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Science Guide

June 2026

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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

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EXECUTIVE LEADERSHIP

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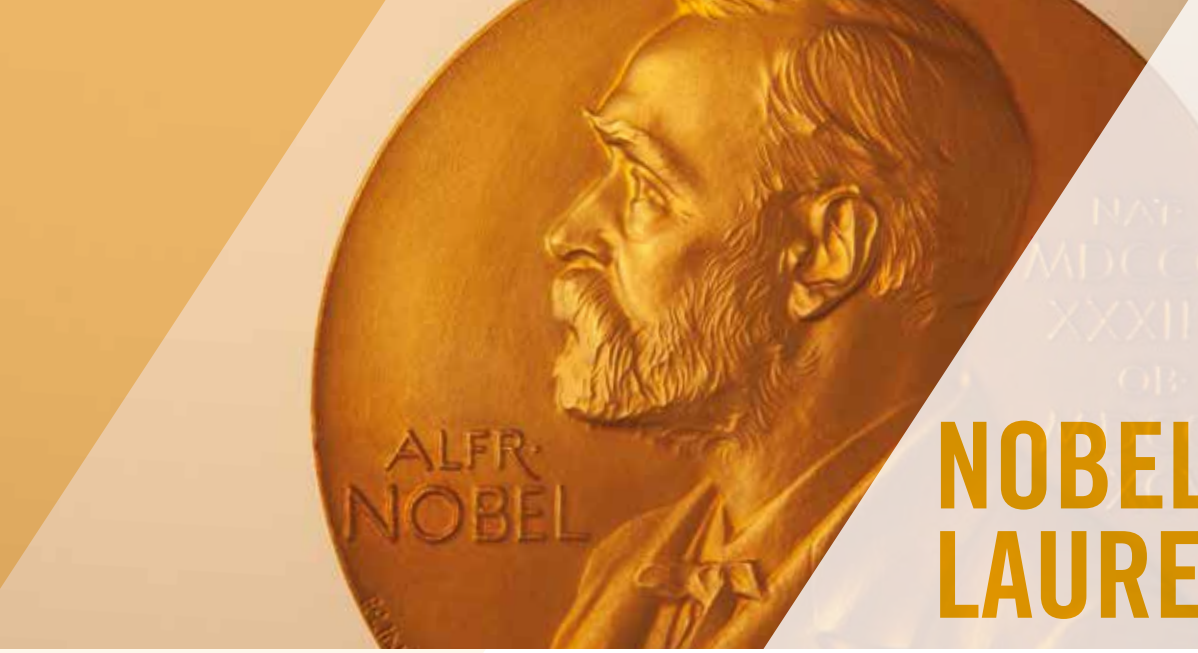

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NOBEL PRIZE LAUREATES

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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NICOLA ALLEN

Professor

Molecular Neurobiology Laboratory
Roger Guillemin Chair

Allen is a neuroscientist who investigates how the brain forms and functions in both health and diseases like autism spectrum disorder or Alzheimer's. Most research on the brain focuses on neurons, but Allen takes a unique approach by asking how non-neuronal cells in the brain—in particular, a class of glial cell called astrocytes—regulate neuronal function.

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 spectrum disorder 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. Her 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 | NEUROSCIENCE
NEUROLOGICAL DISEASE | DEVELOPMENTAL DISEASE

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KENTA ASAHINA

Associate Professor
Molecular Neurobiology Laboratory

Asahina is a neuroscientist who studies the neural mechanisms of behavioral control and social interactions. His lab works to characterize what excites, inhibits, and modulates these circuits, as well as to understand how each neural component contributes to mediating interactions between individuals.

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 spectrum or attention-deficit disorders) is the first step in developing effective and specific treatments for such neurological diseases. 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 do this foundational research, Asahina 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
NEUROSCIENCE | 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
Howard Hughes Medical Institute Investigator
Salk Institute Legacy Chair

Ayres is a molecular and systems physiologist who uses evolutionary theory and microbes to understand how our physiological systems and brains interact with each other to promote optimal health. Her lab looks at health as an active biological process requiring unique endurance and resilience mechanisms—altogether dubbed the *cooperative defense system*.

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 "cooperative 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 cooperative 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 cooperative 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 cooperative 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 cooperative 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 cooperative 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

Azim is a neuroscientist who investigates circuits in the spinal cord and brain to uncover how dexterous movements are controlled and how disease or injury can disrupt the execution of these critical behaviors. Dexterous movements of the arms and hands are often affected by neurodegenerative disease and injury, and Azim's work seeks to lay the groundwork for better treatments and recovery of function.

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

NEUROSCIENCE | LOCOMOTION | NEUROLOGICAL DISEASE

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DANIEL BAYLESS

Assistant Professor
Molecular Neurobiology Laboratory

Bayless is a neuroscientist who studies the social interactions vital to our wellbeing. His research is particularly focused on factors that alter these interactions and how they vary by sex. His work contributes to scientific understanding of neurological conditions, like Alzheimer's disease, social anxiety disorder, and autism spectrum disorder.

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

ALZHEIMER'S DISEASE | AUTISM | NEUROSCIENCE | SEX DIFFERENCES

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MARGARITA BEHRENS

Research Professor
Computational Neurobiology Laboratory

Behrens is a neuroscientist who studies how the environment affects the molecular signatures that define brain cells during development and adulthood. Her discoveries help determine why some individuals develop neurodevelopmental disorders, while others do not.

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 spectrum. 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 (CH_3)—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' lab identifies new subtypes of neurons based on their DNA methylation patterns, called epigenetic markers, using a method known as methylation profiling. Charting the different subtypes of neurons in the brain—and 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 spectrum.

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
NEUROSCIENCE | NEUROLOGICAL DISEASE | SCHIZOPHRENIA

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JAMIE BLUM

Assistant Professor

NOMIS Center for Immunobiology and Microbial Pathogenesis

Blum is an immunologist who studies how the immune system interprets what we eat and why some foods trigger harmful allergic responses while others are accepted as safe. Her research lays the groundwork for new therapeutic and plant-based strategies to address food allergies.

THE CHALLENGE

Food allergies are on the rise globally, yet much remains unknown about how and why they develop. Every day, our diet exposes us to thousands of molecules that can impact our health in both beneficial and harmful ways. The intestinal immune system must constantly survey these dietary inputs to allow for nutrient absorption while also preventing pathogen invasion. In most cases, the body develops oral tolerance, a state in which intestinal immune cells actively recognize the dietary proteins as safe. However, failure to develop this tolerance can lead to life-threatening food allergies. Despite its critical importance, most of what scientists know about oral tolerance comes from a limited number of studies on a single protein found in eggs. Blum is working to change that.

THE APPROACH

While traditional food allergy research focuses on the molecules involved in allergic reactions, Blum's lab is taking a new approach by exploring the mechanisms of oral tolerance, the immune system's default, noninflammatory reaction to most foods. By understanding the molecular signals that help our bodies tolerate most foods, Blum's work could enable entirely new immunotherapy strategies for preventing or treating food allergies.

Notably, Blum's findings show that individual dietary proteins are often insufficient to drive an allergic reaction. The lab is actively identifying adjuvants—food molecules that co-occur with dietary proteins and play a critical role in determining whether the immune response will be tolerogenic or inflammatory. This integrated approach of mapping both dietary protein antigens and other co-occurring molecules addresses key challenges in understanding why some foods induce tolerance while others provoke allergy. To accomplish this, Blum's lab uses cutting-edge tools including high-throughput T cell receptor screening, antigen mapping, and *in vivo* tracking of immune responses in mouse models.

THE INNOVATIONS AND DISCOVERIES

- Blum discovered the first dietary antigens from staple crops corn, soy, and wheat.
- Blum showed that food tolerance is not only driven by the presence of individual dietary proteins but also depends on the gut microbial context and the food's broader molecular matrix.
- Blum established that peanut exposure can provide adjuvant activity, enhancing the body's immune response to unrelated co-exposed antigens.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/JAMIE-BLUM

FOOD ALLERGIES | IMMUNOLOGY | INFLAMMATION | PLANT BIOLOGY

WOLFGANG BUSCH

Professor and Director
Plant Molecular and Cellular Biology Laboratory
Integrative Biology Laboratory
Hess Chair in Plant Science

Busch is a plant biologist who studies the genes and molecular mechanisms that orchestrate interactions between plants and their environments. His research could help grow more resilient food sources and develop root systems that store carbon on a large scale to decrease harmful atmospheric carbon dioxide.

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 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 (CO_2) 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 more resilient crop varieties.

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® that remove excess atmospheric carbon and are more robust in the face of environmental stress.

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 | AGRICULTURE | SYSTEMS BIOLOGY

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EDWARD CALLAWAY

Professor

Systems Neurobiology Laboratory
Vincent J. Coates Chair in Molecular Neurobiology

Callaway is a neuroscientist who studies the intricate brain cell circuitry that responds to and analyzes visual stimuli. Knowledge at this fundamental level will bring a closer understanding of how we visually perceive the world around us, and of how normal perceptive processes are disrupted in cognitive and mental disorders such as schizophrenia.

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 disorders like schizophrenia and autism spectrum, 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 his 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

NEUROSCIENCE | NEUROLOGICAL DISORDERS | SYSTEMS BIOLOGY | VISION

SREEKANTH CHALASANI

Professor
Molecular Neurobiology Laboratory
Jesse and Caryl Philips
Foundation Chair

Chalasani is a neuroscientist who uses models, from a simple worm to more complex mice, to answer questions about how brains function. His lab works to understand how a healthy brain works, so they can then point to specific differences in brains of people with disorders, from autism spectrum to depression.

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 disorders, from autism spectrum to depression. But it's a daunting task: 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 to answer these neuroscience questions, ranging from the simple worm to more complex fish and mice.

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 spectrum 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, Chalasani's lab is studying how an entire brain processes oxygen information. This is particularly relevant as dysfunction in this process can lead to devasting human conditions including sudden infant death syndrome (SIDS).

Chalasani's 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 extended it to mice, and are currently working on translating it to humans.

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 developed a new method to manipulate neurons and other cells non-invasively using ultrasound, a technique he has termed sonogenetics, and is working to get the technology into clinical practice (sonogenetics.salk.edu).

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/SREEKANTH-CHALASANI

SONOGENETICS | ANXIETY | AUTISM | LOCOMOTION
NEUROSCIENCE | NEUROLOGICAL DISEASE

JESSE DIXON

Associate Professor

Gene Expression Laboratory
Helen McLoraine Developmental Chair

Dixon is a molecular biologist who uses molecular and computational approaches to explore how our genomes are organized in cells and how abnormal genome folding leads to human diseases such as cancer. His team is also developing new methods to study gene organization and gene function in single cells.

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

GENETICS | CANCER | CELLULAR BIOLOGY

JOSEPH ECKER

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

Ecker is a plant and molecular biologist who researches genomic and epigenomic regulation in plants and mammals, as well as the application of DNA sequencing technologies for genome-wide analysis in single cells. He is working to chart the epigenetic differences between brain cell types, which will help scientists better understand everything from schizophrenia to Alzheimer's disease.

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 they 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, with particular attention to 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 like 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 | NEUROSCIENCE | MOLECULAR BIOLOGY
PLANT BIOLOGY AND AGRICULTURE | STEM CELLS

DANNIELLE ENGLE

Assistant Professor

Regulatory Biology Laboratory
Helen McLoraine
Developmental Chair

Engle is a cancer biologist who seeks to identify biomarkers and therapeutic targets that will allow for earlier diagnoses and more effective treatments for cancer. Her lab studies the intersection of inflammation and cancer in the pancreas, building upon Engle's discovery that the carbohydrate biomarker, CA19-9, causes pancreatitis and accelerates tumorigenesis.

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

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RONALD EVANS

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

Evans is a microbiologist who is an expert on the essential roles of hormone receptors in reproduction, growth, and metabolism. Evans has identified novel pathways involved in cancer and metabolic diseases that are targetable by drugs—with more than a dozen approved drugs having been developed with Evans' technology for the treatment of leukemia, prostate cancer, breast cancer, liver disease, diabetes, and hypertension.

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. A clinical trial led by the Dana-Farber Cancer Institute demonstrated that a synthetic vitamin D analog can be administered safely in combination with standard-of-care chemotherapy and effectively reprogram the supporting pancreatic tumor microenvironment. The findings provide early evidence that vitamin D analogs can enhance chemotherapy response and improve survival, especially in patients with high tumor vitamin D receptor expression.

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

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

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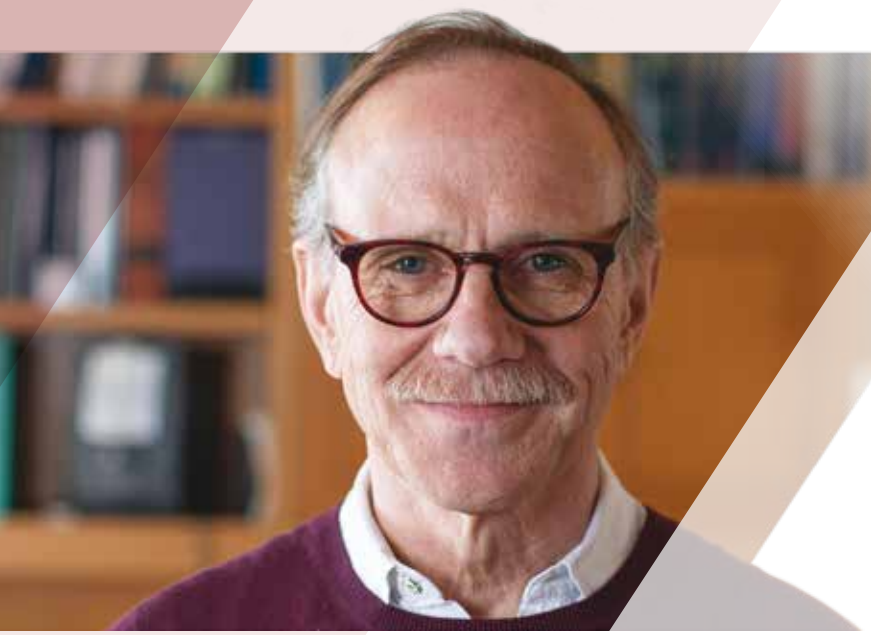

RUSTY GAGE

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

Gage is a neuroscientist who studies the plasticity, adaptability, and diversity of the brain. By reprogramming cells from patients with neurologic and psychiatric diseases into induced pluripotent stem cells, neurons and organoids, he deciphers the progression and mechanisms that lead to diseases and disorders like Alzheimer's, Parkinson's, bipolar, depression, and autism spectrum.

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 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 spectrum.

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

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

MARTYN GOULDING

Professor

Molecular Neurobiology Laboratory

Frederick W. and Joanna J. Mitchell Chair

Goulding is a neuroscientist who studies the sensorimotor circuitry in the spinal cord that controls a range of different motor behaviors from scratching to walking to precise forelimb movements. His lab also investigates how these spinal circuits are altered by spinal injury or by pathologies that lead to chronic pain and itch.

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

Goulding's 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 V0 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 | NEUROSCIENCE
SPINAL CORD INJURY | CHRONIC PAIN | ITCH

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IAN GULDNER

Assistant Professor

Guldner is a neuroscientist and molecular biologist who works to identify the cellular communication mechanisms that regulate brain aging and disease, with the goal of target those interactions to preserve brain health.

THE CHALLENGE

Cells communicate to coordinate tissue and biological function. One way they talk is by transferring proteins from one cell to another—initiating a response in the recipient cell. Dysregulation of this communication is a hallmark of aging and contributes to diseases like Alzheimer's and Parkinson's. Despite its importance, we still lack a comprehensive understanding of which cells communicate, the proteins that mediate these interactions, and how these signaling networks drive aging and disease.

THE APPROACH

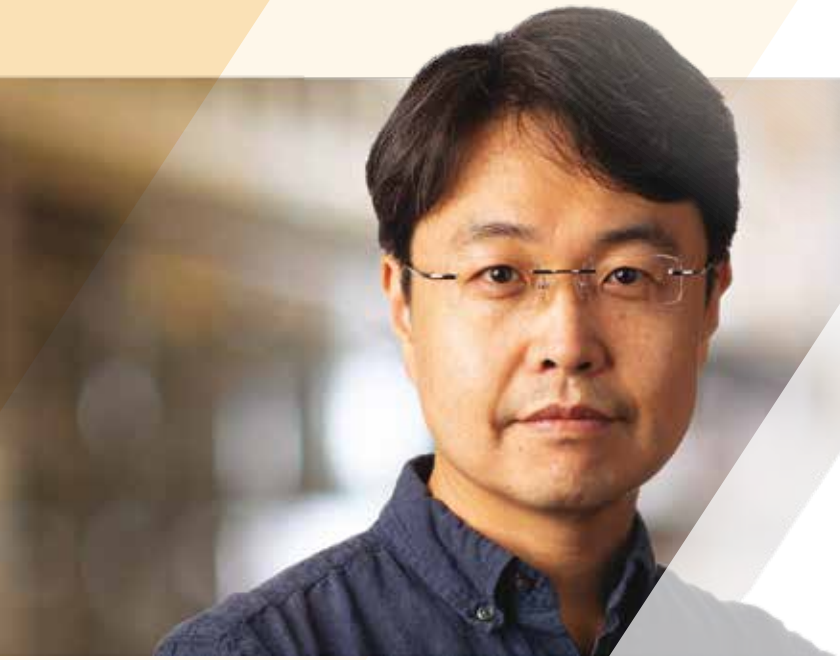
Guldner's lab investigates cell-to-cell communication by directly tracking proteins exchanged between cell types in living organisms. The lab combines cell-specific proteome tagging with advanced cell isolation methods to tag proteins in "sender" cells and recover those transferred to isolated "recipient" cells. This approach reveals which cells communicate, the proteins they exchange, and how these interactions change with aging and disease. The lab also uses genetic and pharmacologic perturbations to test whether modifying these communication networks can delay or even reverse aging, neurodegeneration, and other disorders.

THE INNOVATIONS AND DISCOVERIES

- Guldner demonstrated that cell-specific protein tagging approaches can be leveraged to understand the pace of cellular protein recycling, cellular origins of protein aggregates, and activity of intercellular protein communication—processes central to disease pathologies from Alzheimer's to cancer.
- Guldner tracked how hundreds of proteins were exchanged from neurons to microglia in young and old mice, finding that many proteins accumulate in aged microglia and may contribute to age-related cognitive decline and neurodegeneration.
- Guldner tagged proteins to measure degradation rates of neuron-specific proteins across aging in mice to discover that—on average—proteins in old neurons degrade at half the speed they degrade in young neurons.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/IAN-GULDNER

HEALTHY AGING | NEUROSCIENCE | ALZHEIMER'S DISEASE | PARKINSON'S DISEASE



SUNG HAN

Associate Professor

Clayton Foundation Laboratories for Peptide Biology

Pioneer Fund Developmental Chair

Han is a neuroscientist who investigates small molecules called neuropeptides that are critically involved in brain functions like sensing pain, reward, food intake, and metabolism. His work provides a foundation for understanding and treating anxiety, panic, and autism spectrum disorders, as well as schizophrenia and chronic pain.

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

NEUROSCIENCE | NEUROLOGICAL DISEASE | PAIN | AUTISM

DIANA HARGREAVES

Professor

Molecular and Cell Biology Laboratory
J.W. Kieckhefer Foundation Chair

Hargreaves is a molecular biologist who studies a particular epigenetic regulator, the BAF complex, that uses energy to unpack and unwind DNA from structural proteins to alter DNA accessibility and, in turn, gene transcription. Her lab has identified novel BAF complex variants and new roles for the BAF complex in cancer, inflammation, and pluripotency.

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. Mutations in epigenetic regulators are also commonly found in cancers. But how epigenetic regulators know which genes to turn on when—and how mutations disrupt this process to cause cancer—is not fully understood.

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 and inflammation. Her lab has found that BAF complexes control immune cell function through interactions with transcription factors and other epigenetic machinery. Additionally, her lab explores how BAF complex mutations in cancer affect therapeutic response, specifically to immunotherapies, and how BAF complex inhibitors may be used for cancer therapy. Hargreaves brings her knowledge of epigenetic regulation and molecular biology to investigate these properties in models of cancer and immune cell activation.

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 T cell and macrophage activation.
- Hargreaves discovered a non-canonical form of the BAF complex, which underlies the essential activity of the complex in inflammatory gene expression.
- Hargreaves showed that BAF complexes are mutated in greater than 20% of all human cancers. Her work has demonstrated that mutations in the ARID1A subunit confer sensitivity to cancer immunotherapy, highlighting ARID1A mutation as a potential biomarker of therapeutic response.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/DIANA-HARGREAVES

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

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DANIEL HOLLERN

Assistant Professor

NOMIS Center for Immunobiology and Microbial Pathogenesis
Frederick B. Rentschler Developmental Chair

Hollern merges two disciplines—multi-omics computational analysis and cancer immunology—to find where tumors are vulnerable and how they can be controlled therapeutically by the immune system. His goal is to identify the mechanisms by which B cells operate and to translate these findings into therapeutic strategies that leverage B cells to disarm tumor cells and provide long-term protection against cancer.

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

BIOINFORMATICS | BREAST CANCER | GENETICS | THERAPEUTICS

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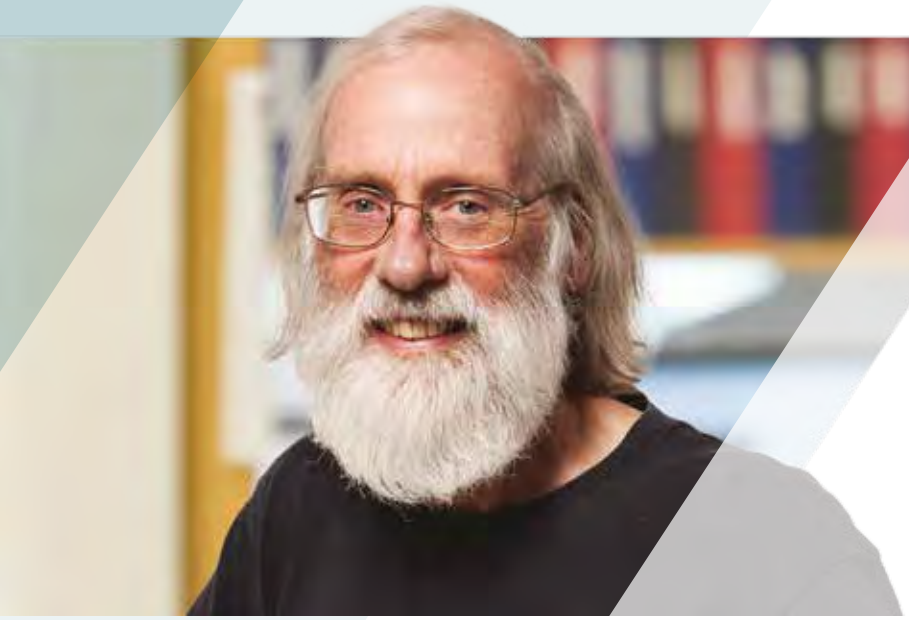

TONY HUNTER

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

Hunter is a cell biologist and cancer researcher who studies how cells regulate their growth and division, and how mutations in genes that regulate cell growth lead to cancer. In 1979, his lab discovered that phosphate can be attached to the amino acid tyrosine in proteins, which led to the development of the drug Gleevec as a targeted therapy for leukemia. This early success led to the development of a new class of cancer drugs that target misbehaving tyrosine kinases. Currently, Hunter's group is focused on identifying growth factors and cytokines produced in the pancreatic cancer microenvironment to promote tumor progression.

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 a 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 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

HEALTHY AGING | CANCER | GENETICS | EPIGENETICS | THERAPEUTICS

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GERALD JOYCE

Salk President Professor

Jack H. Skirball Center for Chemical Biology and Proteomics
Irwin M. Jacobs Presidential Chair

Joyce is a biochemist who has been a pioneer in the field of in vitro evolution. His research program is focused on the development of novel RNA and DNA enzymes and their potential application in clinical diagnostics and therapeutics. His research has led to the development of the first self-replicating RNA enzyme that is capable of exponential growth and evolution.

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 lab 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

EVOLUTION | SYNTHETIC BIOLOGY | CANCER

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SUSAN KAECH

Professor

NOMIS Center for Immunobiology and Microbial Pathogenesis

Kaech is an immunobiologist who 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 during immunization. In particular, 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 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

HEALTHY AGING | CANCER | GENETICS | EPIGENETICS | THERAPEUTICS

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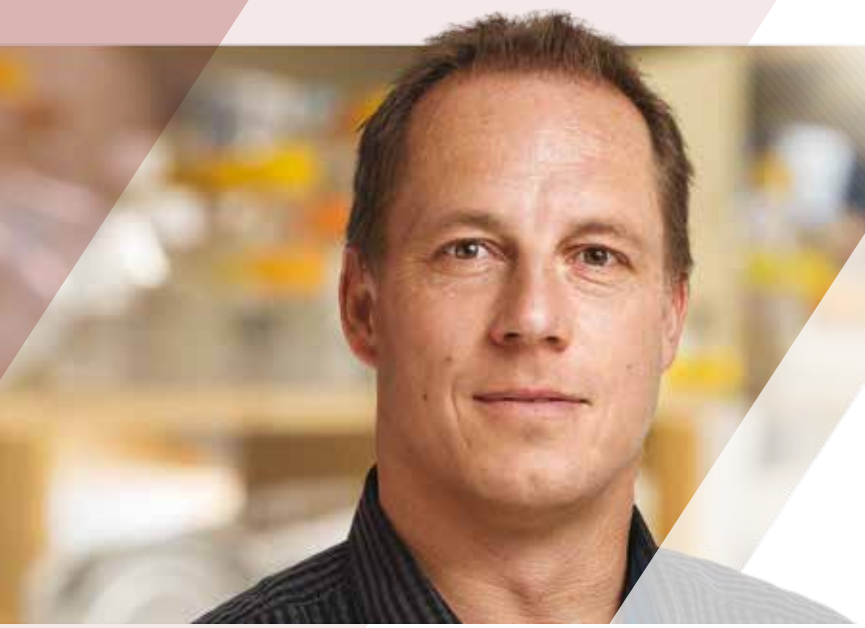

JAN KARLSEDER

Vice President, Chief Science Officer
Professor

Molecular and Cell Biology Laboratory
Donald and Darlene Shiley Chair

Karlseder is a molecular biologist who focuses on understanding the functions of mammalian telomeres—the protective endcaps of chromosomes—and how broken DNA is repaired. Telomeres and DNA repair are key players in aging and cancer, so the more scientists study them, the better they're able to promote healthy aging and create effective cancer therapeutics.

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), Karlseder's lab has exposed novel pathways during the earliest stages of cancer formation, which may yield potential interventions.

THE INNOVATIONS AND DISCOVERIES

- Karlseder's 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

HEALTHY AGING | CANCER | CELLULAR BIOLOGY | EPIGENETICS | GENETICS

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AGNIESZKA KENDRICK

Assistant Professor

Molecular and Cell Biology Laboratory

Kendrick is a biochemist who studies the molecular motors cells use to transport necessities and function. Her work sheds light on the dysfunction of these motors in disease, like cancer and numerous neurological disorders, while also having broader implications due to the prevalence of these motors throughout the body's diverse cell types.

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

ALZHEIMER'S DISEASE | CANCER | MOLECULAR MOTORS

PALLAV KOSURI

Assistant Professor
Integrative Biology Laboratory
Hearst Foundation
Developmental Chair

Kosuri is a bioengineer who studies the movements of molecules and their organization in tissues to create an integrated map of how movement gives rise to function—from the motors inside single cells to the structure of the heart's muscle tissue. For his work, Kosuri designs and builds custom nanoscale devices (millions of which could easily fit within a single cell) that track molecular motion.

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.Poris essi cus int. Temolut dollent perspeliquas utemolu ptaecturest labore,

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

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JULIE LAW

Professor

Plant Molecular and Cellular Biology Laboratory

Law is a plant biologist who studies the mechanisms by which epigenetic modifications are translated into stable expression states—a poorly understood process critical for proper gene regulation, imprinting, genome integrity, and development.

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 | EPIGENETICS | GENETICS | PLANT BIOLOGY | AGRICULTURE

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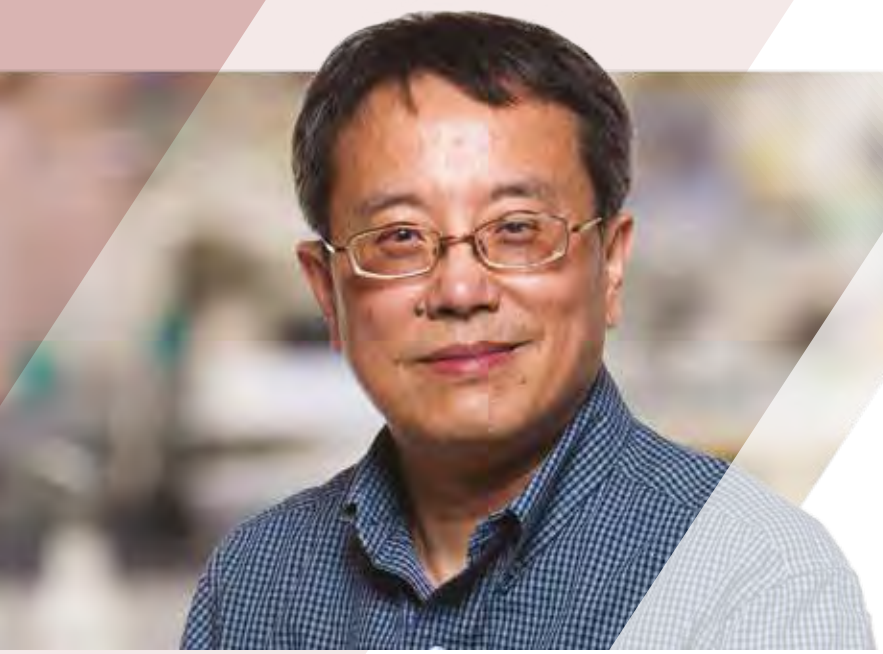

KUO-FEN LEE

Professor

Clayton Foundation Laboratories for Peptide Biology

Helen McLoraine Chair in Molecular Neurobiology

Lee studies the genes and molecules that guide brain cell development. His lab focuses on how disruptions in development and maintenance of nerve cells and their supporting cells can contribute to neurodegenerative diseases such as Alzheimer's disease, neuroendocrine diseases like anxiety, and neuromuscular diseases.

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

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NEUROLOGICAL DISEASE | NEUROSCIENCE

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DMITRY LYUMKIS

Associate Professor
Laboratory of Genetics
Hearst Foundation
Developmental Chair

Lyumkis is a biochemist who uses biochemical, structural, computational, and imaging tools to understand how proteins and protein assemblies function in cells to elicit diverse biological responses. His work focuses on understanding the molecular mechanisms of host-pathogen interactions and gene expression regulation.

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

Maher is a biochemist who studies the intersection of aging and neurodegenerative disease. As part of this work, she screens for compounds that alter processes associated with aging and thereby have the potential to 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 and turmeric, to treat cellular aging and memory loss.

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

ALZHEIMER'S DISEASE | HEALTHY AGING

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GRAHAM MCVICKER

Associate Professor
Laboratory of Genetics
Integrative Biology Laboratory

McVicker is a computational biologist and geneticist who studies how genetic differences between individuals affects molecular features of our cells, such as chromatin state or gene regulation. The knowledge gained from this research can reveal the biological mechanisms underlying disease and support the development of personalized therapies.

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.
- McVicker's lab has developed techniques and analysis methods that leverage CRISPR to scan noncoding portions of the genome for important regulatory functions.
- 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
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CHRISTIAN METALLO

Professor

Molecular and Cell Biology Laboratory
Daniel and Martina Lewis Chair

Metallo is a bioengineer who studies how our body metabolizes molecules like glucose, fats, and amino acids to generate the building blocks and energy needed to perform life-sustaining tasks—and how changes in metabolism contribute to disease. Metallo has made key discoveries about the metabolic pathways that drive cancer progression, peripheral neuropathy, and macular disease, as well as how those pathways can be influenced through dietary manipulations or targeted therapies.

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 that 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

HEALTHY AGING | CANCER | METABOLISM

TODD MICHAEL

Research Professor
Plant Molecular and Cellular Biology Laboratory

Michael is a plant biologist who leverages genetic sequencing technology and computational biology to uncover how genomic differences enable plants to better respond to and exploit their environments. 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 atmospheric carbon deep in the ground.

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 and to grow more food, fiber, and fuel for a burgeoning population.

THE APPROACH

Todd Michael leverages sequencing technology and computational biology to uncover how genomic differences enable plants to better respond to and exploit their environments. 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 extreme weather and other environmental pressures.

THE INNOVATIONS AND DISCOVERIES

- 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.
- 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.
- 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

PLANT BIOLOGY | GENETICS | AGRICULTURE | SYSTEMS BIOLOGY

LENA MUELLER

Assistant Professor
Plant Molecular and
Cellular Biology Laboratory

Mueller is a plant biologist who studies the symbiotic relationship between plants and arbuscular mycorrhizal fungi. Her research reveals the basis for healthy plant symbiosis and can be applied to engineer crops that take up nutrients more efficiently.

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

GENETICS | MICROBIOLOGY | PLANT BIOLOGY | AGRICULTURE

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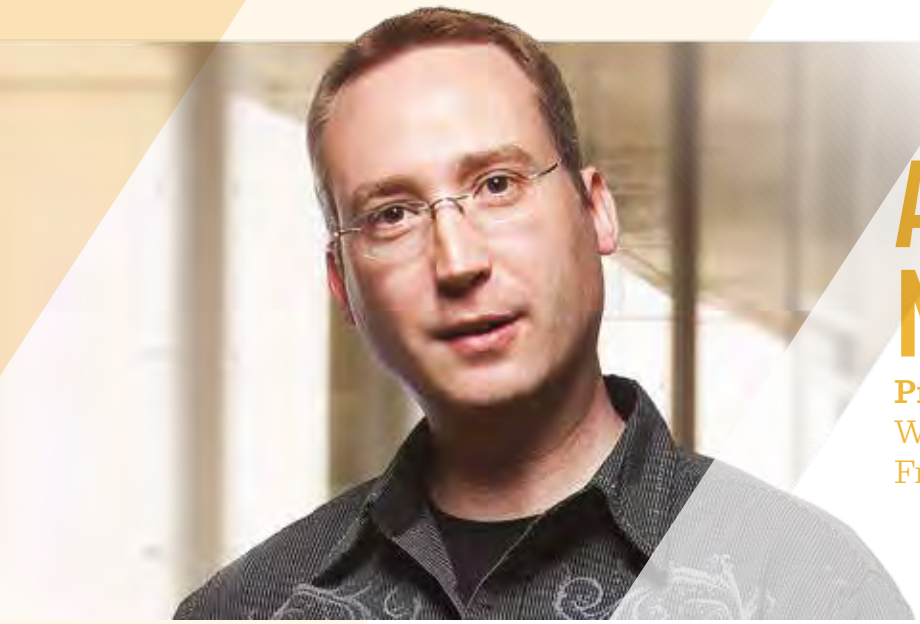

AXEL NIMMERJAHN

Professor

Waitt Advanced Biophotonics Center
Francoise Gilot-Salk Chair

Nimmerjahn is a biologist and physicist who has spearheaded the development of new microscopy techniques to uncover how the central nervous system regulates and maintains function throughout life. He pays particular attention to the brain's glial cells, which are involved nervous system injuries and diseases like viral and bacterial infection, spinal cord injury, Alzheimer's, Parkinson's, cancer, and stroke.

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. 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 breakdown after stroke. His team found that stepwise impairment of different cellular mechanisms accounts for the blood-brain barrier 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 | NEUROSCIENCE | NEUROLOGICAL DISEASE | STROKE
CANCER | PAIN | INFLAMMATION | VISION

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JOSEPH NOEL

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

Noel is a plant biologist who focuses on the chemistry, biochemistry, structural biology, and evolution of metabolism in plants that has given rise over 450 million years to an incredible diversity of natural chemicals. More recently, Noel's research has concentrated on plant natural polymers that may serve as carbon storage devices in plants—ranging from food crops to freshwater and marine wetlands.

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 increase their resiliency. For example, Noel has pieced the structure of a natural plant polymer known as suberin—commonly known as cork—that is rich in carbon atoms derived from the greenhouse gas carbon dioxide and 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 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

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CLODAGH O'SHEA

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

O'Shea is a microbiologist who works to identify the critical molecular drivers of disease and to translate this knowledge into more effective therapies. Her research integrates cancer biology, virology, structural biology, microscopy, synthetic biology, and translational research. She combines her knowledge and creation of new genome assembly technologies to design synthetic viral vectors, vaccines, and therapies that target cancer and inflammation.

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 cells, 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

CANCER | CELLULAR BIOLOGY | THERAPEUTICS | VIROLOGY

SATCHIDANANDA PANDA

Professor
Regulatory Biology Laboratory
Rita and Richard Atkinson Chair

Panda is a biologist who aims to understand the cellular and molecular basis of circadian or ~24-hour rhythms, then to leverage this knowledge to prevent, manage, and reverse chronic diseases that affect our brain and body. His findings suggest that genes and molecules involved in the circadian clock could be drug targets for conditions linked to inflammation, like infections or cancer.

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 eating 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

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

THALES PAPAGIANNAKOPOULOS

Professor

PapaG is a cancer biologist who studies how tumors adapt under stress by rewiring the way cells use nutrients and energy, how those changes shape the surrounding immune environment, and how cancers communicate with distant organs and the nervous system.

THE CHALLENGE

Cancer is not just a disease of uncontrolled cell growth; it is a disease that rewires the entire body. Aggressive cancers, like lung and pancreatic, can alter metabolism, evade immune attack, resist therapy, and even lead to multi-organ dysfunction by disrupting how the brain and body communicate. This disruption contributes to symptoms such as weight loss, loss of appetite, and depression. Yet we still do not fully understand how the genetic mutations that promote cancer also enable tumors to manipulate their surrounding environment and the host's physiology. Papagiannakopoulos (PapaG) studies these unanswered questions to uncover how cancers become so aggressive and how their vulnerabilities can be targeted for better treatment.

THE APPROACH

PapaG's group takes an integrative approach that combines cancer genetics, metabolism, immunology, and systems physiology to understand how tumors grow and interact with the body. His lab uses advanced mouse models and CRISPR genome engineering to study how cancer-causing mutations interact with diets and systemic physiology to reshape tumor behavior and therapeutic response.

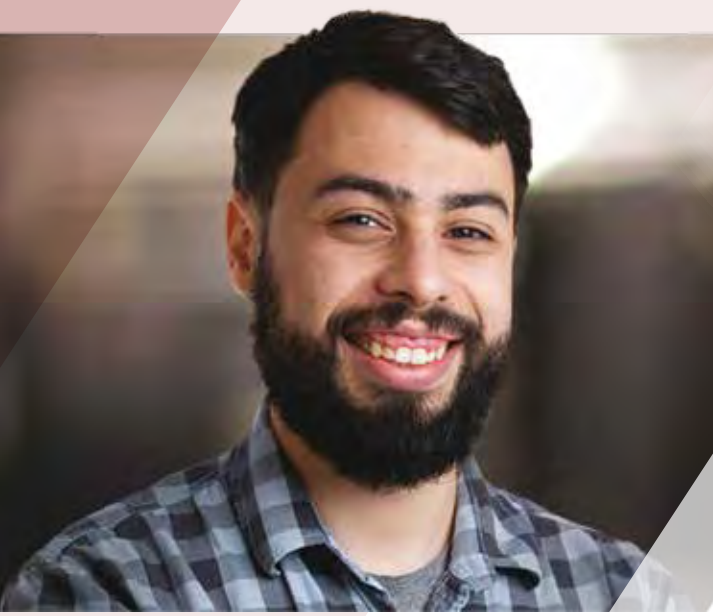
More recently, the lab has expanded into the emerging field of cancer neuroscience, investigating how tumors communicate with the nervous system and the rest of the body. This broad and interdisciplinary strategy allows the lab to uncover not only what drives tumor progression, but also how cancer affects whole-body physiology in ways that could reveal entirely new therapeutic opportunities.

THE INNOVATIONS AND DISCOVERIES

- PapaG's lab pioneered powerful mouse and CRISPR-based models to study how combinations of cancer mutations drive lung tumor initiation, progression, and immune evasion and therapeutic resistance.
- PapaG's lab uncovered how stress response pathways hijacked by cancer cells can promote critical metabolic rewiring and immune evasion to evade death and promote tumor progression.
- PapaG's lab is now uncovering how cancer engages brain-body communication pathways to influence systemic physiology, immune responses, and cancer-associated sickness states, opening a new frontier at the intersection of cancer and neuroscience.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/THALES-PAPAGIANNAKOPOULOS

CANCER | NEUROSCIENCE | LUNG CANCER | PANCREATIC CANCER



TALMO PEREIRA

Assistant Professor

Pereira is a computational neuroscientist who develops and applies artificial intelligence techniques to study how life moves as a window into how it works. By building detailed virtual simulations of how living beings—from plants to animals—move, he aims to tackle tough questions like how brains process information or how early signs of disease manifest in an individual's body language.

THE CHALLENGE

From plants growing roots through soil to giraffes walking through the savanna, all forms of life evolved the ability to move to survive in changing environments. This fundamental aspect of biology is so important that it prompted the development of the nervous system. Despite movement's importance, little is known about this "body language" of life, from its constituent "syllables" to how quirks in its "grammar" may be linked to underlying diseases.

THE APPROACH

Pereira and his lab develop and apply artificial intelligence (AI) techniques to study the processes that give rise to biological motion. By using a form of AI called deep learning, the lab has created computational tools capable of performing "markerless motion capture"—a powerful technology that can extract biological dynamics from video data. Pereira now leverages this approach to make sense of how animals and humans behave during health or disease, how plant root systems sequester carbon, and how the brain coordinates body movements to produce complex behaviors.

THE INNOVATIONS AND DISCOVERIES

- Pereira's pioneering work demonstrated how deep learning could be used to achieve markerless motion capture in animals that enables detailed quantification of behavior.
- Pereira and his team have developed SLEAP, an open-source software tool that makes AI-based motion capture technology accessible to non-technical users. SLEAP is now in use by thousands of researchers all around the world to study everything from subcellular organelles to whale sharks.
- Pereira and his team have shown how artificial neural networks can be used to simulate how real brains process information.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/TALMO-PEREIRA

COMPUTATIONAL BIOLOGY | NEUROSCIENCE | ARTIFICIAL INTELLIGENCE
ALS | PARKINSON'S DISEASE

SAMUEL PFAFF

Professor

Gene Expression Laboratory

Benjamin H. Lewis Chair

Pfaff is a neuroscientist who studies how nerve cells are formed and wire up correctly. His lab focuses uses a combination of genetics, biochemistry, and microscopy with cutting-edge tools to study motor neurons—with particular attention to the fetal development of the spinal cord.

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. Pfaff's lab 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 | NEUROSCIENCE
NEUROLOGICAL DISEASE | POST-POLIO SYNDROME | STEM CELLS

DEEPSHIKA RAMANAN

Assistant Professor

NOMIS Center for Immunobiology and Microbial Pathogenesis

William Scandling Developmental Chair

Ramanan is an immunologist who studies the biology of maternal-offspring relationships, like how maternal microbiota, diet, and environment can shape a newborn's immune development and influence their long-term immune health across generations.

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

- Ramanan discovered that communication between the mother's intestine and mammary glands, called the entero-mammary axis, can impact breast milk composition and influence offspring intestinal immunity in a mouse model.
- 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.
- 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

Reynolds is a neuroscientist who brings together experimental and theoretical neuroscience to understand the mechanisms that mediate sensory perception, selective attention, and memory. By understanding these mechanisms, his work sets the stage for developing new approaches to treat diseases in which perception, attention, and memory fail, like autism spectrum disorder, schizophrenia, and Alzheimer's.

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. 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

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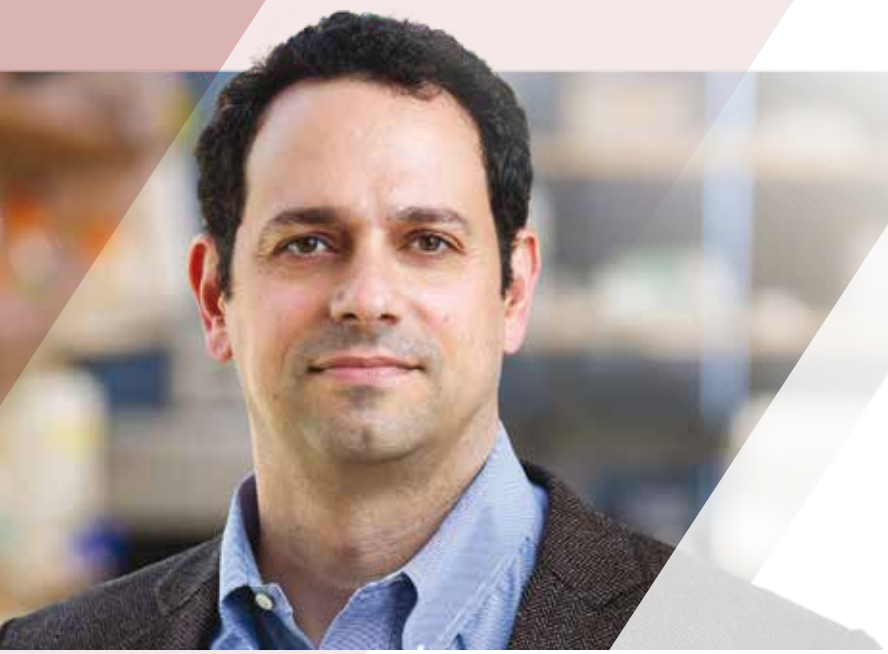

ALAN SAGHATELIAN

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

Saghatelian is a chemist who develops and applies innovative technologies to elucidate the molecular basis of prevalent diseases including diabetes, cancer, and autoimmunity. Key findings from his lab include the discovery of novel metabolites that regulate metabolism and inflammation, and the discovery of thousands of new human genes with potential roles in all disease.

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 finding 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.
- 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

CANCER | DIABETES | IMMUNOLOGY | METABOLISM | NEUROLOGICAL DISEASE

TERRENCE SEJNOWSKI

Professor and Laboratory Head
Computational Neurobiology Laboratory
Francis Crick Chair

Sejnowski is a computational neuroscientist and a distinguished pioneer in his field. Sejnowski's team uses sophisticated electrical and chemical monitoring techniques to measure changes between nerve cells in the hippocampus during a simple form of learning, then take those measurements and instruct large-scale computers to mimic how those nerve cells work. By studying the resulting computer simulations, Sejnowski hopes to gain new knowledge of how the human brain learns and stores memories.

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 (stored in the brain) sleep. Researchers hypothesized some memories are strengthened during sleep, while other memories are deemed less important and 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
NEUROSCIENCE | PARKINSON'S DISEASE | SCHIZOPHRENIA | SYSTEMS BIOLOGY

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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

Shadel is a biologist who studies mitochondria, the dynamic "powerhouses" inside cells that generate energy from the food we eat. He showed a novel role for mitochondrial signaling in regulating aging and discovered that mitochondrial DNA activates the antiviral innate immune system. Using genetic, biochemical, and molecular approaches, Shadel's team continues to focus on the surprisingly diverse roles of mitochondria in aging and diseases like autoimmunity and cancer.

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 | HEALTHY AGING | GENETICS

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TATYANA SHARPEE

Professor
Computational Neurobiology Laboratory
Integrative Biology Laboratory
Edwin K. Hunter Chair

Sharpee is a neuroscientist who studies the fundamental principles behind how the brain processes information. She is interested in how sensory processing in the brain is shaped by the animal's need to create parsimonious representations of events in the outside world, and how these representations are altered in brain diseases.

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. 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.

But as we age, we begin to lose connectivity between neurons and lose molecular balances—all while the environment within which the brain is operating is changing, too. Sharpee and colleagues are working to understand the optimal signals that the brain should pay attention to in its environment, and what we could prescribe to help the brain adapt to these lifelong changes.

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 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 spectrum disorder, 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
Director of the NCI-designated
Salk Cancer Center
William R. Brody Chair

Shaw is a cancer biologist who discovered direct connections between cancer and metabolism. Shaw's lab looks at central metabolism and the AMPK growth pathway discovered by Shaw that underpins cellular response to low nutrients and low energy. Since discovering the AMPK pathway, he has continued working on how nutrient deprivation and cellular energy levels control cancer and other diseases.

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. Shaw's 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, Shaw's studies have led to the discovery of several new therapies for both cancer and metabolic diseases.

THE INNOVATIONS AND DISCOVERIES

- Shaw's 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.
- 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, and 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.
- Shaw's lab discovered how cells trigger repair of their power generators, the mitochondria, following attacks. 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

LUCIA STRADER

Professor

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

Strader is a plant biologist studying how plants sense and integrate environmental cues to shape their growth and development. Her discoveries on the plant hormone auxin are helping scientists design more resilient crops that can thrive in changing environments.

THE CHALLENGE

Plants must constantly adapt to their surroundings. They wait for the right temperature, light, nutrients, and water levels to trigger each developmental stage, shifting their priorities to align with their changing environment.

One of the biggest challenges in plant biology is understanding how plants sense and integrate these complex environmental signals and translate them into growth decisions. At the center of this signal integration is auxin, a hormone that regulates nearly every aspect of plant development. However, many of the systems that interact with auxin remain poorly understood. Without this core understanding, we face significant barriers in developing stronger crops that can thrive under changing climate and nutrient conditions.

THE APPROACH

Strader investigates how plants integrate environmental information with hormone signaling to shape plant growth and development. Her lab is building a molecular understanding of the spatial and temporal control of plant hormone responses, particularly in their regulation of gene transcription. Her multidisciplinary approach combines techniques from plant physiology, genetics, molecular biology, biochemistry, structural biology, biophysics, systems biology, and synthetic biology to understand the mechanisms of auxin regulation.

Strader's lab is also using these insights to develop heartier, more resilient crops that can better withstand extreme weather events, use nutrients more efficiently, and produce reliable yields in the face of environmental stress.

THE INNOVATIONS AND DISCOVERIES

- Strader's team determined a mechanism for regulating the cell-type-specific auxin response, providing a tunable knob for plant growth.
- Strader identified the activation domains of all *Arabidopsis* transcription factors, explaining how these proteins 'turn on' genes in the plant.
- Strader's lab has identified how specific auxin inputs control distinct aspects of plant growth.

For more information, please visit:
WWW.SALK.EDU/SCIENTIST/LUCIA-STRADER

PLANT BIOLOGY | GENETICS | SYSTEMS BIOLOGY
BIOPHYSICS | AGRICULTURE

CHRISTINA TOWERS

Assistant Professor

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

Towers is a cancer cell biologist who uses 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 their own nutrients and power-generating structures called mitochondria to survive. Her goal is to understand the fundamental cancer cell biology that drives cancer cell survival to develop targeted cancer therapies that block cancer cell recycling pathways and kill the cancer cells.

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 patients' 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 gain a broader understanding of these recycling mechanisms that cancer cells use to survive, and then 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

Tye is a neuroscientist who seeks to understand the neural-circuit basis of emotion that leads to motivated behaviors such as social interaction, reward-seeking, and avoidance. Using cellular-resolution recordings, behavioral assays, and optogenetics (a technique that activates certain cells with light), she finds mechanistic explanations for how these emotional and motivational states influence behavior in health and disease.

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

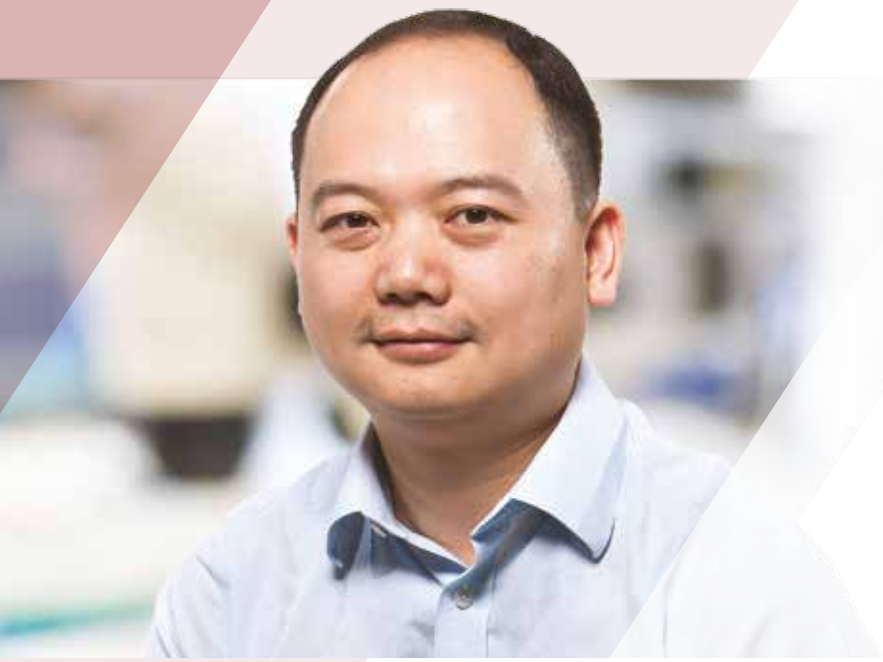
Kay Tye's lab seeks to understand the neural-circuit basis of emotion that leads to motivated behaviors such as social interaction, reward-seeking, and avoidance. Her lab employs a multidisciplinary approach, including cellular-resolution recordings, behavioral assays, and optogenetics—a technique that 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, Tye's 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

NEUROSCIENCE | NEUROLOGICAL DISEASE | ANXIETY | DEPRESSION | ADDICTION



YE ZHENG

Professor

NOMIS Center for Immunobiology and Microbial Pathogenesis

Becky and Ralph S. O'Connor Chair

Zheng is an immunologist who focuses on a specialized set of immune cells called regulatory T cells (Tregs), which help balance and maintain a healthy immune system. He hopes his findings open new avenues in the treatment of autoimmune diseases, improve organ transplant survival, and uncover new cancer therapeutic targets.

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

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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

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.

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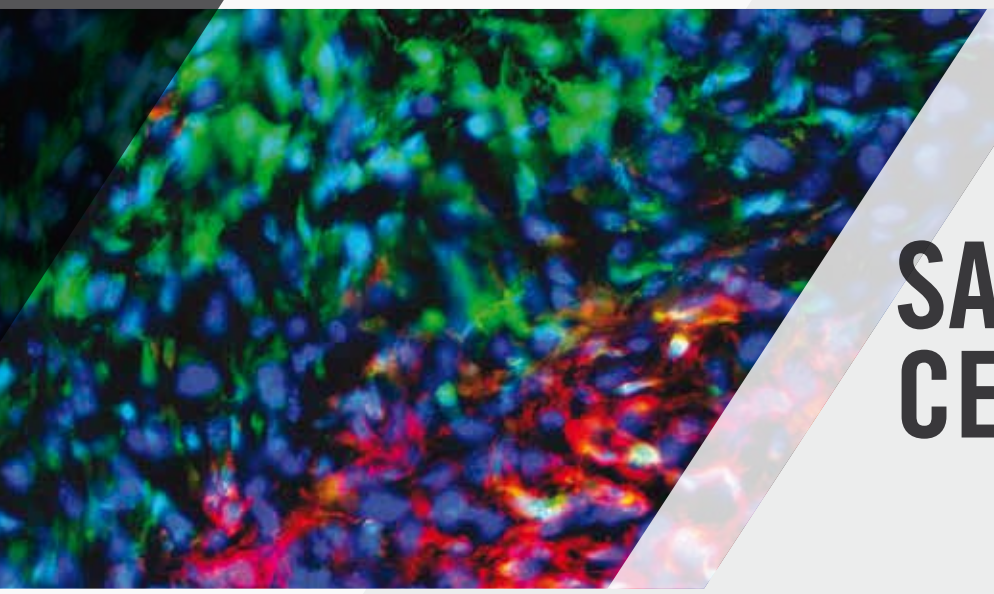

SALK CANCER CENTER

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:
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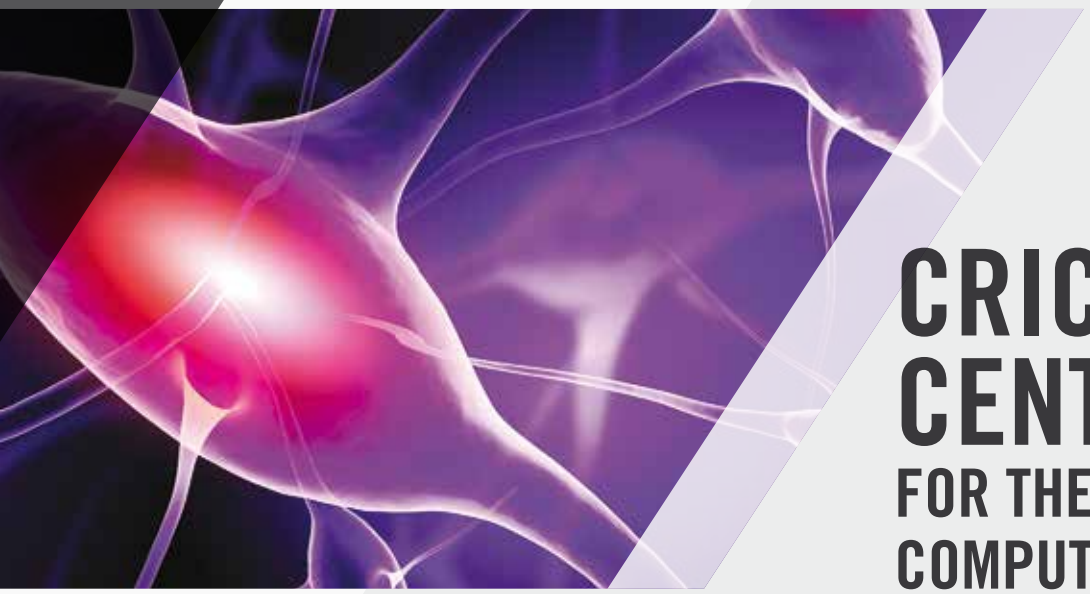

CRICK-JACOBS CENTER
FOR THEORETICAL AND COMPUTATIONAL BIOLOGY

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:
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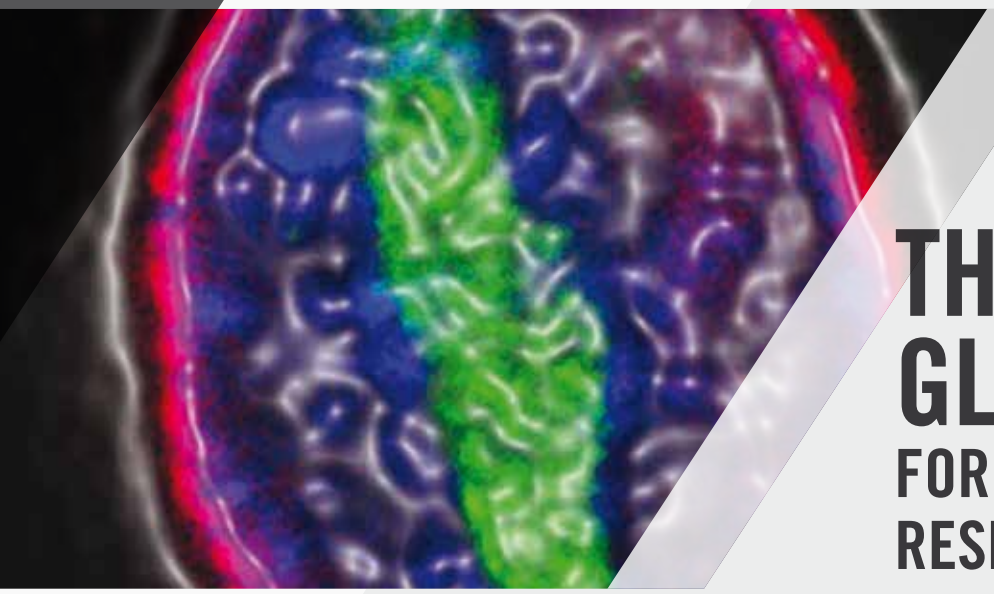

THE PAUL F. GLENN CENTER
FOR BIOLOGY AGING RESEARCH

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:
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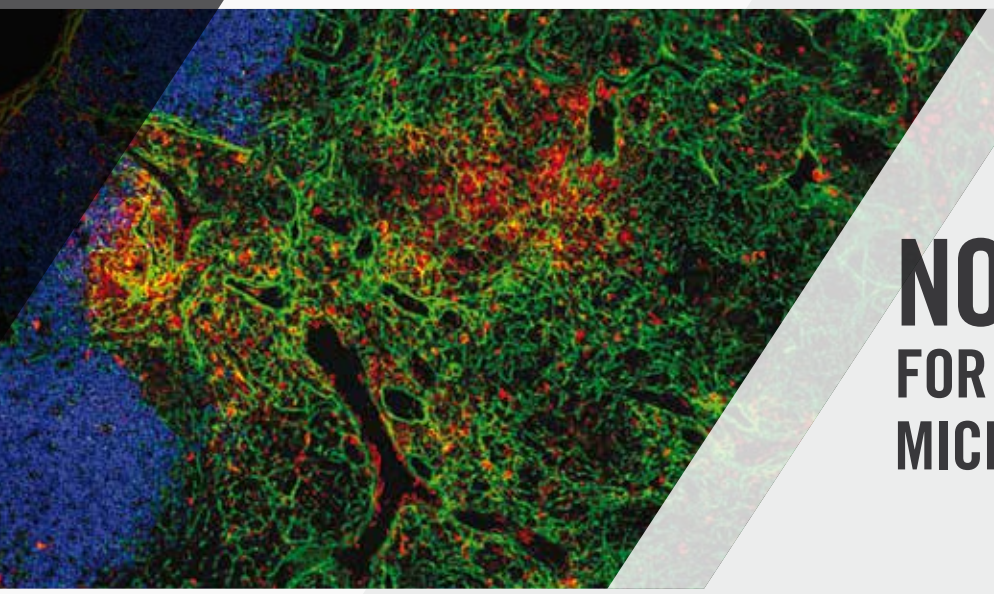

NOMIS CENTER
FOR IMMUNOBIOLOGY AND MICROBIAL PATHOGENESIS

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:
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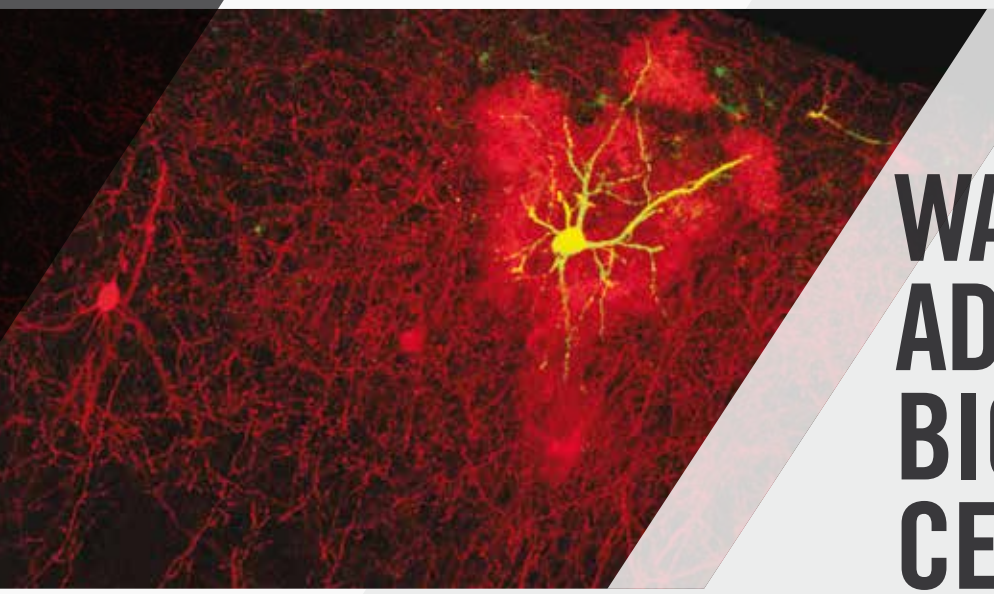

WAITT ADVANCED BIOPHOTONICS CENTER

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

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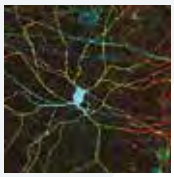
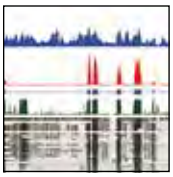
SCIENTIFIC CORE FACILITIES



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.

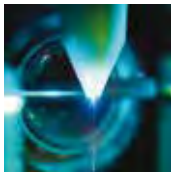
Daniela Boassa, Director
Gerald Shadel, Faculty Advisor



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)

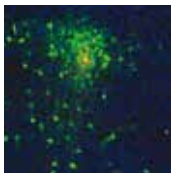
The Flow Cytometry Core facility is dedicated to advancing research projects requiring cell sorting and/or analysis of cell populations by flow cytometry.

Carolyn O'Connor, Director
Ye Zheng, Faculty Advisor

MASS SPECTROMETRY CORE (MASS)

The Mass Spectrometry Core provides both proteomics and metabolomics services through the analysis various biological and plant samples. Services include a variety of untargeted and targeted analysis.

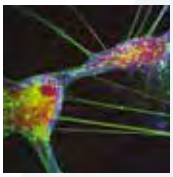
Michael La Frano, Director
Christian Metallo, Faculty Advisor



GENE TRANSFER, TARGETING AND THERAPEUTICS VIRAL VECTOR CORE (GT3)

The Gene Transfer, Targeting and Therapeutics Viral Vector Core 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, Director
Edward Callaway, Faculty Co-Advisor (Neurosciences)
Tony Hunter, Faculty Co-Advisor (Cancer Center)



CELL TECHNOLOGIES AND ENGINEERING CORE (CTEC)

The Cell Technologies and Engineering Core supports the needs of researchers for human ES and reprogrammed iPS cell culture. We offer training and the physical space to carry out experiments using pluripotent cell types.

Jenn Page, Director
Ronald Evans, Faculty Advisor

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EMERITUS FACULTY

DISTINGUISHED EMERITA

THOMAS ALBRIGHT

By combining physiological, neurological, and computational studies, Thomas Albright helped reveal how the brain enables humans to perceive and behave in a world of varying sensory demands. The visual system, he found, has a filter that determines which stimuli reach the brain's visual processing area in the first place. He also pinpointed how sets of neurons in the visual cortex are more or less sensitive than others in different environments to allow for this attention shift. Using brain scans, Albright uncovered hallmark signs of attention span problems in patients with schizophrenia, which aid in screening for new therapeutics. His work also informs how the memory of visual information can be distorted, as well as how to build environments and architecture that encourage learning, productivity, and healing.

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.

EMERITUS FACULTY

DISTINGUISHED EMERITA

GREG LEMKE

Greg Lemke is a neuroscientist who used molecular genetics to study signaling networks that control immune system function and nervous system development. He discovered a family of receptor tyrosine kinases, called TAM receptors, which play a crucial role in telling immune cells how to handle normal cellular debris and infections of bacteria, viruses, and other pathogens. His work showed how problems with the TAM receptors or their pathways are associated with drug-resistant cancer, Alzheimer's disease, inflammation, and autoimmune diseases such as lupus, multiple sclerosis, and rheumatoid arthritis.

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.

DISTINGUISHED EMERITA

MARC MONTMINY

Marc Montminy gave up clinical medicine in favor of following up on his PhD work, which led him to his seminal discovery of the "cAMP response element"—an important stretch of DNA necessary for creating endocrine regulating hormones called somatostatins. This discovery drove him to Salk, where he joined neuropeptide hormone expert Wylie Vale and continued his research into metabolic pathways. He looked at changes in cellular communication during fasting and diabetes, wherein he discovered a key signaling molecular called CREB and a genetic switch called CRTC2. In healthy individuals, both CREB and CRTC2 are responsible for maintaining the right cycle of sugar storage and release throughout the day, so Montminy's work to understand their dysregulation in diabetes paves the way for future diabetes treatments.

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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.

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.

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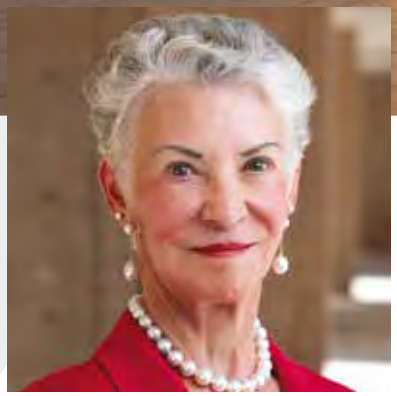

CATHERINE RIVIER

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.

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.

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GEOFFREY WAHL

For decades, Geoff Wahl focused on understanding how tumors acquire genetic and cellular plasticity. These factors lead to treatment failure and underlie metastasis. His work revealed mechanisms and genes that preserve genetic integrity in normal cells that are lost during cancer progression. He also explored links between genetic plasticity, normal development, and tumor development, focusing on breast and pancreatic cancers. His lab generated the first cell-by-cell analysis of the chromatin and gene expression changes occurring in each mammary cell from the fetus to the adult. This molecular road map revealed how genes and pathways involved in normal development are co-opted during malignant progression. Wahl's team also discovered that a rare type of cell generated during pancreatitis, a harbinger of pancreatic cancer, secretes substances that help heal damaged pancreases. These innovative findings opened new paths for treating breast cancer and preventing pancreatic cancer progression.

FACULTY

PRESIDENT
Gerald Joyce

DISTINGUISHED PROFESSORS EMERITI
Thomas Albright
Elizabeth Blackburn
William R. Brody
Greg Lemke
Vicki Lundblad
Marc Montminy

PROFESSORS EMERITI
Beverly Emerson
Katherine Jones
Christopher Kintner
Catherine Rivier
Paul E. Sawchenko
John B. Thomas
Geoffrey Wahl

PROFESSORS
Nicola Allen
Janelle Ayres
Wolfgang Busch
Edward Callaway
Sreekanth Chalasani
Joseph Ecker
Ronald Evans
Rusty Gage
Martyn Goulding
Ian Guldner
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Dannielle Engle
Daniel Hollern
Agnieszka Kendrick
Pallav Kosuri
Lena Mueller
Talmo Pereira
Deepshika Ramanan
Christina Towers

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

ANDREW DILLIN
Professor, Department of Molecular & Cell Biology
University of California, Berkeley

CHRISTOPHER K. GLASS
Professor, Department of Cellular and Molecular Medicine
University of California, San Diego

DOUGLAS R. GREEN
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
Ronald and Deborah Harris Professor in the Sciences
Department of Biological Sciences
Dartmouth College

DAVID JULIUS
Professor
Chair of the Department of Physiology
Morris Herzstein Chair in Molecular Biology and Medicine
UC San Francisco
2021 Nobel Prize in Physiology or Medicine

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

J. ANTHONY MOVSHON
University Professor and Silver Professor
Professor of Neural Science and Psychology
New York University

STEPHEN QUAKE
Professor, Department of Bioengineering
Stanford University

BRENDA SCHULMAN
Director, Molecular Machines and Signaling
Max Planck Institute of Biochemistry

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

DETLEF WEIGEL
Director and Scientific Member
Max Planck Institute for Biology Tübingen

IRVING L. WEISSMAN
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

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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

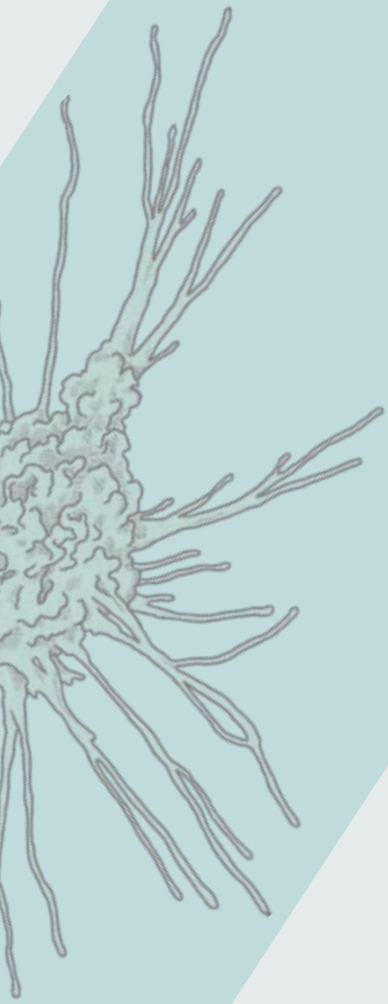
NATIONAL ACADEMY OF SCIENCES*

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
Susan Kaech | 2024
Greg Lemke | 2025
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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Salk Institute for Biological Studies
10010 N Torrey Pines Rd
La Jolla, California 92037-1002
Telephone: (858) 453-4100
www.salk.edu