RESEARCH PROGRAM

Medical Research Abstracts
for Grants Awarded in June 2018

Center for Infectious Disease Research
Seattle, WA
Alexis Kaushansky, Noah Sather
$1,000,000
June 2018

Recently, several promising experimental vaccines have failed to achieve efficacy in the field after they demonstrated high levels of protection in human clinical trials involving pathogen naïve individuals. Early clinical trials typically study the first exposure to infection while in the field, people are often infected with a pathogen multiple times before vaccination. Investigators at the Center for Infectious Disease Research in Seattle, Washington, hypothesize that the resultant partial "immunity" alters the engagements between the pathogen and the host. This impacts the development of potent immune effector cells and in turn reduces the efficacy of vaccine-induced protection. Each of these processes is complicated by the reality that, while most studies evaluate bulk measurements, infection and immunity are both driven by a very small number of individual cells whose characteristics are likely lost in the context of bulk measurements. The team proposes to evaluate changes that occur in host-parasite interactions as a result of pre-existing humoral immunity to malaria infection, as well as determine the impact of these changes on vaccine efficacy. Importantly, assessments will occur at the single cell level, allowing evaluation of how parasites, host target cells and antibody responses interact to yield protection or susceptibility to infection.

University of Chicago
Chicago, IL
Tao Pan, Murat Eren, Eugene Chang, Mitchell Sogin
$1,000,000
June 2018

Genomics-enabled microbiome science has revealed amazing snapshots of globally distributed taxonomic and metabolic diversity, yet current molecular technologies do not describe the dynamic response of microbiomes to environmental shifts. Biological systems generally respond to environmental flux via regulated protein synthesis where transfer RNA (tRNA) serves a key role in decoding genetic information on-demand. These adapter molecules also undergo

posttranscriptional, chemical modifications that add distinct regulatory aspects in decoding as well as reflect levels of microbial metabolic activity. A multidisciplinary team of investigators propose a transformative approach that utilizes high-throughput sequencing technology with novel molecular and computational components that simultaneously report tRNA abundance, modification, and charging states that translate into measures of specific taxon expression and activity levels. The researchers will develop this platform for the application of minute amounts of microbiome samples and generate a complete bioinformatics pipeline integrated into metagenomics platforms such as Anvi'o. The team will also carry out three biological driver studies as proof-of-principle of applying tRNA-Seq for new biological insights and discoveries. These studies will empower investigations of rapid dynamic taxonomic and functional shifts in microbial populations in various biomedical and ecological contexts.

The Rockefeller University
New York City, NY
Erich Jarvis, Shiaoching Gong, Michael Long, Ofer Tchernichovski
$1,000,000
June 2018

Spoken language is critically dependent on the ability to imitate sounds heard, a complex trait known as vocal learning. Despite its independent evolution in only a handful of distantly related avian and mammalian lineages, vocal learning between these lineages shows remarkable convergence in behavioral mechanisms, neurocircuitry, and associated brain gene expression specializations. These specializations include a finite set of over 50 genes that Rockefeller University researchers recently identified as showing convergent, differential expression within vocal circuits in the brains of vocal-learning songbirds and humans. The investigators posit that evolutionary changes in the regulation of these genes are responsible for the emergence of vocal learning and other brain circuits for related complex traits. They will test this hypothesis by developing new molecular tools to modify a rudimentary vocal brain circuit in mice. The researchers will engineer the human versions of these genes into mouse vocal circuits and then determine whether these animals exhibit enhanced vocal-learning associated traits as measured by circuit connectivity, physiology, and vocal behavior. Such studies may generate genetically tractable mouse models with greater vocal learning capacity for studying and repairing human communication disorders, as well as tools for genetically engineering circuits for other complex traits.

University of California, Davis
Davis, CA
Ben Montpetit, Priya Shah, Christopher Fraser, Richard Wozniak
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Zika, Hepatitis C, Dengue, and West Nile of the *Flaviviridae* virus family infect hundreds of millions of people, causing widespread morbidity and mortality. A prominent example is the recently discovered congenital Zika syndrome characterized by severe microcephaly and other developmental defects. Except for Hepatitis C, there are no approved anti-viral treatments for these viruses, despite decades of research. A central tenet of *Flaviviridae* biology, and one that defines therapeutic strategies, is that virus replication occurs within the cytoplasm of host cells. Investigators from the University of California, Davis and the University of Alberta in Canada are challenging this dogma by showing, using highly sensitive and specific detection techniques, that the RNA genomes (vRNAs) of Zika and Hepatitis C enter and leave the host cell nucleus during the course of an infection. This breakthrough requires a paradigm shift away from a cytoplasm centric view of *Flaviviridae* biology and a re-evaluation of how researchers study and combat these viruses. However, before the team can leverage this knowledge for societal benefit (e.g. therapeutics), they must understand, at a molecular and mechanistic level, why these viral RNAs travel through the nucleus and engage nuclear processes, and how this benefits the virus. They will tackle these questions using highly innovative approaches that will allow them to construct dynamic and cell specific systems-level interaction networks between vRNAs and host cell nuclear factors. The investigators expect these high-risk, high-reward endeavors will produce new paradigms and foster novel pan-*Flaviviridae* therapeutic opportunities.

Salk Institute for Biological Studies
La Jolla, CA
Janelle Ayres
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Host-microbe interactions have traditionally been viewed as antagonistic, with most investigators focusing on understanding host resistance mechanisms that kill pathogens. Salk researchers have been characterizing host-microbe interactions from a fundamentally distinct perspective—how do animals survive when interacting with microbes? Health is traditionally believed to be a passive homeostatic state and disease occurs when there's disruption in the system, such as the presence of a pathogen. It would then follow that removal of the pathogen would return the system back to a healthy state. However, in many scenarios, the collateral damage associated with pathogen elimination can do more harm than the pathogen itself, as is seen with sepsis and influenza infection. Salk investigators hypothesize that maintaining health during infection is an

active process, involving mechanisms that coordinate cooperative interactions between the host and pathogens. This is based on Salk researchers' discoveries of co-operative defenses that protect the host during infections by alleviating physiological damage without killing the pathogen. The investigators plan to develop an approach to perform systems level analyses to elucidate the mechanisms contributing to co-operative defenses against two infections in the elderly: sepsis induced by intestinal perforation and influenza. They will also identify novel methods to manipulate these defenses and strategies to determine how cooperative defense therapies influence pathogen virulence, evolution and attenuation. The project could generate a fundamentally different perspective on understanding and treating many infectious diseases.