The power of...

Conversations that drive change

*From the beginning, the structure and culture of the Salk Institute have spurred dynamic conversations among faculty, no matter their discipline. Often this crosstalk—which happens more freely than at other institutions—leads their research in new and unexpected directions.*

The challenge

Biology is tremendously complex, and diseases don’t care about boundaries between academic disciplines. Cancer, for example, has metabolic, genetic and immunologic underpinnings, and is greatly influenced by aging. So it makes sense to tackle the most complex problems of human health—like cancer—using a cross-disciplinary approach.

The Salk approach

Exceptional scientists are attracted to the Salk Institute because it encourages intellectual curiosity and gives faculty the freedom and resources to follow scientific questions wherever they might lead. Collaboration between faculty with different expertise is encouraged, not only in word but also in deed, with grants that support promising ideas at stages too early for traditional funding, and with the technical strength of Salk’s scientific cores—shared facilities with cutting-edge equipment and trained staff experts that enable Salk labs to make world-changing discoveries.

See the Salk approach at work:

Crosstalk between disciplines happens every day

**Aging and cancer.** In most labs, telomeres (the protective DNA caps at the end of chromosomes) and mitochondria (structures that generate energy for cells) are studied as separate drivers of aging. But Professors Jan Karlseder, an expert on telomeres, and Gerald Shadel, an expert in mitochondria, have teamed up to explore crosstalk between the two. So far, they have discovered that shortening telomeres kick off a cascade of molecular signals that reach the cell’s mitochondria. These signals ultimately trigger inflammation and cell death. This way, aging, unstable cells with critically short telomeres are efficiently removed by the body, preventing them from becoming cancerous. Stabilizing this pathway could offer a new approach for preventing age-related cancers.

**Cancer and immunology.** Associate Professor Diana Hargreaves studies how epigenetics—modifications to genes that control cell identity and cell fate. Professor Susan Kaech is director of the NOMIS Center for Immunobiology and Microbial Pathogenesis. They are working together to study how epigenetics can be leveraged to build better immune cells for cancer immunotherapy—an approach that uses the body’s immune system to recognize and destroy cancer.

**Immunology and neuroscience.** Understanding conditions that affect the brain—such as schizophrenia, autism and Alzheimer's—requires understanding how brain cells connect to one another, which can be difficult to tease out. In 2007, Professor Edward Callaway, a neuroscientist, his graduate student, Ian Wickersham, and former Salk professor John Young, a virologist, came up with a technique that revolutionized the process. Callaway was describing to Young the problems with using viruses that naturally infect neurons, such as rabies, to trace connections between the mammalian cells used in the lab. Callaway was having difficulties targeting the rabies virus to specific neurons of interest. Young immediately had a solution: use a protein combination found in a bird virus to help fluorescent proteins selectively enter target brain cells. Using microscopes to follow the fluorescent proteins, researchers can literally see the path traced between connected cells. The method, now known as monosynaptic neural circuit tracing, has become one of the most useful tools in neuroscience research.

**Immunology and aging.** Epigenetics—the chemical modifications to DNA and associated proteins that help determine which genes are “on” or “off”—can be affected by diet, exercise and other aspects of lifestyle. Hargreaves and Kaech, along with Associate Professor Ye Zheng and Assistant Professor Jesse Dixon, think that many of the age-related changes in immune function and inflammation stem from epigenetic dysfunction. As recipients of a 2021 Salk Collaboration Grant, grants that were established specifically to foster collaborative research, the group is working to determine the effects of age on epigenetic factors during a viral infection, identify key factors in aging-associated decline in immunity, and facilitate efforts to improve immune response in older patients.

**Aging and neuroscience.** Alzheimer's disease—an aging-related disorder that results in severe memory loss—represents a global health crisis, with estimates suggesting that 130 million people will be affected by 2050. To date, there are no effective therapies for this disease. A team of Salk Institute researchers led by Professor Rusty Gage is investigating mechanisms underlying Alzheimer's disease and aging-related cognitive decline to uncover new therapies. This bold venture will comprehensively analyze interactions between five areas key to brain health: proteins, genes, metabolism, inflammation and epigenetics, and is funded by $19.2 million from the American Heart Association-Allen Initiative in Brain Health and Cognitive Impairment.
Neuroscience and plants. Plants use sensory proteins to detect and respond to touch signals from animals and neighboring plants. With a 2022 Salk Innovation Grant, Professor Joanne Chory, Associate Professor Sreekanth Chalasani and Staff Scientist Carl Procko will investigate these proteins to assess their ability to sense high-frequency sound waves. The work could lead to new ways of treating conditions such as chronic pain, epilepsy and PTSD, as well to contribute to the growing body of research on “sonogenetics,” a method Chalasani developed for non-invasively controlling cells with sound waves.

Plants and cancer. In a study that might only happen at Salk, Professor Wolfgang Busch, codirector of the Harnessing Plants Initiative, has teamed up with Professor Reuben Shaw, director of the Salk Cancer Center, to study starvation signals in plants. Shaw’s cancer research lab has been studying genes altered in lung cancer whose normal function is to sense when cells are starving for nutrients. It turns out that these genes go so far back in evolutionary time that a common ancestor of plants and animals passed them on to both groups. Thus, the genes also control the response to starvation in plants. The duo’s preliminary work suggests that activators of one of these genes, AMPK, are active in plants, and might prove helpful to the Harnessing Plant Initiative’s effort to increase the amount of carbon plants can store in their roots as a means to mitigate climate change.

Computational biology, theory building and…everything.

Computational biology. Biological studies—across all disciplines—today amass such vast mountains of data, that computational algorithms, machine learning and artificial intelligence are needed to search for meaningful patterns within the peaks and valleys. Fortunately, Salk has long been ahead of the computational curve.

In one example: To understand how the brain controls the body, Associate Professor Eiman Azim needs to record motions and train deep learning algorithms to recognize how body parts, like arms and fingers, move in 3D space. Working with engineers and computer scientists, he is pioneering new, automated ways to collect motion data at a resolution that the traditional process of manual human labeling cannot achieve. Once vast amounts of movement data are gathered, he leverages machine learning and other techniques to explore how circuits in the brain govern motion. This work is providing new insights into how injuries and neurological disorders, such as Parkinson’s disease and ALS, can have such devastating effects on motor skills. He believes that illuminating these processes will help uncover innovative ways to restore healthy movement.

Theory building. In addition to statistically processing and analyzing the vast amount of data currently being generated in Salk labs and elsewhere, we must have a way to put the processed (“reduced”) data into context.

Building mathematical models and theories to test causality and make predictions about the future will enable Salk researchers to make sense of existing data and plan the next set of important scientific questions. For example, Professor Tatyana Sharpee, who studies how the brain’s billions of neurons exchange energy and information, was curious about our sense of smell, which can be affected by diseases like Alzheimer’s and Parkinson’s. But she found there was no good way to categorize odors. Visual input can be organized by wavelengths or colors, and sound can be organized by frequency, but there was no similar system for odors. So Sharpee used mathematical methods to organize known odor molecules based on the unique idea of how often they occur together in nature. Her team then created a 3D map for the data, which revealed specific directions for qualities such as acidity or pleasantness. Along with guiding the development of pleasing new odor mixtures in industry, the work might lead to news ways of studying why people with certain diseases lose their sense of smell.

Professor Terrence Sejnowski, who also studies the brain, develops computer models to test hypotheses on how brain cells process, sort and store information. His lab recently ran a study on working memory—keeping things in mind for just seconds or minutes to, for example, remember what dish we plan to order after closing a restaurant menu. They created a computational model of the brain’s prefrontal cortex, an area known to manage working memory. They discovered that good working memory requires two things: neurons that hold on to information for longer than average, but also strong connections between inhibitory neurons, which suppress brain activity. Their results could inform future studies on why some people with neuropsychiatric disorders, including schizophrenia and autism, struggle with working memory.

Why Salk

For more than 60 years, the Salk Institute has pursued Jonas Salk’s vision of fearless, interdisciplinary science tackling some of the biggest challenges facing humankind. The Institute’s long track record of successful discoveries about complex cellular function—in both animals and plants—makes investing in Salk science a sound bet. Cross-disciplinary studies are bringing fresh perspectives and potential breakthroughs to aging, cancer, immunology, plant biology, neuroscience and more. And supporting them all is Salk’s strong commitment to computational biology, which is necessary for conducting meaningful science in the era of big data, when vast quantities of information too unwieldy for human calculation can be manipulated and analyzed for meaningful patterns using computational algorithms.

Why now

In 2019 the Institute launched the Campaign for Discovery—a seven-year, $750 million effort to accelerate Salk’s critical research.

The campaign is focused on driving discoveries in six Centers of Excellence: Cancer Center, Center for Healthy Aging, Center for Plant Biology, Center for Neuroscience, NOMIS Center for Immunobiology and Microbial Pathogenesis, and Crick-Jacobs Center for Theoretical and Computational Biology.

To continue to lead the field in these areas, Salk is recruiting new faculty and other experts, investing in new technologies, and creating new collaborative spaces, including construction of the Joan and Irwin Jacobs Science and Technology Center.

As it has always been at Salk, there will be no barriers between disciplines. New ideas from multiple areas can mix and flourish, generating the most innovative, multi-pronged approaches to solving some of the world’s most pressing challenges.

Join us

Science is a collaborative pursuit, and we invite you to join us in accelerating life-changing discoveries: www.salk.edu/campaign.