

**one discovery** can have an exponential impact on human health



# ESSENTIAL IMPACT

“

This philanthropic support allows our scientists to pursue unconventional ideas that have the potential to transform our understanding of human biology—and our ability to improve human health.

— **Lloyd B. Minor, MD**

Carl and Elizabeth Naumann Dean  
Stanford University School of Medicine

*As a young physician-scientist, Dean Minor's unconventional research led to the discovery of superior canal dehiscence syndrome, a debilitating disorder characterized by sound- or pressure-induced dizziness. He and his team subsequently developed a surgical procedure that corrects the problem and alleviates symptoms.*

121

innovative new  
research projects

\$947k

average size of a  
follow-on grant

80

new research grants

191

new research papers

200+

national/international  
research presentations

9

new patents

\$75M  
generated in  
follow-on funding

**Discovery Innovation Awards** support early-stage research projects that could exponentially accelerate our understanding of human biology—and our ability to predict, prevent, and cure disease. These competitive seed grants are available to faculty across all 12 of Stanford Medicine’s basic science departments.

Since the launch of this program eight years ago, \$8.17 million in philanthropy has been distributed to fund 121 high-risk, high-reward projects, with an average grant size of just \$70,000 per project.

More than one out of every three faculty recipients have leveraged their findings from these awards to receive additional funding that allows them to continue their lines of investigation.

Of the nearly 40 percent of projects that have received follow-on funding, the average grant size is \$947,097, nearly doubling the average size of grants distributed by the National Institutes of Health (NIH).

Furthermore, faculty recipients and their lab members have published 191 papers in leading scientific journals on their findings from these projects and presented their research at more than 200 national and international conferences.

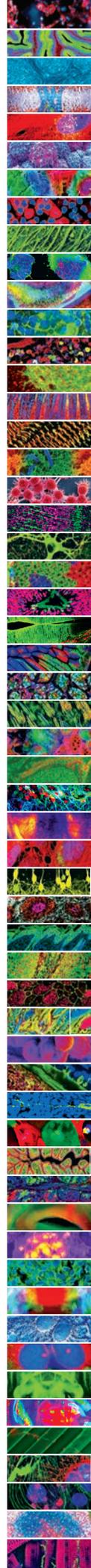
Nine patents have been filed as a result of these projects, and three companies have been founded.

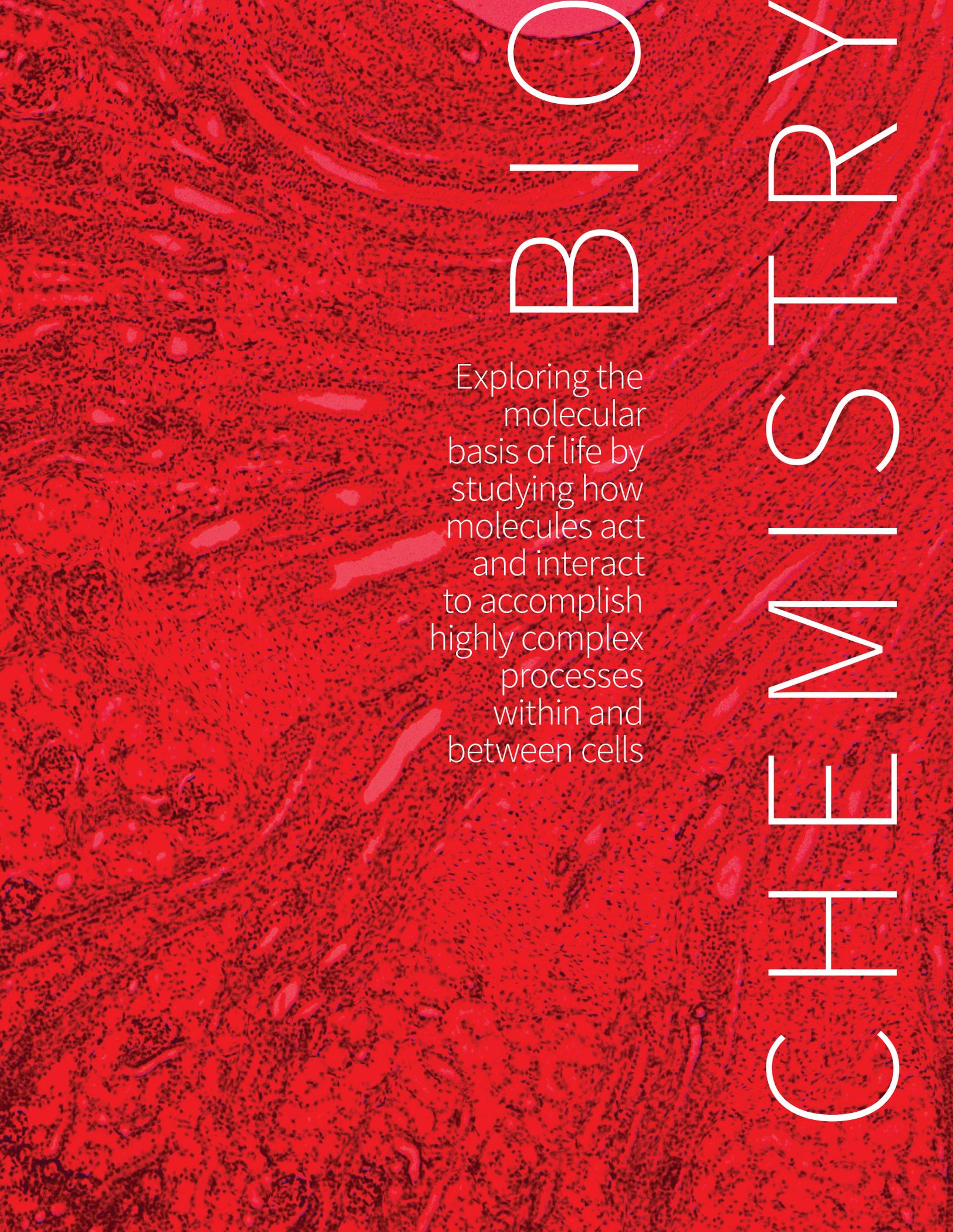
Nine faculty members have received R01 grants from the NIH using preliminary data from their awards, and two faculty members shared that this funding “transformed” their research. From Professor Dan Jarosz: “This funding seeded a line of research that has become the backbone of my laboratory. And I almost let it go because it was deemed too risky by the NIH! Now they are happy to support it, but without the vision of this program nothing would have happened.”

Thank you for your investment in the pursuit of scientific understanding and for believing that one discovery can have an exponential impact.

more than  
9x  
return on  
investment

\$8.1M  
awarded



A detailed electron micrograph of biological tissue, showing various cellular structures, membranes, and organelles in shades of red and pink. The image has a complex, textured appearance with many small, dark spots and larger, lighter areas.

# BIO M CHEMISTRY

Exploring the  
molecular  
basis of life by  
studying how  
molecules act  
and interact  
to accomplish  
highly complex  
processes  
within and  
between cells



## DECIPHERING THE MOLECULAR LANGUAGE OF CELLS AND TISSUES

**Pehr Harbury, PhD**

ASSOCIATE PROFESSOR OF BIOCHEMISTRY

The cells of the human body collaborate with each other to build essential physiological structures, such as an alveolus in the lung, a nephron in the kidney, and a ganglion in the nervous system. A constant “chatter” of molecular signals between the cells allows them to organize a division of labor. Some cells specialize to become muscle, others to form blood vessels, others to create skin, and so forth. Different combinations of molecular signals form the “words” of a cellular language, and the words that each cell hears from its neighbors instruct its behavior.

Deciphering cellular language remains a great challenge, akin to an epigrapher deciphering ancient text written in a lost language. First we must learn all of the letters of the language, which in the case of the cell means deciphering roughly two dozen different molecular signals. This project aims to implement a tool that can read the entire cellular alphabet in a single microscope image. This is an important step toward understanding what cells are saying when the body is healthy, undergoing regeneration, or experiencing disease. By learning how to read this language, we may one day be able to edit or rewrite it, to correct processes gone awry in many disease contexts.



## TARGETING CHEMOTHERAPY TO THE NUCLEUS TO FIGHT CANCER

**Onn Brandman, PhD**

ASSOCIATE PROFESSOR OF BIOCHEMISTRY

Colorectal cancer is the second most common cause of cancer deaths worldwide. A leading treatment for colorectal cancer, called oxaliplatin, acts through a mechanism that has remained unknown while also causing peripheral neuropathy for yet unknown reasons. This knowledge gap has hindered the development of improved therapies and drug combinations that not only limit toxicity, but improve efficacy.

We aim to develop a mechanistic understanding of oxaliplatin in order to improve our ability to trouble-shoot all of these issues with rational, scientifically guided approaches in place of the current trial-and-error strategy, which is clearly failing. We recently discovered that oxaliplatin kills cancer cells by binding to a cellular organelle called the nucleolus. The nucleolus is critical for making proteins, including those that drive cancer cell proliferation, suggesting that oxaliplatin somehow alters protein production to shut down the cell. Yet, how oxaliplatin targets the nucleolus and what exactly it does when it gets there remains unknown.

We now seek to understand these mechanisms and how they interact with that of other cancer therapies given in combination with oxaliplatin. This work will enable clinical improvements in multiple ways. First, medicinal chemists may be able to design structural alterations to oxaliplatin, based on these mechanisms, to improve activity or decrease side effects. Second, this knowledge will also enable scientifically informed pairing of combination therapies for greater efficacy and minimal toxicity. Finally, this mechanistic understanding may enable us to pioneer a whole new class of anti-cancer treatments targeting the nucleoli of cancer cells, which could be broadly applicable across cancer types.



# BIOENGINEERING

Fusing  
engineering and  
the life sciences  
to promote  
scientific  
discovery and  
invent new  
technologies  
and therapies



## DUAL DIAGNOSIS AND TREATMENT FOR LEWY BODY DEMENTIA/PARKINSON'S DISEASE

**Possu Huang, PhD**

ASSISTANT PROFESSOR OF BIOENGINEERING

Lewy body dementia (LBD) is the second most common dementia illness after Alzheimer's disease (AD), for which there are currently no effective diagnostic methods or treatments. LBD afflicts patients with Parkinson's disease, and a separate category of patients suffering dementia with Lewy bodies. The pathological hallmark of LBD is the accumulation of misfolded  $\alpha$ -synuclein ( $\alpha$ S) in the brain. However, this is not unique to LBD; approximately 30 percent of AD cases also have  $\alpha$ S pathology, exhibiting more rapid and severe cognitive decline than AD alone.

The exact cause of  $\alpha$ S misfolding, and how that impacts cognition, are unknown, but there is a clear link to the aging population. Given the prevalence of LBD, and a growing geriatric population in years to come, there is an urgent unmet need to develop methods for the diagnosis, prevention, and treatment of this debilitating disease. Here, we propose to develop a novel strategy to detect LBD early, before disease pathology becomes irreversible and when interventions are more likely to be successful.

Disease progression is often caused by an overactive immune system, which damages cells in the brain. We propose a strategy to detect the link between the disease-causing  $\alpha$ S in the brain and the peripheral immune system and leverage that connection for early-stage diagnosis. Here we develop a novel synthetic protein that targets the major histocompatibility complex, a major activator of immune responses. We hope to not only detect immune activation signals, but also potentially block them with the same molecular mechanism. Investigating this new strategy may therefore yield a dual-pronged approach, where the method of disease detection may also serve as the treatment for LBD, by binding to and dampening pathological immune activation signals.



## DEFINING NEURAL DYNAMICS THAT CONTROL MOTOR FUNCTION AND COMPLEX OPERATIONS

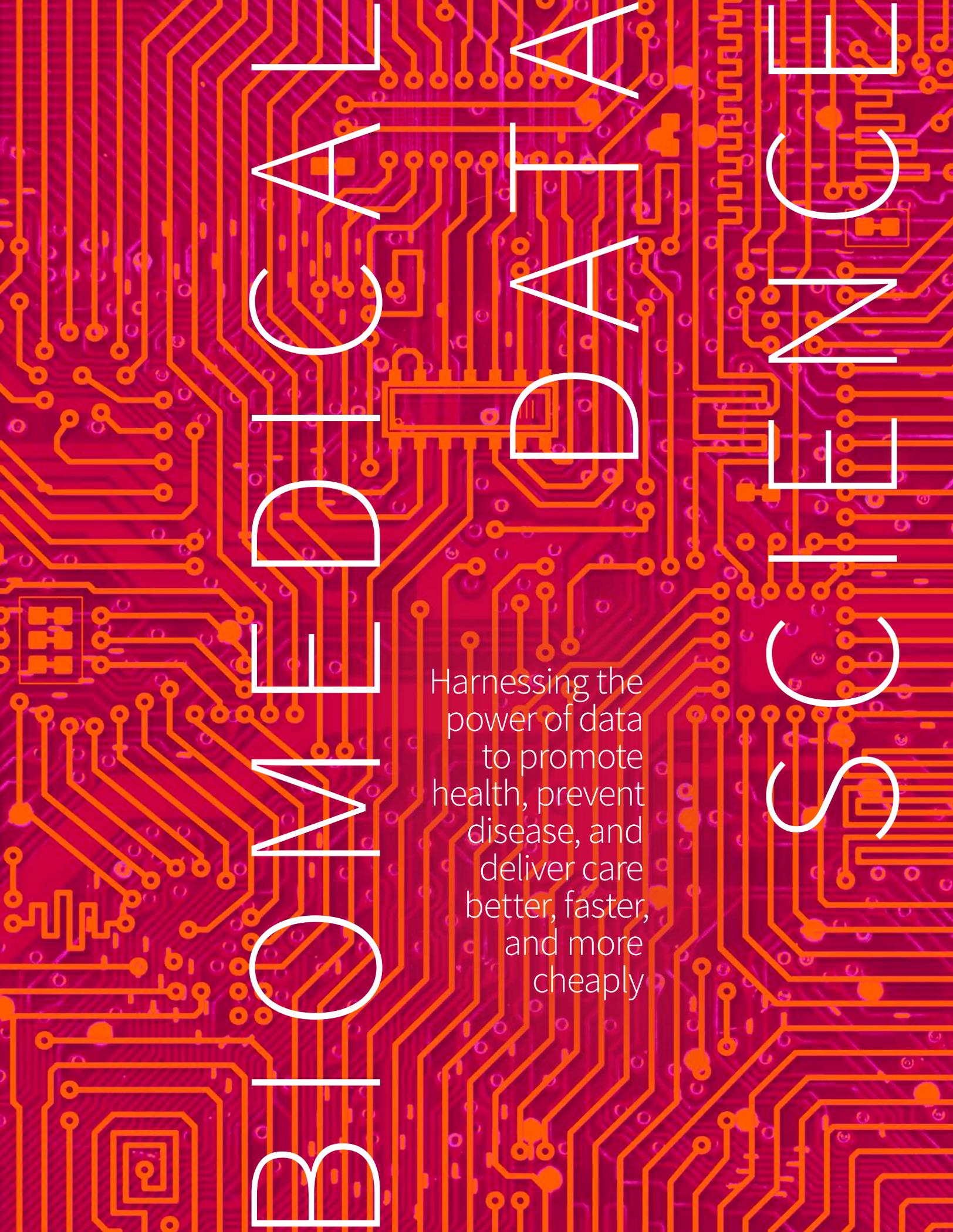
**Paul Nuyujukian, MD, PhD**

ASSISTANT PROFESSOR OF BIOENGINEERING AND OF NEUROSURGERY AND, BY COURTESY, OF ELECTRICAL ENGINEERING

Among all organs in the body, we understand the brain the least—we still do not know how the brain controls movement, let alone complex thought processes. Although much research has gone into studying neuronal signals at a cellular level, understanding the characteristics and behaviors of individual neurons does not facilitate even an elementary understanding of how the brain controls complex operations such as movement, memory, and cognitive function. How populations of neurons come together to form circuits that dictate movements and complex behaviors remains a mystery.

This project seeks to reveal the neurocircuitry underlying voluntary movement by introducing lesions to specific areas of the brain that are implicated in planning and executing motor functions, and examining the impacts on compromised motor activity. Defining neural dynamics necessary for precision movement and preparatory activity will set the stage for both scientific and clinical advances.

These studies will yield greater insight into the neurobiological underpinnings driving voluntary behavior and serve as an example with which to explore other complex cortical regions and their functions. Meanwhile, these discoveries may be leveraged to develop novel clinical devices to treat brain disease. Such devices could measure the activity of neuronal populations to inform treatments and might even be designed to modulate brain activity accordingly to correct pathological brain activity. This novel class of neuromodulatory medical devices has implications for every category of brain disease, from the near-term goals of stroke recovery and epilepsy to treating more complex psychiatric diseases.



# HEALTHCARE INNOVATION DRIVES

Harnessing the power of data to promote health, prevent disease, and deliver care better, faster, and more cheaply



## DISCOVERY OF VIRAL EVOLUTIONARY PROCESSES FOR PANDEMIC PREPAREDNESS

**Julia Salzman, PhD**

ASSOCIATE PROFESSOR OF BIOMEDICAL DATA SCIENCE AND OF BIOCHEMISTRY

The COVID-19 pandemic has brought the basic biology of RNA viruses and their evolution to the forefront of public and scientific inquiry. Yet despite the critical importance to global public health, we still do not understand the mutational processes that dictate the evolution of novel RNA viruses—a critical step in predicting not only how and when pandemics will emerge, but also their trajectory once they have jumped into human populations. While active surveillance of viral strains in zoonotic animal populations is, and has been, ongoing as a means of pandemic preparedness, our inability to foresee viral evolution has prevented us from adequately assessing their risks to human populations. Meanwhile, the emergence of novel COVID-19 strains within human populations presents a constant challenge to public health efforts as the virus morphs to evade our control.

The goal of this project is to leverage massive viral metatranscriptomic data with novel statistical models to infer how RNA virus communities evolve, and how quickly they can do so. These statistical models will enable the prediction of which specific COVID-19 viral communities are evolving most rapidly, to guide public health interventions in specific areas that will prevent the emergence of more virulent or transmissible strains—an incredibly significant real-world impact. This project will also improve the impact of viral surveillance in both human and animal populations by enabling researchers to assess which viruses most likely pose the greatest threat and on what time-scales. In addition, revealing the mutational processes underlying viral evolution has the potential to spur a new generation of molecular tools for bioengineering, analogous to the discovery of CRISPR for modifying DNA.



## COMBINING PHARMACOGENOMICS WITH PHYSICAL INTERVENTIONS FOR RAPID RECOVERY

**Teri Klein, PhD**

PROFESSOR OF BIOMEDICAL DATA SCIENCE AND OF MEDICINE (BMIR)

Traditionally health care in the United States has focused on treating sick patients with medications, but recently other behavioral interventions such as exercise, better eating habits, and limiting alcohol consumption are gaining attention for their role in not only maintaining health, but improving patient outcomes across a range of disease states from cancer to osteoarthritis. In particular, physical therapy and mobility assist devices can greatly benefit those who suffer from debilitating osteoarthritis, which afflicts a large portion of the geriatric population. However, research into the efficacy of such non-pharmaceutical interventions is hard to come by due to limited interest from funding agencies and pharmaceutical companies.

We aim to combine personalized drug therapy with mobility assist devices (i.e., the Alinker) to achieve better outcomes for patients with osteoarthritis. By both optimizing therapeutics with pharmacogenomic insights and assisting patients with a normal walking gait, we expect to accelerate patient recovery while minimizing medical interventions and resulting medical costs.

We are uniquely poised to conduct these studies, which have not been undertaken in the past due to many factors. First, these studies will require cross-disciplinary collaborations between diverse medical professions, from pharmacogenomics to physical therapy, which are traditionally hard to achieve. Second, due to a lack of preliminary studies on the impacts of personalized treatments, both pharmacologic and physical, on osteoarthritis outcomes, funding is difficult to procure. Now is the time to overcome these hurdles. Our studies will pave the way for more effective, personalized treatment approaches that leverage behavioral interventions alongside pharmaceuticals to optimize patient outcomes.

# CHEMICAL AND SYSTEMS BIOLOGY

Discovering the molecular mechanisms that underlie cellular function and contribute to human disease



## VISUALIZING REGULATORY PROTEIN MODIFICATIONS IN REAL TIME

### **Gheorghe Chistol, PhD**

ASSISTANT PROFESSOR OF CHEMICAL AND SYSTEMS BIOLOGY

Our cells make more than 10,000 different proteins to carry out functions required for life. Moreover, cells employ hundreds of custom post-translational modifications to alter the properties and functions of these proteins. These individual modifications can even be linked together to form long linear or branched “chains,” which play critical roles in controlling how cells grow, how cells repair DNA damage, and whether cells die or not. These processes often go awry in the context of cancer, making enzymes that “read” and “write” such modifications excellent targets for anti-cancer drugs.

However, we remain completely oblivious to many important dynamics of long-chain protein modifications. Importantly, protein modification chains grow and shrink very quickly—within only a few seconds—yet the methods used to study them cannot measure these fast dynamics. In fact, we are blind to many important aspects of their regulation and control.

Here we propose to develop a new method to study long-chain protein modifications using advanced imaging. This new technology will enable us to visualize how individual proteins are modified in real time, to study the basic biology of these modifications, and thus gain insights to improve cancer therapies.



## ENGINEERING NEW BIOSENSORS TO VISUALIZE CELLULAR COMMUNICATION

### **Tom Wandless, PhD**

PROFESSOR OF CHEMICAL AND SYSTEMS BIOLOGY AND, BY COURTESY, OF CHEMISTRY

The ability of cells to communicate with each other is essential for multicellular life, including the functioning of complex human tissues and organ systems. For example, a human white blood cell must be able to communicate with surrounding cells to distinguish between self-cells and pathogenic bacteria or parasites. To make these distinctions, the exterior of a white blood cell is decorated with many protein molecules, which constantly interact with nearby cells to distinguish friend from foe. When the white blood cell contacts a foreign cell, the proteins on the surface send a signal into the nucleus telling the white blood cell to activate an attack. The white blood cell itself acts to eliminate the intruder cell and also alerts other nearby white blood cells to come help.

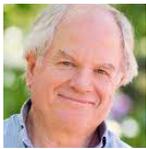
Biologists have made great progress understanding these complex cell communication pathways. Small molecules called “second messengers” rapidly diffuse throughout the cell, spreading the message to proteins to turn on and activate downstream responses. Biologists can visualize many of the proteins involved in these signaling pathways, yet the small, second messengers are invisible. Our inability to know exactly when and where these molecules are produced, and also where they carry their messages, is a critical barrier to progress in this field.

We aim to develop new fluorescent biosensors that will allow biologists to literally see where and when second messengers are produced, in real time and in live tissues, when specific signaling pathways are turned on. These novel biosensors will enable researchers to not only reveal the nuances of how cells communicate, but also to identify aberrant communication signals in the context of various diseases, from cancer to immune dysfunction.



# COMPARATIVE COHORT MEDICINE

Researching  
the biological  
similarities and  
differences  
among species  
to better  
understand the  
mechanisms  
of human and  
animal disease



## STUDYING SENSORY SUPPRESSION TO TREAT NEUROPSYCHIATRIC DISORDERS

**Shaul Hestrin, PhD**

PROFESSOR OF COMPARATIVE MEDICINE

We are constantly exposed to ongoing streams of sensory information, but we react to only a select few of these inputs. Our ability to ignore most sensory information is an important aspect of sensory processing essential to our functioning as human beings. When the mechanisms that suppress sensory inputs fail, sensory overload is experienced and interferes with normal activities and behaviors. Sensory overload has been implicated in many disorders, including attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), obsessive-compulsive disorder, schizophrenia, and autism spectrum disorders.

Although there has been much research on how we process and respond to sensory inputs that do grab our attention, there has been very little investigation into the mechanisms that allow us to suppress most incoming sensory information. Understanding these mechanisms could potentially guide therapeutic approaches targeting specific neuromodulatory pathways or groups of interneurons to treat major neurological and psychiatric disorders.

## IDENTIFYING THE UNDERLYING CAUSE OF NEUROPATHIC PAIN—POTENTIALLY ABNORMAL REWIRING OF SENSORY RECEPTORS

**Corinna Darian-Smith, PhD**

PROFESSOR OF COMPARATIVE MEDICINE

Spinal cord injury (SCI) primarily affects young people, who must endure a lifetime of expensive care, long-term paralysis and chronic pain. Conventional treatments for pain in particular remain inadequate because we do not understand the fundamental cause of the pain, and there is no sufficient animal model in which to develop treatments.

To facilitate progress in understanding and treating chronic pain, we propose to study primates as a suitable animal model with close similarity in sensorimotor systems. Specifically, we will examine specialized sensory receptors in the skin called Meissner's corpuscles (MCs) and how they rewire after injury. These important receptors are particularly abundant in the primate (and especially human) hand and contribute to the impressive dexterity unique to these species. MCs relay signals to the brain via two nerve types—one carrying tactile information and the other pain information.

We will investigate whether the connections to pain nerves increase and become dominant following spinal injury. If so, this would help explain why so many SCI patients develop intractable chronic pain, and importantly, could lead to new therapeutic strategies to improve treatments.



DEVELOPMENTAL BIOLOGY

Advancing our understanding of the molecular mechanisms that generate and maintain diverse cell types during development



## PRECISION MEDICINE FOR MOUSE MODELS

### **Gill Bejerano, PhD**

PROFESSOR OF DEVELOPMENTAL BIOLOGY, OF COMPUTER SCIENCE, OF PEDIATRICS (GENETICS), AND OF BIOMEDICAL DATA SCIENCE

Model organisms are utilized by the scientific community to advance the study of biology and medicine. Over the years, the laboratory mouse has contributed more to science and medicine than any other model organism. For centuries mice have been bred, crossed, and mutagenized to replicate different characteristics resembling human disease conditions. However, in many cases the underlying genetic alterations that cause those disease characteristics in specific mouse strains remain a mystery.

We propose to genetically sequence these mouse models to elucidate the genes and mutations behind specific disease etiologies. With advances in DNA sequencing technologies, it now costs only a few hundred dollars or less to sequence a mouse genome. Our goal is to develop the tools to interpret this sequencing data, and point researchers to the genes and variants that cause disease pathology and/or characteristics of interest. We have already pioneered a suite of tools to interpret the genomes of more than 116,000 patients and pinpoint genes associated with different disease states in humans. Adapting these tools to interpret the genomes of mouse models will bring the precision medicine revolution to the study of mice, enabling thousands of discoveries directly relevant to basic biomedicine and human health.



## ENABLING TRANSLATIONAL RESEARCH FOR GENES ASSOCIATED WITH AUTISM SPECTRUM DISORDER

### **William Talbot, PhD**

PROFESSOR OF DEVELOPMENTAL BIOLOGY

Genome sequencing studies have implicated more than 1,000 genes in—or that may underlie—autism spectrum disorder (ASD) and other neurodevelopmental disorders, but very few animal models are available to study these mutations and how they actually contribute to disease. In far too many cases the discoveries from human genome studies have not translated to clinical improvements in treatment or diagnostics for these diseases due in part to the lack of animal models to elucidate the functions and mechanisms of action of these putative disease-causing mutations.

We aim to rapidly develop such animal models of human disease mutations in order to facilitate these functional studies and accelerate clinical impacts for neurodevelopmental disorders. Specifically, we will use genome-editing techniques to engineer zebrafish models of five ASD genes, enabling us to study their roles in brain development and test the consequences of mutations in these genes. Zebrafish provide many advantages for genetic and cellular studies which will make these goals possible.

After these initial studies, our longer-term goal is to expand our efforts and create many more zebrafish models of other genes implicated in ASD. Ultimately, we aim to thoroughly catalog and characterize the impacts of these genes on neurodevelopment and enable the mechanistic and preclinical studies necessary to yield clinical advances for patients with autism.

EPIDEMIOLOGY  
AND  
PUBLIC  
HEALTH

Leveraging  
economics,  
sociology,  
anthropology,  
political science,  
public health, and  
epidemiology  
to better  
understand  
the broader  
determinants  
of health

POPULATION  
AND  
PUBLIC  
HEALTH



## CLINICIAN INSIGHTS AND BIASES IN DISTINGUISHING LUPUS NEPHRITIS AND PREECLAMPSIA IN PREGNANCY

### **Julia Simard, ScD**

ASSOCIATE PROFESSOR OF EPIDEMIOLOGY AND POPULATION HEALTH AND, BY COURTESY, OF MEDICINE (IMMUNOLOGY AND RHEUMATOLOGY)

Lupus nephritis and preeclampsia are both severe, life-threatening conditions with similar presentations that can occur during pregnancy. They are difficult to distinguish, but accurately identifying each condition is essential as they each require different treatment approaches. Unfortunately, diagnosis falls on clinicians to interpret patient symptoms with their best judgment, as there is no gold standard for diagnosis.

We aim to improve the diagnostic accuracy for these two conditions by studying clinician decision-making processes and biases that may lead to incorrect diagnoses. First, we will examine whether the specialty of the clinician influences how they approach the case by surveying specialists in rheumatology, nephrology, and obstetrics/gynecology. We will present them with clinical vignettes and task them with differentiating the two diagnoses and determining the next steps in case management. Second, we will investigate how cognitive biases impact a physician's interpretation of the data when the age and race of the patient differs. The vignettes will randomly vary according to age and race while the remaining clinical features and relevant history remain unchanged.

Through these studies we hope to glean insight into the factors that influence physician clinical decision-making in order to better inform better medical education, as well as to promote a multi-disciplinary clinical approach to improve patient care.



## CITIZEN-SCIENCE-ENABLED RESEARCH TO PROMOTE HEALTH EQUITY AMONG THE U.S.'S MOST VULNERABLE OLDER ADULTS

### **Abby C. King, PhD**

PROFESSOR OF EPIDEMIOLOGY AND POPULATION HEALTH AND OF MEDICINE (STANFORD PREVENTION RESEARCH CENTER)

Successful aging is strongly dictated by the physical and social environments in which we live, which impact both our mental and physical health. This is particularly true for older adults living in disadvantaged communities, where conditions are not ideal. However, the impacts of these environments, and how to improve them to minimize illness in aging populations, as well as health-care costs to society, are unclear due to lack of data. Current U.S. data systems do track information about physical and social environmental conditions, but only from the national level down to community or zip code levels. Rarely do they include local information that reflects the actual lived experiences of older adults themselves as they go about their daily lives.

We have developed a novel technology-enabled “citizen science” mobile app (Discovery Tool) that allows residents themselves to systematically collect meaningful information about local neighborhood conditions that help or hinder their ability to live healthy lives. We will explore how to most effectively combine these “bottom-up” citizen science data with “top-down” epidemiological data systems to provide a more comprehensive and meaningful understanding of both the barriers to, and enablers of, healthy living in culturally diverse older adults. By developing innovative methods for visualizing our results for researchers, policy makers, and residents themselves, we believe that a better understanding of older adults' circumstances and needs will emerge that can help drive age-friendly community changes. Ultimately this work will improve the health of these vulnerable aging populations while helping to alleviate the financial burden on families and the health-care system.



Studying genes,  
genomes,  
genetic  
variation, and  
heredity in  
organisms and  
populations  
and their  
contributions  
to disease

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## RESCUING PHOTORECEPTORS WITH A NOVEL PROTEIN IN A MOUSE MODEL OF AGE-RELATED MACULAR DEGENERATION

**Douglas Vollrath, MD, PhD**

ASSOCIATE PROFESSOR OF GENETICS AND, BY COURTESY, OF OPHTHALMOLOGY

Age-related macular degeneration (AMD), a common blinding disease of the elderly, starts in a particular type of retinal cell within the retinal pigment epithelium (RPE), which is then followed by subsequent death of neighboring photoreceptors, causing vision loss. The RPE and photoreceptors are like trading partners and their molecular commerce of food molecules is essential for vision. In AMD, the cellular powerplants (mitochondria) in RPE cells dysfunction, creating a shortage in fuel for both RPE cells and photoreceptors that impacts their survival and function.

We previously created a mouse model of AMD by modifying the RPE so that the mitochondria do not function properly and found that photoreceptors die as a result. We have now found that adding a particular mitochondrial protein to the dysfunctional mouse RPE can keep photoreceptors alive. We aim to understand how this protein rescues photoreceptors by studying the trafficking of food molecules between the RPE and photoreceptors in the presence and absence of this protein. Success of this project will define critical aspects of molecular commerce between the RPE and photoreceptors that will point to new avenues for AMD treatments.



## POSSIBLE TOXIC EFFECTS OF METALLIC OXIDE-BASED SUNSCREENS ON CORALS

**John Pringle, PhD**

PROFESSOR OF GENETICS

Coral reefs are biodiversity hotspots of great ecological, economic, and aesthetic importance. Their global decline due to climate change and other anthropogenic stressors has increased the urgency of conservation efforts. Such efforts would be greatly furthered by a better understanding of the underlying molecular and cell biology of the coral animals, the keystone species of these ecosystems, and we have been working to develop such an understanding using both corals themselves and a closely related sea anemone as a model system.

A particular threat that has received much popular and political attention recently is that posed by the organic compounds used as UV-light absorbers in many common sunscreens. These pass into the seawater from the bodies of swimmers and snorkelers and may reach concentrations that are toxic to corals or their larvae. Although it remains uncertain how serious this problem really is, many states and countries have already banned such sunscreens, and alternative sunscreens based on metallic oxides (zinc, titanium) are being widely promoted as “coral safe.” However, the evidence to support this claim remains very limited.

In the studies proposed here, we will launch a study of the levels of toxicity of these compounds using the sea-anemone model system to better inform these policies and provide insight into how to best protect these essential ecosystems.



## RAPID REMODELING OF THE TRANSLATOME FOR TISSUE REPAIR AND REGENERATION

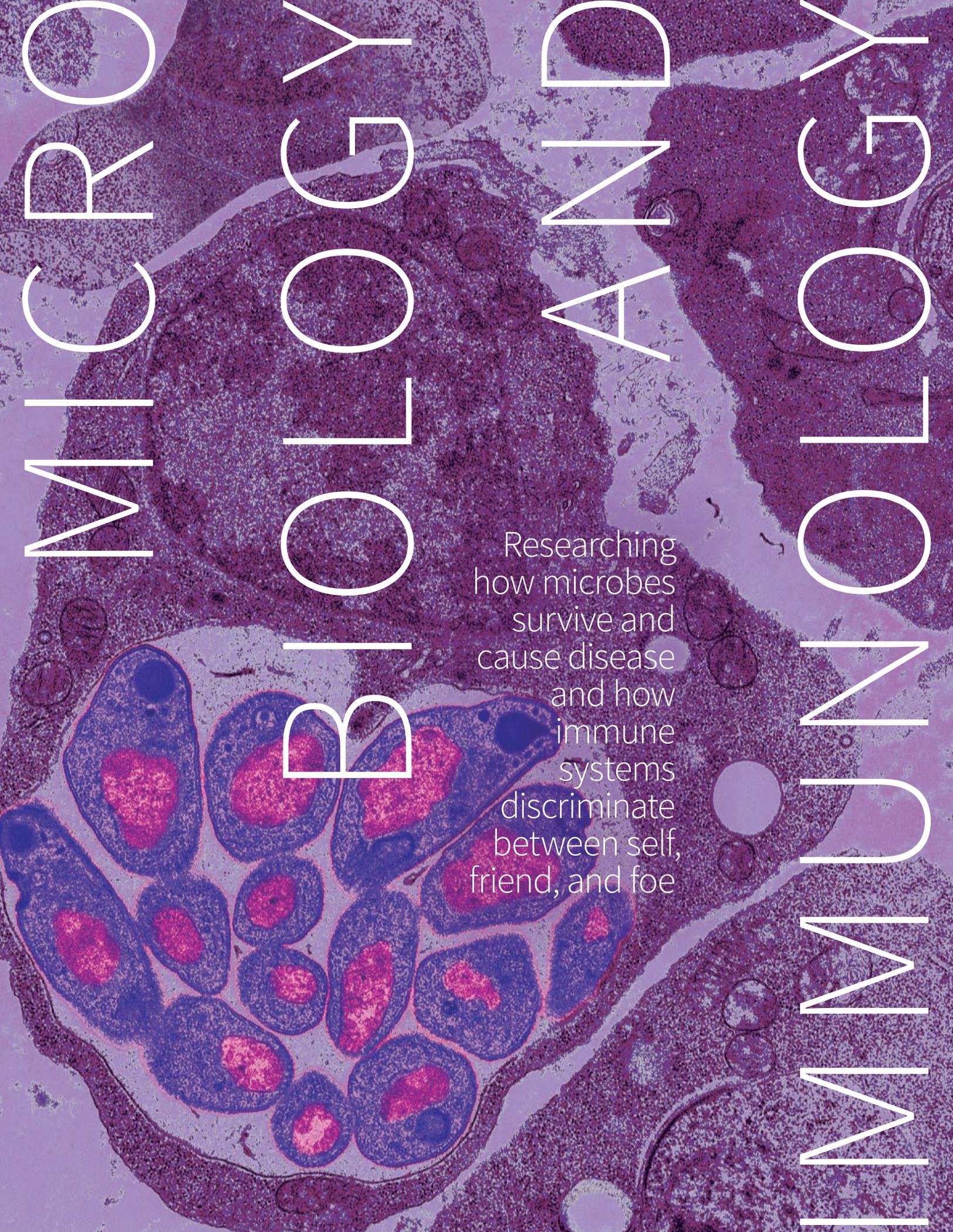
**Maria Barna, PhD**

ASSOCIATE PROFESSOR OF GENETICS

The biggest biomedical challenge of this century is the restoration of diseased organs and tissues. Our goal is to discover how the axolotl, a small salamander endemic to Mexico, rebuilds functional adult tissues in a matter of weeks. Our approach is to focus on molecular factories called ribosomes, which produce all the building blocks that make up our bodies.

When tissues sustain damage, our cells tune these factories to make only essential building blocks that are critical for survival and repair. Until recently, the textbook view has been that ribosomes are rote assembly lines with little control of their production inventory. However, in a paradigm-shifting discovery, touted as the “Breakthrough of the Year” in 2011 (*Science Signaling*), we demonstrated that ribosomes are molecular gatekeepers with tight control over when, where, and which building blocks are made.

Our goal is to reveal how the salamander reprograms its ribosomes into efficient regeneration machines by using cutting-edge, genome-wide deep sequencing and mass spectrometry methods to pinpoint which genes are turned into vital building blocks for rapid healing and regeneration. Unlocking the salamander’s secret to self-healing will open new avenues for human regenerative medicine and advance treatments for many incurable diseases.



M I C R O B I O L O G Y  
B I O L O G Y  
A N D  
I M M U N O L O G Y

Researching how microbes survive and cause disease and how immune systems discriminate between self, friend, and foe



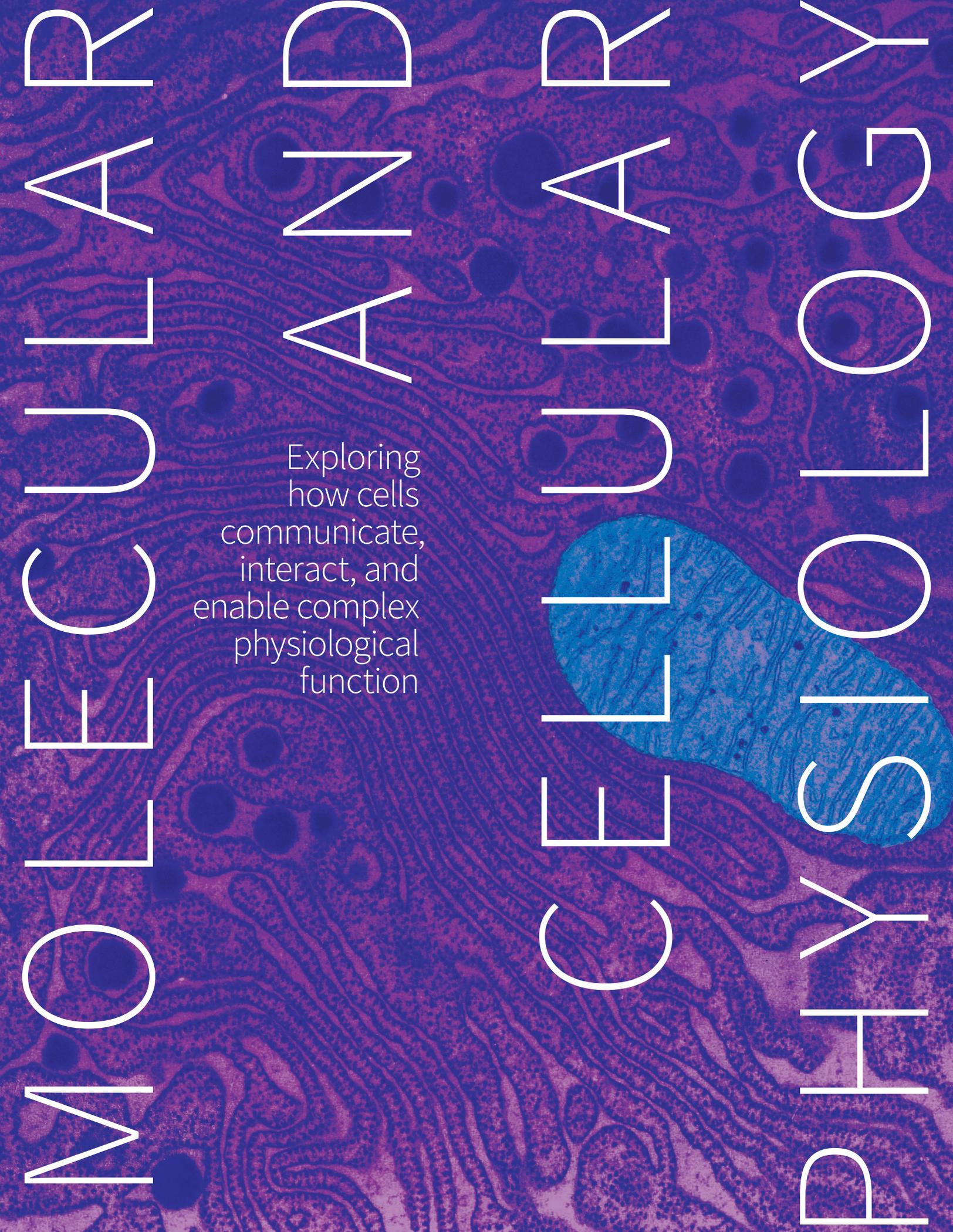
## DECIPHERING MOLECULAR DRIVERS OF IMMUNE SYSTEM AGING

**Juliana Idoyaga, PhD**

ASSOCIATE PROFESSOR OF MICROBIOLOGY AND IMMUNOLOGY

Aging of the immune system results in severe health repercussions for the elderly, including an inability to fight infections such as COVID-19 or influenza. Unfortunately, we still lack a basic understanding of the mechanisms of immune system aging, which impairs our capacity to design interventions that might boost the immune system of older adults.

In this project, we aim to investigate how aging affects dendritic cells, which are key immune cells that play a critical role in the initiation of all types of immune responses. This proposal will take advantage of new technologies in the field of immunology to resolve how aging affects the function of dendritic cells and their capacity to fight viral, bacterial, and parasitic infections. Specifically, we will use single cell approaches to compare the gene expression, phenotype, and epigenetic changes of human dendritic cells obtained from young versus elderly adults. We will investigate the expression of markers known to modulate the phagocytic capacity of dendritic cells and their capacity to activate other cells of the immune system. In addition, we will analyze the expression of transcription factors that regulate the number and function of dendritic cells. We hypothesize that declining expression of these genes during the aging process severely compromises immune function; consequently, bolstering the activity of these genes therapeutically could effectively boost immunity in the elderly and provide unique approaches to fight infections such as COVID-19 or influenza.



# CELLULAR PHYSIOLOGY AND CELLULAR RHYTHM

Exploring how cells communicate, interact, and enable complex physiological function



## SINGLE-NEURON GENE EXPRESSION CHANGES THAT CONTROL SYNAPTIC PLASTICITY

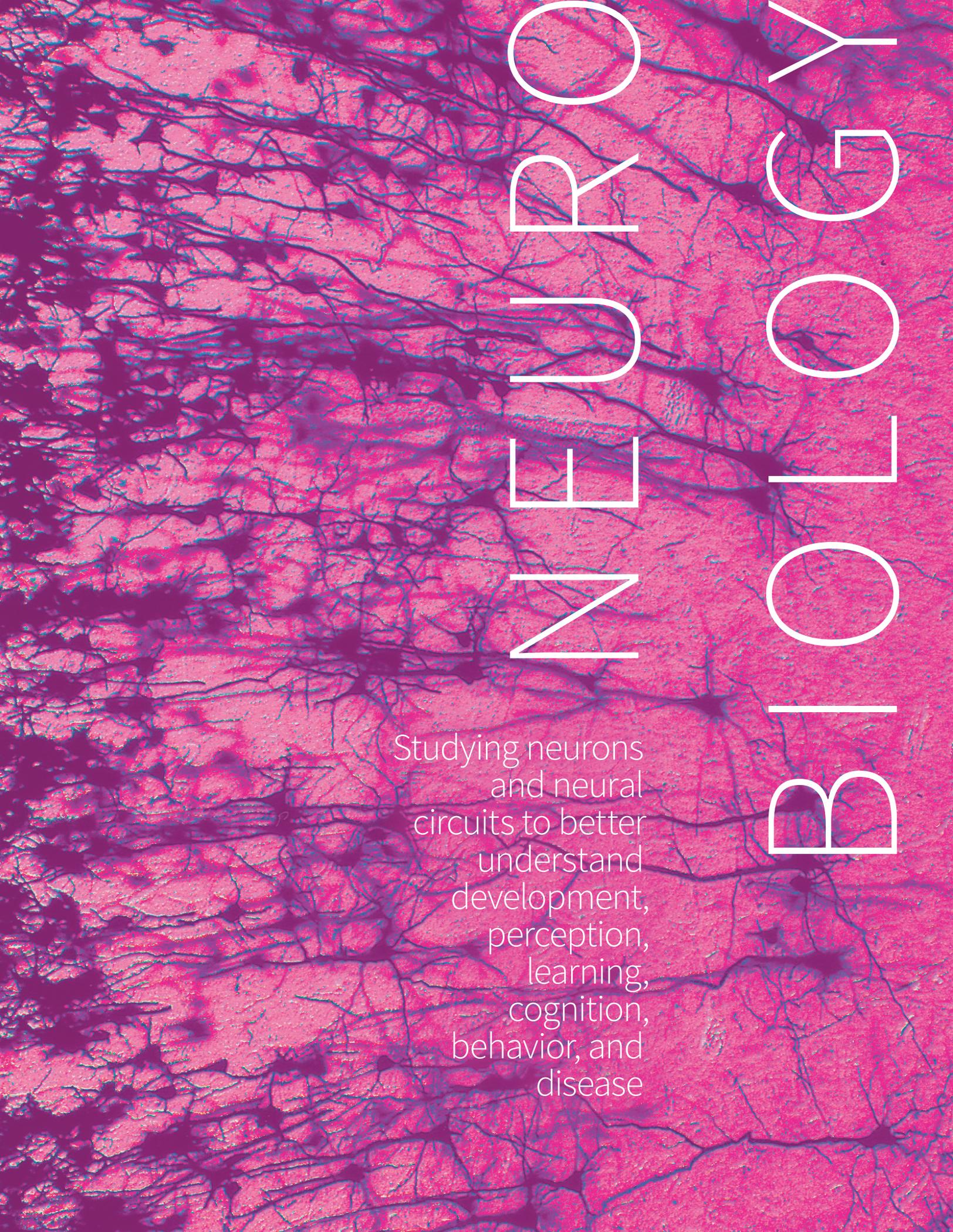
**Daniel V. Madison, PhD**

ASSOCIATE PROFESSOR OF MOLECULAR AND CELLULAR PHYSIOLOGY

As we learn new skills, facts, and faces, the connections between nerve cells are dynamically strengthened or weakened through a process known collectively as synaptic plasticity. Disruptions in synaptic plasticity are associated with a variety of important neurological disorders.

Synaptic plasticity results from alterations in the chemical communication pathways between nerve cells, dictated by the expression of genes that enable those changes. Our laboratory studies these processes by focusing on the most fundamental elements of neural circuitry underlying plasticity: the connection and communication between a single pair of nerve cells. By focusing on the most “quantal” elements of neural circuitry, we have revealed underlying mechanisms of synaptic plasticity that could not have been discovered in any other way.

Now, we aim to multiply the power of this approach by adding the ability to track gene expression with RNA-seq technology in the very same pair of nerve cells. Combining physiological and anatomical data with gene expression information will provide insights into synaptic plasticity that are unattainable anywhere else in the world. In particular, we will study “PV + inhibitory interneurons” that connect to principal cortical pyramidal neurons, because this particular type of cell pair is especially influential in regulating larger neural circuitry of the brain. These cells shape “normal” brain activity that underlies nearly every function of the brain and are implicated in neurological dissociative disorders and schizophrenia. Therefore, illuminating the mechanisms of synaptic plasticity between these specific pairs of cells is of particular significance and will not only advance our scientific understanding of how the brain functions and learns, but also provide translational insights to treat schizophrenia and other neurological disorders.

A microscopic image of neurons, showing a dense network of dark, branching cell bodies and axons against a reddish-pink background. The neurons are interconnected, forming a complex web. Overlaid on the right side of the image is the text 'ROY FLOYD' in a white, sans-serif font, with each letter being a large outline.

# ROY FLOYD

Studying neurons  
and neural  
circuits to better  
understand  
development,  
perception,  
learning,  
cognition,  
behavior, and  
disease





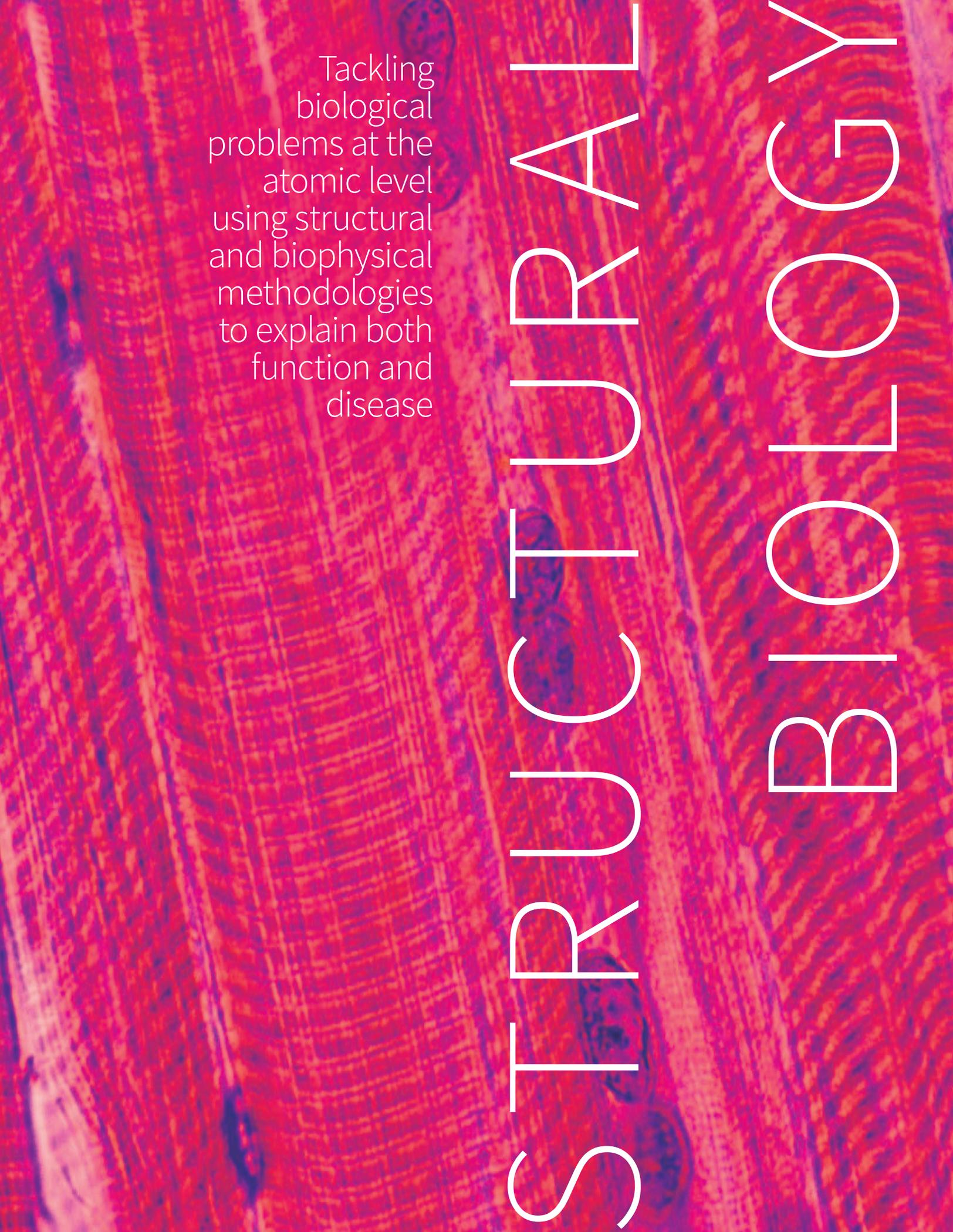
## NEURAL LINKAGE BETWEEN REWARD, SPATIAL MEMORY, AND GOAL-DRIVEN BEHAVIOR

**Lisa Giocomo, PhD**

ASSOCIATE PROFESSOR OF NEUROBIOLOGY

How does the brain use past experience to guide future behavior? A core function of the brain is its ability to form memories that link spatial locations in the world with reward, such as food or home, and use this experience to guide future goal-directed navigation. While this function is critical to an organism's survival, it can at the same time become pathological in mental illness and drug addiction. For example, one potent driver of relapse to drug use in addiction is re-exposure to the spatial environment in which a drug was previously experienced. However, the brain circuits and mechanisms underlying this behavior remain incompletely understood.

Here, we propose to explore how the well-known reward-circuitry, and its associated neuromodulators, interface with the hippocampus, a region that encodes spatial locations. The hippocampus is ideally poised to engage with the reward-circuitry to form memories that later drive behavior based on learned associations. We will apply cutting-edge technology that enables the visualization of both neuromodulators and neurons in the hippocampus that code for spatial locations in live mice. To observe these neural connections in awake, actively behaving mice will provide a completely novel lens into the mechanisms of reward-driven changes to memory processes. Ultimately, this work may guide novel interventions for addiction and mental illnesses where these circuits malfunction.

A microscopic image of muscle tissue, showing striated fibers and nuclei. The image is overlaid with a semi-transparent red color. The text is positioned in the upper left quadrant.

Tackling  
biological  
problems at the  
atomic level  
using structural  
and biophysical  
methodologies  
to explain both  
function and  
disease

# STRUCTURAL BIOLOGY



## AN UNEXPLORED PATHWAY OF CHRONIC VIRAL INFECTION-INDUCED IMMUNE ALTERATION

**Peter Parham, PhD**

PROFESSOR OF STRUCTURAL BIOLOGY AND OF MICROBIOLOGY AND IMMUNOLOGY

Chronic viral infections can alter the host's immune function, causing immunopathologies such as inflammatory and autoimmune conditions that result in a lifetime of health problems. HIV-1, hepatitis C virus, and herpesviruses all interact differently with human immune cells, yet in all cases cause the growth of a subset of natural killer cells called CD56neg cells, known for their potent anti-viral capabilities. Their presence in the context of multiple chronic viral infections suggests a shared pathway through which long-term infections promote an immune response causing this subset to expand.

We aim to expose and understand the pathway that produces CD56neg cells and investigate their role in immunopathologies associated with chronic viral infections. While this population of cells is currently understudied, we will develop new techniques to isolate and grow them in the laboratory in order to study the pathways and targets involved in their expansion. Specifically, we will explore the interactions of CD56neg cells with other cells, in the context of different types of chronic viral infections, to identify the common signals that trigger their growth. In addition, we will investigate the immunological conditions associated with chronic viral infections.

Ultimately, with these studies we hope to reveal a common mechanism that may be targeted to minimize the long-term health consequences of chronic viral infections and improve the lives of many with various viral diseases.

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