NEW INVESTIGATOR RESEARCH GRANTS
$150,000 over two years ($75,000 per year)

GOAL

The goal of the New Investigator Research Grants is to provide research support for innovative basic scientists in Pennsylvania as they transition into an academic position as a new independent investigator. Proposals are required to address basic (fundamental, pure) questions addressing core principles in biology, physics and chemistry or at the disciplinary boundaries between these fields. Applied or clinical studies will not be supported. Competitive applications are expected to be rich in innovative ideas and approaches with the potential for generating transformative intellectual advances.

NEW INITIATIVE RESEARCH GRANTS
Up To: $300,000 over two years ($150,000 per year)

GOAL

The goal of the New Initiative Research Grants is to stimulate existing investigators with strong records of research accomplishments to establish collaborations that facilitate innovative interdisciplinary approaches towards a common research question and that require expertise beyond that of any single researcher. Investigators may be at different institutions or in the same department and institution, provided that different approaches are combined to address a new research initiative. Proposals are required to address basic (fundamental, pure) questions addressing core principals in biology, physics and chemistry or at the disciplinary boundaries between these fields. Applied or clinical studies will not be supported. Competitive applications are expected to be rich in innovative ideas and approaches with the potential for generating transformative intellectual advances.

NEW INVESTIGATOR RESEARCH GRANTS

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Nathan L. Clark, Ph.D.
Assistant Professor, Department of Computational and Systems Biology
University of Pittsburgh

Title: Co-evolutionary Signatures as a Novel Approach to Gene Discovery

Abstract: It is humbling for genetics researchers to acknowledge that even a decade after determining the DNA sequence of the human genome, we still do not understand the basic functional roles of most genes. This lack of knowledge severely hinders our ability to locate genes affecting important biological processes and those responsible for disease. One solution is to blindly screen all ~23,000 genes in the genome; however, only limited cases are scalable enough to do this. As an alternative, we propose to deploy our unique computational biology tools to prioritize the best candidate genes for any biological processes of interest. Our innovative approach is based on a principle of evolutionary biology stating that environmental forces influence or "select" how our genes change over time. Because such forces will similarly affect all genes carrying out a particular biological function, those genes will co-evolve over time, and this correlative signature can be detected in DNA sequences. The central advantage of our novel tools is that they allow us to measure and exploit this co-evolutionary signal and thereby identify functional links between genes. This has permitted us to reveal previously unknown genes as contributors to specific biological functions, and we have published several proof-of-principle articles describing these successes. In this proposal, we use co-evolutionary signatures to discover novel functional links between important cardiac muscle proteins and the genes that regulate them. These new regulatory genes will advance the fields of cardiac physiology and protein trafficking, and suggest new gene targets for therapy. In addition, our project will hone and validate our co-evolutionary tools while simultaneously making them publically available for all biological researchers through a webserver. The core datasets generated in this project will be valuable for prioritizing genetic work in many fields in basic biology, as well as in medical genetics.

Tzahi Cohen-Karni, Ph.D.
Assistant Professor, Department of Biomedical Engineering
Carnegie Mellon University

Title: Investigation of pancreatic islet electrical properties by a high density nanodevices array

Abstract: For centuries efforts have been invested in the exploration of the intricate way cells communicate. Basic research at the tissue level of the heart and brain electrical activity, for example, has led to the development of tools to treat various ailments, such as pacemaker and deep brain stimulation electrodes for the treatment of cardiac arrhythmias and Parkinson's disease respectively. Currently, there is a critical need to develop new ways to explore how cells communicate at the cellular level with exquisite details. The hair sized pancreatic islet (approximately 100□millionth of a meter), is a prime example of such communication. This proposal aims to investigate for the first time the electrical activity of a pancreatic islet using a novel nanomaterial-based sensor array with exquisite resolution. Studying the mechanism of cell-cell communication and understanding the electrical signal propagation within pancreatic islet will reveal the underlying processes leading to glucose level maintenance. The developed nanomaterials-based measurement platform will set the ground for further investigations related to disease abnormalities and will shed light on electrical transduction processes in additional biological systems, such as neuronal and cardiomyocytes communications.

David Pekker, Ph.D.
Assistant Professor, Department of Physics and Astronomy
University of Pittsburgh

Title: Protecting quantum information with disorder

Abstract: Equilibration and thermalization are fundamental ingredients in our description of physical, chemical and biological systems. These processes allow us to make descriptions base don statistical ensembles, in or close to equilibrium, thus resolving the paradox of the 'arrow of time.' In this proposal, we will address the question of how the 'arrow of time' can be broken in a generic interacting quantum many-particle systems with disorder.

A useful way to think about the arrow of time and thermalization has been offered by the field of quantum information theory: the irreversibility of the evolution is connected to the generation of entanglement between subparts of the system undergoing equilibrium. Until recently, it has been thought that interactions in generic quantum systems would always drive this type of entanglement growth, and hence lead to thermalization. In the recently discovered phase of matter – the many-body localized phase – this paradigm is broken down by the interplay of disorder and interactions.

The goals of the proposed research is the combine the tools of quantum information theory and of condensed matter physics to construct a detailed theory of many-body localized systems, their dynamics, and the quantum information contained within these systems. In the process, I hope to learn how to use disorder as a resource for attached the central questions of the two subject areas: condensed matter physics and quantum computation. For condensed matter physics: how to describe and control the dynamics of many-body quantum systems? For quantum computation: how to build qubits that do not become entangled with their environment, even at high temperatures?

Matt Youngman , Ph.D.
Assistant Professor, Department of Biology
Villanova University

Title: Analysis of the role of SMK-1 in the age-dependent regulation of the FOXO transcription factory DAF-16 in *Caenorhabditis elegans*

Abstract: Instead of resulting from wear-and-tear, the age-related changes in immunity may represent an orchestrated reshaping of host defense where some aspects are de-emphasized while others are preserved or bolstered. My studies of evolutionarily conserved innate immunity signaling pathways in the roundworm *Caenorhabditis elegans* suggest that this is true. I have found that while the activity of PMK-1 p38 MAP kinase declines during aging in worms, the activity of the FOXO transcription factor DAF-16 increases in an age-dependent manner and is required for normal resistance to infection in adults. I propose to examine the role of SMK-1, a known genetic interactor of DAF-16, in regulating the activity of DAF-16 during aging. I will test the hypothesis that SMK-1 physically interacts with DAF-16 and influences its target site selection in adult animals. Since FOXO3A, the mammalian orthologue of DAF-16, is essential for the survival of innate immune cells during inflammation and because polymorphisms in FOXO3A are associated with increased longevity in centenarians, I anticipate that my studies will have implications regarding human immunity and aging.

Gregory Lang, PhD.

Assistant Professor, Department of Biological Sciences
Lehigh University

Title: Epistatic Interactions and Constraints on Evolutionary Outcomes in Yeast Experimental Evolution

Abstract: In his 1989 book, *Wonderful Life*, Stephen Jay Gould proposed the following thought experiment. Rewind the "tape of life" and let evolution play out a second time. In doing so, does the replay produce anything like what we see today? In other words, is evolution reproducible, or do chance events (seemingly inconsequential at the time) cause evolutionary paths to diverge, producing wildly different outcomes? With advances in high-throughput biology, we can perform Gould's thought experiment in the laboratory by initiating hundreds—or thousands—of identical populations and observing the distribution of evolutionary outcomes. Such experiments demonstrate that replicate populations tend to find similar (but not identical) solutions to the same selective pressure. The degree to which evolutionary outcomes are reproducible depends critically on underlying parameters that are largely unknown, in particular, the distribution of fitness effects and epistatic interactions. The goal of this proposal is to combine high-throughput experimental evolution with the tools of quantitative genetics to measure quantitatively and comprehensively the distributions of these key parameters and to assess the relative roles of chance and determinism in governing evolutionary outcomes. These results will advance a fundamental understanding of how evolution chooses among a vast number of possible paths.

NEW INITIATIVE RESEARCH GRANTS

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Alison L. Barth, Ph.D. (PI)
Associate Professor, Department of Biological Sciences
Carnegie Mellon University

Marcel Bruchez, Ph.D. (co-PI)
Associate Professor, Biological Sciences and Chemistry
Associate Director, Molecular Biosensors and Imaging Center
Carnegie Mellon University

Title: Neural circuitry of the mammalian neocortex: which neurons are connected to each other, and how can these patterns of connectivity be altered by experience?

Abstract: Neurons in the cerebral cortex communicate with each other using highly specified, hierarchical rules of connectivity. There are more than 30 cell types in the neocortex, and these cell types can be differentiated by their developmental lineage, projection target, or expression of marker genes. Previous studies have attempted to reveal the logic of neural circuits by low-throughput anatomical or electrophysiological methods. Here we propose to develop and employ a novel protein complementation strategy to chemically tag synapses defined by pre- and post-synaptic cell identity. Cell contacts made between genetically specified pre- and post-synaptic neurons will enable assembly of a fluorescence-activating protein that triggers a 20,000-fold increase in fluorescence upon dye application. The outstanding signal-to-noise and spectral properties of the dye will enable quantitative and *in vivo* analysis of cell-type specific synapses in the mammalian neocortex. The long-term goal of this proposal is to develop chemical biology tools for a complete index of cell-type specific synaptic contacts in health and disease states.

Alexander Deiters, Ph.D. (PI)
Professor, Department of Chemistry
University of Pittsburgh

Michael Tsang, Ph.D. (co-PI)
Associate Professor, Department of Development Biology
University of Pittsburgh

Title: Expanding the Genetic Code of Zebrafish

Abstract: In nature, the basic building blocks for proteins are comprised of twenty common amino acids. All life on earth exists on the complexity of how these natural amino acids are assembled in proteins. The template for proteins is encoded in the genetic material (DNA and RNA) and every cell has the machinery to process this information to synthesize proteins. The possibility to expand the complexity of proteins though chemical synthesis of new (unnatural) amino acids with new properties shows significant promise in understanding and improving protein function. The challenge is to alter the machinery that translates the DNA into proteins such that unnatural amino acids can be incorporated into this process. This project will alter the genetic code of the zebrafish, an animal model favored by many researchers, to expand the number of amino acids it can use to build proteins. This will become the first vertebrate animal with an expanded genetic code of 21 amino acids and will be a major advance as it provides novel tools to explore and unravel the mysteries of how cells, tissues, and organs form in first few days of life. By initially focusing on light-activated amino acids, this research will enable precise optical control over protein function with unprecedented spatial and temporal resolution in zebrafish. Controlling protein function using a light switch will provide answers to fundamental biological questions about zebrafish developmental biology that has relevance to human embryogenesis.

Ayusman Sen, Ph.D. (PI)
Distinguished Professor, Department of Chemistry
Penn State University

Anna C. Balazs, Ph.D. (Co-PI)
Distinguished Professor, Department of Chemical & Petroleum Engineering
University of Pittsburgh

Title: Autonomous Interacting Microrobotic Systems

Abstract: The goal of the proposed research is to answer the challenge: Can we design self-powered synthetic materials that self-organize—based on signals from each other and from their environment—and thereby perform complex, coordinated tasks? The specific questions to be addressed are: (a) Can we design purely synthetic materials that autonomously process energy and information and, hence, begin to mimic salient biological behavior? (b) Can these materials effectively "network" to share information and perform cooperative, coordinated activities? These questions lie at the heart of critical issues in both the physical and biological sciences. We will focus on devising *chemically-powered* "motors" and "pumps". Motors are motile objects that transduce chemical energy into mechanical motion. When these motors are anchored onto a surface, they transfer their chemically-generated force to the surrounding fluid and, hence, function as fluidic pumps. By creating systems of autonomous motors and pumps that have the capacity to *transduce energy*, *move* and *communicate*, we will lay the foundations for fabricating self-powered, small-scale robotic systems that can perform *"collaborative"* work. The proposed research involves a *new* collaboration that utilizes knowledge of synthetic chemistry and catalysis (Ayusman Sen, Penn State), as well as fluid dynamics and computational modeling (Anna C. Balazs, Univ. Pittsburgh).

Alison Sweeney, Ph.D. (PI)
Assistant Professor, Department of Physics and Astronomy
University of Pennsylvania

Randall Kamien, Ph.D.
Professor, Department of Physics & Astronomy
University of Pennsylvania

Title: Living Photonic Devices: Self-assembly from Proteins as Patchy Colloids

Abstract: Molluscan animals such as squids, octopuses and clams build an array of living optical devices of astounding photonic sophistication, such as reflective camouflage, graded index lenses, solar radiance distributors, and wavelength-specific light guides. These structures self-assemble from still-enigmatic groups of proteins called "reflectins" or "S-crystallins". Several of our new observations about these systems show that the "patchy colloids" framework recently developed by soft matter physicists is the correct paradigm for explaining the evolutionary emergence and modern routes to self-assembly of these systems. The work proposed here, an unprecedented synthesis of evolution, biochemistry, photonics, and soft matter physics, will allow the field of self-assembly to cut to the chase, as it were, and learn evolution's rules for building complex architectures from colloidal materials without having to find them again through a more laborious and difficult-to-direct design process.