in breast cancer prevention and treatment have come from strategies based on knowledge of mammary cell biology and the unique molecular fingerprints of individual tumors. Despite such advances, however, more than 40,000 patients in the United States and about 500,000 worldwide will die of breast cancer in the next 12 months. In too many cases, treatment failures resulting from emergence of drug-resistant cells and metastases will shorten lifespan and reduce quality of life. The overarching issue the Wahl lab addresses is whether a better understanding of the stem-like cells Wahl and others have found in many breast cancers could provide clues to the development of more effective treatment strategies.

During the 1800s pathologists and developmental biologists emphasized that understanding cancer requires deep knowledge of the principles governing the development of the tissue of origin in which the cancer will arise. Thus, even in the 19th century, scientists appreciated that cancer is a caricature of normal development. Wahl’s group therefore expended considerable effort studying the development of the mouse mammary gland in the hope that it would provide insight into the types of cells and processes that are perturbed in the generation of human breast cancers.

His team recently reported the first identification, isolation and characterization of mouse fetal mammary stem cells (fMaSCs) and their associated gene expression profiles. Significantly, they found that many growth regulatory pathways present in fMaSCs appear to be enriched in specific patients with aggressive and frequently chemoresistant basal-like and triple-negative cancers. This is important, as these cancers currently lack molecular targets around which to build personalized therapeutic agents, such as Herceptin for those breast cancers that overexpress Her2 (a growth factor receptor that Herceptin inactivates). The researchers tested whether currently available targeted therapeutic agents directed against some fMaSC growth factor pathways would inhibit their growth and found that the agents tested worked well to inhibit fMaSC growth.

Wahl and his group are now doing the work needed to extend these studies to the clinic in the hope that this basic research can be translated to the bedside to help patients with breast cancers that currently lack targeted therapeutic strategies. An implication of the work is that cells that fuel cancer progression may revert to, or acquire, gene expression characteristics initially found in the stem cells of the embryonic tissue of origin.

For more information, please visit www.salk.edu/faculty/wahl

From left to right: T. Morrell, Rose Rodewald, Justin La, Payal Desai, Geoff Wahl, Ben Spike, Miranda Cox, Chris Dravis, Leo Li
“We are trying to expand the genetic code and insert artificial amino acids into proteins in mammalian cells and multicellular organisms, which provides novel tools to address questions that are insurmountable with conventional means. We may also use these amino acids to build new proteins as novel therapeutics.”

Cells provide a dazzling variety of functions that cover all of our body’s needs, yet they make do with a very limited number of molecular building blocks. With few exceptions, all known forms of life use the same common 20 amino acids—and only those 20—to make all the proteins necessary to keep organisms as diverse as humans, earthworms, tiny daisies and giant sequoias alive. During protein synthesis, amino acids are brought out one by one by molecules known as transfer RNAs (tRNAs) and added to the growing protein chain according to the instructions spelled out in the body’s genes. This continues until a stop codon—for which no corresponding tRNA exists—lets everybody know that this particular job is done.

By generating a new tRNA to recognize the stop signal, novel amino acids can be attached to this tRNA and inserted into any protein, potentially generating new functions for the protein. However, stop codons also are naturally recognized by proteins called release factors to terminate protein translation, which results in competition between the new tRNA and the release factor. The efficiency for inserting novel amino acids is often less than 10 percent, and it is extremely difficult to put them at multiple places in a protein. These problems have prevented people from creating new protein properties by harnessing the power of the novel amino acids.

Release factors have been thought to be essential for the life of bacteria since the 1980s, but Wang and his team recently discovered that one release factor could be removed from Escherichia coli, a workhorse bacterium for protein expression. They created multiple new E. coli strains, which are able to insert new amino acids at the stop signal with an efficiency of 99 percent, close to that of natural amino acids. In addition, without the competition of the release factor, these new bacteria now allow the novel amino acid to be simultaneously inserted at multiple places, which was not feasible before with any other organisms.

This work introduces the possibility of exploiting novel amino acids to generate new biological functions for therapeutic or industrial applications.

For more information, please visit www.salk.edu/faculty/wang
A major goal of our work is to reveal how host cell proteins either contribute to or defend against infection by important human microbial pathogens, such as HIV, influenza virus, Ebola virus and the bacterium that causes anthrax. Knowledge of the roles played by this cellular machinery provides new insights into the cell biology of microbial infections and could suggest new broad-spectrum antimicrobial approaches.

To identify cellular processes that either facilitate or defend against HIV-1 infection, Young and his collaborators use systems biology approaches to investigate the roles played by individual genes in the genome of host cells. These experiments have uncovered ZASC1, a new regulator of virus gene expression. They have also revealed that sulfonation—a type of chemical modification—regulates viral gene expression. A number of cellular factors they have identified restrict HIV infection, some of which play known roles in innate immunity, one of the body’s defense mechanisms that protect against microbial infections. In addition, virus countermeasures of these host defenses are being identified. Young anticipates that these discoveries will open up new avenues for the development of drugs that specifically interfere with HIV replication.

For more information, please visit www.salk.edu/faculty/young

From left to right: Rose Pilpa, T Morrell, Shannon Seidel, Artuo Diaz, Jeff Murry, John Young, John Naughton, John Marlett, Sebastien Landry, Justine Swann, Melissa Rodgers
"Regulatory T cells play a key role in the immune system to limit excessive immune reactions and prevent autoimmune diseases. Research in my lab is focused on the underlying molecular mechanisms that are involved in regulatory T cell differentiation and their immune suppression function."

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 autoimmune diseases, such as type 1 diabetes, multiple sclerosis and rheumatoid arthritis. There are multiple safeguard mechanisms built into our immune system to prevent an autoimmune reaction. A subset of T cells, named regulatory T cells (Tregs), plays a key role in maintaining immune homeostasis.

Abnormal Treg function has been linked to a number of autoimmune diseases. Recent studies showed that a protein known as Foxp3 is a pivotal regulator for Treg differentiation and function. Mutations of Foxp3 in humans and mice lead to a deficiency of regulatory T cells and fatal autoimmune disease. Zheng’s lab is interested in mapping both the upstream pathways that turn on Foxp3 expression and the downstream genes that Foxp3 regulates. Zheng and his colleagues identified several genes in the area of DNA that codes for Foxp3 and are found in a number of mammalian species. These genes appear to be involved in controlling and maintaining Foxp3 activity and in regulating the development and stability of regulatory T cell lineage.

Using genomic approaches, the researchers were able to map all Foxp3 downstream target genes. They showed that among all Foxp3 targets, a small group of proteins is implicated in Treg-mediated suppression of different subtypes of autoimmune responses.

Zheng and his team are now further exploring the Foxp3 transcriptional network in regulatory T cells and searching for key molecules involved in the Treg suppression function. Since manipulations of Tregs can either weaken or strengthen the immune response, their findings can potentially open new avenues in the treatment of autoimmune diseases, improve organ transplant survival and enhance anti-tumor immunity.

For more information, please visit www.salk.edu/faculty/zheng
Centers
The Crick-Jacobs Center is an interdisciplinary neuroscience research unit named in honor of the late Nobel laureate Francis Crick and chairman of the Salk board of trustees, Irwin Jacobs. The overall goal of the center is to integrate experimental and theoretical approaches to understanding the organization of signaling systems and the functional neuroanatomy of the brain, from the molecular to the systems levels, and how behavior arises from the interactions between the brain’s many components.

Under the leadership of Terrence J. 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 J. Sejnowski
Salk

**Members**
Nicola Allen
Salk
Sreekanth Chalasani
Salk
Xin Jin
Salk
Tatyana Sharpee
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**Senior Fellows**
William Bialek
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David Kleinfeld
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Christof Koch
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Charles F. Stevens
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Susumu Tonegawa
MIT

**Junior Fellows**
Mike McConnell
Krishnan Padmanabhan

**Visiting Fellow**
Rex Kerr

For more information, please visit [www.salk.edu/faculty/crick-jacobs_center.html](http://www.salk.edu/faculty/crick-jacobs_center.html)
The Glenn Center for Aging Research was established in January 2009 with a $5 million gift from the Glenn Foundation for Medical Research. The center draws from nine of Salk’s leading laboratories specializing in genetic analysis, stem cell biology and metabolism research to address the overarching goal of defining a healthy lifespan, or “healthspan,” and answer one of the most elusive questions in biology: Is there a defined biological process of aging that is universal to all organisms?

**Director**  
Jan Karlseder

**Genetic Analysis Group**  
Martin W. Hetzer  
Vicki Lundblad

**Stem Cell Group**  
Fred H. Gage  
Juan-Carlos Izpisua Belmonte

**Metabolism Group**  
Ronald M. Evans  
Marc R. Montminy  
Reuben J. Shaw

For more information, please visit www.salk.edu/glenn/
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 Tony Hunter, researchers in the Cancer Center probe the fundamental aspects of cancer biology, with the ultimate goal of reducing incidence, morbidity and mortality.

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:

**Director**
Tony Hunter

**Metabolism and Cancer**
Ronald M. Evans
Marc R. Montminy
Joseph P. Noel
Satchidananda Panda
David R. Schubert
Reuben J. Shaw

**Growth Control and Genomic Stability**
Beverly M. Emerson
Martin W. Hetzer
Katherine A. Jones
Jan Karlseder
Björn F. Lillemeier
Vicki Lundblad
Clodagh O’Shea
Geoffrey M. Wahl
Lei Wang

**Mouse Models and Cancer Stem Cells**
Senyon Choe
Joseph R. Ecker
Fred H. Gage
Juan-Carlos Izpisua Belmonte
Christopher R. Kintner
Kuo-Fen Lee
Greg Lemke
Axel Nimmerjahn
Samuel L. Pfaff
John B. Thomas
Inder M. Verma
John A. T. Young
Ye Zheng

For more information, please visit www.salk.edu/faculty/cancer_center.html
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 D. Albright

**Members**
Ursula Bellugi
Edward M. Callaway
E. J. Chichilnisky
Sascha du Lac
Sergei Gepshtein
Greg Lemke

Dennis D. M. O’Leary
Satchidananda Panda
John H. Reynolds
Terrence J. Sejnowski
Tatyana Sharpee
Charles F. Stevens
Gene Stoner

For more information, please visit www.salk.edu/cnv/
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. The center will provide 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 D. M. 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 Fred H. 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 E. 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 D. M. O’Leary

**Core Directors**
Fred H. Gage
Kou-Fen Lee
Paul E. Sawchenko

For more information, please visit www.salk.edu/ncc/
The Nomis Center for Immunobiology and Microbial Pathogenesis was launched in 2008 with gifts of $18 million received on behalf of 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 or infection and understand why inflammatory processes spin out of control under some circumstances.

An increasing number of reports show 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 and diabetes.

**Director**
John A. T. Young

**Members**
Melvin Cohn
Ronald M. Evans
Tony Hunter
Katherine A. Jones

Greg Lemke
Björn F. Lillemeier
Clodagh O’Shea
Inder M. Verma
Ye Zheng

For more information, please visit www.salk.edu/faculty/nomis_center.html
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 M. Evans
Marc R. Montminy
Reuben J. Shaw

**Helmsley Fellows**
Weiwei Fan
Evans Lab
Yeddula Narayana
Verma Lab
Mark Huising
Montminy Lab
Erin Quan Toyama
Shaw Lab
Bing Luan
Montminy Lab

For more information, please visit www.salk.edu/cng/
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**
- Nicola Allen
- Thomas D. Albright
- Ursula Bellugi
- Edward M. Callaway
- Sreekanth Chalasani
- E. J. Chichilnisky
- Sasha du Lac
- Martyn D. Goulding

**Sloan-Swartz Fellows**
- Stephen F. Heinemann
- Xin Jin
- Christopher R. Kintner
- Greg Lemke
- Dennis D. M. O’Leary
- John H. Reynolds
- Terrence J. Sejnowski
- Charles F. Stevens
- John B. Thomas
- Sergei Gepshtein
- Jude Mitchell
- Samat Moldakarimov

For more information, please visit www.sloan-swartz.salk.edu/
Waitt Advanced Biophotonics Center

Founded in 2008 with a $20 million challenge grant from the Waitt Foundation, whose president and founder, Ted Waitt, is also the vice-chair of Salk’s Board of Trustees, the Waitt Advanced Biophotonics 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 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 W. Hetzer, a professor in the Molecular and Cell Biology Laboratory, whose research uses advanced imaging methods to investigate cell organization and genome function and their role in cancer and age-related degenerative diseases. The center also is home to three outstanding junior faculty members, Hu Cang, Björn F. Lillemeier and Axel Nimmerjahn. The Cang laboratory is focused on the development of novel nanophotonic devices to enable the tracking of single molecules in living cells. The Lillemeier laboratory is developing a combination of super-resolution imaging and correlation spectroscopy to study signaling 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, led by James Fitzpatrick, 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 close collaborative relationship to further advances in imaging technology and apply and integrate those new methods into the biological research community at Salk.

**Director**
- Martin W. Hetzer

**Members**
- Hu Cang
- Björn F. Lillemeier
- Axel Nimmerjahn

**Core Staff**
- James Fitzpatrick (Director)
- Matthew Joens
- Jamie Kasuboski
- Yury Sigal

For more information, please visit www.salk.edu/biophotonics/
Scientific Core Facilities
“By observing general health and physical performance in laboratory rodents such as motor coordination and learning and memory, we can determine the viability of our animal models and better predict how humans will respond under similar conditions. The Behavior Testing Core at the Salk Institute provides a comprehensive resource for investigators interested in neurobehavioral testing by providing the equipment, trained staff and expert consultation across multiple behavior domains.”

Standardized behavioral testing assesses general health and performance in laboratory rodents and can significantly improve the translation of animal models to humans. The Behavior Testing Core facility provides a centralized resource for investigators who wish to incorporate behavioral phenotyping or neurobehavioral testing into their research.

The facility assesses in mice and rats sensory and motor functions, cognition and complex behaviors related to human neurological disease and disorders, congenital defects and injury or trauma to the nervous system. Various tests measure sensory and motor function, determining function of sensory systems, including visual and somatosensation, as well as motor movement and coordination. Cognitive tests utilize measures of learning and memory that target global or specific modalities of memory, including spatial memory, smell and sound. Complex behaviors are measured by eliciting species-specific social or “emotional” responses from animals, which are often validated by the ability to alter these behaviors with the same psychoactive drugs that mediate the behavior in humans.

The core can assess the neurobehavioral consequences of genetic manipulations in mouse models and gene, immune, vaccine, stem cell and drug therapies, among others. This information can also be used to satisfy requirements for moving from preclinical testing to filing an investigational new therapy application.

Testing of individual behaviors as well as batteries of tests can be carried out, and custom tests can be developed upon request. Assistance is available for the submission of Institutional Animal Care and Use Committee protocols using the core, and data summaries can be provided at the end of testing. The core staff can conduct the testing or staff from the investigator’s laboratory can be trained to carry out testing independently.

The Behavior Testing Core is part of the Salk Institute Neuroscience Core Center, directed by Dennis D. M. O’Leary and 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 www.salk.edu/cores
Flow Cytometry Core Facility
Carolyn O’Connor, Director

“Fluorescence is a key tool in today’s research, and Salk’s Flow Cytometry Core Facility provides access to sophisticated fluorescence technology and expertise in related areas. We train and assist investigators in the use of our equipment, assist with data analysis and presentation and provide advice concerning experimental design and optimization.”

FLOW CYTOMETRY
Flow cytometry may be used to analyze large numbers of cells in a short time and optionally isolate cells of interest. The facility’s two analytical flow cytometers are capable of resolving up to six fluorescent colors simultaneously, while the high-speed digital cell sorter (FACSVantage DiVa) offers up to eight colors; cells separated by the latter may be used for subsequent analyses or may be further expanded in culture. The cell sorter allows investigators to isolate pure populations of rare (<0.1 percent abundance) cells with a throughput of up to 50 million cells per hour.

CONFOCAL MICROSCOPY
Our digital confocal microscope is a high-end Leica TCS SP2 spectral unit with four lasers. This machine provides high-resolution images of cells at the sub-micron level or overviews of large tissue sections, using up to four simultaneous fluorescence colors. One of this machine’s major advantages is that it features freely programmable fluorescence collection, rather than using traditional fixed color filters. This not only saves time because color overlaps can easily be eliminated, it also helps eliminate the unwanted autofluorescence that many samples exhibit.

TWO-DIMENSIONAL IMAGING
Extracts from cells tagged with fluorescent or radioactive compounds may be separated by one- or two-dimensional electrophoresis, and the resultant gels or blots analyzed using the center’s 2-D imagers. In the case of radioactively labeled probes, a radiation-sensitive screen is exposed to the sample and then imaged while fluorescent labels are detected immediately. The facility has two imagers: a Molecular Dynamics Typhoon and a Fuji FLA 5100. The Fuji instrument is newer and can analyze more colors than the Typhoon.

MICROPLATE READING
The FCCF also offers a multi-well plate reader, which is able to quantitate fluorescence or absorbance in standard plate formats ranging from six wells to 384 wells per plate.

For more information, please visit www.salk.edu/cores
The Functional Genomics Core was established at the Salk Institute in 1999 to provide a shared resource for analysis of gene expression using Affymetrix Gene Chip technology and the real-time detection of the polymerase chain reaction (PCR) products for genes of interest. Our mission is to provide Salk investigators with high-quality, state-of-the-art gene expression services in a timely manner.

**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 recently purchased 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 miniprep service for rapid handling of DNA samples—a cost-effective and convenient way for laboratories to analyze large numbers of samples.

For more information, please visit www.salk.edu/cores
Gene Transfer, Targeting and Therapeutics Core
Daniel Gibbs, Director

“Our mission is to promote and support use of recombinant viral vectors and gene transfer technologies that allow genes and other regulatory nucleic acids to be inserted into cells for basic and translational research.”

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 whole 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 common 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 vectors based on a range of viruses, including lentivirus, adeno-associated virus and rabies virus.

The GT3 core facility is housed in the new 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 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, it also produces and distributes functionally validated off-the-shelf induced pluripotent stem cell (iPSC) reprogramming vectors.

For more information, please visit www.salk.edu/cores

From left to right: Anne Beall, Christina Ly, Daniel Gibbs, Helen Fang
“Brain researchers are increasingly focused on the links between genes and behavior, exploring how genetics plays a role in brain development, structure and function, which is ultimately manifested in a person’s 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.”

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 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 mice.

The Genome Manipulation Core is part of the Salk Institute’s Neuroscience Core Center, directed by Dennis D. M. O’Leary and supported by the National Institute of Neurological Disorders and Stroke. Core operations are overseen by faculty director, Kuo-Fen Lee, with day-to-day operations carried out by the core manager, a research scientist and one research technician. It is located within a pathogen-free barrier facility.

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 core is overseen by the Institutional Animal Care and Use Committee.

For more information, please visit www.salk.edu/cores

Genome Manipulation Core
Kuo-Fen Lee, Faculty Director
Tsung-Chang Sung, Core Manager
Histology and Imaging Core
Kim McIntyre, Director

“The Histology and Imaging Core facility provides routine and experimental histological services, as well as training and supervision of various equipment and techniques necessary for pathological analysis and characterization of tissues and cells. Our goal is to provide Salk and SCRM-affiliated scientists with the tools to evaluate biological samples at the microscopic level.”

**HISTOLOGY SERVICES AND EQUIPMENT**
The services provided by the histology core facility include routine tissue processing and paraffin embedding, routine H&E and non-routine special stains. It also has the capability to perform high-throughput automated immunohistochemistry. The histology equipment available for researchers includes two cryostats for sectioning of thin frozen sections, a vibratome for slicing thick live tissues, two rotary microtomes and a sliding microtome for thick slices of fixed tissue.

**IMAGING**
The HIC has a Nikon 80i fluorescent microscope equipped with a CCD camera for color and black-and-white photography, and an Arcturus laser capture microscope. It also has two specialty confocal microscopes: Olympus Fluoview 1000 Multi Photon LSM/MP and Zeiss Laser Scanning Microscope with Spinning Disc LSM/SP.

The HIC facility is located in the Sanford Consortium for Regenerative Medicine, next door to Salk.

For more information, please visit www.salk.edu/cores
“We have provided a reliable, cost-effective source of peptides for Salk investigators to use in their research since 1992. In addition to synthesizing custom peptides, we also provide advice and training for investigators in the design of appropriate peptides, use of protocols and the interpretation of peptide characterization profiles.”

The current peptide synthesizer, a Model PS3 from Protein Technologies, was purchased in June 2006 and is operated by 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 crude peptides to be analyzed 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. 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 100 peptides are synthesized, including phosphopeptides, peptides with chemical modifications such as acetylation or biotinylation, as well as peptides incorporating specially derivatized amino acids to control peptide folding.

For more information, please visit www.salk.edu/cores
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 second purpose of the core is to drive the development of cutting-edge analysis techniques. The core develops novel algorithms and software programs to help groups analyze their data in creative new ways. This work also 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.

For more information, please visit www.salk.edu/cores
The Stem Cell Core Facility (STEM Core) is dedicated to promoting research involving human embryonic stem (hES) cells and induced pluripotent stem (iPS) cells. We maintain existing hES lines and newly derived human iPS cell lines. The STEM Core provides the physical space, dedicated equipment and hands-on training for scientists to use these pluripotent cells for their research goals.

The STEM Core is ideally suited for Salk scientists to perform studies involving existing hES and iPS cell lines (provided by the core) and to support the derivation and propagation of newly reprogrammed iPS cells.

Many Salk scientists use the core’s reprogramming resources for studies aimed at turning an adult patient’s skin, blood or fat cells into iPS cells. These stem cells have the potential to be coaxed into a variety of mature cells, including those that are involved in disease. They retain the same genetic information that may have led to disease in the adult, allowing researchers to generate models of human diseases in a laboratory dish.

The core director and staff provide individualized training in proven techniques for successful culturing of these cells, including reprogramming of patient-derived cells and techniques for differentiating them into targeted cell types. The core staff is available for consultation on experimental design and can assist in getting projects involving hES or iPS cells moving quickly.

All the requisite equipment and resources for successful stem cell culture are found in the STEM Core, including two cell culture rooms, benchtop research space, a microscope room and cryo-storage equipment. One of the cell culture rooms is designated for existing, pre-approved hES and iPS cell lines only. The other cell culture room is designated for work with viral vectors, for reprogramming adult cells to stem cell–like iPS lines, and has dedicated hoods and incubators for quarantined cell culture. The segregation of these spaces is part of a mechanism to provide flexibility for new research projects while protecting the existing cells from external contamination.

The facility is centrally located on the Salk campus, making it convenient for Salk researchers to drop in while staying within easy reach of their laboratories. The STEM Core operates on a recharge rate basis.

For more information, please visit www.salk.edu/cores
“Research at the Salk Institute depends to a high degree on the use of mouse models. The Transgenic Core is dedicated to providing access to cutting-edge technologies to create these models.”

Transgenic and knockout mice have become an integral part of the research programs at Salk. The Transgenic Core provides a variety of services, including microinjection of embryonic stem (ES) cells into blastocysts; microinjection of DNA into one-cell embryos; lentiviral infection and injection; in-vitro fertilization (IVF); cryopreservation and rederivation of mouse lines; providing inbred strains of mice; and establishment of ES cell lines from wild-type and mutant mice. In addition, the core offers injection of human embryonic stem (hES) cells and induced pluripotent stem (iPS) cells into immunodeficient mice to form teratomas, a type of tumor. The facility also develops new techniques and applications, provides immediate access to individuals with knowledge of dealing with transgenic mice and offers the potential for research collaborations.

Over the last year, the microinjection laboratory has generated more than 120 transgenic and knockout mouse lines and rederived and cryopreserved more than 100 lines for investigators at the Institute. These mice are not only important resources for researchers at Salk but also for investigators at other institutions. More than 50 publications have been based on genetically altered mouse lines created by the core.

Operated by a core director, one staff researcher and one research assistant skilled in the appropriate techniques, the Transgenic Core is located within a pathogen-free barrier facility in which only animals from standard 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 facility are overseen by the Institutional Animal Care and Use Committee.

For more information, please visit www.salk.edu/cores
The Mass Spectrometry Center routinely identifies small amounts of proteins that are separated by gel electrophoresis. The facility also performs analyses of complex protein mixtures by two-dimensional chromatography followed by mass spectrometric identification. It is equipped with a hybrid Fourier-transform mass spectrometer with an electrospray source. In addition, a time-of-flight mass spectrometer that employs matrix-assisted laser desorption ionization is available.

**PROTEIN IDENTIFICATION**

During the past year, a number of projects requiring mass spectrometric protein identification were completed. As part of a study elucidating the role of the kinase SIK3 in the regulation of energy balance, proteins interacting with the kinase were identified by mass spectrometry. In another study, our previously developed oligonucleotide pull-down procedure was used to identify proteins interacting with the chromogranin A promoter. Another investigation of protein-protein interaction led to the identification of proteins interacting with the lysine specific demethylase KDM1A. As part of our effort to characterize intact proteins using mass spectrometry, we were able to analyze intact myoglobin into which unusual amino acids were incorporated.

**IDENTIFICATION OF POST-TRANSLATIONAL MODIFICATIONS IN PROTEINS**

The disulfide bridge arrangement is an important feature in proteins and stabilizes the structural topology. During the past year, a large number of synthetic peptide ligands were analyzed to determine their disulfide connectivity. This is part of an effort to correlate specific disulfide arrangements in CART (cocaine and amphetamine regulated transcript) peptides with biological activity.

The determination of phosphorylation sites in proteins continues to be of interest because of the importance of this modification in the regulation of many biological processes. We have recently explored the use of proteases with varying specificity to identify the sites where the modification occurs. Applying these strategies, we were able to increase the number of identifiable sites to obtain a more complete picture of modification patterns.

For more information, please visit www.salk.edu/cores
The Waitt Advanced Biophotonics Center Core facility is dedicated to promoting the use of state-of-the-art imaging technologies in biological research. We provide access to multi-scale microscopy techniques and technical support, and we work collaboratively with Salk investigators to further their specific research aims.

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. We also provide free data storage for all Salk researchers using the core. Current capacity stands at a total of 350 terabytes of data.

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 augmented by support from the Waitt Foundation.

For more information, please visit www.salk.edu/cores

From left to right: Jamie Kasuboski, James Fitzpatrick, Yury Sigal, Matthew Joens
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John B. Thomas, Ph.D.
Inder M. Verma, Ph.D.
Geoffrey M. Wahl, Ph.D.
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Julie Law, Ph.D.
Bjorn Lillemoeier, Ph.D.
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Soon O. Y. Lee, Ph.D.
Innokentiy Maslennikov, Ph.D.
Jude Mitchell, Ph.D.
Marilyn H. Perrin, Ph.D.
Shingo Yoshikawa, Ph.D.
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, Ph.D.
Nobel Laureate, 1975
President Emeritus
California Institute of Technology

Elizabeth H. Blackburn, Ph.D.
Nobel Laureate, 2009
Professor, Departments of Biochemistry and Biophysics
University of California, San Francisco

Caroline Dean, Ph.D.
Professor and Project Leader, Department of Cell & Developmental Biology
John Innes Centre

Thomas M. Jessell, Ph.D.
Howard Hughes Medical Institute
Professor, Departments of Neuroscience, Biochemistry and Molecular Biophysics
Columbia University Medical Center

Eric S. Lander, Ph.D.
President and Director, Broad Institute of Harvard and MIT
Professor of Biology, MIT
Professor of Systems Biology, Harvard Medical School

Jennifer Lippincott-Schwartz, Ph.D.
Bethesda, Maryland

Carla J. Shatz, Ph.D.
Director, BioX James Clark Center
Professor of Biology and Neurobiology
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