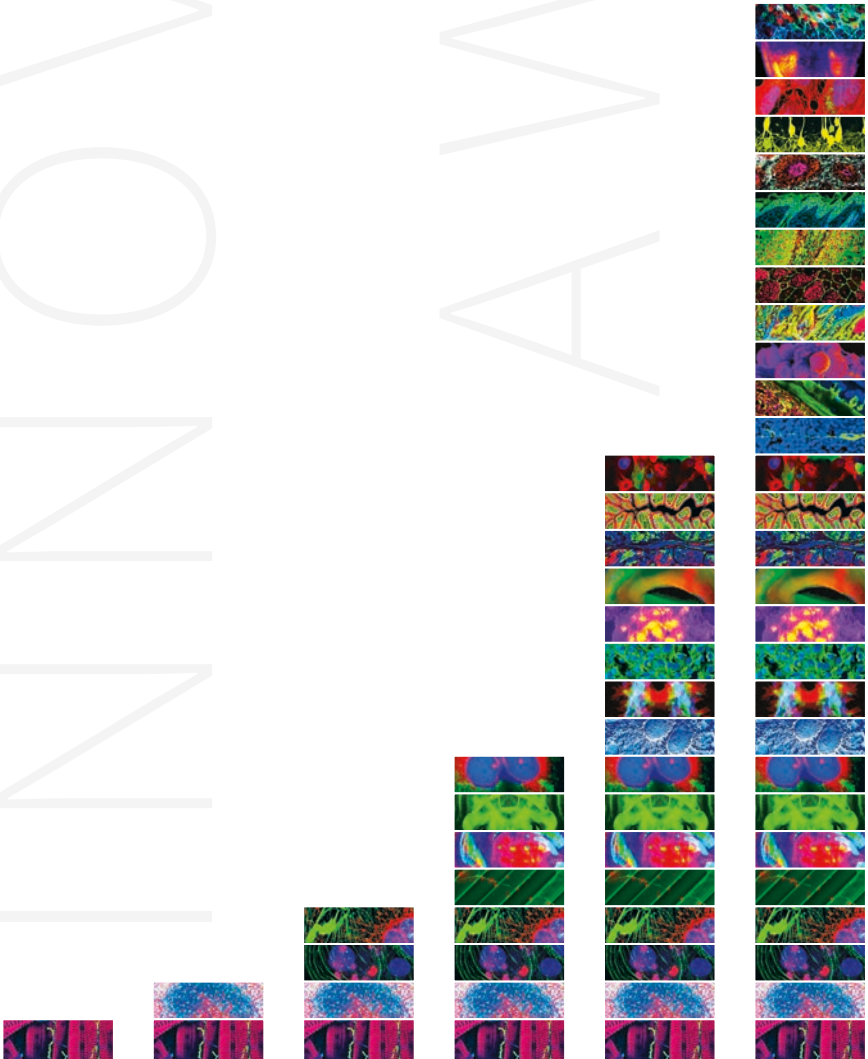
DISCOVERY INNOVATION AWARDS

one discovery can have an exponential impact on human health



Stanford | MEDICINE

EXPONENTIAL 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 the symptoms.

84
innovative new research projects

$900K
average size of a follow-on grant

63
new research grants

157
new research papers

113
national/international research presentations

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.

Funded by philanthropy and designed to drive discoveries about the fundamental mechanics of human health, these competitive seed grants fuel high-risk, high-reward ideas that don’t yet have the preliminary data needed to receive funding from the NIH and other conventional sources. These awards give faculty across Stanford Medicine’s 12 world-renowned basic science departments an opportunity to pursue their most creative, out-of-the-box ideas—ideas with the potential to have an exponential impact on human health.

Over the past five years, nearly $7 million has been awarded to fund 84 new research projects. In turn, these projects have led to 157 research papers and 63 grants totaling more than $57 million in follow-on funding from outside sources.

But the impact is far more than financial—these awards have supercharged Stanford’s already unrivaled atmosphere of entrepreneurial innovation and multidisciplinary collaboration. By giving faculty at all levels chances to pursue ideas that could open up entirely new avenues of discovery, these awards have launched the careers of many talented young researchers and they’ve proven to be a powerful incentive for the best and brightest to join—and stay—at Stanford.

This year, 18 of our researchers received a total of $1,386,499 through these awards. On the following pages, you’ll find descriptions of the winning projects and learn about some of the most innovative work in human biology happening anywhere in the world.

$57M
generated in follow-on funding

more than
8x
return on investment

$7M
awarded

BIOCHEMISTRY

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

cross-section of a human kidney

TISSUE ADAPTATION TO EXTREME ENVIRONMENTS

Rajat Rohatgi, MD, PhD
ASSOCIATE PROFESSOR OF BIOCHEMISTRY
AND OF MEDICINE (ONCOLOGY)

Cells within our bodies constantly battle hyperosmotic pressure, produced when high salt concentrations in tissues draw water out of cells. Consequently, cells undergo rapid shrinkage, with catastrophic consequences for cell health. To mitigate the deleterious effects of hyperosmolar stress, cells have evolved adaptive mechanisms that reverse the loss of cell volume and cell water. The goal of this project is to understand how cells sense hyperosmolarity and how they transmit these signals to the nucleus to activate the genes that control these protective responses.

Discovery of these genes and pathways may provide new targets for drugs to ameliorate diseases where hyperosmolar stress plays a role in cell and tissue damage, such as liver dysfunction, kidney failure, and inflammation.

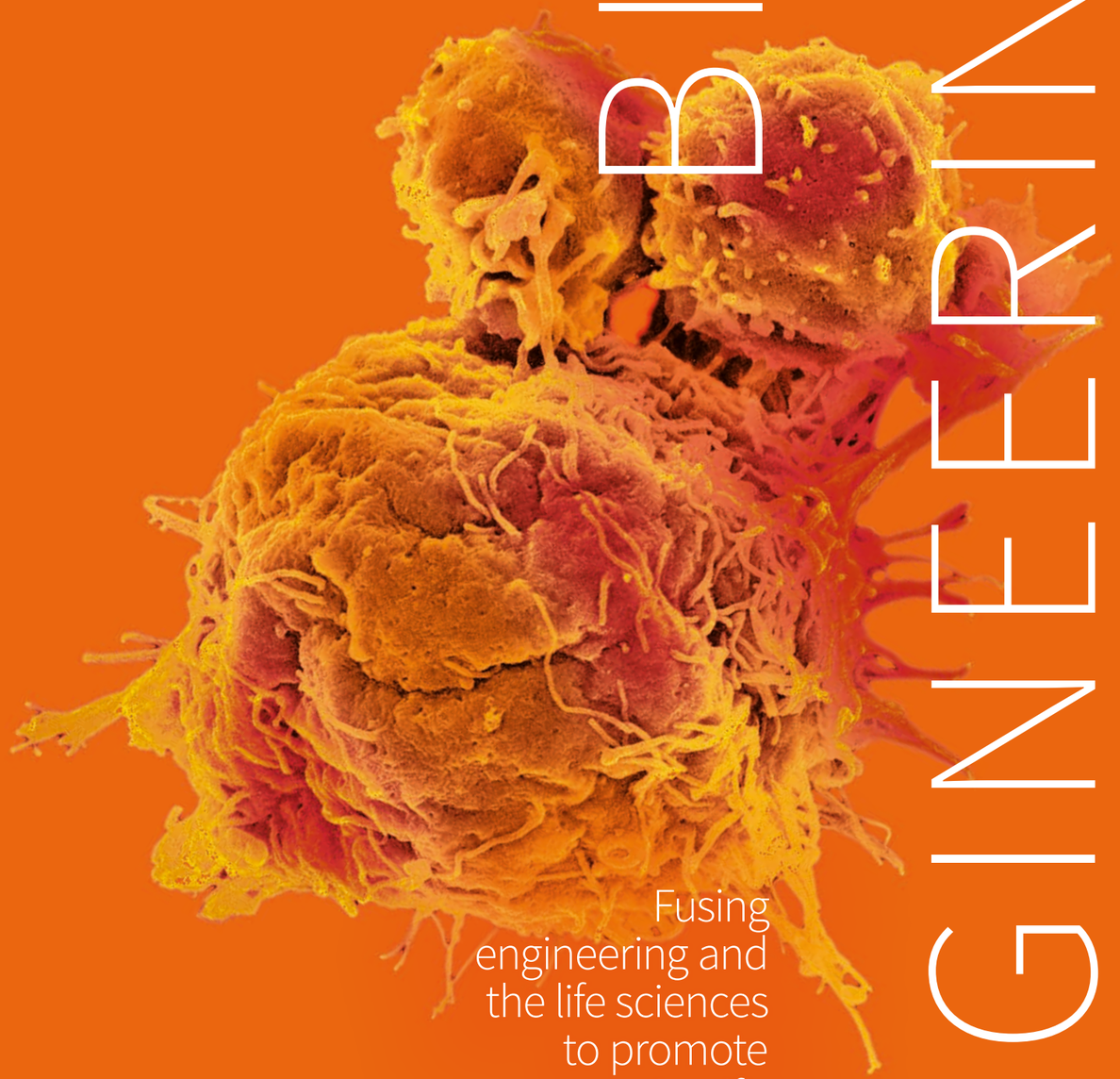
NEW TOOLS FOR UNDERSTANDING STRESS RESPONSE PATHWAYS IN DISEASE PROCESSES

Onn Brandman, PhD
ASSISTANT PROFESSOR OF BIOCHEMISTRY

Cells react to dangerous conditions through an interconnected set of pathways that work together to sense danger and protect the cell. These “stress responses” can be activated by toxins, heat or cold, viral or bacterial infections, and cellular damage. Improper function of stress responses can lead to disease, including cancer, neurodegeneration, and diabetes. Stress responses are difficult to study and poorly understood due to their interconnectedness and complexity.

The proposed work will meet this challenge by developing new experimental and mathematical methods to uncover the molecular machines and high-level wiring of stress responses. By developing general tools, we aim to empower the entire scientific community to accomplish our shared goal of understanding stress responses. These efforts may lead to new insights about the causes of diseases and new strategies to treat them.

BIO ENGINEERING



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

T lymphocyte cells (smaller round cells) attached to a cancer cell

SCREENING FOR ENGINEERED T CELLS AS POTENT CANCER THERAPEUTICS

Jennifer Cochran, PhD
SHRIRAM CHAIR OF BIOENGINEERING PROFESSOR OF BIOENGINEERING AND, BY COURTESY, OF CHEMICAL ENGINEERING

Chimeric antigen receptor T cell (CAR-T) technology represents a new era in cancer therapy, where a patient's own immune cells are trained to recognize and kill tumors. Despite its clinical success, with 50–90% efficacy, this therapeutic approach is limited to treating blood cancers such as lymphoma. Engineering tools are critically needed to develop CAR-T cell therapies against a broader range of tumor types.

We are developing an innovative discovery platform to rapidly screen millions of CAR-T cell candidates for clinically relevant activity against diverse tumor types. This platform will help identify new CAR-T cell treatments, while providing insight into molecular properties of CAR-T cells that effectively attack and kill tumor cells. We hope these insights will open up new avenues of immuno-oncology research and enable us to engineer next-generation designer treatments for patients with difficult-to-treat cancers.

MOLECULAR DYNAMICS OF CRISPR/CAS9 GENE EDITING FOR IMPROVED GENETIC ENGINEERING TECHNOLOGIES

Zev Bryant, PhD
ASSOCIATE PROFESSOR OF BIOENGINEERING AND, BY COURTESY, OF STRUCTURAL BIOLOGY

CRISPR/Cas9 technology is revolutionizing biological research by enabling precise genetic editing. Yet the applications of this technology have in some ways outpaced our understanding of how this nanomachine works. A better understanding of CRISPR/Cas9 molecular mechanisms could yield improved and more controlled genetic engineering technologies that eliminate unwanted side effects like genome editing at spurious locations.

This project utilizes new technology to watch CRISPR/Cas9 gene editing at the molecular level. We will examine the molecular forces that allow CRISPR/Cas9 to search the genome for specific target sites using a "guide" molecule that it carries as a reference, in a process akin to pulling genomic books off the shelf and searching at random for a particular passage. Observing these interactions step by step, while simultaneously measuring molecular forces, will provide fundamental insight to guide engineers in developing future gene-editing technologies with improved functional capabilities.

MICA and SYSBIO

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

DETERMINANTS OF SEASONAL RHYTHMS IN MAMMALS

James Ferrell, MD, PhD
PROFESSOR OF CHEMICAL AND SYSTEMS BIOLOGY AND OF BIOCHEMISTRY

Animals function differently in the summer vs. winter. For example, in the winter, some mammals hibernate and many others enter a so-called torpor, low-activity state. Humans are not exempt from these seasonal changes, with 5-10% of us suffering from seasonal affective disorder and overall mortality increasing 15% in winter months.

These annual or circannual (approximately annual) rhythms, like circadian rhythms, rely on external cues like day length. In addition, internal circannual clocks keep these rhythms cycling in the absence of external cues, for many years, or indefinitely in some animals.

Currently we know very little about how the circannual clock works in any organism. We have launched an effort to discover which hormones and cellular components exhibit annual cycles in mouse lemurs as a mammalian model organism. These cycling components will then be tested for their significance in contributing to circannual behaviors. Insights from this research may guide us to causes and treatments for seasonal affective disorder and other seasonal health problems.

A SYSTEMS APPROACH TO DEFINE THE MOLECULAR ARCHITECTURE OF COMPLEX TRAITS

Dan Jarosz, PhD
ASSISTANT PROFESSOR OF CHEMICAL AND SYSTEMS BIOLOGY AND OF DEVELOPMENTAL BIOLOGY

Understanding how differences in DNA sequence give rise to diversity between individuals is the central goal of genetics. Yet even with the extensive genome sequences available today, it remains challenging to determine which variations in DNA sequence matter. One big challenge is distinguishing mutations that have a meaningful biological effect from neighboring mutations that do not, because large portions of chromosomes are inherited together.

We have solved this challenge by pushing the limits of genetic crossing to improve DNA sequence mapping resolution from megabases to single nucleotides. With this 'super-resolution' approach we have identified hundreds of sequence variants responsible for dozens of biological traits, and overturned many misconceptions about genome function and organization.

Now we aim to take this approach to the next level by combining it with genetic engineering strategies to comprehensively and quantitatively understand the molecular basis of heredity. This high-risk, high-reward research could have a wide range of important biomedical applications in genetic medicine, genome engineering, and the design of custom microorganisms.

EVOLVING NOVEL RESEARCH TOOLS FROM LIGHT-SENSITIVE PROTEINS

James Chen, PhD
PROFESSOR OF CHEMICAL AND SYSTEMS BIOLOGY AND OF DEVELOPMENTAL BIOLOGY AND, BY COURTESY, OF CHEMISTRY

Plants and microbes produce light-sensitive proteins, which can be repurposed as research tools to transform the biomedical sciences. Using these "optogenetic" technologies, we can use light to regulate specific biological pathways with unprecedented spatial and temporal precision, allowing us to explore the molecular basis of health and disease in exciting new ways. For example, optogenetic probes could help uncover the biochemical mechanisms of tissue formation, expedite drug discovery, and perhaps even establish new clinical paradigms.

Realizing the full potential of optogenetics will require faster and easier methods for engineering new light-responsive proteins, as current strategies rely primarily on inefficient trial and error. We are pursuing a new approach, inspired by the natural evolution of light-responsive systems, that involves the random insertion of light-responsive modules into other protein sequences. This method will enable us to rapidly generate thousands of chimeric molecules, which we will then screen for light-sensitive variants and optimize through molecular evolution. This method should be broadly applicable to functionally diverse proteins, creating powerful new tools for basic and translational science.

◀ *DNA sequencing results*

COMPARATIVE MEDICINE

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

◀ *dendritic cell*

BOOSTING ANTI-TUMOR IMMUNITY

Thomas L. Cherpes, DVM, MD
ASSISTANT PROFESSOR OF COMPARATIVE MEDICINE

A major objective of cancer therapy research is to develop methods to fight tumors by activating a patient's immune system. One way is to enlist specialized immune cells called dendritic cells (DC) to present tumor antigens to patient T cells, thereby boosting the ability of these T cells to combat tumors. As such, identifying the molecules on the DC surface that present tumor antigens to T cells can guide development of more effective immunotherapies.

Our lab newly uncovered that DC uptake of activated B cells induces powerful antitumor immunity, but we do not yet understand how DCs recognize and interact with these cells. This award permits us to use unbiased high-throughput approaches to identify the DC surface molecules that interact with activated B cells. Simply put, it will facilitate development of cellular immunotherapies that will enhance a person's ability to mount an effective antitumor immune response.

DEVELOPMENTAL BIOLOGY

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

◀ *neural stem cells*

EPIGENETIC REGULATION OF STEM-CELL FATE SWITCHES IN HEALTH AND DISEASE

Margaret Fuller, PhD
REED-HODGSON PROFESSOR OF HUMAN BIOLOGY AND PROFESSOR OF GENETICS AND OF OBSTETRICS/GYNECOLOGY (REPRODUCTIVE AND STEM CELL BIOLOGY)

Many tissues and organs in our bodies are maintained and/or repaired by tissue-specific adult stem cells. These adult stem cells operate between two different cell programs: they self-perpetuate by proliferating in an undifferentiated state, or they can switch to shut down proliferation and turn on tissue-specific gene programs to generate repair cells.

Failure to appropriately switch between these two programs results in various disease states. If a cell remains in proliferation mode, excessive precursor cell production causes cancers. Meanwhile, premature differentiation can cause small organs or premature tissue aging. Other aberrant programming can cause tissue malformations like cirrhosis or lipomas. Despite its medical importance, the regulatory mechanisms of stem-cell fate switching are poorly understood.

We aim to elucidate these regulatory mechanisms by examining how cells suppress differentiation genes in proliferating precursor states and activate tissue-specific genes to commit to a specialized and proper cell fate. Utilizing the powerful genetic and molecular tools available in the *Drosophila* male germ line model, we will reveal if and how chromosomal and nuclear architecture play novel roles in these key cell state transitions.

These studies will further our understanding of adult stem-cell behaviors in the context of diverse diseases, potentially guiding improvements in stem-cell based therapies. In addition, our model system may more specifically expose new molecular mechanisms underlying male infertility and new targets for male contraceptives.

GENETICS

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

DNA, mRNA, nucleolus and enzymes

CRISPR/CAS9-BASED GENE EDITING FOR CORAL RESEARCH AND REEF CONSERVATION

John Pringle, PhD
PROFESSOR OF GENETICS

Coral reefs are biodiversity hotspots of great ecological, economic, and aesthetic importance. Due to climate change and other anthropogenic stressors, their global decline has increased the urgency of understanding these important ecosystems to guide conservation efforts. Our work focuses on elucidating molecular aspects of coral biology that are essential to their survival, including essential symbiotic interactions with algae that live within the coral tissues, calcium carbonate deposition for reef formation, and the responses to heat and other stresses.

Current coral-biology research is hindered by the lack of rigorous genetic methods for studying corals or relevant model systems—this makes it difficult, if not impossible, to definitively determine gene functions and molecular mechanisms of coral biology. We have recently adapted the CRISPR/Cas9 gene-editing technology to allow the generation of mutations in coral genes. This promising approach requires further development to overcome significant technical and logistical hurdles. Once perfected, this method should allow us to clarify many aspects of basic coral biology and thus provide a solid scientific foundation for coral-conservation efforts.

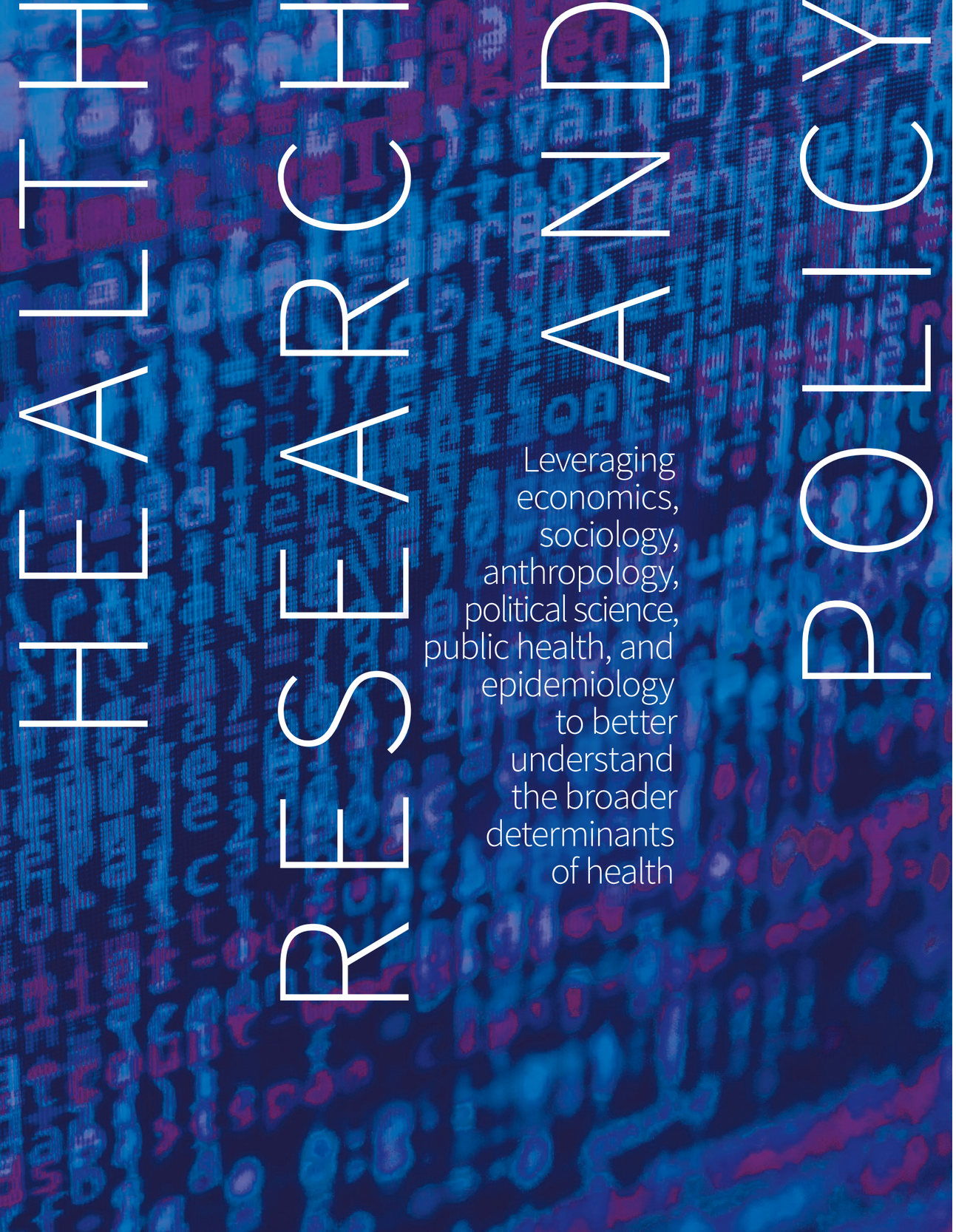
NOVEL COMPUTATIONAL APPROACHES FOR EXAMINING HOW GENETIC VARIATION INFLUENCES PROTEIN ABUNDANCE TO MANIFEST COMPLEX TRAITS

Hua Tang, PhD
PROFESSOR OF GENETICS

A fundamental biological question is how genetic variation manifests into diverse phenotypes, like normal variation in height, or variation in genetic susceptibilities to diseases like cancer, diabetes, or heart disease. While most research has focused on how genetic variation influences differences in mRNA expression, little is known about the influences on protein abundance.

Filling this gap is critical both for understanding fundamental biological processes and for deciphering the genetic basis of complex diseases.

Our goal is to develop computational approaches to elucidate genetic factors that influence protein abundance. We will pursue two complementary directions. First, we will use machine learning to construct predictive algorithms for how RNA locally and distally regulates protein levels. Second, we will construct a protein co-variation network, and search for genetic factors that influence the relationship between proteins within this network. This work will offer new insights into the genetic regulation of protein levels, while pioneering a new systems approach for studying factors that contribute to complex phenotypes.



BIG DATA INSIGHTS TO MEDICAL MALPRACTICE POLICY QUESTIONS

Michelle Mello, JD, PhD
PROFESSOR OF LAW AND OF HEALTH RESEARCH AND POLICY

Medical liability is intended to shape health-care quality by inducing physicians to provide better-quality care. But it can also spur "defensive medicine," which inflates health-care costs. The balance between these effects remains ambiguous because conventional investigatory methods are subject to substantial biases. The advent of big data research provides new opportunities to explore these issues and transform our understanding of the costs and benefits of the medical liability system.

Making novel uses of large proprietary databases, we will investigate how malpractice experiences shape physician behaviors. We will first examine how malpractice claims influence older physicians' decisions to leave clinical practice, and then go on to demonstrate proof of concept for a broader study of the influence of malpractice pressure on physicians' treatment choices.

This "precision" approach to malpractice research will shed light on how American patients benefit, or don't, from the more than $63 billion spent annually on the medical liability system. This unprecedented insight will reveal novel strategies for policy interventions to bring those costs down.

ONLINE RECRUITMENT AND SMARTPHONE DATA COLLECTION FOR PUBLIC HEALTH RESEARCH

Lorene Nelson, PhD, MS
ASSOCIATE PROFESSOR OF HEALTH RESEARCH AND POLICY (EPIDEMIOLOGY)

Population health data informs scientists and policy makers to address community health problems. However, current data and data collection methods are lacking in their actionability. Large national surveys may take years to provide results, delaying action, while also overlooking local population health variations. Meanwhile, local studies suffer from poor recruitment methods, such as phone or mail surveys, which are expensive and increasingly ineffective with diminishing response rates. Improvements in population health surveying methods, to obtain faster, more reliable and geographically localized data, are vitally needed to strengthen the evidence-base for public health efforts and policies.

We propose to study new methodologies using social media recruitment (SMR) for data collection from the general population. We recently completed a pilot study showing successful rapid recruitment of 363 Santa Clara County residents over a 24-day period. The study required participants to download our HealthKey mobile app and complete two brief surveys two weeks apart, with a 74% retention rate for the second survey. However, our results also expose the under-representation of several groups, including men, individuals over age 50, Hispanics, and individuals with a high school education or less. Further research is necessary to explore ways to improve SMR-based strategies to attract and retain a representative sample for population health data collection. Such SMR-based strategies could transform public health research and policy management.

MICROBIOLOGY AND IMMUNOLOGY

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

◀ *malaria* Plasmodium cathemerium *(purple and pink) infecting a blood cell (maroon)*

HOST IMMUNE DEFENSE AGAINST MALARIA INFECTION

Yueh-Hsiu Chien, PhD
PROFESSOR OF MICROBIOLOGY AND IMMUNOLOGY

Patient immune responses after vaccination are commonly used to inform vaccine design strategies to improve vaccine efficacy. However, we find that immune status before malaria vaccination correlates with effective immune protection afterwards. Similar findings have been reported from different patient cohorts, using different malaria vaccine formulations. In these cases, and in studies of natural malaria infection, the patient's initial level of T cells prior to exposure correlates with their subsequent protection against malaria.

T cells are central members of the adaptive immune system. Their presence in all but the most primitive vertebrates suggests an essential role in host immune defense—yet this role remains elusive. We aim to investigate how these T cells function to respond to and control malaria infection. These studies could improve vaccine design against malaria and/or yield new treatment strategies against this worldwide epidemic—alleviating a massive global health burden.

PRO- AND ANTI-HEPATITIS C EFFECTS OF CIRCULAR RNAs

Peter Sarnow, PhD
PROFESSOR OF MICROBIOLOGY AND IMMUNOLOGY

A new form of RNA was recently discovered with novel roles in gene regulation. This new form has a circular, rather than linear, structure, making it extremely stable and capable of interacting with other molecules to perform novel functions in living cells.

We have discovered that certain circular RNA molecules can regulate the growth of hepatitis C virus, in both positive or negative ways. We will systematically study these RNAs and characterize their actions by increasing or decreasing their abundance and observing the impact on hepatitis C virus growth and spread. Hepatitis C virus resides within the liver of the host, so we will conduct these experiments in cultured liver organoids—miniature three-dimensional models of the liver. These organoids will allow us to examine the influence of circular RNAs in both infected cells and uninfected neighboring cells to reveal any communication between them and how that cross-talk may lead to so-called bystander effects.

We anticipate that the circular RNAs may signal to bystander cells that their neighbors harbor a virus, triggering them to initiate defensive antiviral activities. Revealing such functions of circular RNA in dampening viral spread could expose a new Achille's heel to target for novel antiviral therapies.

MOLECULAR AND CELLULAR PHYSIOLOGY

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

◀ *mitochondria (blue) surrounded by endoplasmic reticulum (purple)*

MITOCHONDRIAL MOLECULAR TARGETS TO PROTECT AGAINST NEURODEGENERATION

Merritt Maduke, PhD
ASSOCIATE PROFESSOR OF MOLECULAR AND CELLULAR PHYSIOLOGY

Mitochondria are the powerhouses of the cell, converting food-based fuel into cellular energy. This essential life function produces reactive oxygen species (ROS) as a byproduct, which can damage biological tissues. Mitochondria must strike a delicate balance between the pros and cons of energy production, fulfilling the cell's energy needs while limiting ROS damage. This balance is achieved through mitochondrial regulatory mechanisms, which put the brakes on energy production. When these brakes malfunction, the balance tips and cells experience excessive oxidative damage, resulting in disease. In particular, the brain is extremely sensitive to ROS damage, resulting in neurodegeneration in aging, Alzheimer's disease, Parkinson's disease, depression, and other disorders.

These neurodegenerative disorders might be treated by restoring mitochondrial "braking" function. We aim to study how these mitochondrial brakes work in the brain, focusing on a recently identified central player, uncoupling protein 2 (UCP2). These studies will reveal strategies to augment mitochondria braking and to develop therapies to delay or reverse ROS-related neurodegeneration. This work could lead to new therapies to alleviate devastating neurodegenerative disorders and age-related neurodegeneration for which there are currently no or very limited treatment options, filling a critical need as our population ages.

NEUROLOGY

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

◀ *pyramidal neurons*

A NOVEL VIRTUAL REALITY-BASED PHYSIOLOGY PLATFORM TO UNDERSTAND AND TREAT HUMAN ANXIETY

Andrew Huberman, PhD
ASSOCIATE PROFESSOR OF NEUROBIOLOGY AND OF OPHTHALMOLOGY

Anxiety and dysregulated arousal are at the center of many common human psychiatric conditions, including PTSD, depression, and generalized anxiety. These conditions debilitate a huge percentage of the adult and child population, yet very little is understood about the brain mechanisms and physiological responses underlying them. Our goal is to develop new tools to study the physiological processes of anxiety and to test the efficacy of various anti-anxiety interventions.

First, we'll define objective, non-invasive measures of anxiety by using virtual reality to immerse patients in anxiety-provoking experiences. We'll measure their autonomic responses (heart rate, pupil size, breathing patterns, etc.) and record their brain activity with state-of-the-art physiology technology. Comparing autonomic responses between 'normal' people and patients with generalized anxiety or phobias will reveal how these responses are altered in anxiety disorders.

In addition, we'll test whether several novel anti-anxiety interventions known to decrease activation of the brain's threat detection systems, such as specific breathing patterns and visual eye movements, alter these responses. This may allow patients to consciously maintain control over their internal stress level while re-confronting these anxiety-provoking experiences.

We hope to establish tools and objective criteria to better diagnose and monitor anxiety disorders in the clinic. In addition, we seek ways to better manage these disorders by using novel, non-invasive, and self-generated interventions to regulate arousal states. These advances will significantly improve the diagnosis and treatment of many mental conditions where anxiety plays a major role.

STRUCTURAL BIOLOGY

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

◀ *striated skeletal muscle fibers*

BLOCKING MUTANT GENE TRANSLATION TO TREAT ALS

Joseph Puglisi, PhD
PROFESSOR OF STRUCTURAL BIOLOGY

Amyotrophic lateral sclerosis is one of the cruelest neurodegenerative diseases, typically striking around the age of 50 and progressing devastatingly quickly. The disease causes premature degeneration and death of motor neurons in the spinal cord and brain, resulting in the loss of mobility, dexterity, speech, and swallowing. Patients are left wheelchair-bound, and later bedbound, without the capacity to communicate, eat, or breathe on their own. There is currently no treatment to slow disease progression significantly, and most patients succumb to fatal paralysis within approximately three years of diagnosis.

A recent discovery has elucidated the most common genetic cause of ALS, revealing to researchers a molecular target for potential new treatments. Many patients with ALS have mutations in the gene C9orf72, with a certain DNA sequence abnormally repeated 100s to 1000s of times. When translated into protein, these extra repeating sequences create an unwieldy structure that clumps together. These abnormal proteins gum up the works in motor neurons, eventually causing their death and thereby, the symptoms of ALS. Our goal is to understand how the cellular machinery constructs these gummy proteins, and to find a way to block the machinery from adding problematic repeated sequences. Preventing the production of these mutated proteins could open the door to revolutionary new treatments for ALS.

NOTES

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