RESEARCH PROGRAM

Medical Research Abstracts
for Grants Awarded in December 2018

Scripps Research Institute
La Jolla, CA
Peter Schultz, Angad Mehta
$800,000
December 2018

Almost five decades ago Crick, Orgel and others proposed that RNA might be able to support both genotype and phenotype. Since then, the RNA world hypothesis has been extensively investigated and the function of RNA templates has been studied in terms of evolution, replication and catalysis. Recently, investigators at the Scripps Research Institute engineered strains of *E. coli* in which a large fraction of 2'-deoxycytidine in the genome is substituted with the modified base 5-hydroxymethylcytidine. Subsequently, they generated strains derived from these engineered bacteria, which show significant ribonucleotide content in their genomic templates. In the proposed studies, the investigators will characterize the properties of these chimeric templates and corresponding strains to determine the circumstances under which *E. coli* can incorporate ribonucleotides into its genome. They will also attempt to rationally engineer strains with similar high ribonucleotide content. The team's expectation is that such chimeras may provide deeper insights into the link between the RNA and DNA worlds.

University of California, San Francicso
San Francisco, CA
Diana Laird, Andrew Brack, Saul Villeda
$1,000,000
December 2018

Expansion of the aging population is creating major health and socio-economic challenges. The nascent field of gerontology aspires to develop therapies to extend the human health span and mitigate chronic diseases of aging. However, this goal is stymied by the sparsity of appropriate model organisms and by a lack of insight into mechanisms by which the more than 80 organs in the body regulate aging. A team at the University of California, San Francisco proposes to devise a unique, new, tractable and generalizable model for interrogating the role of individual organs in determining the rate of aging using interspecies chimeras between the mouse and the naked mole rat (NMR). NMRs live >9-fold longer than laboratory mice, and the female

reproductive lifespan is an astonishing 20-30 times longer. The team will consider the specific role of the ovary in regulating aging, and its potential as a fountain of youth. The aims of this project are to understand how the NMR ovary functions 30-fold longer than that of the mouse and to test the capacity of the ovary to prolong youth across the entire organism in chimeric mice with ovarian tissue from NMRs. The investigators will introduce novel and powerful means to reveal and study integrated mechanisms of aging across all tissues and organs, with special emphasis on skeletal muscle and brain, and to evaluate the potential of NMR ovaries to decelerate or reverse aging.

University of Virginia
Charlottesville, VA
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$1,000,000
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Structural biology is a critical component of modern biomedical research. Multiple experimental techniques, primarily X-ray crystallography and cryo-electron microscopy (which has recently advanced remarkably), can yield macromolecular structure at atomic- or near-atomic resolution. The current structural biology paradigm is that high information content samples, yielding large amounts of data per sample, are used to solve the structure. However, obtaining such high information content samples, particularly for more complicated systems such as protein complexes, membrane proteins, or transient conformational states of macromolecules, is often very risky, with concomitantly large amounts of time, money, and effort required to maximize the likelihood of success. An investigator at the University of Virginia, in collaboration with investigators at the University of California, San Francisco and Stony Brook University, proposes an alternative structural biology paradigm: multiple low information content samples, yielding small amounts of data per sample, are used to solve the structure. This alternative structural biology paradigm will be actualized via development of a new integrated experimental/computational approach, Serial Solution Scattering Structure Determination (S4D). S4D will utilize atomic pairwise distances obtained by solution X-ray scattering from protein samples containing electron-dense "R-group" labels incorporated by *in vitro* chemical or *in vivo* unnatural amino acid incorporation methods. These pairwise distances will be utilized by the "sparse constraint" Bayesian structure determination program termed Modeling Employing Limited Data (MELD). The culmination of this approach would permit facile macromolecular structure determination *in vitro* and *in vivo*. Success with this "alternative paradigm" for structural biology would enable true high-throughput structure determination that better keeps pace with the increasingly rapid acquisition of genomic and proteomic data.

Washington University in St. Louis
St. Louis, MO
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$1,000,000
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Structure determines function. A new protein structure is often the milestone that transforms our understanding of basic biological processes. Four Nobel Prizes have been awarded to the scientists who deciphered the structures of membrane proteins, which constitute about one third of all proteins. Membrane proteins, however, are notoriously difficult for structural studies due to their hydrophobicity and instability. The structures of only ~2% of human membrane proteins have been solved, significantly impeding the understanding of their functions. New out-of-the-box approaches for determining their structures would be nothing short of revolutionary for science and medicine. Two investigators at Washington University in St. Louis propose a "termini coupling" method to stabilize membrane proteins for purification and structural determination. Building upon their recent success applying termini coupling to X-ray crystallography, they will develop this novel concept for cryo-electron microscopy, a revolutionary structural tool that overcomes many limitations of crystallography. The team's proposed approach can be universally applied to solve the structures of almost any membrane protein, which will allow them and others to address fundamental questions about the multitude of processes that occur on or through cell membranes. The structures will reveal how signals move between the external and internal environment, how nutrients and ions are sensed and transported, how enzymes catalyze reactions at the membrane interface, and how cells identify and interact with each other to execute a coordinated action. Termini coupling will allow scientists to finally 'see' how human membrane proteins are built and how their functions are executed. Termini coupling is expected to fundamentally transform the current understanding of biology.