PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA FOUNDATION

2010 Annual Report





Supporting Innovative Science for 45 Years

CONTENTS

MISSION STATEMENT

The mission of the PhRMA Foundation is to support young scientists in disciplines important to the pharmaceutical industry by awarding them **COMPETITIVE RESEARCH FELLOWSHIPS AND GRANTS** at a critical decision point at the outset of their careers. The aim is to encourage young scientists who will be the **LEADERS OF TOMORROW** to pursue careers in research and education related to drug discovery.

The program will help to build a larger pool of **HIGHLY-TRAINED, TOP-QUALITY SCIENTISTS** to help meet the growing needs of scientific and academic institutions, government, and the research-intensive pharmaceutical industry.

The Foundation's program is of particular benefit to the pharmaceutical industry in serving its purpose of developing new **LIFE-SAVING, COST-EFFECTIVE MEDICINES** for patients all around the world.

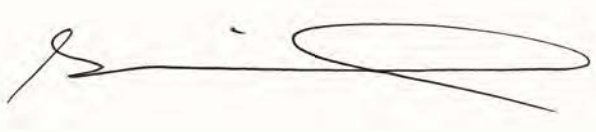
MESSAGE *from the* CHAIRMAN

Talented scientists can best innovate when they have the necessary resources and support. Scientists are curious by nature, fascinated by novel concepts and compelled to resolve problems that have eluded so many others. In the realm of drug discovery and development, these individuals drive the studies that yield new and improved medicines. At the PhRMA Foundation, we provide these innovators the support they need to start their work, and the result has been many long and successful careers.

Our commitment to pharmaceutical scientists, and consequently, better health care, is renewed each year as we develop and implement new initiatives, awards and programs. We measure our impact on the scientific community by consistently evaluating the progress we have made as an organization. In a recent survey of 500 of our former award recipients, we found that more than 88 percent are actively conducting research, and more than 40 percent have published a key concept that affected the pharmaceutical industry. Foundation-supported scientists are leading research and development at top pharmaceutical companies. They are esteemed educators who have trained and mentored nearly 20,000 graduate students—many of them now the researchers and executives of our member companies.

Over the course of 45 years, the Foundation's scientists have together had a major impact on the fields of pharmacology, pharmaceutics, toxicology, informatics and health outcomes. In this report, we will highlight several innovative research efforts. Three former award recipients have contributed to breakthroughs in the prevention, detection and control of cancer. Another is developing tools and treatments that could restrict the transmission of tuberculosis. The novel findings of these scientists are described in detail on pages 4, 5 and 6.

We are proud of this record that has been possible with your support. And we look forward to continuing our mission of seeding and encouraging the scientific curiosity that paves the way for innovation.



Garry A. Neil, M.D.

MESSAGE *from the* PRESIDENT

For 45 years, the PhRMA Foundation has been driven by its mission to start the careers and support the research of young pharmaceutical scientists. This mission defines and distinguishes our organization—it is the cornerstone of every goal that we set out to achieve. We have some clear advantages in fulfilling our strategic goals and succeeding as an organization. We have proven ability to create and cultivate the necessary programs. We have a distinguished reputation as a staunch supporter of education and scientific innovation. Our organization is widely seen as one among the well-respected in the pharmaceutical industry, operating by a code of conduct under principles of integrity, dedication and diligence.

These advantages give us great leverage and have positioned the Foundation to embark on initiatives that will foster public-private partnerships with key outside organizations and help create new education and training programs to fortify the nation's resources in critical areas. The first initiative addresses a critical need for training in the field of comparative effectiveness research (CER). Comparative effectiveness will be an increasingly central component of patient care, but trained personnel are not yet in place in numbers sufficient to meet the expected demand. We intend to help make CER a core subject in medical schools across the country. In 2009, the Foundation convened a panel of 17 specialists from academia, industry and government to develop the framework for a CER training curriculum. The panel's recommendations included training programs for both researchers and decision makers, developed in part by pharmacoepidemiologists well-versed in the essential elements of CER. To promote this training, the Foundation established a new award for schools that integrate CER programs into their core curriculum. We have also partnered with the Agency for Healthcare Research and Quality to develop and promote CER competencies.

A second such initiative involves building enhanced training programs for safe and effective prescribing. Truly safe prescribing requires more than an understanding of best practices. A prescribing physician must possess a keen ability to adapt and respond to constant changes in therapeutics. Our initiative will develop educational modules on pharmacogenomics, medical error prevention and geriatric prescribing, among other topics. In partnership with the Association of American Medical Colleges and the American Society for Clinical Pharmacology and Therapeutics, these modules will be developed by the Foundation's former award recipients—recognized experts in safe and rational prescribing. Our relationships with medical school instructors and administrators throughout the country will propel this initiative forward.

Also, we will focus on building our relationship with the Food and Drug Administration. The PhRMA Foundation has provided crucial bridge funding to the Reagan-Udall Foundation, which will obtain the tools and resources necessary to pursue its long-term agenda in important areas.

As the Foundation embarks on these and other new initiatives, I send my most grateful thanks to our benefactors, who enable our core mission and make these new initiatives possible. I am confident that with full support from all of our member companies, the PhRMA Foundation will succeed in all our efforts to help build the nation's legion of supremely bright and dedicated scientists for generations to come.

Del Persinger

AWARDS *in* EXCELLENCE

The annual PhRMA Foundation Awards in Excellence honor past award recipients who have distinguished themselves through scientific and/or academic achievement. When deciding on a specialty area at the outset of their careers, these scientists received Foundation grants in disciplines important to the research-based pharmaceutical industry. The awardees are dramatic proof that Foundation programs have a critical role in the career development of young researchers and make a substantial difference in their ability to succeed.

The 2010 Award in Excellence recipients exemplify the very best in their fields of clinical pharmacology and pharmacology/toxicology. Having supported these scientists at the beginning of their careers, the PhRMA Foundation is especially proud of their achievements. Their success typifies the outstanding accomplishments of all our award recipients and underscores the importance of continuing to provide support to those who follow in their footsteps.

2010 Award in Excellence in Pharmacology/Toxicology

Roger A. Nicoll, MD
1976 Research Starter Grant in Pharmacology/Toxicology

Roger Nicoll, MD, is a professor of Cellular and Molecular Pharmacology and Physiology at the University of California, San Francisco (UCSF). Now a widely accomplished scientist, scholar and mentor to young neurophysiologists, Dr. Nicoll received a PhRMA Foundation grant at a time when the support was crucial to his career development. At the heart of his research is an exploration of brain function—how brain neurons communicate and regulate learning and memory. His studies have been called scientific breakthroughs in the understanding of brain capability at molecular and cellular levels.

In 1963, Dr. Nicoll graduated from Lawrence University in Appleton, Wisconsin, with a BA in Biology and Chemistry. Three years later, he completed a research fellowship at the National Institute of Mental Health's Laboratory of Neuropharmacology. He received his MD in 1968, graduating with honors from the University of Rochester School of Medicine.

Dr. Nicoll continued his research of the nervous system, illuminating the complexity of neural signaling through electrophysiological experimentation. He spent two years alongside Nobel Laureate Sir John Eccles in the Laboratory of Neurobiology at the State University of New York.

In 1980, Dr. Nicoll joined the Department of Cellular and Molecular Pharmacology at UCSF, where he has been a professor for more than 30 years and served as interim chairman for a one-year appointment.

Dr. Roger Nicoll of the University of California, San Francisco, was selected to receive the 2010 Award in Excellence in Pharmacology/Toxicology. Dr. Nicoll was awarded a Research Starter Grant in Pharmacology/Toxicology in 1976.

Through extensive research of chemical and biological events, the Department of Cellular and Molecular Pharmacology aims to share innovative ideas and information with the next generation of neuroscientists. Studies explore interactions of drugs with receptors, synaptic transmission and cell movement, and analyze the resulting biological impact.

Dr. Nicoll's achievements have been recognized with numerous awards and honors, most recently the J. Allyn Taylor International Prize in Medicine. He received the Luigi Galvani Award in 1993, the Perl/UNC Neuroscience Award in 2005 and the Gruber Award for Excellence in Neuroscience in 2006. Throughout his career, he has also received several awards from the National Institutes of Health for professional development, merit and research excellence. Dr. Nicoll was elected to the National Academy of Sciences in 1994 and the American Academy of Arts and Sciences in 1999. That same year, he was named the Morris Herzstein endowed Chair in Cellular and Molecular Pharmacology. In 2009, he was elected to the Institute of Medicine.

Dr. Nicoll has been widely published, contributing as a

lead or supporting author to more than 300 original articles, reviews and meeting symposia. His research has appeared numerous times in *Nature*, *Science*, the *Journal of Neurophysiology* and *The Journal of Physiology*. He has been an editorial board member for journals such as *Neuron*, *Physiological Reviews* and *Hippocampus*, and has remained on the *Cellular and Molecular Neurobiology* Editorial Board since 1996.

Dr. Nicoll is also a member of eight professional societies, including the American Association for the Advancement of Science, the American Society for Pharmacology and Experimental Therapeutics and the International Brain Research Organization, where he served on the Governing Council.

2010 Award in Excellence in Clinical Pharmacology

Raymond L. Woosley, MD, PhD
1977 Faculty Development Award
1988 Clinical Pharmacology Unit Support Award

Raymond Woosley, MD, PhD, is the founding President and CEO of the Critical Path Institute (C-Path). Prior to this position, Dr. Woosley was Vice President of Health Sciences at the University of Arizona (UA).

C-Path is a non-profit partnership between the UA, SRI International (formerly Stanford Research Institute) and the U.S. Food and Drug Administration. Its goal is to accelerate the development of safe medical treatments by promoting collaboration among industry, academic and government scientists. Dr. Woosley is a well-known medical administrator, scholar and researcher, with extensive expertise in the safe use of medication.

Dr. Woosley earned his BA from Western Kentucky University, his PhD in pharmacology from the University of Louisville and his MD from the University of Miami. In 1968, he was hired as the first scientist at Meyer Laboratories (now GlaxoSmithKline). He completed his residency and internship in internal medicine and a fellowship in clinical pharmacology at Vanderbilt University in Nashville, Tennessee.

As Professor of Medicine and Pharmacology at Vanderbilt University Medical School, Dr. Woosley provided evidence about the importance of cytochrome P450 2D6 in relation to antiarrhythmic drugs. He also chaired the Data Safety Monitoring Committee for the renowned Cardiac Arrhythmia Suppression Trial, which showed that antiarrhythmic drugs are deleterious in the treatment of ventricular arrhythmias following myocardial infarction.

At the 2010 Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics (ASCPT) in Atlanta, Georgia, ***Darrell R. Abernethy, M.D., Ph.D.****, chairman of the PhRMA Foundation Clinical Pharmacology Advisory Committee presented* ***Raymond L. Woosley, M.D., Ph.D.*** *with the 2010 Award in Excellence in Clinical Pharmacology.*

Before joining the University of Arizona faculty, Dr. Woosley was Associate Dean of Clinical Research at Georgetown University and served as chair of the Department of Pharmacology from 1988 to 2000. During his tenure, the department became one of the highest ranked pharmacology departments for research funding and achieved the largest endowment of any pharmacology department in the nation.

While at Georgetown, Dr. Woosley contributed substantially to the awareness that noncardiovascular drugs can

have cardiovascular effects, findings that led to the withdrawal of terfenadine (Seldane) and several other drugs from the market. He championed the development of the Centers for Education and Research on Therapeutics (CERTS), which eventually became a government-funded entity.

Among his many honors and awards, Dr. Woosley received the Harry Gold Award in Therapeutics from the American Society for Pharmacology and Experimental Therapeutics and was the Sir Henry Hallet Dale Visiting Professor in Clinical Pharmacology at Johns Hopkins University School of Medicine. He was a recipient of the FDA Commissioner's Special Citation for his efforts to warn Congress and the public of the dangers associated with dietary supplements containing ephedrine. His colleagues have often nominated him for inclusion in the *Best Doctors in America*.

Dr. Woosley is a member of numerous advisory committees for the NIH and the Department of Veterans Affairs, and serves on the WebMD Editorial Advisory Board and Board of the Society for Women's Health Research. He has been an editorial board member for several medical and pharmacology journals.

SCIENCE, AMBITION AND INNOVATION
the health care trifecta

In the field of drug discovery and development, scientists are breaking the barriers to innovation, creating new opportunities and hope for those stricken with disease.

The PhRMA Foundation has helped bridge the funding gap needed to advance innovation in science and stimulate the development of new drugs, devices and diagnostics. As the first open door in a highly competitive profession, this support proffers a level of confidence to young scientists, lending the authority and recognition needed for continued funding. Without it, vital research may be delayed or halted completely.

The Foundation's award recipients have made extraordinary contributions to the growing fields of pharmaceutics, informatics, health outcomes and clinical pharmacology. The goal of many of these specialists—to end disease—is the ultimate challenge for the medical community. Certainly, every scientist hopes to see the eradication of illness in his or her lifetime, but for patients diagnosed with diseases that are now manageable and treatable, the value of incremental medical developments cannot be overstated.

This report highlights the novel research of five Foundation award recipients, a small sample of the remarkable scientists supported by the Foundation at influential points in their careers.

Hilary Coller, PhD
Assistant Professor, Department of Molecular Biology, Princeton University
Research Starter Grant in Informatics, 2007

The progressive stages of cancer are often characterized by metastasis, the spread of diseased cells from one part of the body to another. Hillary Coller, an Assistant Professor of Molecular Biology at Princeton University, has explored what seemed to be the antithesis of metastatic cancer cells—quiescent, or non-dividing cells.

Dr. Coller studies fibroblasts, connective-tissue cells essential to the body's immune response. Fibroblasts have been associated with cancer cells at all stages of disease progression, and in the Coller Lab, they represent an important target for chemotherapeutics. The research team is applying its knowledge of quiescent fibroblasts to the broader context of cell cycle control, the lack of which can result in rapid tumor growth.

To maintain good health, cells perform certain functions. While uncontrolled cell production can lead to the spread of tumors, there are times when dormant cells must be able to divide—for example, to repair damaged tissue.

Quiescence has traditionally been viewed as a quiet or inactive state, where cells consume little and refrain from producing the proteins that replenish damaged cells. On the contrary, Dr. Coller found that quiescent fibroblasts exhibit rather lively behavior, consistently processing nutrients and producing proteins.


Hilary Coller, PhD

She discovered that quiescent fibroblasts utilize the pentose phosphate pathway, a conduit by which glucose is metabolized or transformed. Hindering this pathway leads to cell self-destruction, which could represent a way to eliminate dormant cancer cells. Her studies suggest that quiescent cells may adopt a number of strategies to survive during non-proliferative times.

"Our efforts to define the pathways invoked by quiescent cells for viability [could] provide insights into the strategies used by quiescent tumor cells for survival," said Dr. Coller. "My hope is that we will be able to take advantage of our findings to target both the proliferating and quiescent cells within a tumor, and thereby achieve a more complete eradication of the disease."

Carrie House, PhD Candidate
Molecular Medicine,
The George Washington University Medical Center
Pre-Doctoral Fellowship in Pharmacology/Toxicology, 2009


Carrie House

Carrie House, a PhD candidate at The George Washington University Institute for Biomedical Sciences, is also examining diseased cell behavior. She has studied the correlation between ion channels and cancer, a link that may be significant in tumor development.

"One of the defining features of malignancy is the ability of cancer cells in the primary tumor site to migrate and metastasize to other parts of the body," said Carrie. "In order to do this, malignant cells must be able to degrade and invade the basement membrane and enter the bloodstream or lymph system. Invasion is therefore essential for metastatic progression and much interest lies in finding drug targets that can prevent this process, which is the major cause of death in patients with cancer."

Ion channels are proteins that exist in the membranes of living cells. They generate signals of the nervous system, aid in blood vessel regulation and as studies suggest, may be involved in cancer growth.

Carrie's research focuses on voltage-gated sodium channels, which could be targets for new lung, prostate, breast and colon cancer drugs. Analyzing colon cancer cells, her team linked high sodium channel expression with increased metastasis. They treated the cell samples with Lidocaine, a sodium channel blocker and local anesthetic. While the drug reduced cellular invasion, it did not affect proliferation, an important distinction that sheds light on the channel's function in metastatic progression.

With additional testing, Lidocaine and other local anesthetics could prove to be effective cancer drugs. "These findings are important, as sodium channels are not typically expressed in normal colon epithelial cells," said Carrie. "The channels become abnormally expressed in colon cancer cells, and they actively participate in malignant progression."

The study also illuminates a novel pathway by which channel activation effects changes in gene expression, Carrie explained. "We showed that SCN5A, the gene that encodes Nav1.5, controls the expression of several genes important for invasion potential. There have been no studies analyzing channel expression or activity and how each relates to gene expression changes in cancer."

By recognizing new genes that regulate invasion, Carrie and her team have highlighted possible new targets for cancer therapy.

Anthony J. Hickey, PhD, DSc
Professor, Division of Molecular Pharmaceutics,
University of North Carolina Eshelman School of Pharmacy
Research Starter Grant, 1989


Anthony J. Hickey, PhD, DSc

In his quest to improve respiratory care, Anthony Hickey has focused on the quality and efficacy of tuberculosis treatments.

According to the World Health Organization, one-third of the world's population is infected with the microbe that causes tuberculosis, and one in every ten people will develop the disease. New drugs and delivery systems such as aerosols may disperse larger doses of medicine to the lungs, providing more effective and shorter therapy. Theoretically, these treatments could prevent the disease from spreading.

In partnership with Dr. David Edwards, a biomedical engineering professor at Harvard University, Dr. Hickey developed a dry powder form of the tuberculosis antibiotic capreomycin. His research has led to clinical trials for a dry-powder inhaler and the creation of Oriel Therapeutics, a company that produces essential respiratory drug products. Furthermore, Dr. Hickey's methodologies reflect the principles of Quality by Design, the FDA's view that extensive product and manufacturing knowledge will ensure high-quality and consistent output.

Evan D. Kharasch, MD, PhD
Russell D. and Mary B. Shelden Professor of Anesthesiology, Washington University School of Medicine in St. Louis
Medical Student Research Fellowship, 1979;
Faculty Award in Clinical Pharmacology, 1993


Evan D. Kharasch, MD, PhD

Each year in the US, 50,000 people are diagnosed with kidney cancer. As the sixth leading cause of cancer death, renal cancer has an alarmingly high mortality rate. But in its early stages, the disease is curable in more than 70 percent of patients.

While there is no diagnostic test for kidney cancer, Washington University Professor Evan Kharasch believes that early detection is absolutely critical for survival. His studies have identified clear indicators of common kidney cancers.

Based on evidence that certain proteins are over-expressed in renal tumor tissue, Dr. Kharasch predicted high concentrations of these proteins in the urine of kidney cancer patients. Along with anesthesiology professor Dr. Jeremiah Morrissey, Dr. Kharasch searched for proteins in urine samples of renal cancer patients undergoing tumor removal. They compared the samples with those from healthy and non-nephrectomy volunteers, discovering elevated levels of two proteins, aquaporin-1 (AQP1) and adipophilin (ADFP). When the tumors were surgically removed, AQP1 and ADFP levels dropped significantly.

"If kidney cancers have grown so large that patients present with blood in the urine, abdominal pain or an abdominal mass, the cancer has already metastasized in 30 to 40 percent of these patients," said Dr. Kharasch. "The real need is for a screening test that can detect kidney cancer very early. A simple urine test, which can be performed annually as part of a routine physical exam, could detect kidney cancers at an earlier, more treatable stage."

Matthew M. Murawski, RPh, PhD
Associate Professor of Pharmacy Administration, Purdue University
Faculty Development Award in Pharmacoeconomics, 1997


Matthew M. Murawski, RPh, PhD

Matthew Murawski has spent years examining the relationship between pharmacists and patients. As the landscape of pharmacies has shifted from local, neighborhood operations to large national corporations, this rapport has changed considerably.

Dr. Murawski realized the time pharmacists spend with patients must be maximized to uncover potential medical risks. He believed pharmacists could better advise patients within a limited time frame if they were well prepared for the discussion.

Along with Associate Professor Brian Shepler and Drs. Mary Kiersma, Aleda Chen and Kristin Villa, Dr. Murawski focused on the primary concerns of the pharmacist—adverse drug events (ADEs) and reactions (ADRs). The team developed a system that organized drugs according to ADEs and ADRs linked to their use.

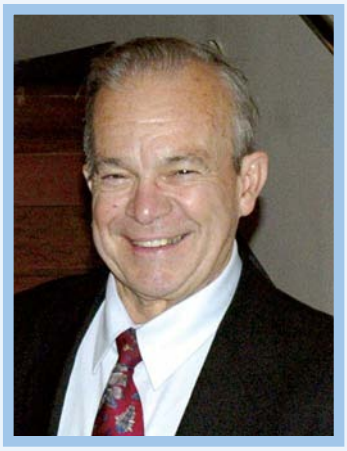
"This immensely innovative way of organizing medication knowledge has allowed us to develop a comprehensive series of short checklists for the top 200 drugs sold in the United States," said Dr. Murawski.

The checklists, easily and quickly completed by patients, are capable of determining up to 87 percent of known potential dangers associated with a range of medications. According to Dr. Murawski, this classification system could eventually cover the entire pharmacopeia.

"Over time, with experience and the accumulation of real information on the effectiveness of drugs in real world circumstances, we hope that use of this system may lead to lower costs, a better match between patient and treatment and, ultimately, better outcomes."

At the confluence of science, technology and innovation are the researchers whose remarkable findings have improved the health and welfare of people throughout the world. In the war against disease, scientists are undeniably the best defense. And innovation is a powerful and promising tool.

In Memoriam
George C. Fuller, PhD
1937 – 2010



On September 23, 2010, the PhRMA Foundation lost George C. Fuller, a dedicated advisor, committee member, chairman and friend.

Dr. Fuller was Professor Emeritus and former Dean of the College of Pharmacy and Allied Health Professions at Wayne State University (WSU). A longtime member on the advisory boards of the PhRMA Foundation and University of Rhode Island, he provided exceptional leadership and service.

Born in Detroit, Michigan, Dr. Fuller earned his BS in pharmacy in 1959 and his MS in 1963, both from WSU. In 1966, he graduated from Purdue University with a PhD in pharmacology. He taught pharmacology at the University of Rhode Island for 14 years, during which time he also held the rank of lecturer in the Department of Medicine at Brown University. In 1980, he joined G.D. Searle & Company as Director of Pharmacology in the Molecular and Cell Biology Research Department.

During his tenure as Dean of WSU, Dr. Fuller's vision and commitment led to the creation of a new pharmacy and health science building, which opened in 2002. In 2011, the university's Board of Governors honored his contributions by establishing the George Fuller Endowed Scholarship. He received Distinguished Alumni Awards from WSU and Purdue University.

Dr. Fuller had a genuine interest in the next generation of scientists and was a teacher and mentor to students of pharmacy, medicine, dental hygiene and nursing. His guidance was invaluable to many young pharmacologists, which made him a core contributor to foundation-sponsored science. He also pursued his own research interests, studying pharmacologic management of inflammation and disease-induced alterations in collagen metabolism. He held two US and corresponding foreign patents.

In July 1989, Dr. Fuller became a member of the Basic Pharmacology Advisory Committee for the PhRMA Foundation. He assumed the position of Chair in 2001 and was active in this role for nearly ten years. The Foundation relied on his leadership while evaluating grant and fellowship applications, program services and new initiatives.

Dr. Fuller was a notable authority in the field of pharmacology, having published 85 original scientific articles and book chapters. He was a member of many professional medical organizations, including the American Society for Pharmacology and Experimental Therapeutics, the New York Academy of Science and the Rho Chi Society, an academic honor society in pharmacy. He was a reviewer for the National Institutes of Health and the Environmental Protection Agency and served on the editorial boards of several scholarly journals.

Dr. Fuller enjoyed playing bridge, reading and sailing. He was devoted to his family, including Margery, his wife of 51 years, his three children and grandchildren.

For more than 21 years, George Fuller was an integral part of the PhRMA Foundation. His leadership, insight and altruism will not be forgotten. As stated by Dr. Jim Swarbrick, "He was a good friend, good colleague and a good scientist, gone before his time." Dr. Fuller will truly be missed.

FELLOWSHIPS *and* GRANTS

INFORMATICS

Pre Doctoral Fellowship in Informatics

The PhRMA Foundation Pre Doctoral programs aim at supporting promising students during their thesis research by providing assistance in the form of stipend and funds to cover costs incidental to the training. This fellowship program provides a stipend of $20,000 annually for up to two years. Up to $500 a year of the funding may be used for incidentals directly associated with the preparation of the dissertation.

The goal of this fellowship is to increase the number of well-trained investigators in pharmaceutical research that incorporates Informatics.

2010 Pre Doctoral Fellowships in Informatics

Alan Barber II
University of California at San Francisco

"Predicting in vivo *cleavage targets of executioner caspases using orthogonal data sets"*

Alan Barber II

Phosporylation and proteolytic cleavage are enzymatic reactions that drive cellular proliferation and programmed cell death (apoptosis). Both of these reactions require molecular recognition between a functional enzyme and small linear motifs in a protein target. Thus, discovery of functional small linear motifs in protein targets provides a strategy to describe the cellular pathways that underlie the progression of cancer and many autoimmune diseases. While recent advances have increased the ability to discover these motifs in protein sequences, it remains difficult to accurately predict such function or translate those predictions into useful knowledge for experimental researchers. One reason is that general methods developed to predict cellular function using computationally predicted motifs have demonstrated daunting false positive rates. It is possible that these general computational models will be unable to overcome signal-to-noise issues because of the uniqueness of each functional system in the cell. Our strategy is to develop specific computational models that use global and local sequence protein characteristics as well as evolutionary information to accurately predict cellular function of small linear motifs in specific *in vivo* systems. To test this strategy on a single model protease system, models are being developed for *in vivo* target recognition of executioner caspases. Activation of executioner caspases is a requirement for cellular commitment into apoptosis and dysregulation of this process is a common feature in cancers. Prospective predictions will be computed and validated experimentally by collaborators. Successful implementation of these models will provide increased understanding of the apoptotic cascade, a new set of potential chemotherapeutic targets for cancer researchers and methods for developing more predictive models for other important cellular processes.

Jamie Duke
Yale University

"Computational Modeling of Genome-Wide Targeting of Somatic Hypermutation"

Jamie Duke

B cells bind foreign antigens through their Immunoglobulin (Ig) receptor, and provide protection from infections by producing antibodies. During the course of an immune response, B cell Ig receptors that initially bind pathogens with low affinity are modified through somatic hypermutation to produce high-affinity memory and plasma cells. The process of somatic hypermutation is initiated by the enzyme activation induced cytidine deaminase (AID)

and involves the action of error-prone DNA-repair machinery resulting in "random" point mutations introduced directly into the DNA of Ig genes. While somatic hypermutation can help create more effective antibodies, it may also cause harm if the wrong genes are mutated. The project has recently shown that AID acts on a surprisingly large number of genes. A major goal of this project is to understand why some genes are targeted for somatic hypermutation, while others are protected. Computational modeling will be used to link the mutational risk of individual genes with cis-elements and DNA structural features. This model will allow a genome-wide screen to be performed which will predict strongly and weakly targeted genes for experimental validation. A second aspect of this project will focus on whether (and how) genes that are targeted by somatic hypermutation have evolved mechanisms to shield themselves against the deleterious effects of AID activity. A specific focus will be placed on the effects seen within proto-oncogenes and tumor suppressors as mutations in these genes have a high potential to cause serious damage.

Jason Rizzo
State University of New York at Buffalo

"Modeling Nucleosome Inhibition of Transcription Factor Binding"

Jason Rizzo

Human genetic information is encoded in DNA sequences and packaged precisely by molecules known as nucleosomes. Nucleosomes inhibit key intracellular interactions that regulate how our genetic information is read, including transcription factor (TF) binding to DNA. At present, aberrations in the way nucleosomes inhibit TF-DNA binding have been implicated in diseases including cancer and viral pathogenesis. In theory, the sterics of nucleosome-DNA interactions could inhibit TF binding to all nucleosome-bound DNA. In reality, however, nucleosome inhibition of TF binding is variable both across a genome and even within a single nucleosome, depending on the context and characteristics of a given TF binding site. Site-specific studies have shown that variables such as nucleosome stability, TF binding site affinity, and TF binding site location can influence protein binding patterns, however, no study has examined the genome-wide contributions of any variable nor their interactions *in vivo*. The objective of this research proposal is to dissect the principles governing nucleosome inhibition of TF binding and to incorporate these findings into the current paradigm for gene regulation. We will evaluate how variables such as TF binding site affinity, TF binding site location, and nucleosome occupancy function individually, cooperatively, and/or competitively to govern TF targeting *in vivo* by using an experimental system that provides for control and consideration of each variable. Briefly, our experimental system allows for the experimental depletion of nucleosomes throughout the model eukaryotic genome of *Saccharomyces cerevisea* (yeast). Genome-wide nucleosome depletion and corresponding TF binding events induced by depletion will be mapped using next generation DNA sequencing technology. Identified TF binding events and locations will provide a dataset to test the genomic variables suggested to regulate the relationship between nucleosome occupancy and TF binding. Findings from this proposal will be directly applicable to emerging epigenetic and genomic alterations implicated in human disease.

Peter Skewes-Cox, Jr.
University of California at San Francisco

"An integrative approach to more sensitive and specific detection of viral sequences within metagenomic data"

This research focuses on the discovery of novel viruses and their role in causing human disease. The project focus has been on improving the computational methods for how researchers go about detecting viruses researchers have never seen before. Traditionally, the detection of viruses was greatly dependent on the ability to grow them in culture in the laboratory, which enabled researchers to produce massive amounts of virus for their subsequent investigation. This works quite well assuming the virus is actually able to be cultured in the laboratory. But for many viruses, there is no known set of culturing conditions that will enable expansion of the viral population, so many viral discovery efforts have begun to take a metagenomics approach. Rather than growing a lot of virus to study its genome, metagenomics approaches study the virus in its natural state, i.e. within the context of *all* of the genetic material derived from host and other natural flora. This metagenomic approach entails performing large scale sequencing runs, which determine the sequence of nucleotides (A, C, G, or T) for every piece of genetic material in a sample. For organisms that have already had their genome sequences determined, matching the sequences in the sample to their genome is a somewhat

trivial task. But for viral sequences, which may mutate greatly to the point where they don't look much like any known relatives, it can be much more difficult to identify them as of viral origin. The project focuses primarily on using special probabilistic models called profile-HMMs to both better detect more mutated viruses, as well as to better distinguish viral sequences from human or bacterial sequences that may be similar to known viruses.

Yat Tang
Washington University in St. Louis, School of Medicine

"Identification and Characterization of Drug-Like Compounds Targeting Two-Component Signal Transduction Regulatory Systems to Inhibit Bacterial Virulence"

Infectious diseases have evolved resistance to most antibiotics in clinical use. Antibiotics currently used in clinical practice either inhibit bacterial growth or kill the bacteria. One promising strategy is to combat virulence without inhibiting growth, so less selective pressure will be presented to bacteria for the generation of resistance. Two-component signal transduction (TCST) regulatory systems are the most prevalent signaling modules used by bacteria to sense and respond to environmental changes in order to survive and proliferate under various conditions. TCSTs consist of a transmembrane histidine-kinase sensor and a response regulator with conserved structural and biochemical properties, allowing it to adapt to various modes of intracellular signaling. These conserved signaling systems couple environmental stimuli to an adaptive response, participating in fundamental processes such as regulating metabolism, and also more specialized ones such as controlling virulence in the pathogen's host. The PhoP/PhoQ system senses and responds to extracellular Mg^{2+} levels by controlling the transcription level of key virulence genes in *Salmonella typhimurium*, in addition to a number of other pathogens. In the signaling cascade, the PhoQ histidine kinase detects an extracellular signal, in this case, Mg^{2+} levels. Under low Mg^{2+} conditions, PhoQ autophosphorylates a histidine residue. PhoQ then interacts with PhoP, the response regulator, by transferring the high-energy phosphate group from the conserved histidine to a conserved aspartate on PhoP. Phosphorylation of PhoP induces a conformational change and mediates homodimerization and activation of the homodimer transcription factor, allowing recognition and binding to its DNA promoter to regulate gene expression. Currently, no known inhibitors of TCST response regulators have been identified, and only recently, have targeting signaling systems shown effective as a means to combat bacterial virulence. The hypothesis is that drug-like compounds targeting the PhoP response regulator will selectively disrupt its function as a transcription factor and inhibit transcription of key virulence genes in humans during infection. The PhoP/PhoQ system will be investigated as a prototype for targeting TCST response regulators to inhibit bacterial virulence. This study uses a hybrid approach coupling computational and experimental methods to search for drug-like compounds that can inhibit the function of the PhoP TCST response regulator. Virtual screening combined with consensus scoring will be employed to prioritize compounds for screening. Electrophoretic mobility shift assays and fluorescence anisotropy assays will test the predictability of the computational method. This study will serve as a proof-of-principle for targeting the TCST response regulator to inhibit its function as a transcription factor and modulate expression of key genes responsible for virulence.

At the 2010 Annual Meeting of The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) in Atlanta, Georgia, the PhRMA Foundation presented their Health Outcomes awards. Pictured from left are Julia Slejko, University of Colorado Denver; Eileen Cannon of the PhRMA Foundation, and Elizabeth Gorevski, Ph.D., University of Cincinnati.

Post Doctoral Fellowship in Informatics

The PhRMA Foundation Post Doctoral program in Informatics provides stipend support for individuals engaged in a multidisciplinary research training program that will create or extend their credentials in informatics.

The intent of this program is to support post doctoral career development activities of individuals preparing to engage in research that will bridge the gap between experimental and computational approaches in genomic and biochemical studies. It is anticipated that this research training will be accomplished in academic and/or industrial laboratory settings where multidisciplinary teams are organized to address problems which span the range of biological complexity rather than focus on the application of single technologies.

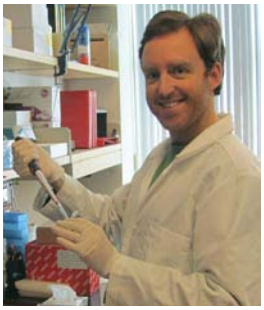
The post doctoral award consists of a $40,000 annual stipend for up to two years. The second year of this award is contingent upon a progress report approved by the Foundation and submission of a financial report. The award is intended solely as a stipend and may not be used otherwise.

2010 Post Doctoral Fellowship in Informatics

Charles Danko, Ph.D
Cornell University

"Exploring the Direct Estrogen-Regulated Transcriptome using a Multidisciplinary Approach"

Breast cancer is the most deadly cancer in women, leading to worldwide mortality rates in excess of 350,000 each year. Estrogen receptor alpha (ERα) is a protein that plays a pivotal role during the early stages of breast tumor growth. ERα activates hundreds of genes in response to its ligand estrogen. Genes that are regulated by estrogen can be classified into two categories: (1) ERα direct targets, which are regulated by the binding of ERα to target sites in the genome; and (2) These primary targets encode transcription factors and noncoding RNA transcripts that are responsible for secondary changes in gene expression. Previous studies do not have the temporal resolution to successfully distinguish between these two categories of estrogen regulated genes. This research project will be using a multidisciplinary approach to distinguish between direct and indirect estrogen target genes. This is accomplished by using a novel molecular technique called GRO-seq in conjunction with state of the art bioinformatic approaches to identify genes that change following very short estrogen treatments (direct targets), as well as longer treatments (indirect targets). Successful completion of these goals will provide a novel set of diagnostic and therapeutic targets useful in the fight against breast cancer.



Charles Danko, Ph.D

Research Starter Grant in Informatics

The purpose of the PhRMA Foundation Research Starter Grant is to offer financial support to individuals beginning their independent research careers at the faculty level.

The program provides a research grant of $60,000 for one year. This program supports individuals beginning independent research careers in academia who do not have other substantial sources of funding. The program is not offered as a means to augment an ongoing research effort.

2010 Research Starter Grants in Informatics

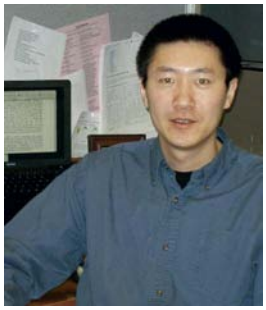
Jun Song, Ph.D
University of California, San Francisco

"Discovering Regulatory Elements Governing the Transcription and Biogenesis of microRNAs"

MicroRNAs are short (~22-nucleotide) non-protein-coding RNAs which form a subunit of the enzyme complex that inhibits the translation of complementary messenger-RNAs into proteins. MicroRNAs play important roles in timing developmental cues and in maintaining the balance of gene expression in changing environments. Deregulation of microRNA activities has been implicated in maladies such as cancer, diabetes, and heart disease. The proposed project aims to study the regulation of microRNA transcription and processing by combining computational and high-throughput experimental methods. In particular, there will be a focus on key transcription factors functioning in the melanocyte lineage and how they regulate tissue-specific microRNAs that are necessary for normal development as well as pathogenesis. The project will use next-generation DNA sequencing to discover novel regulatory sites in human melanocyte and analyze how specific transcription factors are recruited to such regions. Methods will be developed for studying the post-transcriptional processing and evolution of microRNAs. The results of this research may help reveal how oncogenic transcription factors can lead to the aberrant regulation of microRNAs in melanoma.

Kai Tan, Ph.D.
University of Iowa

"Identify Transcriptional Enhancers by Chromatin Signatures"



Kai Tan, Ph.D

Activation of gene expression involves the coordination of a multitude of transcription factors and cofactors on regulatory DNA sequences such as transcriptional enhancers. Therefore, identification of these regulatory DNA elements is of utmost importance for understanding gene regulation in both healthy and diseased cells. Inside the cell, DNA is tightly packaged in the form of chromatin consisting of DNA and histone proteins. Recent studies have demonstrated many characteristic histone modifications occur at enhancers, which in turn play an important regulatory role in the establishment of gene expression programs. In recent years, an enormous amount of genome-wide chromatin modification data has been generated using high throughput assays such as chromatin immunoprecipitation coupled with microarray chip. Currently, there is a pressing need for analytical methods to make sense of these genome-wide histone modification data. The goal of the proposed research is to develop a novel computational method to identify transcriptional enhancers on the basis of their epigenetic characteristics. First, the project will design and test a set of statistical features that enable better representation of histone modification data. Second, the project will design and evaluate the performance of several statistical classifiers in predicting enhancers. Finally, it will apply the computational method to predict novel enhancers in two biomedically important cell types, embryonic stem cell and T cell. Both computational and experimental approaches will be used to evaluate the accuracy of the project predictions.

HEALTH OUTCOMES

Pre Doctoral Fellowship in Health Outcomes

The goal of this program is to increase the number of well-trained investigators in Health Outcomes research. This program is designed to encourage and support promising students during their thesis research and is aimed at those candidates who are within two years of completing their research for doctoral dissertations in Health Outcomes.

The fellowship program provides a stipend of $25,000 annually for up to two years. Up to $500 a year of the funding may be used for incidentals directly associated with the preparation of the dissertation.

2010 Pre Doctoral Fellowship in Health Outcomes

Mindy Cheng
University of Washington

"Oncology orphan drugs: An evidence assessment and cost-utility analysis"

Orphan drugs are difficult to study in clinical trials due to disease rarity. Smaller patient populations and limited knowledge about rare diseases constrain the design, conduct, analysis, and interpretation of orphan drug studies. Although the methodological challenges associated with studies of smaller sample sizes have been established, it remains unclear how these challenges impact the quality and quantity of clinical and economic evidence for marketed orphan drugs. As the U.S. healthcare system moves towards decision-making guided by comparative effectiveness and economic analyses, limited bodies of evidence present major challenges for patients, clinicians, and healthcare payers in assessing the benefits and harms of orphan drug use and the economic value of orphan drug availability. The objectives of this study are to critically assess the clinical and economic evidence for oncology orphan drugs marketed in the U.S. using systematic literature reviews and evidence assessment frameworks and to highlight the challenges and opportunities for evidence development through evaluation of a case study in hairy cell leukemia (HCL). The findings of this study will be useful to stakeholders and decision-makers in developing evidence assessment frameworks, resource allocation strategies and reimbursement policies for oncology orphan drugs.

Julia Slejko
University of Colorado Denver

"Cost-Effectiveness of Expanded Statin Guidelines for Coronary Heart Disease Prevention in the United States"

Julia Slejko

Coronary heart disease (CHD) is the leading cause of death in the United States and one of the most costly conditions. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) Guidelines recommend statin therapy for CHD prevention based on cholesterol levels. Recent evidence from the JUPITER trial shows that individuals with normal cholesterol but elevated high-sensitivity C-reactive protein (hs-CRP) also benefit from statin treatment. This compelling evidence suggests that the treatment guidelines may be expanded to include recommendations for hs-CRP screening and subsequent statin treatment. Canada has already moved in this direction. If the US follows this lead and recommends statins for those with elevated hs-CRP, it is estimated that six to ten million adults would be new statin users, in addition to the 6.5 million adults who are currently statin users. Statin treatment is costly, and the economic burden of this prevention strategy has not been explored. In five years, 260,000 cardiovascular events could be prevented with the JUPITER strategy. While the clinical benefit to society is clear, the cost-effectiveness of expanded guidelines is uncertain. Acute cardiovascular events are expensive and their prevention may present an economic benefit as well. This study will estimate the economic implications and cost-effectiveness of expanding NCEP guidelines to include statin treatment recommendations based on hs-CRP screening. It is expected that, while expanded NCEP guidelines are significantly more costly than existing guidelines, the improved health outcomes and cost savings will contribute to a greater net benefit to society.

Post Doctoral Fellowship in Health Outcomes

The PhRMA Foundation Post Doctoral program in Health Outcomes provides stipend support for individuals engaged in a research training program that will create or extend their credentials in health outcomes. The purpose of this program is to support post doctoral career development activities of individuals prepared (or preparing) to engage in research that will strengthen representation of health outcomes in schools of pharmacy, medicine and public health. To accomplish these goals, support will be provided for a two-year period to selected individuals who are beginning careers in health outcomes research and who give promise of outstanding development as researchers. The award consists of a $55,000 annual stipend for up to two years.

2010 Post Doctoral Fellowship in Health Outcomes

Elizabeth Gorevski, Ph.D.
University of Cincinnati

"Adherence with medications in liver and kidney transplant recipients associated with quality of life, depression and personality"

Medication non-adherence is a major problem in solid organ transplantation, with an estimated 20–50% of transplant recipients categorized as non-adherent. Poor clinical outcomes and significant financial burden on the health care system has been associated with non-adherence of immunosuppresants in these patients. The economic impact of this problem in solid organ transplant recipients has been estimated as $15–$100 million annually. From 1995 until 2009, nine studies were published investigating the predicting factors of non-adherence in transplant recipients. A few factors, poor social support, a history of alcohol abuse, and young, non-white males are all strong predictors of non-adherence in lung, liver or heart recipients. However, overall, the data seeking factors that influence medication adherence in this highly specialized population, is lacking. The purpose of this study is to begin to address some of these unanswered questions. This study investigates whether or not there is an association between non-adherent behavior and the patient's personality traits, state of depression or quality of life in kidney and liver transplant recipients. A cross sectional study of a 100 liver and kidney recipients > 1 year post transplant will be conducted at University Hospital in Cincinnati, OH. Patients' adherence with medications is assessed by using the Immunosuppressive Therapy Adherence Scale (ITAS). Adherence will be further measured with collateral reports, drug level monitoring, adherence to clinic visit appointments and the Karnofsky Performance scale. Depression, personality traits and quality of life will be measured by Patient Health Questionnaire 9 (PHQ-9), NEO-Five Factor Inventory (NEO-FFI) Scale and Short Form-36 (SF-36), respectively. The results of this study will also provide information to begin stratifying the level of a patients' risk for non-adherence after transplant. Identifying high risk patients will allow healthcare professionals to target these patients and provide additional resources needed to improve adherence, improve patient outcome, and avoid the clinical and economic consequences of non-adherence.

Elizabeth Gorevski, Ph.D

Research Starter Grant in Health Outcomes

The purpose of the PhRMA Foundation Research Starter Grant is to offer financial support to individuals beginning their independent research careers at the faculty level.

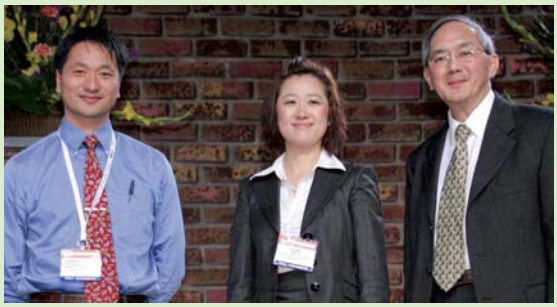
The program provides a research grant of $60,000 for one year. This program supports individuals beginning independent research careers in academia who do not have other substantial sources of funding. The program is not offered as a means to augment an ongoing research effort.

2010 Research Starter Grants in Health Outcomes

Hua Chen, M.D., Ph.D
University of Houston

"The definition, utilization, and development of long term psychotropic polypharmacy in children and adolescents"

Concomitant use of multiple psychotropic drugs, or psychotropic polypharmacy, is on the rise in children and adolescents. Data from specific risk groups have shown that the prevalence of the practice is up to 70% among psychotropic-medicated youth. However, no recent pediatric study has attempted to differentiate short-term combination due to reasons such as cross-titration from long-term, chronic use of multiple psychotropic drugs. Compared to short-term polypharmacy, long-term maintenance treatment with psychotropic combinations raises far more significant questions about safety and tolerability due to the lack of long-term empirical data on psychotropic drugs in the pediatric population. Therefore, the purpose of this research project is 1) to validate the definition of long-term psychotropic polypharmacy and assess the extent of this practice in children and adolescents; and then 2) to describe the course of psychotropic polypharmacy using a multistage Markov process and identify factors that drive the change in the number of concomitant drugs over time. Findings from the proposed study could substantially advance knowledge regarding the utilization and genesis of chronic polypharmacy in pediatric psychiatry. Identification of key factors that drive changes in psychotropic polypharmacy will provide insights for strategies to reduce polypharmacy.



Pictured from left are Changquan Sun, Ph.D., University of Minnesota; Huan Xie, Ph.D., Texas Southern University; and American Association of Pharmaceutical Scientists (AAPS) president, Danny D. Shen, Ph.D. Drs. Sun and Xie were presented with their PhRMA Foundation Pharmaceutics Awards at the Annual Meeting of the AAPS on November 15, 2010 in New Orleans, Louisiana

Nathaniel Rickles, Ph.D.
Northeastern University

"The Impact of a Pharmacist Call Center to Improve Asthma Medication Adherence"

Nathaniel Rickles

There are no known studies evaluating the role of a remote pharmacy call center to improve medication adherence of patients with asthma. The study's primary objective is to determine the feasibility and impact of a pharmacist call center on asthma medication adherence and other outcomes. A pre-post experimental design will be conducted involving 50 adult patients who are insured through a non-profit, community-based health maintenance organization (HMO). Eligible patients will be identified from the HMO's asthma trigger reports indicating patients suspected of having poor asthma control and controller non-adherence. At baseline, the research team will administer an Adherence Barrier Assessment (ABA) to enrolled patients to determine barriers to controller use and mail out

baseline surveys asking patients to complete background medication-related information, the Asthma Control Test (ACT), and the Perceived Control Asthma Questionnaire (PCAQ). The ABA will be used to estimate the patient's risk for asthma controller nonadherence. The ACT and PCAQ measure self-report of asthma symptoms and patient sense of control over asthma condition respectively. The ABA information will be sent to an academic pharmacist call center who will contact study patients at a frequency based on risk for non-adherence. Patients with low, medium, and high risk of non-adherence will receive 1, 2, and 4 calls respectively for a 6-month intervention period. Call center pharmacists will use a variety of techniques including motivational interviewing to help patients understand the value of controller adherence and improve medication adherence. The Call center pharmacists will document all interventions. At the end of the study period, the research team will administer a second ABA and mail out a final ACT and PCAQ. To measure change in medication adherence, Medication Possession Ratios (MPRs) for the asthma controller medications will be calculated a 6-month period before patient enrollment in the study and the 6-month intervention period. Other data at the end of the study will examine patient satisfaction, patient report of communications with pharmacists, and pharmacist experiences towards the pharmacy call center. Descriptive, bivariate, and multivariate statistics will be analyzed using SPSS 18.0.

Jesse Schold, Ph.D.
Cleveland Clinic

"The Impact of Variable Administration of Immunosuppressive Protocols by Kidney and Liver Transplant Centers on Recipient Outcomes"

Jesse Schold, Ph.D

Kidney and liver transplantation are associated with a significant survival benefit for patients with End-Stage Renal Disease (ESRD) and End-Stage Liver Disease (ESLD) respectively. Rates of end-organ disease have significantly increased over the past decades, yet the number of available donors has not kept pace with the need for transplantation. Transplants are performed at one of approximately 280 centers across the United States and even after accounting for patient risk; rates of graft and patient survival significantly vary by center. Understanding the etiology of differences in patient outcomes between centers has been challenging, but is important towards defining best practices of care. One potential source of variation in transplant recipient outcomes may relate to use of immunosuppressive therapies. Immunosuppression is a critical component of transplant patient care, yet there is no clear consensus on use of specific protocols and there remains wide variation in therapies. It is unclear whether transplant centers that utilize standard immunosuppressive protocols versus more individualized and diverse therapies provide more efficacious treatment. From one perspective, homogenous application of therapies may facilitate uniform care, help define complication profiles and treatment and broadly facilitate concordant care practices. Alternatively, well specified use of therapies based on individual patients' risk profile or individual physician expertise may also be advantageous. This study will compare outcomes of patients at centers that utilize homogenous versus diverse immunosuppressive strategies using data from a national cohort of patients in the United States to potentially identify an important source of transplant center-level variation and inform best practices of care.

PHARMACOLOGY/TOXICOLOGY

Pre Doctoral Fellowship in Pharmacology/Toxicology

The goal of this program is to increase the number of well-trained investigators in pharmaceutical research. This program is designed to encourage and support promising students during their thesis research and is aimed at those candidates who are within two years of completing their research for doctoral dissertations in pharmacology and toxicology. The fellowship program provides a stipend of $20,000 annually for up to two years. Up to $500 a year of the funding may be used for incidentals directly associated with the preparation of the dissertation.

Three hundred and fifty fellowships have been awarded under this program since it began in 1978 including the nine fellows awarded in 2010.

2010 Pre Doctoral Fellowships in Pharmacology/Toxicology

Janet Bodmer
University of Cincinnati

"The role of protein kinase C alpha in low molecular weight fibroblast growth factor 2-mediated cardioprotection."

Janet Bodmer

Heart disease remains the leading killer of both men and women in the U.S., and a significant contributor to this mortality rate is cardiac ischemia, the loss of blood flow to the myocardium during a heart attack. Despite the profound and immediate need for therapeutics that can prevent the death of heart tissue and promote better postischemic cardiac function, there are few widely available effective treatments that directly target the myocardium. One promising treatment is fibroblast growth factor 2 (FGF2), a protein that can promote the regrowth of blood vessels and prevent cell death. Among its many roles in the regulation of cardiovascular biology, FGF2 has been shown to protect the heart from dysfunction and damage associated with an ischemic attack, if given prior to the reperfusion of blood flow; this cardioprotection is independent of its angiogenic activity. However, it is unclear what role the different protein isoforms of FGF2 play in this protection, and what signal transduction is used by each type of isoform to produce its effects. Our laboratory has demonstrated that protection against postischemic myocardial dysfunction is initiated by the low molecular weight (LMW) isoform of FGF2, a cytosolic protein that is released to the extracellular space. Conversely, the high molecular weight (HMW) isoforms of FGF2, which are found primarily in the cell nucleus and are not released from heart muscle cells under normal conditions, have been associated with an overall decrease in post-ischemic functional recovery. A candidate that may be responsible for transducing these apparently opposing effects, protein kinase C (PKC), can be activated by FGF2 in the heart and is implicated in the regulation of cardiac dysfunction and protection of the heart from ischemic injury. Of particular interest is the alpha isoform of PKC, which is known to modulate cardiac contractility and to localize to myofibrillar structures that regulate postischemic function. The purpose of this project is to determine, using genetically modified mice, if PKC alpha plays a role in the opposing effects of LMW and HMW isoforms of FGF2 on post-ischemic cardiac recovery in an isolated working mouse heart. This research will further examine how each type of FGF2 isoform modulates PKC alpha to alter the phosphorylation state of candidate downstream contractile and calcium handling proteins. The results of these studies will further elucidate the mechanisms of FGF2-mediated cardioprotection for future therapy in ischemic heart disease.

Noel Yan-Ki Chan
Weill Medical College of Cornell University

"A novel proadrenergic effect of cardiac natriuretic peptides: inhibition by histamine H_3-receptor activation"

Noel Yan-Ki Chan

Preliminary project studies have identified an original cardioprotective effect of histamine$_3$-receptor activation: The inhibition of a previously unsuspected

pro-adrenergic effect of cardiac natriuretic peptides. Natriuretic peptides (NP) are generally viewed as cardioprotective. Yet, NP were recently found to increase myocardial infarct size in mice, while their deletion decreased it. Moreover, a recombinant NP (nesiritide) was shown to increase death risk in heart failure patients. Excessive norepinephrine release may have been pivotal in these unexpected events. Thus, the current project seeks to determine by which mechanisms NP exert a pro-adrenergic effect and further define how H_3-receptor activation inhibits this pro-adrenergic effect. The project will assess whether the catecholamine-releasing effects of NP derive from a cGMP/PKG-mediated prevention of cAMP hydrolysis by PDE3 and whether H_3-receptor activation limits these pro-adrenergic effects by inhibiting PKG and/or stimulating PDE3. Isolated hearts and PC12 cells, both wild-type and PKG- and PDE3-silenced by siRNA, will be used. Collectively, this study will elucidate new mechanisms for the control of norepinephrine release in the heart. As the search for effective cardioprotective drugs continues unabated, the proposed studies will foster the design of new agents (e.g., selective H_3-receptor agonists) to enable a safe and effective treatment of congestive heart failure with NP.

Matthew Costello
University of California-Irvine

"Self-Administration of Cigarette Smoke Extract as a New Model of Tobacco Use."


Matthew Costello

Cigarette smoking remains the leading cause of preventable death in the United States and 20% of Americans continue to smoke, despite recent advances in treatments. For many years nicotine has been considered the component of tobacco smoke that is responsible for addiction and most of the medications for smoking today are designed to block or mimic nicotine's effects on the brain. However, less than 25% of people who take these medications are able to stop smoking for a full year. The animal model used for testing tobacco cessation medications, nicotine self-administration, is also based on the idea that nicotine and tobacco dependence are the same phenomenon. Contrary to this dogma, a growing body of work suggests that some of the 7,000 other compounds in tobacco smoke are important in the rewarding effects of tobacco. For example, this research has found two compounds in smoke, acetaldehyde and norharmane, which enhance nicotine-taking behavior in animals. These non-nicotine components of tobacco smoke may explain the poor success rates of current medications for smoking. The goal of this project is to develop a new animal model of smoking that takes these non-nicotine factors into consideration. The initial experiments focused on norharmane, a reversible monoamine oxidase inhibitor that is present in cigarette smoke. Norharmane enhanced nicotine self-administration, and rats will self-administer it alone. Based on these findings cigarette smoke extract (CSE), a solution made from cigarette smoke which contains both nicotine and many other compounds from the smoke, is more reinforcing than pure nicotine. The goal of these experiments is to establish CSE self-administration as a better animal model of smoking. In early studies animals will work for CSE with a much lower content than they will for pure nicotine; future studies will explore this phenomenon in greater depth. Further experiments will attempt to reveal the brain mechanisms behind CSE's reinforcing effects and test if the non-nicotine factors in tobacco smoke are activating a different set of brain regions than pure nicotine. Finally, nicotinic receptor antagonists will be evaluated in the CSE or nicotine-alone model of drug taking to determine if there are any nicotine-independent effects of CSE. These studies will help establish a new animal model of cigarette smoking which can ultimately be used to develop more effective smoking cessation medications.

Emileigh Greuber
Duke University

"Role of Abl Tyrosine Kinases in Autoimmune Disease and Inflammation"


Emileigh Gruber

Rheumatoid arthritis (RA) is a chronic, degenerative inflammatory disorder that affects 1% of the industrialized world. The advent of tumor necrosis factor-alpha blocking agents has improved patient quality of life from this debilitating disease, but many patients do not respond completely or become resistant to treatment. Recent studies have indicated imatinib mesylate (Gleevec) may be effective for the treatment of RA and other inflammatory disorders. Imatinib is a tyrosine kinase inhibitor that impairs

the activity of multiple kinases including Abl, PDGFR, c-kit, and c-fms. Because imatinib has multiple targets, the mechanism whereby this drug alleviates inflammation remains unknown. The current project investigates how Abl kinase signaling mediates inflammation, focusing the role of these kinases in macrophages, a cell type responsible for amplifying local and systemic inflammation associated with RA. It has been observed that Abl kinases are activated downstream of inflammatory cytokines and that impairing Abl kinase function impairs macrophage-mediated extracellular matrix degradation. This project will specifically address if Abl kinases are required for the pathogenesis and progression of RA in a mouse model of arthritis that lacks Abl kinases specifically in macrophages. This research will explore the role of Abl kinase signaling in inflammation and define the mechanisms underlying the effects of Abl downstream of cytokines that contribute to RA pathology. This project proposes that if Abl kinase activity is required for inflammation that imatinib's clinical use be extended for the treatment of autoimmune and inflammatory conditions. In addition, these studies may provide support for the development of second generation Abl kinase inhibitors with improved specificity.

Melanie Laederich
Oregon Health & Science University

"Defining the role of Hsp90 activity in FGFR3 pathology"

Melanie Laederich

Fibroblast growth factor receptor 3 (FGFR3) is a key coordinator of mammalian development, controlling cellular differentiation and growth. Germline mutations in FGFR3 give rise to a variety of skeletal diseases including the prototypic disorder of skeletal growth, achondroplasia. Somatic mutations in FGFR3 transform it into an oncogene and are observed in a number of cancers including bladder cancer and multiple myeloma. The mutant receptors degrade more slowly that their normal counterparts leading to accumulation of mutant receptor protein and excessive signaling. Our lab investigates the mechanisms responsible for the increased receptor stability as potential targets for therapeutic intervention. Heat shock protein 90 (Hsp90) is a cytoplasmic protein chaperone that facilitates the folding and enhances stability of select 'client' proteins. Interestingly, Hsp90 chaperone activity contributes to many human diseases through stabilization of pathogenic proteins such as oncogenic kinases. Inhibition of Hsp90 function using small molecule inhibitors destabilizes client proteins and induces their degradation. As such, these drugs have potential to modulate the stability of disease causing client proteins. They have reached Phase II clinical trials in cancer therapy. This project has discovered that FGFR3 is a client of Hsp90. It hypothesizes that constitutively activated FGFR3 will require the function of Hsp90 for its uncontrolled activation and stability. In this project, in addition to in vitro experiments, the ability of small molecule Hsp90 inhibitors to alleviate disease manifestations in two preclinical models of FGFR3-mediated disease will be tested. The first is a knock-in mouse model of achondroplasia. Experiments are being carried out in embryonic metatarsal and tibial explant cultures to determine if Hsp90 inhibitors can stimulate bone growth. Additionally, mouse pups will be treated to determine the extent to which the dwarf skeletal phenotype can be rescued by the inhibitors. In the second model involving bladder cancer, Hsp90 inhibitors are being tested for their capacity to reduce the size of xenographs of FGFR3-driven bladder cancer cells in nude mice. These studies should provide insight into the role of Hsp90 chaperone activity in FGFR3-mediated disease and the efficacy of Hsp90 inhibitors in countering this action.

Katie Paul
University of North Carolina at Chapel Hill

"In vivo and in vitro characterization of the mode of action of triclosan-induced hypothyroxinemia"

Katie Paul

The U.S. population is exposed to low concentrations of triclosan through multiple potential exposure routes, including use of ubiquitous consumer products such as hand soaps, and contact with surface waters. Triclosan (2,4,4'-trichloro-2'-hydroxyphenylether) is a chlorinated phenolic antibacterial found as an active ingredient in many hygiene and medical products. Triclosan is an emerging surface water contaminant and has been widely detected in human urine, serum and milk. Initial research demonstrated triclosan-induced, dose-dependent thyroxine decreases in young rats. Disruption of thyroid hormones during development adversely affects neurodevelopment in both rats and humans. Therefore it is critical to determine whether tri-

closan disrupts thyroid hormones during development, to characterize its mode-of-action, and to discern the human relevance of this mode-of-action using comparative *in vitro* models. This work will test the hypothesis that triclosan disrupts thyroid hormone via activation of hepatic nuclear receptors, mediating downstream Phase I-III gene expression and protein changes that result in decreased systemic thyroid hormone concentrations. Three specific aims will be addressed: 1) Determine the impact of triclosan on hepatic catabolism and transport in rats using protein activity and mRNA expression analysis; 2) Evaluate the sensitivity of the developing organism to triclosan-induced thyroid hormone disruption; and, 3) Characterize and compare key molecular events from the rat-based mode-of-action, using rat and human hepatocytes to assess nuclear receptor activation, mRNA expression, and protein activity. These data will play a crucial role in managing the risks to humans from triclosan exposure.

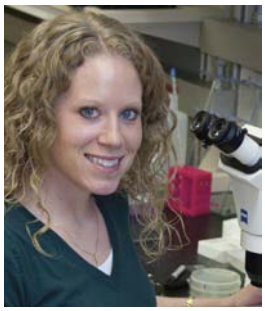
Sarah Schumacher
University of Michigan

"Mechanisms of Antiarrhythmic Drug-induced Internalization of Kv1.5 in Atrial Myocytes"

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States and serves as a major risk factor for increased stroke, heart failure, and cardiovascular morbidity. The usefulness of currently-used antiarrhythmic drugs in the treatment of AF is limited by proarrhythmia in the ventricle due to a lack of ion channel selectivity in combination with an overlap in ion channel expression patterns. The voltage-gated potassium channel Kv1.5 (KCNA5) has emerged as a primary target in both academic and industrial research efforts for treatment of AF. In humans, Kv1.5 is selectively expressed in atrial myocytes where it mediates the ultrarapid delayed rectifier current (I_{Kur}) that is vital for atrial repolarization and participates in the control of action potential duration. Additionally, alterations in the cell surface expression of functional Kv1.5 have been shown to contribute to the pathophysiology of paroxysmal and persistent atrial fibrillation. Although significant effort has been made to identify novel blockers of Kv1.5, compounds with both atrial selectivity and clinical efficacy remain elusive and highlight the need for new potential therapeutic strategies or targets. The lab investigation of the mechanisms regulating the dynamic trafficking of Kv1.5 led to the discovery of a novel paradigm for antiarrhythmic pharmacology in the control of the cell surface stability of channel protein in atrial myocytes. The project found that antiarrhythmic agents, such as quinidine, trigger Kv1.5 internalization concomitant to block of channel current that is both subunit-dependent and stereospecific, presenting a new mechanism for the inhibition of ion current through drug-stimulated endocytosis of channel protein. The current research project will specifically address the structural basis within the channel protein and drug molecule for antiarrhythmic drug-induced endocytosis of Kv1.5. Furthermore, it will expand these studies to include analysis of homomeric versus heteromeric assembled channels. The purpose of this research is to determine the mechanisms of antiarrhythmic drug-induced Kv1.5 channel internalization, and investigate the possibility for new agents that selectively modulate the stability of channel protein in the membrane as an approach for treating cardiac arrhythmias.

Natalia Vanduyn
Indiana University School of Medicine

"Mechanisms of methylmercury-induced cellular stress in Caenorhabditis elegans"


Natalia Vanduyn

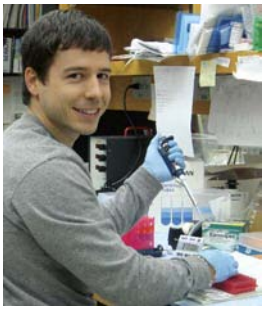
Methylmercury (MeHg) exposure from occupational, environmental and food sources is a considerable threat to public health. The toxicant easily crosses the blood brain barrier and the placenta, and can cause neurological and developmental defects. Although MeHg has been studied on a molecular level for over 50 years, the molecular determinants involved in the cellular pathology are largely unknown. The molecular basis of MeHg toxicity is difficult to evaluate because of the high complexity of the vertebrate brain and lack of facile *in vivo* genetic models to determine and explore the mechanisms involved in the cellular dysfunction. The genetically tractable nematode *C. elegans* is a powerful model to study the molecular, cellular and developmental components involved in MeHg toxicity. The genetic and molecular pathways associated with embryonic development, neurotransmission, and cellular stress are highly conserved between *C. elegans* and humans. The project's preliminary studies show that the nematode is highly sensitive to MeHg, and that as in vertebrate systems, the toxicant causes animal death, delayed development, a decreased brood size and embryonic developmental defects. On the molecular level, MeHg increases the level of reactive oxygen species and induces

stress response genes such as heat shock proteins and glutathione S-transferases. The research has shown that several of these genes are under the control of the cytoprotective transcription factor Nrf2/SKN-1. Futhermore, knockdown of expression of the *skn-1* gene increases sensitivity to MeHg and overexpression of the SKN-1 protein increases resistance to the toxicant. Future work will build on these studies and test the hypothesis that SKN-1 and its down-stream targets can inhibit MeHg-induced developmental defects and neurotoxicity. The study will also determine the involvement of up-stream regulators of SKN-1 activity, like members of the MAP kinase cascade. These studies will include a novel genome-wide, reverse genetic screen to identify genes involved in MeHg toxicity.

Christopher Vellano
Emory University School of Medicine

"Ric-8A as a Novel Regulator of RGS14/G protein Signaling in Hippocampal Neurons"

The **r**egulators of **G** protein **s**ignaling (RGS) proteins are key modulators of G protein-coupled receptor (GPCR) and G protein signaling pathways. RGS14 is a highly unusual brain scaffolding protein that we show is expressed within the hippocampus. Our lab has found that loss of the RGS14 mRNA/protein enhances long-term potentiation (LTP) in certain hippocampal neurons that is associated with enhanced



Chris Vellano

spatial learning and object memory. These findings suggest that RGS14 plays an important role as a suppressor of signaling pathways important for synaptic plasticity. The RGS14 protein contains a complex structure that binds inactive Gαi1/3-GDP, active H-Ras, and Raf kinases, integrating and modulating G protein and mitogen-activated protein (MAP) kinase signaling pathways. How the RGS14:Gαi signaling complex is regulated is unknown. The research has found that native RGS14 co-localizes with native Ric-8A in the same hippocampal neurons. Ric-8A is a guanine nucleotide exchange factor (GEF) known to regulate unconventional G protein signaling pathways independent of GPCRs. The project's preliminary studies find that Ric-8A co-localizes at the plasma membrane with the RGS14:Gαi1 complex, and induces dissociation of Gαi1 from RGS14 in cells. This project will examine how Ric-8A regulates RGS14:Gαi1 signaling mechanistically using both purified proteins and hippocampal stem cells/ neurons. Elucidating the mechanisms behind Ric-8A integration of RGS14:Gαi1 signaling in hippocampal neurons may help identify novel molecular targets in the development of new therapeutics for diseases involving cognitive impairment and deficits in learning and memory.

Post Doctoral Fellowship in Pharmacology/Toxicology

The PhRMA Foundation Post Doctoral program in Pharmacology/Toxicology provides support for individuals engaged in a multidisciplinary research training program that will create or extend their credentials in pharmacology or toxicology. The purpose (intent) of this program is to support post doctoral career development activities of individuals prepared (or preparing) to engage in research that integrates information on the effect of an agent in the intact organism. Recent graduates from pharmacology Ph.D. programs interested in post-doctoral experience that integrates pharmacology with a morphologic specialty (cell biology/anatomy/pathology) are also eligible to apply for this fellowship. It is anticipated that this research training will be accomplished in academic and/or industrial laboratory settings in which multidisciplinary teams are organized to integrate informatics, molecular, cell and systems biology with pharmacology/toxicology research.

The post-doctoral award consists of a $40,000 annual stipend for up to two years. The second year of this award is contingent upon a progress report approved by the Foundation and submission of a financial report. The award is intended solely as a stipend and may not be used otherwise.

2010 Post Doctoral Fellowships in Pharmacology/Toxicology

Francheska Colon-Gonzalez, Ph.D.
Thomas Jefferson University

"GUCY2C at the nexus of obesity and colorectal cancer"

Francheska Colon-Gonzalez, Ph.D.

Dietary factors increase the risk of colorectal cancer, the 3rd most common neoplasm in the U.S., with ~150,000 new cases annually. Obese patients have ~20–60% greater risk of developing the disease and ~1.5–2.0-fold greater risk of dying from it. However, the precise mechanisms relating obesity to colorectal cancer remain undefined. The current scientific model suggests that obesity directly causes colon cancer. In contrast, this project explores the novel hypothesis that obesity and colorectal cancer both reflect a deficiency of hormones that activate GUCY2C, a receptor that suppresses tumor growth in intestine and appetite and body weight in the brain. Early in the development of colorectal cancer, the expression of specific hormones produced in intestine that control GUCY2C activity are lost. This leads to uncontrolled cell growth and genetic mutations underlying cancer development. Unexpectedly, the research has found that the GUCY2C-hormone system also regulates appetite and body weight. Indeed, mice in which the GUCY2C-hormone signaling system has been eliminated in the appetite control centers of the brain eat uncontrollably, and become obese when given a high fat diet. Importantly, the preliminary studies suggest that excess consumption of nutrients, especially fat, reduces the expression of GUCY2C hormones in intestine, making less available for secretion into the circulation and delivery to the brain to control appetite. These observations suggest a model in which GUCY2C is at the intersection between obesity and colorectal cancer, in which excess nutrients reduce the expression of hormones leading to cancer development and uncontrolled appetite. The studies will focus on confirming the effect of nutrients on hormone expression, explore the molecular mechanisms by which this occurs, and explore the efficacy of GUCY2C hormone supplementation to reduce nutrient-induced cancer development. These studies will establish a novel paradigm relating obesity and colorectal cancer, involving nutrient-induced GUCY2C hormone loss, and provide an endocrine-based solution to prevent these diseases, through hormone replacement therapy.

Jonathan W. Theile, Ph.D.
Indiana University School of Medicine

"Pharmacology of sensory neuronal sodium currents in inherited and acquired pain syndromes"

Jonathan W. Theile, Ph.D

Inherited and acquired pain disorders constitute significant health problems affecting millions of Americans each year. Abnormal pain sensitivity occurs primarily through altered excitability of peripheral sensory neurons. Voltage-gated sodium channels (VGSCs) are key determinants regulating action-potential generation and propagation; thus, changes in VGSC function have profound effects on neuronal excitability. Inherited erythromelagia (IEM) and paroxysmal extreme pain disorder (PEPD) are inherited pain syndromes caused by distinct mutations in Nav1.7, a VGSC isoform predominantly expressed in peripheral neurons, that alter the gating properties of the channel resulting in hyperexcitability of these neurons. Additionally, many Americans suffer from chronic pain following contusive spinal cord injury (SCI). Recent studies suggest that SCI results in hyperexcitability of sensory neurons and thus VGSCs may also play a role in pain associated with SCI.

After opening, VGSCs undergo a distinct process termed 'inactivation' in which a cytoplasmic loop of the channel complex enters the pore preventing further sodium influx. Normally, channels cannot reopen after inactivation until they have been hyperpolarized. Thus, alterations in the inactivation process can have profound effects on neuronal excitability. Under rare conditions VGSCs can re-open during repolarization allowing a surge of current (resurgent current), enhancing excitability. This project has recently discovered that a PEPD mutant, which slows inactivation, enhances both the frequency and amplitude of resurgent currents in dorsal root ganglion (DRG) neurons. Enhanced resurgent currents in DRG neurons following SCI were observed. The project can hypothesize that resurgent currents likely contribute to pain associated with PEPD and SCI via enhanced sensory neuron excitability. VGSCs are attractive candidates for the treatment of pain, however many of the currently available modulators are non-selective. Thus, it is necessary to develop drugs that target specific VGSC isoforms or patterns of activity, such as resurgent currents, in peripheral neurons to effectively treat pain while minimizing unwanted side-effects. PEPD and IEM mutants respond differently to certain VGSC modulators and it is proposed that this may be due in part to resurgent currents displayed by PEPD mutants. Therefore, the project aims to identify VGSC modulators that are sensitive to PEPD and SCI induced resurgent currents compared to normal currents. The research will also investigate whether other inherited mutations or post-translational modifications which alter excitability in certain Nav isoforms, such Nav1.3, Nav1.8 and the cardiac isoform Nav1.5, can generate resurgent currents.

Research Starter Grant in Pharmacology/Toxicology

The purpose of the PhRMA Foundation Research Starter Grant is to offer financial support to individuals beginning their independent research careers at the faculty level.

The program provides a research grant of $60,000 for one year. This program supports individuals beginning independent research careers in academia who do not have other substantial sources of funding. The program is not offered as a means to augment an ongoing research effort.

2010 Research Starter Grants in Pharmacology/Toxicology

Luke H. Bradley, Ph.D.
University of Kentucky

"Investigation of the Antiapoptotic effects of Dopamine Neuron Stimulating Peptide – 11"

Luke H. Bradley, Ph.D

Parkinson's disease (PD) is a chronic, disabling neurodegenerative disorder that affects over 1 million Americans and is expected to double in incidence over the next 40 years. This movement disorder, most often diagnosed in people over the age of 50, is characterized by one or more of the following symptoms: bradykinesia, stooped posture, rigidity, resting hand tremors, balance impairments and gait difficulty. These multisymptoms are linked with the dysregulation of the neurotransmitter dopamine resulting from the loss of dopamine neurons in the substantia nigra. Glial cell line-derived neurotrophic factor (GDNF), a neurotrophic factor with protective and restorative effects on dopamine neurons *in vitro* and *in vivo*, has received considerable attention as a potential therapeutic agent for PD. However, GDNF did not progress from PD clinical trials, likely due to the pharmacological disadvantages associated with the invasive delivery of large protein molecules directly to the brain. Thus, a viable approach towards the development of potential PD therapeutics is to construct and evaluate novel smaller molecular alternatives with neurotrophic factor activity. Evidence of propeptides from other neurotrophic factors, that possess alternate apoptosis-mediating functions compared to the mature proteins, provides a wealth of untapped sequences for exploration and evaluation for therapeutic strategies. Our studies hypothesize that an amidated 11 amino acid residue propeptide from GDNF, named human dopamine neuron stimulating peptide-11 (DNSP-11), has similar effects by mediating apoptotic pathways. The goal of the proposed work is to decipher the protective properties of DNSP-11 using molecular, proteomic and cellular biology approaches. The information obtained in this study will pave the way towards utilizing these identified sequences as molecular engineering scaffolds for the further development of novel downstream therapeutics targeting PD and age-related neurodegenerative diseases.

Fereshteh Nugent, Ph.D.
Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.

"Reversal of Opioid-Induced Inhibitory Synaptic Plasticity in the VTA"

Fereshteh Nugent, Ph.D

Drug addiction is a chronic disease with devastating impact on families and society. Treatment options for drug addiction are limited and even if drug use is stopped, chronic craving and relapse are critical problems in drug addiction. Long-term potentiation (LTP) and long-term depression (LTD) are the synaptic models of learning and memory. Mounting evidence now suggests that addiction is a pathological form of learning that involves drug-induced synaptic plasticity in addiction-related areas of the brain including the ventral tegmental area (VTA). Drug-induced alteration of the strength of GABAergic inhibition in the VTA can critically affect the VTA neuronal output and may mediate the long-term effects of drugs of abuse. In this proposal, the project will extend the initial work on opioid-blockade of LTP of GABAergic inhibition in VTA dopamine neurons by examining

the already demonstrated LTD and its modulation by opioids. Furthermore, the project will test whether LTP could reverse LTD. It is anticipated that this research will provide new information on the molecular mechanisms by which opioids can modify the excitability of the VTA neurons that contribute to enhanced drug craving and relapse. It will also lead to potential novel molecular drug targets for prevention and treatment of drug addiction.

CLINICAL PHARMACOLOGY

Paul Calabresi Medical Student Fellowship

This program offers students an opportunity to spend up to two years full-time conducting an investigative project in pharmacology-clinical pharmacology. It is hoped that by having students become involved in investigative projects at a point when career choices are still relatively flexible, they will eventually choose research careers in clinical pharmacology.

The minimum period of the fellowships is six months and the maximum is two years, with a maximum stipend of $18,000. One hundred and seventy Medical Student Fellowships have been awarded since the program began in 1974. This fellowship has been named in honor of Dr. Paul Calabresi who served the PhRMA Foundation as a committee Chairman and member for 25 years.

2010 Paul Calabresi Medical Student Fellowship

Loc Thang
Michigan State University

"Macrophage (Mϕ)-Derived Superoxide Disrupts Sympathetic Nerve Function In Deoxycorticosterone Acetate (Doca)-Salt Hypertensive Rats"

More than 65 million Americans have hypertension (sustained elevation of systolic blood pressure ffi 140 mmHg or diastolic blood pressure ffi 90 mmHg). If uncontrolled, hypertension is a major risk for stroke, heart disease and end-organ damage. Sympathetic nerve activity is elevated in some human hypertensive subjects, and in some animal models of hypertension. Furthermore, local mechanisms regulating neurotransmitters release from sympathetic nerve

Loc Thang

supplying arteries are impaired in hypertension. In the DOCA-salt model of hypertension there is an elevated vascular level of O_2. Mice deficient in macrophage (Mϕ) colony-stimulating factor exhibit reduced vascular inflammation and they are protected against damage caused by DOCA-salt hypertension. The proposed studies will test the hypothesis that as blood pressure increases, Mϕ infiltrate into the adventitia of mesenteric arteries (MA) of DOCA-salt rats. This contributes to the increased O_2 that disrupts sympathetic nerve function causing further increases in blood pressure. The data may have important implications for the development of new drugs for the treatment of hypertension.

Faculty Development Award in Clinical Pharmacology

Through this program, annual awards are made to medical schools for support for full-time junior faculty members in the field of human clinical pharmacology. The level of support is variable, and is aimed at keeping within the existing salary and fringe benefit structure of the applicant university. The award is for two years. Individuals at the associate professor or professor level should not apply for this award.

This program was established by the PhRMA Foundation in 1966 in recognition of the many problems involved in evaluating therapeutic agents. Drug investigation is a demanding task. As in nearly every aspect of the health field, manpower needs are acute. This program is intended to meet some of these workforce needs in the field of clinical pharmacology. The ultimate aim of the awards program is to stimulate teaching, training, and research in clinical pharmacology. It is aimed at providing an opportunity for the development of the research potential of clinical pharmacologists during the years immediately following their formal training programs.

2010 Faculty Development Award in Clinical Pharmacology

Sarah A. Holstein, M.D., Ph.D.
University of Iowa

"Targeting monoclonal protein trafficking in multiple myeloma"

Multiple myeloma is an incurable bone marrow cancer in which patients develop painful bony lesions, kidney damage, and blood count abnormalities. The medical complications of multiple myeloma are largely a consequence of the ability of the malignant plasma cells to secrete substantial quantities of antibodies (monoclonal protein). Despite recent advances in therapeutics, all patients will either eventually become resistant to currently available agents or will be unable to tolerate the therapies because of adverse effects. Therefore, there continues to be a critical need for the elucidation of previously unexploited pathways in malignant plasma cells to allow for the development of novel therapeutics. While it has been demonstrated that inhibitors of the isoprenoid biosynthetic pathway are capable of inducing cytotoxic effects in myeloma cells, the mechanisms underlying these effects remains incompletely understood. This project's

Sarah Holstein, M.D., Ph.D

preliminary studies have revealed that select inhibitors of the isoprenoid biosynthetic pathway (IBP) disrupt monoclonal protein secretion in myeloma cells via inhibition of Rab geranylgeranylation, leading to induction of the unfolded protein response (UPR) pathway and apoptosis. Rab proteins, which are geranylgeranylated geranylgeranyltransferase (GGTase) II, play critical roles in mediating vesicle trafficking. Given the sensitivity of malignant plasma cells to disruption of protein trafficking and endoplasmic reticulum stress, it is proposed that inhibition of Rab geranylgeranylation represents a novel therapeutic strategy for multiple myeloma. Ongoing studies involve the determining the relationship between Rab proteins and monoclonal protein trafficking, developing novel GGTase II inhibitors as potential therapeutic agents, and investigating the effects of combining IBP inhibitors with standard anti-myeloma therapies. This work will lead to a better understanding of the pathophysiology of malignant plasma cells and guide the development of novel therapeutic strategies for the management of multiple myeloma.

The PhRMA Foundation would like to express our thanks to the American Society for Clinical Pharmacology and Therapeutics (ASCPT) for allowing us to present our Clinical Pharmacology Awards. At the 2010 meeting the Foundation presented awards to our 2009 recipients. Mara Becker, M.D., M.S.C.E., Children's Mercy Hospital and Myaing M. Nyunt, M.D.,Ph.D., Johns Hopkins University.

PHARMACEUTICS

Pre Doctoral Fellowship in Pharmaceutics

This program has been in effect for 22 years. It assists awardees who have one or two years remaining in the pharmaceutics pre doctoral training—the time during which they are engaged in dissertation research. We provide the funding during the doctoral program after course work has been completed and the remaining training activity is a student's research project.

The fellowship program provides a stipend and funds to cover costs incidental to the training for up to two years. The level of support is $20,000 per year and up to $500 a year may be used for incidentals directly associated with the preparation of the dissertation. Two fellowships were granted in 2010.

2010 Pre Doctoral Fellowships in Pharmaceutics

Kelly M. Forney
University of Connecticut

"Critical Factors in Biopreservation of Freeze-Dried Protein Formulations"

Due to the susceptibility of proteins to degradation, adequate storage stability is often a challenge, resulting in therapeutic formulations having an inadequate shelf-life and requiring refrigeration to maintain product quality. While both aqueous and solid-state protein formulations are susceptible to chemical and physical instabilities, a freeze-dried solid formulation has superior stability due to the minimization of degradation through limited mobility and the absence of water as a reactant. Formulation is often carried out by molecularly dispersing the protein in a protective excipient (e.g. disaccharides, polymers) matrix, providing mechanical immobilizing and spatial separation of potential reactive sites. However, even at low storage temperatures, degradation can still occur do to local motions within the protein matrix. It has recently been demonstrated that storage stability of several model protein/disaccharide formulations increased with the addition of a small amount of a low molecular weight compound. Low molecular weight compounds (e.g. polyols, amino acids) often have low glass transition temperatures (T_g) and for this reason are often avoided in solid-state formulations. The addition of a compound with a low T_g to a system with a high T_g results in plasticization and a decrease in the system T_g, which in turn would classically be expected to destabilize the product. It is

Kelly M. Forney

hypothesized that the low molecular weight compounds inhibit the local motions of the system, thereby further hindering degradation. The proposed research will investigate the relationship between optimal amount of low molecular weight compound, dynamics of the system, and physical characteristics (free volume, phase chemistry, protein structure), in order to understand the mechanism of stabilization. The knowledge obtained from this research can be applied to allow for long-term stability at ambient temperature, particularly important for military and third world applications.

Taryn Bagby
University of Kansas

"Development of Targeted Nanoconjugates for the Treatment of Head and Neck Cancer"

The purpose of this project is to develop a safer and more effective treatment for locally advanced head and neck squamous cell carcinoma (HNSCC) utilizing unique features of nanoparticles to target disease in the regional lymphatics. Over 30,000 Americans are diagnosed with HNSCC every year, and if discovered while still small and localized (stage I) the cure rate is very high. However, over 60% of patients present with advanced disease that has already metastasized to the rich lymphatic beds of the head and neck, and even with the best care available, most will relapse within two years. HNSCC preferentially metastasizes to the locoregional lymphatics thus making less invasive treatment impossible

Taryn Bagby

with current tools. However, if both the unique transport properties of the lymphatic system along with specially designed nanoparticles are utilized in developing a targeted treatment to the lymphatics of the head and neck, a safe new therapeutic option can be provided to patients that will save them from high dose radiation, reduce the extent and trauma of surgery, and reduce or eliminate systemic chemotherapy in many cases. Thus the project is developing biodegradable star-polymer nanoparticles that can deliver chemotherapeutics, cisplatin and 5-FU, to the lymph bed, where HNSCC disease is most prevalent in early disease and toughest to eliminate with conventional techniques. Platinum chemotherapy can play a role in treatment, but approximately 30% of HNSCC in-treatment deaths are associated with cisplatin toxicity, and surviving patients often experience painful peripheral neuropathy and irreversible hearing loss and tinnitus. Localizing the treatment to the head and neck tissues will eliminate most systemic toxicities and is much simpler to implement than targeted intravenous treatments. Because these particles are designed for local administration, the problems with efficient delivery that plague all systemic treatments (even highly advanced targeted nanoparticles) are overcome.

Post Doctoral Fellowship in Pharmaceutics

This program was initiated to encourage more qualified graduates to obtain the post doctoral research training so vitally needed in the area of Pharmaceutics. The PhRMA Foundation and its Pharmaceutics Advisory Committee recognize the critical need for such well-trained scientific investigators. The post doctoral award consists of a $40,000 annual stipend for up to two years. The second year of this award is contingent upon a progress report approved by the Foundation and submission of a financial report. The award in intended solely as a stipend and may not be used otherwise.

2010 Post Doctoral Fellowships in Pharmaceutics

Andreas Sophocleous, Ph.D.
Purdue University

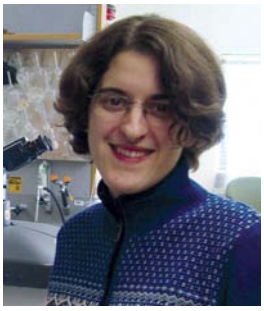
"Hydrogen-Deuterium Exchange-Mass Spectrometry for Predicting Aggregation Propensity of Lyophilized Proteins Formulations"

Andreas Sophocleous, Ph.D

Aggregation is one of the most common routes of inactivation for protein drugs in the solid-state, and can lead to life-threatening immunogenic side effects in patients if undetected. As a result, aggregates must be detected and removed during manufacturing and storage, adding to the cost of producing protein drugs. The broad goal of this research project is to develop amide hydrogen/deuterium exchange (HDX) as a method for assessing aggregation potential in solid formulations of protein drugs. The central hypothesis is that the extent of HDX, measured by mass-spectrometry, is a better predictor of aggregation on long-term storage than conventional protein characterization measures. This project proposes two specific aims: to compare solution and solid state protein HDX patterns in the presence of various excipients or matrix conditions, and to identify the relationship between HDX patterns and protein aggregation in the solid state. To test this hypothesis, stabilizing, neutral, and destabilizing excipients will be investigated and their effect on protein HDX evaluated. The effects of excipient activity, moisture content, and mobility in the solid on the HDX mechanism will be evaluated and compared to solution controls. Information from these studies will be valuable in strengthening our mechanistic understanding of protein aggregation in solids.

Erica Gunn, Ph.D.
University of Wisconsin-Madison

"Surface structure and crystallization of amorphous pharmaceuticals"



Erica Gunn, Ph.D.

Pharmaceutical scientists increasingly face the challenge of delivering highly potent but poorly soluble drugs. Amorphous solids provide a general solution to this problem because they dissolve much faster than their crystalline counterparts, making them more bioavailable. A potential problem with amorphous pharmaceuticals is that they tend to crystallize over time, thus negating their advantages. We seek to understand how this transition occurs, so that we can control and ultimately avoid crystallization in these materials. The surface of an amorphous solid plays an important role in determining its stability; crystals can grow several hundred times faster at the surface than in the bulk. It has been proposed that faster crystallization rates are caused by greater mobility and a different packing arrangement of molecules at the surface of the material as compared to the bulk. If we can understand and control changes to the surface structure, we may be able to prevent crystallization and extend the shelf life of amorphous drugs. We will characterize the surface of model amorphous pharmaceuticals using x-ray diffraction, and will study ways to modify the surface in order to inhibit crystallization and improve drug stability.

Research Starter Grant in Pharmaceutics

The purpose of the PhRMA Foundation Research Starter Grant is to offer financial support to individuals beginning their independent research careers at the faculty level.

The program provides a research grant of $60,000 for one year. This program supports individuals beginning independent research careers in academia who do not have other substantial sources of funding. The program is not offered as a means to augment an ongoing research effort.

2010 Research Starter Grants in Pharmaceutics

Huan Xie, Ph.D.
Texas Southern University

"Targeted Thioaptamer-Nanorod Bioconjugates for Tumor Hypoxia-Associated Carbonic Anhydrase IX"

Huan Xie, Ph.D

Each year millions of American lives are taken by cancer. Currently the standard treatment modality for cancer includes surgeries and systemic therapies such as radiation, chemotherapy and immunotherapy. Each method has its unique strengths yet limitations. Thermal ablation, as alternative interventional techniques, provides a minimally invasive or noninvasive cancer therapy technique that rapidly kills cancer cells by heat. Nanomaterials have been broadly used in advanced pharmaceutical formulation and delivery. Among a lot of newly developed nanomaterials, gold nanorods, with unique dimensions and optical properties, are ideal for targeting and near-infrared thermal ablation of cancer. Most tumors develop areas of hypoxia as a result of proliferating cells outgrowing the new vasculature that feeds them oxygen and nutrients. Hypoxia increases tumor resistance to radiation and chemotherapy. Carbonic anhydrase IX (CA IX), strongly induced by hypoxia, is found to be highly over-expressed in many cancer types but only present in a few normal tissues. Therefore CA IX functions as an intrinsic biomarker of tumor and becomes an attractive target for cancer treatment.

Aptamers are RNA or DNA molecules that fold by intramolecular interaction into unique three-dimensional structures for target recognition. Phosphorodithioate (PS2) modified aptamers (thioaptamers) possess more advantages as attractive therapeutic agents, such as lack of immunogenicity, strong binding affinity, specificity and stability. This project proposes to use a patented bead-based selection method to generate a thioaptamer that binds tightly to CA IX; then develop a multifunctional nanoformulation using gold nanorods as a scaffold and a photo-thermal ablation agent conjugated to the CA IX binding thioaptamers. The plan is to synthesize the formulation and characterize its stabilities and efficiency by bioassays, cell assays and thermal ablation treatment. This work has the potential to develop a cancer therapy that could synergize with radiation therapy and chemotherapy to eliminate residual or recurrent tumor cells.

Changquan Calvin Sun, Ph.D.
University of Minnesota

"Enabling tablet manufacture by direct compression through surface engineering of drugs"

Changquan Calvin Sun

Tablet manufacturing through direct compression is significantly more economical than that through granulation processes. However, most active pharmaceutical ingredients (API), due to their poor compaction and flow properties, are not currently amenable to direct compaction. This project has shown that physical modifications of particle surfaces by coating with suitable polymers or nanoparticles can profoundly enhance powder compaction and flow properties respectively thus potentially enabling direct compression. The surface modification strategy does not involve a change in drug crystal form and can be implemented

at any stage of drug development. Therefore, the goal of the proposed research is to develop an integrated surface modification strategy that enables direct compression for most API. Upon its completion, this study will have demonstrated a universal strategy that can dramatically improve API powder properties so that direct compression is readily achieved. This project will lay the groundwork for designing high quality tablet products through crystal surface engineering. It minimizes dependence of manufacturing process on API properties and places pharmaceutical product development on a firm scientific footing.

On April 24, 2010 at the American Society for Pharmacology and Experimental Therapeutics (ASPET) Annual Meeting in Anaheim, California, the PhRMA Foundation Pharmacology/Toxicology Awards were presented. Pictured from left are Luke Bradley, Ph.D., University of Kentucky; Francheska Colon-Gonzalez, Ph.D., Thomas Jefferson University; Jonathan Theile, Ph.D., Indiana University; Noel Yan-Ki Chan, Weil Cornell Graduate School of Medical Sciences; Matthew Costello, University of California-Irvine; Sarah Schumacher, University of Michigan; and Foundation Executive Director, Eileen Cannon.

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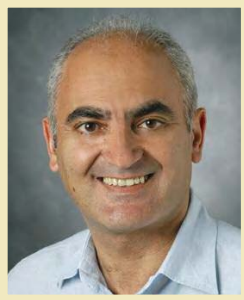

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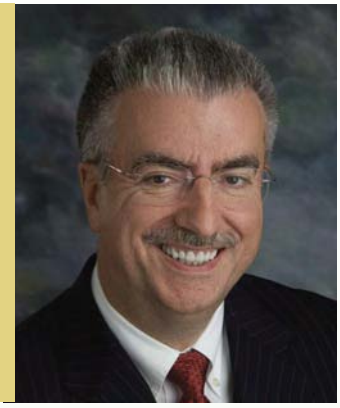
PhRMA
Washington, D.C.

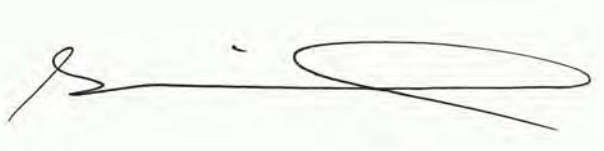
TREASURERS REPORT



The PhRMA Foundation ended 2009 in solid financial shape despite a financially challenging year. Contributions were down 2% from the previous year, to $2.65 million. We awarded over $1.8 million in grants and held down non-grant program and administrative expenses. Total expenditures, at $2.6 million, are 7% below budget. Net assets at December 31 were $14.4 million, a 20% increase from $12.0 million the prior year. The increase in net assets is attributable primarily to a gain of $1.8 million in investments. For the 11th year in a row, we did not need to transfer net assets to cover payment this year of awards granted in previous years. Financial details are shown in the accompanying Statement of Income and Expenditures.

For 2010, contributions were targeted to reach $2.35 million. I can also report that we did not transfer net assets to cover our expenses. On behalf of the Board and staff, I give special thanks for the continuing support of our generous contributors, who are listed in this report. We need the support of all member companies during these challenging financial times. Our programs represent our industry's commitment to innovation in today's research as well as to the young investigators of tomorrow.

The Foundation's financial position as of December 31, 2009, has been audited by the accounting firm of Tate and Tryon of Washington, D.C. A full report can be obtained by contacting the Foundation.



Garry A. Neil, M.D.

STATEMENT OF
INCOME *and* EXPENDITURES

for the year ended december 31, 2009

INCOME	
Contributions	$ 2,650,461
Contributions – in kind from PhRMA	$ 294,806
Interest and Dividends	$ 387,466
(Realized and Unrealized) Gains in Securities	$ 1,409,026
Other Income	$ 160,043
TOTAL INCOME	**$ 4,901,802**

EXPENDITURES	
Programs	
Awards in Excellence	$ 16,029
Clinical Pharmacology Program	$ 156,000
Health Outcomes Program	$ 334,362
Informatics Program	$ 409,500
Pharmaceutics Program	$ 280,000
Pharmacology Programs	$ 567,500
AFPE Fellowship Award	$ 7,500
Other Grants	$ 89,932
Subtotal – Grants	**$ 1,860,823**
Other	
Committee Meetings, Travel and Honoraria	$ 68,880
Publications and Special Projects	$ 37,505
Subtotal – Other	**$ 106,385**
PROGRAM TOTAL	**$ 1,967,208**
Administrative	
Staff, Taxes, Depreciation & Insurance	$ 291,784
Rent & PhRMA Accounting Services (1)	$ 294,806
Professional Services and Investment Expenses	$ 47,260
Office Expenses	$ 13,927
Subtotal – Administrative	**$ 647,777**
TOTAL EXPENDITURES	**$ 2,614,985**

[1] *Rent and Accounting Services are donated by PhRMA*

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Piscataway, New Jersey

PhRMA FOUNDATION
PROGRAMS *for* 2010

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
HEALTH OUTCOMES ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Health Outcomes (2002)	2 budgeted/ 2 years	$100,000 total $25,000 per award per year	October 1, 2010 December 15, 2010 January–August
Post Doctoral Fellowship in Health Outcomes (2002)	1 budgeted/ 2 years	$110,000 total $55,000 per award per year	October 1, 2010 December 15, 2010 January–December
Sabbatical Fellowship in Health Outcomes (2002)	1 budgeted/ 1 year	$40,000 total $40,000 per award per year	October 1, 2010 December 15, 2010 January–December
Research Starter Grants in Health Outcomes (2002)	3 budgeted/ 1 year	$180,000 total $60,000 per award per year	October 1, 2010 December 15, 2010 January 1, 2011
INFORMATICS ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Informatics (2009)	2 budgeted/ 2 years	$80,000 total $20,000 per award per year	September 1, 2010 December 15, 2010 January–August
Post Doctoral Fellowships in Informatics (2002)	2 budgeted/ 2 years	$160,000 total $40,000 per award per year	September 1, 2010 December 15, 2010 January–December
Sabbatical Fellowship in Informatics (2002)	1 budgeted/ 1 year	$40,000 total $40,000 per award per year	September 1, 2010 December 15, 2010 January–December
Research Starter Grants in Informatics (2002)	2 budgeted/ 1 year	$120,000 total $60,000 per award per year	September 1, 2010 December 15, 2010 January 1, 2011
BASIC PHARMACOLOGY ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)	9 budgeted/ 2 years	$360,000 total $20,000 per award per year	September 1, 2010 December 15, 2010 January–August
Post Doctoral Fellowships in Pharmacology/Toxicology (2002)	2 budgeted/ 2 years	$160,000 total $40,000 per award per year	September 1, 2010 December 15, 2010 January-December
Sabbatical Fellowship in Pharmacology/Toxicology (2002)	1 budgeted/ 1 year	$40,000 total $40,000 per award per year	September 1, 2010 December 15, 2010 January–December
Research Starter Grants in Pharmacology/Toxicology (1972)	3 budgeted/ 1 year	$180,000 total $60,000 per award per year	September 1, 2010 December 15, 2010 January 1, 2011

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
CLINICAL PHARMACOLOGY ADVISORY COMMITTEE			
Paul Calabresi Medical Student Research Fellowships (1974)	2 budgeted/ 6 months up to 2 years	$36,000 total $18,000 per award	February 1, 2010 May 15, 2010 July 1, 2010
Faculty Development Award in Clinical Pharmacology (1966)	1 budgeted/ 2 years	$240,000 total $120,000 per award per year	February 1, 2010 May 15, 2010 July 1, 2010
PHARMACEUTICS ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Pharmaceutics (1987)	2 budgeted/ 2 years	$80,000 total $20,000 per award per year	October 1, 2010 December 15, 2010 January–August
Post Doctoral Fellowships in Pharmaceutics (1992)	2 budgeted/ 2 years	$160,000 total $40,000 per award per year	October 1, 2010 December 15, 2010 January–December
Sabbatical Fellowship in Pharmaceutics (2002)	1 budgeted/ 1 year	$40,000 total $40,000 per award per year	October 1, 2010 December 15, 2010 January–December
Research Starter Grants in Pharmaceutics (1972)	2 budgeted/ 1 year	$120,000 total $60,000 per award per year	October 1, 2010 December 15, 2010 January 1, 2011
COMPARATIVE EFFECTIVENESS			
Pre Doctoral	2 budgeted/ 2 years	$100,000 total $25,000 per award	To Be Determined To Be Determined To Be Determined
Post Doctoral	1 budgeted/ 2 years	$110,000 total $55,000 per award per year	To Be Determined To Be Determined To Be Determined

All of the above programs will accept applications for research on drugs for rare diseases.

PhRMA FOUNDATION STAFF

DEL PERSINGER
President and CEO

EILEEN CANNON
Executive Director

CHARLOTTE LILLARD
Associate

BENEFACTORS

The PhRMA Foundation owes its success to the pharmaceutical companies that have provided their generous support over the past 45 years. We thank all of you for continuing to invest in the future of pharmaceutical research and the scientists of tomorrow.

OUR 2010 BENEFACTORS ARE

Abbott Laboratories

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Endo Pharmaceuticals

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Talecris Biotherapeutics

Vifor Pharma

ETHICAL CONSIDERATIONS The Scientific Advisory Committee as well as the program advisory committees of the PhRMA Foundation are dedicated to ensuring the appropriate use of animals and humans in research. In their deliberations, they consider all aspects of a proposal and may deny support for many reasons. Careful consideration is given to ensure the humane use and care of animal subjects. For human and animal research, the project review committee requires, in writing, a statement of adherence to prevailing standards of ethical research practices. Institutional Review Board approval is required before any research project may be initiated. In addition, informed consent is required before any person can participate in a research project.

PhRMA FOUNDATION

PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA FOUNDATION
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