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Science Guide



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INSIDE

PRESIDENT'S MESSAGE

EXECUTIVE LEADERSHIP

NOBEL PRIZE LAUREATES

FACULTY

SALK FELLOWS PROGRAM

RESEARCH CENTERS

SCIENTIFIC CORE FACILITIES

EMERITUS FACULTY

FACULTY LISTING

STAFF SCIENTISTS LISTING

NON-RESIDENT FELLOWS

HONORS



THE PRESIDENT'S MESSAGE

Following his success in developing the first polio vaccine, many people likely expected Jonas Salk to focus his new endeavor, the Salk Institute, on infectious disease research. Yet he instead chose to create a place where researchers could study the fundamentals of life and the root causes of many disease conditions, with the freedom to follow their findings wherever they may lead. He recruited the best scientists, prioritizing people who were eager to work across disciplines and gather differing points of view to illuminate the bigger picture.

Still today, exploration is what we do. One of the defining traits of Salk scientists is curiosity. We seek to understand biology at its deepest levels. Sometimes, these explorations create whole new areas of study, uncovering mechanisms that weren't previously imagined.

Each scientific discovery leads to new, more complex questions that also require answers. And as these questions emerge, investigators must seek out new approaches, technologies, and collaborators to address them. At Salk we form cross-functional teams that work intensively to find answers and reconfigure into new groups as needed—working literally without walls between disciplines, as Jonas Salk and architect Louis Kahn intentionally designed the Institute's iconic buildings.

This Science Guide details the work of each of Salk's faculty members, including the challenges they face, the innovative scientific approaches they are taking, and the important contributions they have made to their fields. Their discoveries are powered in part by the Institute's collaborative research centers and shared technologies, also described within.

Advanced technology,
engineering and computational
science are increasingly becoming
important tools in helping
create new ways of modeling
solutions with potential for
transformative impact.

I'm excited about the future of science at Salk. With the rapid development of new computational technologies that allow us to ask bold research questions and uncover answers faster than ever before, and with the support of our outstanding Salk community, donors, and collaborators, I know we will continue to change the world for the better.



Gerald Joyce | Salk Institute President

EXECUTIVE LEADERSHIP



GERALD JOYCE
President



SUE BACINO
VP, People & Culture



JAN KARLSEDER
SVP, Chief Science Officer



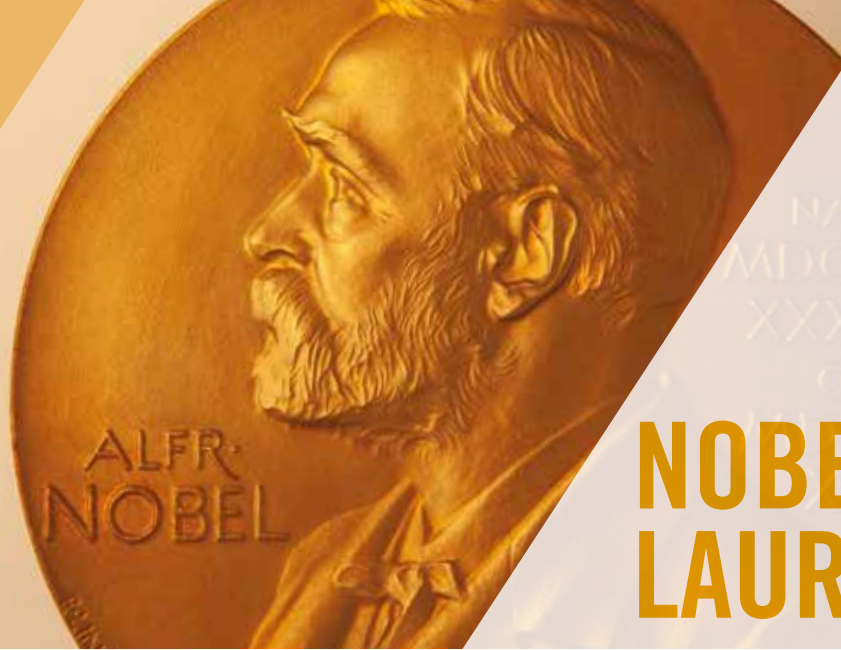
JULIA MILLER
General Counsel



BRYAN ROBINSON
VP, External Relations



KIM WITMER
SVP, Finance & Administration



NOBEL PRIZE LAUREATES

ELIZABETH BLACKBURN

Elizabeth Blackburn won the Nobel Prize in Physiology or Medicine in 2009 for discovering the molecular nature of telomeres, the ends of chromosomes that serve as protective caps essential for preserving genetic information, and for co-discovering telomerase, an enzyme that maintains telomere ends.

ROGER GUILLEMIN (1924 – 2024)

Considered the founder of the field of neuroendocrinology and whose research into brain hormones has led to treatments for disorders ranging from infertility to pituitary tumors, Roger Guillemin was awarded the 1977 Nobel Prize for Physiology or Medicine for his work with hypothalamic hormones.

FRANCIS CRICK (1916 – 2004)

Francis Crick, a molecular biologist, biophysicist and neuroscientist, won the Nobel Prize in Physiology or Medicine in 1962 for co-discovering the structure of the DNA molecule in 1953 with James Watson.

SYDNEY BRENNER (1927 – 2019)

One of the world's pioneers in genetics and molecular biology, Sydney Brenner was one of three recipients to win the Nobel Prize in Physiology or Medicine in 2002 for his contributions in discovering how genes regulate organ growth and the process of programmed cell death. Brenner pioneered research using the translucent microscopic worm *Caenorhabditis elegans* as a model system.

RENATO DULBECCO (1914 – 2012)

Founding Salk fellow and pioneering cancer researcher Renato Dulbecco won the Nobel Prize in Physiology or Medicine in 1975 for his work that provided the first clue to the genetic nature of cancer and described how a tumor virus could insert its own genes into the chromosome of the cell it infects, and “turn on” the uncontrolled growth that is the hallmark of cancer.

ROBERT HOLLEY (1922 – 1993)

Two years after his arrival at the Salk Institute as a professor and fellow, biochemist Robert Holley received the Nobel Prize in Chemistry in 1968 for his work on the structure of transfer-RNA.

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SALK FACULTY





THOMAS ALBRIGHT

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

THE CHALLENGE

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

THE APPROACH

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

disease, Albright's work can inform how the memory of visual information can be distorted, as well as how to build environments and architecture that encourage learning, productivity and healing.

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/THOMAS-ALBRIGHT



NICOLA ALLEN

Associate Professor
Molecular Neurobiology Laboratory

THE CHALLENGE

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

THE APPROACH

Allen studies how astrocytes regulate the formation, function and stability of neuronal connections called synapses. Astrocytes closely interact with neurons and synapses via thousands of fine processes, putting them in a position to regulate these connections. Synapses are essential points of information transfer within neuronal circuits and change throughout life. In the young brain trillions of synapses form, in the adult brain synapses are stabilized, and in the aging brain synapses become less functional and are eliminated. Further, in most neurological disorders, no matter the stage of life, synaptic dysfunction is a key component. This includes autism during youth, schizophrenia in adulthood and Alzheimer's disease in aging. Allen is investigating if life stage-specific properties of synapses are being regulated by the astrocytes the neurons interact with, to identify new therapeutic targets for repairing synapses in the disorders where they are dysfunctional.

THE INNOVATIONS AND DISCOVERIES

- Allen discovered a class of proteins released by astrocytes in the young brain that enables neurons to communicate by making new synaptic connections form. The lab is now asking if re-expressing these signals in the Alzheimer's disease brain is able to rescue synaptic function and delay disease progression.
- Allen discovered a separate class of proteins that astrocytes secrete in the adult brain that stabilizes synaptic connections, leading to an inhibition of plasticity. The lab is currently investigating if blocking this protein in the adult brain will enhance recovery from injury such as stroke by enhancing plasticity.
- Allen discovered that in the aging brain, astrocytes acquire properties that negatively impact neuronal and synaptic function, including increased inflammation and altered metabolism. The lab is now asking if manipulating these targets in astrocytes will be able to delay the progression of cognitive decline and neurodegeneration.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/NICOLA-ALLEN

ALZHEIMER'S DISEASE | AUTISM | STROKE | NEUROBIOLOGY
NEUROLOGICAL DISEASE | DEVELOPMENTAL DISEASE



KENTA ASAHINA

Associate Professor
Molecular Neurobiology Laboratory

THE CHALLENGE

Whether you are a human or an insect, behavior is ultimately supported by functions of genes. Genetic circuitry and molecular interactions give rise to an animal's choice on how to react to its environment. However, animal behaviors can appear highly variable—they can vary dramatically depending on an animal's internal states, experience and reactions from other individuals. Understanding what goes haywire in brains of the socially impaired (such as in autism or attention-deficit disorders) is the first step in developing effective and specific treatments for such neurological disease. It can be difficult, however, to study the basis for behaviors and pathologies in humans, in part because our nervous systems are so complex.

THE APPROACH

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

To unravel the fundamentals of behavior, he is using multidisciplinary approaches, including advanced genome editing, gene expression control, optogenetic techniques for

controlling neurons with light, functional neuronal imaging and computational behavioral analysis. His lab is also interested in expanding the research scope to comparative genomics, evolutionary ethology and social behaviors.

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/KENTA-ASAHINA

**AUTISM | DEMENTIA | GENETICS | MEMORY
NEUROBIOLOGY | NEUROLOGICAL DISEASE**



JANELLE AYRES

Professor and Laboratory Head

Gene Expression Laboratory and the
Molecular and Systems Physiology
Laboratory

NOMIS Center for Immunobiology and
Microbial Pathogenesis

Salk Institute Legacy Chair

THE CHALLENGE

The current approach for treating infections relies on annihilating the pathogen using antibiotics, which has driven the global crisis of antibiotic-resistant infections and does not ensure that a person will survive their infection or return to a healthy state. However, health is an active process between host and pathogen for which microbial mechanisms to promote our health represent an unexplored aspect of host-microbe interactions. This provides an opportunity to uncover novel insights into health and disease.

THE APPROACH

Janelle Ayres is a molecular and systems physiologist who studies evolutionary theory and microbes to understand how all of our physiological systems and our brain interact with each other to promote optimal health. Ayres' research into how our physiologies are regulated by microbes and the mechanisms by which microbes affect us is paving the way to an entirely new understanding of normal and dysfunctional biological processes.

How a host responds to a pathogen determines outcome of infection, and the long-standing belief was that a host needed to kill an invading pathogen in order to survive. Ayres' discovery of the host "co-operative defense" system has challenged this notion. As part of her paradigm-shifting work, Ayres showed that a host can employ disease tolerance defenses executed by the co-operative defense system during

infection that limits pathology and promotes host survival while having no effect on the pathogen.

Ayres made a number of other breakthroughs in this area, revealing not only more about fundamental, dynamic biological processes but also charting discoveries that have potential translational applications for treating a wide array of diseases as well as ways to promote healthy aging.

THE INNOVATIONS AND DISCOVERIES

- In addition to discovering the host co-operative defense system and processes by which it can promote host survival, Ayres also demonstrated that a host can employ anti-virulence mechanisms executed by the co-operative defense system that changes the behavior of pathogens so that they do not cause disease in the host.
- Ayres found that pathogenic and beneficial microbes have evolved mechanisms to promote the host co-operative defense system to support their own survival and transmission—by promoting the health of the host—revealing a beneficial role for microbes in the maintenance of host health.
- Ayres demonstrated that promoting the co-operative defense system drives the evolution of pathogens into a type of symbiotic relationship called commensalism, reducing the overall threat of infections.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/JANELLE-AYRES

**INFECTIOUS DISEASE | INFLAMMATION | METABOLISM | MICROBIOLOGY
PHYSIOLOGY | MICROBIOME | IMMUNOLOGY | NEUROINFLAMMATION | EVOLUTION**



EIMAN AZIM

Associate Professor
Molecular Neurobiology Laboratory
Williams Scandling
Developmental Chair

THE CHALLENGE

The nervous system has an incredible capacity to take in and process complex information, yet the only way it can exert an influence on the outside world is through movement—whether it's kicking a ball, typing an email or using vocal chords to speak. Humans have evolved an astonishingly diverse repertoire of motor behaviors to help translate intents into actions. Even seemingly simple movements require the extensive coordination of dozens of muscles to ensure that physical efforts are successful, but scientists have only begun to scratch the surface of how this is accomplished. Understanding how movements are learned, planned, executed and corrected can teach us more about how neural circuits govern behavior and how evolution has shaped the mammalian nervous system. This type of knowledge could clarify how disease or injury disrupts the normal execution of movement and pave the way for improved diagnosis and treatment.

THE APPROACH

Eiman Azim uses a multidisciplinary approach to identify how neural circuits solve the challenges of motor control, taking advantage of genetic and viral tools, anatomical analysis, electrophysiological recording, imaging and detailed motor behavioral tests. By dissecting the molecular, anatomical and functional diversity of motor pathways one element at a time, Azim aims to pinpoint neural circuits and piece together the underpinnings of movement, especially skilled motions like reaching, grasping and object manipulation.

Dexterous movements of the arms and hands are critical motor functions often affected by neurodegenerative disease and injury, and Azim's work seeks to lay the groundwork for better treatment and recovery of function.

THE INNOVATIONS AND DISCOVERIES

- Azim identified circuits dedicated to controlling specific features of movement, supporting the idea that there is a modular organization to the motor system, meaning that certain circuits control reaching, others control grasping, and so on. His work helps show that this organization is shared across mammal species.
- Azim investigated inhibitory neurons in the spinal cord that control the strength of incoming sensory feedback and showed that this circuit is essential for maintaining the stability of the limb during movement.
- Azim mapped a spinal circuit that conveys copies of motor commands within the nervous system, helping to keep the brain aware of its ongoing output. His research showed that these internal copy signals get channeled through part of the brain called the cerebellum and can be used to update movements very rapidly, supporting the speed and precision of skilled behaviors.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/EIMAN-AZIM



DANIEL BAYLESS

Assistant Professor
Molecular Neurobiology
Laboratory

THE CHALLENGE

Social interactions are vital for wellbeing, social cohesion, and societal progress. Disruptions in social information processing can impact behavior and are often observed in neurological conditions, including Alzheimer's disease and autism spectrum disorders. Many of these conditions are more common in men or women, and the symptom severity can vary by sex. Yet, how these sex differences manifest and how sex hormones affect the brain circuits that underlie these neurological conditions remains poorly understood.

THE APPROACH

Bayless investigates the brain basis of social behaviors, like mating and aggression, by looking at how sex hormones affect brain circuits. His lab uses advanced molecular genetic techniques in mice to study cells that have sex hormone receptors (proteins on cells that receive and pass along messages) throughout the brain. The approach provides insight about three different aspects of social behaviors: 1) which brain circuits control specific social behaviors, 2) how much these brain circuits can change and what initiates that change, and 3) how sex hormones influence brain development and social information processing.

THE INNOVATIONS AND DISCOVERIES

- Bayless identified, for the first time in the vertebrate brain, a group of neurons that designate another mouse as either male or female, which is a necessary step for subsequent mating and aggression behaviors in mice.
- Bayless characterized how neurotransmitter (substance P) signaling in downstream neurons in the hypothalamus that have the receptor Tacr1 underlies the transformation of mate recognition signal into male mating behavior. Moreover, the activation of these Tacr1-expressing neurons can remove the typical 24- to 72- hour rest period after mating, causing male mice to repeat mating immediately.
- Bayless discovered that the same set of Tacr1-expressing neurons also cause an immediate release of dopamine, thereby linking the brain circuits for mating and reward.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/DANIEL-BAYLESS



MARGARITA BEHRENS

Research Professor
Computational Neurobiology
Laboratory

THE CHALLENGE

Within the brain there exists a balance between activating and inhibiting neurons, akin to the balance between accelerating and braking a car. Maintaining this balance (called homeostasis) in brain circuitry is critical for cognitive processes, while disruption of it can lead to disorders such as schizophrenia and autism. Although symptoms of these diseases appear at different times in peoples' lives, they may result from a similar cause: abnormal brain development during critical periods early in life.

THE APPROACH

Margarita Behrens is examining genes, environmental influences and the interplay between the two to determine why some individuals develop a neurodevelopmental disorder while others do not. With her strong background in genomics, neurobiology and physiology, Behrens focuses on neural circuit formation and disruption within the prefrontal cortex, an area of the brain responsible for decision-making and reasoning, from late pregnancy through adolescence.

Her team uses a variety of methods to understand the rules that govern brain maturation during the perinatal period, when neuronal circuits are established. They measure the electrical activity of neuronal circuits; image the formation of neuronal synapses; and study the maturation of subtypes of neurons by looking at a layer of chemical tags on DNA called the epigenome. These tags—methyl groups (CH₃)—bind to DNA to turn genes on and off, and are increasingly thought to play a major role in health and disease. As part of a large consortium, the Behrens team identifies new

subtypes of neurons based on their DNA methylation patterns (epigenetic markers) using a method known as methylation profiling. Charting the different subtypes of neurons in the brain—as well as targeting variations in the epigenome and changes that occur during neuronal maturation—could lead to a better understanding of brain circuits and improved interventions for a host of neuropsychiatric and neurodevelopmental disorders such as bipolar disorder, depression, schizophrenia and autism.

THE INNOVATIONS AND DISCOVERIES

- Interneurons, which transmit signals between neurons, regulate the excitatory and inhibitory balance in the prefrontal cortex. Behrens found that without the critical receptor mGluR5, the interneurons developed abnormally, could not adequately regulate inhibitory circuits, and led to behavioral deficits similar to human neurodevelopmental disorders.
- While identifying normal patterns of DNA methylation in the brain, her lab produced the first whole-genome maps comparing mouse and human prefrontal cortices throughout the life span, tools that help neuroscientists around the world better study this area of the brain.
- Different neurons have variations in methylation patterns (methylomes). When profiling the methylomes, Behrens and colleagues found that neurons in the human frontal cortex formed 21 subtypes, including some subtypes that were not previously identified. Her group is now studying how these cell-type-specific methylome patterns are established during brain maturation, and how the maternal environment affects them.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/MARGARITA-BEHRENS

AUTISM | BIPOLAR | DEPRESSION | DEVELOPMENTAL DISORDERS
NEUROBIOLOGY | NEUROLOGICAL DISEASE | SCHIZOPHRENIA



WOLFGANG BUSCH

Professor

Plant Molecular and Cellular Biology

Laboratory

Integrative Biology Laboratory

Hess Chair in Plant Science

THE CHALLENGE

While flowers and shoots are the more visible features of plants, what lies beneath the surface is just as important: roots. Plants' roots are critical for obtaining water and nutrients from the soil. They also play a major role in the global carbon cycle by transferring carbon that was fixed by plant photosynthesis from the atmosphere into the soil. Despite their high relevance for ecology, agriculture, food security, and carbon cycling, there are many open questions in regard to root systems. For example, why are some root systems shallow and some are deep? How do plants process environmental information? How can roots work with beneficial microbes while fending off harmful microbes? A better understanding of plant roots could help grow more resilient food sources—an increasingly urgent problem in the face of the planet's shifting climate and increasing population—and help develop root systems that can be utilized on a large scale to store carbon dioxide (CO₂) that was captured from the atmosphere by plant above-ground tissue.

THE APPROACH

The flowering plant *Arabidopsis thaliana* is an easy-to-grow weed, popular for plant biology research. Different strains, all with very similar genomes, grow all over the world, making the plant especially useful for studying which genes and genetic variants make plants respond to different environments and help them survive. Wolfgang Busch uses a systems genetics approach, combining techniques from genetics, genomics, and other science fields to understand how root growth in given environments is determined by a plant's genes. Genome-wide association studies correlate genetic variation with physical characteristics, such as having long or short roots. But to be meaningful, studies have to measure the physical characteristic of interest in significant quantities. Because it is difficult to measure roots accurately and in large numbers, Busch has employed a number of cutting-edge technologies and computational

methods for evaluating roots. Using these approaches, Busch was able to uncover several genes and their genetic variants that determine how roots grow and respond to the environment. Studies like these are continuing to inform how roots can be optimized for distinct environments or functions. The lab has also recently expanded its work to some of the most globally relevant crop species with the aim of identifying mechanisms conserved across species that can be engineered to create crop varieties resilient to climate change and its effects.

As executive director of Salk's Harnessing Plants Initiative, Busch aims to help plants grow bigger, more robust root systems that can absorb larger amounts of carbon by burying it in the ground in the form of suberin, a naturally occurring carbon-rich substance. The team will use cutting-edge genetic and genomic techniques to develop these Salk Ideal Plants™ to fight climate change.

THE INNOVATIONS AND DISCOVERIES

- Busch developed novel methods to evaluate hundreds of thousands of roots using imaging and machine vision algorithms to automatically extract root length and shape data.
- He discovered how plants reprogram their cellular activities to withhold iron when bacteria invade root tissues, and characterized the molecular mechanisms that link the iron deficiency signaling pathway with the plant immune system. This has revealed new ways to engineer plant resilience and disease resistance.
- He identified a gene and its variants that can switch shallow root systems to deep root systems, uncovered how this is achieved on a molecular level, and found association of certain variants of this gene with adaption to sparse rainfall conditions.root systems to deep root systems, uncovered how this is achieved on a molecular level, and found association of certain variants of this gene with adaption to sparse rainfall conditions.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/WOLFGANG-BUSCH

GENETICS | PLANT BIOLOGY | CLIMATE CHANGE | AGRICULTURE | SYSTEMS BIOLOGY



EDWARD CALLAWAY

Professor

Systems Neurobiology Laboratory
Vincent J. Coates Chair in Molecular
Neurobiology

THE CHALLENGE

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

THE APPROACH

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

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

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

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/EDWARD-CALLAWAY



SREEKANTH CHALASANI

Professor
Molecular Neurobiology Laboratory

THE CHALLENGE

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

THE APPROACH

Sreekanth Chalasani uses three models comprising a simple worm to the more complex fish and mice to answer questions about neuroscience.

The worm (*Caenorhabditis elegans*) has only 302 neurons and a few thousand connections between these cells. Each neuron is mapped and named, making it easier to study the effect of environment or gene changes at the resolution of individual cells. But despite its simplicity, the *C. elegans* nervous system has commonalities with a human brain: if you give a worm a dose of the antidepressant Zoloft, for example, it becomes less fearful of predators such as the worm *P. pacificus*; and if you mutate a gene linked to autism in humans, the worm shows less interest in other worms. Among other studies, Chalasani's lab is also exploring what these tiny creatures can tell us about human aggressions and fears—emotions and behaviors often necessary for our survival, but which are also sources of great suffering. The

worm's simple nervous system makes it useful for studying human diseases—and testing drugs—in a well-understood model.

The fish (*Danio rerio*) is an ideal model for neuroscience because its larvae are transparent and exhibit a number of robust behaviors. Combining genetics with imaging and bioengineering methods, the Chalasani lab is studying how an entire brain processes oxygen information. This is particularly relevant as dysfunction in this process can lead to devastating human conditions including sudden infant death syndrome (SIDS).

The Chalasani lab recently developed a new method to manipulate neurons non-invasively using ultrasound, a technique they have termed sonogenetics. They demonstrated this technology in worms, and are currently extending it to mice.

THE INNOVATIONS AND DISCOVERIES

- Chalasani used salt-sniffing roundworms to help explain how the nervous system processes sensory information, discovering that insulin plays a role in mediating worms' perceptions and behaviors.
- He also discovered that there was more than one type of neuron involved in processing sensory cues that researchers had previously thought were only sensed by single neurons.
- He recently developed a new method to manipulate neurons and other cells non-invasively using ultrasound, a technique he has termed sonogenetics (sonogenetics.salk.edu).

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/SREEKANTH-CHALASANI

SONOGENETICS | ANXIETY | AUTISM | LOCOMOTION
NEUROBIOLOGY | NEUROLOGICAL DISEASE



JOANNE CHORY

Professor and Director

Plant Molecular and Cellular Biology
Laboratory

Howard Hughes Medical Institute

Investigator

Howard H. and Maryam R. Newman Chair
in Plant Biology

THE CHALLENGE

Climate change is an urgent and immediate threat to the rapidly growing human population. With the accumulation of carbon dioxide (CO₂) in our atmosphere, there is an increased trapping of heat, which causes changes in weather such as more extreme storms, droughts, fires and flooding. The global population recently topped 7 billion and is expected to reach 12 billion by the end of the century. This growing demand, combined with extreme temperature fluctuations, has resulted in widespread environmental damage, economic hardship and famine.

THE APPROACH

Joanne Chory is leading the Salk Institute's Harnessing Plants Initiative (HPI), an innovative, scalable and bold approach to fight climate change by optimizing a plant's natural ability to capture and store carbon and adapt to diverse climate conditions. Chory and the HPI team aim to help plants grow bigger, more robust root systems that can absorb larger amounts of carbon by burying it in the ground in the form of suberin, a naturally occurring carbon-rich substance. The Salk team will use cutting-edge genetic and genomic techniques to develop these Salk Ideal Plants™.

Chory has spent more than 30 years using *Arabidopsis thaliana*, a small flowering mustard plant, as a model for plant growth. She has pioneered the use of molecular genetics to study how plants alter their size, shape and

form to optimize growth and photosynthesis for particular environments. Utilizing plant genetics coupled with biochemical studies has allowed her to determine one of the most complex signaling networks that controls growth and development in response to environmental change.

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/JOANNE-CHORY

**CELLULAR BIOLOGY | CIRCADIAN RHYTHMS | CLIMATE CHANGE
GENETICS | PLANT BIOLOGY | AGRICULTURE**



JESSE DIXON

Assistant Professor
Gene Expression Laboratory
Helen McLoraine
Developmental Chair

THE CHALLENGE

The human genome, the DNA blueprint for life, is organized in three-dimensional space inside of cells. While only two percent of the genome codes for proteins, much of the other 98 percent can serve a regulatory purpose, dictating when genes are expressed. The organization of these noncoding regions plays a critical role for proper gene regulation, yet understanding how genomes are folded and the consequences of folding errors are two extraordinary challenges for scientists.

THE APPROACH

Dixon uses molecular and computational biology to explore how abnormal genome folding leads to errors in critical stretches of noncoding DNA that cause many diseases, such as cancer. His team is also developing new methods to study gene organization and gene function in single cells. By profiling each individual cell, the scientists gain extremely detailed (“high-resolution”) information about the different genes in each cellular system as well as insights into the molecular mutations that lead to disease.

THE INNOVATIONS AND DISCOVERIES

- Dixon’s team described a fundamental feature of how genomes are organized, called topologically associating domains (TADs). These TADs act as genomic “neighborhoods” and function together in units.
- Gene mutations can break and rearrange chromosomes, which carry genetic information in the form of genes. Dixon discovered some of the basic consequences of these mutations on genome folding that lead to cancer.
- Dixon created software and other genome technology tools that allow scientists to extract more genome sequence information than traditional techniques.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/JESSE-DIXON



JOSEPH ECKER

Professor

Plant Molecular and Cellular Biology
Laboratory

Director, Genomic Analysis Laboratory
Howard Hughes Medical Institute Investigator
Salk International Council Chair in Genetics

THE CHALLENGE

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

THE APPROACH

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

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/JOSEPH-ECKER

**EPIGENETICS | GENETICS | NEUROBIOLOGY | MOLECULAR BIOLOGY
PLANT BIOLOGY AND AGRICULTURE | STEM CELLS**



DANNIELLE ENGLE

Assistant Professor
Regulatory Biology Laboratory
Helen McLoraine
Developmental Chair

THE CHALLENGE

Pancreatic cancer is one of the deadliest cancers, both because it is often diagnosed late and because therapies are ineffective. The diagnosis of pancreatic cancer is complicated by a more common condition known as pancreatitis, which is a benign inflammation of the pancreas that can look very similar to pancreatic cancer. Because there is no way to distinguish between pancreatitis and pancreatic cancer, there is no early detection test for pancreatic cancer. Without a way of finding this cancer early, most patients are diagnosed at late stages with metastatic disease. In addition, pancreatic tumors contain a high degree of scar-like tissue, which provides substances that fuel cancer growth and hamper treatment efficacy. The only cure for pancreatic cancer remains surgical resection of the tumor, highlighting our failure to impact patient outcome for this disease. Thus, the challenge of pancreatic cancer consists of finding better ways to both detect and treat this disease.

THE APPROACH

Having lost close family members to pancreatic cancer, Dannielle Engle has a personal connection to the disease. Engle uses her personal and scientific passion as well as her expertise in modeling to facilitate progress in pancreatic cancer research by creating better representations of what actually happens in patients. The identification of biomarkers and therapeutic targets has been hindered by the limited access to pure sample populations and accurate models. When looking at a patient's blood samples, there can be hidden signals from the incipient tumor, but these are masked and diluted by the multitude of other signals from all over the body. In addition, when looking at the pancreatic tumor tissue itself, most of our time is spent looking at signals from non-cancer cell types in the scar-like tissue that takes up the majority of the tumor in human patients. Traditional approaches have used cell lines

that do not accurately represent the early stages of pancreatic cancer. Engle tackles these challenges by using stem-cell techniques to create more accurate models of pancreatitis and pancreatic cancer as well as biochemistry methodology to identify biomarkers that unambiguously differentiate between pancreatic cancer and other inflammatory conditions.

THE INNOVATIONS AND DISCOVERIES

- Engle has devised powerful new mouse models of pancreatitis and pancreatic cancer that improve on existing models by incorporating carbohydrate CA19-9, which is a fundamental aspect of human, but not mouse, pancreatic biology. These models have enabled fundamental advances in our understanding of how CA19-9 causes pancreatic inflammation, accelerates pancreatic tumor development, and increases the aggressive nature of this disease. These new models facilitated the discovery that anti-CA19-9 targeted therapy may be an effective treatment for pancreatic disease.
- Engle developed miniature pancreas organ cultures called organoids. Using both human and mouse cells, organoids accurately recreate the process by which tumors develop and retain defining cancer features over time. The advances in organoid technology provide a renewable resource for the field, enabling a deep dive into the basic biology of pancreatic transformation from the earliest stages of disease, identification of new therapeutic targets, and the discovery of biomarker candidates to discriminate between pancreatitis and pancreatic cancer.
- The presence of CA19-9 can indicate pancreatic cancer. However, because it is also present in pancreatitis, it can result in false positive diagnoses of cancer. Using the organoid culture platform, Engle has established new, improved ways to evaluate CA19-9 that make it possible to distinguish between pancreatitis and pancreatic cancer.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/DANNIELLE-ENGLE

CANCER | EPIGENETICS | GENETICS | THERAPEUTICS



RONALD EVANS

Professor and Director
Gene Expression Laboratory
March of Dimes Chair in Molecular and
Developmental Biology

THE CHALLENGE

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

THE APPROACH

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

In addition, Evans' studies led to a new class of PPAR delta drugs called exercise mimetics, which promote the benefits of fitness without the need to train. Exercise mimetics represent an important advance in addressing problems arising from

excess weight and obesity, such as frailty, muscular dystrophy and type 2 diabetes.

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/RONALD-EVANS

**CANCER | CIRCADIAN RHYTHMS | DIABETES | GENETICS | INFLAMMATION
METABOLISM | PANCREATIC CANCER | THERAPEUTICS**



RUSTY GAGE

Professor

Laboratory of Genetics

Vi and John Adler Chair for Research
on Age-Related Neurodegenerative
Disease

THE CHALLENGE

Variations in the genes we inherit from our parents ensure that each person's brain is uniquely wired, leading to differences in how we think, learn and behave, as well as our susceptibility to some mental illnesses. Understanding how genes and environment come together to guide these processes is crucial to developing better ways to prevent and treat diseases of the brain, such as Alzheimer's, depression or schizophrenia. But studying the human nervous system at the molecular level is challenging due to the complexity of the brain, as well as the difficulty of obtaining live human neurons.

THE APPROACH

Rusty Gage concentrates on the plasticity, adaptability and diversity observed in the brain. He showed that, contrary to longstanding dogma, the creation of new neurons (neurogenesis) does occur in the adult human brain and that environmental enrichment and physical exercise can enhance this growth. His lab demonstrated that neural stem cells exist in the adult hippocampus and can give rise to neurons that are physiologically active.

In addition, Gage discovered that moveable DNA sequences dubbed mobile elements are active during neurogenesis and lead to genomic mosaicism (being composed of genetically different cell types); this genetic variety may contribute to the brain's diverse functions.

Recently, a team of Salk Institute researchers, led by Gage, received \$19.2 million from the American Heart Association-Allen Initiative to analyze the interactions between proteins,

genes, epigenetics, inflammation and metabolism that underlie the aging brain in health and disease. The goal of the project is to investigate the mechanisms of cognitive decline and Alzheimer's to identify new therapies and treatments.

Gage's lab currently models diseases in the laboratory using human stem cells. By reprogramming human skin cells and other cells from patients with neurologic and psychiatric diseases into induced pluripotent stem cells and induced neurons, his work is deciphering the progression and mechanisms that lead to disorders such as depression and autism.

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/RUSTY-GAGE

**AGING | ALZHEIMER'S | AUTISM | DEPRESSION | EVOLUTION | GENETICS
NEUROBIOLOGY | SCHIZOPHRENIA | STEM CELLS**



MARTYN GOULDING

Professor

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

THE CHALLENGE

Movement is a core feature of all animal behavior, from simple behaviors such as locomotion and feeding to more complex tasks of speaking and playing a musical instrument. The control center for movement is the spinal cord, which harbors the neurons that transmit sensory information from the body to the brain. These neurons play key roles in voluntary movement and balance, and in protective motor behaviors such as withdrawing your hand from a hot object or scratching your skin to remove harmful parasites. An in-depth knowledge of how neurons in the spinal cord are connected and function is key to understanding how spinal cord injury or diseases such as ALS and Parkinson's disrupt the ability to move and maintain balance. It is also necessary for devising therapies that restore the ability to walk after injury, and will guide the development of better therapies for chronic itch and pain, which currently rely heavily on opiate-based treatments, with the attendant issues of addiction.

THE APPROACH

The Goulding lab has established a comprehensive genetic toolkit and set of sophisticated behavioral tests that allows them to functionally dissect the circuits in the spinal cord that process sensory information and generate coordinated body movements. Over the past 15 years, Goulding has identified and characterized many of the core interneuron cell types that are required for locomotion, and has delved into the genetics and development of these neurons. Neurons called VO neurons, he discovered, mediate alternating stepping during walking, while two classes of inhibitory neurons

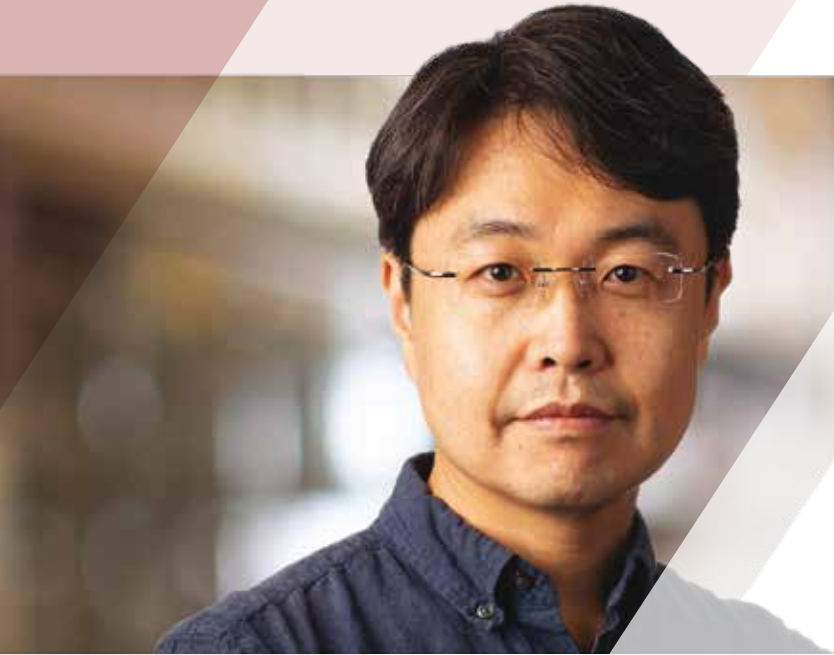
(V1 and V2b) control the alternating patterns of flexor and extensor muscle activity that underlies all movements of the limbs and digits. A knowledge of which neurons are needed for walking and balance can help scientists develop approaches to restore walking in people with spinal cord injuries as well as prevent falls in the elderly and people with Parkinson's. Goulding has also leveraged his expertise in spinal neural circuitry to define the pathways that transmit and gate itch and pain, providing a better understanding of the cellular changes that underlie chronic pain and itch.

THE INNOVATIONS AND DISCOVERIES

- Goulding's lab identified an important neural mechanism in the spinal cord that appears capable of sending erroneous pain signals to the brain. By charting the spinal circuits that process and transmit pain signals in mice, the study lays the groundwork for identifying ways to treat pain disorders that have no clear physical cause.
- Goulding's team mapped the neural circuitry of the spinal cord that processes the sense of light touch. A better understanding of these circuits should eventually aid in developing therapies for spinal cord injury and diseases that affect motor skills and balance, as well as the means to prevent falls in the elderly.
- Goulding's lab has delineated the role that multiple interneuron cell types play in controlling locomotion.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/MARTYN-GOULDING

GENETICS | NEUROLOGICAL DISEASE | LOCOMOTION | NEUROBIOLOGY
SPINAL CORD INJURY | CHRONIC PAIN | ITCH



SUNG HAN

Associate Professor

Clayton Foundation Laboratories for Peptide Biology

Pioneer Fund Developmental Chair

THE CHALLENGE

To escape from potentially harmful situations, the brain has a built-in alarm system. This system first recognizes environmental threats using its sensory systems, and then issues orders to change physiology, metabolism, behaviors and emotions to avoid these threats. However, just as with house or car security technology, the biological system can malfunction and generate false alarms. This hypersensitivity to otherwise normal sensory stimuli is linked to neuropsychiatric disorders, such as PTSD, panic disorders, anxiety disorder, chronic pain disorder, schizophrenia and autism spectrum disorders. Despite its critical involvement for survival and for disease pathogenesis, much remains unknown about how the brain's alarm system works, mainly due to the lack of appropriate tools that show specific neural circuits responsible for behaviors.

THE APPROACH

Recent discoveries show that each type of neuron has its own chemical markers that determine its functional role in the brain. Sung Han examines specific markers called neuropeptides that influence the brain's alarm system. The dysfunction of neuropeptide signaling has been directly linked to a variety of human disorders, ranging from neuropsychiatric disorders to metabolic syndromes. Although hundreds of neuropeptides are identified, their functional roles in the brain are not fully understood. To better understand how neuropeptide signaling encodes and

processes sensory threats, Han is unraveling individual neural circuits using the latest techniques in the field of neuroscience, including optogenetics, chemogenetics, electrophysiology and in vivo and in vitro functional imaging techniques, among others. Understanding the neural circuitry of the brain's alarm system will provide insights for developing therapeutic interventions for a host of neuropsychiatric disorders with sensory abnormalities.

THE INNOVATIONS AND DISCOVERIES

- Han discovered that the mutation of a gene that can make neurons excitable leads to autism spectrum disorder by decreasing the balance between excitatory and inhibitory signals in the brain.
- He also found that a very low dose of benzodiazepine, a tranquilizer drug, relieves symptoms of autism spectrum disorders, including social impairment, repetitive behaviors and cognitive deficits, in multiple mouse models by rebalancing the ratio of neurons activated and inhibited in the brain.
- Han found a neural circuit that contains neurons expressing the neuropeptide calcitonin gene-related peptide (discovered by Salk's Ronald Evans), which mediates emotional and motivational aspects of pain from the periphery to the brain.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/SUNG-HAN



DIANA HARGREAVES

Associate Professor

Molecular and Cell Biology Laboratory

THE CHALLENGE

Our bodies are comprised of several hundred different cell types, yet each cell possesses the same genetic material. This diversity arises from selectively activating genes that are particular to each cell type, whether it is skin, liver or brain. This activation is achieved by proteins called epigenetic regulators, which work to make specific regions of our genome more or less accessible to transcription. Unlike our fixed genome, epigenetic regulation is dynamic and reversible, allowing cells to respond to developmental and environmental cues. However, mutations in epigenetic regulators are commonly found in tumors, indicating that the regulation of cell identity is an important safeguard to prevent cancer.

THE APPROACH

Diana Hargreaves studies a particular epigenetic regulator, the BAF complex, which uses energy to unpack and unwind DNA from structural proteins to alter DNA accessibility and, in turn, gene transcription. Her group has identified novel BAF complex variants and new roles for the BAF complex in cancer, inflammation and pluripotency (the ability of stem cells to become any cell type). She is interested in understanding how the BAF complex is targeted to specific genes, the function of the complex, and the mechanisms by which mutations in BAF subunits cause disease. Additionally, her lab explores the use of epigenetic inhibitors to disrupt BAF complex activity for therapeutic benefit. Hargreaves

brings her knowledge of biochemistry and epigenetic regulation to investigate these properties in models of embryonic-stem-cell pluripotency, cellular differentiation, and macrophage activation and polarization.

THE INNOVATIONS AND DISCOVERIES

- Hargreaves has demonstrated that the BAF complex is an essential regulator of gene enhancers, which are important for the expression of genes involved in cell type differentiation and cancer.
- Hargreaves has discovered a non-canonical form of the BAF complex, which underlies the essential activity of the complex in stem-cell pluripotency.
- By examining the role of the BAF complex in macrophages and inflammatory cells, Hargreaves is beginning to pinpoint changes in packaged DNA to better explain the role of the BAF complex and other epigenetic regulators in inflammation and tumor immunity.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/DIANA-HARGREAVES

**CANCER | DEVELOPMENTAL DISEASE | EPIGENETICS | GENETICS
NEUROSCIENCE | NEUROLOGIC DISEASE**



DANIEL HOLLERN

Assistant Professor

NOMIS Center for Immunobiology
and Microbial Pathogenesis

Frederick B. Rentschler
Developmental Chair

THE CHALLENGE

For many patients with advanced cancers, current treatments can extend life expectancy, but do not control the disease long-term. One of the most deadly cancers, triple-negative breast cancer, is an incredibly complex disease and does not respond to conventional therapies. Because of this, research into new treatment approaches with an enduring ability to control tumor activity is an urgent need for patients.

THE APPROACH

Daniel Hollern aims to identify new therapeutic opportunities for the deadliest cancers. He merges two disciplines, computational medicine and cancer immunology, to find where tumors are vulnerable and how they can be controlled therapeutically by the immune system.

In particular, Hollern is interested in an immune cell type that has not been well-studied, called the B cell. He was the first to demonstrate that B cells help provide long-term immunity and facilitate the anti-tumor immune response coming from treatment. B cells recruit additional cells to attack tumors and also kill tumor cells through the secretion of antibodies. His goal is to identify and develop therapeutic strategies that leverage B cells to disarm tumor cells and provide long-term protection against cancer activity.

THE INNOVATIONS AND DISCOVERIES

- Hollern was the first to show that B cells predict which patients will respond to treatment and functionally control the anti-tumor immune response by secretion of antibodies and support of T cell activity.
- Hollern has developed innovative models that allow researchers to study breast cancer immunotherapy.
- Hollern discovered that immune cells called T follicular helper cells and interleukin 21, a signaling protein, help mediate the anti-tumor immune response and activate B cells.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/DANIEL-HOLLERN



TONY HUNTER

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

THE CHALLENGE

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

THE APPROACH

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

Already, cancer drugs—such as the leukemia therapy Gleevec™—have been designed based on Hunter's

discoveries. Gleevec turns off an enzyme that normally adds phosphates to tyrosines in proteins, thus preventing cancers from growing. As Hunter continues to discover other ways in which cells use chemical additions to proteins to control their growth, he aims to find potential therapeutic targets for cancers.

THE INNOVATIONS AND DISCOVERIES

- Hunter demonstrated that a mechanism called tyrosine phosphorylation (the addition of phosphate molecules to an amino acid in proteins) acts as a master on/off switch for a number of key proteins. This discovery has led to new, successful cancer therapies.
- Hunter helped to explain precisely how cells mobilize their repair crews to fix damaged DNA, an important mechanism for preventing cells from turning cancerous.
- Hunter showed how some cancers find a loophole in the cellular security system that should destroy them, which helps them to recover and resume dividing after treatment with DNA-damaging cancer drugs. In pancreatic cancer, drugs cannot reach the tumor due to an inflammatory barrier created by crosstalk between the tumor and pancreatic cells, but Hunter has found a way to disrupt this communication via a signaling molecule called LIF. LIF could be a useful biomarker or target for the treatment of pancreatic cancer.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/TONY-HUNTER



GERALD JOYCE

**Salk President
Professor**

**Jack H. Skirball Center for Chemical
Biology and Proteomics**

THE CHALLENGE

Many people have heard of DNA as being the code for life, but its single-stranded counterpart, RNA, is just as important in development and disease and likely was the ancestor to DNA during the early history of life on Earth. For many years RNA was thought to be less important in modern organisms, until more sophisticated molecular biology tools began to reveal its complexities. The field of in vitro evolution seeks to re-create the biomolecules of early life in a test tube and to coax the building blocks of RNA to assemble, replicate and evolve. Although we can't know exactly how the first genetic molecules developed 4 billion years ago, re-creating plausible facsimiles in the lab may give some insight into early evolutionary processes as well as how to design synthetic RNA molecules for therapeutic uses in diseases such as cancer, immune defects and viral infection.

THE APPROACH

Gerald Joyce is a pioneer in the field of in vitro evolution. He uses biochemical techniques to explore the potential of RNA to serve as a catalyst in critical reactions and to search for RNA enzymes that have the ability to bring about their own replication. Like their protein counterparts, nucleic acid enzymes have a specific structure that is responsible for their catalytic activity. Unlike proteins, nucleic acids are genetic molecules that can be amplified and mutated in the test tube. Joyce's laboratory has learned to exploit this dual role of nucleic acids to develop RNA- and DNA-based evolving

systems that operate entirely in test tubes. They can carry out many "generations" of in vitro evolution, allowing them to evolve nucleic acid enzymes at a much faster pace than in nature. This allows them to devise molecules whose function is to disrupt disease-related pathways.

THE INNOVATIONS AND DISCOVERIES

- Joyce improved on a synthetic RNA molecule called the class I RNA polymerase, enabling it to replicate short lengths of RNA and to conduct transcription on longer pieces of RNA to make functionally complex RNA molecules, two tasks that RNA is thought to have carried out before the emergence of DNA and proteins.
- He engineered an enzyme made of RNA that makes a mirror-image copy of itself. The molecule, which he termed a "cross-chiral" enzyme, could be how the earliest self-copying molecules emerged on Earth.
- He designed the first and several subsequent examples of DNA enzymes, some of which are now in human clinical trials for the treatment of cancer, asthma and skin diseases.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/GERALD-JOYCE



SUSAN KAECH

Professor and Director
NOMIS Center for Immunobiology and
Microbial Pathogenesis
NOMIS Chair

THE CHALLENGE

Every time we encounter a new infectious pathogen, our immune system preserves a memory of the invader so that it can protect us faster the next time we're exposed to it. In fact, developing immunological memory is one of the three cardinal traits of the mammalian immune system. A specific class of immune cells, aptly named "memory" T cells, is critical for maintaining long-term immunity to a pathogen. In fact, vaccines take advantage of this mechanism to help us develop long-term immunity to viral diseases like polio or measles. Memory T cells also attack and fight cancer. But how exactly T cell activation and memory works—and why it sometimes fails in chronic diseases or cancer—isn't fully understood. Kaech's lab is tackling this problem by identifying the fundamental mechanisms that govern the formation of long-lived memory T cells.

THE APPROACH

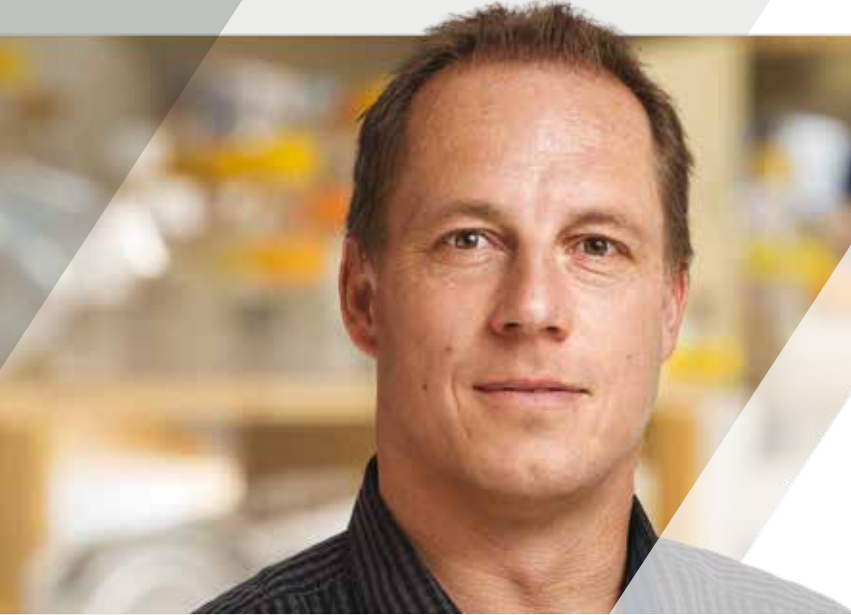
Susan Kaech aims to understand how memory T cells are produced during infection and vaccination, how they function and why they can fail to induce long-term immunity, particularly during chronic disease or cancer. Her lab has been a leader in using genetic and molecular tools to identify the genes and signaling molecules involved in generating two specific types of memory T cells, CD4 and CD8, from precursor cells during both acute and chronic viral infections. She and her team have discovered several gene networks and key molecules called cytokines that shape how memory T cells develop during a viral infection. Kaech is especially interested in how T cells are metabolically regulated, and

how their specialization and function can be altered by the types of nutrients available in infected tissues or in tumors. Related to this, she seeks to learn how T cell behavior is suppressed by tumors, in order to create better therapies for cancer using the body's own immune system—an innovative and rapidly moving field called cancer immunotherapy.

THE INNOVATIONS AND DISCOVERIES

- Kaech discovered the cellular precursors of long-lived memory CD8 T cells that form following viral infection in mice, based on increased expression of a protein receptor called IL-7. IL-7 is required both for T cell development into mature memory cells and for their long-term survival.
- Kaech has identified several key genetic pathways central to how long-lived memory T cells form following infection. Knowledge of these pathways may help to inform strategies to enhance vaccines or create new types of immunotherapies for cancer.
- Kaech discovered that part of how tumors cause immune suppression is by suppressing T cell metabolism. This discovery is opening up an entire new area of cancer biology that focuses on how immune cells and cancer cells influence each other metabolically by competing for nutrients and metabolites within tumors. Kaech's work suggests that efforts to target the metabolism of tumors may actually suppress immunity, due to the metabolic crosstalk that occurs between T cells and cancer.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/SUSAN-KAECH



JAN KARLSEDER

**Senior Vice President,
Chief Science Officer
Professor**

Molecular & Cell Biology Laboratory
Donald and Darlene Shiley Chair

THE CHALLENGE

Just as every photocopy of a copy becomes a little less crisp than the last version, each time a cell copies its genetic material, it loses some details from the ends of each chromosome. These ends, called telomeres, eventually erode and expose vital genes to wear and tear, preventing a cell from growing or causing it to die. Telomeres regulate important proliferative boundaries and limit cellular growth potential—and as a consequence inhibit cancer formation.

However, in many cancer cells telomeres are constantly rebuilt, thereby endowing a cell with immortality. Similarly, the cell's ability to repair broken DNA declines with age, leading to the accumulation of mutations and age-associated disease. If scientists can determine how to stop this telomere extension and improve DNA repair during aging, they may be able to make cancer cells die or render them more susceptible to drugs. On the flip side, keeping telomeres intact and improving DNA repair could treat premature aging syndromes. But first, researchers need to understand the complex ins and outs of normal telomere function and the regulation of DNA repair.

THE APPROACH

Jan Karlseder studies the role of telomeres throughout a cell's proliferative cycle—from the time the cell starts copying its genetic material to the time it divides into two new cells, as well as throughout the cell's life—from when a young cell emerges through cell division to when an old cell permanently "retires" (becomes senescent) or dies.

Cell division limits, such as the ones set by telomere shortening, are essential to restrict uncontrolled cell

division and thereby to prevent cancer formation. The two fundamental limits preventing primary human cells from becoming cancerous are: replicative senescence, a kind of cellular retirement in which cells stop dividing, and crisis, a state that leads to cell death. While these boundaries had been recognized for decades, it remained unclear how cells become senescent and what happens as cells keep dividing when they should senesce.

By discovering and clearly defining the mechanisms regulating cell division of primary human cells (cells taken from living tissue such as a biopsy), the Karlseder lab has exposed novel pathways during the earliest stages of cancer formation, which may yield potential interventions.

THE INNOVATIONS AND DISCOVERIES

- The Karlseder lab discovered that cell death in crisis is executed by the macroautophagy machinery, a cellular recycling mechanism, revealing a novel tumor-suppressive pathway.
- Upon senescence bypass, telomeres shorten further, until chromosomes fuse. Karlseder and his team discovered that these fused telomeres activate a cellular checkpoint (spindle assembly) that causes mitotic cell division to stop, during which the damage signal is amplified and causes cell death in a single cell cycle.
- His lab discovered that telomeres move to the outer edge of the cell's nucleus after they have been duplicated. The findings reveal how our genes are regulated and how gene expression programs are altered during cell division, an important step in understanding aging and diseases that stem from genetic mutations, such as cancer.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/JAN-KARLSEDER



AGNIESZKA KENDRICK

Assistant Professor
Molecular Neurobiology Laboratory

THE CHALLENGE

Cells use molecular motors to transport the necessities for proper cellular function. These highly dynamic, energy-driven molecular machines travel along a cellular highway system—called the cytoskeleton—to transport diverse cargo such as organelles, vesicles, mRNA, and viruses. Cells have different types of motors that can move in opposite directions or on different cytoskeletal tracks. Although transport disruption is linked to cancer and numerous neurological diseases, including Alzheimer’s disease, we still don’t fully understand how these motors work to transport items throughout the cell.

THE APPROACH

Kendrick investigates how cellular motors are assembled, how they handle diverse cellular cargo, and how they communicate with each other. She uses advanced imaging tools like cryogenic electron microscopy (cryo-EM) combined with single-molecule and live-cell imaging methods to piece together the principles of these motors. Her multidisciplinary approach allows her to unravel how cells transport important materials and how regulating or disrupting that transport either prevents or contributes to disease.

THE INNOVATIONS AND DISCOVERIES

- Kendrick discovered a protein that links cellular motors that move in opposing directions and share the same cytoskeletal track.
- Kendrick showed that a cellular motor called cytoplasmic dynein-1 can carry diverse cargo by creating multiple specialized carrying complexes to attach new cargo.
- Kendrick contributed to defining the different steps in cellular motor activation.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/AGNIESZKA-KENDRICK



PALLAV KOSURI

Assistant Professor
Integrative Biology Laboratory
Hearst Foundation
Developmental Chair

THE CHALLENGE

Human health depends on the coordinated movements of an astounding number of molecular components in our bodies. Enzymes pry apart the DNA helix to read and repair our genome, cells transport nutrients to fuel our tissues, and motor proteins in our heart work together to drive circulation. Yet we are far from having a comprehensive understanding of biomechanics across scales, from molecules, to cells, to tissues. Addressing this challenge will pave the way for quantitative models of biomechanical systems that have the power to revolutionize our understanding of human health and disease.

THE APPROACH

Kosuri studies the movements of molecules, as well as their organization in tissues, to create an integrated map of how movement gives rise to function, from the molecular motors inside cells to the muscle tissue of the heart.

In order to reveal the mechanics of single molecules, Kosuri is developing a new kind of measuring technology. Drawing on rapid advances in the field of DNA origami, Kosuri designs and builds custom nanoscale devices (millions of which could easily fit within a single cell) that are able to track molecular motion. Combining this new technology with cutting-edge microscopy techniques, Kosuri is able to visualize and measure previously unseen movements of biological molecules.

Kosuri is also using novel functional imaging methods to create a 3D molecular atlas of the heart. This atlas will improve our understanding of how the molecular and cellular structure of the heart leads to its mechanical function or dysfunction. Using these approaches, he will examine heart tissue remodeling and fibrosis, two hallmarks of heart failure, to identify new avenues for regenerative therapies.

THE INNOVATIONS AND DISCOVERIES

- Kosuri co-discovered a chemical mechanism that tunes the mechanics of muscle by altering protein folding. The study illuminated how protein folding and unfolding effectively controls how a muscle reacts to stretching.
- Kosuri developed the theoretical basis, computational methods and instrumentation—including the co-invention of a specialized atomic force microscope (AFM)—for using force pulses to detect formation of the chemical crosslinks, known as disulfide bonds, within single proteins.
- Kosuri invented ORBIT (origami-rotor-based imaging and tracking), a technology that enables extremely high-resolution measurement of the rotational movements generated by proteins. Using ORBIT, he made the first direct measurements of the rotational steps taken by the enzyme RNA polymerase as it transcribed single letters of the genetic code.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/PALLAV-KOSURI

**BIOMECHANICS | MICROSCOPY | MOLECULAR BIOPHYSICS | BIOCHEMISTRY
SINGLE-MOLECULE BIOLOGY | NANOTECHNOLOGY | DNA ORIGAMI | TRANSCRIPTOMICS | COMPUTATIONAL
BIOLOGY | CARDIAC BIOLOGY | HEART DISEASE | LOCOMOTION | THERAPEUTICS**



JULIE LAW

Associate Professor
Plant Molecular and Cellular Biology
Laboratory

THE CHALLENGE

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

THE APPROACH

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

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

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/JULIE-LAW

CANCER | CLIMATE CHANGE | EPIGENETICS | GENETICS
PLANT BIOLOGY | AGRICULTURE



KUO-FEN LEE

Professor

Clayton Foundation Laboratories for
Peptide Biology

Helen McLoraine Chair in Molecular
Neurobiology

THE CHALLENGE

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

THE APPROACH

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

Lee has uncovered a handful of genes in mice that are vital to the animal's ability to recover from nerve damage. Some are important because they stop the cell death that can occur when a nerve senses it has been injured. Others are more directly involved in nerve regrowth, and another set helps ensure that new nerves are not created just any old place, but in the proper spots of the body.

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/KUO-FEN-LEE

**CANCER | DEMENTIA | DEVELOPMENTAL DISEASE
NEUROLOGICAL DISEASE | NEUROBIOLOGY**



GREG LEMKE

Professor

Molecular Neurobiology Laboratory
Françoise Gilot-Salk Chair

THE CHALLENGE

To keep the body healthy, immune cells rely on proteins, expressed on their surface, that detect signals and threats. These proteins trigger immune cells to take specific actions, such as attacking a pathogen or clearing away dead cells. Changes in the activity of a class of cell-surface proteins, known as receptor tyrosine kinases, can lead to inflammation, cancer growth and autoimmune diseases, such as lupus, rheumatoid arthritis and multiple sclerosis. In order to understand what goes wrong in cell receptor signaling—and how to fix it—researchers must understand how receptors act and react during an immune response.

THE APPROACH

Greg Lemke discovered a family of three-receptor tyrosine kinases, called TAM receptors, which play a crucial role in regulating the response of the immune system to infection from bacteria, viruses and other pathogens. He also discovered how these same receptors mediate the everyday clearance of dead cells and cellular debris. He and his colleagues demonstrated that diminished signaling through TAM receptors (Tyr03, Axl and Mer) or their pathways results in inflammation and autoimmune disease; and conversely, that enhanced TAM signaling leads to the development of cancer. Recently, they have found that the TAM receptors Axl and Mer play a critical role in the immune cells of the brain during the development of Alzheimer's disease. Understanding the specific roles of each TAM receptor may

lead to new classes of drugs to fight infectious, autoimmune and neurodegenerative diseases.

THE INNOVATIONS AND DISCOVERIES

- Lemke's lab unveiled critical differences between the Axl and Mer receptors, and found that they regulate immune cells in inflamed and routine settings, respectively. This distinction points the way to more targeted therapies for autoimmune and cancer treatments.
- The Lemke lab revealed that microglia, the immune sentinels of the brain, require TAM receptors to detect and respond to growing amyloid plaques during Alzheimer's disease. This discovery may lead to new therapeutic approaches for neurodegeneration.
- Lemke discovered a powerful mechanism by which viruses such as influenza, West Nile and dengue fever evade the body's immune response and infect humans. A substance called phosphatidylserine, located on the surfaces of these notorious "enveloped" viruses, directly activates TAM receptors to prevent the immune system from launching a response. The finding could lead to new antiviral drugs that block the interaction.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/GREG-LEMKE

**AUTOIMMUNE DISEASE | CANCER | DEVELOPMENTAL BIOLOGY | INFECTIOUS DISEASE
INFLAMMATION | IMMUNOLOGY | NEUROBIOLOGY | VISION**



DMITRY LYUMKIS

Associate Professor
Laboratory of Genetics
Hearst Foundation
Developmental Chair

THE CHALLENGE

Biological life is organized along a continuum that ranges from complete living organisms down to tissues, cells, large “macromolecular” assemblies composed of proteins and nucleic acids, small “molecular” assemblies or individual molecules, and, finally, atoms. Since the advent of light microscopy several centuries ago, researchers have been unraveling the connection between biological structure and function along this continuum at increasingly finer degrees of spatial resolution. As technology improves, many researchers are finding that directly visualizing the structure of individual macromolecules or their assemblies at resolutions nearing the level of individual atoms can better reveal various types of dysfunction that lead to disease.

THE APPROACH

Dmitry Lyumkis utilizes and develops cutting-edge transmission cryo-electron microscopy (cryo-EM) techniques to determine the structures of macromolecules and macromolecular assemblies, which perform most of the functions inside cells. By observing previously unseen structures under different physiological conditions and at near-atomic resolution, Lyumkis aims to understand and interconnect the complex roles macromolecules play in human diseases such as cancer and HIV.

THE INNOVATIONS AND DISCOVERIES

- Lyumkis determined structures of macromolecular assemblies called “intasomes” from viruses including and related to HIV, which allows them to establish permanent infection in target host cells. These structures further our understanding of the molecular hallmarks of infection and, importantly, provide direct chemical blueprints for improving antiviral therapies used to treat HIV-infected individuals.
- Lyumkis developed new methods to quantitatively evaluate and experimentally improve anisotropic (directionally dependent) resolution in cryo-EM, which frequently plagues attempts to derive meaningful structural information from biological samples. The techniques were shown to yield higher quality data and have broad applicability to structure determination and evaluation.
- Lyumkis and colleagues deciphered the structures and molecular mechanisms of activity of a novel class of CRISPR/Cas enzymes, which has the ability to cut and edit RNA. This work opens novel opportunities for genetic engineering and has broad implications for understanding, and potentially treating, diseases at a molecular level.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/DMITRY-LYUMKIS

CRYO-EM | STRUCTURAL BIOLOGY | IMMUNOLOGY | GENETICS



PAMELA MAHER

Research Professor
Cellular Neurobiology Laboratory

THE CHALLENGE

Alzheimer's disease is the most common form of dementia, yet treatment options remain limited. Current drug therapies on the market treat the symptoms of Alzheimer's but do not halt the progression of the disease. More-effective treatment options are urgently needed in order to slow, stop and reverse the effects of Alzheimer's and other neurodegenerative diseases associated with aging.

THE APPROACH

Maher screens for compounds that could slow or stop the progression of neurodegenerative diseases, with a focus on Alzheimer's. Her novel approach uses compounds derived from natural products, such as strawberries, turmeric and cannabis, in order to treat the cellular aging and memory loss observed in Alzheimer's.

Maher and her team have taken multiple drug candidates from conception in the laboratory into clinical trials. Currently, two compounds, CMS121 and J147, are undergoing clinical trials for the treatment of Alzheimer's. In mice, these compounds were found to protect neurons and prevent the molecular changes that are associated with aging.

THE INNOVATIONS AND DISCOVERIES

- Maher and her team discovered a novel cell death pathway called oxytosis/ferroptosis. This pathway, also identified by another lab, is thought to play a role in Alzheimer's and other neurodegenerative diseases.
- Maher was one of the first to take aging into account for drug discovery in Alzheimer's. She identified a class of compounds known as geroneuroprotectors, which slow the aging process in mice.
- Maher uses natural products as the basis for designing novel drug candidates, which has led to the development of two compounds, CMS121 and J147, which are now in clinical trials for the treatment of Alzheimer's.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/PAMELA-MAHER



GRAHAM MCVICKER

Associate Professor

Laboratory of Genetics and the
Integrative Biology Laboratory

THE CHALLENGE

Human genetic differences, known as genetic variants, are what make people unique. Genetic variation affects traits like hair and eye color and can promote both health and disease. Thousands of genetic variants have now been associated with human diseases; however, the functions of most of these variants are unknown and difficult to determine, since most of them are “noncoding” and lie outside of genes (the portions of the genome that encode proteins). Research now suggests that—rather than altering genes directly—these variants instead influence gene expression by modifying *when* genes are turned off and on and the *amount* of protein that they produce in different cell types and conditions. To understand the genetic underpinnings of complex human diseases, it is essential to understand how these noncoding genetic variants alter the regulation of gene expression.

THE APPROACH

Graham McVicker’s lab studies how human genetic variation affects gene regulation by combining experimental approaches with computational analyses. The experimental side of the laboratory specializes in CRISPR perturbations of the genome, as well as in genomic assays to determine chromatin structure and gene expression. The computational side of the laboratory specializes in analysis of human genetic variation and large experimental datasets using methods from statistics and machine learning.

THE INNOVATIONS AND DISCOVERIES

- As a postdoctoral researcher, McVicker published the first study to identify histone mark quantitative trait loci (QTLs) in the human genome, which are genetic variants that are associated with differences in histone modifications between human individuals. He also developed a software package for analyzing allele-specific expression and discovering molecular quantitative traits, called WASP, which his lab has used to discover genes with recurrent dysregulation in cancer genomes.
- McVicker’s lab has developed techniques and analysis methods that leverage CRISPR to scan noncoding portions of the genome for important regulatory functions. They also use these methods to discover important regulatory sequences that affect gene expression in T cells.
- In current research, McVicker’s lab is using machine learning to predict the regulatory function of noncoding genetic variants in the human genome.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/GRAHAM-MCVICKER

COMPUTATIONAL BIOLOGY | EPIGENETICS | GENETICS
GENE REGULATION | BIOINFORMATICS

A portrait of Christian Metallo, a man with dark hair and glasses, wearing a dark button-down shirt, smiling. The background is a blurred laboratory setting.

CHRISTIAN METALLO

Professor

Molecular and Cell Biology Laboratory
Daniel and Martina Lewis Chair

THE CHALLENGE

Every organism needs food to survive. For humans this food comes in the form of molecules like glucose, fat and amino acids (the building blocks of proteins). Cells throughout the body metabolize, or break down, these molecules to obtain the building blocks and energy needed to perform life-sustaining tasks. When cellular metabolism goes awry, however, it can lead to metabolic catastrophe and diseases that include cancer, diabetes, and neurodegeneration. By studying how these complex metabolic processes work, scientists can design therapies that target metabolic dysfunction and improve human health.

THE APPROACH

Metallo's work focuses on mapping these interconnected metabolic networks to uncover disease-causing pathways. Using tracer molecules and advanced mass spectroscopy techniques, his lab identifies how molecules are broken down and re-built, where metabolites end up in the body, and what regulates these processes. Taking this approach, Metallo has made key discoveries about the metabolic pathways that drive cancer progression and macular disease—pathways, which can then be influenced through dietary manipulations or targeted therapies.

THE INNOVATIONS AND DISCOVERIES

- Metallo discovered new insights into the role that two amino acids, serine and glycine, play in tumor progression and demonstrated that restricting dietary serine and glycine in mice alters lipid (fat) metabolism to decrease tumor growth.
- Metallo's team investigated a metabolic defect that leads to macular telangiectasia type 2. They discovered new biochemical links between peripheral neuropathy and macular disease which may be exploited via diet or pharmacological interventions.
- Metallo uncovered the metabolic origin of lipid molecules called branched-chain fatty acids that correlate positively with body fat metabolic activity and are decreased in patients with fatty liver.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/CHRISTIAN-METALLO

AGING | CANCER | METABOLISM



TODD MICHAEL

Research Professor
Plant Molecular and
Cellular Biology Laboratory

THE CHALLENGE

Plants perform a myriad of extraordinary biochemical functions, including capturing carbon dioxide through photosynthesis as well as extracting and concentrating essential elements, such as nitrogen. Underlying these biochemical abilities are the most diverse genetic codes (genomes) on the planet. Plants have highly complex genomes that result from mixing, reorganizing and restructuring to adapt to diverse and changing environments. For example, the complex genome of bread wheat is six times the size of the human genome due to three wheat relatives' genomes fusing over time. Scientists have only recently been able to read (sequence) these complex genomes, which is opening the door for understanding the genetic basis of plant biochemistry and adaptation. This information will help researchers develop plants that can survive in harsh environments, to grow more food, fiber and fuel for a burgeoning population, as well as to potentially mitigate the negative effects of climate change.

THE APPROACH

Todd Michael leverages sequencing technology and computational biology to uncover how genomic differences enable plants to better respond to and exploit their environment. Michael's team is developing a multi-genome framework to better understand the underlying genetic networks that govern how plant populations interact with their surroundings.

His lab examines plants with unique physical forms, carbon and nitrogen acquisition strategies, and growth patterns to better understand plant genomes. For example, his team pioneered the use of the fastest growing (~1 day to multiply) and smallest (1 mm) flowering plant, *Spirodela polyrhiza*, as a research model to study a diverse array of plant functions. The

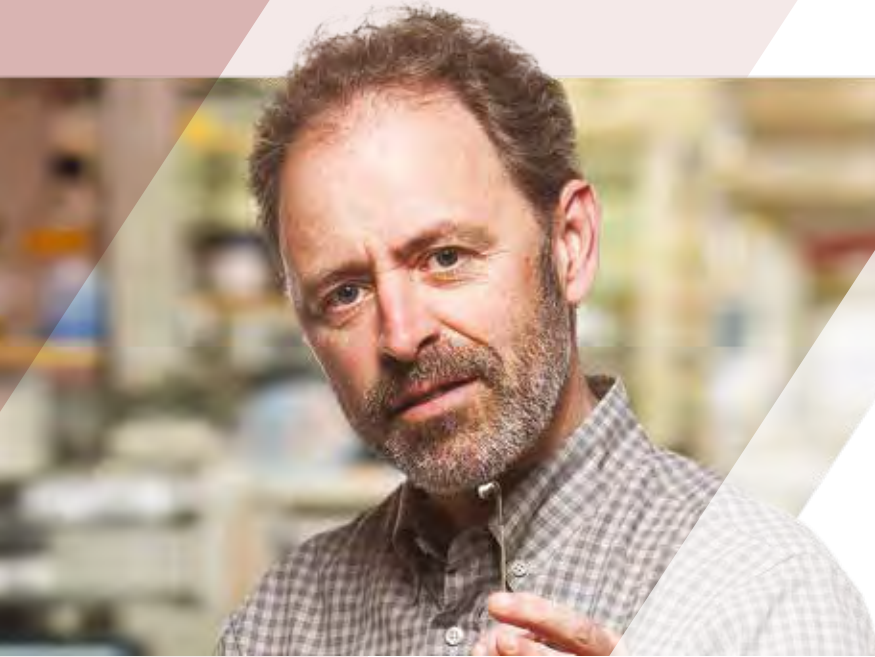
group uses carnivorous and parasitic plants to examine novel nitrogen acquisition strategies. They also study plants that perform alternative photosynthesis such as crassulacean acid metabolism (CAM) to uncover how a genome is rewired to take in carbon dioxide at night and conserve water during the day.

As a member of Salk's Harnessing Plants™ Initiative leadership team, Michael is providing genome sequencing support to create Salk Ideal Plants™, which could store excess amounts of atmospheric carbon deep in the ground. His team is investigating the genetic architecture controlling specific traits, such as deeper rooting, in order to take a "genome-informed" breeding approach to help plants store more carbon and adapt to climate change.

THE INNOVATIONS AND DISCOVERIES

- **Plant genomics:** Michael published the first near-complete plant genome of *Oropetium thomaeum*, a type of grass that can survive extreme drought, by pioneering the use of new sequencing technologies and genome analysis tools.
- **Time of Day (TOD) expression:** Using the model plant *Arabidopsis thaliana*, Michael provided molecular evidence that the circadian clock enables plants to anticipate changes in their environment such as daily light-dark cycles as well as seasonal changes. His group also showed that TOD gene expression networks are conserved by evolution across higher plants, which enables advanced breeding for next-generation crops.
- **New plant models:** Michael's team has been instrumental in introducing several key model plant systems, such as *Brachypodium distachyon* and *Spirodela polyrhiza*, to the research community, which can help further reveal details into a diverse array of plant functions.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/TODD-MICHAEL



MARC MONTMINY

Professor

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

THE CHALLENGE

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

THE APPROACH

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

Montminy discovered one of these key signaling molecules, called CREB, and has described many of its functions. His lab also deciphered the role of another genetic switch,

CRTC2. In healthy individuals, both are responsible for maintaining the right cycle of sugar storage and release throughout the day. Understanding how the signals—as well as many other molecules that interact directly with CREB and CRTC2—are regulated incorrectly in diabetics could reveal new targets for drugs. Montminy works to reveal these connections and mechanisms by identifying the role of different genes, studying which genes are turned up or down during different metabolic states, and testing how signaling molecules interact within isolated muscle or liver cells.

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/MARC-MONTMINY

CIRCADIAN RHYTHMS | DIABETES | GENETICS | METABOLISM | THERAPEUTICS



LENA MUELLER

Assistant Professor
Plant Molecular and
Cellular Biology Laboratory

THE CHALLENGE

Most terrestrial plants, including many crops, engage in mutually beneficial relationships with soil microbes—like arbuscular mycorrhizal fungi—that provide nutrients in exchange for carbon. Leveraging these microbes in agriculture has great potential to reduce our reliance on chemical fertilizers and make agricultural production more sustainable. To accomplish this, scientists must understand how the symbiotic relationship between plants and arbuscular mycorrhizal fungi is controlled by plant and fungal genes, as well as the environment.

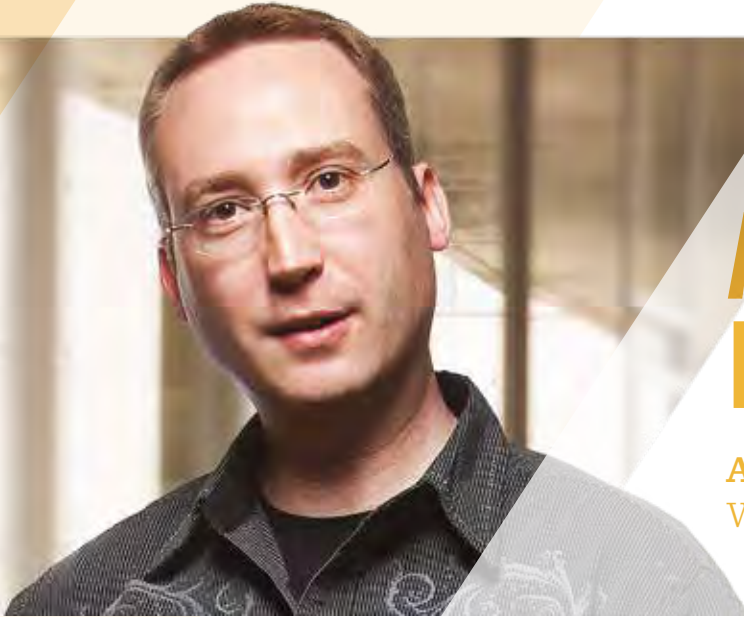
THE APPROACH

Mueller works to uncover the genetic basis of how plants initiate and maintain symbiosis with arbuscular mycorrhizal fungi. To do so, she looks at 1) the molecular signaling pathways that allow plants to perceive and transmit information about fungus presence and quality, 2) how these long- and short-distance signals are integrated with other physiological signals to ensure that carbon cost and nutrient uptake are optimally balanced, and 3) the genetic factors that determine symbiotic success in a changing environment. Mueller hopes to use what she learns to engineer crops that are optimal hosts for arbuscular mycorrhizal fungi, allowing them to take up more nutrients or transfer more carbon underground to their roots and microbial partners.

THE INNOVATIONS AND DISCOVERIES

- Mueller described the molecular mechanism of arbuscular mycorrhizal symbiosis autoregulation, which allows plants to regulate the number of fungi in their roots and may help plants maintain an optimal balance between giving carbon and receiving nutrition from a fungus.
- Mueller contributed to a better understanding of the transcriptional networks that govern the establishment of fungal feeding structures in plant roots, finding that transcriptional regulators can be manipulated to increase the symbiotic capacities of plants.
- Mueller identified different “supermycorrhizal” plant lines, which harbor more arbuscular mycorrhizal fungi in their roots. Such genotypes can be utilized to enhance plant nutrition and improve fungal carbon sequestration in soils.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/LENA-MUELLER



AXEL NIMMERJAHN

Associate Professor

Waitt Advanced Biophotonics Center

THE CHALLENGE

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

THE APPROACH

Axel Nimmerjahn has spearheaded the development of new microscopy techniques to visualize the structural and functional dynamics of glial cells and their bi-directional interaction with other cells. To enable cellular-resolution measurements under naturalistic conditions, his lab has worked to shrink the size of microscopes to make them wearable. Their tiny microscopes weigh less than 2.5 grams, are only a few millimeters in size, and have allowed the team to reveal how cellular activity encodes sensory and motor information. Additionally, they have created new tools for

cell type-specific staining and genetic manipulation and for analysis of large-scale imaging data. This has allowed them to address long-standing questions regarding the role of glial cells in the intact healthy or diseased CNS (see below). Resolving these fundamental questions has broad implications for our understanding of CNS function and the treatment of neuroinflammatory and neurological disorders.

THE INNOVATIONS AND DISCOVERIES

- Nimmerjahn discovered that microglia, the resident immune cells in the CNS, continuously survey the cellular environment with their fine branches. He showed that through this behavior, microglia provide the first line of defense against tissue injury and infection, and he identified mechanisms that regulate this inflammatory response (patent pending).
- Nimmerjahn's lab used cutting-edge microscopy approaches to visualize the blood-brain barrier (BBB) breakdown after stroke. His team found that stepwise impairment of different cellular mechanisms accounts for the BBB deficits in stroke. The findings could lead to new ways to treat the disease.
- Nimmerjahn uncovered that astroglia, a major regulatory cell type in the CNS, respond to painful stimuli with large-scale coordinated excitation suited to initiate macroscopic changes in CNS network dynamics, and showed how antinociceptive drugs disrupt this activity. This makes astroglia potential new targets for treatment of painful conditions.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/AXEL-NIMMERJAHN

**BIOPHOTONICS | NEUROBIOLOGY | NEUROLOGICAL DISEASE | STROKE
CANCER | PAIN | INFLAMMATION | VISION**



JOSEPH NOEL

Professor and Director
 Jack H. Skirball Center for
 Chemical Biology and Proteomics
 Arthur and Julie Woodrow Chair

THE CHALLENGE

Plants use a remarkable diversity of capabilities to respond to their environment—they can sense light, water, chemicals and even wind flows, and, in turn, speak with other plants and organisms in their environment using the language of chemistry. Over millions of years, plants evolved to harness the energy of the sun, survive in a myriad of challenging environments, absorb carbon dioxide (which most other organisms find toxic) and gather nutrients from decaying life in the soil, all while firmly planted in the ground. But farmers want to further improve how plants grow, fight off pests, generate natural medicines and produce healthy food crops. To improve plants' health and yield in globally sustainable ways, scientists first need to understand how plants have already optimized their biology and chemistry through the process of evolution over nearly 450 million years.

THE APPROACH

Joseph Noel studies the structure and chemistry of compounds produced by plants as well as how plants have evolved unique ways to make their own specialized products adapted to nearly every ecosystem on Earth. He uses biological assays to test how a plant's behavior is altered by genetic changes. He also employs chemistry techniques to replicate a plant's production pathways in the lab. The knowledge he gains includes clues about how to improve plants' chemical reactions or combat climate change. For example, Noel has pieced the structure of a natural plant polymer known as suberin—aka cork—that is rich in carbon

atoms derived from the greenhouse gas carbon dioxide, and that also protects plants from environmental stressors including drought, floods, disease and salt. Because these natural plant molecules are densely packed with carbon atoms and resist decomposition in soils, they enhance the vitality of soils and serve as carbon storage devices to possibly mitigate the deleterious effects of climate change associated with excess atmospheric carbon dioxide.

THE INNOVATIONS AND DISCOVERIES

- Using tricks he learned from plant biology and biochemistry, Noel engineered the enzyme plants use to make the anti-aging compound resveratrol, commonly found in red wine. This technology has been used to produce resveratrol and related molecules in other plants to arm them in their constant battle against environmental pathogens while offering potential dietary benefits to humans as well.
- Noel's group uncovered a more complete chemical structure of a natural carbon storage device found in all plants known as suberin that explains why it resists decomposition and protects plants from a myriad of environmental stresses.
- Noel's team uncovered how an enzyme called chalcone isomerase evolved to enable plants to make products vital to their own survival. The researchers hope that this knowledge will inform the manufacture of products that are beneficial to humans, including medications and improved crops.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/JOSEPH-NOEL

BIOPHOTONICS | CANCER | CLIMATE CHANGE | NEUROBIOLOGY
NEUROLOGICAL DISEASE | STROKE



CLODAGH O'SHEA

Professor

Molecular and Cell Biology Laboratory
Howard Hughes Medical Institute
Faculty Scholar
Wicklow Chair

THE CHALLENGE

Cancer is a leading cause of death in the United States. Most cancer patients are treated with non-specific chemotherapies that have devastating side effects and do not always cure their disease. To conquer a disease as complex as cancer requires a therapeutic agent that is as sophisticated as the disease itself. As one approach, scientists are turning to nature to find ways to harness and redesign biological systems and devices to combat disease.

THE APPROACH

Clodagh O'Shea is at the forefront of cutting-edge technologies to design synthetic viruses and other genetic devices that are controlled and able to selectively target cancer cells. Viruses are nature's nanomachines: Their outer coats enable them to enter specific tissues in our body where they express proteins that hijack the cell's growth controls, forcing the cell to replicate and unwittingly reproduce the virus at the same time. O'Shea has revealed that many of the same cellular controls are targeted by mutations in cancer. She is exploiting this knowledge to redesign viruses that act like guided missiles, specifically infecting and replicating in tumor cells. Each time a virus infects a cancer cell and multiplies, the virus kills the cell by bursting it open to release thousands of viral progenies, which go on to target other cancer cells. Such intelligent viral therapies leave normal cells unharmed and have enormous potential in improving the treatment of patients suffering from cancer.

To successfully redesign and program synthetic viral therapies, O'Shea is uncovering the deep-rooted secrets of how viruses, normal and tumor cells work and can be made to work. In addition, she is combining these fundamental insights with new technologies developed in her lab that enable viral gene delivery devices, cancer therapies and vaccines to be assembled using libraries of modular DNA parts, akin to using LEGO® pieces to build a sculpture or

robot. O'Shea proposes to further develop these genetic machines as diagnostic "drones" that identify the earliest traces of cancer; synthetic viruses that act like guided missiles to destroy tumor cells while preventing therapeutic resistance; and viruses that home in on damaged tissues to promote wound healing and stave off infection.

Another aspect of O'Shea's research is to unravel the structural code that determines if DNA can be accessed and used in the cell nucleus. A cell's genomic material is not a simple helix: DNA is coiled around proteins to form complex three-dimensional packages called chromatin to fit into the small space of a cell nucleus. Charting and determining the structure of chromatin at multiple scales is a vital step in understanding how viruses access genetic material to replicate and kill cells. To this end, her lab is developing new techniques to visualize the structure-function of DNA in time and 3D space. These studies have the potential to reveal the structural code that determines if a gene is in an "on" or "off" state in health and how to make a cancer cell "remember" how to be normal again through novel epigenetic therapies.

THE INNOVATIONS AND DISCOVERIES

- O'Shea's lab discovered critical details into how a cell's response system tells the difference between damage to its own DNA and the foreign DNA of a virus. The discovery could help in the development of new cancer-selective viral therapies and may explain why aging and certain diseases seem to lead to more viral infections.
- Her team discovered a mechanism used by adenovirus to sidestep the cell's suicide program. This could help explain how tumor suppressor genes are silenced in tumor cells, and could pave the way for a new type of targeted cancer therapy.
- O'Shea is developing new methods to visualize cell nuclei's bundles of DNA and proteins (chromatin) in three-dimensional space to better understand gene activity and viral infections.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/CLODAGH-OSHEA



SATCHIDANANDA PANDA

Professor

Regulatory Biology Laboratory
Rita and Richard Atkinson Chair

THE CHALLENGE

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

THE APPROACH

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

In the process of exploring how the liver's daily cycles work, Panda found that mice who eat within a set amount of time (8-12 hours) resulted in slimmer, healthier mice than those who ate the same number of calories in a larger window of time, showing that when one eats may be as important as what one eats. If the benefits of this "time-restricted eating"

(TRE) hold true in humans, it could have profound impacts on treating overeating disorders, diabetes and obesity.

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

THE INNOVATIONS AND DISCOVERIES

- Panda's lab discovered that confining caloric consumption to an 8- to 12-hour period—as people did just a century ago—might stave off high cholesterol, diabetes and obesity. He is exploring whether the benefits of time-restricted eating apply to humans as well as mice. By preventing and better managing these age-related chronic diseases, one can extend healthy life span and promote healthy aging.
- Panda's team discovered the essential function of a blue-light sensitive protein, melanopsin, in regulating our circadian clock, sleep and alertness. This discovery is fueling a new lighting revolution to enrich our exposure to blue light during the daytime and reduce blue light at night to improve mood, alertness and sleep.
- His lab discovered that hundreds to thousands of genes in our genome turn on and off in different organs at specific times during the 24-hour day. The findings imply that hundreds of existing drugs to cure many different types of diseases from joint pain to cancer may work better if they are administered at the right time of the day or night.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/SATCHIDANANDA-PANDA

AGING | CELL BIOLOGY | CIRCADIAN RHYTHMS
DEPRESSION | GENETICS | METABOLISM



SAMUEL PFAFF

Professor
Gene Expression Laboratory
Benjamin H. Lewis Chair

THE CHALLENGE

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

THE APPROACH

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

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

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/SAMUEL-PFAFF

**BIRTH DEFECTS | DEVELOPMENTAL DISEASE | LOCOMOTION | NEUROBIOLOGY
NEUROLOGICAL DISEASE | POST-POLIO SYNDROME | STEM CELLS**



DEEPSHIKA RAMANAN

Assistant Professor
NOMIS Center for Immunobiology and
Microbial Pathogenesis

THE CHALLENGE

For babies: A mother's microbiota, diet, exposure to infections, and other environmental factors are crucial for a newborn's early development and long-term immune health. But it remains unclear exactly how these maternal factors influence a person's susceptibility to autoimmune disorders such as inflammatory bowel disease later on. Studying the underlying biological mechanisms will help us better understand the causes of autoimmune and inflammatory diseases and enable researchers to develop interventions to prevent and treat them.

For moms: How the maternal immune system changes during pregnancy and breastfeeding is poorly understood. Studying the ways immune cells function during these crucial times, especially in the intestine and the mammary glands, will help advance our understanding of women's health. This information will also help us understand how maternal changes during these stages affect breast milk and offspring health for multiple generations.

THE APPROACH

Ramanan's lab uses a combination of single-cell techniques, metabolomics, and metagenomics in mouse models, human tissue samples, and breast milk to study the immune cell landscape and other maternal factors. Her team is interested in how the immune system influences both maternal health and offspring immunity for multiple generations.

THE INNOVATIONS AND DISCOVERIES

- **Entero-mammary axis:** Ramanan discovered that communication between the mother's intestine and mammary glands can impact breast milk composition and influence offspring intestinal immunity in a mouse model.
- **Host-microbe interactions in early life:** Ramanan found that the way mouse maternal antibodies coat an offspring's intestinal microbes in the first week of life can determine the offspring's intestinal immune landscape in adulthood.
- **Multigenerational immune transfer:** Ramanan discovered that immune traits can be maternally transferred for multiple generations in mice.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/DEEPSHIKA-RAMANAN

AUTOIMMUNE DISORDERS | BREAST MILK | DIGESTION
DIGESTIVE DISORDERS | IMMUNOLOGY



JOHN REYNOLDS

Professor

Systems Neurobiology Laboratory
Fiona and Sanjay Jha Chair in
Neuroscience

THE CHALLENGE

Perception is a constructive process in which the brain integrates sensory information to build an internal representation of the external world. This occurs so quickly and effortlessly that we are unaware it has happened at all. The idea that the brain endlessly creates an internal model of the external world is key to our modern understanding of perception. The Reynolds lab wants to know how the brain achieves this remarkable feat.

THE APPROACH

Vision is the most well-developed sensory system in humans, and arguably the most well-studied system in the brain. Since the neurons that make up its circuitry are found throughout the brain, vision acts as an exemplar for understanding the rest of the brain.

Reynolds develops models of the neural mechanisms underlying vision, perception, and consciousness to gain insight into the brain. Reynolds then leverages those models to derive specific hypotheses that can be tested using a variety of experimental techniques, such as quantitative studies of perception, neurophysiology, and neuroanatomy. His lab is also one of the world leaders in the application of optogenetics, a research tool that uses light to activate specific brain cells and networks to study their roles in neural computation.

THE INNOVATIONS AND DISCOVERIES

- Reynolds developed the leading computational model of attention, providing a unified, quantitative framework for understanding attentional selection in healthy brains, and how this selection fails in some brain diseases.
- Reynolds discovered that brain activity fluctuations are reduced when attention is directed to a stimulus, resulting in improved perception of that stimulus.
- Reynolds found that patterns of neural signals, called traveling brain waves, exist in the visual system of the awake brain, and are organized to allow the brain to perceive objects that are faint or otherwise difficult to see.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/JOHN-REYNOLDS

**ALZHEIMER'S DISEASE | ATTENTION | MEMORY | DEMENTIA | NEUROLOGICAL DISEASE
COMPUTATIONAL NEUROSCIENCE | NEUROBIOLOGY | VISION**



ALAN SAGHATELIAN

Professor

Clayton Foundation Laboratories
for Peptide Biology
Dr. Frederik Paulsen Chair

THE CHALLENGE

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

THE APPROACH

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

discoveries, including the recent finding of a novel human lipid that reduces inflammation and reverses the symptoms of diabetes. Saghatelian hopes to use the knowledge gained from his lab's work to accelerate the development of new medicines in the area of diabetes. He is also collaborating with many laboratories at Salk to understand the roles of peptides and metabolites in cancer and neurodegenerative and immunologic disorders.

THE INNOVATIONS AND DISCOVERIES

- With collaborators, Saghatelian analyzed changes in metabolite levels in mice that are resistant to diabetes, which led to the discovery of a lipid called a FAHFA. FAHFAs are also found in humans. Administration of these lipids to mice reduces inflammation and improves the symptoms associated with diabetes, making these interesting therapeutic candidates and revealing a new disease-associated metabolite.
- Saghatelian also identified a previously unknown cluster of human genes that produce peptides that control fundamental cellular processes, such as DNA repair, highlighting their potential importance in cancer.
- In recent work, Saghatelian's team discovered thousands of additional human genes that will increase our understanding of the molecular pathways that regulate many diseases such as cancer and autoimmunity.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/ALAN-SAGHATELIAN



TERRENCE SEJNOWSKI

Professor and Laboratory Head
 Computational Neurobiology
 Laboratory
 Francis Crick Chair

THE CHALLENGE

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

THE APPROACH

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

To collect data on brain function, Sejnowski records the electrical activity of select sets of cells, as well as analyzes thin slices of autopsied brains. He uses that information to create and refine computational models on how the brain

stores information for different activities. Through these models, he gets a better understanding of what information different cell types encode, what molecules are needed and how signals move throughout the brain. At the same time, he learns how diseases such as schizophrenia or Parkinson's might alter these patterns.

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/TERRENCE-SEJNOWSKI

**ALZHEIMER'S DISEASE | COMPUTATIONAL BIOLOGY | NEUROLOGICAL DISEASE | MEMORY
 NEUROBIOLOGY | PARKINSON'S DISEASE | SCHIZOPHRENIA | SYSTEMS BIOLOGY**



GERALD SHADEL

Professor

Molecular and Cell Biology Laboratory
Audrey Geisel Chair in Biomedical
Science

Director, San Diego-Nathan Shock
Center of Excellence in the Basic
Biology of Aging

THE CHALLENGE

Life cannot exist without energy. For us to move, think and withstand stress and infections, the cells in our body must generate energy from the food we eat. This occurs in dynamic “powerhouses” inside cells, called mitochondria. Mitochondria are also involved in cellular signaling and immunity via pathways that are only starting to be identified. However, harboring mitochondria comes at a cost—they wear out with age, produce damaging metabolites and contain their own DNA (mtDNA) that can cause inherited diseases. A greater understanding of these complex organelles is essential to unravel their role in human disease and aging.

THE APPROACH

Gerald Shadel studies the basic biology of mitochondria and mtDNA, and, in doing so, has identified novel ways that mitochondria contribute to disease, aging and the immune system. He is also interested in understanding how mitochondria are involved in cellular signaling processes. He seeks to identify what the signals are, what pathways they trigger and how they play a part in aging, cancer and metabolic and degenerative diseases. His group takes a multidisciplinary view, exploring mitochondrial function—and dysfunction—via cultured cells, model organisms and other genetic and biochemical approaches.

THE INNOVATIONS AND DISCOVERIES

- Shadel has elucidated context-specific ways that mitochondria and the reactive oxygen species (ROS) they produce are involved in the neurodegenerative disease ataxia-telangiectasia (A-T), maternally inherited deafness, aging and cancer.
- He also discovered that mtDNA, which is derived from an ancient bacterium, can trigger the immune system if exposed to the rest of the cell, causing antiviral and other defensive responses.
- He is currently studying adaptive responses to mitochondrial stress in mammals, based on his discovery in yeast that mitochondrial ROS signals induce changes in gene expression in the cell nucleus that extend this organism’s life span.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/GERALD-SHADEL

MITOCHONDRIA | AGING | GENETICS



TATYANA SHARPEE

Professor

Computational Neurobiology

Laboratory

Integrative Biology Laboratory

Edwin K. Hunter Chair

THE CHALLENGE

Tatyana Sharpee's lab seeks to understand how the brain and other biological systems work while their components are constantly changing. For example, when a baby is growing, new neurons are added to circuits. During adulthood, connections between neurons are constantly added and removed as we learn new skills and information. As we age, we begin to lose some functionality of these connections. Despite these changes, we maintain a constant sense of self and can remember events for decades. Even within individual neurons, proteins are constantly updated, yet the right balance is achieved to ensure appropriate signaling by them. Nevertheless, we maintain the same sense of "self" and can remember events for decades. Further exacerbating the problem, the environment in which the brain operates is constantly changing, so Sharpee and colleagues are working to understand optimal signals that the brain should pay attention to in the environment, and to understand optimal prescriptions for adaptation to changes in the environment.

THE APPROACH

Tatyana Sharpee is using advanced methods from mathematics, statistics and physics to chart the principles by which the brain's billions of neurons exchange energy and information. In particular, she uses information theory (a set of mathematical concepts commonly employed in communications and finance systems) to quantify the activity of neurons and, in one area of research, works to determine how features are organized within parts of the brain that are responsible for conveying our senses, including vision, hearing and the sense of smell. Revealing the workings of

these core senses would help lead to new treatments and brain-machine interfaces for patients with disruptions to these systems that can happen as a result of stroke, dementia or with schizophrenia. Furthermore, Sharpee and her group are using disruptions in sensory systems as diagnostic tools to find new treatments for a number of neurological disorders that affect the brain more broadly, including autism, Alzheimer's disease, schizophrenia, depression and anxiety.

THE INNOVATIONS AND DISCOVERIES

- Sharpee's group revealed a new way to organize odors and the sense of smell. They found that odors from the natural environments can be described by a curved surface, similar to a Pringle's potato chip, and mathematically known to have a hyperbolic metric. They also found that our perception of smell is organized similarly, in ways that facilitate accurate estimation of fruit content based on odors.
- Sharpee developed a concise scheme for how visual neurons can combine selectivity to shapes and textures of visual objects.
- Sharpee and collaborators have generated a theory that explains when it becomes advantageous for an organism to use new types of neurons. This theory could help catalogue and determine the number of separate neuronal types in the brain. Extensions of this theory make it possible to compute how much information large numbers of neurons jointly convey about incoming stimuli. Previously, this was only possible to do for a few neurons, and now the method can keep up with the capacity of experimental methods that record thousands of neurons simultaneously.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/TATYANA-SHARPEE

**ALZHEIMER'S DISEASE | AUTISM | SCHIZOPHRENIA | NEUROLOGICAL DISEASE
VISION AND OTHER SENSES | COMPUTATIONAL BIOLOGY**



REUBEN SHAW

Professor

Molecular and Cell Biology Laboratory
William R. Brody Chair

THE CHALLENGE

Lung cancer and type 2 diabetes are two leading causes of death in the United States. It turns out they have something else in common: both diseases involve a mishap in how cells use energy. In tumors, mutated cells usurp energy to grow aggressively. In diabetes, cells can no longer properly process and store two key sources of energy—sugar and fat (lipids).

Now, scientists have discovered a common set of biochemical pathways that normally suppress both cancer and type 2 diabetes. In the past decade there has been an explosion of interest in the details of how cancer pathways connect to metabolism, and, conversely, how metabolic pathways control development of cancer and diabetes. This has led to a number of new discoveries into how cells maintain their energy balance and couple their metabolism to their growth needs. Researchers are observing that multiple medications for diabetes and other metabolic disorders may help treat drug-resistant cancers and vice versa.

THE APPROACH

Fifteen years ago, Reuben Shaw discovered that a gene frequently mutated in cancer (LKB1) regulates an enzyme named AMPK. This enzyme is critical for the therapeutic benefit of metformin, which is currently the most widely used frontline type 2 diabetes medication. Ever since this discovery, Shaw wondered if drugs originally designed to treat metabolic diseases could also work against cancer.

This intriguing connection between cancer and metabolism coincided with emergent interest in metabolism in cancer, which rapidly moved to the forefront of cancer research. The Shaw lab focuses on uncovering new aspects of a central metabolism and growth pathway that underpins how all

cells respond to low nutrients and low energy. This AMPK pathway, which Shaw discovered, halts cell growth and reprograms metabolism when nutrients are scarce. The same pathway also helps to mechanistically connect the benefits of exercise, metformin and diet to the suppression of both cancer and diabetes. In the past decade at Salk, the lab's studies have led to the discovery of several new therapies for both cancer and metabolic diseases.

THE INNOVATIONS AND DISCOVERIES

- Targeting fat to treat cancer: The Shaw lab has discovered a way to target and stall fat synthesis to halt cancer growth. They developed the novel fat synthesis inhibitor drug called ND-646, which is promising when paired with common treatments for non-small-cell lung cancer. This discovery could lead to new therapeutic treatments for a variety of types of cancer such as liver or other lung cancers.
- A magic bullet for metabolism: Shaw developed a new system to study how, where and when AMPK carries out its molecular and therapeutic functions such as reversing diabetes, improving cardiovascular health, treating mitochondrial disease—even extending life span. This novel model provides a new way to define the health benefits of AMPK, a master regulator of metabolism, for a variety of diseases.
- How the cell's power station survives attacks: The Shaw lab discovered how cells trigger repair of their power generators, the mitochondria, following attacks by, for example, poisons. When cells are exposed to mitochondrial damage, the enzyme AMPK sends an emergency alert to the mitochondria instructing them to break apart into many tiny mitochondrial fragments to be reassembled into new, usable units. This finding provides insight for disorders such as Parkinson's disease, which is linked to dysfunctional mitochondria.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/REUBEN-SHAW

CANCER | DEVELOPMENTAL DISEASE | DIABETES | GENETICS
LUNG CANCER | METABOLISM | THERAPEUTICS



CHRISTINA TOWERS

Assistant Professor

Molecular and Cell Biology Laboratory
Richard Heyman and Anne Daigle
Endowed Developmental Chair

THE CHALLENGE

Cancer cells can recycle their own nutrients to grow unchecked. Ongoing clinical trials are trying to target these processes, but so far, the trials have been somewhat disappointing. Scientists still believe that targeting these recycling pathways may increase cancer patient life span, but it remains unclear how to best accomplish this. In particular, cancer cells can adapt after treatment with different therapeutics, causing patients to relapse, yet the adaptations that might occur after blocking recycling pathways remain unknown. Patients need more effective cancer-killing drugs, but first scientists must (1) gain a broader understanding of these recycling mechanisms that cancer cells use to survive, and (2) leverage this knowledge to find the best ways to target these pathways with drugs.

THE APPROACH

Towers is using a combination of DNA-editing techniques, light-based genetic manipulation (optogenetics), three-dimensional miniature organs (“organoids”), and detailed imaging to uncover how

cancer cells recycle both their own nutrients and the power-generating structures called mitochondria in order to survive. Her goal is to work with local clinicians to develop new targeted cancer therapies that can block the cancer cell recycling pathways that allow these cells to survive. Towers’ research could lead to decreased cancer recurrence and improved cancer patient outcomes.

THE INNOVATIONS AND DISCOVERIES

- Towers paired the DNA-editing technology CRISPR-Cas9 with live-cell imaging to monitor cancer cells’ ability to survive in real time.
- Towers discovered that cancer cells dependent on recycling pathways for survival can adapt when these pathways are blocked and co-opt other pathways to grow.
- Towers developed a novel technique to measure the recycling of the powerhouses called mitochondria, in cancer cells.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/CHRISTINA-TOWERS

**CANCER | GENETICS | METABOLISM
CELLULAR BIOLOGY | THERAPEUTICS**



KAY TYE

Professor

Systems Neurobiology Laboratory
Howard Hughes Medical
Institute Investigator
Wylie Vale Chair

THE CHALLENGE

The ability to respond to environmental stimuli, such as avoiding a predator or approaching a food source, with appropriate choices is critical for survival. There are two classes of motivated behaviors: seeking pleasure and avoiding pain. Although most animals are capable of learning to associate either positive or negative valence to environmental cues to help them thrive, we are only beginning to understand the neural circuit mechanisms governing the formation, retrieval or extinction of an associative memory.

When the neural circuits mediating reward-processing, fear, motivation, memory or inhibitory control are perturbed, we may observe a number of disease states such as substance abuse, attention-deficit disorder, anxiety and depression. These are among the most prevalent neuropsychiatric disorders, and show a high rate of co-occurrence, as patients diagnosed with anxiety or mood disorders are approximately twice as likely to develop a substance abuse disorder.

THE APPROACH

Kay Tye's lab seeks to understand the neural-circuit basis of emotion that leads to motivated behaviors such as social interaction, reward-seeking and avoidance. Her lab employs a multidisciplinary approach including cellular-resolution recordings, behavioral assays and optogenetics, a technique that activates certain cells with light, to find mechanistic explanations for how these emotional and

motivational states influence behavior in health and disease. She focuses on an area of the brain called the amygdala as well as an interconnected circuit called the limbic system, which is implicated in emotional states such as fear. By using optogenetics, she can control specific neurons in the amygdala to decipher their function, genetic signature and communication patterns. Her lab has shown that these differences lead to either positive or negative reinforcement in the brain. This may explain why, for example, the sound of a gunshot is stressful for a refugee who has experienced war, but induces excitement in a runner about to start a race. The findings from Tye's lab may help to inform treatments for a multitude of neuropsychiatric conditions such as anxiety, depression, addiction and impairments in social behavior.

THE INNOVATIONS AND DISCOVERIES

- Tye pioneered the use of projection-specific optogenetic manipulations for the study of neural circuits and behaviors related to anxiety and social interaction.
- Using these advanced imaging techniques, the Tye lab discovered how distinct amygdala circuits can increase or decrease anxiety-related behavior and social interactions. Manipulating certain circuits could lead to treatments for neuropsychiatric disorders.
- Tye has uncovered the neural circuit mechanisms underlying compulsive reward-seeking behaviors (for sucrose, food, alcohol).

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/KAY-TYE

**NEUROBIOLOGY | NEUROLOGICAL DISEASE | ANXIETY
DEPRESSION | ADDICTION**



GEOFFREY WAHL

Professor
Gene Expression Laboratory

THE CHALLENGE

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

THE APPROACH

Geoffrey Wahl's team is using state-of-the-art approaches to better understand breast and pancreas cancers in order to develop more individualized therapies. First, his lab is studying whether the most aggressive forms of breast cancer are fueled by deranged versions of the stem cells that generate the mammary gland. They are using the most sophisticated molecular and tumor modeling approaches to determine whether the risk factors for breast cancer, such as obesity, actually cause adult cells to reprogram themselves into more plastic, stem-like variants that generate metastatic tumors. Important differences between reprogrammed tumor cells and normal cells may reveal uniquely targetable vulnerabilities.

Secondly, some cancers, like pancreatic, are encased in a protective covering of cells that both prevents drugs from reaching the tumor cells and provide substances that fuel cancer growth. The protective covering arises due to interactions between the cancer cells and the normal cells that surround it. Like breast cancers, pancreatic cancers also "evolve" from one mutant rogue

cell. How this evolution occurs, and how the original "initiated" cell generates the diverse types of variant cells within the cancer, remains unknown. The Wahl lab is using advanced methods that interrogate the individual cells formed at each stage of evolution from normal to cancer to understand how the process occurs, to identify vulnerable intervals amenable to interception. Already, their studies are uncovering rare cell types generated during the cancer evolution that produce substances that may be helpful for slowing tumor development or in aiding the immune system to fight the growing cancer before it has a chance to spread.

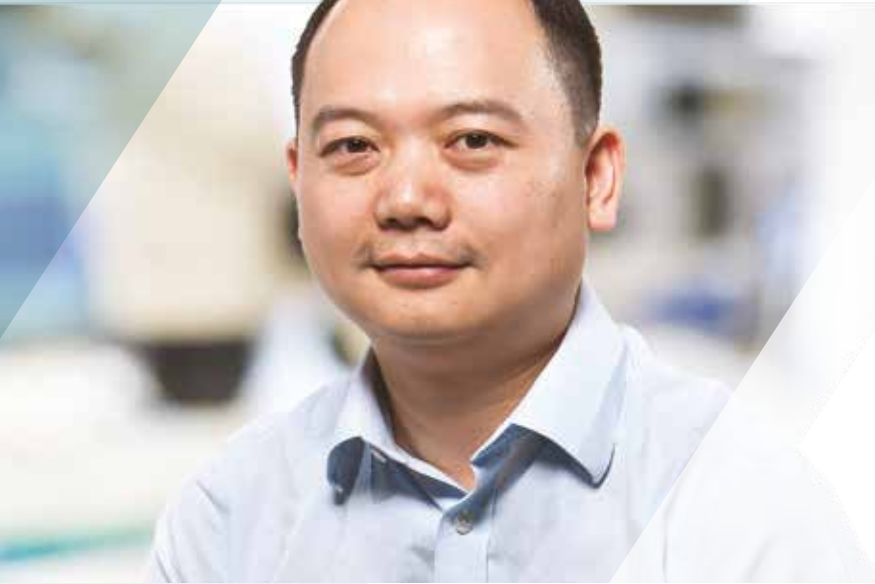
THE INNOVATIONS AND DISCOVERIES

- Wahl's lab discovered striking similarities between genetic signatures found in certain types of human breast cancer and those of stem cells in breast tissue in mouse embryos. The findings may lead to new ways to predict and personalize the diagnosis and treatment of some of the most aggressive forms of breast cancer.
- His lab examined mammary development, cell by cell, to provide a road map from the fetus to the adult to show how the mammary gland arises. This provided the first comprehensive analysis of all the genes that are expressed during mammary development. And they provided the first single-cell-resolution map of how the chromatin changes in each cell during development. Together, these studies provide a road map for understanding how normal processes are perturbed in the genesis of breast cancer.
- Wahl's team found that a rare type of cell generated during pancreatitis, a harbinger of pancreatic cancer, appears to act by secreting substances that aid the healing of the damaged pancreas. Harnessing this knowledge may provide a way of preventing pancreatitis from turning cancerous, or of slowing the progression of pancreatic cancer.

For more information, please visit:

WWW.SALK.EDU/SCIENTIST/GEOFFREY-WAHL

BREAST CANCER | PANCREATIC CANCER | GENETICS
STEM CELLS | THERAPEUTICS



YE ZHENG

Professor

NOMIS Center for Immunobiology and
Microbial Pathogenesis

THE CHALLENGE

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

THE APPROACH

To learn how to strengthen or correct the immune system, Ye Zheng focuses on a specialized set of immune cells called regulatory T (Treg) cells. Tregs control the immune response, telling the more aggressive immune cells when to stop their frenzied attack. Abnormal Treg cell function has been linked to multiple autoimmune diseases and tumors. In particular, a key molecular component of these cells, a protein called Foxp3, is often responsible for deficient Tregs. Zheng is making advances in understanding the genes that control Foxp3—as well as genes that Foxp3 controls—to ultimately lead to ways to manage Treg cell function. Since manipulations of Treg cells can either weaken or strengthen

the immune response, his findings can potentially open new avenues in the treatment of autoimmune diseases, improve organ transplant survival and uncover new cancer targets.

THE INNOVATIONS AND DISCOVERIES

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

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/YE-ZHENG

**AUTOIMMUNE DISEASE | CANCER | DIABETES
IMMUNOLOGY | INFLAMMATION | METABOLISM**

SALK FELLOWS PROGRAM

The Salk Institute's Salk Fellows Program brings scientists from broad disciplines to the Institute to trigger innovation and perpetuate the collaborative spirit of the Institute. Most fellows will come directly from a PhD or MD program and have expertise in a wide range of innovative technologies. Their work will have a combination of novelty, originality and risk, factors that often lower the chances of obtaining support through traditional channels.



SALK FELLOW

TALMO PEREIRA

Talmo Pereira comes from Princeton University, where he developed computational methods for quantifying animal behavior through motion tracking technology that leverages artificial intelligence (AI).

Pereira is interested in building and using computational tools that leverage AI to solve biological problems that would not be tractable otherwise. At Salk, he plans to develop new computational methods to quantify and model biological dynamics across a diverse set of application areas, including social behavior, motor control, plant morphology, and single cell states throughout development and disease.



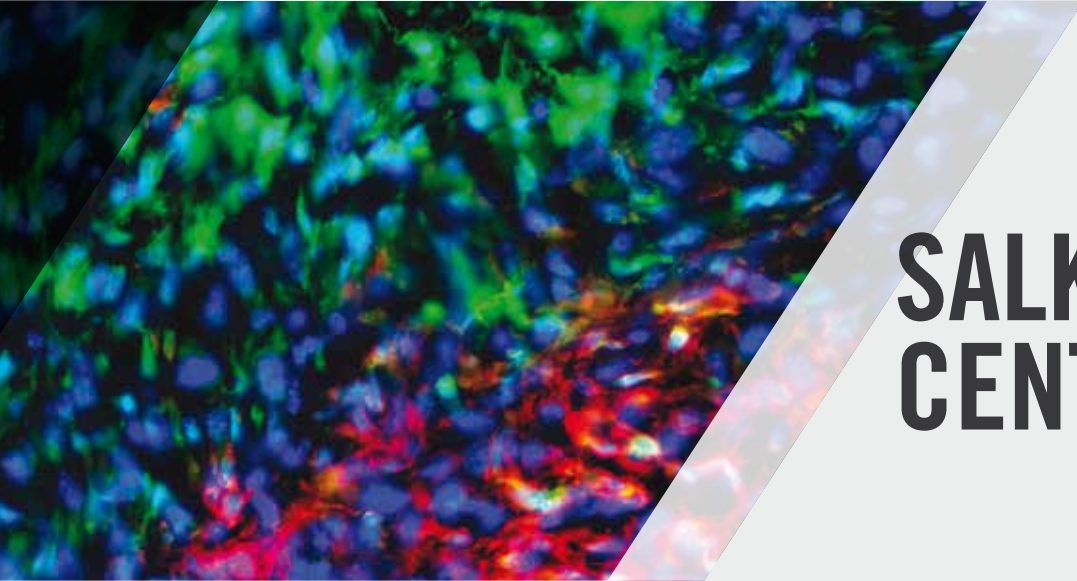
SALK FELLOW

ADAM BOWMAN

Adam Bowman is an applied physicist who develops microscopy techniques to study signals within live cells and tissues. His work allows scientists to capture high-speed images and to gain quantitative insight into how communication underlies biological function.

RESEARCH CENTERS





SALK CANCER CENTER

A National Cancer Center Institute-designated basic research center, Salk's Cancer Center probes the fundamental aspects of cancer biology, with the ultimate goal of reducing cancer's incidence, morbidity and mortality.

For more information, please visit:
WWW.SALK.EDU/CANCERCENTER

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Susan Kaech

DEPUTY DIRECTOR, TRANSLATION

Ronald Evans

DEPUTY DIRECTOR, EDUCATION & TRAINING

Geoffrey Wahl

DEPUTY DIRECTOR, DIVERSITY, EQUITY & INCLUSION

Dmitry Lyumkis

DEPUTY DIRECTOR, SHARED RESOURCES

Gerald Shadel

SENIOR ADVISOR TO THE DIRECTOR

Tony Hunter

DEPUTY DIRECTOR, RESEARCH ADMINISTRATION

Leona Flores

PROGRAM LEADERS

Genome Stability, Epigenetics & Aging in Cancer Program

Diana Hargreaves

Jan Karlseder

Tumor Immunology, Metabolism & Therapeutics Program

Janelle Ayres

Christian Metallo

MEMBERS

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Joseph Ecker

Dannielle Engle

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Satchidananda Panda

Talmo Pereira

Samuel Pfaff

Deepshika Ramanan

Alan Saghatelian

Gerald Shadel

Reuben Shaw

Christina Towers

Geoffrey Wahl

Ye Zheng

CRICK-JACOBS CENTER FOR THEORETICAL AND COMPUTATIONAL BIOLOGY

The Crick-Jacobs Center for Theoretical and Computational Biology is where Salk scientists use computational approaches and engineering to solve biology's biggest challenges in cancer, immunology, metabolism, neuroscience, aging and plant biology. We identify better ways to interpret complex data to better understand health and disease as well as find new targets for therapeutics.

For more information, please visit:
WWW.SALK.EDU/CRICK-JACOBS

DIRECTOR

Terrence Sejnowski
Salk Institute

SENIOR FELLOWS

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Princeton University

Edward Callaway
Salk Institute

Sean Eddy
Harvard University

David Kleinfeld
University of California San Diego

Christof Koch
Allen Institute

Mel Simon
California Institute of Technology

Susumu Tonegawa
Massachusetts Institute of Technology

FELLOWS

Nicola Allen
Salk Institute

Sreekanth Chalansani
Salk Institute

Rusty Gage
Salk Institute

Tatyana Sharpee
Salk Institute

JUNIOR FELLOW

Krishnan Padmanabhan
University of Rochester



THE PAUL F. GLENN CENTER FOR BIOLOGY AGING RESEARCH

The Paul F. Glenn Center for Biology of Aging Research draws from 13 of Salk's leading laboratories to address the overarching goal of defining a healthy life span and understanding the biological processes of aging.

For more information, please visit:
WWW.SALK.EDU/GLENN

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Jan Karlseder

ASSOCIATE DIRECTOR

Gerald Shadel

MEMBERS

Nicola Allen
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Rusty Gage
Susan Kaech
Julie Law
Christian Metallo
Marc Montminy
Satchidananda Panda
John Reynolds
Reuben Shaw
Ye Zheng

NOMIS CENTER FOR IMMUNOBIOLOGY AND MICROBIAL PATHOGENESIS

The NOMIS Center for Immunobiology and Microbial Pathogenesis aims to shed light on the molecular mechanisms that cause infectious diseases; define key molecules involved in the body's response to injury and infection; clarify the rules of engagement between the body's microbiome and immune system; and provide a better understanding of why inflammatory processes can spin out of control—all of which are critical to being able to address challenges to human health and wellness.

For more information, please visit:
WWW.SALK.EDU/NOMIS-CENTER

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Dmitry Lyumkis
Graham McVicker
Axel Nimmerjahn
Clodagh O'Shea
Deepshika Ramanan
Gerald Shadel
Reuben Shaw
Ye Zheng



SAN DIEGO NATHAN SHOCK CENTER

With a ultimate goal of understanding how individuals age at different rates, the San Diego Nathan Shock Center of Excellence in the Basic Biology of Aging provides research resources to analyze the heterogeneity of human aging at the molecular, cell and tissue level. The center also coordinates training, mentoring and outreach activities to promote basic biology of aging research.

For more information, please visit:
WWW.SALK.EDU/SAN-DIEGO-NATHAN-SHOCK-CENTER

DIRECTOR

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Salk Institute

HUMAN CELL MODELS OF AGING CORE DIRECTORS

Rusty Gage
Salk Institute

Anthony Molina
University of California San Diego

HETEROGENEITY OF AGING CORE DIRECTORS

Christian Metallo
Salk Institute

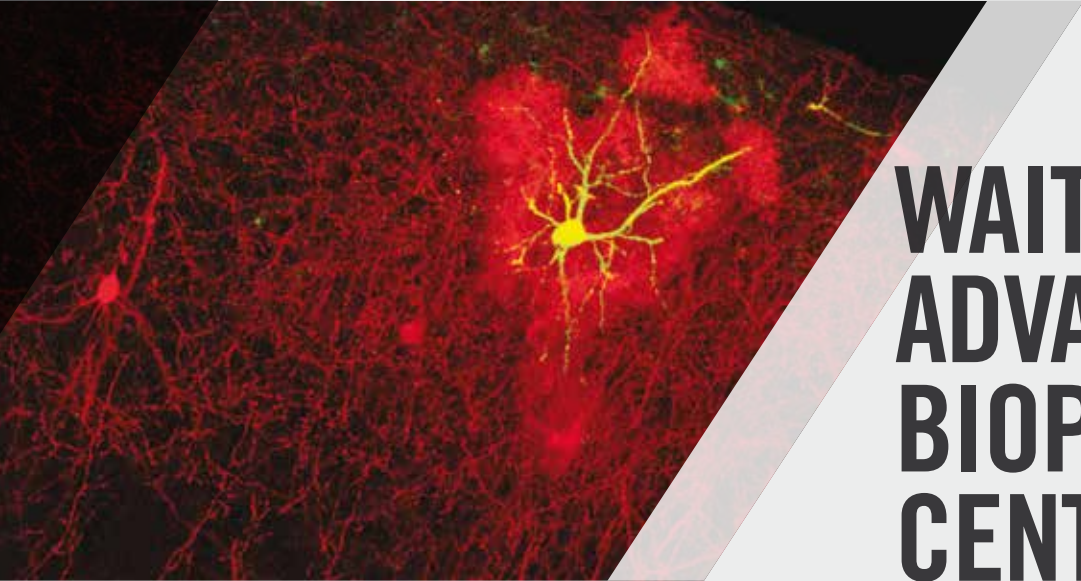
Peter D. Adams
Sanford Burnham Prebys Medical
Discovery Institute

INTEGRATIVE MODELS OF AGING CORE DIRECTOR

Tatyana Sharpee
Salk Institute

RESEARCH DEVELOPMENT CORE DIRECTOR

Alessandra Sacco
Sanford Burnham Prebys Medical
Discovery Institute



WAITT ADVANCED BIOPHOTONICS CENTER

The Waitt Advanced Biophotonics Center is a state-of-the-art research hub that enables investigators from many disciplines to gain unprecedented insight into the inner workings of cells and tissues by observing how single molecules and cells function in real time.

For more information, please visit:
WWW.SALK.EDU/BIOPHOTONICS

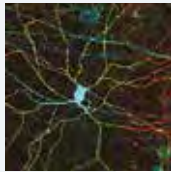
DIRECTOR

Axel Nimmerjahn

MEMBERS

Edward Callaway
Rusty Gage
Martyn Goulding
Samuel Pfaff
Terrence Sejnowski
Tatyana Sharpee

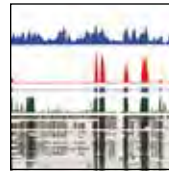
SCIENTIFIC CORE FACILITIES



ADVANCED BIOPHOTONICS CORE (BPHO)

The Waitt Advanced Biophotonics Center Core facility provides technical and logistical access for Salk faculty to advanced fixed and live-cell fluorescence imaging and charged-particle imaging methods.

Daniela Boassa, Director



THE RAZAVI NEWMAN INTEGRATIVE GENOMICS AND BIOINFORMATICS CORE (IGC)

The Razavi Newman Integrative Genomics and Bioinformatics Core facility focuses on the analysis of next-generation sequencing (NGS) and other genomics data as well as develops novel analysis algorithms.

April Williams, Director

*Graham McVicker, Faculty Advisor
(Cancer Center)*



FLOW CYTOMETRY CORE (FCCF)

The Flow Cytometry Core facility is dedicated to advancing research projects requiring cell sorting and/or analysis of cell populations by flow cytometry.

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

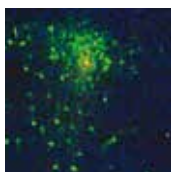


MASS SPECTROMETRY CORE (MASS)

The Mass Spectrometry Core for Proteomics and Metabolomics offers an array of services from protein identification and proteomic profiling to more complex studies using state-of-the-art instrumentation.

Jolene Diedrich, Director

Alan Saghatelian, Faculty Advisor



VIRAL VECTOR CORE

The Viral Vector Core - Gene Transfer, Targeting and Therapeutics (GT3) facility provides design, consultation and production services for retrovirus (MMLV/MSCV), lentivirus (HIV/EIAV), adeno-associated virus (rAAV2 with multiple capsids), adenovirus (Ad5), rabies virus (g-deleted SAD B19) and vesicular stomatitis virus (VSV)-based viral vector systems.

*John Naughton, Assistant Director
Edward Callaway, Faculty Co-Advisor
(Neurosciences)*

*Tony Hunter, Faculty Co-Advisor
(Cancer Center)*



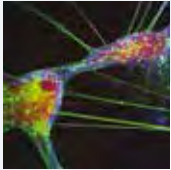
NEXT GENERATION SEQUENCING CORE (NGS)

The H.A. and Mary K. Chapman Charitable Foundations Genomic Sequencing Core's mission is to help facilitate cutting-edge genomics by providing rapid high-throughput sequencing services, consultation and expert assistance in strategic planning and method development.

Elsa Molina, Director

Ronald Evans, Faculty Advisor

SCIENTIFIC CORE FACILITIES



STEM CELL CORE (STEM)

The Stem Cell Core supports the needs of Salk researchers for human ES and reprogrammed iPS cell culture. Offers training and the physical space to carry out experiments using pluripotent cell types.

Jennifer Page, Director
Rusty Gage, Faculty Advisor



TRANSGENIC CORE (TGC)

The Transgenic Core provides services to create transgenic and knockout mouse models. Core services include DNA and ES cell microinjection, lentiviral injection, in-vitro fertilization (IVF), cryopreservation, rederivation and teratoma formation.

Yelena Dayn, Director
Kuo-Fen Lee, Faculty Advisor

EMERITUS FACULTY



DISTINGUISHED EMERITA

ELIZABETH BLACKBURN

Elizabeth Blackburn won the Nobel Prize in Physiology or Medicine in 2009 for discovering the molecular nature of telomeres, and for co-discovering telomerase, an enzyme that maintains telomere ends. In addition to the Nobel Prize, Blackburn has received nearly every major award in science, including the Lasker, Gruber and Gairdner prizes. She is a member of numerous prestigious scientific societies, including the National Academy of Sciences, the National Academy of Medicine and the Royal Society of London. She also served as president of both the American Association of Cancer Research and the American Society for Cell Biology, and has served on the editorial boards of several scientific journals, including the journals *Cell* and *Science*. Blackburn was a non-resident fellow at Salk from 2001 to 2016 and the Institute's President from January 2016 through the summer of 2018.



DISTINGUISHED EMERITUS

WILLIAM R. BRODY

Renowned for his achievements in biomedical engineering and the field of medical instrumentation, William Brody is a member of the National Academy of Engineering and the National Academy of Medicine. He has authored more than 100 articles in US medical journals, holds two US 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 was the President of the Salk Institute from 2008 to 2015, after 12 years as president of Johns Hopkins University.



DISTINGUISHED EMERITA

VICKI LUNDBLAD

Lundblad's interest in telomere biology initiated with her discovery that a defect in telomere replication in budding yeast leads to an eventual block to cell division (referred to as replicative senescence), well before telomere shortening was shown to be the causative factor for senescence in mammalian cells. She subsequently showed that this block to cell proliferation could be bypassed through a recombination-based pathway that provides an alternative means of replenishing chromosome ends. She has been recognized with numerous awards, including the 2008 Pearl Meister Greengard Prize, together with Carol Greider and Elizabeth Blackburn. In 2015, Lundblad was elected to the National Academy of Sciences, considered one of the highest honors accorded to a United States scientist.



EMERITUS FACULTY



SUZANNE BOURGEOIS

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



BEVERLY EMERSON

Beverly Emerson studied how different genes are turned on and off through the course of a cancer—from the time cells become precancerous until the time they develop into a mature cancer and spread to new organs. Many researchers look for genes that are mutated in tumors, as these mistakes in the DNA code can lead to cancer. Emerson’s lab looked at other ways genes can be turned on and off to allow a tumor to grow in order to discover new drug targets that may be used to prevent or treat cancers.



KATHERINE JONES

Katherine Jones studied the genetic processes involved in the expression of HIV and cancer genes, as well as conducting other disease research. She discovered two critical proteins required for HIV gene expression. In addition, she found that the APC protein, which is mutated in colon cancers, regulates the expression of important growth control genes. Her work focused on a process called transcription elongation, which controls the expression of HIV and cancer genes. The Jones lab identified a class of proteins, called elongation factors, which play a pivotal role in the expression of cellular and viral genes. These proteins potently induce HIV in activated T (immune system) cells, determine whether embryonic stem cells will differentiate to specialized cell types, and are mutated in leukemia and other cancers. Her research has led to understanding how these proteins function and may help suggest new approaches to intervene in many human diseases.

EMERITUS FACULTY



CHRISTOPHER KINTNER

Christopher Kintner, PhD, studied the genes that govern how different cell types are generated during organ formation. For 35 years his work focused on neuronal cells in the developing nervous system as well as on cells that extend motile cilia, hair-like structures used to produce fluid flow.



DENNIS D.M. O'LEARY

Dennis O'Leary probed how the brain maps its sensory areas, with distinct brain sections for specific body parts, and made several discoveries surrounding healthy brain development. His work helped to better understand the genes and molecules responsible for helping neurons form and find their place in a developing brain. He focused on genes that aid neurons in a developing brain to connect from one place to another, following chemical cues to find their target. O'Leary also integrated stem-cell research into his laboratory in order to develop therapies tied to the genes he studied.



CATHERINE RIVIER

Catherine Rivier studied hormones that shuttle messages between the periphery and the brain, in particular how the brain perceives and responds to external stressors, such as infection, exposure to psychological threats or alcohol. Her laboratory identified mechanisms through which the occurrence of stressors is conveyed to specialized areas of the brain. For example, she showed that exposure to alcohol during adolescence causes permanent changes in areas of the brain associated with the development of drug abuse in adulthood and identified a new pathway through which the brain controls the activity of the testes, a discovery that offered insights into puzzling cases of low testosterone secretion connected to stressors or diseases.



EMERITUS FACULTY



PAUL E. SAWCHENKO

Paul Sawchenko uncovered many insights in neurobiology, including the relationship between stress hormone receptors and the development of the plaques and tangles associated with Alzheimer's disease. He used cell biology and genetic approaches in animal models to study how stress-responsive systems are organized at a molecular level within the body, particularly the brain. His work helped shed light on how stress signals reach the brain and on the pathways and molecules involved in conveying this information to different brain centers. His lab also helped unravel brain circuitry related to past experience, emotion and stress in hopes of better understanding a range of psychiatric disorders, including depression and post-traumatic stress disorder (PTSD).



JOHN THOMAS

John Thomas developed a fruit fly model of brain tumors to study the molecules that help the brain grow in a developing embryo and which are later reactivated in many aggressive cancers of the nervous system. Thomas discovered some of the chemical road signs that guide growing neurons on their paths through the brain in a developing embryo. The tracks that these neurons take ultimately shape organisms' thoughts and behaviors for the rest of their lives. He also showed how mutations in two genes, EGFR and PI3K, set off a cascade of events that cause the growth of glioblastomas, one of the most common types of brain tumors, in flies. Thomas demonstrated how one step in this cascade—the activation of a set of proteins—could be blocked with drugs to weaken the cancer. Additionally, he examined how molecular pathways in the brain are involved in metabolism, to better understand diabetes and obesity.



FACULTY

PRESIDENT

Gerald Joyce

DISTINGUISHED PROFESSORS EMERITI

Elizabeth Blackburn
William R. Brody
Vicki Lundblad

PROFESSORS EMERITI

Suzanne Bourgeois
Beverly Emerson
Katherine Jones
Christopher Kintner
Dennis D.M. O'Leary
Catherine Rivier
Paul E. Sawchenko
John B. Thomas

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Janelle Ayres
Wolfgang Busch
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Sreekanth Chalasani
Joanne Chory
Joseph Ecker
Ronald Evans
Rusty Gage
Marty Goulding
Tony Hunter
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Samuel Pfaff

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Alan Saghatelian
Terrence Sejnowski
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Tatyana Sharpee
Reuben Shaw
Kay Tye
Geoffrey Wahl
Ye Zheng

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Pamela Maher
Todd Michael

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Dannielle Engle
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Agnieszka Kendrick
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SENIOR STAFF SCIENTISTS

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Giancarlo Costaguta
Michael R. Downes
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Manoj Hariharan
David Horning

STAFF SCIENTISTS

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Antonio Currais
Zac Davis
Weiwei Fan
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Gaoyang Liang
Natalie Luhtala
Emily Manoogian
Sarah Parylak
Matthieu Platre
Carl Procko
Ben Stafford
Sam Van De Velde
Bang-An Wang

SALK NON-RESIDENT FELLOWS

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

LEWIS C. CANTLEY, PHD

Professor of Cell Biology
HMS Cell Biology
Dana-Farber Cancer Institute

CATHERINE DULAC, PHD

Samuel W. Morris University Professor
Lee and Ezpeleta Professor of Arts and Sciences
Howard Hughes Medical Institute
Department of Molecular and Cellular Biology
Harvard University

DOUGLAS R. GREEN, PHD

Member, St. Jude Faculty
Co-leader, Cancer Biology Program
Peter C. Doherty Endowed Chair of Immunology
St. Jude Children's Research Hospital

MARY LOU GUERINOT, PHD

Ronald and Deborah Harris Professor in the Sciences
Department of Biological Sciences
Dartmouth College

JENNIFER LIPPINCOTT-SCHWARTZ, PHD

Senior Group Leader and Head of Janelia's 4D
Cellular Physiology
Howard Hughes Medical Institute –
Janelia Research Campus

STEPHEN L. MAYO, PHD

Bren Professor of Biology and Chemistry
Merkin Institute Professor
Caltech

J. ANTHONY MOVSHON, PHD

University Professor and Silver Professor
Professor of Neural Science and Psychology
New York University

CARLA J. SHATZ, PHD

Sapp Family Provostial Professor
Professor of Biology and Neurobiology
Catherine Holman Johnson Director, Stanford Bio-X
Stanford University

IRVING L. WEISSMAN, MD

Emeritus Director, Institute for Stem Cell Biology and
Regenerative Medicine
Director, Stanford Ludwig Center for Cancer Stem Cell
Research and Medicine
Professor of Pathology and Developmental Biology, and
by courtesy, Biology and Neurological Surgery
Stanford University

HONORS

NOBEL PRIZE

Elizabeth Blackburn | 2009
Sydney Brenner (1927 – 2019) | 2002
Renato Dulbecco (1914 – 2012) | 1975
Roger Guillemin (1924 – 2024) | 1977
Francis Crick (1916 – 2004) | 1962
Robert W. Holley (1922 – 1993) | 1968

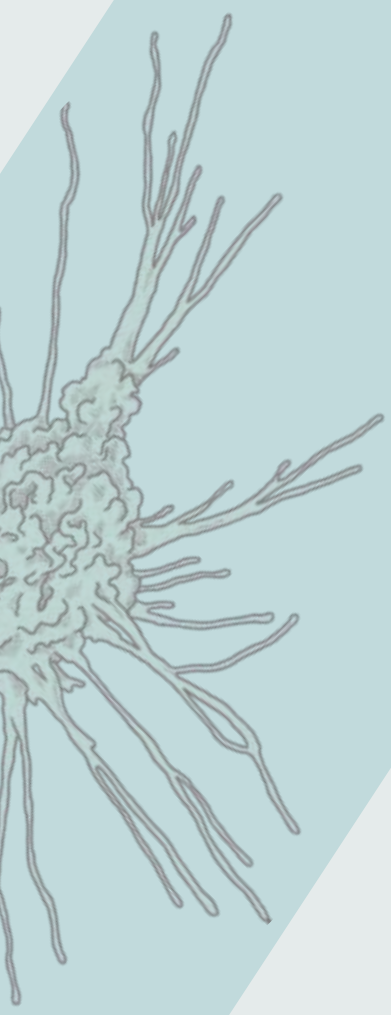
NATIONAL ACADEMY OF SCIENCES*

Thomas Albright | 2008
Elizabeth Blackburn | 1993
Edward Callaway | 2019
Joanne Chory | 1999
Joseph Ecker | 2006
Ronald Evans | 1989
Rusty Gage | 2003
Tony Hunter | 2001
Gerald Joyce | 1998
Vicki Lundblad | 2015
Marc Montminy | 2009
Terrence Sejnowski | 2010

NATIONAL ACADEMY OF MEDICINE*

Elizabeth Blackburn | 2000
William Brody | 1992
Ronald Evans | 2003
Rusty Gage | 2001
Tony Hunter | 2004
Gerald Joyce | 2014
Terrence Sejnowski | 2008

*Elections to the National Academies of Sciences or Medicine are considered one of the highest honors accorded a US scientist.



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