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The world’s leading biomedical research university, dedicated to making transformative discoveries in basic and translational bioscience.
Focus on Bioscience

At Rockefeller, our only mission is to understand life. From the tiniest microbe to the most intricate society, our scientists study the proteins, genes, cells, and organisms that give life on Earth its complexity, its wonder, and its diversity. We study the processes that keep us alive and the conditions that lead to disease. We conduct science for the benefit of humanity.
Biomedical science is The Rockefeller University’s singular priority. Our laboratories conduct basic and translational research and study a broad range of biological processes. Rockefeller scientists work to further our understanding of life, and to generate the knowledge needed to fight disease.

The university’s formula for success is simple: We recruit the very best scientists and provide them with the resources they need to do extraordinary work. Over the years, this recipe has led to an international reputation for excellence and innovation. Despite our small size, we have an impact that reaches far beyond our New York City campus. By any number of measures — awards, publications, citation rates, grants — faculty and alumni from Rockefeller are among the world’s most prolific contributors to scientific progress.
Rockefeller Scientists

Each of our 81 faculty members heads his or her own independent laboratory. Rockefeller scientists report directly to the president and have the latitude to direct their research as they see fit.

Our unique laboratory-based culture is one of our best assets. Because each laboratory functions independently, without departmental boundaries or administrative interference, Rockefeller scientists have the flexibility to ask complex questions and apply a broad range of tools and techniques to their research. As the science evolves, so too can the scientist. Although fields of inquiry serve as useful descriptions of our scientists’ interests and goals, they do not confine researchers within a particular intellectual framework.

Despite their freedom, Rockefeller scientists also have tremendous support as well as opportunities to form creative and productive collaborations. Labs are staffed by postdoctoral researchers, graduate students, and technicians and their work is supported by specialists in core facilities devoted to genomics, bio-imaging, cryo-electron microscopy, high-throughput screening, and precision fabrication, among others. The university’s 11 interdisciplinary centers provide links between clusters of labs working in particular areas of scientific interest, including cancer biology, neuroscience, and digestive diseases. In addition, a rich program of open lectures and seminars, with both internal and external speakers, helps Rockefeller scientists keep abreast of their colleagues’ work.
A History of Innovation

Rockefeller invented the modern bioscience institute and has spent the last 117 years perfecting it. Born out of a frustration with the state of medicine at the turn of the twentieth century, the institute’s founders launched an organization that functioned like no other.

1897
John D. Rockefeller Sr., his son John D. Rockefeller Jr., and his chief philanthropic advisor, Frederick T. Gates, discuss proposals to fund biomedical research as a path toward improving medicine, which Rockefeller felt lacked scientific rigor.

1900
Rockefeller Sr.’s first grandchild, three-year-old John Rockefeller McCormick, becomes ill with scarlet fever, from which he soon dies. Rockefeller decides to create a research institute devoted to the study of infectious disease.

1901
The Rockefeller Institute for Medical Research is founded, emphasizing diversity in the biomedical sciences. Breaking away from major European centers of its day, the Institute simultaneously pursues research in multiple areas. Rockefeller Sr. pledges $200,000 to the planned institute.

1902
Bolstered by the success of early grant recipients, Rockefeller Sr. increases his pledge to $1 million. Simon Flexner, a newly appointed professor of pathology at the University of Pennsylvania, is named the institute’s first director.

1903
The institute purchases one of the last tracts of the Old Schermerhorn Farm and starts planning its first permanent building.

1906
Founders Hall, the institute’s first building, is completed. Flexner begins recruiting scientists, offering independence, generous salaries, well-equipped facilities, and capable assistants.

1909
Welch Hall is built as the university’s library and dining room, in which scientists gather daily for lunch and to have freewheeling discussions of work in progress.

1911
Peyton Rous makes the discovery that cancer can be caused by a virus.

1912
Alexis Carrel becomes the first scientist affiliated with Rockefeller to win a Nobel Prize, for his achievements in suturing blood vessels.

1916
A department of animal pathology is established in Princeton, New Jersey, in response to an outbreak of hog cholera that was devastating American farmers.

1917
Work at the Rockefeller Institute is given over to the war effort. Classrooms are built to train military medical officers in wound treatment and techniques of pathology.

1929
Oswald Avery, Colin MacLeod, and Maclyn McCarty publish their landmark paper identifying DNA as the "transforming" substance of heredity.

1944
A History of Innovation

Welch Hall is built as the university’s library and dining room, in which scientists gather daily for lunch and to have freewheeling discussions of work in progress.
From the beginning, founder John D. Rockefeller Sr. and director Simon Flexner rejected the structures of the day’s academic and medical institutions. Flexner proposed that the institute be organized around independent investigators, without departments, and that its mission include the study of any science that might shed light on health and disease. He made scientific talent, not field of study, the chief criteria for his hiring.

For well over a century, these principles have guided Rockefeller and have paved its path to success. After early, dramatic advances in the treatment of infectious disease, Rockefeller researchers went on to modernize the science of cell biology; to establish the basis of genetics; and eventually to conduct pathbreaking studies in immunology, neuroscience, and structural biology.
Award-Winning Science

Rockefeller faculty have been recognized for their accomplishments with the world’s most prestigious prizes and awards. We have had a remarkable 25 Nobel Prize winners in the sciences, but that’s not the whole story. Our scientists are also recognized by scholarly societies, receive highly competitive early career awards, and are honored by the world’s most prestigious scientific organizations.

Rockefeller's record of achievement dates back to 1912, when the first Rockefeller scientist was awarded a Nobel Prize in medicine just 11 years after the university’s founding. Since then, an additional 24 scientists have received Nobels, most recently in 2017. In addition, 23 scientists have been presented with the Albert Lasker Award, 18 have received the Canada Gairdner International Award, and 20 have been given the National Medal of Science, the nation’s highest scientific honor.

The legacy of awards has continued into the modern era. Three Rockefeller scientists have been recipients of the Breakthrough Prize in Life Sciences, established in 2013; at $3 million, it is the largest monetary award in the sciences. Rockefeller also has winners of the Wolf Prize, the Robert Koch Award, the Japan Prize, the Benjamin Franklin Medal, the Pasarow Foundation Award, the Blavatnik Award, the MacArthur Fellowship, and many others. Thirty-eight members of the current faculty — 40 percent — are members or foreign associates of the U.S. National Academy of Sciences, a body of distinguished scholars that give advice on scientific issues of national importance to both the federal government and the public. Eighteen have been elected to the National Academy of Medicine, which advises on health and science policy.
State-of-the-Art Campus

Seen from overhead, Rockefeller’s campus appears as an oasis of parkland abutting the glass, brick, and limestone of New York City. But behind our mature trees and beneath our vibrant gardens, laboratories buzz with activity. Our campus, which is growing by two acres with the construction of a dramatic new extension over the FDR Drive, is a place of both quiet contemplation and intense scientific energy. It’s also one of our most unique assets.

The university’s existing facilities include a modern research complex, completed in 2012, designed to foster interdisciplinary collaboration, and a recently renovated five-story library with a grand, historic reading room. With the new extension, known as the Stavros Niarchos Foundation–David Rockefeller River Campus, the university is just over 16 acres, a landscaped oasis on Manhattan’s Upper East Side. Our facilities include nine research buildings, two student residences, faculty housing, administrative buildings, lecture halls, and Caspary Auditorium, a neighborhood landmark. The centerpiece of the $500 million extension is the Marie-Josée and Henry R. Kravis Research Building, a 160,000-square-foot laboratory building capable of housing 26 labs. The new campus also has new administrative offices, a café, and a conference facility.

Rockefeller’s location across the street from Memorial Sloan Kettering Cancer Center, Weill Cornell Medicine, and NewYork-Presbyterian Hospital facilitates interinstitutional collaboration and allows it to share core facilities, housing, and even faculty and students. We also have connections with more than a dozen other institutions with bioscience programs in the New York City region, including major universities, research hospitals, and nonprofit institutions. As a burgeoning hub of bioscience activity, New York has become an attractive location for biotech startups that are redefining medicine for a new era.
Financial Support

The Rockefeller family gave the seed money to establish The Rockefeller Institute in 1901, and they have provided generous support for operations, endowment, and capital projects over the ensuing years. Today, the university is funded primarily by government grants and contracts, income from its endowment, and private grants and philanthropy.
Many foundations, corporations, and individuals support the research and educational programs of the university, helping to make possible modern laboratories, essential technologies, and affordable housing for young scientists. Private funding is especially important because it allows the university to provide investigators with the resources to pursue promising leads and undertake innovative research that would be considered too risky, unconventional, or controversial to qualify for federal grants. Support is also provided by the Howard Hughes Medical Institute (HHMI), which maintains a scientific unit on the Rockefeller campus. Fifteen members of the Rockefeller faculty are HHMI-supported investigators.

The university is currently engaged in a campaign to raise funds for faculty recruitment; investment in basic research, medical sciences, and new technologies; current operations including graduate and postdoctoral education; and the construction of the Stavros Niarchos Foundation–David Rockefeller River Campus, a two-acre extension of the campus.
81 scientists who are changing the face of biomedicine.
C. David Allis, Ph.D.

TRI-INSTITUTIONAL PROFESSOR • JOY AND JACK FISHMAN PROFESSOR, LABORATORY OF CHROMATIN BIOLOGY AND EPIGENETICS

All the cells in the human body have the same genes, but only a small percentage of genes are active in any given cell at any given time. Allis studies chromatin, the DNA–histone protein complex that packages the genetic information within each cell. Chromatin can facilitate or restrict access to specific genes, and serves as a means of gene regulation that lies outside of the DNA itself—the basis of a principle known as epigenetics.

Chromatin is the physiological template of the human genome. The histone proteins within chromatin, their posttranslational modifications, and the enzyme systems responsible for generating them are highly conserved through evolution. Meanwhile, nature has evolved sophisticated mechanisms to alter chromatin, and as a result, to regulate gene expression and other biological processes.

One such mechanism involves the addition or loss of chemical groups. The Allis lab is investigating how covalent histone modifications regulate biological processes in a variety of unicellular and multicellular eukaryotic models. Through enzymatic processes such as acetylation, methylation, phosphorylation, and ubiquitylation, histones are believed to function like master on/off switches that determine whether particular genes are active or inactive. Insights into the mechanisms that turn particular genes on or off could lead to better treatments.

The fact that histone proteins are often subject to frequent, high-density posttranslational modifications (PTMs) has led members of the Allis lab to hypothesize that PTMs are found in strategic locations along the histone tail as a way for the cell to deal, reversibly, with gene silencing or activation. The lab has been a front-runner in deciphering elaborate cross-talk relationships in the same histone tails (cis) or across distinct histone (trans) tails. These combinatorial changes appear to govern chromatin function in a variety of processes, and have been termed the “histone or epigenetic code,” a widely cited and influential hypothesis.

More recently, researchers in the Allis lab proposed that the mammalian genome is indexed by H3 variants to control whether genes are constitutively expressed or remain silent. Using biochemical approaches, the group has identified chaperone complexes that engage H3.3 selectively, depositing it into distinct regions of the genome. One of these chaperone systems is mutated in a significant fraction of patients who suffer from pancreatic cancers. H3 mutations are also highly enriched in pediatric gliomas. Allis and his colleagues hypothesize that these so-called oncohistone mutations can alter the recruitment and activity of histone-modifying and “reader” complexes, and therefore change the epigenetic landscape and gene expression. Recent studies have associated PTM “reader” dysregulation in human leukemia; efforts are in progress to develop new drugs that target this interaction.

Given the restricted distribution of H3 oncohistone mutations to various cancers, the Allis lab further hypothesizes that a cell lineage–specific cellular context is crucial for the ability of these mutations to mediate oncogenesis. Active investigations are underway to test this hypothesis with collaborators in clinically relevant settings, including human patients.

SELECTED PUBLICATIONS


Cells are constantly subjected to mechanical forces that originate either externally from the environment or internally from cellular machinery. The Alushin lab studies how cells use changes in the conformation of actin filaments within their internal skeletons to sense and respond to those forces. Over the long term, his group seeks to understand how changes to actin are linked to alterations in gene expression in development and disease.

Cells are supported by a cytoskeleton made of protein filaments that provide it with an internal structure and facilitate movement. Microtubules and actin are two of the predominant classes of filaments, and each has distinct roles. For instance, the intrinsic dynamics of microtubules drive cell division by separating duplicate sets of genetic material, while those of actin filaments power cellular movement. Both types of filaments additionally interact with hundreds of binding partners and serve as tracks for molecular motor proteins, providing the infrastructure for organizing and shaping the cell.

Alushin studies how these filaments, themselves macromolecular assemblies composed of repeating protein subunits arranged like steps in a spiral staircase, physically interface with collaborating proteins. To investigate these interactions, Alushin employs cryo-electron microscopy along with biochemical and biophysical approaches. During his doctoral studies, he and his colleagues produced the then-highest resolution images of microtubule structures. His graduate work also explored the basis for microtubules’ dynamic growth and shrinkage, as well as structures that attach chromosomes to microtubules to position them during cell division.

Alushin’s lab now focuses on actin’s contribution to cellular mechanosensation. Previous research suggests the pushing and pulling forces generated by a cell’s environment and its movement may cause actin subunits to change shape. To investigate these changes, his group is developing a novel approach to reconstruct and visualize deformations of the filaments at a structural level as they are pulled in opposite directions by myosin motors.

Alushin hypothesizes that cells gather information about the forces they are experiencing by “reading” these structural changes, and his lab seeks to identify the actin binding proteins that act as sensors to detect these changes. These sensors are believed to transduce mechanical forces into signals that prompt responses from the cell, such as migration or differentiation. Alushin is using cryo-electron microscopy to further define the interactions between actin and its many binding partners in order to better understand the context in which these sensors work.

Taken together, Alushin’s studies support a broader goal: to understand the means by which mechanical forces influence both a cell’s characteristics and its behavior. Short-term exposure to mechanical force can prompt cells to migrate, or, in the case of cancer, metastasize. Over the long term, meanwhile, forces can alter gene expression, causing new cells to mimic an existing environment. Alushin’s long-term goal is to explore this link between sustained mechanical forces and gene expression.
Cori Bargmann, Ph.D.
TORSTEN N. WIESEL PROFESSOR, LULU AND ANTHONY WANG LABORATORY OF NEURAL CIRCUITS AND BEHAVIOR

Genes, the environment, and experience interact to shape an animal’s behavior. *Caenorhabditis elegans*, a worm with just 302 neurons, shows considerable sophistication in its behaviors, and its defined neuronal wiring and genetic accessibility make it an ideal subject in which to study these interactions.

Using *C. elegans* as a model, Bargmann’s laboratory characterizes genes and neural pathways that allow the nervous system to generate flexible behaviors.

How do genes and the environment interact to generate a variety of behaviors? How are behavioral decisions modified by context and experience? The Bargmann lab is studying the relationships between genes, experience, and behavior in the nematode *C. elegans*, whose nervous system consists of only 302 neurons with reproducible functions, morphologies, and synaptic connections. Despite this simplicity, many of the genes and signaling mechanisms used in the nematode nervous system are similar to those of mammals. The ability to manipulate the activity of individual genes and neurons in *C. elegans* makes it possible to determine how neural circuits develop and function.

The animal’s most complex behaviors occur in response to smell, and these are at the heart of the lab’s research. *C. elegans* can sense hundreds of different odors, discriminate among them, and generate reactions that are appropriate to the odor cue. These behaviors can be traced from molecules, to neurons, to circuits, to behavioral decisions. In *C. elegans*, as in other animals, odors are detected by G protein coupled odorant receptors on specialized sensory neurons. The odors that activate one sensory neuron regulate a behavioral output such as attraction or avoidance. The lab studies the pathways from sensory input to behavioral output by quantitative analysis of behavior under well-defined conditions, genetic manipulation of animals or individual neuronal cells, and calcium imaging from neurons in living animals.

The lab also asks how a fixed nervous system generates flexible behaviors. For example, *C. elegans* is capable of learning the odors of different bacteria and avoiding those that previously made it ill. These learned olfactory behaviors are associated with neuromodulatory signals that lead to behavioral remodeling. Other neuromodulators shape spontaneous behaviors in reversible patterns over minutes or hours. This reversible rewiring occurs without apparent changes to the fixed anatomy of the nervous system, and uses conserved molecules like dopamine, serotonin, and oxytocin, which are implicated in human motivational and emotional states. The lab is currently studying how neuromodulatory systems affect the flow of information between neurons across different timescales.

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**SELECTED PUBLICATIONS**


The biology and evolution of retroviruses and eukaryotes are closely linked. Bieniasz seeks to define how host genes influence the replication of retroviruses, with an emphasis on human and primate immunodeficiency viruses. His lab seeks to characterize the host functions that retroviruses mimic, manipulate, and otherwise exploit, as well as the defenses cells have evolved against retrovirus infection.

The consequences of retroviral infection are diverse, and range from lethal immunodeficiency to benign insertion into the host genome. In addition to determining the functions of viral genes and proteins, Bieniasz’s research seeks to define how the replication of retroviruses is influenced by host genes and pathways. Some host functions are manipulated or exploited by retroviruses to enable replication, while others have evolved specifically to provide defenses against retrovirus infection.

A central aspect of Bieniasz’s work is to define how virus components are generated and assembled into infectious particles. His earlier work, using biochemical, genetic, and imaging approaches, revealed many details of the virus particle assembly process, including the recruitment of host proteins that drive assembly and particle budding. He is currently interested in defining how viral RNA splicing, stability, transport, translation, and packaging into virions are regulated.

Another major area of interest is the intrinsic host defenses against retroviruses. Throughout their evolution, most eukaryotic organisms have frequently been colonized by retroviruses, and selection pressures imposed by ancient retroviral infections are likely responsible for shaping the array of host defense mechanisms that currently influence susceptibility to modern retroviruses such as HIV-1. The Bieniasz lab works on several types of intrinsic defenses to understand the mechanistic details by which these processes inhibit retrovirus replication. Two such inhibitors, discovered in the Bieniasz lab, include tetherin, which inhibits the release of a wide range of enveloped viruses from the surface of infected cells, and Mx2, which targets the capsid of HIV-1 to inhibit viral entry into the nucleus of target cells. New types of antiretroviral defenses and the mechanisms by which they work are currently being investigated.

Infection of germ line cells has left a fossil record of ancient retroviruses, andBieniasz has pioneered the field of “paleovirology” by reconstituting functional versions of extinct retroviral proteins. Understanding how ancient retroviruses were extinguished may give clues about how to combat modern viral infections.

The Bieniasz lab is also working to derive more useful animal models of AIDS virus infection in monkeys and mice. Recently, his lab developed an HIV-1 strain that can cause AIDS in macaques. These new animal models should provide testing grounds for new forms of therapy and vaccination.
The Birsoy lab studies how metabolic pathways regulate biological processes and contribute to diseases including cancer, mitochondrial disorders, and inborn errors of metabolism. Using genetic and metabolomic tools, Birsoy studies the mechanisms by which human cells alter their uptake and use of nutrients to adapt to the genetic and environmental stresses observed in these disorders.

Through a series of chemical reactions collectively known as metabolism, an organism extracts and harnesses energy from organic matter. While the core components of this process are relatively well understood, little is known about how an individual cell rewires its metabolic pathways under varying circumstances, including disease. Using forward genetic approaches, Birsoy's lab studies the regulation of metabolism in mammalian cells with the long-term goal of developing therapies for relevant diseases. His group studies cellular metabolism in the contexts of cancer, mitochondrial disorders, and inborn errors of metabolism.

There is increasing evidence that genetic alterations modify the metabolic program of cells. Since cancer cells are dependent on these changes in metabolism for proliferation, there has been a great interest in exploiting these metabolic liabilities for cancer therapy. As a postdoc at the Whitehead Institute of MIT, Birsoy investigated cancer cells' metabolic response to the nutrient-deprived environment found within tumors. Using the Nutrostat, an instrument he designed to test cells’ response to low-nutrient environments, Birsoy discovered several biomarkers, including mitochondrial mutations for glucose sensitivity among different cancer cells. Subsequent experiments showed that these mutations conferred susceptibility to mitochondrial inhibition by biguanides, a class of diabetes drugs.

To expand upon his previous work, Birsoy's lab is systematically mapping out cancer cell dependencies on other nutrients, such as amino acids and lipids, while simultaneously looking for opportunities to exploit them for cancer therapy. Understanding the molecular basis for these dependencies will help unveil new metabolic programs and may aid in the development of innovative strategies for cancer treatment, including traditional compounds designed to inhibit intracellular enzymes as well as nutritional approaches to eliminate cancer-feeding metabolites from the blood.

Birsoy is also interested in understanding mitochondrial dysfunction, a common feature of many diseases including cancer and mitochondrial disorders. Current therapies are limited for mitochondrial disorders, which are characterized by multi-organ dysfunction, and symptom management remains the primary treatment option. This is due in part to a lack of validated drug targets and the absence of relevant disease models. Using a combination of genetic and metabolomic tools, Birsoy's lab is examining how mitochondrial dysfunction affects cellular metabolism to give rise to these various disease phenotypes.

In addition, the Birsoy lab studies inborn errors of metabolism, rare genetic disorders like organic acidurias, in which metabolites accumulate to toxic levels. This metabolite buildup causes a wide array of symptoms, including damage to the liver and brain. Birsoy's lab aims to better understand the mechanisms by which metabolites damage specific organs. A fuller understanding of these mechanisms may lead to novel therapeutic strategies for rare genetic disorders.
Sean F. Brady, Ph.D.

TRI-INSTITUTIONAL PROFESSOR • EVNIN PROFESSOR, LABORATORY OF GENETICALLY ENCODED SMALL MOLECULES

Natural products, especially genetically encoded small molecules, have a wide range of functions in biology and have proved very useful in the development of therapeutic agents. Brady’s research centers on the discovery and characterization of new, genetically encoded small molecules from microbial sources, with a special focus on those produced by uncultured soil bacteria, human commensal bacteria, and pathogenic bacteria.

One of the key revelations originating from large-scale sequencing of bacterial genomic DNA is that the approaches traditionally used for identifying new natural products only provide access to a small fraction of the biosynthetic gene clusters present in nature. These studies indicate that essentially all bacteria—from those with fully sequenced genomes to those that have not yet been cultured—are rich sources of unstudied natural products.

Using methods from molecular biology, organic chemistry, and microbiology, Brady is working to access the biosynthetic gene clusters responsible for these previously inaccessible natural products. The development of methods to do so should significantly increase the number and diversity of natural products available to test as probes of biological processes and therapeutic agents.

Brady's first research focus is the development of new strategies for studying genetically encoded small molecules produced by bacteria that have not been grown in the lab. Soil microbes that have not yet been cultured outnumber their cultured counterparts by at least two to three orders of magnitude, making uncultured bacteria one of the largest pools of genetic diversity that remain unexamined for potentially useful natural products. Brady has worked extensively on the development of genetic strategies to access the vast chemical and biosynthetic potential of uncultured bacteria. His approach—which involves extracting this previously inaccessible DNA directly from environmental samples and cloning it in easily cultured bacteria—has allowed for the construction of large libraries of environmental DNA, as well as the development of methods to screen these libraries. His work has shown that these libraries are a promising source of both new derivatives of pharmacologically important classes of natural products, as well as completely novel families of bioactive natural products.

Brady’s group is now mapping the presence of promising microbial gene clusters found in soil samples collected around the world. These maps may help guide the discovery of natural products by directing investigators to certain regions and environments.

The second focus of the Brady lab pertains to the chemistry of human microbiome-associated and pathogenic bacteria. It could one day lead to a better understanding of how commensal bacteria interact with their human hosts, and potentially address the problem of drug-resistant pathogenic bacteria. Brady uses phenotypic screening and bioinformatics methods to examine the small molecules produced by commensal and pathogenic bacteria. By studying the complex collections of small molecules used by these bacteria, he hopes to gain new insight into how bacteria interact with the world around them, and draw from these insights to determine how to better control both commensal and pathogenic bacteria.

**SELECTED PUBLICATIONS**


**AWARDS**

- Sinsheimer Fund Scholar, 2007
- Beckman Young Investigator, 2007
- Irma T. Hirschl/Monique Weill-Caulier Trust Research Award, 2007
- Searle Scholar, 2007
- Kenneth Rainin Foundation Innovator Award, 2013

**EDUCATION**

- B.A. in molecular biology, 1993
- Pomona College
- M.S. in organic chemistry, 1999
- Ph.D. in organic chemistry, 2002
- Cornell University

**POSTDOC**

- Cornell University, 2002

**POSITIONS**

- Fellow, 2002–2006
- Harvard Medical School
- Assistant Professor, 2006–2012
- Assistant Professor, 2012–2018
- Professor, 2018–
- The Rockefeller University
- Early Career Scientist, 2009–2015
- Howard Hughes Medical Institute
Atherosclerotic disease, the hardening of the arteries that underlies coronary heart disease, stroke, and peripheral vascular disease, is a complex genetic condition responsible for about 40 percent of the deaths in the United States each year. Breslow’s laboratory explores the genetic and environmental bases of atherosclerosis to determine what makes certain individuals more or less susceptible to this disease, and also pioneers novel therapies.

Susceptibility to atherosclerosis is associated with abnormal levels of plasma lipoproteins. Breslow’s studies have focused on molecules called apolipoproteins, which coat lipoprotein particles and determine their synthesis, processing, and breakdown.

His laboratory cloned the genes for most of the apolipoproteins and made induced mutant mouse models, including the first mouse model of atherosclerosis, to study how these genes function in vivo. The atherosclerosis model was made by knocking out the gene for apolipoprotein E (apo E), which is found on the surface of several lipoproteins. By breeding the apo E knockout trait to different inbred genetic backgrounds, Breslow and his colleagues produced varying amounts of atherosclerosis and evidence for modifier genes. Using these methods, the lab is identifying new genes and pathways involved in atherosclerosis susceptibility.

By using gene expression microarrays to identify mouse liver genes whose expression is regulated by dietary cholesterol, the Breslow lab has uncovered a new subclass of START-domain containing genes linked to cholesterol transport within cells. Using the same approach, they also discovered another cholesterol-regulated gene coding for a protein called PCSK9. His lab showed that PCSK9 was capable of destroying the LDL receptor, which clears LDL from the bloodstream. These findings helped the development of two monoclonal antibody inhibitors of PCSK9, approved by the FDA in 2015 for further lowering LDL cholesterol levels in patients receiving statins, as well as in patients with statin intolerance.

Other past accomplishments include discovering that human genetic variation in apo E resulted from three different apo E types. Specific patterns of inheritance of these apo E types are linked to LDL cholesterol levels, atherosclerosis, Alzheimer’s disease, and even longevity. Breslow was the first to identify, at the molecular level, a human mutation causing atherosclerosis susceptibility, an apo A-I mutation that caused HDL deficiency and premature coronary heart disease. His research has also shown that overproduction of apo CII is a major determinant of high triglyceride levels and that triglyceride-lowering drugs called fibrates act mainly by decreasing apo CII production.

Recently, the Breslow lab discovered a serum peptide, generated at sites of inflammation by factor XIIa, that dramatically promotes CCR7-induced leukocyte migration. A medicinal chemistry effort has generated sensitive and specific small molecular weight inhibitors of factor XIIa that prevent the generation of this peptide, and preliminary in vivo studies have shown efficacy in mouse models of inflammatory disease.

In a collaborative project with Jeffrey M. Friedman and investigators at Columbia, Harvard, MIT, and Yale, Breslow has studied an isolated population on the Micronesian island of Kosrae. Through family data, clinical and laboratory tests, and determination of genetic markers in each adult Kosraen, the investigators have identified genes that predispose an individual to obesity, diabetes, abnormal lipid levels, and high blood pressure.
Ali H. Brivanlou, Ph.D.

HUBERT AND HARRIET HEILBRUNN PROFESSOR, LABORATORY OF STEM CELL BIOLOGY AND MOLECULAR EMBRYOLOGY

Brivanlou uses in vitro attached human embryos and genome-edited “synthetic embryos” derived from human embryonic stem cells to unveil the molecular, cellular, and embryological basis of early human development. His studies employ high-resolution quantitative approaches, and span both theoretical physics and molecular embryology. The lab is particularly interested in the emergence of the human brain and modeling neurodegenerative diseases.

A fertilized egg and embryonic stem cells are the only naturally occurring cells that have the potential to generate all cell types in an organism, both of the adult and the embryo. The emergence of discrete cell fates and key structures in the early embryo occurs gradually by cell-to-cell communication that is highly orchestrated in time and space. Brivanlou’s research focuses on deciphering this signaling network. His work has contributed to key discoveries in developmental biology, including the surprising fact that in the absence of signaling from their neighbors, all embryonic cells will default to a telencephalic fate and give rise to the most anterior structure of the brain.

Previous work conducted in animal models has provided a strong foundation for Brivanlou’s research involving human embryonic stem cells. Current work focuses on the molecular dissection of embryonic stem cells, including their capacity for self-renewal and their ability to differentiate into a broad range of cell types.

The Brivanlou lab has helped establish a groundbreaking system to study the molecular and cellular processes that occur during human embryo implantation, a critical stage of development when the forming embryo attaches to the uterus. The technique vastly expands scientists’ ability to answer basic questions about human development and understand early pregnancy loss. The work has unveiled an unexpected self-organizing ability of the human embryo that can be studied for up to 1.4 days of human development. This ability can be induced in human embryonic stem cell colonies grown in geometrically defined substrates to generate self-organizing “synthetic human embryos” that allow studies after the second week of development.

Fundamental studies in the Brivanlou laboratory are not only offering insights into human reproductive biology and development, but also into specific diseases. The group has demonstrated that the origin of Huntington’s disease can be traced to the earliest stage of human development and the formation of the nervous system, and thus is a developmental disorder that ultimately manifests its destructive effects in adulthood.

As an international leader in the effort to understand the intricacies of human embryonic stem cells and to harness their therapeutic potential, Brivanlou has also played a key role in establishing scientific standards for human embryonic stem cell research. In addition, he and his colleagues have derived several human embryonic stem cell lines that were among the first to be included in the National Registry at the National Institutes of Health, and are now used in laboratories worldwide.

The Brivanlou lab has a tradition of collaborating closely with the theoretical physics groups at Rockefeller. A close and synergistic collaboration for the past decade with Eric D. Siggia has led to the development of high-resolution quantification tools that have been instrumental in studying synthetic human embryos. Brivanlou’s lab has both molecular embryologists and theoretical physicists working side-by-side to unravel the molecular network involved in human development.
Casanova studies the human genetic determinism of pediatric infectious diseases, including viral, bacterial, fungal, and parasitic infections. He is interested in identifying single-gene mutations that compromise the immunity of otherwise healthy children, adolescents, and young adults who are vulnerable to specific infectious diseases.

Casanova’s laboratory aims to understand why some children, adolescents, and young adults develop a severe clinical illness in the course of infection, while most people exposed to the same microbe remain unharmed. Work in the laboratory has revealed that single-gene inborn errors of immunity in young people can confer severe and selective vulnerability to certain infectious illnesses during primary infection. Conversely, the genetic basis of corresponding illnesses during secondary infections that typically occur in older patients is unclear and may result more from complex inheritance mechanisms. This work provides theoretical and experimental support for a human genetic theory of infectious diseases.

With Laurent Abel, at the Imagine Institute of the Necker Hospital for Sick Children in Paris, Casanova’s work identifying and characterizing these genetic defects has modified the field’s dominant paradigm, which for decades has associated rare single-gene defects to vulnerabilities to multiple infectious diseases, and multiple genetic variations to common infectious diseases. Abel is leading the mathematical “dry lab” at Necker and Rockefeller, whereas Casanova heads the experimental “wet lab” in both locations.

Casanova’s team has identified inborn errors of immunity conferring increased susceptibility to a variety of pathogens. For example, they discovered that mutations in IRF7 provide the molecular genetic basis for a predisposition to severe influenza. Likewise, they have found that errors in IL-17 immunity confer unusual vulnerability to chronic mucocutaneous candidiasis; that disruptions in the TLR3 pathway predispose patients to herpes simplex encephalitis; and that mutations in CARD9 contribute to invasive fungal disease.

In identifying errors in IFN-γ immunity responsible for a vulnerability to mycobacterial infections, Casanova and Abel discovered the first cases of monogenic predisposition to tuberculosis in children.

These discoveries have revealed that many immunological circuits that were previously thought to play a broad role in host defense are largely redundant and essential for immunity against one or a few specific infections only. They contribute to defining the function of host defense genes in the natural ecosystem in which human populations live and are subjected to natural selection.

Revealing monogenic holes in the immune defense of otherwise healthy children also has profound clinical implications, offering medical worldwide the possibility of molecular diagnosis and genetic counseling, as well as treatments aimed at restoring a deficient immune response. Children with impaired IFN-γ production, for example, are prone to tuberculosis and benefit from IFN-γ, whereas patients with impaired IFN-α/β production are prone to herpes simplex encephalitis or severe influenza and may benefit from IFN-α.
Mass spectrometry is a powerful analytical technique that can accurately measure the molecular masses of individual biomolecules, including peptides, proteins, and large intact protein assemblies. Chait’s lab specializes in the development of mass spectrometers and other tools and methods for investigating a variety of biological and biochemical phenomena.

Knowledge of the makeup, structure, and dynamics of protein assemblies is key to understanding many cellular processes. The Chait lab devises new tools, including those based on quantitative mass spectrometry, to identify and study the protein interactions within these assemblies. Another primary goal of the lab is to derive a functional definition of cellular protein assemblies.

The lab has recently developed potent approaches for elucidating proximal, distal, and transient protein–protein interactions in cellular milieus, and for determining distance restraints between amino-acid residues within large protein assemblies by chemical cross-linking and mass spectrometry. The long-term goal of this research is to develop a molecular microscope for defining cellular systems with scales spanning all the way from the dimensions of a cell to the atomic resolution of molecules.

The Chait lab also serves as the National Resource for the Mass Spectrometric Analysis of Biological Macromolecules, now in its 44th year of funding from the National Institutes of Health. Its major areas of activity are basic research in mass spectrometry and ion chemistry. Work is currently under way in Chait’s lab to develop novel tandem mass spectrometry (MS/MS) instrumentation for ultrasensitive, rapid, and comprehensive characterization of proteins. Most MS/MS is inherently extremely wasteful, since, at any given time, all ion species except for the one that is specifically isolated are thrown away. The Chait lab is investigating new strategies for overcoming this inefficiency using high-capacity traps to produce MS/MS information on all the trapped ion species without the usual scanning losses. The lab is also developing novel instrumentation for carrying out massively parallel mass spectrometry.

Another aim of the lab is to develop new methods to study viral–host protein interactions during the progression of highly dynamic viral infections. In particular, members of the Chait lab are developing techniques for simultaneously visualizing individual viral proteins in host cells and identifying their interacting macromolecular partners in space and time. Some of these techniques are already facilitating a greater understanding of both the molecular details of viral infections and the biology of the cell.

Most recently, the lab has developed new mass spectrometric techniques for defining repertoires of high-affinity antibodies that develop within humans and llamas against any given antigen, including endogenous human antibodies that are protective against HIV. They have also developed new methods for improving the sensitivity of electrospray ionization mass spectrometers.
Jue Chen, Ph.D.

Cells use certain membrane proteins to pump molecules in or out of cellular structures, moving them from areas of low concentration to high concentration. Chen studies ABC transporters, a class of membrane transporters that power themselves using a form of chemical energy known as ATP. She investigates these proteins’ role in normal cellular processes and in disease, including drug resistance and cystic fibrosis.

Scientists have identified about 2,000 ATP-binding cassette (ABC) transporters found in all types of cells; 48 of these occur in human cells. These proteins play a role in many important cellular processes, pumping an array of molecules—from nutrients to toxins and cellular building material—through the membrane bilayer. Because this molecular cargo is moving from low to high concentration, the transporter protein consumes energy.

The maltose transporter protein, a type of ABC transporter, brings a sugar known as maltose into a bacterial cell to support growth. Using x-ray crystallography, Chen and her colleagues have devised a way to visualize how this transporter converts the chemical energy of ATP hydrolysis into mechanical work through a series of conformational changes.

Chen’s interests have recently shifted to ABC transporters involved in the immune system and disease. For example, her lab now focuses on an ABC transporter known as P-glycoprotein. Discovered in the 1970s, P-glycoprotein recognizes an array of structurally related compounds and pumps them out of the cell. It plays a Jekyll-and-Hyde role in human health: When the cell in question is cancerous and the compounds are therapies targeting some aspect of the cell’s internal machinery, P-glycoprotein’s action reduces the effectiveness of chemotherapy. But, by doing essentially the same thing, P-glycoprotein also helps maintain the integrity of the blood–brain barrier by keeping certain types of molecules from entering the central nervous system.

However, this latter function can create problems for drugs that need to get into the central nervous system. Using x-ray crystallography, Chen’s lab resolved the structure of P-glycoprotein and continues to study how it works.

Her lab has also begun investigating another drug-resistant transporter known as MRP1. Like P-glycoprotein, MRP1 removes chemotherapy agents and contributes to the blood–brain barrier. It also ejects hormones, pro-inflammatory molecules, and antioxidants from cells. Using electron cryo-microscopy, her lab has generated detailed reconstructions of MRP1, uncovering the structural basis for its ability to transport such a wide variety of cargo, as well as capturing the first chemical interactions between a drug-resistant transporter and a cargo molecule, leukotriene C₄.

In other recent work, her lab has resolved long sought-after molecular structures for the cystic fibrosis transmembrane conductance regulator (CFTR), mutations that can give rise to the genetic disorder cystic fibrosis. This work revealed why CFTR is the only ABC transporter to function as a channel, and offered new insight as to how it opens and closes. Chen and her colleagues have also explored how mutations interfere with CFTR to cause disease.

Chen’s goal is to continue to combine structural and functional work to reveal the molecular mechanisms of these multidrug transporters and CFTR, with an eye toward developing new, improved therapies for a variety of disorders, including cancer and cystic fibrosis.

SELECTED PUBLICATIONS
Living populations have “ensemble properties,” such as birth rates, death rates, and growth rates, that are not characteristics of any individual. Cohen develops concepts helpful for understanding ensemble properties of human and non-human populations, and tests these concepts in applications to human fertility, mortality, and migration; farms, fisheries, forests, weather patterns, and wildlife; infectious diseases; and food webs.

The human species is a node in a network of feeding relationships, known as a “food web,” with thousands of other species. Species that humans eat are conventionally studied as part of agriculture. Species that eat humans, which are mainly the agents or vectors of infectious diseases, are studied in epidemiology. Humans, the species humans eat, and the species that eat humans are nodes in a global food web, studied in ecology. The global food web includes many species not directly linked to humans by feeding and strongly interacts with the physical and chemical environment.

Cohen and his colleagues aim to offer insights that can help manage the global food web for the well-being of humans and other species. They combine the perspectives of demography, agriculture, epidemiology, ecology, and environmental sciences. Their work uses concrete problems to motivate the development of new concepts for understanding populations and aims to crystallize these concepts into mathematical, statistical, and computational tools applicable to scientific and practical problems.

For example, Cohen and colleagues study Chagas disease (also called American trypanosomiasis), an insect-borne chronic infectious disease that affects children in Latin America and eventually kills many young adults in their prime years of work and family rearing. No vaccine is currently available to prevent infection because the affected people are poor and commercial incentives to develop a vaccine are weak. Also, the drugs available for treatment are toxic. Cohen collaborates with Argentine colleagues who conduct field studies of Chagas disease to understand the ecology of disease transmission within and among households in poor rural villages in northwest Argentina. Based on data from these field studies, they develop mathematical models of the relations among humans; domestic animals like dogs, cats, chickens, and goats; the insects that transmit infection; and the trypanosome that causes disease. Their findings lead to specific recommendations of low-technology, low-cost interventions to prevent infection of people at risk.

Cohen’s lab also views weather patterns as a population. Cohen and colleagues showed recently that severe tornado outbreaks have become more common over time, not necessarily because of a changing climate. Both the average and variance of tornadoes per outbreak increased during the last half-century, suggesting that outbreaks with an extreme number of tornadoes are more likely in the future. The relationship between the average and variance in this case follows a power law known in population ecology as Taylor’s law.

This same power-law relation of variance to mean occurs not only in ecology, but also under other names in other fields of science, and has provided insights into many systems. Cohen and colleagues are studying Taylor’s law theoretically and empirically in bacteria, trees, fish, voles, humans, and other species, including the insects that transmit Chagas disease, and are exploring its practical applications to sampling, projection, and management.
Obesity has been estimated to threaten the health of more than 600 million people worldwide and more than one-third of the U.S. population. As a physician-scientist focusing on obesity and metabolic disease, Cohen investigates the molecular origins of metabolic dysfunction related to obesity with the ultimate goal of developing therapies to break the link between them.

Obesity can bring with it myriad serious and even potentially fatal health problems, including cardiovascular disease, type 2 diabetes, and cancer. But these conditions and the timing of their onset are not universal; they develop much later for some patients than others, and some escape almost entirely. A number of reasons—genetics, diet, physical activity, and type of fat—contribute to this variability. Cohen focuses on understanding the molecular underpinnings of obesity-related diseases.

Epidemiological studies have shown visceral adipose tissue, stored around the abdomen, increases risk for illness and death. Meanwhile, subcutaneous adipose deposits around the hips and buttocks do not raise these risks and may even be protective. Evidence suggests the type of adipocytes within these two tissues is responsible for the dichotomy.

In visceral fat, white adipocytes warehouse triglycerides in large droplets. In obesity, this tissue is marked by inflammation and an increased accumulation of immune cells. However, other types of adipocytes may have neutral or even beneficial effects. Brown adipocytes can defend body temperature by converting the chemical energy in glucose and triglycerides into heat and may also make significant contributions to adult metabolism. Likewise, a third type, beige adipocytes, can dissipate energy just like brown adipocytes when activated by cold or certain hormones. In rodents, beige adipocytes occur in clusters surrounded by white adipocytes in subcutaneous fat, suggesting the reason for the neutral to beneficial effects of that tissue. The location and physiological role of beige adipocytes, which are also present in humans, is not yet fully defined.

Using animal and cellular models and translational approaches in humans, Cohen investigates the transcriptional basis for the harmful and health-protecting effects of fat deposits and the adipocytes they contain. Ultimately, he hopes to develop ways to engineer healthier fat by manipulating the regulation of traits associated with different types of adipocytes.

As a postdoc, Cohen identified a promising target for this approach, PRDM16, which binds in a complex with other proteins to regulate gene expression. Cohen and his colleagues found PRDM16 acts as a molecular switch that determines some of the key functional differences between visceral and subcutaneous fat. It does so by activating beige adipocytes, prompting them to burn calories rather than store them. When they knocked out the PRDM16 gene in mice, beige adipocytes no longer functioned properly, and the animals developed obesity, insulin resistance, and fatty liver. Meanwhile, their subcutaneous fat came to resemble visceral fat, both on molecular and morphological levels.

Cohen is now investigating whether a lack of PRDM16 produces the negative health effects associated with visceral fat or whether some other regulatory factor is involved. With mouse models developed as part of his work on transcriptional control, Cohen is also studying the interactions between adipocytes and conditions such as hypertension, cardiovascular disease, and cancer.
When blood vessels break, platelets stop the bleeding by adhering to the damaged vessel walls. Coller’s research focuses on molecular interactions between blood cells and blood vessels, and on new therapies for thrombotic diseases such as heart attack and stroke.

Because platelets play a vital role in blood coagulation, deficiencies in their numbers or function can result in excessive bleeding. But when platelets adhere to and aggregate on blood vessels narrowed by atherosclerosis, they can close off the blood vessel and cause a myocardial infarction (heart attack) or stroke.

By studying the receptors responsible for platelet aggregation and patients who genetically lack the receptors, Coller established the platelet αIIbβ3 (GPIIb/IIIa) receptor as an important target for antithrombotic therapy. This led him to develop monoclonal antibodies to the platelet αIIbβ3 receptor that inhibit platelet aggregation. Working with scientists at Centocor, Coller helped develop a derivative of one of these antibodies into the drug abciximab, which was approved in 1994 to prevent ischemic complications of percutaneous coronary interventions, such as stent placement in patients with myocardial infarction and related conditions. More than five million patients worldwide have been treated with abciximab.

Current research in Coller’s lab focuses on multiple areas of platelet physiology. Among them is the genetic disorder Glanzmann thrombasthenia, which produces hemorrhage as a result of an abnormality of the platelet αIIbβ3 receptor. Coller and his lab members are studying the precise genetic and protein abnormalities responsible for the disease, as well as variants in the genes for the receptor (ITGA2B and ITGB3) identified in the general population by next-generation sequencing, such as stent placement in patients with myocardial infarction and related conditions. More than five million patients worldwide have been treated with abciximab.

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Other areas of blood and platelet physiology that the lab is studying include:

- **Integrin structure and activation.** Integrins, including platelet αIIbβ3 and αVβ3, are transmembrane glycoprotein receptors. Through site-directed mutagenesis, molecular dynamics, electron microscopy, and x-ray crystallography studies, the lab is studying the mechanisms by which the receptors undergo a transition from an inactive to an active conformation with high affinity for ligands. Most recently, nanodisc technology coupled with electron microscopy and three-dimensional reconstruction have been employed to address these questions.

- **High-throughput screening and structure-guided design.** The Coller lab identified a compound, RUC-1, that inhibits ligand binding to platelet αIIbβ3. Structure-guided modifications of it led to the development of another compound, RUC-4, that is approximately 100 times more potent and has a novel mechanism of action as a pure antagonist. RUC-4 is currently being developed for prehospital therapy for myocardial infarction.

- **Platelet TGF-β1.** The Coller lab discovered that platelet TGF-β1 can be activated by shear forces, and studies are under way to assess the biological significance of this finding in several model systems.

- **Integrin αVβ3.** With support from the Tri-Institutional Therapeutic Discovery Institute, the Coller lab is studying the impact of pure antagonists of αVβ3 on a variety of pathological processes, including sickle cell disease, osteoporosis, and herpes virus infection.
Cell cycle control involves coordinated production and destruction of proteins that activate cyclical events required for precise cell duplication. Cross uses a variety of approaches to investigate cell cycle control at the molecular level.

Using budding yeast as a model system, Cross uses both genetic and biochemical approaches to investigate the molecular basis of cell cycle control. He seeks to understand how critical regulatory proteins called cyclins control cell cycle progression, both through their timely degradation and through their ability to be highly selective of the molecules with which they interact.

The laboratory is interested in systematic approaches to cell cycle control, including mathematical modeling. Researchers in the Cross lab are developing mathematical models that represent control of the cell cycle and are creating single-cell imaging methods for regulation of gene expression and protein localization through the cell cycle.

A second project concerns cell cycle control in the green alga Chlamydomonas, which is a good microbial genetic model for the plant superkingdom. Plant genetics is challenging because of long generation times, diploid genetics, and ancient polyploidizations that result in many genes being present in multiple functional copies, masking loss-of-function phenotypes. Chlamydomonas, with essentially a full plant genome with respect to core cell biology including cell cycle regulation, has almost all of its genes in single copy, is haploid, and is amenable to classic microbial genetics, as well as modern molecular methods. The lab is creating a systematic collection of mutations in all genes involved in Chlamydomonas cell cycle control, and is using these mutants and other tools for focused studies on similarities and differences in eukaryotic cell cycle control across kingdoms.
Darnell's work identifying the target proteins for a group of rare brain disorders has led to an emerging understanding of the roles of RNA regulation, including the discovery that neurons make a unique set of RNA-binding proteins. These interests grew from studies of paraneoplastic neurologic disorders (PNDs), diseases thought to arise when certain tumors—typically breast, ovarian, or lung cancers—start making proteins normally unique to the brain.

Using a combination of biochemical and genetic approaches, Darnell's lab discovered that the immune systems of PND patients thwart tumors with what is essentially an antiviral response: CD8+ killer T cells that recognize the neuronal antigens present within their tumors. The lab also found that apoptotic tumor cells serve as potent instigators of the T cell immune response and has worked on developing cancer vaccines to mimic PND tumor immunity. Their work demonstrating that killer T cells mediate naturally occurring human tumor immunity has provided key support for the emerging field of immuno-oncology.

This research merged with studies of PND antigens: What is their normal role in neurons, and why do tumors induce their expression? These questions led Darnell's lab to discover and explore the function of neuron-specific RNA-binding proteins in the mammalian brain. Core studies of RNA regulation focused on the neuronal actions of the PND antigens Hu (nElavl), Nova, and the related protein FMRP whose function is lost in fragile X syndrome. The lab then expanded these investigations to include other proteins, such as Argonaute (which works with microRNAs to regulate messenger RNA), as well as Pbp2, Mbln2, and Rfox. To understand the biochemistry of these proteins in the brain, the lab developed a general and powerful method called cross-linking immunoprecipitation, or CLIP, to create genome-wide maps of RNA-binding protein interaction sites in living tissue. CLIP, together with the analysis of knockout mice and bioinformatic approaches, led to the discovery that the position of protein binding in the messenger RNA is a prime determinant of the outcome of alternative splicing or polyadenylation, general rules applicable to many splicing factors. Recent computational improvements in the analysis of CLIP maps have allowed robust genome-wide predictions of combinatorial RNA regulation and single-nucleotide resolution of such sites in the brain.

The lab has also developed functional insight into RNA dysregulation in disease, including that mediated by FMRP in autism spectrum disorders, by Aga in hepatitis infection, by nElavl in Alzheimer's disease, and by Nova in axonal guidance and brain development. Studies with Nova have led to insights into the balance of neuronal inhibition, excitation, and control of spinal motor neurons, leading to new approaches to study neurodegenerative disorders such as Lou Gehrig's disease.

Darnell's interest in applying high-throughput genomics to better understand RNA regulation in human disease led to his leadership role at the New York Genome Center.
RNA, the blueprint for proteins, is made by a complex molecular machine, the DNA-dependent RNA polymerase, present in all cells. Using bacteria as a model organism, Darst’s research explores the mechanism and regulation of transcription by determining three-dimensional structures of RNA polymerase and associated proteins. This work has implications for understanding how gene expression is controlled in many organisms.

In all cellular organisms, RNA is synthesized by a complex molecular machine, the DNA-dependent RNA polymerase (RNAP). In its simplest bacterial form, this enzyme comprises four subunits with a total molecular mass of approximately 400 kDa. The Darst lab focuses on highly characterized prokaryotic RNAPs, which share their basic structure and catalytic function with more complex archaeal and eukaryotic enzymes but are controlled by a much simpler set of regulatory factors.

The basic elements of the transcription cycle—initiation, elongation, and termination—were elucidated through the study of prokaryotes. The RNAP catalytic core combines with initiation factors (called α factors in bacteria) to generate a holoenzyme. It locates promoter sequences within the duplex DNA, forms the open promoter complex (RPo) by unwinding the DNA surrounding the transcription start site, initiates the synthesis of an RNA chain, and elongates the RNA processively in an elongation complex (TEC) while translocating itself and the transcription bubble along the DNA template. Then, finally, it releases itself and the completed transcript from the DNA when termination signals are encountered.

The Darst lab used x-ray crystallography and cryo-electron microscopy to determine the structure of all stable RNAP complexes that mark the transcription cycle (the RNAP core enzyme, holoenzyme, open promoter complex, and elongation complex). These complexes interconvert through transient intermediates involving large conformational changes in the nucleic acids, RNAP, or both. At every stage of the transcription cycle, RNAP function is modulated by interactions with extrinsic regulatory factors. Even in “simple” bacteria, more than 100 RNAP regulators have been identified. Moreover, bacteriophage have evolved extrinsic factors that use ingenious mechanisms to subvert the host transcription process for their own purposes.

Darst and his colleagues are seeking a detailed structural and functional understanding of the entire transcription cycle—knowledge that will be essential to explain the fundamental control of gene expression and to target RNAP with small-molecule antibiotics. Moreover, a complete understanding of how the cycle is driven by a complex molecular machine that uses binding and chemical energy to effect conformational changes—and it is modulated by regulators—is of fundamental interest. The researchers are using a combination of x-ray crystallography, cryo-electron microscopy, and other biophysical and biochemical approaches to fill the gaps in our understanding of the bacterial transcription cycle, particularly with regard to the large regulatory complexes and unstable transition states between the cycle’s stable states.

A related research program in the laboratory, led by senior research associate Elizabeth A. Campbell, seeks to understand the transcription cycle of the human pathogen Mycobacterium tuberculosis to aid in the development of new antibiotics.
The lab studies telomeres, protective elements at the ends of chromosomes critical for the stability and maintenance of genetic information. Flawed telomere function can cause genomic alterations found in cancer, and the gradual loss of telomeres contributes to the aging of human cells. de Lange seeks to understand how telomere protection is established and what happens when telomere function is lost during the early stages of tumor formation.

Research in the de Lange lab focuses on mammalian telomeres, which are made up of long arrays of double-stranded TTAGGG repeats that end in a single-stranded 3' overhang. These telomeric repeats wither away in a shortening process associated with cell proliferation. Telomerase can counteract this attrition and stabilizes telomeres by adding back telomeric repeats. However, this enzyme is absent from most human somatic cells, which eventually die due to the depletion of their telomere reserve.

Cancer cells, on the other hand, usually reactivate telomerase to achieve unlimited proliferative potential. The goal of de Lange's research is to understand how telomeres protect chromosome ends, and what happens when telomere function is lost during the early stages of tumorigenesis before telomerase is activated.

The lab identified a six-subunit protein complex, which they named shelterin, that specifically binds to telomeres. Using Cre-mediated conditional deletion in mouse embryo fibroblasts, de Lange and her colleagues determined the fate of telomeres lacking one or more of the six shelterin subunits. This work showed that cells lacking shelterin perceive their natural chromosome ends as sites of DNA damage.

Six distinct DNA damage response pathways are repressed by shelterin. Two DNA damage signaling pathways, initiated by the ATM and ATR checkpoint kinases, inappropriately respond to chromosome ends that lack shelterin. In addition, shelterin represses three DNA double-strand break repair pathways at telomeres as well as two types of nonhomologous end joining and homology-directed repair, which have detrimental outcomes at telomeres. Finally, shelterin protects telomeres against a sixth threat: the inappropriate resection of the telomeric DNA by nucleases.

de Lange's group is now working to determine the mechanism by which each shelterin protein inhibits its designated pathway, and how loss of telomere protection contributes to genome instability in human cancer. The researchers provided a major mechanistic insight in identifying the t-loop structure of telomeres in which the single-stranded overhang is inserted in the double-stranded repeat array of the telomere, thereby hiding the telomere end from the DNA damage response. Recent data has shown that the TRF2 component of shelterin is required to establish or maintain this structure. Since TRF2 is responsible for the repression of the ATM kinase pathway and non-homologous end joining, it is likely that the t-loop structure is critical to prevent these two pathways from acting inappropriately on chromosome ends.

SELECTED PUBLICATIONS
Wu, P. et al. Telomeric 3' overhangs derive from resection by Exo1 and Apollo and fill-in by POT1b-associated CST. Cell 150, 39–52 (2012).
The description and prediction of natural events that exhibit erratic behavior, such as whorls in fluids, remain challenges in physics and mathematics. Feigenbaum's laboratory helped establish the field of chaotic dynamics, which seeks the understanding of just such phenomena. Its overall goal is to enlarge the applicability of mathematics to science.

Feigenbaum is a pioneer in the science of "chaos," the mathematics of erratic dynamical systems—objects with unpredictable behavior and an attendant fractal geometry.

Chaotic motion shows a lack of predictability despite the total absence of any random ingredients. While the various constraints on a system, such as bounded resources, can allow it to move regularly on a smooth space, its chaotic motion lies in a highly complicated subspace—a so-called strange attractor.

Using computers and inventing mathematics, Feigenbaum developed a full, precise mathematical description of systems during their transition from order to disorder—for example, a dripping faucet changing from a steady drip into an erratic one. The mathematics that underlies this changeover holds true for all systems undergoing this "period doubling" onset of chaos, with all scaling details identically independent of a system's precise nature, including fluctuating animal populations, electrical signals in circuits, lasers, and various chemical reactions. Feigenbaum has shown that all these phenomena prominently exhibit numbers determined by his theory, for example 4.6692016…, a constant of nature called Feigenbaum's constant that determines the rate of onset.

A fractal is a complex object built hierarchically of finer and finer details, all similar apart from their successively reduced scales. These intricate formations in space, reminiscent of objects such as mountains and snowflakes, as well as complex formations in time, can be described by mathematical rules called scaling functions, which Feigenbaum discovered. Scaling functions describe the evolution of an object, whatever its current form or size, and so, unchanged, can be repeatedly reapplied.

In this circumstance, the object produced is scale invariant: as it evolves from a given size, its details remain loosely proportional to that size, and so, are fractal. Looking at systems from this perspective, Feigenbaum has made important contributions to numerous fields, including cartography: as a consultant to the Hammond Corporation, he developed techniques that allow computers to draw, with unprecedented accuracy, maps of archival quality using a dataset of just one high, fixed resolution. This atlas, published in 1992, contains Feigenbaum's optimal conformal projections for arbitrarily chosen regions on Earth, and these projections are at least three times more accurate than all previous ones. The computer-automated labeling of maps of adaptive forms in nature, that determines the rate of onset.

At Rockefeller, Feigenbaum has taken part in numerous collaborations. Among them are efforts to study the electrical fluctuations of single neurons to quantitatively determine their chaotic properties; measure the way fibroblasts travel to the site of injury, observing that as their path appears not to be random, they are moving chaotically; and analyzing the outcome of optical imaging of cortical activity.
The Fischetti lab exploits the evolution of bacteria-killing viruses, known as phages, to develop new ways to prevent and treat bacterial infections. This strategy has revealed bacteria-killing enzymes and novel immunotherapies that can overcome antibiotic-resistant bacteria.

Fischetti works with both gram-positive and gram-negative bacteria, such as streptococci, staphylococci, anthrax, and acetobacter, to develop unique treatment strategies to prevent infection. His approach involves novel immunotherapies and the use of phage lytic enzymes to both prevent infection and remove pathogenic bacteria from infected tissues.

Fischetti's lab uses recombinantly produced phage lysins that will kill the major gram-positive and gram-negative pathogens including Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus, Clostridium difficile, Bacillus anthracis, and Acinetobacter baumannii. The enzymes are extremely potent; micrograms can destroy millions of organisms within seconds. They are also highly specific and, unlike antibiotics, only kill the disease-causing bacteria, without harming the beneficial bacteria.

Fischetti's studies have shown that when small amounts of phage lysins are administered to infected mice, disease-causing bacteria are rapidly destroyed. In an animal model of pneumococcal pneumonia, Fischetti and his collaborators have shown that systemic administration of the phage enzyme Cpl-1 can rescue infected mice and completely reverse lung tissue damage if given within 24 hours post-infection. Similarly, experiments involving antibiotic-resistant S. aureus causing serious bacteremia in mice returned similar results after treatment with a staphylococcal-specific lysis. This lysis technology has been licensed and is currently in human clinical trials.

Using lytic enzymes as a tool, Fischetti's lab developed a method of drilling through the thick cell walls of gram-positive bacteria while keeping the cells intact. The technique enabled the researchers to access the bacterial cytoplasm with labeled antibodies to study intracellular molecules that were previously inaccessible.

As a result of the high variability and plasticity of S. aureus, vaccine development has been challenging and has yet to be accomplished. Using the high-affinity binding domain of phage lysins directed to S. aureus, the Fischetti lab has successfully developed fusion immunoglobulins (called lysibodies) with the capacity to bind to the common cell wall of all Staphylococci, resulting in efficient phagocytic killing by human white blood cells. Lysibodies may be used to boost the immune response of Staphylococcus-infected patients.

Because bacteria use their surface molecules to attack and invade human tissues, a better understanding of how they anchor these molecules in their cell walls could lead to new strategies to prevent infection. The M surface protein is the major virulence factor of group A streptococci because of its ability to impede human white blood cells. Analysis by Fischetti's lab shows that the region used to attach the M protein to the streptococcal cell surface is highly conserved in all gram-positive bacteria, indicating that the mechanism for anchoring surface proteins in bacteria is also conserved. Since bacteria cannot cause infection without surface proteins, a molecule that blocks surface protein attachment would be broadly applicable to different gram-positive bacteria.
Winrich Freiwald, Ph.D.

PROFESSOR, LABORATORY OF NEURAL SYSTEMS

Faces are our primary source for recognizing people and reading their emotional and mental states. Freiwald is interested in how the brain's visual system extracts social meaning from a face and then drives other brain circuits to generate emotional reactions, activate memories, direct attention, and drive social actions.

From patterns of light received by the eyes, the brain constructs our perception of a three-dimensional world, inhabited by objects with shape, color, and motion. To understand the mechanisms that make this happen, Freiwald studies attention and a particular category of objects, faces, using functional imaging of the entire brain and electrophysiological recordings from single cells. Because a dedicated circuit exists for processing them, faces offer a unique opportunity to study object recognition. Likewise, as potent stimuli for attention, emotion, memories, and thoughts, faces provide a powerful means to study social cognition.

Using functional magnetic resonance imaging (fMRI), Freiwald has discovered specialized neural machinery for face processing. By combining fMRI with electrophysiological techniques, he and his colleagues showed that this machinery is composed of a fixed number of face-selective regions, each dedicated to a different dimension of facial information. Yet all except one of these regions are interconnected to form a face-processing network. Because this system is specialized to process only one class of complex forms, and because its computational components are spatially segregated, it offers a unique opportunity to dissect the neural mechanisms and computational principles of object recognition.

Freiwald's lab aims to understand the inner workings of this system, from the level of individual cells to the interactions of brain areas, to answer questions such as: How does face selectivity emerge in a single cell? How is information transformed from one face area to another? What is the contribution of each face area to different abilities, such as the recognition of a friend or a smile, and how do the face areas interact?

The lab uses the face-processing network to uncover fundamental principles of brain organization: Why is visual information processing organized in hierarchies? How do populations of neurons extract and integrate information? And how does activity propagate through the cortex? Furthermore, by studying how the face-processing system is functionally embedded in the brain, the Freiwald lab is exploring its links to social behavior: How does a smile elicit an emotional response and cause someone to smile back? How does a face activate old memories? Understanding the circuits of the social brain that implement these complex functions may aid in understanding disturbances of social behavior in disease, such as autism.

The Freiwald lab is also interested in how the brain exerts attentional control, how attention interacts dynamically with the environment, and how attention and object representations interact. Vision is an active process, aided by attention, and it selects what is relevant and dismisses what is not. Freiwald uses fMRI to determine the entire network of brain areas involved in attention, its connections, and functional properties. The group has also identified a new cortical area for attention control. Faces, due to their high social importance, give rise to specific attentional deployments, and the lab aims to utilize this link to better elucidate general attention mechanisms.
Jeffrey M. Friedman, M.D., Ph.D.

Friedman studies the molecular mechanisms that regulate food intake and body weight. Genetic studies in mice led him to identify leptin, a hormone made by fat tissue that plays a key role in controlling appetite and weight. His current work explores the mechanisms by which leptin mediates these functions, and seeks to identify other key regulators of body weight.

Leptin is a hormone secreted by adipose (fat) tissue in proportion to its mass that in turn modulates food intake relative to energy expenditure. Increased fat mass increases leptin levels, which in turn reduces body weight; decreased fat mass leads to a decrease in leptin levels and an increase in body weight. By this mechanism, weight is maintained within a relatively narrow range. Defects in the leptin gene are associated with severe obesity in animal models and in humans.

Leptin acts on sets of neurons in brain centers that control energy balance to regulate appetite. Leptin also plays a general role in regulating the physiologic responses that are observed with changes in nutritional state, with clear effects on female reproduction, immune function, and the function of many other hormones, including insulin.

The recent identification of the hypothalamic cells that express the leptin receptor is enabling Friedman and his colleagues to delineate the precise neuronal effects of leptin and the mechanisms by which this single molecule can alter a complex behavior. Recent studies have revealed that leptin reduces food intake by decreasing the pleasure associated with food. Friedman’s lab has identified a specific neural population in the hypothalamus that expresses a bioactive peptide known as MCH, which plays a key role in sensing the reward value of food. His ongoing studies seek to understand how leptin modulates the activity of these neurons as well as to identify additional neural populations that regulate feeding.

The Friedman lab is also using transgenic mice to identify DNA regulatory elements that change expression of a reporter gene controlled by the leptin gene proportionately with changes in adipose tissue mass. They have modified a series of leptin bacterial artificial chromosome clones so that the leptin DNA regulatory elements direct the expression of luciferase, enabling them to identify DNA regulatory sequences that control leptin gene expression. The goal of these studies is to identify a novel lipid-sensing signaling pathway in adipocytes and possibly other cell types.

Leptin has potent metabolic effects to improve insulin action and reduce the retained lipid content of peripheral tissues and is now an FDA-approved drug for the treatment of severe lipodystrophy, a form of diabetes. The Friedman lab is studying the mechanism responsible for leptin’s antidiabetic function; current data suggest it interferes with both the production and action of glucagon, a hormone that acts to increase blood glucose by opposing the effects of insulin.

In collaboration with Tayfun Ozcelik at Bilkent University in Ankara, Turkey, the Friedman lab is conducting studies of consanguineous families that include patients who are either morbidly obese, extremely lean, or have polycystic ovary disease (PCOS), which is associated with resistance to insulin. The team expects that analyses of the DNA sequences from these populations will reveal DNA mutations that contribute to differences in weight or that lead to PCOS.
Elaine Fuchs, Ph.D.

INVESTIGATOR, HOWARD HUGHES MEDICAL INSTITUTE - REBECCA C. LANCEFIELD PROFESSOR, ROBIN CHEMERS NEUSTEIN LABORATORY OF MAMMALIAN CELL BIOLOGY AND DEVELOPMENT

The largest reservoirs of adult stem cells reside in skin. Throughout life, they renew the body’s protective barrier, regenerate hair in cyclical bouts and repair surface wounds. Fuchs studies where stem cells come from and how they make and repair tissues. She explores how stem cells communicate with immune, dermal, and other cells in their environment, and how communication malfunctions in aging and cancers, with an aim to advance therapeutics.

Fuchs’ lab couples in vitro studies with classical genetics, RNAi, and CRISPR-Cas technologies in mice to study the biology of skin stem cells. Her research employs high throughput genomics, single cell sequencing, live imaging, cell biology and functional approaches to unravel the pathways that balance stem cell maintenance and differentiation and to explore aberrant routes in aging and cancers. Her team investigates how stem cells establish unique chromatin landscapes and programs of gene expression, and how this shifts in response to changes in their local environment. They seek to discover the activating signals from neighboring cells that instruct skin stem cells when to make hair and when to repair epithelial injuries. Conversely, inhibitory cross talk tells the stem cells when to stop making tissue and rest. Their findings are accelerating the development of therapeutics to enhance wound repair.

After elucidating the positive and negative signaling pathways that need to be turned on and off at the right time and place for adult skin stem cells to become activated to regenerate tissue, Fuchs’ group focused on what happens when these signals are deregulated. They learned that cancer cells hijack the basic mechanisms that enable stem cells to replenish dying cells and to repair wounds.

A major focus of the lab is on squamous cell carcinomas, among the most common and life threatening of human cancers worldwide. The first group used high throughput genomics to delineate the features of so-called cancer stem cells. They then devised technology that permits high-throughput functional screens for oncogenes, tumor suppressors, and microRNAs in mice. By identifying mutations that selectively fuel cancer growth and showing that these alterations also occur in related human cancers, Fuchs hopes her research will lead to new therapeutics that target cancer stem cells without affecting tissue stem cells.

By studying early steps in malignancy, the group discovered that invading blood vessels and associated inflammatory cells transmit aberrant signals. Nearby tumor-initiating cells respond by reducing proliferation, invading stroma, and resisting chemotherapy. Further away, tumor stem cells grow faster but are more sensitive to drugs. This leads to differences in stem cell behavior within developing tumors that arises from heterogeneity in the microenvironment rather than from variations in genetic mutations.

How do these stromal aberrations affect the transcriptional, epigenetic, and translational programs of stem cells during tumor progression? How do these changes confer drug resistance, and how do they affect epithelial polarity, adhesion, and invasiveness within the tumor? Does the epigenetic and translational heterogeneity in tumor stem cells that arises from local variations in the stroma contribute to subsequent genetic heterogeneity within cancers? What is the importance of immune cell cross talk with stem cells in wound repair versus cancer? As the group answers these questions, they will continue to uncover new links to understanding the process of wound repair, as well as tumor progression and metastasis.
During mitosis, a full set of chromosomes must be equally transmitted to the offspring of each dividing cell. Failures in this process can result in numerous disorders, including birth defects and tumor progression. Funabiki studies how chromosomes signal to spatially and temporally orchestrate rapid assembly and disassembly of macromolecules that ensure accurate chromosome segregation.

Mitosis involves rapid macromolecule assembly and disassembly at the right place, at the right time, and in the right order. Upon entry into mitosis, the nuclear envelope encapsulating the chromosomes disassembles, while a bipolar spindle composed of dynamic microtubule polymers assembles on chromosomes. The kinetochore forms at each chromosomal centromere to capture the microtubule ends, ensuring chromosomal segregation. At the end of segregation, the spindle and the kinetochore disassemble, while the nuclear envelope reforms. The Funabiki lab studies the spatiotemporal mechanisms that control changes to these molecular architectures.

The structural and signaling roles of the nucleosome during mitosis. Nucleosomes are the major constituents of chromosomes, and each nucleosome is composed of about 146 base pairs of DNA and the histones H2A, H2B, H3, and H4. To understand how nucleosomes function in mitotic processes, the Funabiki lab has developed a strategy to reconstitute the nucleosome using recombinant histones in the physiological cell-free system of Xenopus egg extracts. This system has made it possible to establish the molecular roles of the nucleosomes in spindle assembly and nuclear pore complex formation on chromatin. They have also demonstrated the importance of mitosis-specific histone H3 phosphorylation in the activation of Aurora B kinase, which provides a spatially controlled mechanism for regulating mitosis.

The Funabiki lab now combines quantitative mass spectrometry and innovative imaging techniques to define how architectural and functional organizations are modulated by cell-cycle regulators and histone modifications.

Transduction of microtubule attachment into the chemical signal for chromosome segregation. In order to segregate chromosomes, microtubules must attach to the kinetochore, which assembles at each chromosome's centromere. If not attached, kinetochores activate a signaling pathway called the spindle assembly checkpoint to delay sister chromatid separation and exit from mitosis. Funabiki aims to understand the mechanism by which the microtubule attachment status is recognized and how this physical difference is converted into checkpoint signaling. Furthermore, using super-resolution microscopy, his lab is studying how the three-dimensional architecture of the kinetochore is modulated by microtubule attachment status.

Centromere integrity. Human centromeres are composed of long arrays of repetitive sequences, called alpha-satellite DNAs. There are diverse variations of centromere size and organization within and across species, and why and how centromeres maintain this repeat organization remains enigmatic. Recently, the Funabiki lab revealed that human centromeric repeats become relatively unstable in cancer cell lines or primary cells undergoing replicative senescence. In characterizing the key mechanism that helps maintain the repeat sequences, Funabiki aims to unveil the functional consequence of centromere instability and its relevance to disease.
Charles D. Gilbert, M.D., Ph.D.

ARTHUR AND JANET ROSS PROFESSOR, LABORATORY OF NEUROBIOLOGY

Gilbert has pioneered studies into the mechanisms underlying visual perception and perceptual learning at the level of cortical circuits. To this end, he has studied the role of the brain’s visual cortex in analyzing images and in memory. His lab has also explored how the circuitry of the brain and the interactions between neuronal ensembles contribute to visual perception.

The Gilbert lab studies the visual cortex, including a series of areas mediating object recognition and perceptual tasks. The job of the visual cortex is to take signals from the retina, group features belonging to objects, and determine their shapes. The lab investigates the mechanism by which this occurs at the level of cortical circuitry. Efforts to map this circuitry have led to a seminal contribution in the field: the discovery of a plexus of long-range horizontal connections that mediate the assembly of contours and the parsing of visual scenes into objects and background. Using a combination of techniques, Gilbert has found close correspondence between the geometry of these connections, the functional properties of visual cortical neurons, and the perception of visual stimuli.

The lab also studies the way visual experience shapes the strategy by which the cortex analyzes sensory information, a process known as perceptual learning. The group has found that, even in adults, the visual cortex is capable of altering its functional properties and circuitry. These long-term changes aid in analyzing visual scenes as a result of normal experience and assist recovery from injury. For example, following a retinal lesion that initially silences parts of the visual cortex, the cortex gradually regains its ability to respond to visual stimuli. The lab is studying the molecular mechanisms underlying experience-dependent changes in cortical circuits. Understanding adaptive changes in cortical function provides important insights into the mechanism of recovery after brain lesions and neurodegenerative disease, including macular degeneration.

Research in the Gilbert lab suggests each cortical area is an adaptive processor that runs different programs according to the immediate demands of the perceptual task. Object recognition, for example, involves a countercurrent process of feedforward and feedback interactions. The top-down signal conveys information, a process known as perceptual learning. The group has found that, even in adults, the visual cortex is capable of altering its functional properties and circuitry. These long-term changes aid in analyzing visual scenes as a result of normal experience and assist recovery from injury. For example, following a retinal lesion that initially silences parts of the visual cortex, the cortex gradually regains its ability to respond to visual stimuli. The lab is studying the molecular mechanisms underlying experience-dependent changes in cortical circuits. Understanding adaptive changes in cortical function provides important insights into the mechanism of recovery after brain lesions and neurodegenerative disease, including macular degeneration.

Gilbert and his colleagues use electrophysiology, imaging, and molecular approaches to understand the mechanisms of adult cortical plasticity. This research includes examining the contribution of different neuronal types and circuit components to experience-dependent changes, the circuitry and synaptic mechanisms underlying the dynamic changes in cortical cells in behaving animals, and using human psychophysics to explore the perceptual consequences of dynamic changes in cortical properties.
Aiming to understand the creation and evolution of the universe, Goulianos and his colleagues study the basic constituents of matter by analyzing data from collisions of sub-atomic particles accelerated to very high energies. Their research is currently conducted at CERN in Geneva, Switzerland, using the Large Hadron Collider, the world’s largest sub-atomic particle accelerator.

A large fraction of the energy in particle collisions is converted into a variety of new particles flying away from the collision like exploding fireworks. Most of the created particles have an ephemeral existence, decaying after a brief period of time into more stable ones. Detailed studies of all known particles have revealed an inner order that has been coded into a theoretical framework known as the Standard Model. Matter in all its forms, from stars to living organisms, is described in terms of twelve fundamental particles, six quarks and six leptons, interacting by exchanging force particles—gluons, photons, or W and Z bosons—following strict mathematical rules based on symmetry principles.

The Goulianos laboratory has made substantial contributions to establishing the Standard Model as the premier theory of particle physics. Their experiments at the Intersecting Storage Rings at the European Organization for Nuclear Research (CERN) provided early evidence for the existence of quarks. In other experiments conducted at the Brookhaven National Laboratory, they discovered and measured the rate of neutrino-proton elastic scattering, confirming the neutral-current interactions predicted by the Standard Model. In the collider detector at Fermilab (CDF) experiment, which used proton-antiproton collisions from the Tevatron machine, the Goulianos laboratory contributed to the discovery of the top quark.

The Goulianos team currently participates in the international collaboration of the Compact Muon Solenoid (CMS) experiment at the Large Hadron Collider at CERN. On July 4, 2012, CMS and ATLAS, another CERN experiment, announced the discovery of the Higgs particle, which could explain the diversity of quark masses. This result was corroborated by a CDF measurement. The Higgs discovery marks the end of a half-century’s hunt for its existence by thousands of scientists around the world and motivates the effort to conduct higher precision experimental tests to look for violations that might come from new physics.

Other physics activities of the Goulianos team at CDF and CMS have included working on phenomenological models aimed at accommodating gravity in the Standard Model and explaining dark matter and dark energy. Presently, the team is studying diffractive phenomena, which provide a window to a component of the Standard Model important for understanding the structure of particles like the proton.

Carrying over the experience gained at the Tevatron to their research at the Large Hadron Collider, Goulianos and his team are uniquely positioned to make new discoveries in areas of physics beyond the Standard Model to advance “Scientia Pro Bono Humani Generis.”
The Greengard laboratory studies the molecular defects responsible for neurological and psychiatric disorders, including Alzheimer’s disease, Parkinson’s disease, schizophrenia, and major depressive disorder. In addition, the lab investigates the molecular mechanisms by which neuro- and psychoactive drugs produce their pharmacological actions in these disorders.

Research from the Greengard laboratory has demonstrated that most neurotransmitters and neuromodulators achieve their actions and interactions on postsynaptic neurons through a process called “slow synaptic transmission.” This process involves activation of highly complex signal transduction cascades. For the last 15 years, the group has applied this knowledge to the study of the molecular pathways underlying various neurological and psychiatric disorders.

One major area of activity in the Greengard laboratory involves a search for the molecular and cellular basis of major depressive disorder. They recently found a protein called p11 (S100A10, a member of the S100 family of proteins) that plays a central role in the regulation of mood. Constitutive removal of p11 from neurons in the brain causes a depressive phenotype and a loss of behavioral response to antidepressant agents. The antidepressant action of p11 is mediated through binding of p11 to a chromatin-remodeling factor, SMARCA3. SMARCA3, in turn, regulates the transcription of many genes. In one current project, the lab is determining which of these genes is necessary for the therapeutic actions of various antidepressants and the molecular mechanisms of action of these gene products.

A second major area of interest is the analysis of the enzymatic pathways involved in the synthesis and degradation of amyloid-β, the prime suspect in the etiology of Alzheimer’s disease. The enzyme γ-secretase catalyzes the formation of amyloid-β, the substance believed to be responsible for the death of nerve cells in Alzheimer’s. The group has recently discovered a protein, which they named γ-secretase activating protein (GSAP), that selectively regulates the trafficking of the amyloid precursor protein, APP, and the formation of amyloid-β. Reductions in the levels of GSAP prevent formation of amyloid-β. GSAP represents an attractive target for therapies to inhibit amyloid-β formation and thus prevent Alzheimer’s disease. In other studies in the laboratory, other pathways involved in regulation of amyloid-β degradation have been found, and their mechanisms of action are now being investigated.

A third area of the laboratory’s activity involves determining the molecular basis for the differences between vulnerable cells and non-vulnerable cells in Alzheimer’s disease and in Parkinson’s disease. This approach is based on identifying all expressed proteins in individual nerve cell types in the brain using bacTRAP technology, which was developed in collaboration with Rockefeller’s Nathaniel Heintz. Proteins highly expressed in vulnerable cells are introduced to non-vulnerable cells to see if they cause vulnerability. Conversely, proteins highly expressed in non-vulnerable cells are introduced to vulnerable cells to see if they afford protection.

SELECTED PUBLICATIONS
Infections by microbial pathogens continue to be a major burden on global health. The Hang laboratory aims to better understand host-microbe interactions in order to prevent and treat infectious diseases. They are interested in developing new chemical approaches to functionally dissect how endogenous and environmental metabolites regulate host immunity and microbial pathogenesis, and in discovering and characterizing novel anti-infectives.

To elucidate specific mechanisms regulated by key metabolites, the Hang laboratory has developed chemical reporters to image and profile the biochemical targets of metabolites in bacteria, yeast, and mammalian cells. At the heart of this chemical approach is the design and synthesis of specific chemical reporters—metabolites bearing uniquely reactive groups—that can be chemically or enzymatically incorporated into biomolecules in vitro and in vivo and then selectively labeled with bioorthogonal imaging or affinity reagents. Using this strategy, a variety of chemical reporters based on important metabolites (nucleosides, amino acids, lipids, and other cofactors) have been developed for the sensitive detection and analysis of metabolite–protein modifications (short- and long-chain fatty-acylation, prenylation, AMPylation, and ADP-ribosylation).

The Hang laboratory has been especially interested in the protein targets of short- and long-chain fatty acids in host-microbe interactions. They have focused on understanding how fatty-acylation of specific proteins (IFITMs, TLRs) regulates host immunity, and how microbial pathogens co-opt or subvert these pathways for infection. Hang has also employed site-specific fluorophore labeling and photocrosslinking methods to functionally characterize specific cellular pathways. These studies highlight how chemical approaches can be used to explore and understand the mechanisms of host immunity and microbial pathogenesis.

To discover novel anti-infectives, the Hang lab is working to develop inhibitors of bacterial virulence pathways and to explore the protective mechanisms of beneficial bacteria. The type III protein secretion system (T3SS) is an important virulence mechanism for many Gram-negative enteric pathogens, but has thus far been challenging to specifically target with small molecules. Using a high-throughput assay for T3SS, Hang and colleagues discovered that specific medicinal plant metabolites (flavonoids) can covalently label and inactivate T3SS substrates to attenuate bacterial virulence. These researchers are continuing to explore these and other small molecule inhibitors.

To complement these studies, Hang has employed C. elegans as a model system for exploring the protective activity and complex mechanisms of specific commensal bacteria and probiotics. The lab has discovered that a secreted peptidoglycan hydrolase (SagA) from E. faecium is sufficient to trigger innate immune pathways, improve intestinal barrier function, and protect worms from enteric pathogens (S. typhimurium). Working with Rockefeller’s Daniel Mucida, they also showed that the SagA protection mechanisms are conserved in mice and can be used to enhance the activity of existing probiotics to prevent enteric infections, including C. difficile. With these studies, the Hang lab continues an ongoing effort to establish more efficient systems to discover and characterize novel anti-infectives.
Mary E. Hatten, Ph.D.

FREDERICK P. ROSE PROFESSOR, LABORATORY OF DEVELOPMENTAL NEUROBIOLOGY

Hatten studies the development of the complex cellular architecture of the mammalian brain. Her research on how neurons differentiate and migrate has implications for the genetics of brain disease, as well as conditions that are partially due to developmental abnormalities, such as autism, attention deficit disorder, and childhood epilepsy. Her work has also provided insights into medulloblastoma, a prevalent childhood metastatic brain tumor.

Using the mouse cerebellar cortex as a model, Hatten studies the mechanisms of cerebellar neurogenesis and migration during central nervous system (CNS) development. Her lab pioneered the development of video imaging methods to view the dynamics of CNS neuronal migration along glial fibers. Using these methods, Hatten has revealed several key steps including the extension of a highly polarized, leading process in the direction of migration, the assembly of an interstitial adhesion junction beneath the cell soma, the formation of a perinuclear tubulin cage to maintain posterior positioning of the nucleus, and the localization of actomyosin contractile motors ahead of the nucleus.

Functional studies in her lab have shown that the conserved polarity protein complex mPar6 controls the actomyosin contractility in the leading process, propelling the neuron along the glial guide. Current studies focus on the small Rho GTPase Cdc42, an upstream regulator of mPar6, and on the polarized trafficking of neuron-glial adhesion receptors during migration.

To analyze global changes in gene expression in postmigratory neurons, Hatten has used a method known as translating ribosome affinity purification (TRAP) to reveal dramatic changes in multiple chromatin remodeling reagents of postmigratory neurons during the formation of cerebellar circuitry. Notably, the Tet genes and a DNA demethylation product, 5-hydroxymethylcytosine (5hmC), are upregulated. Genome-wide analysis of 5hmC distribution revealed the highest levels at exon start sites of most highly expressed genes. The activation of Tet enzymes elevated 5hmC levels in axon guidance and ion channel genes and knockdown of Tet1 and Tet3 by RNA interference markedly inhibited dendritic arborization of developing granule cells. Thus, her work has shown that changes in chromatin remodeling genes in postmigratory neurons are critical for the formation of cerebellar circuitry.

The Hatten lab has extensively studied the neuron-glial adhesion protein astroactin (ASTN1), a receptor she discovered in 1987. The Astn1 gene is expressed by neurons migrating along glial fibers in both the cerebellum and the cerebral cortex, and genetic studies provide evidence Astn1 functions in neuronal migration. The lab has also characterized Astn2, which has been identified as a risk factor in autism, attention deficit hyperactivity disorder, and other neurodevelopmental disorders. Recent experiments show that ASTN2 localizes to synapses, binds to the synaptic protein neuroligin, and functions in synaptic protein trafficking. Thus, mutations, known as copy number variants, in Astn2 may affect synaptic output due to trafficking defects.

To study neurons with Astn2 and Tsc1 lesions from autism patients, as well as other neurogenetic defects that affect cerebellar development, Hatten has developed protocols to differentiate induced pluripotent stem cells (iPSCs) into cerebellar neurons. To characterize iPSC-derived neurons, she uses bacTRAP technology developed in the lab of Nathaniel Heintz and an implantation assay developed in her own lab to test whether implanted human cerebellar neurons will migrate to the correct layer and incorporate into the mouse cerebellar circuitry.
Research in the Heintz laboratory aims to identify the genes, circuits, cells, macromolecular assemblies, and individual molecules that contribute to the function of the mammalian brain and to its dysfunction in disease. Understanding the distinct classes of neurons and the circuits that control specific aspects of cognition and behavior can lead to more targeted treatments for central nervous system disorders.

Cognition and behavior emerge from hundreds of different classes of cells in the mammalian brain, arranged into specific circuits that control various functions of the nervous system. Heintz has developed a suite of tools to investigate the molecular mechanisms that contribute complexities of the mammalian brain, enabling the characterization of different cell types and furthering our understanding of the biochemical basis behind this diversity.

As a first step in identifying the mechanisms that are essential for normal brain functioning and those that go awry in disease, the Heintz laboratory invented a method to reproducibly target defined central nervous system (CNS) cell types using genetics. The system is based on manipulating bacterial artificial chromosomes (BACs) to engineer DNA by homologous recombination in E. coli, a process now known as “recombineering.”

Working with Mary E. Hatten, Heintz launched the NINDS Gene Expression Nervous System Atlas project (www.gensat.org), a large-scale screen using BAC transgenic mice to create an atlas of cellular CNS gene expression. It includes detailed anatomical data on cell types targeted in over 1,500 BAC transgenic mouse lines and a library of verified BAC vectors and transgenic mouse lines, offering the scientific community experimental access to CNS regions, cell classes, and pathways. The information gleaned from this project serves as the foundation for many of the studies currently pursued in the Heintz lab.

Many of the genes involved in neurological and psychiatric disorders are ubiquitously expressed throughout the brain, but Heintz proposes that disease-linked genes differentially impact finely-tuned biochemical pathways controlling specific neurons and circuits. To shed light on the elements that are most affected in a given disorder, the laboratory, in collaboration with Paul Greengard, developed the translating ribosome affinity purification (TRAP) technique. By fusing an affinity tag to a ribosomal protein, TRAP enables the isolation of bound messenger RNAs from a targeted cell type without requiring isolation of that cell type from tissue.

The laboratory employs TRAP to determine molecular constitutions of a wide variety of cell types in the mouse brain and the molecular phenotypes of select cell types in mouse models of common disorders. TRAP profiling has led to the definition of biochemical pathways whose altered activity contributes to the pathophysiology of CNS disorders, including autism-spectrum disorders, obsessive-compulsive disorder, Parkinson’s disease, addiction, anxiety, and depression. Recent studies have also revealed that the circuits involved in these disorders work differently in male and female mice.

Another focus of Heintz’s work centers on an epigenetic modifier discovered by the lab, called 5-hydroxymethylcytosine (5hmC), which is present in the mammalian genome and specifically enriched in neurons. The researchers are currently addressing the potential significance of 5hmC, a novel epigenetic mark not previously observed in metazoans, on epigenetic mechanisms of neurological and psychiatric disease.
Ho has spent decades researching the pathogenesis of HIV infection, in particular the dynamics of HIV replication, and his work has led to the development of life-prolonging combination antiretroviral therapy. Currently, his group focuses on developing vaccines as well as other innovative prevention strategies. As head of the China AIDS Initiative, Ho seeks to comprehensively address the HIV/AIDS crisis in that country.

The Ho lab has been actively engaged in AIDS research for 36 years and has published more than 400 papers on the subject. The lab’s work helped pioneer the field of HIV quantitation in infected people. In the last decade, his research team extended this work and revolutionized the paradigm for AIDS pathogenesis by demonstrating the highly dynamic nature of HIV replication in vivo. Their elegant studies on HIV dynamics formed the foundation for combination antiretroviral therapy, which Ho also helped to champion. Such a treatment approach has transformed a death sentence to a manageable disease and is now being applied widely throughout the developing world.

A major focus of the Ho lab today is the design and testing of candidate vaccines to induce immune responses that could block HIV transmission. The team is currently pursuing multiple vaccine strategies, and manipulating the viral envelope glycoprotein to determine whether neutralizing antibodies could be induced.

Under a Vaccine Discovery Center grant from the Bill and Melinda Gates Foundation, Ho’s latest focus is a unique approach to HIV prevention. He and his colleagues are studying the passive administration of a humanized monoclonal antibody, ibalizumab, that potently and broadly blocks HIV infection by binding to domain 2 of human CD4, the principal receptor for HIV. Ibalizumab is being tested in clinical studies in HIV-infected individuals, showing a good safety profile and a well-documented antiviral effect, and is now being applied widely throughout the developing world.

Moreover, many bispecific antibodies have been constructed and tested, several of which have unprecedented breadth and potency against HIV. Ho’s group is also pursuing the use of gene transfer methods to express second-generation forms of this antibody that offer improved antiviral potency and breadth, and enhanced pharmacokinetic properties.

In addition, Ho and colleagues are actively studying long-acting antiretroviral drugs that are promising as prophylactics against HIV.
A. James Hudspeth, M.D., Ph.D.
INVESTIGATOR, HOWARD HUGHES MEDICAL INSTITUTE • F.M. KIRBY PROFESSOR, LABORATORY OF SENSORY NEUROSCIENCE

The majority of the hearing-impaired suffer from sensorineural hearing loss resulting from damage to the sensory hair cells of the inner ear. The human cochlea contains about 16,000 of these cells, which do not regenerate after damage. In an effort to prevent or reverse deafness, Hudspeth’s group is working to better understand the normal hearing process, the causes of hearing deterioration, and possible means to regenerate hair cells.

Within the cochlea, mechanical signals representing sound are converted into vibrations along the basilar membrane, upon which stand some 16,000 hair cells. Each hair cell is endowed with a few hundred fine “feelers,” or stereocilia, that collectively constitute its hair bundle. Sound-induced vibrations set the hair bundle in motion, evoking electrical responses by opening and closing mechanically sensitive ion channels. As a result of the direct mechanical connection between the hair bundle and ion channels, the transduction process of hair cells is remarkably rapid; we can consequently hear sounds at frequencies as great as 20 kHz. The direct nature of auditory transduction also makes the process highly sensitive.

The extraordinary sensitivity of our hearing suggests that the cochlea amplifies its mechanical inputs, and researchers in Hudspeth’s research group are exploring how human hearing benefits from a tiny mechanical amplifier in each hair bundle. They have found that bundles are spontaneously active, oscillating through an approximate distance of 30 nm. When an active bundle is subjected to a small stimulus force, its motion becomes synchronized with the stimulus. Measurement of the mechanical work performed in this situation confirms that a hair bundle can amplify and tune its mechanical inputs. Members of the research group are now extending these results to the mammalian ear. Using a theoretical approach to model the cochlea, they are also exploring the mechanism by which it amplifies sounds. Identifying the active process in the human cochlea is especially important because hearing loss usually begins with deterioration of this amplifier.

In an effort to learn how hair cells develop, Hudspeth’s group is conducting molecular-biological experiments on the larval zebrafish. In the lateral line of this species, new hair cells continually arise to replace those that die as a result of aging or chemical toxicity. The division of a precursor cell consistently produces a pair of hair cells, one of which responds to water movement toward the animal’s anterior while the other is sensitive to posterior flow. To establish which signaling pathways lead to the production of new hair cells, members of the group are isolating hair cells and their precursors, and examining their gene expression. The investigators hope to identify pathways that might be activated in the human ear to foster the replacement of hair cells.

The team is also studying how individual nerve fibers distinguish between hair cells of the two functional polarities, selectively innervating only one of the two sets. Finally, some members of the lab are investigating the regeneration of hair cells in the inner ear of the mouse, a preparation that resembles the human inner ear.

Hudspeth’s research has led to a deepened understanding of the receptor cells of the inner ear and how they contribute to hearing and hearing loss. He hopes that further investigation will indicate both the causes of and potential remedies for certain forms of human hearing impairment, an affliction that affects 10 percent of the American population.
The ability to speak has allowed our species to pass knowledge between generations, articulate complex ideas, and build societies. Jarvis uses song-learning birds and other species as models to study the molecular and genetic mechanisms that underlie vocal learning, including how humans learn spoken language. He is interested in how their brains, and ours, have evolved to produce this complex behavior.

Unlike songbirds, the vast majority of animals—including common model organisms like mice and fruit flies—cannot imitate novel sounds and have limited vocal flexibility, reducing their usefulness in the study of spoken language. To advance research in this field, the Jarvis lab has developed a suite of experimental tools for songbirds designed to probe the underlying genetics of vocal learning. By using an integrative approach combining behavioral, anatomical, electrophysiological, and molecular biological techniques, Jarvis hopes to advance knowledge of the neural mechanisms of vocal learning and, more broadly, gain a deeper understanding of how the brain generates, perceives, and learns complex behaviors.

Beyond his work with songbirds, Jarvis is interested in using genomics to develop a comprehensive understanding of how vocal-learning and vocal non-learning species are related, providing insight into how vocal learning and other complex behaviors have evolved. As the co-leader of a consortium of over 200 scientists, from 101 institutions in 20 countries, Jarvis helped oversee the sequencing of genomes of species representing nearly all avian orders. These findings led to an overhaul of the bird family tree, and suggest that vocal learning evolved at least twice among birds: once in hummingbirds and once in a common ancestor of songbirds and parrots. Jarvis’s aspiration is to sequence the genomes of each bird species, a total of 10,500, and eventually the genomes of all 66,000 vertebrates, in order to understand how species are genetically related and how their unique characteristics evolved.

Working with results from the avian genomics project, Jarvis and his colleagues have discovered that hundreds of genes have similarly evolved in both the song-learning circuits of songbirds and the speech circuits of humans, and that many of the changes to these genes are not found in the brains of their close living bird and primate relatives. Some of these genes, when mutated, are associated with speech disorders in humans, and are predicted by Jarvis’s studies to control the development of speech brain circuits. These findings have significant implications, suggesting that an entire body of work in songbirds has direct relevance to humans.

Most recently, the Jarvis lab has begun to study the molecules that guide neuronal connections, called axon guidance molecules. Jarvis hypothesizes that these molecules make the difference between a vocal learner and non-learner by directing the formation of a crucial neural circuit. This motor circuit, which has been linked to vocal organs, is believed to make fine motor control in the larynx possible, allowing the production of imitated speech. The Jarvis lab and others predict that the presence or absence of this neural circuit is one of the key transformations in the brain that enables vocal learning, and that axon guidance molecules are responsible for its creation. One of the Jarvis lab’s long-term goals is to use these molecules to induce a vocal-learning circuit in a species that can’t normally imitate speech, such as a mouse.

**SELECTED PUBLICATIONS**

Some biological processes, such as development, take months or years to play out while others require only minutes or even seconds. Kapoor’s lab devises ways to use chemistry to study rapid cellular processes, focusing on those that drive cell division or involve members of the AAA+ family of proteins. His lab also seeks to develop some of these fast-acting compounds into new therapies for disease.

To study a biological process, scientists often need to disrupt the function of key proteins involved in it. The most effective tools to do so block protein function over the same time scale as the process itself. Examining rapid cellular activities—such as the preparations for division or assembly of ribosomal precursors—requires equally fast-acting interventions. The Kapoor lab develops chemistry-based tools and approaches to study these dynamic processes over brief time scales, and much of their effort focuses on small-molecule inhibitors. These compounds can often have potential clinical applications, and when possible, the lab uses them to develop new therapies.

Using two approaches, the lab has identified a number of first-in-class inhibitors, including ribozinoindoles (Rbins), which arrest ribosomal assembly in yeast. One strategy, which mimics forward genetics, employs a cell-based screen to identify a chemical that perturbs a given process. Researchers then determine the mechanism by which the compound achieves its effect. In a second approach, the group develops compounds for a selected protein target. When possible they use rational design, identifying and modifying a chemical scaffold that can interact with a target protein, much like shaping a key to fit a lock.

The means by which many bioactive compounds achieve an effect in cells can be difficult to decipher. To identify a compound’s physiologiclal target in human cells, the Kapoor lab has developed an approach known as DrugTargetSeqR. High-throughput sequencing is used to identify the mutations that confer resistance specifically to the compound of interest. So-called gold standard proof of target is obtained when the same mutation protects cells from the compound also suppresses protein binding or activity inhibition in a biochemical assay.

A major focus of the lab has been to study cell division using multidisciplinary approaches. Recently, the lab has shown how two proteins, PRC1 and kinesin-4, mark the plus ends of microtubules with tags proportional to the length of the microtubules. These tags may help the cell select and organize microtubules to position the cell division plane and keep chromosomes segregated during the final stages of division.

The lab discovered the first cell-permeable and selective inhibitors for the motor protein dynine, a member of the highly conserved family of AAA+ proteins. They continue to identify other AAA+ inhibitors and use them to study the functions of their targets, an effort that includes using Rbins to examine Mdn1’s role in ribosomal assembly. Working with the Tri-Institutional Therapeutics Discovery Institute, Kapoor’s group has begun developing an antifungal drug based on Rbins.

In addition to inhibitors, the Kapoor lab develops and applies other chemistry-based approaches to dissect biological mechanisms. For instance, they have developed a chemical proteomics approach and used it to identify reader proteins that initiate a response to a double-strand break in DNA. This study combined the use of mass spectrometry, high-resolution microscopy, and biochemistry techniques.

SELECTED PUBLICATIONS

- Steinman, J.B. et al. Chemical structure-guided design of dynaprazoles, cell-permeable dynein inhibitors with a unique mode of action. 
Ribosomes are giant molecular machines that produce all proteins necessary for life. In eukaryotic cells, their assembly is a highly elaborate and carefully coordinated process. The Klinge lab’s research is aimed at understanding the molecular mechanisms that govern early stages of eukaryotic ribosome assembly.

Ribosomes are responsible for decoding the information contained in messenger RNA to synthesize proteins used in all domains of life. Ribosome assembly, the process by which ribosomes are synthesized, involves approximately 200 protein and RNA factors in eukaryotes, most of which are essential. These factors are involved in all stages of ribosome assembly, from transcription of ribosomal RNA in the nucleolus to export into the cytoplasm, where the final stages of maturation and quality control occur. As ribosome assembly progresses, more and more of this machinery is released from intermediate complexes until the ribosomal subunits complete maturation.

The structure of this molecular machinery and the mechanisms by which it functions remain poorly understood. The Klinge lab’s major focus is to elucidate them in the context of intermediate complexes formed during the early stages of ribosome assembly, using the model system Saccharomyces cerevisiae. The group combines yeast genetics with novel biochemical tools, x-ray crystallography, and cryo-electron microscopy.

Klinge’s lab has studied the temporal order by which 70 factors associate with nascent pre-ribosomal RNA to form the small subunit processome, a giant pre-ribosomal particle. By studying ribosome assembly as a function of transcription, his lab has assigned proteins to particular stages of early ribosome assembly. In parallel, the researchers have used biochemical and structural biology methods to elucidate the functions of multi-protein complexes within the small subunit processome. More recently, they used cryo-electron microscopy to obtain the first architectural view of the S. cerevisiae small subunit processome, the earliest stable precursor of the small ribosomal subunit.

The lab ultimately aims to define the sequence of events that drive the formation of the eukaryotic ribosome at an atomic level.
Everything we see is the result of light-induced patterns of electrical activity in the nerve networks of the retina and brain. These patterns are then processed into an intelligible form by complex transformations within these networks. Knight works to develop a description of these networks in mathematical equations that will allow scientists to predict how the system will respond to specific visual patterns.

Knight and his colleagues study the visual part of the central nervous system, applying technology and theoretical means refined in their own laboratory. The visual sense provides unique opportunities for highly structured input, making it a suitable system for understanding how the nervous system processes input information.

Knight is specifically interested in the broad multicellular interactions among biophysical processes, which individually lie at the subcellular level. His laboratory's efforts involve the conjoined development of experimental procedures that induce and record detailed neural responses and theoretical tools, including dynamical equations and computer simulation, which may then describe those neural responses quantitatively.

Vision occurs when a moving pattern of colored light arrives from the external world and induces dynamical patterns of electrical activity in a sequence of neural processing networks—starting with the retina, which is specialized brain tissue, and continuing into the brain. At each step, profound signal transformations occur that ultimately reduce the input to a form useful for action. Knight and his colleagues study that process with computer-generated stimuli, including modified natural-scene movies, designed with theoretical considerations that facilitate the interpretation of response features in terms of the responding system's predictive dynamical laws. Their data include single-cell recordings from identified nerve cells.

A detailed analysis of responses of retinal ganglion cells to time-dependent naturalistic stimuli have recently revealed that these responses may be classified within a special subset of neurons that might be descriptively called “faithful copy neurons.” A population of such neurons produces an aggregate firing rate that far better mimics its neural input than would different choices of neuron design. The way a network of such neurons behaves depends critically on the nature of interconnections and only insensitively on variations in the dynamics of the individual neurons. The generality of this feature and its implications for network design are currently under study.

Recently, Knight's associates have been able to record simultaneously from numerous cells in the lateral geniculate nucleus. The responses of these cells naturally classify them into several categories. By the creation of a new data analysis technique, it has proven possible to quantitatively measure the rate of information transfer through a group of such cells and also to measure the degree to which information transmitted by different cell groups is independent or redundant.
Mary Jeanne Kreek, M.D.

SENIOR ATTENDING PHYSICIAN • PATRICK E. AND BEATRICE M. HAGGERTY PROFESSOR, LABORATORY OF THE BIOLOGY OF ADDICTIVE DISEASES

An estimated 25 to 33 percent of people who take a short-acting opiate drug such as heroin develop an addiction to it. This suggests some people are naturally more vulnerable to addiction than others, and that genetics may play a role in the condition. Kreek investigates how specific genetic factors, as well as drug-induced molecular neurobiological alterations, factor into addictive diseases such as opiate, cocaine, alcohol, nicotine, and marijuana addictions.

Kreek investigates the biological basis of addictive diseases as well as existing and novel treatments for these conditions. Her lab also researches the medical complications of drug abuse, such as hepatitis C and AIDS. In 1984, her group discovered that the second most common risk group for HIV-1/AIDS is parenteral drug users.

Kreek’s research focuses on the endogenous opioid system, which modulates stress, pain, and reward, and the roles that specific opioid peptides and their receptors play in normal and abnormal circumstances. Heroin and morphine, as well as cocaine and alcohol, activate these different opiate receptors either directly or indirectly. Kreek and her colleagues are examining gene expression changes in rodents that are given a drug of abuse, or are allowed to self-administer it, to study how this exposure impacts the brain’s neurochemistry, neurobiology, and circuitry, and to identify targets for potential new treatments. The lab also studies the epigenetic, physiologic, and behavioral effects of drug self-administration on the endogenous opioid system and related signaling networks. They perform microdialysis in rats and mice for dynamic studies of neurotransmitter release and peptide processing in the brain.

The lab studies the roles of the \( \mu \) and \( \kappa \) opioid receptor systems and the CRF/CRFR1 and vasopressin/V1b receptor systems in "binge"-like alcohol drinking models using rats and inbred strains, and genetically modified mice. Additionally, since illicit oxycodone use in adolescence has become a major public health problem, the lab is investigating behavioral and neurobiological changes in adolescent versus adult mice during and after self-administration of oxycodone. The researchers are also working on the synthesis and study of new chemicals, primarily \( \kappa \) opioid receptor ligands, which could become new treatments for specific addictive diseases and co-occurring depression.

Kreek’s team is also conducting clinical studies in cocaine- and alcohol-addicted people, and in former heroin addicts in treatment with long-term methadone or buprenorphine-naloxone, focusing on the neurobiology components of these addictive diseases. In these studies, gene polymorphisms that may play a role in addiction, or genes that may alter responses to medications (pharmacogenetics) and affect normal physiology (physiogenetics), are identified. For example, Kreek identified and characterized a functional single-nucleotide polymorphism (A118G) in the \( \mu \) opioid receptor that increases vulnerability to developing opioid and alcohol addictions and significantly alters stress responsiveness in healthy humans; a mouse model of this variant is currently used in studies.

Kreek is well known for her pioneering 1960s work developing methadone maintenance therapy for heroin addiction. The therapy has been documented to be the most effective treatment for any addiction, and is now commonly used to treat opiate addiction throughout the world, with 1.4 million people in daily treatment. Kreek was also one of the first to document, in 1985, that drugs of abuse significantly alter the expression of specific genes in certain brain regions, resulting in neurochemical and behavioral changes.

SELECTED PUBLICATIONS


Daniel Kronauer, Ph.D.

Kronauer studies social evolution and behavior within complex societies. The sophisticated behavior, communication, and division of labor within ant colonies make these social insects ideal model systems for this work. His lab uses an integrative approach to understand how natural selection shapes the evolution of insect societies and how social life is regulated at the levels of genes, individuals, and colonies.

Insect societies are socially integrated to such an extent that they are often portrayed as “superorganisms” in which different morphological or behavioral castes have different functions, similar to the tissues of an organism. The Kronauer lab uses ants to study a number of broad questions: How did complex animal societies evolve from solitary ancestors? How does behavioral and developmental plasticity give rise to division of labor? How do individual ants produce, perceive, and process social signals? And how does the composition and network structure of social groups affect group-level properties and fitness?

To address these questions, the lab uses molecular genetics and neuroscience in combination with quantitative behavioral and morphological measurements under controlled laboratory conditions. In particular, the researchers are developing and using the clonal raider ant *Ooceraea biroi* as a new model system for social behavioral genetics.

The clonal raider ant is a powerful model system because it uniquely combines the rich biology of social insects with unparalleled experimental accessibility. Colonies consist of totipotent, clonally reproducing, genetically identical workers, while queens are absent. This allows researchers to set up many experimental colonies of arbitrary sizes from stock colonies, precisely controlling and replicating the genetic composition of social groups. Different clonal genotypes can be mixed in experimental colonies. Moreover, all individuals in a colony undergo synchronized behavioral and reproductive cycles, alternating between reproductive phases during which workers lay eggs, and brood care phases during which different workers specialize on different tasks, such as nursing and foraging. Because of this reproductive synchrony, larvae develop in discrete cohorts, providing unparalleled experimental control over individual age and group demography. Taken together, the unusual biology of the clonal raider ant makes it possible to control and replicate the size, genotypic composition, and age structure of colonies—the three central factors affecting individual behavior, division of labor, and social networks in ants. The Kronauer lab has recently published the species’ genome and has developed protocols for genome editing along with automated tracking setups that allow precise quantification of individual behavior and social interaction networks.

**SELECTED PUBLICATIONS**


Caused when the immune system attacks the skin, psoriasis is one of the most accessible human diseases in which to examine how the activation of white blood cells called T cells leads to autoimmune disorders. Krueger uses psoriasis as a model to study inflammatory diseases that involve Th17 cells, a set of T cells. His work has implications for other common inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease.

Krueger's group focuses on the study of cutaneous inflammation and autoimmune mechanisms in human skin. Their research is fundamentally rooted in “bench-to-bedside” science, combining the clinical study of new medical therapeutics with laboratory study of relevant immunopathogenic mechanisms in human cells and tissues. The laboratory conducts clinical research on patients with psoriasis vulgaris at The Rockefeller University Hospital. They treat patients with a wide variety of engineered immune agonists or antagonists in order to stimulate or inhibit molecular control points for the restoration of normal immune responses. By combining novel immune-directed therapeutics with large-scale study of gene expression, an approach called pharmacogenetics, the researchers seek to elucidate the molecular pathways that cause pathogenic inflammation and regulate normal human immune responses.

More experimental immunotherapeutics have been assessed in clinical studies in psoriasis than any other human inflammatory disease. Krueger's group has pioneered a number of successful treatments, including some that act on T cells. One of these therapies antagonizes specific inflammatory cytokines; another utilizes a type of ultraviolet light with immunomodulatory properties.

The lab-based research accompanying Krueger's clinical trials includes the study of T cell, dendritic cell, and keratinocyte activation responses using techniques such as cell culture, flow cytometry, and biochemical analysis. His group is also studying the expression of a defined set of proinflammatory genes using real-time PCR, and that of many other genes using genome-wide statement studies with DNA arrays. The lab defined the first disease classification set for psoriasis using chip-based approaches, and recently determined a specific genetic and immunological signature that differentiates psoriasis from atopic eczema, a closely related skin disorder.

Krueger's research in healthy skin has shown that a previously unknown population of dendritic cells exists alongside macrophages in the skin. Other recent work by members of the lab has shown that a newly discovered immune cell, Th17, plays a central role in psoriasis and could serve as a target for future therapies. This T cell subset is regulated by IL-23, a protein shown by the group to be upregulated in psoriasis. IL-23 antagonism has produced major improvements in psoriasis, suggesting a new class of therapeutics. And by investigating the contribution of activated T lymphocytes, Krueger has found that psoriasis may be induced by tissue-infiltrating T lymphocytes, which trigger keratinocytes into a physiologically regulated wound repair pathway of hyperplasia and altered differentiation.

In order to place inflammatory pathways discovered in psoriasis in the context of other T cell mediated diseases and tissue rejection responses, the team is collaborating with investigators of other inflammatory cutaneous diseases. They are attempting to define molecular pathways that control cellular immune responses in order to broaden our understanding of organ-specific autoimmune diseases.
Even the simplest of organisms, such as bacteria, are capable of processing information in a highly sophisticated manner, adapting to varying environments and evolving new functions. Leibler is interested in the quantitative description of microbial systems, both on cellular and population levels.

In recent years, the field of molecular biology has moved away from the study of individual components and toward the study of how these components interact—a systemic approach that seeks an appropriate and quantitative description of cells and organisms. Leibler's laboratory is developing both theoretical and experimental methods to conduct studies on the collective behavior of biomolecules, cells, and organisms. In selecting a number of basic questions about how simple genetic and biochemical networks function in bacteria, his lab is beginning to understand how individual components can give rise to complex, collective phenomena.

Recent research topics in the laboratory include quantitative studies of interacting microorganisms. In particular, the question of how microbial populations survive in varying environments is being addressed both experimentally and theoretically. Leibler and his collaborators are developing new experimental techniques that will facilitate the quantitative analysis of long-time population dynamics in microbial populations. They are using statistical methods to analyze the long-term dynamics of closed microbial ecosystems, while applying theoretical approaches to other problems such as protein assemblies or the evolution of protein families.
Albert J. Libchaber, Ph.D.

When considered from a broad perspective, many events that appear to occur at random, such as weather, are in fact part of recurring patterns subject to mathematical principles. Libchaber applies a type of mathematics called nonlinear dynamics to biological systems in order to understand how an object and its surrounding environment act on one another to produce a specific result.

Libchaber studies mathematical patterns in biology at the organismal, cellular, and molecular levels. His work examines the interactions and dynamics between organism and environment, including the effects of moving boundary conditions on fluid flow. A moving fish, for example, involves a complicated interaction of a dynamic object with the surrounding fluid, with forces by both elements acting on one another. Additionally, Libchaber has shown how temperature and oxygen gradients as well as bacterial concentrations finely tune and control the bacteria’s motility and genetics. The research firmly established that an organism’s environment affects its genes and behavior.

Libchaber’s lab has also undertaken experiments at the single-molecule level to define the minimal conditions needed to produce an artificial cell. Within a phospholipid vesicle, which mimics a cell membrane, he places DNA containing the necessary genes and their regulatory sequences. This cell, which is in contact with a feeding solution through its semipermeable membrane pores, is then the environment for testing different gene networks and elementary logic circuits for their ability to reproduce essential events in a cell’s life, such as producing proteins and transporting them to the cell’s surface. The research may hold clues to the origin of life: the ultimate aim is to produce an artificial cell that reproduces itself following a genetic program.

Another important concept concerning the origin of life is the development of a genetic code that relates the 20-amino acid world to the four-nucleotide one. Libchaber has shown that an RNA molecule of a stem-loop structure, acting as a ribozyme, can load an amino acid to its 3’ end. This amino acid corresponds to the anticodon in the loop, and this whole process can be done without enzymes.

Past research in Libchaber’s lab has elucidated the effects of temperature on DNA. In a detailed study on the effects of thermophoresis on DNA in solution, they found that when far infrared lights are focused on the center of a chamber, DNA moves from a hot region to a cold one. As the heat is increased, however, convection sets in and causes the opposite occurrence: the DNA collects and accumulates at the bottom center of the chamber. Because this phenomenon could be used to sustain very high concentrations of DNA or proteins, it sheds light on how critical concentrations of DNA may have been reached amid early primordial-soup chain reactions. The laboratory then showed that DNA amplification by polymerase chain reaction is essentially a thermal convection process.

Currently, Libchaber’s work focuses on subsurface microbial ecosystems. Mud, a porous medium, contains a high density of diverse organisms. Despite this complexity, microbes in nature self-organize into simple reproducible patterns. His lab is conducting experiments in which the dynamics of natural mud coming to a steady state are observed and modeled.
Richard P. Lifton, M.D., Ph.D.

The pathogenesis of most human diseases, and the consequence of mutation of 80 percent of human genes, is unknown. By developing and implementing robust exome sequencing, Lifton has provided evidence that loss of nearly every gene will have large effect on the risk of specific traits. These findings expand the scope of human genetics, provide insight into pathophysiology, and define new targets for risk determination, prevention, and therapy.

The prevention and treatment of human disease rests upon understanding disease mechanisms. Despite extensive efforts, the pathogenesis of most diseases remains poorly understood. Genomic approaches provide a means to establish causal relationships between genotypes and phenotypes by enabling the determination of the mechanisms that link them and identifying new targets for prevention, treatment, and diagnosis. The Mendelian era identified the consequence of mutation of only 3,000 of the 20,000 human genes. The conservation of human genes among vertebrates suggests the vast majority of the remainder will have large effects when mutated.

To explore this possibility, Lifton developed rapid and inexpensive exome sequencing and new analytic approaches, enabling large-scale discovery of rare mutations with large effects on human traits. His lab has identified hundreds of new disease genes causing known or previously undescribed diseases. These include de novo mutation of large numbers of genes that cause congenital diseases, including malformations of the heart, the fusion of skull bones that prevent normal brain growth (craniosynostosis), and autism. Unexpectedly, mutations in chromatin modifiers are major contributors to both congenital heart disease and autism, explaining the frequent co-occurrence of these traits.

The lab has also developed methods to identify genes with incomplete penetrance, including new telomere maintenance genes for pulmonary fibrosis (e.g., PARN) that require inhalational exposure for disease expression; and rare mutations in SMAD4 that have low penetrance for craniosynostosis without the presence of a common BMP2 risk allele.

Similarly, the lab has been able to dissect a number of previously unsolved problems, including mutations that cause a variety of primary cancers and determinants of metastatic disease; and single mutations that cause hormone-producing tumors and diverse skin diseases.

In the case of hypertension, the most frequent global cause of death, Lifton has shown that mutations that cause extremely high or low blood pressure act by modulating renal salt reabsorption, providing the scientific basis for global efforts to reduce cardiovascular mortality by altering salt balance. Recent studies have shown that renal tumors that constitutively produce aldosterone—a common cause of severe hypertension—arise from single somatic mutations in a potassium ion channel that causes cell proliferation and hormone production. Chemical screens have identified macrolides that selectively inhibit mutant channels, providing new opportunities for the diagnosis and treatment of these tumors. Genetic studies also identified a new physiologic pathway regulating the balance between salt reabsorption and potassium ion secretion. Biochemical studies have revealed the mechanisms that regulate this balance, which explains how increased dietary potassium lowers blood pressure.

These results collectively demonstrate a path to determine the consequence of mutation of every gene in the human genome, showing that much more genomic discovery lies ahead than behind.
Shixin Liu, Ph.D.

ASSISTANT PROFESSOR, LABORATORY OF NANOSCALE BIOPHYSICS AND BIOCHEMISTRY

The cell’s biomolecular complexes are often coupled to each other in time and space, giving rise to new forms of function and regulation. Using single-molecule fluorescence- and force-based methods, Liu investigates the coordination and competition among principal machineries involved in gene expression. The goal is to elucidate how cellular processes collectively respond to changing conditions during growth, development, and disease.

Virtually all aspects of the cellular life involve the operation of nanometer-scale machines, commonly known as molecular motors, which convert chemical energy into mechanical work. The advent of single-molecule techniques has made it possible to examine these tiny machines in unprecedented detail by following each individual movement, pull, and twist in real time. It is thus not surprising that, over the past decade, a soaring number of molecular motors have been subjected to single-molecule interrogation, uncovering a wealth of novel information and, oftentimes, unexpected phenomena.

However, much less attention has been paid to how these machines interact or cooperate—and these questions represent a crucial next step toward connecting insights from in vitro experiments back to the cellular environment. Liu’s research takes this step, using state-of-the-art single-molecule tools, sometimes in combination with genomic approaches, to understand how motor-driven processes are integrated into a coherent network in the cell, and how their interplay evolves in response to environmental changes.

Through his training, Liu has established expertise in two primary classes of single-molecule methods: fluorescence-based detection and force-based manipulation. As a graduate student at Harvard University, he used single-molecule fluorescence spectroscopy to examine the movement of HIV reverse transcriptase, the target of many anti-AIDS therapies, as it makes a DNA copy of viral RNA. During his postdoc, Liu utilized high-resolution optical tweezers to investigate the bacteriophage phi29 DNA packaging motor, which is a ring-shaped ATPase, a common type of molecular motor. His research revealed the precisely coordinated chemical and mechanical transitions that its five ring subunits must undergo, as well as an unexpected division of labor among these subunits—insights that may apply to many molecular motors with similar structures.

Liu’s current research focuses on the fundamental gene expression process, during which a series of molecular machines act in concert to convert genetic DNA code into RNA messages, and subsequently into protein products. Among the specific interests of his laboratory is the interplay between bacterial transcription, translation, and the RNA degradation machineries that controls the fate of RNA transcripts and the output of protein synthesis.

Another area of focus for the lab lies within more complex eukaryotic cells. Liu is designing experiments to investigate how RNA polymerase reads through eukaryotic chromatin, a process regulated by transcription factors, the remodeling of chromatin, and epigenetic modifications. In addition, he is interested in chromatin replication, a process in which the replisome not only faithfully duplicates the genetic code but also helps transmit epigenetic information from parental to daughter strands. The lab is seeking to visualize the hierarchy of molecular events involved in this process, and the fates of its players.
Roderick MacKinnon, M.D.

INVESTIGATOR, HOWARD HUGHES MEDICAL INSTITUTE • JOHN D. ROCKEFELLER JR. PROFESSOR, LABORATORY OF MOLECULAR NEUROBIOLOGY AND BIOPHYSICS

Electrical signals play many roles in the body: They control the pace of the heart, regulate the secretion of hormones, and transfer information between neurons. The MacKinnon lab studies the physical and chemical principles of biological electricity with a special focus on the passage of inorganic ions, such as potassium and chloride, across cell membranes.

Ion channels catalyze the diffusion of inorganic ions down their electrochemical gradients across cell membranes. Even though ions move passively through them, ion channels are sophisticated systems responsible for electrical signaling in living cells, an essential component of many physiological processes. MacKinnon aims to understand the physical and chemical principles of ion channel function.

Like enzymes, ion channels have specific substrates: Potassium, sodium, calcium, and chloride channels permit only their namesake ions to diffuse through their pores. The MacKinnon lab has used mutational analysis to show that potassium channels are tetramers of identical subunits and that specific “signature sequence” amino acids form a selectivity filter that allows only these ions to pass through.

To understand how the selectivity filter conducts potassium ions, the MacKinnon lab determined the x-ray structures of numerous potassium channels, including the KcsA potassium channel at a resolution higher than 2.0 Å, and has proposed a mechanism for their function. His lab has also investigated anion selectivity by determining the atomic structures of prokaryotic and eukaryotic members of the CLC chloride channel family. Although built on a completely different architectural plan than that of potassium channels, these transport proteins use many of the same basic physical principles.

The diverse members of the potassium channel family have evolved to open in response to specific triggers in their environments. To understand the atomic basis of potassium channel gating, the MacKinnon lab has analyzed the function and determined the structures of several different members of the family. For example, studies of MthK and BK have begun to reveal how the free energy of calcium binding is harnessed to open the pore. In addition, the lab has advanced the understanding of how the inward rectifier Kir2 opens in response to a lipid and Kir3 in response to a G protein by resolving these channels’ atomic structures. MacKinnon’s group has also determined structures of both archaebacterial and eukaryotic voltage-dependent potassium (Kv) channels and has posited several fundamentally new ideas about their mechanism.

Recently, his group has begun to study mechanical gating, which underlies sensory detection in touch and hearing as well as basic physiological processes such as cell volume regulation and blood pressure control. MacKinnon and others have observed significant mechanosensitivity in the gating of certain potassium and calcium channels. Now, they seek to understand how mechanical forces elicit electrical signals, and if mechanosensitivity is physiologically relevant in these channels.

For much of this ongoing work, lab members employ cryo-electron microscopy, taking advantage of new, highly sensitive direct electron detectors and other advances. By obviating the need for crystals, this technology has made it possible to determine detailed structures of long-inaccessible channels such as Slo1 and Slo2, Eag1, hERG, KcnQ, and HCN to gain new insights into their function.
Magnasco’s group uses living beings as a source of inspiration for creating new mathematical descriptions of nature. The lab’s main focus is on computational and experimental neurophysiology, primarily in the context of auditory function but also touching on vision, memory, olfaction, and other sensory processing, as well as studies of dolphin communication in aquaria and in the wild.

Magnasco uses both computational and experimental methods to model the complexity, organization, and information-processing properties of living organisms. The lab concentrates on sensory processing, employing experimental techniques to investigate the auditory representation of complex objects in laboratory animals as well as in humans. They also study communication in dolphins. Using computer modeling, they work to understand how and where sound is processed in the mammalian brain, as well as more general models of brain function.

Magnasco’s computational studies include both abstract modeling and data analysis. Modeling work is underway on neural architectures of auditory processing, including frequency discrimination and spatial perception models. These efforts also address neural function and memory, such as mechanisms employed by the brain to balance excitatory and inhibitory activity in neural circuits. Data analysis work concentrates on methods to analyze large-scale neurophysiological datasets to demonstrate the footprints of such critical balancing during wakefulness and its absence during loss of consciousness, anesthesia, epilepsy, and normal sleep.

The laboratory’s effort to study dolphin communication and cognition is carried out both in aquaria and with wild animals at several field stations. The scientists are seeking to understand both the natural extent of dolphins’ vocal repertoire and communication ability, and their ability to acquire novel signals. This work involves extensive data analysis efforts as well as fieldwork to develop novel acquisition techniques.

Prior work from the Magnasco lab has touched on many aspects of sensory processing, including auditory, visual, and olfactory functions. For example, together with A. James Hudspeth, he created a mathematical model of a “trapdoor amplifier” in the hair cells of the inner ear—a concept that challenged some of the most basic assumptions about how the human ear processes sound. His work studying birdsong, which followed the expression of the ZENK gene, allowed researchers to watch learning and memory at the cellular level in the brains of canaries. And in a sound analysis breakthrough, Magnasco created an algorithm that transforms sound into visual representations—with far more accuracy than any method previously available—closely replicating the system used by the human brain.

In addition, the group has studied venation of tree leaves as a model system of a complex biological network with interesting topological and geometrical features, and has recently created methods to section whole rodent livers and reconstruct their three-dimensional vascular structure in unprecedented detail.

**SELECTED PUBLICATIONS**


The Maimon lab aims to understand how brains internally compute and store the value of quantitative variables—like heading angles, spatial distances, time intervals, and event probabilities—and then use these variables to guide behavior. By studying this topic in Drosophila, a classic genetic system, the team’s long-term goal is to better understand how molecules, through their effect on cellular electrophysiology, impact memory and cognition.

Explaining animal behavior requires more than defining stimulus–response relationships. Rather, cognitive processes like spatial attention, reward expectation, sensory prediction, and the construction of internal spatial maps have a fundamental role in modifying these relationships. Conceptual frameworks for thinking about such internal processes, and our understanding of their neural implementation, are only starting to emerge.

Work in the Maimon lab is inspired by the observation that insects, despite having tiny brains, are capable of performing specific cognitive operations extremely well. For example, desert ants know if they are 30 or 90 meters away from their nest. Honeybees communicate, with their waggle dance, if a flower patch is 30 or 90 degrees to the left of the sun. By seeking comprehensive descriptions of how insect brains perform such quantitatively accurate internal calculations, the Maimon lab aims to provide inspiration on how to better understand cognition in larger brains.

The lab studies the genetically tractable fruit fly, Drosophila melanogaster, and has pioneered one of the primary approaches it uses. The technique involves monitoring or perturbing activity in neuronal circuits in flies as they perform flight or walking behaviors, glued to a tiny platform.

In recent work, the Maimon lab found that flies are partially blind each time they make a rapid flight turn. This happens because every time a fly turns, the image of the world sweeps over the retina and the fly needs a mechanism to ignore this large self-generated sensory stimulus. The lab has discovered that fly visual neurons receive a quantitatively tailored, internally generated silencing input during turns. When humans make rapid eye movements, our brains face the same problem: We need to ignore the self-generated sensory stimulus caused by these movements. The silencing mechanism discovered in flies may illuminate similar processes in our own visual system.

In another line of work, the Maimon lab has described how the fly brain constructs an internal sense of angular orientation. Humans, too, have a robust sense of orientation, and its importance is made clear when we become disoriented upon exiting a subway station, or in the early stages of Alzheimer’s disease.

Specifically, the Maimon lab has characterized a neuronal circuit in the Drosophila central complex—a set of structures in the middle of the fly brain—that allows flies to build and update an internal compass-like signal. This circuit operates even in complete darkness, wherein flies must internally integrate how much their legs are turning to update their sense of angular heading. The central features of this biological circuit are analogous to computational models proposed for how rodents build an internal sense of orientation, and may thus inform how any neural system performs mathematical integration.

The lab continues to study how flies calculate quantitatively accurate, spatial and nonspatial variables, and use these to guide behavior. This research program provides a platform for discovering basic mechanisms of how brains integrate, think, and decide.
CRISPR-Cas systems enable bacteria and other microbes to acquire immunity against viruses by capturing snippets of their DNA. Marraffini investigates the molecular mechanisms that make CRISPR immunity possible, as well as its evolutionary implications. His lab also explores genome editing and other potential applications for CRISPR-Cas systems.

Sequence-directed genetic interference pathways control gene expression and preserve genome integrity in all kingdoms of life. In many bacteria and most archaea, CRISPRs—clustered, regularly interspaced, short palindromic repeats—specify a recently discovered genetic interference pathway that protects cells from phages and conjugative plasmids. Within CRISPR sequences, the repeats are separated by short spacer sequences that match phage or plasmid genomes and specify the targets of interference.

Spacer sequences are transcribed into CRISPR RNAs (crRNAs)—small RNAs that, through base-pairing interactions with the target sequence, guide Cas nucleases to the invasive nucleic acid. Upon infection, CRISPR arrays can acquire new repeat-spacer units that match the infecting phage or plasmid. In this way, CRISPR-Cas systems provide adaptive and inheritable immunity to the bacterial cell. The spacer content of CRISPR arrays reflects the many different invaders encountered by the host and can be expanded rapidly in response to new ones. Accordingly, CRISPR loci constitute a form of genetic memory that ensures the rejection of new, returning, and ever-present invading DNA molecules.

Marraffini uses Staphylococcus epidermidis and Streptococcus pyogenes as model systems for studying CRISPR immunity. The clinical isolate S. epidermidis RP62a harbors a CRISPR spacer that matches the nickase gene (nes) that is present in nearly all staphylococcal conjugative plasmids and prevents their spread. Using this system, Marraffini revealed that the CRISPR-Cas machinery targets DNA, rather than RNA, directly. Work in the Marraffini lab also demonstrated that the S. pyogenes crRNA-guided Cas9 DNA nuclease constitute a formidable tool for genetic engineering.

Marraffini's current research employs molecular genetic and biochemical approaches to analyze the genesis and function of CRISPR-Cas systems. He ultimately hopes to answer fundamental questions about how CRISPR-Cas systems destroy their targets, how the genetic memory is generated, and how CRISPR-Cas immunity affects the evolution of bacteria and archaea.
Bruce S. McEwen, Ph.D.

ALFRED E. MIRSKY PROFESSOR, HAROLD AND MARGARET MILLIKEN HATCH LABORATORY OF NEUROENDOCRINOLOGY

Throughout life, hormones alter behavior and mood, regulate neuroendocrine activity, protect the brain from stress, and regulate brain aging and certain disease processes. McEwen’s laboratory takes an interdisciplinary approach to investigate how stress and sex hormones act on the brain. His work has wide-ranging implications for understanding how the brain changes from embryonic development through adult life.

The neuroendocrine system links behavior and experience with hormone secretion. Hormones, in turn, regulate body functions such as reproduction, fluid and mineral balance, metabolism, and immune activity. They also help shape the developing brain, affect mood and behavior, and contribute to aging and disease.

In studying the cellular and molecular mechanisms underlying the effects of stress and sex hormones on the hippocampus and other regions of the adult or developing brain, the McEwen laboratory has helped create a new understanding of how the brain changes in adult life and in development. Their work has implications for understanding the impact of stress on the brain and sex differences in human brain function as well as in Alzheimer's disease, depression, posttraumatic stress disorder, and normal aging.

In relation to stress, the McEwen lab has shown that hormone actions on structural plasticity are intertwined with the actions of excitatory amino acid transmitters, NMDA receptors, other neurotransmitters, and BDNF.

McEwen has also found that chronic stress reduces the number of neurons in the dentate gyrus. In the hippocampus, the lab has shown that chronic stress causes neurons to undergo remodeling of dendrites, and excitatory amino acids are important regulators of this neuronal remodeling, acting in concert with glucocorticoids. Stress-induced remodeling is largely reversed once the stress is removed, although gene expression patterns continually change with experience and resilience declines with aging.

The hippocampus is involved in the formation of episodic, spatial, and contextual memories, and is one of the first brain structures to degenerate in Alzheimer’s disease. The McEwen lab has recently shown that age-related impairment of cognitive function can be reduced by treatment with riluzole, a drug that reduces glutamate overflow.

In studying the action of sex hormones, the researchers have identified sex hormone receptors in the hippocampus that regulate signaling pathways associated with synapse formation and maturation. These “nongenomic” forms of the classical sex hormone receptors work in concert with the more classical genomic actions of sex hormones on gene expression, and they increase excitatory synapse formation and exert neuroprotective effects in the hippocampus and other brain regions.

The McEwen lab has recently expanded its scope of study to investigate stress-induced structural remodeling in the amygdala, which is involved in fear and strong emotions, and the prefrontal cortex, which is involved in working memory, self-regulation, and extinction of fear learning. In animals, aging leads to loss of the ability to promptly extend dendrites of the prefrontal cortex after cessation of stress.

Work conducted as part of the Neuroimmune-Physiology Program, headed by Karen Bulloch, has led to the discovery of dendritic-like cells in the brain that are activated by interferon-γ to present antigens. These cells increase in number in the aging brain, and are induced by viral infections and simulated stroke.

SELECTED PUBLICATIONS
At the surface of the intestinal lining, immune responses are carefully balanced: Invasive pathogens must be eliminated or excluded, while nutrients and trillions of commensal microbes must be tolerated. Mucida studies how the immune system associated with intestinal mucosae maintains this careful balance by generating efficient protective responses without jeopardizing its tolerance to innocuous foreign substances.

The human intestinal mucosae, with an area of about 300 square meters, form the largest body surface exposed to the outside world. Within the gut, an estimated 10 trillion commensal bacteria reside, and each day, about 100 grams of dietary protein passes through. Although the great majority of these potential antigens are harmless, the intestine is a major entry point for viruses, pathogenic bacteria, fungi, and parasites.

To mediate immunity over such a large and active area, the intestine contains more lymphocytes than the entire rest of the human body. These cells must act rapidly and efficiently to protect the gut, while also avoiding unregulated or excessive immune responses that potentially could lead to allergies and severe inflammatory bowel diseases. In a healthy gut, the immune system strikes a perfect balance between responsiveness and tolerance.

Mucida studies the mechanisms behind these two competing immunological functions within intestinal tissue, and what happens when either is compromised. His lab is testing the hypothesis that distinct signals from lymphocytes' spatial niches within intestinal tissue determine these cells' pro- or anti-inflammatory activity. Currently, the nature of such environmental cues and the mechanisms by which they influence immune cells' adaptation are not well understood.

A major focus of the lab is the development and function of leukocytes that are stimulated by antigens and other cues from the surrounding intestinal tissue. These include intraepithelial lymphocytes (IELs), a class of specialized T cells found within and just below the intestinal epithelium. Mucida's work has shown that the presence of TGF-β, retinoic acid, and microbiota can induce CD4 T cell plasticity, leading, for instance, Foxp3-expressing regulatory T cells (Tregs) to differentiate into tolerance-promoting IELs. His ongoing work continues to define how IELs contribute to the immunological balance within the gut, including their role in protecting against infection.

Located within the intestinal muscularis, neurons that innervate the gut's lining also send signals to gut immune cells, and Mucida's lab is investigating the hypothesis that the enteric neurons may provide a means to quickly sync immune responses across a large area. A recent study from the lab found that, in a luminal infection, norepinephrine from sympathetic neurons activates a tissue-protective gene program in muscularis macrophages. Mucida continues to study how such neuro-immune communication might help control inflammation, and how its loss can lead to severe tissue damage and inflammatory disorders.

Cues from within the intestinal lumen can also affect tolerance of innocuous antigens throughout the body. Mucida is working to better understand the mechanisms behind this phenomenon, known as oral tolerance. His lab has determined that only classical dendritic cells are required to generate the tolerance-inducing peripheral Tregs necessary for oral tolerance, and he is now further investigating the means by which signals derived from the intestinal lumen are disseminated.
Nottebohm is interested in the origin and evolution of ideas, and he examines the genesis of concepts as a biological process. He holds that a full understanding of a phenomenon requires that we know its origins and evolution, and that this holds true for our understanding of matter, space, time, people, life, the universe, gods, and science.

For decades, the Nottebohm laboratory has worked on the basic biology of vocal learning in birds. This research described the stages of vocal learning and the underlying circuitry, which was found to include anatomically discrete nuclei that seem to have no function other than their involvement in the acquisition and production of learned song. Several of these nuclei are larger in males, which do most of the singing, than in females. Furthermore, in males the size of these nuclei changes seasonally, a finding that has led to the discovery that some of these nuclei accommodate a constant production and replacement of the very cells whose circuits encode the learned song, and that this replacement peaks at times of peak memory load.

The discovery of this phenomenon in songbirds has led to a rethinking of the elements that set limits on how much can be learned: the replacement of seemingly healthy neurons suggests that long-term memory involves not only changes in synaptic efficacy and number, but also changes in DNA expression, affecting a cell’s performance in a circuit. Such permanent changes would, however, use up memory space, thus setting the need for periodic replacement of whole cells. Conceived in this manner, the management of memory space emerges as a key principle of brain function and suggests that neuronal replacement can also be thought of as a process of brain rejuvenation.

In recent years, Nottebohm has switched his attention from hands-on experimental work to an ambitious review of the genesis of key ideas in science, philosophy, and religion. His work treats the phenomenon of culture formation as a biological process, with laws of its own and emergent patterns and paradoxes. His focus is on big questions, including the origins of people, of life, of the universe, and of God. Nottebohm argues that such questions—aimed to understand how some of the thoughts and beliefs at the center of our culture came to be and the rhythm and rules of their creation and modification—constitute a legitimate scientific challenge.
Nurse’s research focuses on the molecular machineries that control eukaryotic cell reproduction, cell growth, and cell form. Using the fission yeast *Schizosaccharomyces pombe* as a model system, his studies have led to the co-discovery of cyclin-dependent kinase as the key regulator molecule controlling S phase and mitosis—findings that have had implications for understanding reproduction, development, and cancer.

Currently, the Nurse laboratory pursues work in three areas: the controls over the cell cycle, cell growth, and nuclear size homeostasis. The lab is split on two sites, with the major activity located at the Francis Crick Institute in London, and a smaller group located at The Rockefeller University. The Rockefeller group works mainly on combining chemical biology and genetics to investigate problems of cell biology and cancer.

In collaboration with Tarun Kapoor, the Nurse lab works on the development and use of fission yeast for chemical biology. A fission yeast strain has been constructed with compromised multidrug resistance, allowing chemical drug screens and experiments to be carried out efficiently. This strain has been used in synthetic lethal approaches to identify chemicals that influence the course of the cell cycle and cell growth. Several chemical drugs and their targets have been identified and characterized, including a chemical that inhibits fatty acid synthase and reduces nuclear membrane growth, and another that inhibits Aurora protein kinase. The latter compound has been used to demonstrate that the various functions of this kinase are inhibited by different levels of activity. More recently, the researchers identified a drug inhibiting the AAA+ ATPase Midasin, a protein that has a role in assembling nucleolar precursors of the 60S ribosomal sub-unit.

Presently, the lab at Rockefeller is focused on identifying novel small molecules that influence cell proliferation and cell growth, both to better understand these processes and to generate drugs with the potential for cancer chemotherapy. The lab has established live imaging for screening of both fission yeast and human cells. A variety of small molecules have been discovered that result in delays of the cell cycle, some with effects on microtubules. The lab is now further characterizing these chemicals to determine their molecular targets, their mechanisms of action, and their potential for therapeutics.
Michel C. Nussenzweig, M.D., Ph.D.

In the laboratory, Nussenzweig’s studies focus on the molecular aspects of the immune system’s innate and adaptive responses using a combination of biochemistry, molecular biology, and genetics. His work on adaptive immunity, particularly on B lymphocytes and antibodies to HIV-1, while his studies of innate immunity focus on dendritic cells.

The immune system protects vertebrates from a multitude of pathogens. Two types of immune responses have evolved to accomplish this task: innate and adaptive. Lymphocytes are the primary effectors of adaptive immunity and assemble a diverse repertoire of immune receptors using a somatic gene recombination process known as V(D)J recombination. This process enables the production of a very large number of unique receptors that recognize almost any antigen, as well as self-reactive receptors, which must be silenced to prevent autoimmune diseases.

The multitude of antigen receptors produced by V(D)J recombination are relatively low-affinity and must be refined by somatic hypermutation and class switch recombination to produce the high-affinity antibodies that protect against most pathogens, including HIV-1. Hypermutation and selection occur in specialized micro-anatomical compartments called germinal centers. Nussenzweig’s laboratory investigates the molecular basis of such hypermutation, and the selection for high affinity antibody-producing cells in the germinal center.

Understanding the rules that govern hypermutation and selection is especially relevant to effective vaccine responses. Nussenzweig’s research aims to understand these processes with the goal of creating vaccines for pathogens such as HIV-1. As part of that effort, his laboratory has cloned highly potent human antibodies to HIV-1 that are currently being used in clinical studies of HIV-1 prevention and therapy.

A second area of interest is the physiological function and development of dendritic cells. Current studies focus on outlining the pathway of human dendritic cell development and differentiation.

Nussenzweig’s experiments are consistent with the notion that self-antigens induce tolerance. In contrast, pathogens taken up by dendritic cells in the context of activation stimuli, such as those found during inflammation or tissue destruction, induce prolonged T cell activation. This steady-state tolerizing function of dendritic cells may be essential to their role in eliciting immunity. During inflammation or infection, they present self-antigens simultaneously with non-self-antigens. By establishing tolerance to self-antigens before challenge with pathogens, dendritic cells can focus the adaptive immune system entirely on the pathogen, thereby avoiding autoimmunity. The ability to target antigens to dendritic cells and control their function in vivo has significant implications for the development of vaccines and therapies for autoimmunity. Recently, the lab has defined distinct progenitor lineages for classical spleen dendritic cells, plasmacytoid dendritic cells, and monocytes, a step toward antigen-specific targeting.

SELECTED PUBLICATIONS


Duplication of chromosomes requires numerous proteins acting together to unwind and replicate the two strands of duplex DNA. O’Donnell’s laboratory studies these replication mechanisms with the goal of understanding how the protein gears act together to make copies of DNA, and how they function with repair and recombination factors to ensure that these copies are accurate.

Over the years, research from O’Donnell’s lab has provided an overview of how the replication machine functions in *Escherichia coli*, yeast, and humans. A circular protein that he and his colleagues refer to as a sliding clamp completely encircles duplex DNA, acting as a mobile tether to hold the replication machine to the chromosome and sliding along behind the machinery for long distances.

The sliding clamps of prokaryote (β) and eukaryote proliferating cell nuclear antigen (PCNA) have similar structure and function. O’Donnell solved the structures of these ring-shaped proteins in collaboration with John Kuriyan’s laboratory (now at the University of California, Berkeley) and showed that they comprise six domains organized on a dimer or trimer surface.

To become attached to DNA, sliding clamps require a multiprotein clamp loader machine that uses adenosine triphosphate (ATP) to open and place the circular clamp on DNA. The lab has studied the detailed workings of these clamp loaders in both prokaryotic (γ complex) and eukaryotic (RF-C) systems. New and recent studies into other, accompanying processes include how the replication machinery interfaces with proteins in repair, DNA damage checkpoint paths, and recombination.

The eukaryotic replisome is much more complex than its prokaryotic counterpart. O’Donnell’s lab recently succeeded in reconstituting the eukaryotic replisome from over 30 different polypeptides—a project that has held his fascination over the past few years. O’Donnell and his colleagues have determined the architecture of the eukaryotic replisome, a feat not yet accomplished in a prokaryotic system. Eukaryotic replisomes must deal with histones, which organize the DNA in eukaryotic cells. The histones also regulate how the genome is expressed in different tissues of an organism, a process referred to as epigenetic inheritance. The replisome structure has implications about how the process of replication deals with histones, and how it may conserve the inheritance of epigenetic information.

Studies of eukaryotic replisome function have also outlined the rules by which distinct DNA polymerases act on the two strands of DNA during replication. The lab is applying techniques such as single-molecule technology and single-particle reconstruction by electron microscopy to understand how the replisome functions with other factors. These studies can be expected to provide new insights into eukaryotic replication, repair, and epigenetic inheritance.

Michael O’Donnell, Ph.D.

INVESTIGATOR, HOWARD HUGHES MEDICAL INSTITUTE • ANTHONY AND JUDITH EVNIN PROFESSOR, LABORATORY OF DNA REPLICATION

EDUCATION
B.S. in biochemistry, 1975
University of Portland
Ph.D. in biochemistry, 1982
University of Michigan

POSTDOC
Stanford University, 1982–1986

POSITIONS
Assistant Professor, 1986–1991
Associate Professor, 1991–1993
Professor, 1993–1996
Weill Cornell Medical College
Professor, 1996–
The Rockefeller University
Assistant Investigator, 1990–1993
Investigator, 1993–
Howard Hughes Medical Institute

HONORARY SOCIETIES
National Academy of Sciences

SELECTED PUBLICATIONS
Pfaff uses molecular, neuroanatomical, and neurophysiological methods to study the cellular mechanisms by which the vertebrate brain controls behavior. His laboratory’s research has focused on steroid hormone effects on nerve cells as they direct natural, instinctive behaviors, as well as the influences of hormones and genes on generalized brain arousal.

The Pfaff lab, which investigates the cellular control mechanisms for behavior, has two areas of focus: steroid hormones’ influence on the brain and generalized arousal of the central nervous system. In four distinct steps, previous work in his lab has shown how specific chemicals, the steroid hormones, act in certain parts of the brain to direct natural, instinctive behaviors. First, he identified in rodents the exact cellular targets in the hypothalamic and limbic forebrain for steroid hormones, opening the door for the discovery of similar sex hormone receptor systems in species ranging from fish to primates.

Second, Pfaff’s lab worked out the neural circuitry for hormone-dependent female reproductive behavior, the first behavior circuit elucidated for any vertebrate. Third, they followed up on this discovery by using estrogen to turn on several genes in the forebrain. Fourth, Pfaff has shown these gene products facilitate reproductive behavior. For example, knocking out the estrogen receptor gene prevents female reproductive and maternal behaviors.

Current work in Pfaff’s lab focuses on the question: Why do animals or humans do anything at all? His work seeks an answer through the concept of generalized arousal (GA). He offered the first operational definition of GA, which activates all behavioral responses, enabling scientists to measure arousal quantitatively. In humans, deficits in GA contribute to a wide variety of cognitive and emotional problems, from depression to dementia.

Pfaff and physicist Jayanth Banavar have gathered large amounts of precise behavioral data suggesting the onset of GA is a phase transition. Now the lab is following individual mice through this phase transition at 20-millisecond resolution to describe the behavioral change in mathematical terms, and to follow up on a preliminary discovery of a striking sex difference.

The cellular origins of central nervous system arousal, GA, reside deep in the hindbrain, in the nucleus gigantocellularis (NGC). Using the developing mouse brain, the lab is investigating the transcriptional regulation responsible for NGC neuron birth and migration. Meanwhile, cultured NGC neurons are being recorded on multi-electrode arrays and lab members are working to reconstruct reticulospinal systems, which arise from the NGC, in the dish.

Lee-Ming Kow is testing the hypothesis that first expression of the delayed rectifier, a class of potassium channel, accounts for the initial burst of heightened excitability seen in young NGC neurons in the mouse and in culture. From postnatal day 3 to 6, pups’ arousal increases dramatically as does NGC excitability, suggesting delayed rectifier expression is responsible.

Meanwhile, Inna Tabansky is endeavoring to derive these crucial neurons from mouse embryonic stem cells. Collaborating with the Friedman lab, she has determined the transcriptome of these GA master cells with special attention to mRNAs within axonal projections to the thalamus responsible for “waking up” the cerebral cortex. She has so far uncovered one transcript unique to this subpopulation of NGC neurons and several that suggest how these NGC neurons manage their metabolism to survive challenges and prevent GA failures.
The ability to faithfully store and retrieve memories is an important adaptive quality that allows humans to reflect on, engage with, and respond to an ever-changing environment. Research in the Rajasethupathy lab focuses on observing and manipulating large-scale neural dynamics in real-time in behaving animals, to understand memory processing in the mammalian brain during health and disease.

Neuroscience seeks to understand how computations in the brain give rise to meaningful behavior, and in many ways, memory lies at the heart of this endeavor. Research in the Rajasethupathy lab is focused on understanding neural-circuit mechanisms of memory storage and retrieval in guiding adaptive behavior. The lab explores fundamental questions regarding the distributed nature of memory representations as they form, stabilize, and reorganize over time, an approach that requires the simultaneous monitoring of neural dynamics spanning multiple brain regions over multiple timescales.

More specifically, the Rajasethupathy lab uses fast volumetric cellular resolution imaging approaches for observing neural dynamics, as animals engage with complex virtual environments, to dissect dynamic and distributed population codes of memory representations. These experiments are then coupled with real-time optogenetic manipulation of neural dynamics to appropriately bias the animal’s neural activity and resulting behavior. The eventual goal is to understand not only how memories are allocated and maintained in neural circuits, but ultimately to understand how they are appropriately (or inappropriately) retrieved to guide adaptive (or maladaptive) behavior.

Another goal of the Rajasethupathy lab is to complement neural-circuit approaches with genomic and transcriptomic approaches, to untangle the scale and complexity of the molecular genetic features that drive circuit properties underlying memory-guided behaviors. The Rajasethupathy lab works to develop and apply methodologies that provide molecular annotation to activity-defined cell populations, with the hopes of identifying molecular logic that enables specialized circuit architectures and circuit computations, which in turn support memory allocation, maintenance, and retrieval. Over the long term, they hope to fill a long-standing need in neuroscience of bridging the gap between genes and circuits in order to better understand cognitive behaviors.

While pioneering studies of memory have illuminated the molecular and physiological mechanisms that occur in individual synapses, the next frontier in memory research will require, among other approaches, a more circuit-level and genome-scale understanding of memory processes in the brain, tackling questions such as: How is information encoded and integrated across multiple brain regions during learning and recall? How do top-down memory circuits form and engage with bottom-up circuits to faithfully retrieve memory representations? What are the gene-regulatory mechanisms that enable allocation and maintenance of neurons within these memory ensembles? And how are these circuit-level and genome-wide properties of memory ensembles disrupted during disorders of memory? By leveraging transformative technologies at the convergence of systems genetics and systems neuroscience, the Rajasethupathy lab hopes to address these questions to further our understanding of memory processes in health and disease.
Jeffrey V. Ravetch, M.D., Ph.D.

By binding to receptors on immune cells, antibodies mediate immune responses ranging from neutralizing pathogens to suppressing inflammation. The Ravetch lab investigates the complex biology of these antibody-Fc receptor interactions, and their roles in normal immune function and disease. These studies are providing novel approaches to treating infectious and inflammatory diseases, as well as cancer.

Pairs of activating and inhibitory molecules, known as Fc receptors, are found on the surface of nearly all immune cells. The Ravetch lab’s studies of Fc receptors has led to the discovery that, by binding to these receptors, antibodies coordinate the immune system’s effector responses. The lab continues to investigate the roles and mechanisms of Fc-mediated interactions, and applies its findings to improve treatments for disease.

By disrupting activating receptors, lab members found they could ablate antibody-dependent inflammatory reactions, such as those characteristic of lupus. Subsequent studies established Fc receptors’ pre-eminence in the pro-inflammatory activity of both protective and pathogenic immunoglobulin G (IgG) in vivo. Even classical neutralizing antibodies for bacterial toxins and viruses require Fc receptor engagement, and ongoing studies are examining its role in the response to the Ebola virus.

Likewise, the lab’s work has shown that therapeutic anti-tumor antibodies, including rituximab, Herceptin, and others, achieve their effects through Fc receptor-dependent pathways. Fc receptor-mediated effector activity is now accepted as the dominant mechanism for anti-cancer antibodies in humans.

The lab has sought to enhance effector activity by engineering antibodies’ Fc domains, and a number of the modified antibodies developed by the group have been approved or are awaiting approval for clinical use against cancer. Lab members continue to dissect Fc interactions with the goal of enhancing antibodies’ ability to both kill tumors and activate a memory response to them.

Interactions with inhibitory Fc receptors, meanwhile, enable antibodies to mediate tolerance to harmless antigens. Experiments in animal models and human populations have shown that when this mechanism breaks down, autoimmunity ensues. This condition can be reversed, however, by restoring the inhibitory Fc receptor pathway. The lab has defined and is characterizing a family of Fc receptors, Type II FcRs, involved in immune suppression.

These inhibitory and activating mechanisms alone do not fully explain how antibodies mediate the full range of effector responses. The discovery that modifications to antibodies can alter Fc interactions has provided the final piece to the puzzle. When investigating the anti-inflammatory activity of high doses of IgG, the lab discovered that a fraction of it contained a specific modification: the addition of a sialic acid to an Fc domain glycan. Sialylation switches the binding specificity from the canonical activating Fc receptors to Type II FcRs.

The lab has since begun investigating the role of Fc domain modifications in responses to infection and vaccination, including those for flu, dengue, and malaria. Fc sialylation is correlated with the production of higher affinity antibodies after the flu vaccine, and is being studied as a mechanism for a “universal” flu vaccine. Meanwhile, Fc afucosylation appears to contribute to severe secondary dengue infections. The lab is currently dissecting its role in antibody-dependent enhancement in dengue and developing strategies to mitigate it.
George N. Reeke Jr., Ph.D.
ASSOCIATE PROFESSOR, LABORATORY OF BIOLOGICAL MODELING

Signals exchanged between cells contribute to the complexity that makes the behavior of biological systems hard to predict. Reeke employs computer simulations to investigate how the components of biological systems work together to carry out complex functions. He is specifically interested in modeling neuronal systems to better understand how physical phenomena within them give rise to perception, motor control, and memory.

As the nervous system develops, it must acquire adaptive behavior through interactions with the environment. Reeke’s research simulates neural systems based on experimental neurophysiology with simulated or real sensors and locomotor organs. It then challenges those systems to perform various tasks, shedding light on sensory integration, perceptual categorization, motor control, and aspects of memory in both normal and damaged or diseased brains. These models have shown how the ability to recognize objects and events in the environment can arise in the nervous system as a result of the operation of selective processes guided by innate value systems. Reeke’s research indicates that there is no need for built-in representational codes or computational algorithms, nor for feedback of error signals from omniscient external teachers. The results call into question the popular theory that the brain is a kind of computer.

Areas of particular interest in Reeke’s lab are perception, control of locomotion, and the development of analytic tools appropriate for the characterization of these activities in space and time. He is focusing on neural mechanisms for the recognition and recall of temporal patterns, which are of fundamental importance for planning and navigation, language, and music. The lab has developed novel information-theoretic measures, based on the temporal intervals between events of interest, that help to quantify the temporal characteristics of the signals exchanged among neurons and the spatiotemporal discharge activity of neuronal assemblies.

Reeke has shown that these same measures can be used to analyze data obtained from behavioral animal experiments. In a collaborative project with Rockefeller’s Donald W. Pfaff, Reeke helped measure the contribution of estrogens to exploratory behavior in female mice. The method could also be adapted to measure the contribution of a range of genes to behavior, as well as to understand the effects of different genotypes or pharmacological manipulations on behavior.

Reeke’s lab has also developed a composite approach to modeling neurons in which the degree of detail employed in modeling different membrane conductances is adapted to the dynamical complexity of each neuron. For example, their analysis of a model cerebellar Purkinje cell shows that when both the rate and the timing of a stimulus are varied, novel cell discharge behavior emerges. Studies of large-scale systems incorporating these techniques provide a greater understanding of how different types of neurons in both normal and diseased brains function at the integrated system level. Members of the lab have applied these methods to study non-classical responses of cells in the primary visual cortex, the process by which juvenile birds learn their songs, how general anesthetics affect the activities of neuronal clusters in the cerebral cortex, and the generation of descriptive models of sensorimotor contingencies and their relationship to reward in the cerebellum and other brain regions.

SELECTED PUBLICATIONS
Charles M. Rice, Ph.D.

MAURICE R. AND CORINNE P. GREENBERG PROFESSOR IN VIROLOGY, LABORATORY OF VIROLOGY AND INFECTIOUS DISEASE

Millions of people are infected with hepatitis C or hepatitis B viruses, which cause liver cancer and liver failure. Meanwhile, other RNA viruses such as Zika, yellow fever, dengue, and chikungunya cause significant morbidity and mortality. Rice’s lab works to understand virus replication and innate immune responses that limit infection. His group is also developing new in vitro culture and animal models to facilitate this work.

Hepatitis C virus (HCV) infects the liver and is a major cause of cirrhosis and liver failure. Conventional virus culture methods are unsuccessful for HCV, and creative new approaches have been required to study it. Rice is among those who pioneered such techniques, and his group continues to unravel how HCV infects liver cells, replicates, assembles, and causes disease. Ongoing studies in his lab are revealing how the virus exploits hepatocyte lipid and protein secretory pathways to promote its own growth. These and other findings are being applied to develop new technologies, such as 3D culture and induced pluripotent stem cell culture, which will be used to efficiently grow HCV and other viruses.

The Rice lab also studies the host side of the virus-cell interface, and has identified and characterized host proteins that make cells permissive for infection by HCV. In addition, cellular micro RNAs, which are important in translational control, also regulate HCV RNA in cells. With innovative bioinformatic methods that map these interactions with unprecedented precision, the lab has discovered further complexities in the host-pathogen relationship.

Rice’s work on HCV can be applied to other liver viruses, such as the hepatitis B virus (HBV), which is often refractory to treatment due to viral genome persistence as a covalently closed circular DNA (cccDNA). His team’s development of a mouse model with a human liver and immune system, as well as new in vitro culture methods, are revealing new strategies to potentially target cccDNA.

It has long been recognized that the immune response to pathogens includes an innate, rapidly activated component. Rice’s group studies how infection impacts pathways induced by interferon, triggering innate immune responses. To conduct these investigations, Rice has developed high-throughput screening assays to identify interferon-stimulated genes (ISGs) that limit or, in some cases, enhance virus infection. Understanding how ISGs work may lead to improvements in prevention and treatment of infectious diseases. In that context, the Rice lab has focused on viruses of global health concern, such as HCV, HBV, influenza A, dengue, yellow fever, Zika, and chikungunya. Collectively, these pathogens are responsible for hundreds of millions of infections, and enormous human suffering every year. Another area currently under investigation is the mechanisms of attenuation of the yellow fever vaccine, and the possible human genetic causes of a rare yellow fever-like illness that can occur after vaccination.

In studies led by research associate professor Margaret R. MacDonald, the mechanistic details of an ISG known as zinc-finger antiviral protein (ZAP) are under investigation. ZAP potently inhibits alphavirus and filovirus replication, and how it functions with other ISGs will reveal another aspect of virus-cell engagement. MacDonald, in collaboration with others, is also investigating the human antibody response to the Zika virus with the goals of developing an antibody reagent for therapeutic use, while gaining insight into successful immune responses that will guide vaccine development.
The way a stretch of DNA is organized inside the cell—whether it is loosely or compactly packaged by associated proteins—is believed to reflect the activity level of the genes it contains. The Risca lab studies how the three-dimensional architecture of the mammalian genome helps to precisely control transcriptional programs and genome maintenance in both healthy cells undergoing differentiation and in cells exposed to stressors, such as DNA damage.

The 46 chromosomes of the human genome would measure almost two meters if stretched out end-to-end as pure DNA. To fit into the roughly five-micron-wide cell nucleus, DNA is wrapped around histone proteins into repeating bobbin-like structures called nucleosomes, which make up the chromatin fiber. Chromatin organizes the genome within the nucleus to control transcription, DNA replication, and DNA repair. Defects in chromatin organization can perturb gene expression, leading to serious consequences that include developmental disorders and cancer.

The Risca lab investigates the three-dimensional architecture of chromatin and the basic biophysical mechanisms by which it defines and maintains stable states in the regulation of transcription and other DNA-based processes.

Risca’s postdoctoral studies helped to fill a significant gap in the field of chromatin biology: The high density of chromatin packing made it challenging to study how nearby nucleosomes fold together in the chromatin fiber. Risca and her colleagues developed a technique, called RICC-seq, capable of examining the configuration of one to three nucleosomes. This length scale is particularly important because it corresponds to the length of genetic elements that contain binding sites for transcription factors.

RICC-seq uses ionizing radiation to create spatially distinct clusters of DNA strand breaks within intact cells. DNA fragments spanning break sites are sequenced and the resulting data aggregated across many cells to create a high-resolution map of DNA folding. Using RICC-seq, Risca and colleagues uncovered accordion-like compaction of chromatin fibers within repressed regions of chromosomes. Meanwhile, within active regions, they found evidence of looser folding with few contacts between neighboring nucleosomes, consistent with previous data.

In addition to RICC-seq, the Risca lab uses computer simulation, microscopy, and other sequencing-based methods to study genome architecture in order to understand how it is regulated and how it, in turn, controls regulatory molecules’ access to DNA.

To better understand these relationships, the lab focuses on two natural perturbations in chromatin states. First, they study X-chromosome inactivation, which occurs when female mammalian cells must repress large portions of one of their X chromosomes during development. Using mouse embryonic stem cells, Risca is interested in the biophysical mechanisms that control this large-scale silencing of transcription. Secondly, the lab investigates senescence, a state in which cells irreversibly exit the cell cycle and undergo associated changes in genome organization. Because senescence can shut down the replication of cells in response to DNA damage or oncogene activation, it acts as a first line of defense against cancer.

The new mechanistic insights that result from this work may make it possible to better understand how cells respond to perturbations brought on by mutations or chromatin-targeting drugs, potentially leading to more precise tailoring of cancer therapies and control of cell differentiation.

**Viviana I. Risca, Ph.D.**

**ASSISTANT PROFESSOR, LABORATORY OF GENOME ARCHITECTURE AND DYNAMICS**

**EDUCATION**

B.S. in physics, 2004
Stanford University
Ph.D. in biophysics, 2012
University of California, Berkeley

**POSTDOC**

Stanford University School of Medicine, 2012–2018

**POSITIONS**

Assistant Professor, 2019–
The Rockefeller University

**SELECTED PUBLICATIONS**

Jeremy M. Rock, Ph.D.

Assistant Professor, Laboratory of Host-Pathogen Biology

Mycobacterium tuberculosis is the leading cause of death due to infectious disease and infects one-third of the world’s population. By investigating the mechanisms that enable this bacterium to cause tuberculosis and evade current antibiotics, the Rock lab aims to lay the foundation for new therapeutic strategies to improve control of this pandemic.

Despite the discovery of effective antibiotics, tuberculosis (TB) remains an enduring global public health threat. New drugs, drug regimens, and innovative approaches to limit drug resistance are desperately needed—and to facilitate their development, the Rock lab seeks to provide a more complete understanding of the genetic and biochemical basis of Mycobacterium tuberculosis (Mtb) pathogenesis.

Genetic studies of this bacterium have thus far been hampered by the difficulties associated with conventional genetic tools. To fill this methodological gap, Rock and colleagues developed a CRISPR interference (CRISPRi) gene knockdown method for Mtb. This transformative tool will enable the systematic interrogation of gene function in Mtb using high-throughput approaches to previously intractable problems in the field. The Rock lab uses this and other methods to study, among other things, the mechanisms that enable chronic infection, antibiotic tolerance and resistance, and large-scale genetic and chemical interactions.

TB is a chronic, progressive disease, often with a long period of latency following initial infection. In most cases, the host immune system is capable of restraining but not eliminating Mtb, leading to lifelong infection. The mechanisms that enable the pathogen to persist in the face of a robust adaptive immune response, sometimes for decades, are incompletely understood. The Rock lab is using new approaches to define the genetic basis for persistent Mtb infection.

Mtb infection can be treated with antibiotics. However, effective TB treatment requires a combination of four drugs taken for a minimum of six months. This lengthy treatment, necessitated by the presence of antibiotic-tolerant bacilli that arise during infection, is one of the most important roadblocks to effective TB control. Moreover, antibiotic tolerance can ultimately facilitate the evolution of antibiotic resistance, thereby fueling the growing problem of drug-resistant TB. As a postdoctoral fellow, Rock discovered an ancient mechanism of DNA replication proofreading in Mtb that is central to controlling the drug-resistance rate. His lab is currently investigating the molecular mechanisms of antibiotic tolerance, as well as the mechanisms by which the bacterium can ultimately evolve antibiotic resistance.

Finally, the lab is interested in using genome-scale genetic and chemical interaction mapping to improve Mtb chemotherapy. The current four-drug combination to treat TB was developed in the 1960s. Rock seeks to identify new antibiotic combinations that leverage drug target synergies to create more potent antibiotic regimens, thereby reducing treatment time and limiting the emergence of drug resistance.
Gene expression is controlled primarily at the level of transcription, the process by which genes are copied into RNA before being translated into proteins. A central question in biology is how the transcription of the human genome's approximately 25,000 genes is regulated in a gene- and cell type-specific manner. Roeder studies the transcription factors, including epigenetic factors, and underlying mechanisms involved in this regulation.

Differential gene expression, regulated primarily at the level of transcription, underlies key events in an organism's development, cell growth, differentiation, and homeostasis, as well as in pathologies such as cancer. The transcription programs central to these events are governed by cell-specific master transcription factors bound to specific enhancer and promoter elements. The extraordinary power and significance of such factors is profoundly demonstrated by the ability of very small subsets to reprogram somatic cells to a pluripotent state. Roeder's major objectives are to determine the mechanisms by which such factors, acting ultimately upon the general transcription machinery, activate or repress specific target genes in various physiological processes.

The lab's multipronged experimental strategy emphasizes powerful cell-free systems, pioneered by Roeder, that recreate the essence of transcription in a test tube with cloned genes and factors purified from cellular extracts. The structure, function, mechanism of action, and regulation of these factors is then studied by a combination of biochemical, cell-based, and genetic analyses.

The actual transcription of protein-coding genes is mediated by RNA polymerase II and coactivator initiation factors (TFIIA, TFIB, TFID, TFIE, TFIF, and TFIIH) that form functional preinitiation complexes on promoters via an ordered assembly pathway. The process begins with the recognition of common core promoter elements (e.g., TATA box) by the multisubunit TFIID. These initiation factors, which comprise the general transcription machinery, represent the ultimate targets of various gene-specific factors. However, other "cofactors" are essential for functional communication between the gene-specific factors, to which they bind, and the general transcription machinery.

Roeder's current work is heavily focused on these cofactors, many of which are structurally complex. They include cofactors that alter the structure of the natural chromatin template (e.g., multi-subunit histone acetyl- and methyl-transferase complexes), others that act directly on the general transcription machinery (e.g., the 30-subunit Mediator), and a variety of cell/activator-specific cofactors (e.g., the B cell-specific OCA-B and the inducible PGC-1 implicated in energy metabolism).

The lab's current activities focus on transcriptional activators important for homeostasis (nuclear hormone receptors); lymphoid cell differentiation (E2A, OCT1/2, OCA-B); lymphoid malignancy (E2A-PBX1, AML1-ETO, and MLL1-AF9 leukemogenic fusion proteins); and tumor suppression (p53).

In addition to detailing the mechanisms by which specific target genes are activated by individual transcriptional activators and associated cofactors, the Roeder laboratory is interested in determining the basis for differential usage of cofactors by individual activators in varied contexts. They are also discovering how variations in cofactor usage can dictate cell fate (e.g., growth arrest versus apoptosis in p53-dependent DNA damage responses), and, in the case of leukemic fusion proteins generated in acute myeloid leukemia, potential therapeutic targets.
Michael P. Rout, Ph.D.
PROFESSOR, LABORATORY OF CELLULAR AND STRUCTURAL BIOLOGY

Nuclear pore complexes control the passage of molecules into and out of the nucleus, regulating how DNA communicates with the rest of the cell. Rout is interested in how the pore complex mediates this transport, and in the nature of the many diseases associated with alterations in it. Together with collaborators, his lab is also working to develop technology to map and interpret the dynamic molecular interactions within a cell.

Using a variety of techniques, Rout and his colleagues are studying the structure of nuclear pore complexes (NPCs) and relating their structure to sites of interactions and reactions with soluble nuclear transport factors. Ultimately, they hope to gain a better understanding of the roles NPCs play in gene expression, nuclear regulation, and maintenance.

A full understanding of how NPCs mediate transport requires a comprehensive inventory of their molecular components, knowledge of how each component contributes to the overall structure, and information on the interactions NPC proteins have with components of the soluble phase. Rout and his colleagues have catalogued the components of the yeast NPC and determined that it is composed of a surprisingly small number of proteins whose size and high degree of overall symmetry account for the NPC’s large mass.

By systematically isolating and analyzing the subcomplexes of proteins making up the NPC, and by isolating the entire NPC as a whole, the scientists have computed three-dimensional maps of its architecture, sufficient to resolve its molecular organization. This mapping has exposed similarities between structures in coated vesicles and those in the NPC, supporting a hypothesis for their common evolutionary origin in a progenitor protocoatomer. Moreover, the map reveals an extensive underlying modularity in the architecture of the NPC, suggesting that repeated duplication events led to the evolution of its final architecture. They have also shown how the scaffold of the NPC resembles the structure of a suspension bridge, providing both strength and flexibility to the assembly. The lab is now continuing their work to characterize the NPC’s architecture with the highest level of precision.

In a similar fashion, Rout and his colleagues are studying members of the mobile phase, focusing on the kinetic behavior of nup-transport factor and transport factor-cargo interactions using a variety of in vitro and in vivo approaches. These results have already suggested a mechanism for nuclear transport. Rout’s ultimate goal is to integrate ultrastructural and biochemical studies to understand the molecular basis of the translocation of different transport factors across the NPC. He aims to reconstitute key reactions of these processes in vivo, study the high-resolution structures mediating the transport processes, and test possible mechanistic models in vivo to understand the complete sequence of events during a transport cycle.

With support from the National Institutes of Health, Rout has formed the National Center for Dynamic Interactome Research (www.ncdir.org), which includes several collaborating laboratories at Rockefeller and other institutions. The center will develop the methodology required to obtain a comprehensive map of protein interactions within any organism, and to study their dynamic behaviors. This will allow researchers to explore the utility of the technology for functional elucidation of complex biological processes, with an initial focus on cell cycle control, transcription, oncogenesis, and viral infection.

SELECTED PUBLICATIONS

EDUCATION
B.A. in zoology, 1986
M.A. in zoology, 1989
Ph.D. in molecular biology, 1989
University of Cambridge

POSTDOC
The Rockefeller University, 1990–1997

POSITIONS
Assistant Professor, 1997–2002
Associate Professor, 2002–2008
Professor, 2008–
The Rockefeller University

AWARDS
Irma T. Hirschi/Monique Weill-Caulier Trust Research Award, 1999
Rita Allen Foundation Scholar, 2000
Sinsheimer Fund Scholar, 2000
Presidential Early Career Award for Scientists and Engineers, 2001
The Rockefeller University Distinguished Teaching Award, 2018
Animal behavior reflects the interplay of two types of responses: those that arise innately, from neural circuits pre-programmed into the genome, and those acquired by learning from past experience. Using the fruit fly *Drosophila melanogaster*, Ruta works to define the neural-circuit mechanisms that generate innate and learned behaviors.

Animal behavior arises from an interplay between instinct and learning. Certain behaviors are innate and invariant across members of a species, suggesting they are genetically programmed into the nervous system. However, behavior must also be highly flexible to allow individuals to adapt to their unique and changing experience of the world. A major focus of the Ruta lab is to delineate the distinct neural circuits and computations that underlie innate and learned behaviors, and to reveal how these circuits can be modified through evolution or individual experience to generate novel behavioral adaptations. To accomplish this, the group uses a multidisciplinary toolkit—including optical tracing techniques, electrophysiology, functional imaging, and behavior—to study the concise chemosensory circuits of the fly, with the goal of revealing how they mediate fixed and flexible behaviors at the level of synapses, cells, and circuit motifs.

In recent work, the Ruta lab has examined how the nervous system is wired to flexibly encode and assign meaning to the complex and vast chemical world. By examining the functional architecture of the Drosophila mushroom body, an associative brain center in the fly that is essential for olfactory learning and memory, they shed light on the synaptic and circuit mechanisms that mediate flexible odor processing, demonstrating how neuromodulation can act to rapidly reconfigure circuit properties and allow the same odor to drive alternative behavioral responses. In parallel, the Ruta lab has used Drosophila courtship as a paradigm to explore how innate behaviors emerge from genetically specified neural circuits and are modified through evolution to generate species-specific variations in mating behavior.

All olfactory behaviors in the fly, whether innate or learned, are initiated through the same molecular recognition events: the binding of volatile chemical cues to odorant receptors expressed in peripheral sensory neurons. Odorant receptors in insects, unlike in mammals, are thought to function as heteromeric odor-gated ion channels. To begin to reveal how the binding of odorant ligands is coupled to ion flux in this large and diverse family of membrane proteins, the Ruta lab is performing biochemical, electrophysiological, and structural studies on insect odorant receptors. The aim is to provide insight into the molecular basis for odorant signaling in insects and to lay the foundation for the development of novel strategies to prevent the transmission of insect-borne diseases.
A ubiquitous family of cell-surface receptors called G protein coupled receptors act as transducers for myriad processes, ranging from color vision to hormone signaling to synaptic transmission. These receptors are also the targets for approximately one-third of therapeutic drugs. The Sakmar laboratory examines the molecular mechanisms by which G protein coupled receptors work and develops new technologies to advance drug discovery.

The primary research focus of the Sakmar laboratory is to study the biology and chemistry of heptahelical G protein coupled receptors (GPCRs). The mechanism of transmembrane signaling by heptahelical receptors is an area of intense scientific interest that has tremendous biological and pharmaceutical relevance.

The laboratory has pioneered novel methods, including genetic code expansion to introduce unnatural amino acids into expressed receptors, as a tool for GPCR-targeted drug discovery. The researchers recently adopted a variety of ancillary experimental approaches, including targeted photocrosslinking to map ligand and antibody binding sites; bioorthogonal labeling reactions to introduce site-specific fluorophores; and monoclonal antibody epitopes to facilitate single molecule imaging studies. These strategies can be combined with traditional approaches to study GPCRs, channels, and other difficult-to-express membrane proteins.

Sakmar's work has focused primarily on family A GPCRs, also known as the rhodopsin family, as a model system for biophysical studies, and chemokine receptors for studies of ligand recognition and proteomics. Chemokine receptors control cell migration and also act as coreceptors for HIV-1 cellular entry. Other receptors and aspects of G protein-mediated signaling are also under investigation. In particular, the lab is studying downstream cytoplasmic components of G protein signaling pathways, with a particular interest in defining protein-protein interactions that modulate crosstalk between signaling pathways. In addition, the lab has studied how mutations in genes encoding GPCRs result in expressed receptors with high levels of basal activity. One such gene, CYSLTR2, causes a rare ocular cancer called uveal melanoma, and is the first known example of a GPCR “driver” oncogene.

A new area of research in the Sakmar lab focuses on human protein folding disorders and amyloid syndromes. Members of the lab have discovered novel chaperone-like amyloid-binding proteins that can be used to stabilize transient intermediates and create unique panels of monoclonal antibodies with diagnostic or therapeutic potential.
Research in Shaham’s lab focuses on two areas: the control of programmed cell death during animal development and the roles of glial cells in nervous system development and function. The lab uses the roundworm *C. elegans* for both areas of research, and has demonstrated that their underlying cellular programs were maintained through evolution from *C. elegans* to humans.

Nervous systems consist of two major cell types: neurons and glia. The basic properties of neurons and the mechanisms governing neuronal development and function are well studied. In contrast, the functions of glia, the most abundant cell type in vertebrate nervous systems, remain mostly unexplored, and few mediators of glial function are known. Glia are important in disease: 95 percent of brain malignancies are of glial character, and glial defects are associated with neurodegenerative diseases including amyotrophic lateral sclerosis and Alzheimer’s disease, suggesting that understanding glial functions, and how these functions go awry, is indispensable for comprehending brain functions and dysfunctions.

One explanation for the gap in understanding glia may lie in their neurotrophic properties. Glial manipulation often results in neuronal loss, precluding investigations of other effects glia might have on neuronal morphogenesis or activity. The Shaham lab has discovered that glia of the nematode *C. elegans* bear striking morphological, anatomical, and molecular similarities to vertebrate glia. Importantly, *C. elegans* glia are not required for neuronal survival, making *C. elegans* a unique model for deciphering glial roles in the nervous system and allowing, for the first time, manipulation of these cells in vivo without the complication of neuronal loss.

The researchers have shown that glia are essential for neural development, promoting axon outgrowth and dendrite extension, and that glia are required for morphological plasticity of neuronal receptive endings; in fact, some sensory receptive structures fail to form in their absence. The lab has also uncovered morphology-independent roles for glia in sensory neuron function, showing that animals lacking glia exhibit profound sensory deficits. To understand the bases of these functional interactions, Shaham and his colleagues have identified glia-enriched proteins and studied their roles in neuronal development and function.

Although *C. elegans* glia do not control neuronal survival, the Shaham lab has explored the death of other *C. elegans* cells to understand the principles by which vertebrate glia might control neuronal viability. In addition to discovering novel transcriptional and protein degradation-mediated controls of apoptotic cell death, the lab has identified a novel cell death program independent of known apoptotic regulators. The unique morphology accompanying this cell death program is conserved during the development of the vertebrate nervous system. The Shaham lab identified many genes promoting this new cell death form, all of which are conserved among vertebrates, raising the possibility that the mechanism of this novel cell death program is also conserved.
During development, cells must arrange into particular tissue patterns in order to become functional organs. Shyer studies the emergence of biological form, or morphogenesis, using the chicken embryo as a model system. By focusing on physical dynamics, the lab is able to gain insight into critical symmetry-breaking events that control how tissues and organs take shape.

As an organism develops, homogenous tissues gradually give rise to complex morphological features. Understanding this process is crucial to enhancing fundamental knowledge about development. In recent decades, the prominence of genetic models has led to an assumption that patterns of gene expression, more than any other factor, govern tissue formation. Taking an alternative course, the Shyer lab focuses on the mechanical forces that influence morphogenesis. Her team takes an integrative approach to developmental biology, melding physical and molecular perspectives.

To better understand the dynamics of morphogenesis, the lab measures and perturbs physical aspects of cells in chicken embryos. The group conducts experiments in eggs, whole tissue explants, and primary cells extracted from embryos. Using these techniques, Shyer seeks to determine whether, given the appropriate physical and chemical contexts, researchers can reconstitute tissue dynamics from cellular components.

The emergence of feather follicles in birds is analogous to that of hair follicles in mammals. The Shyer lab therefore uses avian skin as a model for investigating questions about pattern formation that may be relevant in human skin. An applied goal of the lab is to uncover tactics for generating lab-grown tissues that more faithfully mimic their natural counterparts. Though scientists can already generate tissue from cultured cells, these products have limited clinical usefulness because they often fail to develop important morphological features. For example, skin grafts made from cultured cells using existing techniques do not form hair follicles or sweat glands—a shortcoming that may cause health issues if used to replace damaged skin. A lack of sweat glands, for instance, can lead to problems with thermoregulation.

Previously, Shyer and co-author Alan Rodrigues showed that avian follicle morphology and gene expression patterns depend on contractility-driven cellular mechanics. These findings corroborate the scientists’ view that mechanical processes can precede and trigger cell fate-determining gene-expression changes. Shyer and Rodrigues ultimately aim to build unified models that integrate mechanical and molecular perspectives of morphogenesis. To test the generality of these mechanisms, they hope to explore whether other tissue types demonstrate patterning dynamics similar to those observed in skin.
Developmental genetics has furnished the parts list for vertebrate development, but it is not remotely possible to reassemble those parts and predict the outcome. Embryonic stem cells can recapitulate slices of development and thus provide a rich readout of the signaling pathways that pattern the embryo. Siggia wishes to quantify the genetic signals that define morphogenesis.

Genetics and genome sequencing have supplied an extensive parts list for how to create an embryo, yet it is still impossible to construct a precise description of the process from genome-scale data. Existing models of signaling pathways have too many parameters to fit experimentally, and they ignore the complexities of cell biology. Siggia’s group recently developed mathematical descriptions for embryonic patterning that encapsulate how a field of cells can react to an external signal and choose between three discrete fates. The resulting mathematics is geometric and naturally meshes with the phenomenological concepts from the pre-molecular era of embryology.

To test this model, Siggia’s group worked with Shai Shaham to develop a microfluidic device for long-term imaging of larval development in C. elegans. The device permits the timed application of genetic stimuli, offering a sensitive test of dynamical models of development.

Vertebrate signaling pathways are another area where pathway dynamics in single cells has lagged behind genetic and biochemical findings. In collaboration with Ali H. Brivanlou, Siggia’s group found that the TGF-β pathway is adaptive: in response to a step increase in ligand, the transcriptional response of the pathway turns off and the output varies with the time derivative of the ligand. In the embryo, positional information can be conveyed by the rate of ligand changes, not merely its level.

To take a step closer to the embryo, Siggia’s lab has begun investigating early differentiation in human embryonic stem cells confined on micropatterned substrates. In response to the ligand at the top of the signaling hierarchy uniformly mixed in solution, all three germ layers emerge in reproducibly ordered patterns. Because cell communication via secondary signals is an essential part of morphogenesis, stem cell differentiation provides a quantitative assay for this process.

Geometric descriptions of biodynamics are not always evident by inspection, and Siggia, together with colleagues at McGill University, has developed computational evolutionary methods to discover them. These findings have led to proposals for how circadian oscillators can both have a temperature-independent period and the ability to entrain and phase lock to a temperature oscillation. Together with Michael W. Young, Siggia conducted experiments motivated by this theory. In a related project, his group worked with Frederick R. Cross to demonstrate that the yeast cell cycle is phase locked to a temperature oscillation. Together with Michael W. Warmflash, A. et al. Dynamics of TGF-β signaling reveal adaptive and pulsatile behaviors reflected in the nuclear localization of transcription factor Smad4. Proc. Natl. Acad. Sci. U.S.A. 109, E1947–E1956 (2012).

Siggia wishes to encapsulate how a field of cells can react to an external signal and choose between three discrete fates. The resulting mathematics is geometric and naturally meshes with the phenomenological concepts from the pre-molecular era of embryology.
The Simon lab has two areas of focus. One is pediatric cancer, for which their work runs the gamut from identifying oncogenic drivers and studying malignant transformation to coordinating clinical trials. The lab’s second endeavor is to examine individual events to gain insight into biological systems. Using imaging and other tools, these studies include the movement of individual cellular components and the activity of single nuclear pores and proteasomes.

The Simon lab uses imaging techniques to observe and clarify dynamics and interactions in living systems. Imaging enables his group to study molecules in isolation, in the living cell or animal. In addition, it often makes it possible to detect alterations of single molecules that produce pathological changes in the whole animal. Imaging single molecules or cells provides the means to report not only the average behavior of populations, but also the diversity of their individual behaviors.

A major new initiative of the lab is on cancers affecting children and young adults. This work includes population studies in patients with fibrolamellar hepatocellular carcinoma, a type of liver cancer, aimed to identify the alterations in the genome responsible for tumorigenesis. The biophysical and imaging tools developed in the lab are being used to characterize the molecular dynamics of the oncogenic drivers, as well as cellular alterations. At the same time, the lab is designing diagnostics, identifying potential therapeutics, and organizing clinical trials.

Another part of the lab focuses on the study of individual events in cellular function. The study of populations, whether of molecules or people, provides important insights into biological processes. However, valuable information is lost when one examines the population average. For example, if a cellular machine exists in two discrete states, the macroscopic measure is the average of the two states. Such a measure has shortcomings: it may reflect activity states that do not exist at the individual level, miss transient active states, or make it difficult to put different steps in a proper temporal order and to resolve between two microscopic mechanisms. A microscopic approach, however, does not face these problems.

Single phenomena that Simon and his lab members have followed include individual vesicles docking and fusing to the membrane, single proteins translocating across the endoplasmic reticulum, and single cells metastasizing in the lung. They have also succeeded in imaging the birth of individual HIV particles, and the activity of single nuclear pores and proteasomes.

Another key area of research in the lab is to develop new technologies that can improve the spatial or temporal resolution of images obtained through microscopes or other modalities. Simon and his colleagues are working to improve the sensitivity of the imaging systems they use so that molecules can be followed for longer time periods, and they are developing new reporters that can follow biological processes and act as actuators for these processes.
Agata Smogorzewska, M.D., Ph.D.

ASSOCIATE PROFESSOR, LABORATORY OF GENOME MAINTENANCE

Throughout its lifetime, a cell’s DNA is under constant metabolic and environmental assault that can lead to damage. If left unchecked, the resulting genome instability can initiate cancer and a variety of other human disorders. Using Fanconi anemia and other genetic diseases as a backdrop, Smogorzewska’s research aims to elucidate the pathways that protect organ function and prevent cancer, with a focus on those that replicate and repair DNA.

Research in the Laboratory of Genome Maintenance is focused on DNA repair, with special emphasis on repair that takes place during replication. The group’s interests are broad, ranging from the molecular function of proteins involved in the DNA damage response to the cellular and in vivo consequences of deficiencies in proper DNA replication and repair.

The DNA interstrand crosslink (ICL) is the prototype DNA lesion repaired during replication. ICLs covalently link the Watson and Crick strands of the DNA, and the repair of these lethal lesions requires a dual excision of the crosslinked bases as well as repair of the resulting double-strand breaks. This feat is accomplished in a multi-step process mediated by the Fanconi anemia (FA) pathway and factors that promote homologous recombination (HR), including BRCA1 and BRCA2. FA patients lack components of this pathway and suffer from bone marrow failure and infertility due to failures in the maintenance of hematopoietic and germline stem cells. FA is also associated with a very high incidence of cancer, most likely due to the mutagenic nature of incorrectly repaired ICLs.

In recent years, the lab has identified SLX4, RAD51, and UBE2T as genes mutated in Fanconi anemia patients. By identifying these and other novel genes in patients with FA and related disorders, the group is able to use insights and patient-derived tools in the quest to understand the mechanism of DNA repair at the cellular level. Currently, the prevention and treatment of tumors are the major clinical challenges for the disease. The lab is using next generation sequencing and functional analysis of identified variants to investigate the etiology and vulnerabilities of cancers in FA patients, with the goal to identify biomarkers or treatment targets.

ICL repair deficiency is also associated with kidney and liver dysfunction. A rare human disease called karyomegalic interstitial nephritis (KIN) develops when FAN1, a nuclease that functions in ICL repair, is deficient. The lab recently developed a mouse model of KIN that is being used to gain insights about the pathogenesis of the disease, as well as to obtain more global understanding of how genome maintenance pathways protect organ function.
Hermann Steller, Ph.D.

Cell death plays an important role in sculpting a developing organism, and in eliminating unwanted and potentially dangerous cells throughout life. Steller’s research focuses on how programmed cell death is regulated and how its dysfunction contributes to disease, including cancer. He also studies the nonlethal use of cell death proteins for cellular remodeling and the mechanism of protein degradation in development, aging, and disease.

Central to both development and tissue homeostasis, apoptosis is intimately associated with a variety of human diseases including cancer, autoimmunity, AIDS, neurodegenerative disorders, and liver diseases. This makes cell death proteins promising drug targets. Using both Drosophila melanogaster and mice as model organisms, Steller’s lab investigates the molecular mechanisms that govern the decision between cell death and survival.

Apoptosis has been conserved throughout evolution, from worms to insects to humans. Steller’s team discovered and characterized a family of proteins that act as integrators of many different signaling pathways to ensure that the death program is activated. Reaper, Hid, and Grim activate apoptosis by binding to and inactivating inhibitor of apoptosis (IAP) proteins, which in turn directly inhibit caspasases, the key executioners of apoptosis. A conserved IAP-binding motif originally discovered in these proteins has provided the basis for a novel class of cancer therapeutics currently in clinical trials.

Many organs and tissues can repair wounds and regenerate cells lost upon injury. Steller discovered that cells undergoing apoptosis in response to stress or injury can stimulate their own replacement by secreting mitogens to induce proliferation of adjacent progenitor cells. These mitogen pathways have been highly conserved throughout evolution, and similar phenomena have been observed in mammals with profound implications for cancer therapy, stem cell biology, and regenerative medicine.

The cell death machinery can also serve nonlethal functions for cellular remodeling in Drosophila and mammals. Steller’s work initially revealed the importance of this process for the generation of mature sperm. Subsequently, similar mechanisms were shown to operate during nervous system development. Steller defined the role of enzymes that control protein degradation by the apoptosis machinery, and his work has revealed that two major proteolytic systems, caspasases and proteasomes, are coordinated to achieve “controlled demolition” of unwanted cellular structures. These findings are relevant for human diseases, including muscle-wasting diseases, neuronal degeneration, and cancer.

More recently, work in Steller’s lab has focused on the mechanisms by which cells degrade unwanted or toxic proteins. The long-term health of cells critically relies on selective protein degradation since damaged or aggregated proteins cause proteotoxic stress that can impair cell function and cause cell death. Many neurodegenerative diseases—including Alzheimer’s, Parkinson’s, Huntington’s, ALS, and retinitis pigmentosa—are caused by the accumulation of protein aggregates. Steller and his colleagues discovered a mechanism that enables cells to boost their proteolytic capacity by stimulating the assembly of proteasomes, the multi-protein protease complex responsible for the regulated degradation of intracellular proteins. Manipulating the activity of this pathway may lead to novel therapeutics for the treatment of age-related neurodegenerative diseases.
The brain is critically dependent on sufficient blood flow. Strickland’s laboratory investigates how dysfunction of the circulatory system contributes to neurological conditions such as Alzheimer’s disease in humans and in mice.

Neurological disorders of the central nervous system represent profound medical problems worldwide. For example, Alzheimer’s disease affects millions of people and has severe physical, psychological, and financial consequences. By studying patients and mouse models with neurological diseases, Strickland is working to elucidate the molecular mechanisms by which neural function is disrupted.

In investigating neurovascular dysfunction, the Strickland lab studies the mechanisms underlying the pathogenesis of Alzheimer’s disease. Cerebrovascular defects contribute to the progression of Alzheimer’s pathology, and members of the lab are using transgenic mouse models of Alzheimer’s to evaluate blood-brain barrier damage and the roles that blood clot formation and degradation play in this disease. Their research has determined that the $\beta$-amyloid peptide, which is considered to be a causative factor in Alzheimer’s, interacts with fibrinogen to promote irregular fibrin accumulation in the brain and increase brain inflammation. This peptide also hinders blood clot degradation, which could compromise blood flow, exacerbate inflammation, and lead to neuronal death. These findings suggest that fibrin and the mechanisms involved in its accumulation and clearance may present novel therapeutic targets for slowing the progression of Alzheimer’s disease.

The Strickland lab has also recently found that $\beta$-amyloid can activate coagulation Factor XII (FXII) in the plasma of both Alzheimer’s patients and mouse models. The activation of FXII initiates fibrin clotting as well as inflammatory processes, both of which are recognized pathologies in Alzheimer’s disease. Promotion of FXII activation by $\beta$-amyloid could help explain the association between Alzheimer’s disease and vascular diseases. This knowledge may ultimately identify new pathogenic mechanisms that could disrupt neuronal function, aiding in the discovery of novel diagnostic and therapeutic approaches.
Encounters with pathogens can alter the function of immune-cell genes in a number of ways including alterations to chromatin, the complex formed by DNA and its packaging proteins. The resulting changes in gene expression can produce persistent traits. The Tarakhovsky lab studies the mechanisms by which pathogens affect chromatin function, and their effect on long-lasting immune and non-immune cell responses to the environment.

An organism’s response to environmental stresses has both a predetermined and an adaptive nature. The predetermined response reflects the cell-type specific differences in signaling pathways and gene expression programs, while adaptive responses reflect the ability of individual cells within a given lineage to integrate distinct environmental cues and respond to them in a well-calibrated fashion. Both types of responses depend largely on tightly controlled gene-expression programs that operate within limits imposed by a gene-specific chromatin environment. In the immune system, changes in chromatin are associated with, and contribute to, the differentiation of hematopoietic stem cells into highly diverse immune-cell subpopulations. Cell-type specific programs that drive responses of differentiated immune cells to pathogens differ significantly between B and T lineage cells, as well as between cells of the adaptive and innate immune systems. The Tarakhovsky laboratory studies the mechanisms by which pathogens affect the function of chromatin, as well as how they affect long-lasting immune and non-immune cell responses to the environment.

Several years ago, the laboratory proposed the “histone mimicry” paradigm as a novel mechanism for regulation of gene expression. According to this paradigm, the regulation of gene expression could be controlled by histone-like entities present in non-histone proteins that can compete with histones for the regulators of gene expression. The foundation of this model originates from the identification of the histone mimic within the histone methyltransferase G9a, which plays the important role of gene silencing. Further studies demonstrated the presence of histone mimics in a large number of human and mouse proteins. The laboratory found that pathogenic microorganisms carry histone mimics in the proteins that critically contribute to pathogen-mediated suppression of the host immune response. This finding led them to propose a mechanism according to which histone mimics in bacterial and viral proteins may serve as histone surrogates, hijacking chromatin-based pathways of the immune response. The histone mimics concept led the Tarakhovsky laboratory to develop synthetic histone mimics that regulate inflammatory gene expression by interfering with the association between histones and transcriptional regulators. In the future, the laboratory plans to extend its research toward the mechanism of epigenetic conditioning of host cells by pathogens. This work may help to elucidate the basis of chronic inflammatory disorders that are initiated by infection but can persist in the absence of infectious agents.
Metastasis is responsible for the majority of cancer deaths. The Tavazoie laboratory employs a systems biology approach that integrates molecular, genetic, cellular, organismal, and clinical observations to discover and characterize key molecular regulators of metastasis, with the goal of developing new therapeutics for its prevention and treatment. This work is also uncovering basic insights into the mechanisms of gene regulation.

Metastatic disease is the primary cause of cancer mortality but remains poorly understood at the molecular level. The Tavazoie lab studies the molecular and cellular mechanisms underlying this process. Their work on metastasis has also uncovered previously unknown, fundamental mechanisms of gene regulation.

The lab employs unbiased genome-wide technologies to identify recurrent molecular alterations associated with enhanced metastatic capacity. Molecular and genetic studies in mice are used to implicate causal and critical genes that regulate this process, with clinical association studies confirming human relevance and biochemical studies implicating signaling pathways involved. This has led to the discovery that modulation of tissue-specific sets of small non-coding RNAs (microRNAs) drives metastasis formation in distinct cancer types by altering expression levels of critical downstream genes. These genes activate pathways that alter the cellular, metabolic, or matrix composition of the metastatic microenvironment; changes to the microenvironment may enhance the survival, immune-evasive, and invasive capacity of cancer cells. The lab’s findings have been applied toward the development of first-in-class metastasis-preventive therapeutics that target critical genes. Their long-term goal is to achieve broadly curative regimens in common cancers.

Furthermore, by studying how rare cancer cells are able to achieve extreme gene expression programs that enable metastasis formation, Tavazoie and his colleagues have gained basic insights into gene regulatory mechanisms. For example, modulation of specific transfer RNAs (tRNAs) has been shown to alter the expression levels of specific downstream target genes and to drive cancer progression. This has led to the discovery of specific tRNA-driven pathways. Moreover, mechanistic insights into gene regulation by an unusual class of small-RNAs, called tRNA-fragments, have also been uncovered. In addition to their relevance for metastatic disease, these basic studies are providing fundamental new insights into gene regulation mechanisms.

Sohail Tavazoie, M.D., Ph.D.

**EDUCATION**
- A.B. in molecular and cell biology, 1995
  University of California, Berkeley
- M.D., 2003
  Harvard Medical School
- Ph.D. in neuroscience, 2003
  Harvard University

**MEDICAL TRAINING**
- Internship in internal medicine, 2003–2004
  Brigham and Women’s Hospital/Harvard Medical School
- Fellowship in oncology, 2005–2008
  Sloan Kettering Institute

**POSTDOC**
- Harvard Medical School, 2004–2005
- Sloan Kettering Institute, 2006–2008

**POSITIONS**
- Assistant Professor, 2009–2015
- Associate Professor, 2015–2018
- The Rockefeller University
- Senior Attending Physician, 2009–
  The Rockefeller University Hospital

**AWARDS**
- NIH Director’s New Innovator Award, 2009
- ASCO/AACR Young Investigator Award, 2009
- Rita Allen Foundation Scholar, 2009
- Emerald Foundation Young Investigator Award, 2009
- Era of Hope Scholar, Department of Defense, 2010
- The Rockefeller University Distinguished Teaching Award, 2013
- Pershing Square Sohn Prize, 2015
- Howard Hughes Medical Institute Faculty Scholar, 2016
- Gabrielle H. Reem and Herbert J. Kayden Early-Career Innovation Award, 2017
- Emerging Leader in Health and Medicine, National Academy of Medicine, 2018

**SELECTED PUBLICATIONS**
The cell walls of pathogenic bacteria are the site of molecular events responsible for many symptoms of bacterial disease, as well as the target for antibiotics. Focusing on *Streptococcus pneumoniae* and *Staphylococcus aureus*, Tomasz studies how bacteria cause disease and resist antibiotics, often through mechanisms involving their cell walls.

The Tomasz laboratory uses biochemistry and molecular genetics in combination with firsthand medical knowledge to study three basic problems: how the bacterial cell wall is assembled and replicated, how bacteria respond to antibiotic treatment and ultimately gain resistance, and how bacteria cause disease. This work focuses on *S. pneumoniae* and *S. aureus*, two major human pathogens with multidrug-resistant clones that have spread globally.

A significant conceptual contribution from the laboratory came in the late 1960s with the discovery that pneumococci secrete a polypeptide that allows foreign DNA to pass through cell walls. This finding has been cited as the first evidence that bacteria “talk” to one another, a concept later called quorum sensing.

Cell walls may be envisioned as vast networks of covalent bonds organized into macromolecular sheets. Tomasz is interested in how these “super” molecules are reproduced with precision during each cell division. Using conditional mutants of key cell wall biosynthetic genes, the lab aims to identify genetic determinants and protein catalysts involved in this morphogenetic process.

Antibiotic resistance is a growing problem. Treatment of *S. pneumoniae* and *S. aureus* with penicillins or glycopeptide antibiotics triggers a kind of programmed cell death for these cells. A mechanism named antibiotic tolerance, which enables bacterial cells to evade this suicidal pathway, was discovered in the Tomasz lab in the mid-1970s.

Tolerant bacteria survive the antibiotic but are still inhibited by it, while antibiotic-resistant bacteria can overcome even the inhibitory effects of these agents. In the mid-1990s, building off its much earlier discovery of the first quorum sensing factor, the Tomasz lab was the first to demonstrate that penicillin resistance in *S. pneumoniae* involves the reengineering of penicillin-binding proteins (PBPs) using blocks of foreign DNA that reduce PBPs’ affinity for the antibiotic. Pneumococci with the reengineered PBPs are not only resistant to penicillin, but show an altered chemical structure of their cell walls.

A number of other projects in the Tomasz lab have focused on the role of the cell walls in disease and antibiotic resistance. Recent data on *meca*, a foreign gene critical to methicillin resistance in *S. aureus*, suggests it originated as a cell wall synthetic gene ubiquitous in the animal commensal species *S. sciuri*. The Tomasz lab is also investigating alterations in the chemical structure of the cell wall that can have a profound impact on bacterial virulence. For instance, mutants of *S. pneumoniae* that produce a cell wall lacking phosphoryl choline residues suffer a profound loss in virulence.

Other work includes using whole-genome sequencing to identify specific mutations that accompanied the evolution of antibiotic resistance in an *S. aureus* strain from a patient undergoing extensive chemotherapy by vancomycin. The lab is also tracking the spread of antibiotic-resistant clones of staphylococci and pneumococci, often in collaboration with labs in Europe and South America.
RNA functions not only as a carrier of genetic information, but also as a catalyst and guide for the processing or regulation of other RNA molecules. Tuschi is investigating gene-regulatory mechanisms that include non-coding RNA and RNA-binding proteins in human cells, with the goal of developing treatments for genetic diseases.

Eukaryotic cells express a variety of classes of small RNA molecules. The Tuschi lab has identified these classes and their many members using a variety of RNA-sequencing (RNA-seq) techniques. Their discoveries include the molecular characterization of small interfering RNAs (siRNAs), a class of double-stranded, 21-nucleotide-long molecules that guide sequence-specific gene silencing. Tuschi was the first to demonstrate their utility for knocking down human gene expression.

Two additional RNA classes uncovered by his lab, called microRNAs (miRNAs) and piwi-interacting RNAs (piRNAs), have great importance to human biology. piRNAs are specifically expressed in male and female germ line cells and are required for normal germ cell development. Although researchers know that knocking out the piwi protein-coding genes in mice causes male infertility, the targets and molecular function of piRNAs remain unknown. Efforts to characterize their biogenesis and targets are ongoing.

During its life cycle, messenger RNA interacts in a sequence-specific manner with many ribonucleoprotein complexes (RNPs) and RNA-binding proteins (RBPs). In order to understand these complex regulatory networks, the Tuschi lab has developed experimental approaches to precisely define the binding sites of RNPs and RBPs on coding and non-coding RNA and its precursors. Current studies focus on characterizing RBPs implicated in genetic diseases such as fragile X syndrome as well as those with unknown functions. The identification of RNA interaction networks sheds light on the biological function of these proteins and may contribute to the design of new therapeutic agents for controlling gene expression.

The Tuschi lab catalogs and annotates all cellular coding and non-coding RNAs in a global effort to clarify their roles in human development and various diseases. The ultimate goal is to host and mine all existing RNA-seq information in a database searchable by read, and to establish a non-redundant human reference transcriptome. As the project nears completion, residual unmapped reads hold promise for the discovery of new pathogens or rare genetic aberrations contributing to disease.

RNAs have been difficult to visualize and measure in archival tissue sections using traditional histological techniques. The lab continues to develop fluorescence-based methods to visualize RNA molecules in tissue sections while also exploring single-cell RNA-seq methods for characterization. This work will help researchers better understand the crosstalk occurring among cell types in inflammatory diseases and cancer.
Brain functions rely on the coordinated dynamics of a vast number of highly interconnected neurons. To discern how these dynamics lead to behavior, Vaziri seeks to capture neuronal activity over large brain volumes at high speed and single-cell resolution across species. His lab develops and uses imaging techniques addressing these demands to generate functional maps of neuronal circuits up to the level of a whole brain in behaving animals.

To fully understand how sensory input leads to behavior, it is necessary to not only map connections between neurons, but also examine how these cells interact in real time and how their collective dynamics influence behavior. To do so, new tools are required to excite neurons in specific spatiotemporal patterns, while capturing their activity across entire functional networks on a physiologically relevant timescale and at single-cell resolution.

Vaziri develops new high-speed functional optical techniques that meet this challenge. With these tools, he seeks to uncover the biological mechanisms and ultimately the computational and theoretical principles by which sensory inputs are represented and interact with internal states to generate behavior.

One of these tools, light sculpting, uses temporal focusing to disperse the spectrum of femtosecond laser pulses, which are then brought back into register, generating a wide-field two-photon excitation that is axially highly confined. Three-dimensional data can be obtained by scanning the wide-field two-photon in the axial direction. Using genetically encodable calcium sensors, the lab has developed a microscope that can capture brain-wide dynamics in C. elegans at high speed.

Applying a variation of this approach to neurons engineered to express light-sensitive channel rhodopsin, Vaziri and his colleagues have also shown that individual cells can be selectively activated at high speed. Variations on this technique have made it possible to mimic the excitation patterns target neurons would receive from the environment.

Another technique developed by Vaziri and his collaborators makes it possible to record signals on even greater scales and at higher speeds than has been possible previously. Light-field deconvolution microscopy employs an array of microlenses to simultaneously capture views from a large number of angles, without any moving components. These views are then recombined to generate a three-dimensional representation. This technique has made it possible to capture the activity of thousands of neurons across the entire brain of the larval zebrafish, which the lab uses as a model to understand the emergence of high-level feature recognition and action selection.

The Vaziri lab continues to refine these and other techniques, and extend their use across species. One of the main frontiers in the field is the creation of tools to capture the functional dynamics of large-scale neuronal circuits in awake, behaving rodents. Working toward this goal, Vaziri’s lab has recently demonstrated an unbiased high-speed calcium imaging technique based on light sculpting that has made it possible to capture the majority of a mouse cortical column at single-cell resolution.

Ultimately, Vaziri hopes to examine the computation algorithms with which the brain performs various tasks. In addition, his lab is broadly involved in using other optical tools, such as single-molecule techniques, and exploring new ways of applying quantum optics to other biological questions.
Victora studies germinal centers, structures within lymphoid organs where antibodies mutate and improve their targeting capabilities. This process, called affinity maturation, allows the immune system to produce antibodies that are precisely targeted at invaders, resulting in faster and more robust responses upon subsequent exposures.

When a pathogen invades the human body, the immune system responds by producing proteins called antibodies that are precisely targeted at the invader. Antibody production creates an immunological memory that allows for a faster and more robust response to the invader upon subsequent exposures. It is also the basis for vaccination.

Antibodies are tuned to efficiently recognize a specific invader through affinity maturation, in which a small region of the antibody undergoes random hypermutation, followed by the proliferation of mutants with high affinity to the pathogen. The Victora lab is currently investigating the mechanistic details of this process. His research could lead to more effective vaccines against pathogens such as influenza or HIV, and could help explain how affinity maturation can malfunction in diseases such as allergies.

In previous work, Victora developed techniques to label and observe cells within the lymph nodes of live mice, and was able to shed light on how B cells with high-affinity antibodies are selected and amplified. In addition to defining the types of B cells in GCs and their migration patterns, the research identified another major component of the immune system, T cells, as the regulators of this process. His work also showed that, unlike B cells, T cells are not physically restricted to individual GCs and can help maintain diversity in the antibody response.

To gain a deeper understanding of how high-affinity antibodies are generated and evolve during this complex process, the Victora lab is now exploring three complementary perspectives: those of molecules, cells, and whole organs. On the molecular scale, research is underway to identify the key genes involved in how B cells choose between two fates—to remain within the GC or to differentiate into another cell type. At the cellular level, the lab is exploring how a cell's history of interactions with other cells contributes to affinity maturation and GC development. Finally, Victora and colleagues are investigating how different GCs within the same lymphoid organ may vary in terms of the antibodies they carry, and how these antibodies change over time to produce an effective antibody response.

By applying a broad scope in their work—from individual genes to the dynamics within the spleen and lymph nodes—the Victora lab hopes to gain insight into the critical evolutionary processes by which the immune system refines its response to an infection or vaccine.
Leslie B. Vosshall, Ph.D.

The Vosshall lab studies how complex behaviors are controlled by cues from the environment and modulated by the internal physiological state. Working with the dengue and Zika vector mosquito, Aedes aegypti, and human subjects, Vosshall’s research has yielded new knowledge about how sensory stimuli are perceived and processed.

Vosshall’s lab takes a multidisciplinary approach spanning neurobiology, behavior, genetics, and genomics. The early focus of the lab was to study how the brain interprets olfactory signals associated with food, danger, or potential mating partners using three model organisms: flies, mosquitoes, and humans. The lab identified the genes that mediate odor and carbon dioxide perception in insects, including Orco, a member of the odorant receptor gene family, which is uniquely expressed in a majority of olfactory sensory neurons and highly conserved across insect evolution. The researchers pinpointed Orco as a potential target for chemical inhibitors, which could potentially be used to fight mosquito-transmitted infectious diseases.

Beginning in 2008, the group established a mosquito genetics research program to understand host-seeking and blood-feeding behaviors in the mosquito. They focus on Ae. aegypti, the mosquito associated with yellow fever, dengue, and Zika viruses. These mosquitoes have evolved an intense attraction to human body odor, body heat, and carbon dioxide—the gas exhaled in human breath—and serve as deadly vectors of infectious disease. Olfactory cues guide mosquitoes toward humans, from which female mosquitoes derive the blood they need to complete egg development. Although a genome for this mosquito has been available since 2007, it is highly fragmented. Research associate Ben Matthews has led an international effort to produce a complete genome assembly that will catalyze investigations throughout the world.

The Vosshall lab has also developed genome-editing techniques for targeted mutagenesis in Ae. aegypti using the CRISPR-Cas9 system to enable the tracing of neural pathways and functional imaging of circuits activated by sensory cues. The establishment of loss-of-function genetics in mosquitoes has opened up new pathways of investigation in vector biology, including the neurobiology of host-seeking and egg-laying, and the mechanisms of insect repellents. A particular focus is to understand why some humans are more attractive to Ae. aegypti than others, and the role of the skin microbiome in this differential attraction. Mosquitoes transmit deadly infectious diseases to humans both in the United States and around the world, and understanding the rules by which these animals target human hosts will enable the development of tools to reduce their capacity to spread disease.

Another broad area of interest is olfactory perception in humans. The Rockefeller University Smell Study has been carrying out large-scale research on human subjects to combine olfactory psychophysics with genetic analysis in order to understand the mechanisms of olfactory perception in humans. Recent work has challenged the assumption that humans have a comparatively poor sense of smell compared to animals, leading to the finding that the human nose has the power to discriminate between a very large number of olfactory stimuli. Ongoing work aims to link variation in olfactory perception to genetic polymorphisms, probe the basic perceptual logic of human smell, and develop novel diagnostic tests for patients suffering from olfactory dysfunction.
Walz is interested in processes that involve biological membranes, ranging from vesicular transport that distributes cargo molecules throughout the cell to the effects of lipids on the structure and function of membrane proteins. To explore these processes, he applies cryo-electron microscopy to image macromolecular complexes and membrane proteins, aiming to visualize their dynamics and determine their structures at the atomic level.

Biological membranes surround cells and cellular compartments, and have to relay signals and allow cargo transport. They also catalyze reactions and mediate all interactions cells have with their environment and with other cells. These functions are performed by proteins embedded in the membranes, and increasingly, structures of these membrane proteins reveal how they can carry out their activities. However, most of this structural work is being conducted on isolated membrane proteins in solution, without the lipid bilayer that is the native environment of a membrane protein. Meanwhile, cellular membranes contain thousands of different lipids. It is increasingly being recognized that this diversity affects most membrane processes as well as many aspects of the embedded membrane proteins.

Walz is broadly interested in processes related to cellular membranes, and much of his current work focuses on exploring how lipids affect the structure and function of membrane proteins. He uses single-particle cryo-electron microscopy and nanodiscs, a biochemical tool that makes it possible to explore the structure and function of membrane proteins in the context of lipid bilayers.

An exceptionally exciting development in electron microscopy is the introduction of direct electron detector device (DDD) cameras that record images of unprecedented quality. Together with new image processing algorithms, DDD cameras have opened up new avenues for structural investigations. The Walz group aims to exploit these new developments to study the structure and dynamics of proteins within the membrane, and to visualize the effects that lipids and other membrane characteristics exert on these proteins.

Nanodiscs are small patches of lipid bilayer stabilized by a scaffold protein that recreate the native environment of a membrane protein and its associated characteristics—something that cannot be achieved by detergents, which are traditionally used to prepare membrane proteins for electron microscopy. The Walz group uses nanodiscs to visualize lipid-induced conformational changes in membrane proteins, asking, for example, whether the thinning of a membrane is sufficient to open certain channels.

The lab is also investigating other membrane-related processes, such as membrane repair and vesicular transport. For example, they are exploring how multisubunit tethering complexes help ensure that transport vesicles fuse with the appropriate target membrane.

Walz’s earlier work includes the use of electron crystallography to determine the structure of the archetypal water channel, aquaporin-1, and as an approach to study how membrane proteins interact with their annular lipids.
Michael W. Young, Ph.D.

VICE PRESIDENT FOR ACADEMIC AFFAIRS • RICHARD AND JEANNE FISHER PROFESSOR, LABORATORY OF GENETICS

The Young lab studies 24-hour circadian clocks, which time the recurring, daily activities observed in most organisms. These cellular clocks are active in most animal tissues and establish daily rhythms in physiology and behavior. The lab's findings have implications for sleep and mood disorders as well as for dysfunctions related to the timing of gene activities underlying visual functions, locomotion, metabolism, immunity, learning, and memory.

Internal biological mechanisms, called circadian clocks, control the timing of a host of biological functions in organisms from fruit flies to humans. Studies of the molecular basis for this circadian rhythmicity began in the early 1980s in Young's lab at Rockefeller, and in the labs of Jeffrey C. Hall and Michael Rosbash at Brandeis University. Over the past 30 years, these investigators learned that the circadian clocks of Drosophila are formed through the actions of a small group of genes including per (period), tim (timeless), dbt (double-time, casein kinase 1), cik (clock), cyc (cycle), sgg (shaggy), Pdp1 (PAR domain protein 1), vri (vrille), cry (cryptochrome) and ck2 (casein kinase 2). Mutations in any of these "clock" genes—six of which were first characterized in the Young lab—can lengthen or shorten the period of behavioral, physiological, and molecular circadian rhythms, or abolish the rhythms altogether.

The expression of several clock genes oscillates in wild-type flies. Two of the proteins encoded by these genes, TIM and PER, regulate their own expression through a feedback loop. TIM binds to and stabilizes PER, and allows both proteins to move to the nucleus, where their presence switches off their further synthesis. After several hours, PER and TIM decay, reinitiating the 24-hour cycle of synthesis and inhibition.

The circadian clock adjusts to environmental light through CRY, which in flies is a novel photoreceptor that binds to TIM in the presence of light and promotes TIM’s rapid degradation, pausing the clock until TIM can re-accumulate in the dark. Young’s lab has discovered that the enzyme casein kinase 1 (DBT) further regulates the pace of this 24-hour molecular clock by limiting the longevity of the PER protein during each circadian cycle, and especially by removing PER when TIM is absent. Most of the genes composing the Drosophila clock, and the cycling intracellular mechanism they direct, are well conserved throughout the animal kingdom.

The Young lab has found that approximately seven percent of all genes active in the Drosophila head are expressed with a circadian rhythm. Genes composing this large circadian program influence almost every aspect of the fly’s biology, and subsets are switched on and off with phases representing every hour of the day and night. When genes that compose the circadian clock are mutated, this program of temporally sequenced gene expression disappears even if environmental cycles are present, indicating that the temporal program is thoroughly dependent on the molecular oscillator.

Members of the lab have identified genes that affect the homeostatic regulation of sleep in Drosophila. They are also studying how sleep and circadian rhythms are regulated at the genetic and molecular levels in humans. Young’s lab recently identified a CRY variant associated with a form of delayed sleep phase disorder (DSPD) that may affect approximately one in 75 individuals of non-Finnish European ancestry. The most commonly diagnosed type of circadian rhythm sleep disorder, DSPD is characterized by a persistent and intractable delay of sleep onset and offset times relative to the societal norm.

SELECTED PUBLICATIONS
Recent evidence suggests new genes can emerge from ancestrally noncoding sequences. These de novo genes acquire functions and, if they provide a selective advantage, spread within a population until they become fixed. Zhao studies the origin and evolution of de novo genes, as well as their contribution to adaptive evolution, in both flies and humans.

Research in the Zhao lab addresses a central question in evolutionary biology: What is the molecular genetic basis of biological diversity? Natural selection acts upon traits, yet it is poorly understood how these traits evolve in relation to genes. Zhao’s group seeks to delineate the molecular changes and mechanisms responsible for phenotypic divergence and adaptation.

She is particularly interested in de novo genes, which emerge from noncoding DNA. Work in her lab aims to uncover how these and other new genes originate, spread, and contribute to adaptive evolution; to determine how differences in gene expression alter phenotypes; and to identify the genetic basis for adaptation to local environmental conditions.

The Zhao lab employs a range of next-generation sequencing, computational, and analytical approaches to generate and study large-scale population genomic and transcriptomic data in systems that include Drosophila and humans. The hypotheses generated from these data-rich analyses are then tested using genetic and experimental manipulations.

While previous work in the field has focused on the origins of genetic novelty through the duplication of genes, recent studies have uncovered an alternative path whereby ancestrally noncoding sequences are co-opted by evolution, producing novel genes. However, nothing was known about the earliest steps in the birth of these de novo genes within species. Using genomic and population analyses, Zhao and her colleagues discovered a large number of de novo genes segregating and evolving in Drosophila melanogaster populations under the influence of directional selection. Zhao has since expanded her analyses to identify de novo genes that contribute to multiple fly tissues and developmental stages. Using CRISPR-Cas9 and other technology, her lab also is investigating the functions of individual de novo genes.

Over the long term, Zhao aims to compile the first comprehensive description of de novo gene evolution within a species. She also seeks to use novel genes as an entry point from which to investigate the evolution of genes and genomes, as well as human cancer biology.

Zhao is also interested in how species adapt to variable environments. To better understand how variation in gene expression is maintained within and between species, she studies its evolution in heterogeneous, natural environments. In a recent study, Zhao and her colleagues observed substantial parallels in gene expression between fly populations, suggesting that spatially driven selection contributes to these differences. The Zhao lab will extend this work by investigating variation in the genomics, transcriptomics, and transcription factor binding in Drosophila populations using flies collected from a variety of environments.
Colleagues, collaborators, and additional members of our scientific village.
Tri-Institutional Professors

Based at Memorial Sloan Kettering Cancer Center or Weill Cornell Medicine, Tri-Institutional faculty hold joint appointments to facilitate interaction with colleagues and students at all three institutions.
Hening Lin, Ph.D.

INVESTIGATOR, HOWARD HUGHES MEDICAL INSTITUTE • TRI-INSTITUTIONAL PROFESSOR • DEPARTMENT OF CHEMISTRY AND CHEMICAL BIOLOGY, CORNELL UNIVERSITY

SELECTED PUBLICATIONS

Lin's research focuses on NAD-consuming reactions in eukaryotic cells. His lab combines organic synthesis, biochemistry, and genetics to discover new reactions that consume NAD and new biological pathways that are regulated by known or new NAD-consuming reactions.

Lin's lab is currently studying sirtuins, a family of enzymes with NAD-dependent deacylase activity that are important for aging, transcriptional regulation, and metabolism. His lab discovered that mammalian Sirt5 is a NAD-dependent desuccinylase and demalonylase. His lab also discovered the defatty-acylase activity of sirtuins, and it continues to identify novel activities of other mammalian sirtuins. These discoveries in turn enable his lab to design potent and selective inhibitors for specific sirtuins. Some of these inhibitors have demonstrated interesting and broad anticancer activities. Lin also studies poly(ADP ribose) polymerases, or PARPs, that catalyze protein poly(ADP-ribosylation). PARPs are known to be required for DNA repair, transcriptional regulation, telomere extension, and mitosis. Lin's lab uses organic synthesis to make various NAD analogues that, combined with biochemistry and RNA interference, allow the tagging and identification of substrate proteins of PARPs, which allow the discovery of biological pathways that are regulated by PARPs.

Alexander Y. Rudensky, Ph.D.

INVESTIGATOR, HOWARD HUGHES MEDICAL INSTITUTE • TRI-INSTITUTIONAL PROFESSOR • PROGRAM IN IMMUNOLOGY, MEMORIAL SLOAN KETTERING CANCER CENTER

Rudensky's research is focused on understanding how T cells develop and their role in immunity and tolerance. Major areas of interest in his laboratory include the molecular and cellular mechanisms governing the differentiation and function of CD4 T lymphocytes, and the roles these cells play in controlling autoimmunity, cancer, and immunity to infections, and in the maintenance of nonlymphoid organs in the settings of injury and stress.

Rudensky is particularly interested in understanding the role of the forkhead family transcription factor Foxp3 in establishing and maintaining regulatory T cell transcriptional and functional programs, and in the molecular mechanisms of regulatory T cell lineage stability. In these studies, the Rudensky laboratory employs a wide range of experimental techniques, including traditional biochemical and molecular biological analyses; genetic approaches including conventional and conditional gene targeting and transgenesis; mass spectrometry; large-scale gene expression analyses and bioinformatics; and classical immunological analyses utilizing both cellular in vitro techniques and whole animal experimentation.

SELECTED PUBLICATIONS

Alexander Y. Rudensky, Ph.D.
Ryan’s laboratory is interested in the molecular basis of synaptic function, the essential point of communication between neurons. Ryan and his colleagues focus on presynaptic biology, in which neurotransmitter-containing synaptic vesicles fuse with the plasma membrane at the synapse in response to electrical stimulation. His lab develops optical techniques to measure synaptic function in real time. Combined with molecular and chemical tools, this approach allows them to address fundamental questions about how synaptic communication is controlled. Areas of interest include the processes that determine the abundance and control of synaptic voltage-gated calcium channels, how the supply of fuel needed to support synaptic function is regulated, and how synaptic vesicles are rebuilt after the release of a neurotransmitter.

Through his studies on synapse function, Ryan hopes to gain insight into how information is controlled both in normal and diseased states of brain function.

Advances in genomics have revealed myriad new potential therapeutic targets. However, existing small-molecule drugs address only a small set of approximately 550 protein targets encoded in the human genome. Efforts to expand have been thwarted by a heavy focus on a correspondingly narrow range of complementary chemical structures in drug discovery. To address this problem, Tan’s lab leverages insights from natural products in diversity-oriented synthesis and rational drug design to identify novel small-molecule ligands for a variety of targets. They leverage multidisciplinary collaborations with biologists to evaluate the molecules they synthesize to probe complex biological processes and pursue new therapeutic opportunities in cancer and infectious diseases.

In the area of diversity-oriented synthesis, Tan’s lab uses structural motifs found in biologically active natural products as starting points for library design. At the core of these efforts is the development of new synthetic routes to provide flexible, efficient, systematic access to these structures. The resulting libraries access distinct regions of chemical space compared to conventional drug-like libraries and are screened against a wide range of biological targets.

In the area of rational drug design, Tan’s lab designs natural product-based sulfonyladenosine inhibitors of adenylation enzymes, a mechanistic superfamily implicated in a wide range of biological processes. Leveraging structural and mechanistic information, they have developed new antibiotic lead compounds that inhibit enzymes required for bacterial virulence and semisynthetic protein inhibitors of ubiquitin-family E1 activating enzymes that have revealed dramatic active site remodeling during catalysis.

SELECTED PUBLICATIONS


The Weinstein lab studies complex systems in physiology with methods of molecular and computational biophysics, bioinformatics, and mathematical modeling. The focus is on the structural and dynamic mechanisms of cellular components, including macromolecular assemblies of proteins and the membranes of the cell. Computational modeling and simulation provide insight into the involvement of these cellular components in fundamental biological processes such as signal transduction, neuronal signaling, and regulation of cell physiology and growth. The lab then examines how these mechanisms, studied at the molecular scale, and the macromolecular processes they underlie, coalesce into physiological functions of organized systems in tissues and organs. The work combines theoretical and computational methods of biophysics with experimental designs in large-scale collaborations. New theory and advanced methods of computational simulations, based on quantum and statistical mechanics, mathematical modeling, and informatics, are developed and employed in these studies.

Current research themes include the mechanisms of molecular recognition and allostery of micromachines of the cell, such as G protein-coupled receptors, secondary transporters, scramblases, and multi-domain scaffolding/adaptor proteins. The lab studies how macromolecular dynamics, oligomerization, and encounter-complex formation execute cellular functions and signaling, and how it is possible to modulate, remodel, and repair these mechanisms through molecular and genomic interventions. The biomedical end points for these particular studies are neurotransmission in health and disease, drug abuse mechanisms, and cancer.

**SELECTED PUBLICATIONS**


Because they can't pick up and move, plants must react rapidly to changes in their environment. Doing this requires a complex network of signaling pathways that can involve epigenetic factors, such as noncoding RNA molecules. An emeritus professor, Chua is focusing on the function of these long, noncoding RNAs in Arabidopsis.

Previously, the Chua lab found that the Arabidopsis genome encodes around 8,000 long intergenic noncoding RNAs (lincRNAs) and 36,000 natural antisense transcripts (NATs). Critically, Chua established several of the basic tools necessary to conduct molecular research in plants, and he subsequently found key proteins involved in Arabidopsis's response to the transition from light to dark. His research has also led to the identification of proteins that play a role in a plant's reaction to drought.

The knowledge Chua generated through the use of Arabidopsis shows promise for improving crops to reduce hunger around the world, as well as to create sustainable agriculture in regions that currently are poorly suited for it.

Chua received his B.Sc. in botany and biochemistry from the University of Singapore, and his Master's and Ph.D. from Harvard University. He was a lecturer at the University of Singapore before joining Rockefeller as a research associate in 1971. He was made a member of the faculty in 1973. Chua is a member of The Royal Society, the Chinese Academy of Sciences, and Academia Sinica.
George A.M. Cross, Ph.D.
ANDRE AND BELLA MEYER PROFESSOR EMERITUS, LABORATORY OF MOLECULAR PARASITOLOGY

Trypanosomes remain a problem for humans and other animals throughout large regions of Africa and South America. African sleeping sickness and Chagas disease are invariably fatal, though it may take weeks or years to succumb, depending on the species and the strain. Cross’s research focuses on how the African trypanosomes evade our immune systems, which has prevented the development of a vaccine, and on the novel biochemical and genetic mechanisms employed by these organisms. Trypanosomes branched very early in eukaryotic evolution, and they have significant and sometimes bizarre variations from the conventional mechanisms of gene expression. Research on trypanosomes can shed light on how more complex, higher eukaryotic regulatory systems have evolved.

Trypanosoma brucei causes African sleeping sickness and is transmitted by the Glossina species, commonly known as the Tsetse. Ten million copies of a single glycoprotein form the surface coat of the parasite, a dense structure that surrounds the entire cell body and the flagellum. Using recombinatorial mechanisms, trypanosomes possess an infinite capacity for switching among the thousands of genes that encode members of the variant surface glycoprotein (VSG) family, allowing infections to evade the host immune system, so the parasites proliferate indefinitely, until death of the host.

Cross was the first to identify the VSG family, which led to the discoveries of trans-messenger RNA splicing and a mechanism for protein anchoring to the cell membrane, called glycosphatidylinositol (GPI) anchoring, which has since been found to be used for numerous proteins in a wide range of organisms. Trypanosomes use GPI anchoring to a greater extent than any other cell type, and there are some unique features of GPI anchoring in these parasites that are still not well understood.

Born in Cheshire, England, Cross received his undergraduate degree in 1964 and his Ph.D. in biochemistry in 1968 from the University of Cambridge, where he held a Medical Research Council Research Training Scholarship, and was an Imperial Chemical Industries Fellow during his postdoc. From 1970 to 1977 he worked in the Medical Research Council Biochemical Parasitology Unit in Cambridge.

He then joined the Wellcome Research Laboratories of the Wellcome Trust in England, where he was the head of the department of immunochemistry and molecular biology. Cross came to Rockefeller in 1982. In 1984 Cross was a recipient of the Paul Ehrlich and Ludwig Darmstaedter Prize, awarded in Germany, and he received the Chalmers Memorial Medal of the Royal Society of Tropical Medicine and Hygiene in 1983. He is a fellow of The Royal Society.

James E. Darnell Jr., M.D.
VINCENT ASTOR PROFESSOR EMERITUS, LABORATORY OF MOLECULAR CELL BIOLOGY

The Darnell laboratory studies how signals from the cell surface affect the transcription of genes in the nucleus. Using interferon as a model cytokine, the group discovered that transcription of specific genes is quickly changed by binding of cytokines to the cell surface. The bound interferon leads to the tyrosine phosphorylation of latent cytoplasmic proteins called STATs (signal transducers and activators of transcription), which dimerize by reciprocal phosphotyrosine–SH2 interchange. These transcription factors accumulate in the nucleus, bind DNA, and drive transcription. The pathway has proved to be of wide importance, with seven STATs now known in mammals. These proteins take part in a wide variety of developmental and homeostatic events in all multicellular animals.

Crystallographic analysis defined functional domains in the STATs, and the lab’s attention is now focused on two areas: how STATs complete their cycle of activation and inactivation, requiring regulated tyrosine phosphorylation and dephosphorylation; and how the persistent activation of STAT3 that occurs in a high proportion of human cancers contributes to blocking apoptosis and promoting metastasis in cancer cells. Current efforts are devoted to inhibiting STAT3 with cell-penetrating small molecules, and to more detailed mutagenesis to expose potential sites for possible therapeutic inactivation.

Darnell received his M.D. in 1955 from the Washington University School of Medicine. His career has included research at the National Institute of Allergy and Infectious Diseases; at the Pasteur Institute in Paris; and academic appointments at the Massachusetts Institute of Technology, the Albert Einstein College of Medicine, and Columbia University. In 1974, he joined Rockefeller as Vincent Astor Professor, and from 1990 to 1991 he was vice president for academic affairs.

A member of the National Academy of Sciences since 1973, Darnell has received numerous awards, including the 2012 Albany Medical Center Prize in Medicine and Biomedical Research, which he shared with Robert G. Roeder; the 2002 National Medal of Science; the 2002 Albert Lasker Special Achievement Award in Medical Science; the 1997 Passano Award; the 1994 Paul Janssen Prize in Biotechnology and Medicine; and the 1986 Canada Gairdner Foundation International Award.

Darnell was the coauthor with S.E. Luria of General Virology, founding author with Harvey F. Lodish and David Baltimore of Molecular Cell Biology, now in its ninth edition, and author of RNA: Life’s Indispensable Molecule. He is a fellow of the American Academy of Arts and Sciences, a member of the American Philosophical Society, and a foreign member of both the Royal Society and the Royal Swedish Academy of Sciences.
Cell membranes contain millions of embedded proteins that control ion movements into and out of the cell. This ion flow underlies such vital functions as electrical signaling in nerve, heart, and muscle cells; cell volume regulation; secretion of hormones and neurotransmitters; fertilization; and kidney function.

Two principal classes of proteins regulate ion movement across membranes: pumps and channels. Channels allow ions to flow rapidly down their electrochemical gradients, while pumps move ions relatively slowly, thermodynamically uphill, thereby building up those gradients.

Gotschlich has used position-specific mutagenesis, combined with structural modeling and biochemical and electrical measurements, to examine the mechanisms of two biomedically important ion transport proteins. One, the Na+/K+/adenosine triphosphatase, is a pump crucial to animal cell life, and the other, CFTR (cystic fibrosis transmembrane conductance regulator), is a Cl− ion channel. Mutations in the CFTR gene are responsible for cystic fibrosis. Mutations in the Na+/K+ pumps of brain neurons have been found responsible for childhood neurological disorders.

Gotschlich’s work has suggested that, whereas an ion channel can be viewed as a transmembrane ion pathway controlled by a gate at one end, an ion pump can be viewed as a modified ion channel governed by gates at both ends. A pump’s gates must be tightly coupled so that both are never open simultaneously. In both the Na+/K+ pump and CFTR Cl− channel, these conformational changes are driven by binding and hydrolysis of adenosine triphosphate (ATP).

Gotschlich’s lab has found that during the normal Na+/K+ transport cycle, a certain conformation of the Na+/K+ pump can be hijacked by extracellular protons to access the cell interior. The probability of proton entry through any given Na+/K+ pump depends on the extracellular proton concentration. The Na+/K+ pump is thus a hybrid transporter, a protein with two distinct functions.

Gotschlich received his Bachelor’s and Master’s degrees from Trinity College at the University of Cambridge, and his Ph.D. in physiology from University College London. He joined Rockefeller as an assistant professor in 1978. He is a member of The Royal Society.
David Mauzerall, Ph.D.
PROFESSOR EMERITUS, LABORATORY OF PHOTOBIOLOGY

Mauzerall’s research focuses on the photochemistry, origin, and evolution of photosynthesis. His lab has developed photoacoustic methods to determine the enthalpy and volume changes of individual photoreaction steps in these processes. These methods allow for a very simple and rapid measure of the efficiency of photosynthesis. By quantifying the enthalpy and volume changes in photosynthetic systems and in the photocycle of the proton pump bacteriorhodopsin, the Mauzerall lab has found that, unlike simple reaction systems, those of photobiology using proteins can contain a large entropy component. Certain steps in the photosystems during photosynthesis and in bacteriorhodopsin are driven by entropy instead of the usual energy or enthalpy. His lab is now extending these measurements to the thermodynamics of the crucial oxygen-forming system of photosynthesis. Preliminary results show that the enthalpy is constant in the four electron transfer steps required to form oxygen from water, indicating that evolution has not only solved the problem of “splitting” water but has also succeeded in developing the minimum energy path for the formation of oxygen. The understanding of this system is crucial to the use of photosynthesis as a source of energy.

With Steven Mielke, a research associate in the lab, Mauzerall has also determined the efficiency of a unique cyanobacterium that uses chlorophyll d, which absorbs at longer wavelengths than the usual chlorophyll a. They have found that the efficiency at the wavelength of light absorbed by chlorophyll d is at least equal to, if not more than, that in chlorophyll a organisms. These results indicate that the long wavelength limit to the photosynthetic formation of oxygen has not yet been reached, a finding that is of interest to astrobiologists studying the possibility of life-supporting planets located near common stars that are substantially redder than the sun. The efficiency of photosynthesis in the red region has now been determined with unprecedented resolution (1 nanometer or 0.001 eV) and accuracy (one percent). Analysis of the data not only determines the efficiency of each of the two photosystems separately but also the energies of their “traps.” This is where the photexcitation energy is converted to chemical oxidation-reduction species by charge separation. The determination is absolute since it is in terms of energy itself; this is particularly important for the oxygen-generating system, as its redox potential is too oxidizing to be determined directly.

Mauzerall received his B.S. in chemistry from Saint Michael’s College in 1951 and his Ph.D. in physical-organic chemistry from the University of Chicago in 1954. He joined Rockefeller in 1954 as a research associate. He became assistant professor in 1959, associate professor in 1964, professor in 1969, and professor emeritus in 2001. He is a fellow of the American Association for the Advancement of Science and various scientific societies.
Miklós Müller, M.D.  
PROFESSOR EMERITUS, LABORATORY OF BIOCHEMICAL PARASITOLOGY

Jürg Ott, Ph.D.  
PROFESSOR EMERITUS, LABORATORY OF STATISTICAL GENETICS

Until the closing of his laboratory in 2005, Müller's research concerned several important human parasites: *Trichomonas vaginalis*, *Giardia intestinalis*, and *Entamoeba histolytica*. These organisms lack typical mitochondria—they are “amitochondriate”—and have an unusual anaerobic fermentative metabolism. The Müller lab's research focused on the molecular and biochemical exploration of this metabolism with the goal of understanding its adaptive significance and evolutionary history. In the course of these studies, Müller and his colleagues identified in trichomonad flagellates a novel cell organelle, the hydrogenosome. This organelle produces hydrogen as a metabolic end product. Similar organelles have been found subsequently in several other anaerobic unicellular organisms, while others contain a smaller structure—the mitosome—that lacks a role in metabolism. Typical mitochondria, hydrogenosomes, and mitosomes are currently regarded as closely related cell organelles, which derive from the ancestral promitochondrion by divergent evolution.

Leaving experimental work behind, Müller continues the comprehensive analysis of the metabolic organization and evolutionary history of these divergent types of mitochondrion-related organelles. This analysis has led to novel insights into the origin of the ancestral eukaryotic cell and its diversification.

Müller also turned his interest in recent years to the history of 20th-century biology. His current work, conducted in archives and libraries in different countries, concerns two topics: the life and works of Hungarian theoretical biologist Ervin Bauer (1890–1938), who successively worked in Hungary, Czechoslovakia, Germany, and the Soviet Union; and the impact of Soviet pseudoscientific distortions of biology (Trofim Lysenko and Olga Lepeshinskaya) on the subject in Eastern Europe in the 1940s and 1950s.

A native of Hungary, Müller received his M.D. from Budapest Medical University in 1955 and continued on the medical faculty as an instructor and assistant professor, where he studied food vacuoles in protozoa. In 1964 he joined Rockefeller as a research associate in the cell biology laboratory of Christian de Duve and later became a tenured associate professor and head of laboratory. He was promoted to full professor in 1999 at the age of 68. In 2007, Müller received the Knight's Cross of the Order of Merit of the Republic of Hungary for his scientific work and support of art in Hungary. In 2006, he was the sixth recipient of the Eduard Reichenow Medal from the German Society for Protozoology, awarded for his life's work in the comparative analysis of energy metabolism, its evolution, and its organellar localization in parasitic anaerobic protists. He is an external member of the Hungarian Academy of Sciences.

The Ott laboratory focuses on the interpretation of genomic data, such as results from microarrays and single-nucleotide polymorphisms (SNPs), Ott develops new mathematical-statistical methods for human gene mapping and builds computer programs to implement them. He uses the resulting information to study the interactions among multiple disease loci that underlie complex traits, as well as to study how environmental risk factors modify disease loci effects.

Ott's work falls into three broad categories: improving existing statistical analysis methods and developing new ones; creating computer programs to implement these methods; and applying the techniques to genetic data, most of which is collected by outside investigators.

Academic and industry researchers are most interested in heritable complex traits—such as heart disease and schizophrenia—that are believed to be under the control of multiple interacting susceptibility loci, each with relatively small effect. One of the challenges is in identifying sets of such disease loci. Ott carried out data analysis with collaborating drug companies, identifying nine SNP markers associated with post-angioplasty artery narrowing in one case and a gene associated with an adverse drug reaction in another.

Ott is also interested in improving analysis techniques that were developed in the lab. His set association analysis method, for example, is currently designed for case-control data or binary outcome variables. The approach grew out of scientists' increasing need to work with a quantity of genes that can far outnumber the quantity of observations, such as that found in genomic screens for disease loci or in microarray experiments.

Ott is a pioneer in the field of genetic linkage and authored the first publicly accessible computer program on human linkage analysis (LIPED). His work provided the statistical framework for newer approaches to haplotype-relative risk methods. He has analyzed gene linkages for disorders including hypertension, macular degeneration, Creutzfeldt-Jakob disease, multiple sclerosis, and retinitis pigmentosa.

Ott earned his Ph.D. in zoology from the University of Zurich in 1967 and his master's degree in biomathematics from the University of Washington in 1972. In 1986 he accepted positions as professor of genetics and development at Columbia University and research scientist and director of the department of statistics at the New York State Psychiatric Institute. Ott came to Rockefeller in 1996 as professor and head of the Laboratory of Statistical Genetics.

Ott was a MERIT awardee of the National Institute of Mental Health from 1991 to 2003. He received a medal of honor from the German Society for Human Genetics in 2007, the Ming Tsuang Lifetime Achievement Award from the International Society of Psychiatric Genetics in 2008, and the Allan Award from the American Society of Human Genetics in 2010. He was a visiting professor at the Institute of Psychology in Beijing, Chinese Academy of Sciences, in 2015, and has been the recipient of two four-year project grants from the Natural Science Foundation of China.
Since retiring as president of The Rockefeller University in 1998, Wiesel has turned his attention to international science advocacy. From 2000 to 2009, Wiesel was secretary general of the Human Frontier Science Program, established in 1989 to support international, innovative, and interdisciplinary basic research in the life sciences. He was chairman of the board of governors of the New York Academy of Sciences from 2000 to 2006 and continues to serve as lifetime honorary chair. Wiesel served from 1994 to 2009 as chair of the scientific advisory committee of the Pew Scholars Program. He also assisted in the creation of the Pew Latin American Fellows Program in the Biomedical Sciences and served as a chair of its review committee from 1992 to 2018. He is a founding member of the Israeli-Palestinian Science Organization, a nonprofit alliance established in 2004 to support collaborative research between scientists in Israel and Palestine to promote positive interactions between the two communities. Wiesel has done much work as a global human rights advocate. He is a founding member of the International Human Rights Network of Academies and Scholarly Societies, and he also served for 10 years as chair of the committee on human rights of the National Academies of Sciences. He chaired the board of the Okinawa Institute of Science and Technology for 15 years and serves as a lifetime trustee on the Hospital for Special Surgery’s board, as well as on the president’s council of the accredited online University of the People.

Born in 1924 in Uppsala, Sweden, Wiesel received his M.D. from the Karolinska Institute in 1954, after which he taught in the institute's department of physiology and worked in the child psychiatry unit of the Karolinska Hospital. He began a fellowship in ophthalmology at Johns Hopkins University Medical School in 1955 and became an assistant professor there in 1958. The following year, he became an instructor in pharmacology at Harvard Medical School, and he became professor in the new department of neurobiology in 1968 and its chair in 1973. Wiesel moved to Rockefeller in 1983 as Vincent and Brooke Astor Professor and head of the Laboratory of Neurobiology. He was president of Rockefeller from 1991 to 1998, during which time he was instrumental in the recruitment of 16 new faculty members, the establishment of six interdisciplinary research centers, and the formation of a collaborative relationship with the Aaron Diamond AIDS Research Center. He is currently co-director of the Shelby White and Leon Levy Center for Mind, Brain and Behavior at Rockefeller.

Wiesel's awards include the 1981 Nobel Prize in Physiology or Medicine, which he won with David Hubel for studies of how visual information is transmitted to and processed in the brain's visual cortex. Their investigations identified specialized functions and mapped the functional architecture of individual cells in the visual cortex. Hubel and Wiesel also studied the development of the visual cortex and the role of innate and experiential factors, research that has had important clinical implications, including more effective treatments for congenital cataracts. Wiesel was also a recipient of the National Medal of Science in 2005.

Torsten N. Wiesel, M.D.

PROFESSOR EMERITUS • VINCENT AND BROOKE ASTOR PROFESSOR EMERITUS, LABORATORY OF NEUROBIOLOGY

Victor Wilson, Ph.D.

PROFESSOR EMERITUS, LABORATORY OF NEUROPHYSIOLOGY

Wilson is a neurophysiologist whose first experiments were on reflex circuitry in the mammalian spinal cord. He discovered a type of synaptic interaction known as disinhibition—excitation by removal of inhibition, previously observed only in an invertebrate, the horseshoe crab, by the laboratory of H. Keffer Hartline. Subsequently, his studies concentrated on the vestibular system, which acts as a “sixth sense,” contributing to an animal’s perception of its position in space and to its control of balance and posture. His particular interests included the circuitry and behavior of groups of vestibular neurons in the brain stem and their influence on spinal circuits controlling the neck and limbs.

Wilson is also the coauthor of Mammalian Vestibular Physiology, published in 1979, one of the seminal books on the vestibular system, and is a contributor to The Vestibular System, A Sixth Sense, published in 2012. Wilson received his undergraduate and master’s degrees from Tufts College and, after a year doing research at the University of Cambridge, obtained his Ph.D. from the University of Illinois. He was appointed a research associate at Rockefeller in 1953 and then served in the United States Army as a physiologist at the Walter Reed Army Institute of Research until 1956. He was named assistant professor in 1958, associate professor in 1962, and professor in 1969.

William Agosta, Ph.D.
Professor Emeritus
Laboratory of Organic Chemistry

Attallah Kappas, M.D.
Physician in Chief Emeritus
Sherman Fairchild Professor Emeritus
Laboratory of Pharmacology

Purnell W. Choppin, M.D.
Professor Emeritus
Laboratory of Virology and Infectious Disease

Te Piao King, Ph.D.
Associate Professor Emeritus
Laboratory of Biochemistry
Karen Bulloch, Ph.D.

RESEARCH ASSOCIATE PROFESSOR, HAROLD AND MARGARET MILLIKEN HATCH LABORATORY OF NEUROENDOCRINOLOGY

Bulloch heads the Neuroimmunology and Inflammation Program, which works to characterize a novel immune cell population, termed brain dendritic cells, in the normal and diseased central nervous system (CNS). Dendritic cells, initially discovered by Rockefeller's Ralph M. Steinman and Zanvil A. Cohn, are essential in orchestrating the body's immune response to pathogenic and toxic antigens. Dendritic cells also play an important role in maintaining tolerance in the body to protect against autoimmune diseases.

Brain dendritic cells were identified using a transgenic mouse model developed at Rockefeller, which expresses enhanced yellow fluorescent protein under the control of the CD11c gene promoter, a marker for dendritic cells throughout the body. Bulloch and the program's scientists further characterized brain dendritic cells in neonatal, young, adult, and aging brains as well as their presence following seizures and stroke. It was further shown that brain dendritic cells are competent inducers of the T cell immune response.

Currently, the program's scientists are working on evaluating the function of brain dendritic cells following viral infection and in mouse models of inflammation and neurodegenerative diseases. Additional work seeks to understand the role of these cells in development and in neuroendocrine–immune interactions.

Their data now indicate that these immune cells, which are both CNS and peripheral in origin, are capable of responding to points of injury and infection in the brain. The goal of Bulloch's program is to elucidate the molecular mechanisms underlying immune responses in the brain and to develop new targets for therapies for a wide range of CNS damage.
A major focus of Butelman's work is the behavioral and neurobiological impact of the κ-opioid receptor (KOPr) system, and of the endogenous agonists that activate it, the dynorphins. The KOPr system is thought to be involved in several neuropsychiatric disorders, including anxiety, depression, and specific addictive diseases. His long-term goal is to open the door for the development of new pharmacotherapeutic approaches for these neuropsychiatric disorders, and for opiate and cocaine addiction, based on a better understanding of their etiology and their interaction with the KOPr–dynorphin system.

Butelman has also focused on characterizing the pharmacology of salvinorin A, a powerful hallucinogenic compound from the plant Salvia divinorum. This plant, originally used in ethnomedical practice, has more recently become widely available and abused, especially in adolescents and young adults. Butelman and his colleagues confirmed in vivo that salvinorin A is a KOPr agonist, by showing that its discriminative (subjective-like) effects are shared with known synthetic KOPr agonists. He further showed that KOPr blockade could both prevent and reverse behavioral effects of salvinorin A. Furthermore, a classic serotonergic hallucinogen did not share the discriminative effects of salvinorin A. Overall, these findings indicate that the behavioral and hallucinogenic effects of salvinorin A are thus completely separate from those of known “classic” hallucinogens, and implicates the KOPr–dynorphin system as a powerful mechanism underlying higher functions.

Caskey's work focuses on the development and clinical evaluation of novel immunotherapeutic strategies against infectious diseases, with a special emphasis on HIV. Despite the success of combination antiretroviral therapy in suppressing viral replication and preventing disease progression, HIV incidence remains high, and current treatment modalities do not eradicate the infection. A new generation of highly potent, broadly neutralizing antibodies may represent a novel strategy to combat HIV infection, potentially providing long-term control of infection, prevention of new infections, and guidance for vaccine development. Over the last four years, Caskey has led a series of first-in-human studies with two of the most promising broadly neutralizing anti-HIV-1 antibodies: 3BNC117 and 10-1074, which were isolated from HIV-infected individuals by the Laboratory of Molecular Immunology. These first studies aim to evaluate the safety, pharmacokinetics, and antiviral activity of these molecules in both HIV-infected and HIV-uninfected individuals. In addition to controlling viral replication and preventing infection by blocking viral entry, these molecules have the potential to interfere with the latent reservoir of infected cells that is not eliminated by standard treatment.

Studies of neutralizing antibodies, in combination with other immunologic strategies directed toward achieving HIV cure or long-term remission, are also being pursued by Caskey's team. These initial studies, conducted at The Rockefeller University Hospital, have begun to elucidate the in vivo activity of these molecules in humans and have generated supportive data to advance their development to larger clinical studies with the goal of determining their efficacy in preventing HIV infection in high-risk populations.

Cells must dispose of unneeded proteins but spare others, requiring precise discrimination. Disposal usually involves ubiquitin tagging for delivery to proteasomes, the site of destruction. Coffino recognized alternate ways to tag proteins for destruction. He and his colleagues discovered that ornithine decarboxylase (ODC) contains a 37–amino acid region responsible for ODC's degradation. Removing this so-called degron stabilizes ODC, while adding it to other proteins destabilizes them in a broad variety of organisms.

ODC's degron couples two properties required for protein disposal: It attaches to proteasomes, and it provides an unstructured region big enough to thread into the proteasome region, an ATPase ring, that actively reels in the target, thrusting it toward the site of destruction.

This understanding made it possible to design novel target substrates to systematically test hypotheses about the proteasome's function. For example, Coffino's work demonstrated that substrate mechanical stability determined how long it takes to unwind, dismantle, and destroy a protein. Other experiments showed that a viral sequence, which frustrates immune system attack, impairs the grip of the proteasome ATPase ring on substrates. Follow-up work found that similar polypeptides frustrated bacterial ATP-dependent proteases, indicating that functional properties have been conserved for protease translocation machines across a broad swath of biology.

At Rockefeller, Coffino is continuing his studies of ATPase motors, augmenting biochemistry with single-molecule analysis to better understand mechanisms by which these motors impel their substrates.
Darnell is a leading authority on fragile X syndrome, the most common monogenic cause of intellectual disability and autism. Fragile X is usually caused by the loss of an RNA-binding protein, FMRP. However, two patients have been identified with missense mutations that occur in FMRP's RNA-binding domains. By reproducing one mutation in mice, Darnell confirmed that the mutation causes fragile X symptoms due to loss of function of the RNA-binding domain in translational control, and provided a new mouse model for the field.

Darnell applied a new technique developed in the lab to determine the set of messenger RNAs that FMRP binds. The technique, called CLIP-Seq provides an unbiased snapshot of where FMRP binds RNA across the transcriptome in living cells. Darnell found that FMRP binds to messenger RNAs encoding many important synaptic proteins as well as chromatin regulatory enzymes and transcription factors. These categories of FMRP-regulated genes have a high overlap with candidate genes for autism spectrum disorders and schizophrenia. Darnell is now extending the CLIP-Seq studies to single neuronal cell types using a new mouse model that she and her colleagues developed in which endogenous FMRP can be conditionally tagged for CLIP-Seq experiments.

To understand the function of FMRP in translational control, Darnell developed a unique translation assay designed to preserve endogenous FMRP-RNA interactions in the brain, and showed that FMRP inhibits the translation of the same messenger RNAs in association with stalled ribosomes. Darnell is now working to determine whether FMRP stalls ribosomes or stabilizes ribosomes stalled by something else. Uncovering why and how FMRP accomplishes this, as well as how this translational repression is relieved, is an area of great interest in her work.

Darnell’s work is furthering our understanding of how FMRP regulates messenger RNA translation important for normal synaptic function, and is opening new avenues for therapy based on a deeper understanding of FMRPs function.

Flajolet is interested in the molecular and cellular mechanisms underlying neuronal signaling, both in healthy brains as well as in neurodegenerative diseases, with a focus on Alzheimer’s disease. He has studied several classes of signaling components including G protein coupled receptors (GPCRs) and their regulatory factors, and protein kinases. Out of about 400 non-sensory GPCRs present in the human genome, about a fifth are still orphan, meaning that their natural ligands are not known. Furthermore, these 120 receptors are vastly uncharacterized: their coupling to secondary messengers is often not established, and their biological functions haven’t been uncovered. The phylogenetic clustering of some of these receptors, and the absence of strong similarities to other subfamilies of GPCRs, may indicate that entirely new biological functions and neurotransmitter systems will be discovered.

Flajolet has studied important and well characterized GPCRs, such as metabotropic glutamate, serotonin, and adenosine receptors, identifying novel signaling routes and regulatory proteins. In a search for key regulatory proteins, novel neuronal pathways, and possibly entirely new neurotransmitter systems, Flajolet's current research is focused on orphan GPCRs that are enriched in the hippocampal formation, an important brain region responsible for learning and memory that is involved in, among other things, fact recollection and spatial memory formation. The two major goals of his research are to identify ligands (natural ones or pharmacological tools) for these orphan receptors and to uncover the functions of these receptors in vivo in the brain. Because of their localization in the brain, these receptors might be relevant for various mental disorders and diseases involving memory, neurogenesis, and developmental dysfunction in general. The putative novel neurotransmitter systems associated with these orphan GPCRs represent important untapped opportunities to develop new paradigms to better understand, and ideally treat, diseases of the central nervous system.

Glickman is interested in discovering molecules that can be developed into medicines, and in the technologies associated with drug discovery. One of the main barriers to translating basic research into treatments for disease is the amount of time required to test medical hypotheses. To speed up this trial-and-error process, Glickman focuses on instrumentation and software that automates and miniaturizes molecular and cellular testing. Among these approaches is high-throughput screening, in which large numbers of random small molecules are rapidly tested in disease-relevant bioassays to identify starting molecules for drug development. Additionally, new technologies that allow for dramatically increased speed and accuracy in the measurement of biomolecular interactions are improving the efficiency of the drug discovery process.

Glickman is working with various researchers to identify and develop novel assays for drug discovery, and then apply screening strategies to identify compounds for further therapeutic development. His High Throughput and Spectroscopy Resource Center conducts a variety of sophisticated approaches for measuring the interaction of small molecules and antibodies with their molecular targets. The information generated is critical for understanding the underlying mechanisms of disease and for beginning to identify drug-like molecules based on this understanding.
Ibañez-Tallon investigates the habenula, an ancient and highly conserved brain structure associated with compulsive and impulsive behaviors. All vertebrates possess this small midbrain structure; however, until recently, it has received little attention. The habenula links the forebrain and limbic system with the brainstem, acting as a relay station for the regulation of emotion, motivation, and cognition. It appears to play a role in psychiatric disorders including drug addiction, depression, and obsessive-compulsive disorders.

While studying nicotinic receptors, Ibañez-Tallon uncovered some of the first evidence implicating the habenula in nicotine addiction. She discovered that cholinergic neurons in the medial habenula play a critical role in nicotine consumption in mice, a result bolstered by genome-wide association studies of human tobacco use. Ibañez-Tallon and another group independently demonstrated that nicotine consumption in mice could be altered via nicotinic receptors in medial habenular neurons.

Ibañez-Tallon is currently investigating the molecular mechanisms, neural circuits, and behaviors associated with the habenula. She has recently identified novel receptors and membrane proteins present only in specific habenular neuron populations, in which these molecules control neuronal activity and synaptic transmission. Her work has also uncovered a high concentration of rhythmic activity-generating pacemaker channels in habenular neurons.

Ibañez-Tallon applies a variety of techniques to investigate habenular structure and function, including genetically encoded venomous peptide toxins, translating ribosome affinity purification, electrophysiology, and behavioral tests in mice. She is also involved in circuit mapping elsewhere in the central nervous system to better understand addiction and other psychiatric conditions.

Hatziioannou's research is guided by the premise that understanding the mechanisms by which lentiviruses avoid and/or counteract inhibitors in their natural host is fundamental to determining the primate lentivirus host range. To successfully colonize a species, lentiviruses have to adapt to optimally use host factors critical for virus replication. Equally importantly, viruses have to overcome host proteins, known as restriction factors, that inhibit virus replication in a species-specific manner. Hatziioannou has shown that although such restriction factors are generally beneficial, as they protect humans from viruses infecting other primates, they may also account for our inability to generate optimal animal models for research on HIV and AIDS.

Understanding how host protein variation drives lentivirus adaptation provides important insights into the evolutionary history of lentiviruses and, moreover, suggests paths toward the development of novel animal models for HIV-1 to facilitate the evaluation of clinical therapies, prevention strategies, and other interventions.

This understanding of the interactions between primate lentiviruses and their hosts has allowed Hatziioannou and her colleagues to manipulate HIV-1, becoming the first to develop an HIV-1-based virus that is able to cause AIDS-like disease in a non-hominid. In parallel, these collaborative studies continually reveal novel aspects of the molecular biology of interactions between primate lentiviruses and their hosts.

This is exemplified by the recent determination of the crystal structure of one such restriction factor, APOBEC3H.

Kost develops innovative strategies, infrastructure, and service models to accelerate the design and ethical conduct of translational research. She has broadened approaches to engagement of diverse populations into research through a research volunteer repository and a collaborative community-engaged research navigation model that fosters research partnerships between basic scientists and communities. Kost also creates tools and measures to improve participant experiences, recruitment, and research integrity.

Kost's work focuses on creating data-driven assessments and novel measures of the research process, so-called "research-on-research." She led a 15-center collaboration that developed a suite of validated participant-centered measures of informed consent, trust, and other aspects of research participation, now adopted at centers across the NIH Clinical and Translational Science Award (CTSA) institutions for both internal and external benchmarking. Kost is applying these measures to evaluate approaches to broad consent in genomics research, and other aspects of human protections. She also developed a simple measure of the timeliness of study accrual, the Accrual Index, to normalize inter-protocol and inter-institutional comparisons of study enrollment methods. The CTSA Consortium recently adopted the Accrual Index as a common metric. The community-engaged research navigation process has produced sustainable partnerships that effectively joined basic researchers with patients, clinicians, and public health collaborators to address antibiotic-resistant infections, healthy aging, and the impact of nutrition on pregnancy outcomes in teens.

In addition to conducting research, Kost chairs the Action Committee for Community Engaged Research, facilitates ethics discussions in the Responsible Conduct of Research course, lectures in the Certificate in Clinical and Translational Research course, and serves as vice-chair of the Institutional Review Board. She is director of the Clinical Research Support Office and co-director of the Community Engaged Research Core in the Center for Clinical and Translational Science. She currently serves on a national committee examining the ethical and regulatory context that would inform return of research results to individual study participants.
Leibowitz is interested in understanding the neurobiology of substance abuse and addiction. She and her colleagues study the most commonly abused substances, namely alcohol and nicotine, in addition to palatable fat- and sugar-rich foods that may have addictive-like properties. Her current research in rodents investigates neural mechanisms that mediate the transition from casual use to abuse and ultimately dependence on these substances. It reveals marked similarities between neurochemical mechanisms in different brain areas that control the consumption of fat, alcohol, and nicotine and also various emotional behaviors, such as novelty seeking, impulsivity, and anxiety, which promote their consumption.

Substance use disorders are heterogeneous in nature, with users exhibiting different patterns of intake varying from cycles of binging to chronically elevated intake. Leibowitz's research links these patterns to distinct neurochemical systems. It demonstrates that individuals prone to abusing these substances, identified by particular behaviors and biomarkers, exhibit specific neurochemical abnormalities that may be causally related to their excessive consumption. Abusers are highly susceptible to relapse, and her findings associate this with specific neuroadaptations that come to precede binging behavior and persist in the absence of substance exposure.

Leibowitz also finds that exposure to fat, alcohol, and nicotine early in life, before puberty or during pregnancy, induces this predisposed phenotype in the offspring. Her recent studies suggest that this is attributed to a similar stimulatory effect of these substances on neurodevelopment, neuroimmune function, and lipid metabolism. Live-imaging studies in zebrafish are also allowing a more in-depth understanding of how these substances affect the birth and migration of brain neurons that promote substance abuse.

With the diversity of mechanisms underlying substance use disorders in adults, Leibowitz's research is focusing on developing methods for prevention of early exposure and brain reprogramming, early detection of abuse propensity, and personalizing pharmacotherapy for distinct subpopulations of prone or addicted individuals.

Drug addiction is a chronic brain disease with a significant genetic contribution and a complex inheritance mode. Only a small percentage of individuals meeting criteria for heroin dependence are able to succeed in maintaining long-term abstinence without medication. Levran's research in the laboratory of Mary Jeanne Kreek focuses on heroin and cocaine addiction, and includes population-specific association studies and pharmacogenetics studies of methadone maintenance treatment. Her aim is to better understand the mechanisms of drug addiction, develop new pharmacotherapeutic approaches, and improve treatment options.

Levran has identified multiple susceptibility loci for heroin and cocaine addiction (e.g., PKBPS, CSKNT1, DRD2, CHRM4, and HTR3B) in several pathways including stress response, circadian rhythm, synaptic plasticity, and the reward system. She has demonstrated that some loci are population-specific or drug-specific. She has also identified susceptibility loci that are associated with methadone dose requirement (e.g., ABCB1, CYP2B6, and NGRB), a step toward personalizing treatments for individuals using genetic tools.

Levran's goal is to expand this research by studying additional populations, unique cohorts, and epigenetic factors, and by using new tools, including genome-wide association studies and region-specific deep sequencing.

MacDonald and her colleagues use two well-studied positive-strand RNA viruses representing the Alphavirus and Flavivirus genera to gain insights into viruses and the hosts they infect. Sindbis virus is an Alphavirus genus member within the Togaviridae family, which causes severe, untreatable illness including arthritis and encephalitis. The zinc-finger antiviral protein (ZAP) is a cellular factor with powerful inhibitory activity against several pathogens, including Sindbis, hepatitis B, HIV, Ebola, and Marburg viruses. While its mechanism of action is not fully elucidated, ZAP expression blocks translation of the incoming Sindbis virus genome and promotes degradation of retrovirus and filovirus genomic RNA. MacDonald's group has shown that ZAP synergizes with interferon, an innate immune defense system that creates an antiviral state. Genes synergizing with ZAP were identified by coexpressing ZAP with over 350 interferon-stimulated genes. To further elucidate ZAP's antiviral mechanism, a genome-wide screen was conducted, revealing a role for TRIM25 in ZAP action. The group is also studying two new ZAP isoforms to determine their biological activity against a panel of viruses.

Infection with the yellow fever virus, a member of the Flaviviridae family, leads to severe disease, including hemorrhagic fever and death. The live, attenuated yellow fever vaccine is a highly successful vaccine, providing life-long protection. MacDonald and her colleagues, in collaboration with Charles M. Rice, are investigating the mechanisms of attenuation of the vaccine strain. Knowledge gained will help improve the vaccine's safety and aid the development of vaccines against other flaviviruses.
Mojsov's long-standing interests are in understanding how peptides and small proteins regulate physiological processes in healthy and disease states. She applied her expertise in the chemical synthesis of peptides and small proteins to a wide range of studies, starting with the discovery of glucagon-like peptide 1 (GLP-1) and its key role in insulin secretion and glucose metabolism. Based on Mojsov's work, Novo Nordisk developed a GLP-1 analogue as a new therapeutic agent for type 2 diabetes approved for use in Europe, Japan, China, and the United States under the trade name Victoza. Close to two million individuals with type 2 diabetes use Victoza to control their glucose levels. Recently, Victoza was approved for the treatment of obesity under the trade name Saxenda. Mojsov's work with gluco-regulatory hormones include studies on the diversification, during vertebrate evolution, of the functions of genes encoding GLP-1-related peptides and their G protein coupled receptors.

Mojsov has collaborated with members of Ralph Steinman's and Brian Chait's groups on developing a proteomic approach to identify the peptide repertoire presented by the major histocompatibility complex on dendritic cells after immunizations with proteins that are specifically delivered to dendritic cells. This work is part of the effort to develop dendritic cell-based vaccines against HIV and other infectious agents.

Malik studies how eukaryotic genes are spatially and temporally regulated. Building on the work of Robert G. Roeder, his research aims to delineate how orchestrated action of numerous transcription factors controls messenger RNA synthesis by RNA polymerase II. These factors include polymerase-interacting general transcription factors; tissue- and gene-specific activators, which target specific DNA sequences; as well as various coactivators. Working with Roeder's group, Malik was among the first to isolate and characterize the multi-subunit Mediator coactivator complex, which functionally couples activators and the general polymerase machinery. The Mediator has since emerged as the cell's singular “integrative hub” for transcription regulation, assimilating multiple signals feeding into a gene and modulating the appropriate transcriptional response.

Malik's group currently focuses on Mediator-dependent transcriptional mechanisms at loci controlled by the nuclear receptor HNF4α, a critical regulator of liver organogenesis and physiology. Malik's research emphasizes reconstitution of HNF4α- and Mediator-regulated transcription in vitro and biochemical dissection of the underlying mechanisms. Most recently, his group established a fully defined system reconstituted from purified components that recapitulates transcription of a model liver gene in the context of nucleosomes that package cellular DNA. This system has revealed novel Mediator-controlled steps that determine when and where the gene will be turned on. Toward further elucidating Mediator mechanisms for delivering precise transcriptional outputs to HNF4α-regulated genes, these studies are being complemented with genome-wide and 3-D structural analyses of Mediator-containing complexes.

North joined The Rockefeller University in 2000 to establish and direct its Bio-Imaging Resource Center, one of the world’s most comprehensive facilities for state-of-the-art microscopy and scientific imaging. North, a cell biologist whose research has included using immunoelectron microscopy to study muscle defects caused by Duchenne muscular dystrophy and ultrastructural studies of the cellular organization of epidermal cell-cell junctions, advises and trains hundreds of researchers from Rockefeller and other institutions in a wide variety of optical microscopy techniques.

A native of Yorkshire, UK, she was an undergraduate at the University of Cambridge and received her doctorate from Oxford University. She undertook postdoctoral research in Salzburg and then Manchester, where she was later awarded a Wellcome Trust Career Development fellowship. North's images and movies have been exhibited worldwide, including in science exhibits at the International Center of Photography in New York and on the public television science series Nova. She has also acted as judge for both the Olympus BioScapes and Nikon Small World photomicrography competitions.
Schlesinger chairs The Rockefeller University Institutional Review Board and the research education and training committee, which is part of the Center for Clinical and Translational Science. She also serves as director of the Clinical Scholars Program and the Certificate in Clinical and Translational Sciences Program. Previously, Schlesinger was involved in clinical trials of 11 HIV vaccines and vaccine adjuvants. She is now conducting the first HIV vaccine trial based on dendritic cells, which were discovered at Rockefeller in 1973 by Ralph M. Steinman and his mentor, Zanvil A. Cohn.

In the steady state, dendritic cells capture antigens and travel to immune or lymphoid tissues, where they present the antigens to T cells, stimulating a robust immune response. But dendritic cells also play a seemingly opposite role, immune tolerance, silencing dangerous immune cells and preventing them from attacking the body’s own tissues. Working with Steinman, Schlesinger used dendritic cells to study and design treatments that can either enhance the immune system or silence its functions in an antigen- or disease-specific manner.

Davide F. Robbiani, M.D., Ph.D.
RESEARCH ASSOCIATE PROFESSOR, LABORATORY OF MOLECULAR IMMUNOLOGY

Robbiani studies B lymphocytes, which are crucial to immune defense because they produce infection-fighting antibodies—the key to the efficacy of most vaccines. Using a combination of experiments with human samples, high throughput antibody cloning, and in vivo animal models of vaccination and infection, Robbiani aims to understand how protective antibodies are formed and to use this information to advance vaccine design. His current work focuses on immune responses to the Zika and dengue viruses, mosquito-borne viruses that are transmitted globally and are responsible for severe human disease. These studies are conducted in association with Margaret MacDonald of Rockefeller’s Laboratory of Virology and Infectious Disease, and in collaboration with researchers in South and Central America.

Robbiani is also interested in the malignant biology of B lymphocytes. B lymphocyte–derived cancers—leukemia, lymphoma, and multiple myeloma—frequently bear characteristic DNA aberrations. To understand the genesis of lymphoma-associated chromosome aberrations, particularly the contribution of immune enzymes such as RAG1/2 and AID to the genomic damage associated with these events, Robbiani and his colleagues use mouse genetics along with deep-sequencing techniques, mouse lymphoma models, and computational analysis of human cancer genomes.

Marjorie Russel, Ph.D.
ADJUNCT ASSOCIATE PROFESSOR

Russel’s research interests relate to how proteins and protein complexes are translocated across biological membranes in prokaryotes. More specifically, she studies how filamentous phage are assembled at the bacterial cytoplasmic membrane and extruded across the both cytoplasmic and outer membranes. She uses genetic, biochemical, physiological, and imaging techniques to determine the individual roles of phage-encoded proteins required for virion assembly and secretion. Taken together, this work has found that protein multimers in each membrane form a trans-envelope structure through which the assembling phage passes. It has identified two cytoplasmic membrane proteins which interact with host thioredoxin and a packing signal in the phage DNA and hydrolyze ATP. The outer membrane protein has a cylindrical structure composed of 14 identical subunits and forms a gated channel large enough to accommodate the phage. Furthermore, variants of this protein with mutations in the gate region cause the channel to open more frequently, thereby rendering bacteria highly sensitive to antibiotics. Homologous proteins encoded by pathogenic bacteria are components of secretion systems that export wide range of virulence factors, and significant functional and structural similarities between the phage and bacterial proteins suggest that findings in the former will be broadly applicable to bacterial pathogenesis.

Sarah J. Schlesinger, M.D.
SENIOR ATTENDING PHYSICIAN • ASSOCIATE PROFESSOR OF CLINICAL INVESTIGATION, LABORATORY OF CHEMICAL BIOLOGY AND SIGNAL TRANSDUCTION

Schlesinger chairs The Rockefeller University Institutional Review Board and the research education and training committee, which is part of the Center for Clinical and Translational Science. She also serves as director of the Clinical Scholars Program and the Certificate in Clinical and Translational Sciences Program.

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In the steady state, dendritic cells capture antigens and travel to immune or lymphoid tissues, where they present the antigens to T cells, stimulating a robust immune response. But dendritic cells also play a seemingly opposite role, immune tolerance, silencing dangerous immune cells and preventing them from attacking the body’s own tissues. Working with Steinman, Schlesinger used dendritic cells to study and design treatments that can either enhance the immune system or silence its functions in an antigen- or disease-specific manner.
Tolwani oversees the Gene Targeting Resource Center and Transgenic Services Laboratory of the Comparative Bioscience Center (CBC). The CBC provides expertise in animal models, research design and methodology, generation and evaluation of genetically engineered mouse models, and other collaborative efforts. It also provides training to Rockefeller investigators.

Tolwani holds a D.V.M. in veterinary medicine from Auburn University. After two years in private practice in Nashville, Tennessee, he turned to research, completing a Ph.D. in cellular and molecular pathology and a postdoc fellowship in laboratory animal/comparative medicine at the University of Alabama. For his research, he developed a mouse model to study a common illness in humans associated with an enzyme deficiency in fat metabolism. Tolwani later earned an M.Sx. degree in management from the Stanford Graduate School of Business.

Tolwani joined Rockefeller in 2007. From 1994 to 2007, he served on the faculty of the Stanford University School of Medicine, where his laboratory focused on understanding the molecular mechanisms of brain plasticity.

Sinha's research focuses on the development of natural and non-natural products as tools and potential treatments for neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Accumulation of misfolded peptides and proteins, such as amyloid-β peptide and hyperphosphorylated tau protein in Alzheimer's disease and α-synuclein in Parkinson's disease, are likely causative to these diseases, and compounds reducing the levels of misfolded peptides and proteins are highly desirable.

In recent years, Sinha has focused on compounds that reduce amyloid-β production through shifting the amyloid precursor protein (APP) metabolism from the amyloidogenic to the non-amyloidogenic pathway. Some of these compounds also induce autophagy, such as the related Brc-Abl kinase inhibitor nilotinib, but do so independent of kinase inhibition. Nilotinib is currently undergoing clinical trials for treatment of Parkinson's disease. The other class of compounds are CK1γ2 autophosphorylation inhibitors that mediate autophagy through increasing PS1 Ser-367 phosphorylation. Sinha and his team are collaborating with Paul Greengard's lab, which has recently identified PS1 Ser-367 phosphorylation as playing a key role in amyloid-β production through mediating autophagic degradation of its precursor, the APP β-CTF.

Sinha and his colleagues are also developing a DNA-encoded library that can be used to screen various targets of interest, including phosphorylation-related enzymes and receptors, relevant for central nervous system diseases. There are vast opportunities in these areas for the understanding of enzyme functions and drug development. Similarly, they are exploring the possibility of selective and effective treatment of central nervous system disorders using G protein coupled receptors.

Zhou's research in Mary Jeanne Kreek's lab focuses on the roles of central arginine vasopressin/V1b receptor, endorphin/mu opioid receptor (MOP-1), dynorphin/kappa opioid receptor (KOP-1), and cannabinoid systems in drug addiction.

Using genetically selected Sardinian alcohol-preferring rats, Zhou and colleagues at the Institute of Neuroscience in Italy have found that pharmacological blockade of V1b receptor attenuates alcohol drinking in a rat model of human alcoholism. A phase II clinical trial with colleagues at the National Institute on Alcohol Abuse and Alcoholism found that V1b antagonists reduce alcohol relapse in alcohol-dependent patients, especially in ones experiencing high stress.

In another study, using transgenic mice with hypothalamic-specific deletion of endorphin/proopiomelanocortin (POMC) expression, Zhou and colleagues at the University of Michigan have found that POMC-deficient mice have decreased "relapse" drinking after escalated alcohol intake, suggesting that hypothalamic endorphins play essential roles in alcohol relapse via an endorphin/MOP-1-mediated mechanism.

To explore the potential of functionally selective KOP-1 antagonists with fewer side effects in alcoholism treatment, Zhou and colleagues at the University of Kansas are actively testing novel Salvinorin A analogs in alcohol dependent-like drinking behaviors in mice. Zhou and colleagues at the University of Guelph in Canada have found that either V1b or KOP-1 antagonists dose-dependently block stress-induced heroin-seeking behavior. Finally, using knockin mice with human FAAH C385A SNP, Zhou and colleagues at Weill Cornell Medicine have found that FAAH+/- mice had greater alcohol intake than FAAH野生-type mice, consistent with clinical reports that human FAAH+/- carriers have higher alcohol intake and more severe alcohol dependency.
Our commitment to scientific education is a natural extension of our leadership in biomedicine.
Graduate and Postgraduate Programs

Rockefeller’s advanced scientific training programs are designed to educate and inspire tomorrow’s scientific leaders. Our philosophy of investing in brilliant, innovative individuals extends to our students and postdocs, who collaborate as equals with their mentors and receive the scientific foundation they need to succeed in academia, in industry, and as policy makers.
The David Rockefeller Graduate Program

The David Rockefeller Graduate Program offers rigorous training in the biomedical sciences. Designed to accommodate students with diverse interests and needs, the Ph.D. program is highly flexible. Students are encouraged to chart their own course, whether that means joining a lab immediately or rotating through several labs to gain exposure to different fields and approaches.

Students also design their own curricula in consultation with their mentors and the Dean's Office. Four required courses taken during the first year serve to develop students' abilities to interpret scientific data, to apply quantitative and statistical techniques to the analysis of experimental data, to promote awareness of research ethics, and to introduce students to research going on in the university's labs. In addition, several classes each semester offer foundations in particular specialties.

Most training, however, takes place in a collaborative laboratory setting. Degrees are awarded based on the satisfactory completion of academic requirements and the submission, presentation, and successful defense of a thesis comprising a body of novel scientific research. Throughout the program, the Dean's Office provides careful mentoring to students.

Since its beginning over 60 years ago, the Ph.D. program has recruited the very best students from around the world. Each year the university receives applications from approximately 800 prospective students, around 25 of whom enroll. All students are fully supported by the university, which provides stipends and remission of tuition. Students are also given subsidized housing, free health insurance, and annual research budgets, which can in part be used for attending scientific meetings and for the purchase of computers, books, and journals.

Clinical Scholars Program

Rockefeller supports approximately 15 to 20 early career physician-scientists each year who train in clinical and translational investigation in a unique three-year master's degree program, designed for M.D. or M.D.-Ph.D. degree holders or those with health-related doctoral degrees who wish to begin a career in patient-oriented research. Scholars join a laboratory and develop a clinical investigation protocol under the mentorship of the head of that laboratory. They also participate in a weekly core curriculum devoted to learning about clinical investigation and new translational research studies conducted by investigators from both the university and other institutions.

The Clinical Scholars Program was begun in 1976 and is supported in part by a Clinical and Translational Science Award from the National Center for Advancing Translational Sciences, part of the National Institutes of Health.

Postdoctoral Opportunities

The university has a strong commitment to the full involvement of postdoctoral trainees in all aspects of the scientific, educational, and cultural activities of the community. Each year approximately 325 postdoctoral investigators are associated with the research of the university's laboratories, where they are encouraged to continue their scientific training and pursue their research interests. In addition, postdoctoral trainees typically participate in the many seminars and colloquia held at the university. Many candidates for postdoctoral training obtain funding from a private or governmental granting agency; the university awards about 15 to 20 postdoctoral fellowships, made possible by philanthropic support, each year.

The Fellows Program at The Center for Studies in Physics and Biology

The Center for Studies in Physics and Biology was founded in 1994 to accelerate the contributions that physics can make to biomedical science, building bridges between scientific communities traditionally separated by steep barriers of language and technique. The center's fellows program recruits outstanding postdoctoral researchers trained in theoretical physics, mathematics, and computer science who demonstrate an interest in biological problems. Appointments are for two to three years.

One of the aims of the fellows program is to support theoreticians in their first steps as experimentalists. In working toward their goals, fellows are encouraged to seek mentors and collaborators among the university's biologists. Fellows apply physics-based and computational approaches to a range of fields, such as cell biology, evolution, and sensory neuroscience.
Tri-Institutional Programs

Rockefeller’s location adjacent to two other world-class institutions—Weill Cornell Medicine and Memorial Sloan Kettering Cancer Center—provides a unique opportunity for prospective students with an interest in medicine or chemistry to access the combined resources of all three facilities.

Tri-Institutional M.D.-Ph.D. Program

The mission of the Tri-Institutional M.D.-Ph.D. Program is to educate and train physician-scientists, who are able to bridge the gap between laboratory research and clinical medicine and thereby contribute toward improving health and reducing disability and death from disease.

Approximately 18 students enroll in this highly competitive program every year, and at any one time, 35 or so are performing thesis research in Rockefeller University laboratories.

Tri-Institutional Ph.D. Program in Chemical Biology

The Rockefeller University, with Weill Cornell Medicine and the Sloan Kettering Institute, trains graduate students to use chemical approaches and technologies to answer fundamental biological questions. Students, who receive graduate-level training in both chemistry and biology, are recruited from top undergraduate chemistry programs worldwide and train with faculty at one of the participating institutions.
Precollege and Undergraduate Research Opportunities

In addition to its degree-awarding programs, the university has several programs that support secondary and undergraduate science education. The programs are designed to engage students directly with hands-on, mentored science and to provide secondary education teachers with the tools they need to instill a passion for science in their students.

RockEDU Science Outreach

RockEDU Science Outreach (RockEDU) is a cornerstone for community engagement in New York City. Sitting at the intersection of basic science research and K-12 science education, this innovative program also serves as a pioneering model for science outreach across the globe. Designed to provide opportunities for K-12 students and teachers to undertake genuine engagements with science, RockEDU programs create innovative and flexible science resources and lead activities that promote equitable access to and an appreciation for the scientific process. Participants learn from working scientists, including volunteers from within the Rockefeller community, and gain hands-on experience in an authentic laboratory. RockEDU is also a resource for the scientific community, aiding in the development of mentoring, teaching, and science communication skills, and connecting scientists to educational career opportunities. RockEDU programs include:

- **RockEDU Presents**: A monthly science café series geared to high schoolers.
- **LAB Jumpstart**: A combined after-school and summer science research experience for high school students.
- **Summer Science Research Program (SSRP)**: A rigorous seven-week program in which high school students are embedded in Rockefeller labs to conduct real research.
- **LAB Experiences**: An immersive one-day science research experience for middle and high school classes of up to 34 students.
- **Science Saturday**: An interactive science festival for children and their families (hosted in collaboration with the Development office).
- **K-12 Teacher Professional Development**: Engaging workshops and classes designed to link the practice of science to the classroom setting.

Summer Undergraduate Research Fellowship (SURF)

The Summer Undergraduate Research Fellowship (SURF) program provides qualified, highly motivated college students majoring in the life or physical sciences an opportunity to experience laboratory research. The program offers intensive research training in the biomedical sciences and provides an opportunity for exceptional undergraduates to experience life as a graduate student. Participants in the program are matched with laboratories according to their interests and work on projects under the direct supervision of faculty, postdoctoral fellows, and/or senior graduate students. The program runs for 10 weeks each summer, and SURF students receive a stipend and free housing. Annually, more than 700 students apply for admission into the SURF program and approximately 20 are accepted.

Bard–Rockefeller Program

The Bard–Rockefeller Program is a collaboration between Bard College and The Rockefeller University. Among many joint ventures, the university offers specialized science courses and research opportunities to Bard undergraduates, allowing more advanced graduate students and postdoctoral fellows to gain teaching experience and creating the opportunity for Bard undergraduates to study the sciences through one of the world’s premier research universities.
Investment in smart people and in advanced technology drives our success.
The Rockefeller University Hospital

One of just two dedicated clinical research hospitals in the country, The Rockefeller University Hospital gives our scientists the ability to conduct human studies that would be difficult to do anywhere else. With its entire staff trained specifically to support clinical research, and no other mission to dilute its focus, The Rockefeller University Hospital can carry out experimental protocols with precision and compassion.

Cross talk between basic research and clinical investigation is an essential feature of Rockefeller’s culture, and The Rockefeller University Hospital provides an independent facility to study the scientific basis of disease and test new therapies; as such, it serves as a crucial link between laboratory investigation and bedside observation. This link works in both directions: discoveries made at the bench can be developed into new therapies to benefit patients, and research on the cause of disease in patients can lead to important insights into the basic process of life. The facility is vital to the University’s mission, with more than 40 percent of the university’s labs engaged in human studies.

With its goal to uncover the scientific basis of disease, including its detection, prevention, and treatment, The Rockefeller University Hospital is dedicated to providing outstanding patient care in the context of clinical research. It receives funding from both The Rockefeller University and a Clinical and Translational Science Award (CTSA) from the National Center for Advancing Translational Sciences of the National Institutes of Health.

The hospital’s facilities include a 20-bed inpatient unit, which operates 24 hours a day, 365 days a year, and the Robert and Harriet Heilbrunn Outpatient Research Center, which has nine examination rooms and is open weekdays from 7 a.m. to 5 p.m. Additional facilities include a four-room procedure suite suitable for endoscopy and biopsy procedures, a sleep study unit, a broadband/narrowband ultraviolet lightbox for psoriasis treatment, and a digital radiology suite. The hospital’s administrative staff supports investigators at every stage of the clinical research process, from the development of protocols to patient recruitment and data analysis; it also has a strong commitment to providing robust patient protections and to delivering exceptional patient service at every step of the way.

The hospital’s unique environment is especially well suited for long inpatient stays under carefully controlled conditions, facilitating the study of pathologic processes in patients and normal physiological processes in healthy volunteers. The facilities are also designed for high-intensity, high-complexity protocols such as pharmacokinetics and metabolic studies in Phase 1 and Phase 2 clinical trials. The hospital’s strengths include a specialized Research Bionutrition Department, special rooms for studies of patients in altered states of consciousness, and an on-site Research Pharmacy. Full clinical laboratory services are provided via contract with Memorial Sloan Kettering Cancer Center, radiology and EKG interpretations are provided by arrangement with physicians at New York-Presbyterian Hospital, and on-site apheresis services are provided by contract with the New York Blood Center.

The hospital, which was founded in 1910, has a rich history of innovation driven by interactions between clinical and basic scientists. Some of the more than 100 major contributions it has made to medicine include methods for blood storage and transfusion, methadone therapy, and multiple-drug treatment of HIV infection.
Interdisciplinary Centers

To facilitate collaborations, Rockefeller’s interdisciplinary centers promote research at the interfaces between fields of study and use multidisciplinary methods to address specific biomedical challenges. By uniting researchers and labs with common goals and providing opportunities—such as retreats and seminars—to foster an exchange of ideas, these centers help to unite basic biology labs around specific clinical goals.

Anderson Center for Cancer Research
Titia de Lange, Ph.D., Director

To advance knowledge of cancer, improve treatments of the disease, and find cures, scientists are working to understand some of the most basic principles that govern life, including how cells normally grow and divide, how they differentiate into various types of cells, how genes switch on and off, and how the body’s immune system interacts with cancer.

The Anderson Center for Cancer Research was established to encourage and support cancer-related investigations that span a range of disciplines: cell and developmental biology, immunology, medical genetics, virology, chemistry, structural biology, bioinformatics, genomics, and proteomics. The approximately 30 laboratories that conduct cancer-related investigations constitute fertile ground for the kinds of collaborations and cross-disciplinary approaches most likely to produce breakthroughs.

The Anderson Center provides funding and infrastructure to support promising interdisciplinary approaches to cancer-related research, including graduate and postdoctoral fellowships for individuals working at the leading edge of cancer research.

Center for Basic and Translational Research on Disorders of the Digestive System
Barry S. Coller, M.D., Director

Diseases that affect the digestive system are among the most prevalent health problems in the world today, but little is known about the fundamental causes and basic biology of these disorders. The Center for Basic and Translational Research on Disorders of the Digestive System (CDDS), established in 2012, brings together faculty for intensive interdisciplinary collaboration intended to result in new treatments for a broad range of health conditions including hepatitis; inflammatory bowel disorders such as Crohn’s disease and ulcerative colitis; obesity and metabolic disorders; and many forms of cancer, notably fibrolamellar hepatocellular carcinoma and gastrointestinal stromal tumors, as well as colorectal, liver, and pancreatic cancer.

The center promotes interdisciplinary basic research and collaborations among some 20 Rockefeller labs that study biological processes related to the digestive system, including its interactions with resident microorganisms and its interconnections with the immune, circulatory, and neuroendocrine systems. The CDDS also encourages translational research that integrates basic studies and clinical investigations centered in The Rockefeller University Hospital, with the goal of making major contributions to the medical management of metabolic diseases, cancers, infections, and inflammatory disorders.
Center for Studies in Physics and Biology
Mitchell J. Feigenbaum, Ph.D., Director

The Center for Studies in Physics and Biology was conceived by physicists and biologists to increase communication between their disciplines, with the goal of developing innovative solutions to biological questions. Much of the work at the center aims to understand how physical laws govern the operation of biochemical machinery and the processing of information inside cells. To this end, researchers study both the basic physical properties of biological systems (such as elasticity of DNA and DNA-protein interactions) and the application of physical techniques to the modeling of neural, genetic, and metabolic networks.

Christopher H. Browne Center for Immunology and Immune Diseases
Michel C. Nussenzweig, M.D., Ph.D., Director

An understanding of the immune system—the body’s intricate and essential defense network—is key to progress in many critical areas of biomedical research. The Browne Center focuses the efforts of Rockefeller researchers who explore the immune system in health and disease, promoting new collaborative research on autoimmunity, infectious diseases, cancer immunotherapy, and allergies. Goals include the creation of effective therapies and preventive measures against AIDS, tuberculosis, hepatitis C, and other infectious diseases, as well as cancer; the development of gene therapies and new transplantation techniques; and the design of better approaches to combat diabetes, rheumatoid arthritis, and other autoimmune disorders that can result when the immune system misguided attacks the body’s own healthy tissues.

Cooperative Center for Human Immunology
Jeffrey V. Ravetch, M.D., Ph.D., Director

The goal of The Rockefeller University Cooperative Center for Human Immunology (CCHI) is to perform directed investigations into the evolution of lasting, protective immune responses in order to better understand the requirements of effective vaccines and adjuvants. CCHI research projects are designed to test mechanistic hypotheses that examine novel aspects of the regulation of human immune responses in the context of vaccination against infectious disease. The program utilizes the resources of The Rockefeller University Hospital, the Zanvil Cohn Vaccine Center, and The Rockefeller University Clinical and Translational Science Award.
Fisher Center for Alzheimer’s Disease Research
Paul Greengard, Ph.D., Director

The Fisher Center is a nexus for Alzheimer’s disease research at Rockefeller. Its scientists work to expand and accelerate Alzheimer’s research and lay the foundation for new treatment strategies. In particular, the Fisher Center’s investigations build on research that explores various aspects of the disease including: 1) the processing of amyloid precursor protein (APP) that contributes to amyloid plaque formation; 2) the regulation of presenilin 1, one of the two major enzymes involved in the processing of APP; 3) the identification and characterization of genomic differences between nerve cells that are vulnerable and those that are resistant to the disease; 4) the evaluation of the importance of microglia in the disease; and 5) attempts to create in vitro stem cells (iPSCs) corresponding to the nerve cells that are most vulnerable in the disease.

F.M. Kirby Center for Sensory Neuroscience
A. James Hudspeth, M.D., Ph.D., Director

Research on the senses is dedicated to understanding how the brain gathers information through the eyes, ears, and other sensory organs, and how it processes that information to create a coherent representation of an organism’s surroundings.

Using tools from molecular genetics, biochemistry, computer science, microscopy, and brain imaging, scientists at the F. M. Kirby Center pursue studies of vision, hearing, smell, and taste both in vertebrates and in medically important arthropod pests. Members of the center collaborate to conduct genetic, biomolecular, and cellular studies of the components of sensory systems; to explore the development of sensory systems during embryonic growth and the regeneration of such systems after damage by illness, injury, or aging; and to determine the neural basis of perception that enables the brain to organize sensory information.

Kavli Neural Systems Institute
Leslie B. Vosshall, Ph.D., Director
Alipasha Vaziri, Ph.D., Associate Director
Mary E. Hatten, Ph.D., Senior Advisor
Roderick MacKinnon, M.D., Senior Advisor

Neuroscience is undergoing a convergence with fields such as bioengineering, nanoscience, and computer science that is expected to accelerate in the coming decades. The Kavli Neural Systems Institute (Kavli NSI) at Rockefeller University aims to be at the forefront of that shift, where multidisciplinary teams of scientists work to develop new tools and novel approaches to meet the very biggest challenges in neuroscience.

The Kavli NSI fosters collaboration among Rockefeller University’s dynamic community of scientists, including faculty, postdoctoral fellows, and graduate students. Together, they seek to generate new knowledge about the brain at many levels, from molecules to cells and from circuits to the whole brain. The ultimate goal is to integrate these different neural systems into a comprehensive view of the brain.

Pels Family Center for Biochemistry and Structural Biology
Taran Kapoor, Ph.D., Director

The Pels Family Center provides infrastructure and training for interdisciplinary studies of important biological and medical problems, using complementary tools from chemistry, physics, and the computational sciences. Center members have access to synchrotron beamlines for x-ray protein crystallography, high-speed computing facilities, and cryo-electron microscopes. The Pels Center facilitates studies on chromosomal DNA replication, nuclear transport, messenger RNA transcription, RNA processing, protein translation, signal transduction, ion channel and transporter protein structure and function, protein folding, peptide/protein chemistry, chemical biology, and computational and structural genomics.
Sackler Center for Biomedicine and Nutrition
Jan L. Breslow, M.D., Director

Founded in 2014, the Sackler Center for Biomedicine and Nutrition is dedicated to understanding how nutrition combined with other factors—including an individual's genetic profile and the influence of microbiota—may lead to healthy metabolic function or to such adverse health conditions as obesity, heart disease, diabetes, and cancer. The center supports basic research conducted at the biochemical, genomic, and molecular levels as well as patient-based studies. The Sackler Center encourages scientists to focus on questions of critical importance in nutrition research.

Topics under examination include: the biological effects of diets weighted toward higher fat, carbohydrate, or protein; obesity and associated inflammation as factors that contribute to cardiovascular disease and cancer; brown and beige adipose tissue, and their connection to weight gain or loss, and associated conditions; the epigenetic regulation of metabolic functions; the impact of supplementation with vitamin D and other micronutrients, rigorously studied; and neuroendocrine pathways that help to regulate appetite and energy expenditure. The center is also collaborating with the Sackler Institute of Nutritional Sciences of the New York Academy of Sciences, the Clinical Directors Network, and eight New York City based Community Health Centers to study nutrition in teenage women and—in those who become pregnant—the effects of nutrition on their offspring. The center offers pilot grants for innovative projects, stimulates interaction among scientists through seminars and meetings, and trains future leaders in nutrition research through its prestigious program of Sackler Fellowships.

Shelby White and Leon Levy Center for Mind, Brain, and Behavior
Mary E. Hatten, Ph.D., Co-director
Torsten N. Wiesel, M.D., Co-director

The human brain generates our perceptions, emotions, memories, and actions. Brain and behavioral disorders, including drug and alcohol abuse, afflict about 50 million Americans, and psychiatric illnesses account for approximately 20 percent of all hospitalizations in the United States. Significant progress in the prevention and treatment of neurological disorders will depend on major breakthroughs in understanding the brain's basic biology. Laboratories in the Shelby White and Leon Levy Center use the latest technological developments to reach deep insights into the function of the brain in health and disease. The center encompasses the work of more than 20 laboratories studying neural systems, neurogenetics, neurochemistry, and neural development.
Scientific Resource Centers

Many of the best tools in biology are too expensive, too complex, or simply too big to house in a single lab. To make such equipment available—and to provide the expertise needed to maximize its utility—the university’s laboratories enjoy access to more than a dozen shared resource centers that provide convenient, affordable access to key technologies and services.

Antibody and Bioresource Core Facility

The Antibody and Bioresource Core Facility develops and produces custom monoclonal antibodies (mAbs) to meet researchers’ experimental needs. A large selection of in-stock mAbs are ready for immediate delivery and use. Other services include purification and conjugation of mAbs, testing for mycoplasmal contamination, and distribution of antibodies and Rockefeller developed cell lines worldwide. The latter is designed to assist investigators with requests they receive for reagents they have developed. The facility supports researchers from The Rockefeller University and Memorial Sloan-Kettering Cancer Center.

Bioinformatics Resource Center

The Bioinformatics Resource Center provides bioinformatics analysis, experimental design consultation, software infrastructure, and training. With a specific expertise in the processing and analysis of high-throughput genomic sequencing data, and in collaboration with both wet and dry lab biologists, the center aims to support and accelerate the diverse and cutting-edge research conducted at the university through the creation of analytical pipelines; the analysis of data via direct collaborations; and the training of Rockefeller’s faculty, students, and scientific staff.

Bio-Imaging Resource Center

The Frits and Rita Markus Bio-Imaging Resource Center provides a wide spectrum of microscopy equipment and offers extensive training. Staff members are available to advise users on instrument selection, sample preparation, and image capture. Research can also be performed on a collaborative basis with the staff.

- 3D-SIM super-resolution system (OMX/GE)
- STORM super-resolution system (Nikon)
- Upright multiphoton microscope (Olympus)
- Inverted multiphoton microscope (Zeiss)
- Light sheet microscope (LaVision)
- Three inverted point-scanning confocal microscopes (Zeiss/Leica)
- TIRF/FLIM microscope (Nikon/Lambert Instruments)
- Two DeltaVision image restoration microscopes (GE)
- Spinning disk confocal microscope (Yokagawa/Zeiss)
- CellVoyager spinning disk system for long-term live imaging (Yokagawa/Olympus)
- VivaView incubator microscope (Olympus)
- Inverted microscope for long-term live cell imaging (Olympus)
- Upright microscope suitable for fluorescence and transmitted light techniques (Zeiss)
- Laser microdissection system (MMI)
- Image processing workstations
Comparative Bioscience Center

The Comparative Bioscience Center (CBC) provides a comprehensive program of animal care and animal model development and characterization in support of the university's in vivo research. The center is capable of maintaining a variety of common and unique laboratory animals and offers veterinary, diagnostic, and research technical services. The center is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Within the CBC, the Gene Targeting Resource Center and Transgenic Services Laboratory provides expertise on animal model development via CRISPR/Cas9 gene-editing technologies, gene targeting by homologous recombination, Cre-mediated genomic engineering, transgenic services, mouse in vitro fertilization, and cryopreservation.

The Laboratory of Comparative Pathology offers anatomic phenotyping of unique mouse strains, postmortem specimen investigation, and clinical pathology services.

- Facilities for in vivo imaging, gene editing, pathology phenotyping, and transgenic services
- Vevo microimaging ultrasound system
- IVIS imaging system for detection of fluorescent or bioluminescent signals
- RS 2000 biological irradiator
- Behavior equipment for behavior characterization of rodent models
- 3 Tesla and 7 Tesla MRI imaging systems (with Weill Cornell Medicine)
- Combined positron emission tomography and computed tomography (PET/CT) system (with Weill Cornell Medicine)
- Small animal PET system (with Weill Cornell Medicine)
- Medical cyclotron facility for production of radiotracers (with Weill Cornell Medicine)

Cryo-Electron Microscopy Resource Center

The Evelyn Gruss Lipper Cryo-Electron Microscopy Resource Center makes sophisticated new tools available to university researchers, allowing for the visualization of three-dimensional structures of molecules and macromolecular complexes in solution. Staff members train users and consult on experiments, enabling scientists to collect exceptionally high-resolution data.

- FEI Talos Arctica 200kV transmission electron microscope with Gatan K2 Summit direct electron detector (1.4 Ångstrom resolution)
- FEI Titan Krios 300kV transmission electron microscope with Gatan K2 Summit direct electron detector (1.0 Ångstrom resolution)
- FEI Titan Krios 300kV transmission electron microscope with Gatan K3 direct electron detector, Falcon 3 electron counting detector, spherical aberration corrector, electron energy filter, volta phase plate (1.0 Ångstrom resolution)

Electron Microscopy Resource Center

The Electron Microscopy Resource Center houses transmission and scanning electron microscopes, along with ancillary equipment, to support imaging studies of tissues, cultured cells, and subcellular fractions. The staff can conduct imaging studies directly or provide full training for users who prefer to conduct their own studies.

- FEI TECNAI G2 BioTwin 120kV transmission electron microscope with Gatan 4K x 4K digital camera
- JEOL 1400 Plus transmission electron microscope with Gatan 2K x 2K digital camera
- ZEISS LEO 1550 scanning electron microscope
Flow Cytometry Resource Center

The Flow Cytometry Resource Center (FCRC) offers a wide variety of multi-laser/multi-color flow cytometry sorters and analyzers, including spectral and imaging flow cytometers. The FCRC staff provides assistance with experimental design, advice on sample preparation, instrument operation training, troubleshooting, and data analysis consultation as well as ongoing instrument maintenance.

High-speed cell sorting is performed by FCRC staff. Researchers can independently operate benchtop analyzers after completing training.

- Three BD FACSAria (operated by FCRC staff)
- ImageStream-X (operated by FCRC staff)
- Cytek Aurora
- BD LSR-Fortessa and two BD LSRIIs
- ThermoFisher Attune NxT
- BD Accuri C6

Genomics Resource Center

The Genomics Resource Center offers comprehensive services and instruments, including technical support and project consultation, to support The Rockefeller University community's genomics research.

- Illumina HiSeq 2500 sequencers
- Illumina NextSeq 500 sequencers
- Illumina MiSeq sequencer
- Library preparation service for DNA-seq and transcriptome sequencing, specialized on ultra-small amount of input materials
- 10X Genomics Chromium system for single cell analysis
- Affymetrix microarray systems
- QuantStudio 12K Flex real-time PCR system
- Bioanalyzer, TapeStation, Qubit fluorometer, and NanoDrop spectrophotometer for DNA/RNA quantity and quality assessments

Glasswashing Services

This facility provides labware washing, drying, baking, and autoclaving to the laboratories, assists in the maintenance and use of autoclaves, and manages a centralized pipette calibration service. Pickup and delivery of glassware is generally same day.

- Six Steris Reliance laboratory glass washers
- Four Steris Reliance laboratory dryers
- Four Steris Reliance laboratory sterilizers
- Two Gruenberg ovens

High Energy Physics Instrument Shop

Staffed by master machinists, the Instrument Shop fabricates precise and unique instruments in support of the university's research needs. The staff is also available to assist in instrument design. The shop is open to all Tri-Institutional researchers.

High Performance Computing

Information Technology offers high-performance computing resources for the Rockefeller community. Resources within the environment include a shared HPC computing cluster with more than 4000 cores, and a hosted HPC environment in which labs may invest in dedicated resources. Large-scale data storage is also available. HPC staff can consult on computational and data science projects.

High Throughput and Spectroscopy Resource Center

The High Throughput and Spectroscopy Resource Center supports researchers in improving the efficiency of bioassays, identifying tool compounds and drug candidates, and utilizing core technologies typically applied to biochemical analysis. The center has a collection of over 380,000 diverse, drug-like compounds; automated liquid transfer devices; and it supports a broad diversity of assay development techniques typically found in drug discovery programs.

The center is configured for processing microplates through the use of automated liquid dispensers. For assay technologies, it has the capability to support cellular and biochemical assays using absorbance, fluorescence kinetics, fluorescence anisotropy, time-resolved fluorescence, time-resolved fluorescence resonance energy transfer, AlphaScreen, bioluminescence, scintillation proximity, and cellular imaging. Assay targets can include ion channels, receptors, enzymes, protein interactions, signaling pathways, and cellular processes.

- HighRes Biosolutions automated library storage system
- PerkinElmer Janus automated liquid handling workstation
- Tecan Freedom EVO 150 automated liquid handling workstation
- Thermo MultiDrop Combi reagent dispenser
- Malvern auto-ITC200 microcalorimeter
- Biotek Synergy NEO microplate reader
- LICOR Odyssey infrared microplate reader
- Molecular Devices ImageXpress high content screening system
- Bio-Rad ProteOn XPR36 surface plasmon resonance system
- NanoTemper MST monolith 115 microscale thermophoresis detector
- Aviv model 202 CD spectrometer
- Bruker Avance DPX600 MHz NMR spectrometer
- Agilent RapidFire 360 high throughput solid phase extraction mass spectrometer
- Wyatt Dynapro dynamic light scattering microplate reader
- BioRad differential scanning fluorimetry analyzer
- Hammamatsu FDSS fluorescence kinetics analyzer
- PerkinElmer TriLux scintillation proximity microplate reader
- Biotek EL406 automated microplate washer
- SeaHorse XF96 extracellular flux analyzer
Precision Fabrication and Instrument Design and Fabrication Facilities

The fabrication facilities provide access to various fabrication and rapid prototyping tools for qualified users. The instrumentation engineering staff of the Precision Fabrication Facility is available for consultation and to help design and fabricate custom microscope parts, behavior chambers, PDMS molds, printed circuit boards, and other equipment.

- ProJet 3510 HDPlus 3-D printer
- VLS6.60 laser cutter
- Roland MDX 540 CNC mill
- Jet 17-inch drill press
- Bridgeport Series I standard mill
- South Bend 28-inch bench lathe
- Jet 8201-k 1HP band saw
- Makerbot Replicator 5th gen 3D printer
- Carbon3D M2 3D printer

The Instrument Design and Fabrication Facility (IDFF), a major initiative of the Kavli Neural Systems Institute, has cutting-edge equipment and is staffed with engineering and machinist staff who enable high-end modern instrument design and fabrication. The IDFF provides end-to-end service from conceptualization to application to all labs on campus. The IDFF’s 5-axis Hermle C22 CNC mill can create functional prototypes using subtractive machining techniques in metals, aerospace materials, and engineered plastics to high precision tolerances (e.g. optical components, microscope stage adapters, mounts, precision tools, and surgical aids).

Proteomics Resource Center

The Proteomics Resource Center offers analysis and synthesis of biomolecules. The focus of the center is identification of protein complexes and assemblies, identification and characterization of protein posttranslational modifications, protein profiling and quantitation, analysis of oligonucleotides and oligosaccharides, characterization and quantification of phospholipids and glycolipids, identification of metabolites, and metabolic profiling by liquid chromatography and mass spectrometry.

The center synthesizes single peptides, with or without modifications and/or stable isotope labeled residues, as well as peptides for arrays. Examples includes peptide antigens, modified peptides, and peptide library synthesis.

The facility is equipped with high mass accuracy/high resolution Orbitrap mass spectrometers including QExactive+ and Fusion Lumos. The center also houses a triple quadrupole, A GCMS, off-line HPLC, and a Typhoon scanner are available for walk-up use.
Stem Cell Derivation Core

The main goal of the university's derivation unit is to isolate, characterize, and maintain new human embryonic stem cell (hESC) lines. It uses classical methods and also works to develop new derivation methods that bypass the requirements of feeder influence and improve the condition of maintenance of hESC pluripotency. A second goal is to reprogram human somatic cells into induced pluripotent stem (iPS) cells using a reversible transpositional strategy. Finally, the facility is developing unbiased, forward genetic approaches to hESCs and iPS cells.

Structural Biology Resource Center

The Structural Biology Resource Center (SBRC) is an expert resource for protein expression and purification and has equipment needed for the determination of the three-dimensional structures of biological macromolecules via x-ray crystallography. The center provides training and expert guidance for researchers undertaking protein purification and crystallographic structure determination. The center is also the liaison between the university and national synchrotron facilities.

The SBRC offers assistance with experimental design in crystallography, protein expression, and protein purification; individualized training on protein expression and purification; consultation and troubleshooting of purification protocols; and hands-on guidance on x-ray structure determination with consultation on structural information, specialized software support, and data analysis.

- X-stream cryosystem on a Rigaku Micromax 007 HF generator for cryo-preservation and diffraction
- JANSi UVEX microscope and Nikon stereomicroscope for crystal evaluation
- Robotic liquid handlers Formulatrix formulator for creating arrays of chemicals in 96-well format and Art Robbins Phoenix for dispensing protein/precipitant nano volumes
- Stocked tissue culture laboratory
- State-of-the-art FPLC chromatography, with in-line multi-wavelength detection
Vertebrate Genome Laboratory

The Vertebrate Genome Laboratory (VGL) specializes in high molecular weight DNA and long read genomic technologies. Researchers can assemble genomes, decipher transcriptome complexity, and discover structural variants with unmatched quality and accuracy.

- PacBio Sequel Sequencing Systems
- BioNano Genomics Saphyr instrument for DNA optical mapping
- 10X Genomics Chromium Plus for linked-read sequencing prep (in conjunction with the Genomics Resource Center)

In addition, the VGL is involved in an international collaboration known as the Vertebrate Genomes Project (VGP). The VGP aims to produce near error-free, high-quality, phased, chromosome-level, annotated, reference genome assemblies of all extant 66,000 vertebrate species that can be used to address fundamental questions in biology and disease, to identify species most genetically at risk for extinction, and to preserve genetic information of life. Phase 1 of the VGP focuses on completing the genomes of 266 species, representing all vertebrate orders.
Tri-Institutional, Regional, and Scientific Collaborations

Rockefeller is an active collaborator with other academic and scientific institutions in New York City and beyond. These partnerships provide Rockefeller scientists with access to tools, resources, and expertise not available on campus, and they create opportunities for moving discoveries beyond the laboratory.

Aaron Diamond AIDS Research Center

The Rockefeller University has a close affiliation with the Aaron Diamond AIDS Research Center (ADARC), and its researchers, including David D. Ho, a head of laboratory at Rockefeller. While ADARC is an independent organization with its own governing board, its scientists conduct clinical research at The Rockefeller University Hospital and pursue collaborative studies with Rockefeller faculty members, among other activities. ADARC’s mission is to find solutions to end the AIDS epidemic by conducting basic discovery research and by developing novel therapies, vaccines, and other prevention strategies. ADARC has played an important role in breakthroughs that have helped redefine our understanding of HIV and changed the course of clinical care for AIDS patients. Ongoing studies at ADARC include a wide range of basic investigations on HIV.

Bridge Medicines

Bridge Medicines is a drug discovery company focused on advancing promising early technologies in major academic institutions from human proof-of-concept to clinical development. The company was formed in 2017 by Rockefeller and its Tri-Institutional partners, Weill Cornell Medicine and Memorial Sloan Kettering Cancer Center, along with Takeda Pharmaceutical Company, in partnership with two venture capital firms, Deerfield Management and Bay City Capital. For projects that originate in Tri-Institutional labs, Bridge Medicines provides an unbroken, fully funded, and professionally staffed path from discovery to drug candidate.

Field Research Center for Ethology and Ecology

Situated on 1,200 acres in Dutchess County, about 80 miles north of New York City, the Field Research Center in Ethology and Ecology provides a setting for studying various organisms living under natural or seminatural conditions. Its facilities allow field and laboratory observations to be conducted in parallel, and include an indoor space for breeding and housing animals, laboratories and behavioral rooms for research, a conference room, and housing for students and guests. The center serves as a nexus for research on animal communication within various species, from birds to non-human primates, and has been the site of many first discoveries. For example, center investigators have gained insights into the vocal learning brain systems of birds, with parallels to human speech brain pathways; echolocation in bats; stress in natural animal populations; and adult neurogenesis in free-ranging animals. Current work focuses mainly on the neurogenetics of vocal learning in birds and on communication among ants, including both field and laboratory studies. In addition, the center serves as a resource for breeding transgenic songbird lines for the scientific community and for conservation genomics of wild animals.
Howard Hughes Medical Institute

The Howard Hughes Medical Institute (HHMI) conducts biomedical research on campus, provides financial support, and helps foster scientific interaction. HHMI supports the research of Rockefeller faculty who have HHMI appointments with funding for salaries, supplies, equipment, and laboratory personnel, including postdoctoral associates, technicians, and administrative assistants. HHMI investigators and early career scientists maintain their faculty appointments at the university and pursue their research in HHMI laboratories on campus. Rockefeller’s collaboration with HHMI began in 1986; it is currently home to 15 HHMI investigators and three HHMI faculty scholars.

New York Genome Center

The New York Genome Center (NYGC) is an independent, nonprofit research center devoted to providing collaborative genomics services to its member institutions, including Rockefeller. Located in SoHo, NYGC serves as a state-of-the-art hub for genome sequencing, analytics, bioinformatics, high-performance computing, and genomics research. Its 170,000-square-foot facility features a sequencing lab housing 12 Illumina HiSeq 2500 sequencers, 16 Illumina HiSeq X sequencers, and five NovaSeq sequencers. In addition, it houses a bioinformatics support service, a data storage annex, translational research labs, an innovation lab to test new technologies, a CLIA/CLEP lab to service clinical needs, and conference and event spaces. Launched in 2013, NYGC connects, services, and collaborates with academic, research, and medical institutions as well as with pharmaceutical, biotech, and IT companies.

New York Structural Biology Center

The New York Structural Biology Center (NYSBC) is a nonprofit consortium founded by Rockefeller and eight other academic research institutions with a mission to provide advanced resources in structural biology and to conduct independent research. NYSBC also offers high throughput gene-to-structure analysis and the production of soluble and membrane proteins, available on a fee-for-service basis to academic and for-profit investigators. NYSBC’s main site, a 45,000-square-foot facility in Manhattan, houses advanced instrumentation for cryo-electron microscopy, nuclear magnetic resonance spectroscopy, x-ray crystallography, and high throughput protein production.

In 2017, NYSBC added two new Krios electron microscopes to its microscopy suite and will be completing its new beamline at the National Synchrotron Light Source NSLS-2, at the Brookhaven National Laboratory. NYX, the new microdiffraction beamline, was developed to exploit the brightness of NSLS-2. NYSBC gives its member institutions access to its resources and expertise, training in instrumentation and techniques, and accredited classes. It also offers research services in all aspects of structural biology and protein production.

Starr Cancer Consortium

Supported by The Starr Foundation, the Starr Cancer Consortium is a collaborative enterprise that leverages the combined resources and expertise of five institutions—The Rockefeller University, the Broad Institute of Harvard and MIT, Cold Spring Harbor Laboratory, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medicine—to strengthen research aimed at the understanding, prevention, diagnosis, and treatment of cancer. Key areas of focus for the consortium include the accelerated development of technologies designed to unravel the genetic and molecular basis of cancers; application of these technologies in joint projects aimed at developing new approaches to diagnosis and treatment; and support for basic biological research into the fundamental cellular processes underlying cancer. The Starr Cancer Consortium was established in 2006.

Tri-Institutional Stem Cell Initiative

Along with Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, Rockefeller participates in the Tri-Institutional Stem Cell Initiative, launched in 2005 and supported by The Starr Foundation. The initiative funds collaborative research projects that involve faculty from the three institutions and also works to develop new resources and expertise in stem cell research. It supports both ongoing studies and new investigations into the molecular processes that are responsible for human cellular diversity, and it seeks to accelerate the development of cell-based therapies for a wide range of conditions. As part of this effort, the initiative has provided funds for the support of postdoctoral fellows working in stem cell biology, as well as for the operation of the university’s Stem Cell Derivation Core, which derives human embryonic stem cell lines to serve the needs of Tri-Institutional investigators.

Tri-Institutional Therapeutics Discovery Institute

The Tri-Institutional Therapeutics Discovery Institute (TDI), a partnership of The Rockefeller University, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medicine, works to accelerate the development of therapeutics that arise from discoveries made in basic science labs. With a focus on early-stage drug discovery, the institute provides expertise in medicinal chemistry and biologics drug development with the goal of conducting proof-of-concept studies, the type of investigations needed to demonstrate that drug candidates can successfully alter the course of a disease. TDI also provides high-quality training opportunities to students, postdoctoral fellows, and faculty to increase their involvement in drug discovery and to support translational research.

An independent, nonprofit corporation with its own board of directors and scientific advisory committees, TDI facilitates efficient sharing of core facilities between the three institutions. It works to form industry partnerships with pharmaceutical and biotech companies to further advance drug research, and seeks to create intellectual property for its parent institutions that can be developed by an open field of industry collaborators.
Information Technology

The Department of Information Technology (IT) provides both commodity and specialized computing resources and services in support of scientific research to the Rockefeller University community. In addition to the continued support of the traditional portfolio of services including technical support, media and graphical design, voice services, application development, information security, and cyber-infrastructure, IT is implementing a new strategic plan which attempts to better leverage cloud computing and to provide more direct support of the university's business and research objectives through the implementation of decision support systems, data visualization frameworks, and big data capable infrastructure.

Laboratory Safety and Environmental Health

Laboratory Safety and Environmental Health's (LS&EH) role at The Rockefeller University is the development and management of the university's environmental health and safety programs. LS&EH works with the university's researchers, administration, and outside regulatory and advisory agencies to ensure that the university is a safe and compliant place to work. In addition to providing support and services to the university, LS&EH conducts research in the health and safety fields. Aimed at minimizing waste, environmental impacts, and laboratory hazards, the staff's research spans the radioactive, biological, and chemical aspects of laboratory safety and has resulted in the publication of two books and numerous journal articles.

Library and Scientific Information Commons

The mission of the Rita and Frits Markus Library is to support and enhance the university's research programs by facilitating access to the world's scientific literature in multiple formats, providing an environment that promotes creative thinking and collaboration, and offering proactive custom research support. By managing high-quality research collections in areas of Rockefeller University expertise as well as access to resources beyond the university, the library is able to link faculty, students, and staff with the information they need to advance their research goals. The Markus Library, located in Welch Hall, is available to members of the Rockefeller community 24 hours a day, 365 days a year. The Markus Library contains technology resources, comfortable spaces for meeting and studying, public access computers, campus Wi-Fi, and physical and digital collections. The Markus Library is part of the Anne T. and Robert M. Bass Center for Community Life.

Other Programs and Facilities

Rockefeller’s administrative functions are dedicated to supporting and advancing the university’s science. Steady investment in infrastructure, technology, training, and staff allow Rockefeller to provide outstanding service to laboratories.
Robertson Therapeutic Development Fund

With a mission to develop medically significant basic research discoveries into new therapies, the Robertson Therapeutic Development Fund awards grants, from $25,000 to $1 million or more, to advance innovative projects to a stage where they can attract outside capital or industry partners. The fund, established by the Robertson Foundation, has a flexible, multi-tiered structure designed to support projects that have the greatest likelihood to benefit patients and bridge critical gaps in the drug discovery process. Grant requests are reviewed by an independent committee drawn from the pharmaceutical, biotech, and life sciences investment industries. Awards have focused on developing novel treatments for viral and bacterial infections, autoimmune disorders, cancer, heart attacks, and many other health conditions. The Fund’s support has enhanced scientific entrepreneurship at Rockefeller, leading to numerous invention disclosures, patent filings, and the founding of several startup companies.

Rockefeller University Press

For more than 100 years, Rockefeller University Press (RUP) has provided scientists and the public with peer-reviewed results of groundbreaking research and vital news and information they can trust. Run by a staff of 35 and financially self-sustaining, RUP publishes four biomedical journals: Journal of Experimental Medicine, founded in 1896; Journal of General Physiology, founded in 1918; Journal of Cell Biology, founded in 1955; and Life Science Alliance, launched in 2018 in collaboration with Cold Spring Harbor Laboratory Press and EMBO Press. With a strong commitment to quality and integrity, RUP strives to publish excellent science that stands the test of time using the latest technologies. All four journals are edited by leading, active scientists in conjunction with professional scientific editors. Editors at RUP journals conduct rigorous peer review, applying the highest standards of mechanistic insight, novelty, and general interest, and securing transparency of the process and data integrity. RUP provides the public free online access to many article types immediately and to research articles no later than six months after publication, with archival content accessible for each journal since inception. Authors retain their copyright, with the option of publishing under either a Creative Commons Attribution-Noncommercial-Share Alike License (CC-BY-NC-SA) or a Creative Commons Attribution 4.0 International License (CC-BY). RUP has also published more than 50 books, many of which are made freely available in eBook format.

Office of Sponsored Programs Administration

The Office of Sponsored Programs Administration (OSPA) facilitates and streamlines extramural grant and contract administration in compliance with pertinent policies and regulations. Driven by the university mission, OSPA applies specialized knowledge in regulatory, statutory, and organizational matters to enable the university’s pioneering research, partnering with investigators to promote collaborative and single investigator projects, as well as to pursue institutional training and infrastructure funding. OSPA anticipates and responds to research needs and shifting funding trends, and assists investigators and their staff in identifying funding resources, navigating the sponsored research landscape, and applying for and managing research and other sponsored awards.

Office of Technology Transfer

The Office of Technology Transfer (OTT) is responsible for technology management and industry partnerships. Through engagement of and partnering with industry collaborators, OTT facilitates the licensing of Rockefeller University’s discoveries, positioning university assets for further development, adoption, and commercial implementation. Patentable inventions, tangible materials, and copyrighted materials that may have commercial relevance are among the types of intellectual property that are managed and licensed by OTT. Often, successful licenses result in a return to the university of unrestricted funds that can be used to support the school’s research and teaching, as well provide a benefit to people, society, and the economy. In addition to licensing, OTT performs a suite of other activities, including negotiating “enabling agreements;” such as confidentiality and material transfer agreements; educating the university community about protecting and partnering commercially relevant translational research; and promoting local and regional entrepreneurship.
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