RESEARCH PROGRAM

Medical Research Abstracts for Grants Awarded in June 2020

University of California, Santa Barbara
Santa Barbara, CA
Songi Han, Kenneth Kosik, Joan Shea, Scott Shell
$1,000,000
June 2020

The aggregation of the abundant neuronal protein tau into neurofibrillary brain deposits is directly diagnostic of a large family of neurodegenerative human diseases. These are collectively known as tauopathies and include Alzheimer's Disease. Stunning new cryo-electron microscopic images of tau fibril structures from post-mortem tauopathy patients now define the fibril shape with atomic resolution that uniquely identifies different tauopathies. However, none of these pathological fibrils have ever been replicated in the laboratory, which is a prerequisite for developing therapeutic strategies. Current drug developments for tauopathies operate under the premise that pathological tau fibrils serve as competent seeds to "infect" native tau and transmit their disease-defining shape from cell to cell. However, the fundamentals of this premise are entirely unknown. A team of University of California, Santa Barbara investigators, consisting of a computational biophysicist, an engineer, a spectroscopist and a neurobiologist, will join their unique expertise to uncover the biophysical and molecular bases for tau aggregation and fibril shape transmission. Questions to be addressed include the identity and composition of competent seeds and the mechanisms of protein shape transmission from mother to daughter fibrils. The team's ambitious endeavor is to establish a new paradigm of dynamic pathway design to control protein shape transmission along a defined aggregation pathway, challenging decades of focus on static end-fibril structures. Answering these research questions will, at last, place the testing of therapeutic strategies for tauopathies on a firm scientific foundation. It will also transform our ability to tune the shape of other fibril-forming proteins critical to numerous diseases and functions.

University of Utah
Salt Lake City, UT
June Round, Chun-Jun Guo
$1,000,000
June 2020

Most people have heard the term "microbiome" and have a vague working knowledge that microbes may be doing something good for us. This has led to a surge of papers, grants, and even companies that are working to harness the power of the microbiome to benefit human health. However, most of these endeavors are focused on one component of the microbiota, the bacteria, despite the presence of archaeal, fungal, and viral members. Indeed, the most numerically prominent biological entity within the gut are viruses that are capable of infecting bacteria, termed bacteriophages (phages). These bacterial viruses can either kill bacteria directly or integrate within the host genome to control bacterial expression of genes. It is estimated that each bacterium may harbor up to five distinct phages within its genome, making the genomic capacity and plasticity of bacteriophages much larger than that of their bacterial hosts. The study of integrated, commensal bacteriophages represents a large research gap and offers the potential to discover novel gene functions. Two investigators, one at the University of Utah and the other at Cornell University, seek to address this gap using cutting-edge technologies to identify, purify, and manipulate commensal bacteriophages found within an important class of human-associated bacteria which, as the team discovered, protect from metabolic disease. The investigations will lay the foundational groundwork to seed a new field of study and establish novel paradigms in the ever-growing microbiome research field.

Vanderbilt University
Nashville, TN
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The current paradigm for the metastatic progression of solid tumors is that cells from a primary tumor migrate into the surrounding tissue, enter blood vessels, and travel to a secondary site. Cell migration is widely viewed as a critical step in metastasis, which is evident based on the prolific number of published research papers involving cell migration in cancer. Contrary to this understanding, investigators at Vanderbilt University have generated surprising data, which show that the ability of cells to migrate does not correlate with metastasis. In this proposal, the overall goal is to identify the key facets of cells which are critical for metastasis and, separately, which are critical for migration. The search for cancer cell biomarkers is typically performed using molecular screens across cell populations. Using an engineering approach, the investigators will sort cells based on behavior first (a phenotypic screen), focusing on the outliers to identify the

most robust drivers of cell migration and metastasis. The proposed engineering-based approach has the potential to uncover previously hidden targets to prevent metastasis. This work directly challenges the prevailing paradigm that migration is essential for metastasis, which has motivated tens of thousands of journal papers and millions of research dollars, and it will significantly expand our knowledge of cell migration and drivers of metastasis.