RESEARCH PROGRAM

Medical Research Abstracts
for Grants Awarded in December 2019

Huntington Medical Research Institutes
Pasadena, CA
Michael Harrington, Linda Petzold, Brian Stoltz
$1,000,000
December 2019

An interdisciplinary team of investigators at the Huntington Medical Research Institutes, the University of California, Santa Barbara, and the California Institute of Technology proposes a new fundamental biological mechanism in which varying sodium levels in cerebrospinal fluid (CSF) or brain tissue alter local neuronal firing rates, resulting in fluctuation of brain performance. Their initial studies of migraine pathophysiology revealed that CSF sodium regulation is a key factor in migraine: CSF sodium levels are higher near specific cranial nerves at the time that their excitability increases. Moreover, based on animal and cell culture studies, the team predicts that fluctuating sodium levels are responsible for fluctuating brain performance in health and disease. For example, altered sodium in the frontotemporal cortex may change executive and memory functions, while sodium fluctuations in the limbic system, amygdala, and prefrontal cortex may alter mood or cause anxiety or panic attacks. To test their hypothesis, the investigators will measure sodium and ATPase activity in well-characterized individuals using multinuclear magnetic resonance imaging and will identify symptoms that match the changing biochemistry. Furthermore, the team will develop new compounds to modulate the sodium/potassium ATPase at different sites to improve neurological functions. Lastly, they will generate a physics-based model of the data to further our understanding of when, where and how specific episodic neurological functions arise. Thus, modeling will establish the key rate-limiting steps in a complex brain network to predict failure of brain homeostasis. Successful completion of this project will ascertain a new paradigm for health or brain pathology, whereby fluctuating neurological functions arise from fluctuating sodium levels.

Louisiana State University
Baton Rouge, LA
Alyssa Johnson, Adam Bohnert
$1,000,000
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Lysosomes are digestive organelles that govern cellular metabolism and homeostasis. Despite their importance to animal health and disease, the current model of lysosome structure and function is quite simplistic: lysosomes are thought to exist mainly as discrete vesicles, each with similar degradative capacity. Recently, two early career investigators at Louisiana State University discovered a new class of lysosomes that challenges this model. In multiple species and cell types (including mammalian cells), the team has identified an interconnected, dynamic network of tubular lysosomes (TLs) that are exceptionally degradative. Notably, these TL networks suppress age-related tissue degeneration, highlighting their biomedical relevance. This study will utilize two genetically tractable model organisms, the nematode *C. elegans* and the fruit fly *Drosophila melanogaster*, to develop a comprehensive picture of this unique organelle. Live-animal imaging will be used to track TL biogenesis and activity in different tissues throughout life and in response to metabolic stimuli. In addition, the investigators will utilize fluorescent sensors to assess cargo turnover in TLs and they will perform unbiased screens to identify TL regulators. These studies have the potential to redefine the landscape of a cell, while also hinting at natural disease-fighting mechanisms based on lysosomal plasticity.

Memorial Sloan-Kettering Cancer Center
New York, NY
Adrienne Boire, Christine Iacobuzio-Donahue, Dana Pe'er
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Spread of cancer cells into the spinal fluid, or leptomeningeal metastasis (LM), is an increasingly common complication of cancer that results in rapid neurologic disability and death. The molecular mechanisms that underlie cancer cell entry into this space remain poorly understood. Preliminary data from both patient samples and mouse models suggest that certain cancer cells exploit the immune system to gain characteristics that enables them to live and grow in the spinal fluid, which is nutritionally sparse with limited oxygen, protein, glucose, lipids, and micronutrients essential for cell growth. A team of three investigators at Memorial Sloan-Kettering Cancer Center plans to determine the mechanisms by which cancer cells become able to survive and grow within the spinal fluid environment. The team hypothesizes that circulating cancer cells enter a structure called the choroid plexus. Once in this structure, immune cells kill many cancer cells, but certain cells survive this selection, follow immune cells into the spinal fluid and live within this unfavorable environment. To study these processes, the team proposes

to subject patient spinal fluid samples and tissues to advanced analytical techniques to generate an LM "atlas" that describes molecular characteristics of cancer cells capable of living within the spinal fluid. They will also employ their established mouse models of LM to further investigate the molecular characteristics of these populations of cancer cells. This translational approach will improve understanding of the essential steps that govern cancer and immune cell entry into the spinal fluid and could provide new insights into therapeutic approaches for cancer metastasis.

University of California, Davis
Davis, CA
Johannes Hell, Kit Lam, James Ames, Manuel Navedo
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The exact location of proteins inside a cell is critical for their function. Antibodies are powerful tools for protein detection and have been developed against a multitude of proteins. However, because of their size, defining the exact location of a protein is limited to 20 nanometers (10^{-9} m, nm) when most protein dimensions are in the range of 4-10 nm. Thus, to accurately map the spatial relationships between individual proteins, new technology is required for their detection. The first goal of this project is to develop groundbreaking technology for detection of protein targets with a resolution in the 1-5 nm range. Investigators at the University of California, Davis will do so by combining a technology for screening peptides with dyes that fluoresce only if in contact with another protein. Their approach would generate highly specific reagents for detection of a particular protein and could also address the – often underappreciated – issue of antibodies binding to proteins other than their intended targets. The team will use this technology to develop peptides directed against key proteins at the synapse, the contact site of neurons. They will focus on the AMPA-type glutamate receptor (AMPAR), which mediates most of the signal transmission between neurons in the brain. Its exact localization within synapses determines the strength of the signal transmission, which in turn can be modified under physiological conditions such as learning and under pathological conditions such as drug addiction and post-traumatic stress disorder. Identifying the exact location of AMPARs would advance our understanding of their function in health and disease.

University of Colorado at Boulder
Boulder, CO
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Biomarkers, or biological markers, are measurable indicators of biological state or condition. The measurement and characterization of mechanical biomarkers (mechanical properties) of cells, such as mass, compressibility, viscosity, stiffness and density, has been of great interest to biomedical researchers and could have profound impact in cellular biology, drug research, cancer and other diseases. The cell mechanical properties are useful indicators of changes in cytoskeleton and nuclear organization. They could serve as label-free biomarkers for determining cell states or properties such as metastatic potential, cell cycle stage, degree of differentiation, and leukocyte activation. In this project, investigators at the University of Colorado aim to develop a newly conceptualized technology, termed acoustic activated flow cytometry, to simultaneously measure multiple mechanical biomarkers of individual cells at a high throughput of up to millions of cells per hour. Surface acoustic wave (SAW), a kind of sound, is a mechanical wave that propagates at the interface of a solid and a liquid medium. Its propagation is highly sensitive to the mechanical properties of the cells passing through the propagating pathway of SAW. By measuring the SAW signal change when cells continuously flow through, the team would be able to collect the details of multiple mechanical properties of individual cells at a high rate. The measurement of multi-dimensional mechanical biomarkers of individual cells in high throughput is beyond the capability of any current technology and could provide an entirely new foundation for both fundamental cell biology and clinical research.

Washington State University
Spokane, WA
James Krueger, Cheryl Dykstra-Aiello, Ilia Karatsoreos, Alexander Panchenko
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In all humans, host cells and microbes live in a delicate symbiotic balance. The gut microbiome affects cognition, emotion, sleep, circadian rhythms, and additional brain functions. Yet, the causal brain mechanisms behind these effects are unknown. A small literature, including past work by Washington State University (WSU) investigators, indicates that bacterial cell wall peptidoglycan (PG) is present in normal brain and changes with sleep loss. These findings provide an intriguing new understanding of what it means to be human – bacteria participate in human neurobiology. The WSU investigators posit that PGs regulate physiological brain functions including sleep and circadian rhythms. They further expect that non-pathological alterations of sleep or circadian rhythms, e.g. acute sleep deprivation or simulated jetlag, induce

dynamic changes in brain PG levels which, in turn, could induce changes in the expression of genes associated with sleep/wake cycles and circadian rhythms. Using mouse models, the WSU investigators have demonstrated that the mRNA of a PG-binding peptide in the brain increases after acute sleep deprivation. This peptide induces the expression of sleep regulatory cytokines involved in circadian rhythms. In this project, the WSU team plans to measure the levels of PG and of the PG-binding peptide in the mouse brain under normal circadian rhythms and sleep-wake cycles. They would determine how disrupting sleep or circadian rhythms drives changes in the levels of PG and PG-binding peptide along with other proteins related to circadian rhythms. Lastly, using *in vitro* neuronal/glial co-cultures that simulate sleeplike states, the investigators would characterize the molecular mechanisms linking PG levels to cytokines and sleep. Successful completion of this project would advance our understanding of the relationship among the microbiome, immune responses, sleep, and circadian rhythms.