2006 ANNUAL REPORT

PhRMA FOUNDATION

Pharmaceutical Research and
Manufacturers of America Foundation

PhRMA FOUNDATION

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Photographs throughout this year's Annual Report highlist some of the current and forme PhRMA Foundation annual recipients.

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.

CHAIRMAN'S MESSAGE 2006

The PhRMA Foundation has been investing in bright and talented young scientists for more than four decades, providing fellowships, grants and Center awards to encourage them to pursue a career in pharmaceutical research. At the same time, our individual companies have been supporting scientists with their own valuable programs that assist young researchers with their career objectives.

As Chairman of the PhRMA Foundation Board of Directors, I believe the time has come to combine the knowledge and financial resources of the PhRMA Foundation and our companies so we can significantly enhance our industry's impact on the landscape of pharmaceutical science. With team work and integration, we will more effectively identify special needs within the areas of drug discovery and drug development, and make a true difference in these critical disciplines.

My fellow Board members concur that, by collaborating and combining our efforts and resources, we can take the Foundation programs to a new level, greatly strengthening recognition of the industry's commitment and leadership in innovative research to serve patients worldwide. Over the next year, we will be pursuing this with member companies.

One exciting new initiative is to go beyond our traditional fellowships and research grants to provide training grants. These training grants will demonstrate the industry's commitment to young scientists as well as provide the skills they need to contribute within their discipline.

We will be able to provide the needed support by pooling our resources. Our companies already support training programs on their own. By working together, we can significantly enhance and better coordinate what the pharmaceutical industry is able to offer. We will be able to reach more young scientists and create a larger pipeline in disciplines that are underrepresented in industry today.

These new programs will succeed because they will be built on:

- Our track record of more than 40 years of providing grants and fellowships to young scientists. Many have gone on to illustrious careers in academia, government and some have made major pharmaceutical discoveries and others have mentored many scientists over their careers.
- The prestige of receiving a PhRMA Foundation award. A recent survey shows that 80% of our awardees went on to receive funding from a larger institution—proof of the status our awardees are accorded.
- Our unique network of committee members from academia and industry, who help create a vital program and evaluate applicants, and former awardees, who promote the program and encourage worthy scientists to apply.

Even as we undertake new and innovative training programs, the Foundation continues to facilitate important PhRMA efforts. The Foundation is working together with PhRMA to support researchers in two new grant programs in the areas of travel for sabbaticals or teaching and for small research projects that would be of benefit to public health and meet our goals and objectives. We are also assisting in the education of academics and the public at large to the complexity of the overall biomedical research and development process leading to the availability of new, more effective medicines. If you would like a free DVD entitled "The Biomedical Research & Development Guide," please contact Eileen McCarron at the PhRMA Foundation (emccarron@phrmafoundation.org).

The themes for the PhRMA Foundation are collaboration, teamwork, and integration with the work of PhRMA and our member companies. We ask you, our contributors, for your continued strong support, and thank you for the many contributions you have made to allow us to enhance our programs on your behalf.

Peter B. Corr, Ph.D.

Laird Forrest, Ph.D. (left) of the University of Wisconsin, Madison and Josh Ramsey, Ph.D. (right) of the University of Illinois are recognized for receiving PhRMA Foundation Post Doctoral Fellowships in Pharmaceutics at the AAPS Annual Meeting in October in San Antonio, Texas. Pictured with Eileen McCarron from the PhRMA Foundation.

PRESIDENT'S MESSAGE 2006

The PhRMA Foundation continues to be a significant asset to the pharmaceutical industry. Contributions were at a record high for the sixth straight year—surpassing the $3 million milestone for the first time. Many member companies contribute according to our recommended formula, recognizing that we have a vital program that truly makes a difference in the world of research. This high level of support is particularly impressive considering the additional financial obligations many PhRMA members are currently facing.

We are delighted to report that our applicant pool this past year was especially strong in Pharmacology/Toxicology, Pharmaceutics, Clinical Pharmacology and Health Outcomes. Each of these disciplines identified strong candidates and used their full budget for the 2006 awards.

We are working on new strategic directions this year. Proposed programs include adding large-scale training grants in disciplines important to the industry and pooling company resources to do this. We are working with PhRMA to offer and administer research grants and travel grants. And we have established more of a presence within the academic and scientific communities through our scientists who step up to help us in our efforts to promote drug discovery and development within academia and the medical community

Our programs make a difference because they support important new and innovative research. We have been told time and time again that if we had not supported scientists when we did in their careers, they would have had to drop out of research. These scientists acknowledge the fellowships and grants that enabled them to make a career in scientific discovery.

We take immense pride in the accomplishments of former award recipients and the leadership qualities they have displayed repeatedly over the years. We surveyed former award recipients recently and have heard from nearly 700 of them. From these responses, we learn that:

- 90% are still active in research
- 80% are in academia
- 14% are in industry
- 4% are in government

Fully 80% have received major funding–usually from NIH—after our award got them started. The total for this follow-on funding over the years—just for the 700 who have responded—is nearly $2 billion. Most of our awardees have referred someone else to our programs. And most are willing to speak on the importance of scientific research to key audiences, such as legislators.

This success and commitment on the part of our awardees demonstrates that our program remains strong and vital and continues to enrich the scientific pharmaceutical environment. Our program helps produce teachers of young scientists. It produces researchers and innovators within industry as well as within NIH, FDA and other vital government agencies that serve the pharmaceutical community and ultimately patients.

I want to acknowledge the hard work and dedication of our committee members who over the past 41 years have supported our programs by giving their time and expertise, even as they have managed their own demanding career and institutional goals.

We particularly value our contributors and benefactors. Without the support of our member companies, this vital organization would be unable to contribute to the scientific world as it has for more than four decades. The PhRMA Foundation has enabled scientists to thrive within their laboratories as well as in the classrooms. We have supported thousands of investigators and educators and we are proud to continue to do so.

All of these outstanding accomplishments are a testament to the continued generosity of the pharmaceutical companies and their total commitment to our organization and to the drug discovery efforts and innovation that it supports.

Thank you for your unwavering support of our program.

Del Persinger

Leah K. Lyons of the University of Miami is a recipient of the 2004 Pre Doctoral Fellowship in Pharmacology and Toxicology.

CENTER OF EXCELLENCE IN CLINICAL PHARMACOLOGY

2006

We awarded our third Center of Excellence in Clinical Pharmacology in July 2006. This program will provide $250,000 of funding per year for up to two years.

The goal of this award program is to encourage the further development of and provide unrestricted financial support for clinical pharmacology programs with commitment for significant expansion in faculty and training. Because of the financial structure at most academic medical centers, there has been a reluctance to invest in programs in clinical pharmacology, even though it is likely that many such programs could become self-supporting when provided with sufficient time and resources. It is also recognized that the needs at each academic institution may differ. In some cases, faculty support for recruitment or to provide protected time could be most important, while in other centers support of fellows or a key piece of equipment might be needed for leveraging the support for the program. This award is designed to provide substantial flexible support over a relatively brief timeframe to permit the program to become an essential and viable entity within the institution. The information for this center is as follows:

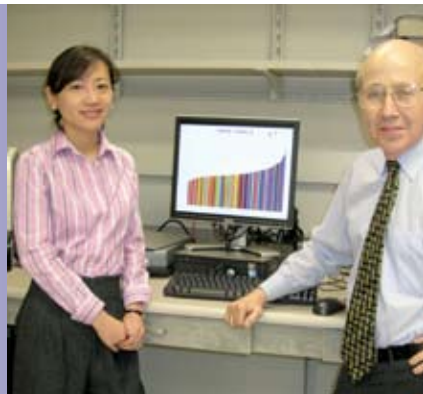
The 2006 Center of Excellence in Clinical Pharmacology was awarded to Mayo Clinic College of Medicine, under the direction of Richard M. Weinshilboum, M.D., Director, Division of Clinical Pharmacology.

Research Objectives:

The goals of the Mayo Division of Clinical Pharmacology are to perform outstanding Clinical Pharmacology research, both translational and basic, that incorporates the "New Biology", and to train the next generation of investigators and educators in Clinical Pharmacology. Achieving these goals will require the active incorporation of the evolving disciplines of genomics, proteomics and metabolomics into both Clinical Pharmacology education and research. The Mayo Clinical Pharmacology Unit—designated as a "Division" only during the past year—has a long-standing record of excellence, with the two present "core faculty" members, Drs. Richard Weinshilboum and Andre Terzic, both having served as Past-Presidents of

the American Society for Clinical Pharmacology and Therapeutics. Mayo also has an NIH-Clinical Pharmacology Training Program, and Mayo Clinical Pharmacology has been a member of the NIH Pharmacogenetics Research Network (PGRN) since the inception of that multi-institutional research network. However, even though the Mayo Division of Clinical Pharmacology has a large number of joint appointees with primary appointments in other Departments and Divisions, there is a critical need for an expanded core faculty for the Division to meet the ever-growing educational and research needs of a large academic medical center.

Therefore, the PhRMA Foundation Center of Excellence in Clinical Pharmacology Award will be used to recruit two junior core faculty members with research programs that involve the application to Clinical Pharmacology of new and evolving research techniques such as those of genomics and metabolomics. The first of these new faculty members, Liewei Wang, M.D., Ph.D., has already been recruited, and an active search is underway for the second new Clinical Pharmacology core faculty member. Dr. Wang's area of expertise is pharmacogenomics, with a background and experience in genomics and cell biology as applied to Clinical Pharmacology. The process of "renewal" represented by the recruitment of these new core faculty members will make it possible for the Division of Clinical Pharmacology at Mayo to move vigorously to incorporate bioinformatics, genomics, proteomics and metabolomics into Clinical Pharmacology to help assure that our discipline will participate in, and contribute to the biomedical scientific revolution that is currently reshaping medical research, education and practice worldwide.



Dr. Richard Weinshilboum pictured with Dr. Liewei Wang at the Mayo Clinic.

AWARDS IN EXCELLENCE 2006

The annual PhRMA Foundation Awards in Excellence honor past awardees who have gone on to distinguish themselves through their scientific and/or academic achievements. At the outset of their careers, when they were deciding on their area of specialization, these scientists received PhRMA Foundation grants in a discipline important to the research-based pharmaceutical industry. These awardees are dramatic proof that our foundation program fills a critical need in the career development of young researchers and makes a huge difference in their ability to succeed.

The two awardees for 2006 exemplify the very best in their chosen fields of clinical pharmacology and pharmacology/toxicology. The PhRMA Foundation is proud of their achievements and is gratified to have been of assistance to them at the beginning of their outstanding careers. Their successes typify the outstanding achievements of all of our awardees and underscores the importance of continuing support to those who follow in their footsteps.

The recipients of the PhRMA Foundation Awards in Excellence for 2006 are David H. Robertson, M.D. and Daniel Acosta, Jr., Ph.D.

2006 Award in Excellence in Clinical Pharmacology

David H. Robertson, M.D.

Director, Clinical Research Center, Vanderbilt University

David Robertson is an Elton Yates Professor of Medicine, Pharmacology and Neurology at Vanderbilt University, where he is director of the General Clinical Research Center. Dr. Robertson graduated from Vanderbilt University with a major in Germanic and Slavic Languages and remained at that institution for his medical degree. He did his house staff training at Johns Hopkins Hospital, serving as Chief Resident on the Osler Medical Service. He returned to Vanderbilt in 1978 and established the Autonomic Dysfunction Center which became a major international referral clinic for autonomic disorders. His clinical investigations with collaborators at Vanderbilt led to the discovery of 2 genetic disorders (DBH deficiency and NET deficiency) and elucidation of 2 acquired disorders (neuropathic postural tachycardia syndrome and selective baroreflex failure). Many agents for treatment of autonomic disorders were pioneered by physicians at Vanderbilt. In 1989 Dr. Robertson founded the American Autonomic Society as an international organization for autonomic neuroscience. He and his colleagues also conducted studies on autonomic effects of microgravity and had experiments aboard the Neurolab Mission of the Shuttle Columbia and on the Mir Space Station in the late 1990's. He is author of 4 books and many scientific articles. His *Primer on the Autonomic Nervous*

At the 2006 Annual Meeting of American Society for Clinical Pharmacology and Therapeutics (ASCPT) in Baltimore, Maryland, Darrell R. Abernethy, M.D., Ph.D. (right), the Chairman of the Clinical Pharmacology Advisory Committee, presented David H. Robertson, M.D. (left) with the 2006 Award in Excellence in Clinical Pharmacology.

System, now in its second edition, has been a widely used text on autonomic neuroscience since 1996. His trainees have become the leaders in autonomic research in this country and abroad. Teaching and mentoring medical students has always been important to Dr. Robertson and his elective in clinical management, which he developed in 1979 as a full-time, month-long course each February, has been the most highly subscribed senior elective at Vanderbilt Medical School for most of the last 25 years. ACRTPD, the American national organization representing training programs in clinical research, presented their inaugural annual Teaching Award to Dr. Robertson in March 2003 for his contributions to teaching medical students, clinical research fellows, and for his role in establishing the Association for Patient-Oriented Research. Dr. Robertson's laboratory focuses on autonomic neuroscience. The autonomic nervous system mediates the brain's control of most organ systems. The laboratory uses homologous recombination mouse models to discover the underlying mechanisms of central and peripheral regulation of heart rate, blood pressure, and the response to stress. Using a bench-to-bedside approach that merges findings from our basic and clinical research, these investigators have identified the previously unrecognized disorders of dopamine beta-hydroxylase deficiency, selective baroreflex failure, and norepinephrine transporter deficiency. Discovery of new therapeutic strategies for these disorders has flowed from these observations. Robertson's basic laboratory focuses on transgenic and knockout mice as models for hypothesis-testing. Investigative strengths of the laboratory are emphasis on systems biology and use of frontier technologies like radiotelemetry, power spectral analysis, microneurography, and biochemical and pharmacological tools to address research questions. Dr. Robertson currently serves on the Board of Advisors for the World Life Foundation, the NASA Microgravity Human Research Committee, the Merck Advisory Board, and the editorial boards of American Journal of Medicine, Autonomic Neuroscience and Clinical Autonomic Research. He is also associate editor for the Journal of Pharmacology and Experimental Therapeutics.

Dr. Robertson received a Medical Student Research Fellowship at Vanderbilt University in 1971 from the PhRMA Foundation.

2006 Award in Excellence in Pharmacology/Toxicology

Daniel Acosta, Jr., Ph.D.

Dean, College of Pharmacy, University of Cincinnati–Medical Center

Daniel Acosta, Jr. is the 4th dean of the University of Cincinnati's College of Pharmacy. He was a member of The University of Texas College of Pharmacy faculty for 22 years where he helped develop a nationally ranked program in toxicology as the first Director of the Toxicology Training Program. Dr. Acosta was also responsible for encouraging minority students to consider careers in pharmacy and biomedical research through several federal and private grants. He received a Research Starter Grant in Pharmacology/ Toxicology at the University of Texas from the PhRMA Foundation in 1976.

Dr. Acosta was presented with the Award in Excellence at the 2006 Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics (ASPET) on April 1, 2006 in San Francisco, California.

As Dean of the College of Pharmacy (first appointed in the fall of 1996) at the University of Cincinnati, he has worked closely with the faculty, staff, and administration to implement a new entry-level Pharm.D. program, which admitted its first class into the four-year curriculum in the Fall of 2000. During his tenure as Dean, he has provided direction and resources to enhance the research and scholarly activities of the faculty, such that annual external grant funding has increased from $350,000 to close to $2,000,000. Through his leadership efforts, several new degree programs have been implemented in the professional and MS/PhD programs of the college, including one of the first national Master programs in drug development. He is the first and only Hispanic dean at the University of Cincinnati and the only Hispanic dean of pharmacy among the research intensive colleges of pharmacy across the country.

His research program focused on the development of *in vitro* cellular models to explore and evaluate the mechanisms by which chemicals and drugs damage or injure specific cell types of various organs and tissues. His laboratory has developed primary culture systems of liver, heart, kidney, nerve, skin, and eye cells as experimental models to study the cellular and subcellular toxicity of selected xenobiotics. He has supervised the training of 29 MS, PhD and postdoctoral students, and over 50 high school and undergraduate students have had a research experience in his laboratory. He has published over 125 original papers in peer-reviewed journals, has authored 28 book chapters or reviews, and has edited three books. He is the editor of the third edition of *Cardiovascular Toxicology* (2001), the primary monograph in this specialty area of toxicology. He is also the editor of the journal *Toxicology in Vitro,* which is recognized for its significant scientific impact in this relatively new area of research.

He is active in numerous scientific and professional organizations, serves on several editorial boards of toxicology and *in vitro* journals, and has been appointed to a number of government and private committees. For example, he is the chairman of the FDA Scientific Advisory Board for the National Center for Toxicology Research, Past Chairman and current member of the Texas A&M External Advisory Board of the NIEHS Center for Environmental and Rural Health, a past member of the Board of Scientific Advisors for the Office of Research and Development of the Environmental Protection Agency, a past member of the National Advisory Committee to the Director of the Center for Environmental Health of the Centers for Disease Control and Prevention, a member of the NIEHS Scientific Advisory Committee on Alternative Toxicological Methods, and was recently appointed to the Committee on Toxicity Testing and Assessment of Environmental Agents for the National Academy of Sciences, which charged the committee to review the role that the U.S. Environmental Protection Agency plays in public health protection.

He is the recipient of several awards and honors, including the Burroughs Wellcome Toxicology Scholar (1986-1991), Colgate Palmolive Visiting Professor in In Vitro Toxicology (1996-97), and several endowed professorships at the University of Texas. He was elected President of the Society of Toxicology (2000-2001), which is the largest toxicology organization in the world. His most recent honor is his selection to receive the Society of Toxicology's Enhancement of Animal Welfare Award, which recognizes outstanding career contributions made by SOT members to the scientifically sound and responsible use of animals in research.

Eberechukwu Akobundu, Ph.D., 2005 Post Doctoral Fellow in Health Outcomes from the University of Maryland, Baltimore in the Department of Pharmaceutical Health Services Research.

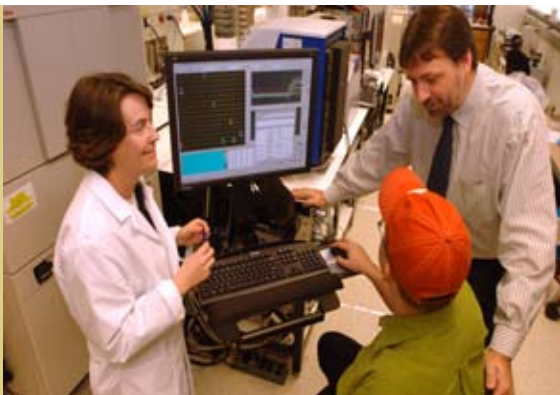
Members of Innovative Drug Discovery Team Grateful for PhRMA Foundation Support

Dr. P. Jeffrey Conn moved to Vanderbilt University in 2003 to start a new and highly innovative Program in Drug Discovery. He and key members of his program have received, or are now receiving, support from the PhRMA Foundation—an investment in training and producing young, cutting-edge scientists by the Foundation that may ultimately lead to the development of novel therapeutic strategies for a variety of serious diseases.

Dr. Conn and his associates are working to develop a detailed understanding of the cellular and molecular mechanisms involved in regulating chemical and electrical signaling in the central nervous system (CNS). Such changes in neuronal function are likely to play important roles in all normal physiological processes in the brain and are critical for development of a variety of brain diseases, including Alzheimer's disease, Parkinson's disease, schizophrenia, epilepsy, drug dependence and other neurological and psychiatric disorders.

Over the past three years, these scientists have created the infrastructure and environment needed to support discovery of small molecule reagents. They use these compounds in rigorous studies needed to directly test hypotheses coming from basic science efforts that are required to help validate a novel drug target or therapeutic approach. This is a highly multidisciplinary endeavor in which they employ a broad range of techniques including electrophysiology, biochemistry, imaging, anatomy, molecular biology, and behavioral techniques. Their facilities are now available for all Vanderbilt investigators and are supporting exciting translational efforts of a range of projects that include efforts in neuroscience, oncology, and diabetes.

Dr. Conn received a PhRMA Research Starter Grant in Pharmacology/Toxicology in 1989 when he was on the faculty of the Department of Pharmacology at Emory University. His associates, Dr. Colleen B. Niswender and Dr. Ashley E. Brady, each received Pre-Doctoral Fellowships in Pharmacology/Toxicology when they were students at Vanderbilt. Dr. Niswender also received a 1997 Post Doctoral Fellowship in Pharmacology/Toxicology from the Foundation. Dr. Carrie K. Jones received a Post- Doctoral Fellowship in Pharmacology/Toxicology in 2006 and continues to receive our support.



Here they are in their own words:

Dr. P. Jeffrey Conn

"The past decade has witnessed unparalleled advances in our understanding of basic biological processes that contribute to a host of human disorders. Today, we have an unprecedented understanding of the mechanisms underlying complex human disease, such as Alzheimer's disease, diabetes, multiple cancers, schizophrenia, and others. This provides key new insights that could provide paths to fundamental advances in care or even cures for patients suffering from these disorders.

Despite this progress, use of this knowledge to realize practical gains in health care has moved slowly. A major challenge facing today's biomedical research community is translation of the extraordinary progress of recent years into fundamental advances in human health and patient care. To realize the promise of recent advances in biomedical research, there must be a greater focus by academic scientists on rigorously testing hypotheses related to novel therapeutic approaches and taking these to a point at which they can be seamlessly adapted into full drug discovery and development programs in industry settings.

These critical issues were the major motivating factors in my decision to move to Vanderbilt to launch a new Program in Drug Discovery. As academic scientists, we do not see our mission as taking a program all the way from early basic science findings to discovery and development of a clinical candidate. This full range of drug discovery and development must rely on the expertise and infrastructure present in the pharmaceutical industry. Our translational efforts are successful when they directly lead to launching of full drug discovery efforts by our industry colleagues.

My own research is highly focused on discovery of novel approaches to treatment of serious disorders of the central nervous system. To insure that our resources are focused on programs that will have direct impact on discovery of therapeutic agents, most of our work is driven by findings from clinical studies that provide compelling insights for novel approaches to development of clinically active drugs. This "bedside to bench" approach to driving basic research provides a powerful and proven paradigm for discovery of new medicines."

Dr. Colleen Burns Niswender

"I obtained my Ph.D. in 1996 in the lab at Vanderbilt University Medical Center. I was awarded a PhRMA Predoctoral Fellowship in Pharmacology which funded my graduate training from 1994 until 1996. My studies expanded upon my interests in molecular biology and gave me direct hands-on training in basic pharmacology and signal transduction. I was then awarded a PhRMA Postdoctoral Fellowship in Pharmacology from 1997 to 1998.

Funding from the PhRMA Foundation was critical to the success of both my pre- and early postdoctoral careers and to my move to a postdoctoral position at the University of Washington. My postdoctoral studies

focused on the study of signal transduction mediated by the enzyme Protein Kinase A. These studies were funded by a National Research Service Award (NRSA) from the NIH. This grant that was secured, in part, by the novelty of the project but also because of my previous track record in obtaining funding--a factor for which I am most grateful to my previous grants from PhRMA.

In 2004, my husband and I were recruited back to Vanderbilt and I joined the Conn laboratory. I am excited by the translational design of the Conn group. We have assembled a highly collaborative team of molecular pharmacologists, electrophysiologists, and behavioral pharmacologists to generate and validate new tools and potential lead therapeutics for several central nervous system targets.

I am particularly interested in investigating the therapeutic potential of the group III mGluRs for the treatment of CNS disorders. Work by the Conn group and other labs has shown that direct activation or "potentiation" of several of the group III mGluRs can be effective in both modulating circuitry within brain regions critical for regulating movement and in reversing movement deficits in preclinical models of Parkinson's disease."

Dr. Carrie K. Jones

"Over the course of my professional training, I have taken a multidisciplinary approach while working both in academia and industry to understand the underlying pathophysiology of two important areas of neuroscience--specifically schizophrenia and chronic pain.

As a graduate student, I investigated the role of the muscarinic cholinergic system and its interactions with the dopaminergic system in the mechanisms of prepulse inhibition of the acoustic startle reflex in rodents, a preclinical model used to assess the cognitive impairments observed in individuals with schizophrenia and other psychiatric disorders. These findings not only contributed to the ongoing drug discovery efforts at Lilly Research Laboratories but also resulted in several publications in well-refered journals. This experience solidified my long-standing interest in schizophrenia research and stimulated my interest in drug discovery and development.

During my graduate training, I also worked full-time as an in vivo pharmacologist and key contributor on several scientific teams focused on the development of novel therapeutics for the treatment of chronic pain in the Neuroscience Division at Lilly Research Laboratories. My research contributed to the development of the antidepressant serotonin/norepinephrine reuptake inhibitor duloxetine which has been found to have efficacy in the treatment of fibromyalgia and painful diabetic neuropathy.

As a postdoctoral fellow working in the Lilly Research Laboratories, I became convinced that my scientific interests and career development would be best served by a transition from pharma to a translational pharmacology program in academia. As a recipient of a postdoctoral fellowship this year from the PhRMA

Foundation, I have been able to make a successful transition to academia and have recently been awarded an NRSA training grant from the NIMH. I am grateful for the PhRMA Foundation funding, which has made it possible for me to take optimal advantage of, and extend, my training in Dr. Conn's laboratory in order to more rapidly transition to being an independent investigator."

Dr. Ashley E. Brady

"An early interest in biology and chemistry led me to pursue an undergraduate degree in biochemistry and molecular biology. During my studies, it became clear to me that I was particularly interested in the mechanisms by which signal transduction pathways allow hormones and neurotransmitters to communicate with intracellular molecules to effect changes in cells. What was even more exciting to me was the fact that a better understanding of these mechanisms would allow us to target specific molecules within these signaling systems as therapeutic targets. With this goal in mind, I decided to enter a graduate program in biomedical research.

I obtained my Ph.D. in pharmacology in 2003 in the laboratory of Dr. Lee E. Limbird at Vanderbilt University. My graduate work focused on understanding the role of the interacting protein spinophilin on $_2$-AR trafficking.

Currently I am a post-doctoral research fellow in the laboratory of Dr. Conn at Vanderbilt University where I continue to pursue my interest in G protein-coupled receptor pharmacology. My work is now focused on drug discovery and translational neuropharmacology. Dr. Conn is a highly accomplished pharmacologist with experience in both academia and industry--thus he brings a very unique perspective to traditional academic research.

I am particularly motivated to be a part of the scientific community actively engaged in bridging the gap between basic science and therapeutics, specifically in the area of neuroscience, and I felt that he and his laboratory were among the best places for me to gain this experience. The laboratory environment is highly collaborative and allows for me to interact with and learn from a diverse team of molecular pharmacologists, electrophysiologists, *in vivo* animal behavioral pharmacologists, and chemists."

The PhRMA Foundation is proud of the support it has been able to provide to Dr. Conn and his team of innovative young scientists. Breakthroughs by researchers like them and others supported by the Foundation pave the way for the new and novel therapeutic approaches that will be a hallmark of the pharmaceutical industry of the future.

2006 FELLOWSHIPS AND GRANTS

The PhRMA Foundation's primary mission is to encourage young scientists to pursue careers in research and education related to drug discovery by providing funding to university-based scientists, and educators for scientific and medical research. The Foundation's current program includes a Center of Excellence—in Clinical Pharmacology. Pre Doctoral, Post Doctoral, and Sabbatical Fellowships are offered as well as Research Starter Grants. Fellowships and Research Starter Grants are offered in Health Outcomes, Informatics, Pharmaceutics, and Pharmacology, which includes Toxicology, and Clinical Pharmacology. The Foundation accepts applications in all program areas for research on drugs for rare diseases.

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 pharmacuetical research that incorporates Informatics.

Receiving the fellowship that began between January and December 2006 is:

Debbie W. Lin, University of California, San Francisco: **"Tenofovir Induced Nephrotoxicity."** The antiviral reverse transcriptase inhibitors, adefovir and cidofovir, have been found to produce direct renal tubular toxicity in clinical trials. Recent studies have found that a third generation nucleotide reverse transcriptase inhibitor, tenofovir is also associated with nephrotoxicity; however, studies in isolated human proximal tubule cells have failed to support a direct tubular toxicity for this drug. Isolated cells in culture may not mimic the *in vivo* situation. In particular, function of transporters that mediate influx of potentially nephrotoxic agents may be lost. Tenofovir, a potent and less nephrotoxic analog of adefovir and cidofovir, is now widely used for the treatment of HIV infection and is being studied as a treatment for hepatitis B infection. The risk of nephrotoxicity due to tenofovir as reported in cohort studies remains unclear. Some studies have reported little or no risk. Previous reports on the incidence of tenofovir-induced nephrotoxicity have been limited to clinical case studies, however; in recent studies, the cumulative incidence of tenofovir-associated renal impairment is greater than the previously reported 1 percent. Finally, the follow-up on these studies is now approximately three years; given the time-dependent emergence of renal toxicity with adefovir, it is possible that renal disease may emerge with long-term follow-up. Ms. Lin proposes to conduct an epidemiological study of tenofovir associated renal impairment in a nationwide prospective cohort of HIV infected women. Laboratory and drug related data from this cohort will be used to answer questions about risk factors, demographics, and prevalence associated with tenofovir associated renal impairment. The main goals of this project are to take both a population-based and phenotype to genotype approach to determine the frequency of tenofovir associated renal impairment in patients on HIV therapy, to determine the contributing risk factors of tenofovir associated renal impairment, to determine whether or not the combined tenofovir and ritonavir regimen is associated with increased nephrotoxicity as compared to tenofovir only, and to understand the effect of genetic variation on tenofovir associated nephrotoxicity.

Michael A. Thomas, Ph.D., Assistant Professor, Department of Biological Sciences Idaho State University. Dr. Thomas is a recipient of the PhRMA Foundation 2005 Research Starter Grant in Informatics.

Research Starter Grants in Informatics

This program supports individuals beginning independent research careers in academia. Applicants must be appointed to an entry-level tenure-track or equivalent permanent position in a department or unit responsible for Informatics activities as part of its core mission.

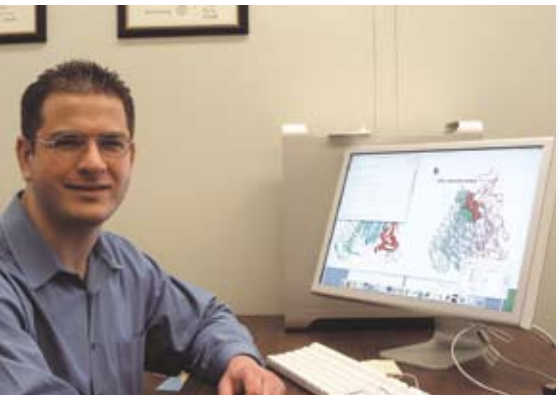
The program provides a research grant of $30,000 per year for up to two years. The "starter" aspect of the program strives to assist those individuals who are establishing careers as independent investigators.The program is not offered as a means to augment an ongoing research effort.

Receiving the grants that began in January 2006 are:

Atul J. Butte, M.D., Ph.D., Stanford University School of Medicine: **"Identifying Novel Therapeutic Indications Using a Genomic Nosology."** They hypothesize that microarrays, now commonly used to measure the amounts of tens of thousands of genes, can be used to classify diseases in a new, more precise way. They propose to build the first data-driven classification scheme for one-hundred diseases across all of medicine, using publicly-available gene measurements. These diseases include HIV infection, Parkinson's disease, Marfan's syndrome, cocaine dependence, leishmaniasis, congestive cardiomyopathy, pulmonary hypertension, clear cell carcinoma of kidney, multiple sclerosis, familial combined hyperlipidemia, and many others. After building this new classification scheme, they will compare this scheme to a pathologist-driven classification scheme used world-wide and which has been in development for nearly a century. Our classification scheme will be particularly useful to find diseases that have very similar gene patterns, but that are currently not thought of as being similar diseases. They hypothesize that they will be able to take drugs for such diseases and use them for alternative diseases with similar gene patterns.

Amar K. Das, M.D., Ph.D., Stanford University School of Medicine: **"Knowledge-Driven Discovery of Drug Resistance Patterns in Biomedical Databases."** The objective of the proposed research is to develop a computational method for the automated discovery of scientifically meaningful temporal associations in biomedical genomics databases. The study focuses on the discovery of drug resistance patterns using the Stanford HIV Database (HIVdb), which contains longitudinal data on HIV genotype test results, drug regimens, and clinical outcomes. There are major gaps in what is known about HIV drug resistance in patients receiving the complex drug combinations that represent the standard of care today. Clinical investigators are particularly interested in establishing which mutations are likely to arise after a given treatment history and which mutations are predictive of poor clinical response to a particular treatment. Investigators are often challenged by the need to apply biomedical knowledge repeatedly to extract such patterns from time-course data. The proposed research efforts will first create a computable knowledge model, or ontology, of drug resistance patterns. The work will then develop a temporal association-rule mining algorithm that uses the ontology to search efficiently among hundreds of thousands of temporal associations in HIVdb for those patterns that make biological sense. The mining algorithm will be next built into general database querying facilities that allow direct use of the computational method. Investigators can maintain the results of a data-mining session in a knowledge repository structured by the ontology. Preliminary analysis of protease gene mutations in HIVdb indicates that the approach reveals clinically meaningful drug resistance patterns, the novelty of which can be readily assessed against findings from prior studies. Through tailoring of the ontology, the proposed computational method can be adapted to other biomedical genomics databases.

Zhijun Li, Ph.D., University of the Sciences in Philadelphia: **"Understanding Membrane Protein Packing Through Network Analysis."** Membrane proteins account for approximately 30% of the human genome and are targets of roughly 50% of drugs currently available in the marketplace. They are essential to many cellular activities and defects in their structure may cause disease. Despite their importance to health, there are less than 100 unique high-resolution structures determined experimentally for these proteins, mainly due to technical difficulties. Understanding membrane protein packing and developing structure modeling tools based on the packing knowledge are thus critical to studies of the biological roles of membrane proteins and to the development of new drugs targeting them. The long-term objective of this project is to elucidate the underlying principles governing membrane protein packing in the lipid bilayer environment. The work proposed here includes two principal parts. First, developing and implementing computational network tools for the characterization of the global and local properties of membrane protein structures. Various aspects of the protein structures will be examined using these tools. Features common to all transmembrane regions will be identified and utilized as basic rules governing native membrane protein folds. Second, applying the new knowledge obtained to the differentiation of



Ian J. Laurenzi, Ph.D., from Yale University, received a 2004 Post Doctoral Fellowship in Informatics.

native membrane protein folds from non-native ones and to the modeling of membrane protein structures. The proposed work will provide the first opportunity to examine and analyze membrane protein structures from the perspective of networks. Comparable studies on globular proteins strongly suggest that it will significantly advance our understanding of membrane protein packing.

HEALTH OUTCOMES

Pre Doctoral Fellowships 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 $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.

Receiving the fellowships that began between January and March 2006 are:

Andrea M. Ireland, M.P.H., The University of North Carolina, Chapel Hill: **"The Effect of Family Adaptive Resources on Asthma Emergency Department Utilization for Urban, African-American Children."** Asthma is a lung disorder that involves chronic inflammation of the pulmonary airways. This inflammation causes children to experience recurrent episodes of wheezing, shortness of breath, cough, chest tightness, and sputum production. Emergency department utilization for acute episodes of asthma represents an adverse health outcome for children because these events are preventable. Racial differences in pediatric asthma ED utilization are well-documented in the literature. These disparities may signal problems in the health care system infrastructure that prevent optimal health services utilization not only for African-American children but potentially all children. Risk factors of pediatric asthma emergency department utilization are disproportionately represented among African-American children and their families. In an effort to address the methodological limitations of race-stratified studies, this research project will focus this research inquiry solely on African-American families. Ms. Ireland's project is noteworthy because it will represent the first study to investigate risk factors of asthma emergency department utilization for over 1,000 African-American children. Using data from Phase 1 of the National Cooperative Inner City Asthma Study (NCICAS), this study will explore the association of two non-economic family resources, social support and family functioning, on pediatric asthma-care utilization. The results from this study could advance public health practice by providing guidance in the development of innovative, culturally competent asthma interventions tailored to the family's psychosocial assets and vulnerabilities.

Lisa M. Meckley, University of Washington School of Pharmacy: **"Clinical Utility, Cost Effectiveness, and Provider Perceptions of CYP2C9 and VKORC1 Genotyping for Chronic Warfarin Therapy."** Currently, there is tremendous interest in pharmacogenetic testing for a variety of drugs. One drug with evidence of a pharmacogenetic effect is warfarin, which is an effective anticoagulant with narrow therapeutic range. Recent studies have identified two genes, CYP2C9 and VKORC1, which influence warfarin dose in addition to demographic and medical characteristics. An algorithm including genetic tests may allow for more accurate warfarin initiation doses. It is unclear whether clinicians would use an algorithm either including or excluding genetic information before initiating warfarin dose. The purpose of this study is to determine the utility and usefulness of genetic testing for warfarin management. The first objective is to determine the added value of knowledge of CYP2C9 and VKORC1 genotypes in initiating warfarin dose. This will be accomplished by developing a dose initiation algorithm using a retrospective cohort. The second objective is to gather information about the range of practice patterns with respect to warfarin as well as to ascertain clinicians' perceptions toward the use of genetic testing to guide warfarin therapy. Key informant interviews will be used to elicit this information. The final objective of this research to assess the potential cost effectiveness of using CYP2C9 and VKORC1 genotype information to help guide warfarin therapy by developing a decision analytic model. The findings of this research will provide a concrete example of the utility of pharmacogenomics as well as potentially improve anticoagulant patient care.

David K. Blough, Ph.D., Research Associate Professor, Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy, University of Washington. In 2003 Dr. Blough received a Research Starter Grant in Health Outcomes.

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 $40,000 annual stipend for up to two years.

Recipient of the Post Doctoral Fellowship that began in September 2006 is:

Basit I. Chaudhry, M.D., University of California, Los Angeles, Division of General Internal Medicine: **"The Impact of a Comprehensive Health Information Technology System of Quality of Care."** Information technology holds the potential to transform the healthcare system. Despite this potential, most care is delivered through paper charts. New technologies such as electronic health records and computer order entry systems offer new ways of managing healthcare information and data. Dr. Chaudhry's project examines the impact that the Veterans Health Administration's (VHA) Computerized Patient Record System (CPRS) has had on improving quality of clinical care. CPRS is currently the most widely used clinical information technology system in the U.S. However, the system was adopted gradually by different facilities at different times. This study evaluates how care improved as CPRS was implemented over time.

Research Starter Grants in Health Outcomes

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

The program provides a research grant of $30,000 per year for up to two years. 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.

Recipients of the Research Starter Grants that began in January 2006 are:

Duska M. Franic, Pharm.D., Ph.D., The University of Georgia College of Pharmacy: **"Stuttering Therapy and Neurophysiological Interaction."** Effective outcome measures in stuttering are critical in the assessment, treatment and understanding of stuttering. Although such variables have been discussed in this discipline, effective tools to assess quality of life have eluded the field. Measurement and improvement of quality of life has also been identified as one of the central public health goals for the nation in Healthy People 2010. The broad long-term objective of this proposal is to assist clinicians and researchers in evaluating their patients' progress to stuttering therapy, from their patients' perspective. The two primary goals of this proposal are: (1) to compare the short and long term patient reported outcomes of two treatment approaches (prolonged speech, PS and modifying phonation intervals program, MPI) in adult stutterers based on the psychometric criteria presented by McHorney and Tarlov (1995) as required for individual decision making in clinical and research applications including reliability, validity, and responsiveness; and (2) to conduct an economic analysis: a cost utility analysis. The results of this study will add to the understanding of the burden of stuttering both in terms of the impact on the stutterers' quality of life and also in terms of the burden of the costs of stuttering treatment programs. Methods to test the first goal involve incorporation of standard quality of life measure. Methods to test the second goal involve conducting an economic analysis. It is anticipated that from the results of this study recommendations can be made to decision makers regarding the costs and outcomes of a new treatment approach, MPI, versus the standard of care, PS, allowing stuttering to benefit from economic and quality of life methods used widely in other areas of healthcare. Establishing the value of outcomes assessment in stuttering will support innovative pharmaceutical approaches in the future. This is of importance in a discipline known for its limited reimbursement by benefit managers for treatments.

Winghan Jacqueline Kwong, Pharm.D., Ph.D., The University of Georgia College of Pharmacy: **"Effect of Continuity of Migraine Care Following Emergency Department Visit on Health Care Resource Use and Expenditures."** The dwindling supply of emergency department (ED) services and increasing demand from patients have led to overcrowding in many EDs, and potentially lengthening the waiting time for the seriously ill and injured who deserve the urgent attention of health care professionals. The overcrowding problem is further exacerbated by over-utilization of the emergency

The PhRMA Foundation presented the 2006 fellowships and grants in Health Outcomes at the 11th Annual Meeting of the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) on May 23, 2006 in Philadelphia, PA. Pictured from left to right; Duska M. Franic, Pharm.D., Ph.D., University of Georgia, Jackie Kwong, Pharm.D., Ph.D., University of Georgia, Amy L. Pakyz, Pharm.D., M.S., Virginia Commonwealth University, James W. Shaw, Ph.D., Pharm. D., M.P.H., Thomas Jefferson University, Basit I. Chaudhry, Ph.D., University of California Los Angeles, and Lisa M. Meckley, University of Washington School of Pharmacy.

departments for non-urgent medical problems. Although patients seeking care from the ED are often instructed to follow up with their primary care physicians at the time of ED discharge, patient compliance with follow-up care is uncertain. The effectiveness of follow-up care on reducing future ED visits and improving patient outcomes is also unknown. In a 2004 report from the Centers for Disease Control and Prevention, headache was noted as the sixth most common reason for visit to the emergency room. Although not all headaches are migraines, previous studies have found that migraine sufferers used emergency services more often than non-migraine patients. Using migraine patients as a study sample, the purpose of this study is to estimate the prevalence of follow-up care following ED discharge, and assess the effectiveness of follow-up care on reducing future emergency department visits for migraine. A retrospective analysis of medical and pharmacy administrative claims data of Medicaid beneficiaries will be performed. The results of this study will inform health policy on improving access of emergency care, and facilitate the development and evaluation of program interventions to reduce inappropriate ED visits.

Amy L. Pakyz, Pharm.D., M.S., Virginia Commonwealth University: **"Incidence and Risk Factors for *Clostridium difficile*-associated Diarrhea (CDAD) in Patients within University HealthSystem Consortium Hospitals."** Diarrhea in hospitalized patients is commonly associated with infection by the *Clostridium difficile* bacteria. CDAD has a large impact on patient morbidity and health care resources. Recent reports have indicated the extent to which CDAD has become a particular microbial threat in health care institutions. These reports show an increase in the number of resistant CDAD cases that do not respond to first-line antibiotic treatment. In addition, there is an increase in the risk of relapse after treatment of CDAD, and an increase in the number of cases of CDAD causing complications such as toxic megacolin, perforation, colectomy, shock, and death. Improved surveillance of CDAD is needed in hospitals, but it is difficult to establish large and reliable surveillance systems. The purpose of this project is to characterize the incidence of hospital-acquired CDAD in a network of university hospitals and to identify links between hospital antimicrobial usage, hospital demographic factors and CDAD incidence rates. Additionally, a case-control study will identify patient factors associated with CDAD, including previous antimicrobial treatment. CDAD occurs almost entirely in patients who have received previous antimicrobial treatment and therefore antibiotic therapy is generally regarded as the main consistent modifiable risk factor for CDAD. Almost all antibiotics have been implicated with CDAD in hospitalized patients, but the risk of promoting CDAD is not considered equal among different antibiotics. This project will allow us to identify which antibiotic classes, or antibiotics in particular, are the most important in the development of CDAD. This will lead to targeted interventions to reduce risk of developing CDAD, decrease rates of CDAD, and subsequently reduce CDAD related morbidity and mortality.

James W. Shaw, Ph.D., Pharm.D., M.P.H., Jefferson Medical College, Thomas Jefferson University: **"Development of the Smoking-Related Quality of Life Questionnaire (SRQLQ)."** Each year roughly 440,000 Americans die as a result of smoking-related illnesses. Although the health consequences of cigarette smoking are known, there have been few efforts to assess its impact on quality of life. The Smoking Cessation Quality of Life (SCQoL) questionnaire was developed to assess the impact of smoking and its cessation on health-related quality of life. In spite of its popularity, the SCQoL suffers from a number of problems that limit its usefulness as an outcomes measure. The goal of the proposed research is to develop a novel Smoking-Related Quality of Life Questionnaire (SRQLQ) with improved conceptual and measurement properties relative to the SCQoL. Items will be generated through a series of focus groups and the resulting draft questionnaire pilot tested at sites in Philadelphia, Pennsylvania and Tucson, Arizona. At an initial clinic visit, participants will be classified by smoking status and intent to quit as precontemplative smokers (SM1), preparatory smokers (SM2), former smokers (FS), or never smokers (NS). Data will be collected from participants in all four groups at baseline. Those in the SM1, FS, and NS groups will be reassessed at 2 weeks after the baseline evaluation. Clinic staff will assist members of the SM2 group in developing a quit plan and setting a quit date within 1 month of the baseline assessment. Follow-up assessments will then take place at various time points after the quit date. Exploratory factor analysis will be used to evaluate the dimensional structure of the draft SRQLQ. Test retest reliability will be assessed by estimating the correlation of baseline and 2-week scale scores for the SM1, FS, and NS groups. Validity will be assessed by comparing baseline scale scores among the SM1, FS, and NS groups. Finally, using data collected from the SM2 group, responsiveness will be evaluated by comparing changes in scale scores at 6 months between abstainers and current smokers. Once validated, the SRQLQ may be used in randomized trials of pharmaceutical and behavioral smoking cessation interventions as well as observational studies of the effects of smoking cessation.

Del Persinger and Eileen McCarron congratulate Lisa Meckley (center) from the University of Washington on receiving a 2006 Pre Doctoral Fellowship in Health Outcomes at the ISPOR Annual Meeting in Philadelphia, Pennsylvania.

PHARMACOLOGY

Pre Doctoral Fellowships 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 disserations 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 disseration.

Three hundred and seventeen fellowships have been awarded under his program since it began in 1978 including he ten fellows awarded in 2006.

Those who received fellowships that began between January and August 2006 are:

Sarah N. Barnes, University of Connecticut: **"Regulation of Hepatic Transporter Expression by Inflammatory Mediators During Drug-Induced Liver Injury."** Hepatocytes exhibit enhanced resistance to acetaminophen (APAP) or carbon tetrachloride (CCl_4) following pre-exposure to sublethal doses of the same hepatotoxicant or a different one. It is likely that this resistance involves multiple compensatory mechanisms. Alterations in the expression and function of efflux transport proteins (e.g. multidrug resistance-associated proteins, Mrps) and proteins mediating chemical influx (e.g. organic anion transporting polypeptides, Oatps; Na^+-taurocholate co-transporting polypeptide, Ntcp) may lead to xenobiotic resistance by preventing the accumulation of potentially toxic compounds in the liver. While the changes in transporter expression following chemical injury (caused by APAP or CCl_4) have been well characterized by this laboratory, the regulatory mechanisms involved are not yet fully understood. They propose that inflammatory mediators generated during chemical-induced liver injury and recovery are involved in regulating hepatic membrane transporter expression. The research will specifically address the potential for IL-6 and TNF cytokine signaling to regulate uptake and efflux hepatic transporter levels following APAP and CCl_4 treatment. In addition they will investigate the cellular source of cytokines responsible for transporter regulation, specifically focusing on Kupffer cell-derived inflammatory mediators. Hepatobiliary transporters are important determinants of the disposition of xenobiotics, therefore understanding the mechanisms underlying altered expression during chemical liver injury may help to predict the susceptibility of individuals with acute liver disease to further damage by drugs whose disposition from the liver is transporter-dependent.

Damon B. Bowe, The University of Alabama at Birmingham: **"The Role of O-G1cNAc in Mammary Development and Oncogenesis."** Breast cancer is a genetic disease developing from dysregulation of hormone-dependent transcription factors. Hormone-induced gene transcription is enhanced by coactivators and repressed by nuclear hormone co-repressors, such as mSin3A. The enzyme, O-GlcNAc transferase (OGT) associates with the co-repressor mSin3A to inhibit gene transcription. By modifying transcription activators via O-GlcNAcylation, OGT cooperates with histone deacetylase to shut-off hormone-dependent transcription. NCOAT (Nuclear and Cytoplasmic O-GlcNAcase and Acetyltransferase), a bifunctional enzyme with both O-GlcNAcase and histone acetyltransferase activities, may associate with proteins involved in repression. The current project investigates the role of NCOAT in governing cellular processes dependent upon nuclear hormone receptor activation. Preventing the removal of O-GlcNAc from intracellular proteins appears to repress expression of nuclear hormone receptors. Moreover, overexpression of a NCOAT variant that cannot remove O-GlcNAc residues from proteins in the mouse mammary gland causes a phenotype related to aberrant expression of progesterone receptors. These studies provide insight into the fundamental regulation of nuclear hormone receptors and serve as a basis for this development of a novel therapeutic intervention strategy for breast cancer which exploits the O-GlcNAc regulatory system.

Jennifer B. Dennison, Indiana University School of Medicine: **"Vincristine Metabolism and the Role of CYP3A5."** Although vincristine has been used clinically for cancer chemotherapy since the 1960's, clinical outcomes of vincristine therapy, both neurotoxicity and efficacy, continue to be unpredictable. One explanation for this inter-individual variation is that vincristine systemic exposure varies between individuals. Because interracial differences in efficacy have been reported, certain genetic factors may also influence clinical outcome. This research explores the possibility that vincristine metabolism and ultimately drug exposure are affected by genetic polymorphisms of CYP3A5, one enzyme in the CYP3A subfam-

Aliasger K. Salem, Ph.D., from the University of Iowa, received a Research Starter Grant in Pharmaceutics in 2005.

ily thought to metabolize vincristine. CYP3A5 genotype may be a clinically significant factor in the interracial and inter-individual variation of vincristine disposition and response. Understanding of the variation in vincristine exposure caused by the polymorphic expression of CYP3A5 may allow identification of patient-specific risk factors for neurotoxicity or even individualized therapy options to minimize patient relapse.

Katherine W. Figueroa, University of California, Irvine: **"Use of Intrinsic Relative Activity Values to Determine if Agonist-receptor Complexes Direct Signaling Through Promiscuous G Proteins."** Drugs that interact with G protein coupled receptors represent approximately 40–50% of marketed drugs; consequently, research designed to enable improved characterization of ligands with less laborious calculations is likely to have a substantial impact on the drug development process. This lab has developed a method of analysis for estimating the product of the affinity and intrinsic efficacy of an agonist expressed relative to that of a standard agonist. This estimate, termed *intrinsic relative activity*, is independent of downstream signaling events and is dependent entirely on the receptor-G protein interaction. All that is required for the estimation of intrinsic relative activity is the concentration-response curve of the agonist. An aim of this research is to investigate how the pharmacological activity of an agonist at a G protein coupled receptor is influenced by the nature of the specific G protein with which the receptor interacts and how this interaction influences the response of the organ to receptor activation. If an agonist has a differential effect on the nature of the G proteins with which the receptor normally interacts, it should be possible to detect this phenomenon using the measure of intrinsic relative activity. These studies will enable a direct correlation between the action of a drug in a highly defined recombinant system with that in a natural tissue or organ utilizing the same signaling pathway, from which reasonable conclusions can be drawn about pharmacological activity in the living animal. Also, the use of mutant G proteins in this research has direct relevance to drug discovery programs where these G proteins are used as transducers for orphan receptors whose endogenous ligands and signaling pathways are unknown.

Elizabeth A. Hackler, M.S., Vanderbilt University School of Medicine: **"The Role of 5-HT_{2C} Receptors in Drug-induced Anxiety States."** The 5-Hydroxytryptamine 2C (5-HT_{2C}) receptor is a member of the 5-HT_2 subfamily of G- protein coupled receptors. Activation of 5-HT_2 receptors by the nonselective 5-HT_2 receptor agonist, m-chlorophenyl piperazine (m-CPP), elicits anxiety in humans and anxiety-like behavior in animals. However, the 5-HT_{2C} receptor contribution to m-CPP-induced anxiety remains unclear. M-CPP has been proposed as a pharmacological probe for 5-HT_{2C} receptor activation *in vivo*, via fMRI studies in both rats and humans. Since m-CPP is nonselective, studies with a specific 5-HT_{2C} receptor antagonist should be performed to verify that the regional brain activation observed is solely due to 5-HT_{2C} receptors. Furthermore, activation of 5-HT_{2C} receptors modulates GABA-A receptor function by reducing inward ionic current. This suggests interplay between these two receptors and that 5-HT_{2C} receptor activation is integral to generating anxiety. The goal of this project is to evaluate m-CPP as a pharmacological fMRI (phMRI) probe for measuring 5-HT_{2C} receptor activation in rats, as well as to assess the role of this receptor in anxiety-like behavior elicited by FG-7142, a GABA-A receptor inverse agonist. To address the involvement of the 5-HT_{2C} receptor in drug-induced anxiety-like states, anxiogenic doses of both m-CPP and FG-7142 will be established in rats by the social interaction behavioral test. The anxiogenic dose of these substances will be systemically administered in rats for subsequent fMRI studies. By utilizing m-CPP and FG-7142 to mimic pathological anxiety-like states, this lab will analyze regional and temporal brain activation looking for commonalities. Pretreatment with a selective 5-HT_{2C} receptor antagonist will reveal the extent to which this receptor contributes to BOLD signal changes induced by m-CPP and FG-7142. *They hypothesize that pretreatment with SB 242084, a selective 5-HT_{2C} receptor antagonist, will significantly blunt neuronal activation elicited by an anxiogenic dose of both m-CPP and FG-7142.* Findings from this project will advance the understanding of anxiogenic neural circuitry in the brain and the role of the 5-HT_{2C} receptor in activating that circuitry. Since anxiety disorders are the most common type of mood disorder in humans, it is imperative that scientists discover and design better therapeutics.

Kerri A. Holick, Columbia University: **"Investigation of Mechanisms Underlying Delayed Onset of Therapeutic Efficacy of Antidepressant Drugs."** Selective serotonin reuptake inhibitors (SSRIs) are an effective class of antidepressant drugs, yet treatment of mood disorders with these compounds is impaired by a delayed onset of the therapeutic efficacy of these compounds in patients. The goal of this work is to study the underlying mechanisms of the therapeutic efficacy of antidepressant drugs in order to identify novel drug targets for improved antidepressant treatments. Many antidepressant compounds modulate the serotonergic system, in addition to enhancing neurogenesis in the adult mammalian brain. However, changes both in the serotonergic tone and in adult hippocampal neurogenesis are time-dependent, requiring

Recipients of the PhRMA Foundation Grants and Fellowships in Pharmacology/Toxicology receive their awards at the 2006 Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics (ASPET). Pictured from left to right are Brian W. Jones, University of Rochester, Katherine W. Figueroa, University of California, Irvine, Elizabeth A. Hackler, Vanderbilt University School of Medicine, Damon B. Bowe, the University of Alabama at Birmingham and Elvira L. Liclican, New York Medical College.

weeks of sustained drug administration in animals to emerge. First, selective ablation of adult hippocampal neurogenesis will permit the exploration of whether the birth of new neurons in this brain region is required for the behavioral effects of SSRIs in mouse models sensitive to the chronic administration of these drugs. Secondly, the role of a specific neurotransmitter receptor, the 5-HT_4 receptor, in mediating these same behavioral effects of SSRIs in mice will be investigated. The 5-HT_4 receptor is a Gs-coupled GPCR that activates adenylyl cyclase to upregulate cAMP. Through cAMP, PKA is activated and subsequent phosphorylation of the transcription factor CREB results. CREB binding to DNA can upregulate the expression of BDNF and other genes that promote neuroplasticity. Taken together, it is proposed that 5-HT_4 receptor activation may promote neurogenesis or other plastic changes within the brain that may be necessary for the slowly developing therapeutic response to SSRIs. Compounds that promote neuroplasticity in the adult brain and/or activate the 5-HT_4 receptor may yield novel, and perhaps faster-acting, antidepressant treatments.

Brian W. Jones, University of Rochester Medical Center: **"Phosphorylation of the Thyrotropin-releasing Hormone Receptor in Pituitary Cells and Tissues."** The thyrotropin-releasing hormone (TRH) receptor is a member of the large family of signaling proteins known as G protein-coupled receptors (GPCRs). In the anterior pituitary, the TRH-signaling pathway controls the synthesis and release of thyroid-stimulating hormone, and is essential for proper thyroid regulation. After becoming activated, most GPCRs are phosphorylated by second-messenger-activated kinases or by GPCR kinases that recognize the active state of the receptor. Phosphorylation coordinates receptor desensitization and internalization. Resensitization, which is believed to be dependent on dephosphorylation, is particularly important for GPCRs like the TRH receptor that likely respond to pulsatile agonist secretion. In order to determine when the TRH receptor is utilized *in vivo,* this research will use phosphorylation as a marker of receptor activity. In order to study phosphorylation of endogenous receptors, a phosphosite-specific polyclonal antibody was generated against the TRH receptor by immunizing a rabbit with a peptide phosphorylated at four residues. This novel tool has been used to detect endogenous phosphorylated TRH receptor in GH3 rat pituitary cells and in rat pituitary tissue. Ongoing studies will measure the kinetics of phosphorylation and dephosphorylation and identify the associated kinases and phosphatases, respectively. In order to understand the role of phosphorylation on receptor trafficking, subcellular localization of phosphorylated TRH receptors will be visualized by immunofluorescence. In order to determine *in vivo* spatial and temporal phosphorylation, pituitary tissue slices from rats kept under various physiological conditions will be immunostained with the phosphosite-specific antibody. Understanding the role of phosphorylation will be vital to improving treatments that target GPCR signaling pathways.

Elvira L. Liclican, New York Medical College: **"Role of Adenosine in the Adaptive Natriuretic Response to Salt Loading".** Cardiovascular disease (CVD) is a leading cause of death in the United States; hypertension is the most common CVD. Sustained arterial hypertension damages blood vessels, which increases the risk of renal failure, cardiac failure and stroke. The majority of people with hypertension are said to have essential hypertension, in which no specific cause of hypertension can be found. Though the etiology is unknown, an important feature of essential hypertension is salt sensitivity, as defined by blood pressure elevation in response to a dietary salt load. Normally, increased salt intake results in increased renal salt excretion. This adaptive process prevents progressive salt retention and volume expansion, with elevation of blood pressure; however, the mechanisms underlying this process are not well understood. Adenosine, a product of ATP metabolism, has been implicated in the renal functional responses to potentially catastrophic events (i.e. hypoxia, hemorrhage and ischemia). However, there is now evidence supporting the contribution of adenosine to renal mechanisms that respond to nonpathological challenges to renal function. The adenosine A_{2A} receptor ($A_{2A}R$) subtype mediates endothelial-dependent vasodilation and natriuresis. Previously, they have shown that the $A_{2A}R$ selective agonist, CGS21680, stimulates cytochrome P450 (CYP) epoxyeicosatrienoic acids (EETs) release from rat preglomerular microvessels (PGMV), and the vasodilator action of CGS21680 in arcuate arteries is inhibited by a selective epoxygenase inhibitor. As EETs are renal vasodilator and natriuretic compounds and can account for the biological actions of adenosine acting on $A_{2A}R$, they propose that adenosine contributes to the adaptive natriuretic response to salt loading. Activation of $A_{2A}R$ and stimulation of EET levels in PGMV can affect renal vascular resistance, renal interstitial pressure and medullary blood flow. Since the tone and reactivity of PGMV are key components in renal autoregulation and tubuloglomerular feedback, $A_{2A}R$ activation can serve in mechanisms that contribute to the regulation of blood pressure.

Matthew S. Marengo, The University of Wisconsin, Madison Medical School: **"Cell Stress Signals Regulate the Splicing and Promoter Affinity of TAF1."** After a

Christine C. Quirk, Ph.D., from Indiana University School of Medicine and Tony R. Hazbun, Ph.D., from Purdue College of Pharmacy, Nursing and Health Sciences are congratulated for receiving 2006 Research Starter Grants in Pharmacology/ Toxicology at the ASPET Annual Meeting in April 2006 by George Fuller, Ph.D., the Chairman of the Basic Pharmacology Advisory Committee, and Eileen McCarron.

gene is transcribed, elements called introns are spliced out of the pre-messenger RNA (pre-mRNA), leaving elements called exons, which are expressed at the protein level. Many pre-mRNAs also include alternate exons, which may be spliced in or out of a pre-mRNA in a regulated fashion. Alternative splicing can change the function of a gene product, and thus is an important regulatory mechanism during development and tumoregenesis. However, cellular signaling networks that regulate alternative splicing are poorly understood. Drug treatment, which perturbs cellular signaling networks, may therefore have unpredictable effects on gene expression. This laboratory has determined that *TBP-associated factor 1 (TAF1)* pre-mRNA is alternatively spliced in the fruit fly, *Drosophila melanogaster. TAF1* is an essential protein for gene transcription in flies and humans. They have found that the alternative forms of *TAF1* differ in their ability to bind DNA, and that the DNA-binding affinity of *TAF1* correlates with its ability to turn on gene transcription. Interestingly, *TAF1* alternative splicing is changed by cellular insults, including treatment with the anticancer drug camptothecin. They hypothesize that this alternative splicing of *TAF1* regulates the response to camptothecin. The lab has shown that alternate forms of *TAF1* are expressed as proteins and associate with another essential transcription factor, TATA binding protein. They have identified an element in a *TAF1* intron that is essential for camptothecin-triggered changes in splicing. They are currently using the genetic and biochemical power of *Drosophila* to identify the molecular players in the regulation of alternative splicing by camptothecin and other cellular insults.

Nicole L. Zandy, Duke University Medical Center: **"Role of Abl Tyrosine Kinases in Invasion and Metastatic Progression in Breast Cancer."** In the United States this year, an estimated 216,000 new cases of invasive breast cancer will be diagnosed, and 40,000 women will die of breast cancer. For patients whose cancers progress to stage IV metastatic breast cancer, the 5-year survival rate is only 16%; patients with stage III non-metastatic breast cancer have a 50% survival rate. Thus it is critical to identify new therapeutic targets aimed specifically at preventing metastatic progression, thereby increasing long-term patient survival. The proposed study focuses on the Abl family of nonreceptor tyrosine kinases, composed of c-Abl and Arg, as such a target. Abl kinases have been implicated in the regulation of events that occur during cancer progression, and increased levels of Arg expression correlate with metastatic potential of colorectal cancer. Abl and Arg are also important for rearrangements of the actin cytoskeleton that contribute to enhanced cell motility. Furthermore, our new findings establish a role for Abl kinases in the regulation of adherens junctions. We have shown that Abl kinase activity is required for the disruption of adherens junctions in response to hepatocyte growth factor (HGF). Upregulation of the receptor for HGF, Met, has been observed in breast cancer and is implicated in metastatic progression. Similarly, epidermal growth factor (EGF) stimulates Abl activity, and EGF receptor (EGFR) signaling is often upregulated in breast cancers. Therefore it is likely that Abl kinase activity is elevated in many breast cancers. They hypothesize that increased Abl kinase activity contributes to metastatic phenotypes in breast cancer by disrupting cell-cell adhesion, increasing cell motility through cytoskeletal rearrangements, and promoting the acquisition of an invasive phenotype. This study aims to determine whether pharmacological inhibition of Abl kinase activity or Abl/Arg knockdown can inhibit breast cancer metastasis in a mouse model and to determine what parts of the metastatic program may be regulated by Abl kinases. In addition, they will perform experiments directed at uncovering the molecular mechanism underlying the Abl kinase family's effects on metastasis. If the results of this study implicate Abl activation downstream of EGFR and Met hyperactivation during metastatic progression, the FDA-approved Abl kinase inhibitor Gleevec could be used in conjunction with conventional therapies to decrease metastasis and increase breast cancer patient survival. Because amplified signaling from both EGFR and Met is common in many types of cancer, the Abl kinases may represent a novel therapeutic target in a broad range of cancers.

Post Doctoral Fellowships in Pharmacology/Toxicology

The PhRMA Foundation Post Doctoral program in Pharmacology/Toxicology provides stipend 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 molecular or cellular mechanisms of action with 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 where mul-

Dr. Darrell Abernethy presents the Center of Excellence Award to Dr. Liewei Wang and Dr. Richard Weinshilboum, of the Mayo Clinic at the ASCPT Annual Meeting in Baltimore, Maryland in March 2006.

tidisciplinary 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.

Receiving the fellowships that began between January and December 2006 are:

Carrie K. Jones, Ph.D., Vanderbilt University Medical Center: **"*In Vivo* Characterization of mGluR5 Allosteric Potentiators for Schizophrenia."** Schizophrenia is a severe neuropsychiatric disorder that afflicts approximately 1% of the world population, and is characterized by a complex set of symptoms, including positive and negative symptoms and cognitive impairments. Over the last several decades, important advances have been made in the treatment of schizophrenia. Yet, despite these advances, the functional outcomes and quality of life for individuals with this disorder remain poor, with few patients able to live independently or hold full employment. Given this overall poor functional prognosis, the development of novel therapeutic approaches remains a critical unmet medical need. One potential approach may be through the indirect activation of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors within the CNS. This approach is based on clinical evidence demonstrating that noncompetitive, use-dependent NMDA receptor blockers such as phencyclidine exacerbate the positive and negative symptoms and cognitive impairments observed in individuals with schizophrenia and cause psychosis in healthy individuals. Previous studies have demonstrated that the metabotropic glutamate receptor subtype 5 (mGluR5) regulates the function of NMDA receptors (NMDAR) in brain regions implicated in the pathophysiology of schizophrenia. Recently, a series of small molecules have been developed that potentiate mGluR5 function and result in enhanced activity of the NMDAR. This class of potentiators is represented by the molecule 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (CDPPB). CDPPB does not activate mGluR5 receptors directly but acts at an allosteric site on the receptor to potentiate glutamate-induced activation of the mGluR5 receptor. The advantage of this approach is that it would potentiate endogenous NMDA receptor function without continuously activating the receptor and thereby potentially producing overexcitation and neurotoxicity. The focus of the present research project is to first characterize the effectiveness of CDPPB to potentiate mGluR5-mediated activation of NMDAR currents in hippocampal CA1 pyramidal cells, a region that has been implicated in the symptoms of schizophrenia, particularly the cognitive deficits; and secondly, to determine whether CDPPB produces mGluR5-mediated behavioral effects in rodent models predictive of antipsychotic efficacy and enhancement of cognition.

D. Scott Witherow, Ph.D., Duke University Medical Center: **"Modulation of T cell Signaling by Abl Tyrosine Kinases."** Abl kinases are important proteins that regulate normal cell function and specifically are also known to play a role in regulating T cell signaling, which is fundamental to the formation of an immune response. Overactive Abl proteins lead to uncontrolled cell growth, resulting in variety of different leukemias, including chronic myelogenous leukemia (CML) and T-cell acute lymphoblastic leukemia. Treatment of CML with a drug that targets Abl kinases (Gleevec®; STI-571) has been shown to suppress immune function in patients. This proposal aims to understand the role of Abl kinases in T cell signaling pathways. By understanding how normal Abl proteins work in T cells, the changes that occur in leukemia can be better understood. Of particular interest in this proposal is the role of Abl kinases in the formation of the immunological synapse, a structure formed when a T cell is activated following its binding to a target antigen-presenting cell. Additionally, results from that proposed experiments will aid in understanding the basis for the immune suppression effect of Gleevec®, allowing patients to be treated more effectively.

Research Starter Grants in Pharmacology/Toxicology

The purpose of the PhRMA Foundation Research Starter Grants is to offer financial support to individuals beginning their independent research careers at the faculty level. The program provides a research grant of $30,000 per year for up to two years. The "starter" aspect of the program strives to assist those individuals who are establishing careers as independent investigators. The program is not offered as a means to augment an ongoing research effort.

The first Research Starter Grant awards were made in 1972; and a total of six hundred and four have been awarded, including the grants beginning on January 1, 2006.

Miller B. Jones, Ph.D. from the Department of Pharmacology at the University of North Carolina at Chapel Hill received a 2003 Post Doctoral Fellowship in Pharmacology/Toxicology.

Recipients of the Research Starter Grants that began in January 2006 are:

Tony R. Hazbun, Ph.D., Purdue College of Pharmacy, Nursing and Health Sciences: **"Uncovering the Proteomic Networks Surrounding the Yeast Aurora Kinase, Ipl1."** Chromosomal instability due to aberrant chromosome segregation is a hallmark of cancer, suggesting that a better understanding of the molecular processes that control the faithful segregation of chromosomes will lead to new therapeutic strategies to control cancer. An example of this promise is evident in the Aurora kinases, which are important regulators of chromosome segregation. Several specific Aurora kinase inhibitors have demonstrated anti-proliferative activities and are proceeding to clinical trials even though they do not understand the multiple roles of this kinase. This proposal will use a systems biology approach in the baker's yeast, *Saccharomyces cerevisiae,* to focus on the proteomic networks surrounding the yeast Aurora kinase, Ipl1. Established yeast-based functional genomics tools will be used to elucidate the genetic and protein interaction relationships within the Ipl1 proteomic network. The substrates of Ipl1 and the downstream effects these phosphorylated substrates have on protein-protein interactions will be determined using novel two-hybrid technology. Identification of genetic interactions, protein-protein interactions, and post-translational modifications (PTMs) related to Ipl1 and it's control of mitosis and chromosome segregation in yeast, should serve as a guide toward the analysis of and ultimately, intervention in, the abnormal mitotic pathways that propagate cancer. Cancerous cells have many dysregulated biological pathways that drive proliferation and subsequent tumor progression. Using the data from this proposal they will build an integrative model that will define what cellular networks are essential when Ipl1 is dysregulated. The high level of conservation between yeast and higher eukaryotic protein networks presents the opportunity of using yeast to predict relationships between abnormal chromosome segregation pathways underlying tumor viability. The long-term outcome of this research is that it may be possible to combinatorially target cellular components essential for cancer.

Christine Campion Quirk, Ph.D., Indiana University School of Medicine: **"Determining the Molecular Role of p8 in Tumorigenesis."** Strict regulation of the cell cycle is critical for the health of all cellular organisms and loss of cell cycle regulation often results in abnormal cell proliferation and cancer. The cyclin-dependent kinase inhibitor p27, a candidate tumor suppressor that is down-regulated in a number of cancers, plays a vital role in blocking the G_1 to S transition of the cell cycle. In health, levels of p27 are regulated strictly throughout the cell cycle. During G_1, p27 localizes to the nucleus where it inhibits cell cycle progression. Upon stimulation to re-enter the cell cycle, Jun activating binding protein 1 (Jab1) binds p27 and mediates its nuclear export and degradation, allowing entry into S phase and cell cycle progression. Recently, the protein p8, a member of the high mobility group (HMG) A family of architectural transcription factors, was found to play a role in Jab1-mediated p27 degradation. Like HMGA proteins, p8 is upregulated during development and the stress response in multiple tissues. p8 expression is normally low in post-mitotic tissues and its re-expression has been linked to a variety of pathologies including cancer. A major mechanism by which p8 facilitates abnormal cell growth may be through its interaction with Jab1 to cause p27 degradation and cell cycle progression. However, the molecular details by which this occurs is unknown. The aim of this study is to elucidate the mechanism by which p8 acts with Jab1 to facilitate p27 degradation.

Sabbatical Fellowship in Pharmacology/Toxicology

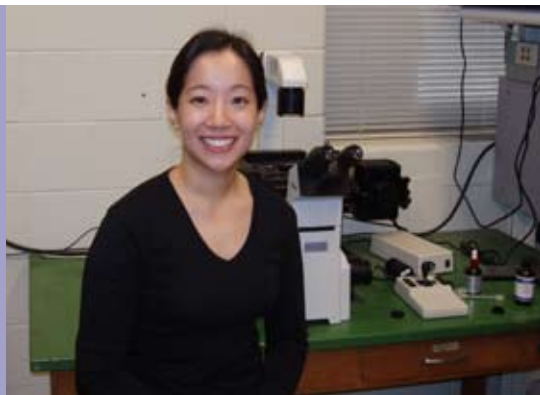
This program provides stipend funding to enable faculty members at all levels with active research programs an opportunity to work at other institutions for periods of six months to one year to learn new skills or develop new collaborations that will enhance their research and research training activities in pharmacology.

The Sabbatical Fellowship provides up to $40,000 for one year of stipend funding.

Receiving the fellowship that began in January 2006 is:

Lee M. Graves, Ph.D., The University of North Carolina at Chapel Hill: **"Application of Protein Arrays and Proteomics to Investigate Signaling Complexes Involved in Cell Metabolism."** Cells are composed of networks of "wires" that allow signals to be transmitted to their appropriate destinations. Aberrant signal transduction through these wires can lead to a host of problems including inflammatory disease and cancer. Hence considerable effort is underway to discover and design inhibitors that selectively uncouple aberrant signal transduction pathways. This research is directed towards understanding how the "wiring diagram" of the cell is connected to basic processes of metabolism necessary for cell growth. They have chosen to concentrate on 2 enzymes, CAD and CTP synthetase that make pyrimidines, essential building blocks for many cellular functions. These studies

2005 Pre Doctoral Fellow in Pharmaceutics, Vivien Y. Chen from the University of Michigan.



show that these enzymes are regulated by protein-protein interactions and phosphorylation and are thus connected to specific wiring diagrams. The objective of this sabbatical research project was to apply novel protein chip technology to elucidate the protein binding partners of CAD and CTP synthetase. In this regard, the recently developed Invitrogen ProtoArray™ Protein Chips was used to investigate CAD and CTP-synthetase binding proteins. Dr. Graves chose to work directly with Professor Richard Christopherson (University of Sydney), a world-renowned expert on protein chip technology. During this time they have also been experimenting with custom made protein chips to specifically study changes in cellular signal transduction. In addition they are exploring how novel inhibitors of specific signal transduction wiring pathways influence the regulation of CAD and CTP synthetase. Ultimately this research is expected to assist in the development of new methods to study protein-protein interactions and function. In addition they anticipate developing methodology to evaluate the function of emerging inhibitors of cell signaling pathways for application to a host of diseases.

Paul Calabresi Medical Student Fellowships

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 fellowship is six months and the maximum is two years, with a maximum stipend of $18,000. One hundred and sixty four 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.

The recipients of the Paul Calabresi Medical Student Fellowships that began in July 2006 are:

Lucienne Marie Ide, Emory University School of Medicine: **"Gene Therapy for Hemophilia A."** Hemophilia A (HA) is an X-linked recessive genetic disorder leading to a deficiency of clotting factor VIII (fVIII) molecules and, therefore, a crippling hemorrhagic condition. One in 10,000 males born worldwide is affected by HA. In its severe form (50% of cases), this disease is life-threatening. Current treatment involves repeated intravenous administration of either plasma-derived or recombinant factor VIII protein. While modern protein replacement therapy has allowed most hemophiliacs to enjoy a normal life expectancy, it is not without risks and disadvantages nor is it curative. In the 1980's and 1990's many hemophiliacs were infected with human immunodeficiency virus and/or hepatitis C virus due to the use of infected human plasma derived fVIII concentrate. With the introduction of new viral inactivation techniques and recombinant technologies, protein-based therapy has become much safer, but patients still bear the psychological burden of potential factor contamination or fVIII shortage due to safety precautions. In addition, recombinant therapy can be extremely costly, with the average patient using up to $100,000 of factor concentrate per year. Given that HA is a monogenic disease for which the gene of interest has been cloned, it is an ideal candidate for gene therapy. This can be accomplished using *ex vivo* genetic modification and transplantation of bone marrow-derived stem cells. The current project aims to show that using a high expression fVIII construct in a clinically relevant bone marrow transplantation model will potentially be curative for HA. Transplantations of genetically engineered bone marrow will be performed in a mouse model of HA to determine which transduction conditions and pretransplantation conditioning regimen will maximize long-term expression of fVIII.

John T. Lucas, Jr., Medical University of South Carolina: **"Relationships between Semaphorins and Vascular Endothelial Growth Factor Signaling in Angiogenesis: A Possible Feedback Regulation Mechanism for Angiogenesis in Breast Cancer?"** VEGF, a potent angiogenic factor and prognostic indicator for breast cancer, and its competing antagonistic ligand SEMA3F have been shown to be involved in a potential paracrine signaling loop between the breast tumor parenchyma and stroma. Concurrently, the VEGF receptor Neuropilin 1 (Np1) has also been shown to be preferentially expressed on breast tumor cells over classical VEGF receptors. These findings correlate with increased intratumor vascularity, and tumorigenic potential. While causal connection between these markers is established, the mechanisms governing their interactions are unknown. This study seeks to use a proteomics approach to explore VEGF and SEMA3F signaling mechanisms and their corresponding dependence on Np1 in MCF-7 breast cancer cells. This will be accomplished by first confirming which VEGF and SEMA3F associated receptors are expressed, and subsequently analyzing their ligand specific signaling events

Lee M. Graves, Ph.D., from the Department of Pharmacology at the University of North Carolina at Chapel Hill, received the 2006 Sabbatical Fellowship in Pharmacology and Toxicology in San Francisco, California at the Awards Ceremony of ASPET in April 2006.

by identifying phosphotyrosine-containing proteins with nLC/MS/MS. The dependence of these signaling events on associated receptors will be determined using receptor specific inhibitors. By comparing the protein profiles of each sample, they will be able to establish which signaling events are specific to each stimulus and receptor. Elucidation of the mechanistic components specific to each receptor will provide new potential targets for cancer prevention and control.

Sunita N. Misra, Vanderbilt University School of Medicine: **"Characterization of Mutant Human Brain Sodium Channels Associated with Familial Epilepsy."** Epilepsy is a common, complex brain disease characterized by abnormal neuronal electrical signaling. To help clinicians diagnose and treat patients, subcategories of epilepsy have been defined based on age of onset, types of seizures, duration of symptoms, severity, and etiology. Channelopathies are a subset of familial epilepsy syndromes with associated mutations in genes encoding various voltage-gated and ligand-gated ion channels such as potassium and sodium channels. The gene *SCN2A* encodes the human brain voltage-gated sodium channel α_2 subunit ($Na_V1.2$). Mutations in *SCN2A* are associated with inherited forms of epilepsy including febrile seizures (FS) and benign familial neonatal-infantile seizures (BFNIS). The epilepsy syndromes associated with mutations in *SCN2A* tend to have a mild phenotype. In contrast, mutations in other neuronal voltage-gated sodium channels are often associated with more severe clinical phenotypes. For this gene family, the underlying link between mutation, biophysical characteristics, and disease severity remains unclear. The aim of this project is to characterize the functional properties of wildtype and BFNIS mutant sodium channels. The laboratory will use site-directed mutagenesis to create BFNIS mutants in *SCN2A* for electrophysiological and biochemical analysis. The electrophysiological characteristics of the BFNIS mutants will be compared to wildtype to look for biophysical defects. If any BFNIS mutants are non-functional or have decreased function by patch-clamp analysis, the cell surface expression will be assessed. Pharmacological rescue experiments using anticonvulsant therapeutics are planned for mutations that have decreased cell surface expression. Characterization of BFNIS mutants will aid in establishing a genotype-phenotype correlation. These studies will also help to promote a greater understanding of the molecular basis of epilepsy, lead to improved classification of epilepsy disorders, and enable better targeting of anticonvulsant medications.

PHARMACEUTICS

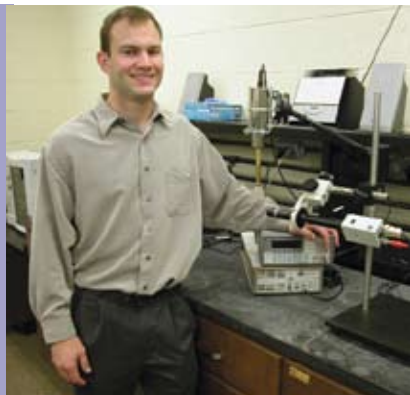
Pre Doctoral Fellowships in Pharmaceutics

This program has been in effect for 19 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. Three fellowships were granted in 2006.

Those who received fellowships that began between January and June 2006 are:

Dongmei Lu, The University of North Carolina at Chapel Hill: **"Aerosol Delivery of Recombinant Antigen 85B in Microparticulate Vaccine Systems for Protection Against Tuberculosis."** A major scientific effort over the past several years has produced many potential antitubercular vaccines. The protein subunit antigen 85B is a promising vaccine candidate. However, there has been little research into alternative delivery systems and routes of administration for vaccination to elicit effective immunity against infection with Mycobacterium tuberculosis. The site of antigen exposure will determine the immune response and circulating antigen-specific T cell specificity. The pulmonary route, by which most patients acquire their primary infection, is a promising route for vaccination. Aerosol immunization with recombinant antigen 85B, and immunostimulatory adjuvants in microparticles is proposed. It is proposed in this project to: encapsulate recombinant antigen 85B/adjuvants for aerosol delivery; optimize and manufacture of microparticulate formulations with different release profiles; initiate studies on alveolar macrophage targeted pulmonary delivery and related immune responses; elucidate the importance of vaccine protein conformation on its antigenicity and characterize the protection effects in a guinea pig model. These studies may result in the first compelling evidence for the protection afforded by a protein subunit vaccine delivered to the lungs against tuberculosis, which has significant implication for worldwide disease control.



Dr. Cory J. Berkland, from the University of Kansas, received a 2005 Research Starter Grant in Pharmaceutics.

Michael G. Spelios, Arnold & Marie Schwartz College of Pharmacy, Long Island University: **"Biophysical and Physicochemical Characterization of a Novel Series of Bivalent 1,3-diamino-2-propanol Cationic Amphiphiles for Gene Delivery."** Gene therapy holds the promise of treating human diseases at the genetic level through the insertion of therapeutic genes into target cells. The project focuses on cationic lipidic vectors for gene delivery, with a primary emphasis on the relationship between aggregate structure and transfection activity. To produce efficient gene expression, the cationic lipid must possess suitable structural features that promote effective transfection. The current project is based on the idea that increasing the intramolecular distance between the hydrophobic chains of a double-chained cationic surfactant will result in a membrane bilayer of enhanced hydration and increased fluidity, which is essential for high transfection efficiency. Physicochemical characterization is essential in elucidating the structural properties of these double-chained surfactants that confer superior *in vitro* lipofection activity. The physical studies comprise a variety of techniques, including gel electrophoresis mobility shift assay, particle size determination, ethidium bromide displacement assay, Langmuir monolayer studies, differential scanning calorimetry, and fluorescence anisotropy. The results of the studies will contribute to the long-term goal of the project, that is, to elucidate the structural requirements of cationic lipids for potent gene delivery and expression. The achievement of this goal is dependent on the physical and chemical characterization of lipid aggregates in isolation and with plasmid DNA, and the correlation between the physicochemical assessment and *in vitro* transfection activity.

May P. Xiong, University of Wisconsin, Madison: **"Design of a pH Sensitive Block-copolymer, Poly(aspartate-hydrazine)-b-poly(l-lysine) for Gene Delivery."** The non-mammalian enzyme yeast cytosine deaminase (yCD) has shown potential in activating the prodrug 5-fluorocytosine (5FC) into cytotoxic 5-fluorouracil (5FU) in several tumor models. Unfortunately yCD's instability limits its bolus delivery in enzyme-prodrug type applications. The current project aims at enhancing the delivery of yCD's gene to solid tumors through a novel non-viral gene carrier system. Any non-viral carrier system should have low toxicity, immunogenicity and should provide a mechanism for pDNA escape from endolysosomes of cells into the cytoplasm. The current application proposes the design of a degradable block-copolymer poly(aspartate-hydrazide)-b-poly(L-lysine) with attachment of acid-labile PEG formation via Schiff bases. PEG will provide 'stealth properties' to the complex, minimizing immunogenic responses and prolonging systemic circulation, followed by pH-triggered release from the polymer under acidic endolysosomal conditions (pH 4-5). This system has two important advantages: (1) PEG will be attached to poly(aspartate-hydrazide) and will not hinder poly(L-lysine) condensation with pDNA, resulting in more stably shielded complexes; and (2) release of PEG may help unpackage the pDNA from the block-copolymer and simultaneously provide free hydrazide groups (pKa 3-4) for an enhanced proton sponge effect.

Post Doctoral Fellowships 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 is intended solely as a stipend and may not be used otherwise.

Receiving the fellowships that began between January and October 2006 are:

M. Laird Forrest, Ph.D., The University of Wisconsin, Madison: **"Targeted Nanoparticle Formulation of the Investigational Anticancer Agent Geldanamycin."** The severe side effects induced by toxic chemotherapy agents make traditional chemotherapy a debilitating and traumatic experience for cancer patients. The toxic nature of many chemotherapeutics and the excipients used to deliver them can severally limit the therapeutic window, increasing the difficulty in treating aggressive carcinomas. Newer antitumor agents in clinical practice and development are increasingly selective in their action, acting on molecular targets that are integral in the progression of cancer and minimally disruptive to normal cells and tissues. Hence, investigational anti-cancer agents, such as Hsp90 inhibitor geldanamycin (GA), possess novel mechanisms of action, which are being exploited for treatment of cancer. Subsequently, the highly targeted action of these compounds can decrease nonspecific toxicity at the tissue level, leading to lesser side effects and greater tolerability in clinical practice. However, many of these newer antitumor agents are poorly water soluble and have poor stability once administered, limiting the levels

2004 recipient of the Post Doctoral Fellowship in Pharmacology/Morphology, Bradley A. States, Ph.D. from the Burnham Institute, Center for Neurosciences & Aging.

of agent that can reach tumors. Traditional formulation techniques have failed compounds such as GA, hampering its progression into the clinical stage. This research seeks to develop the investigational anti-cancer agent geldanamycin as a safe and efficacious nanoparticle formulation. The research will address whether combination the "directed therapeutic" geldanamycin with a nontoxic micellar delivery system can result in increased efficacy and reduced side effects over toxic traditional formulations in murine models of breast cancer.

Josh D. Ramsey, Ph.D., University of Illinois at Urbana-Champaign: **"Protein Stabilization Based on an Empirical Phase Diagram Which Incorporates Static *and* Dynamic Protein Structural Data."** The goal in pharmaceutical protein formulation is to find a condition for protein storage that maintains biological activity over a shelf life of two to three years. Stable formulations of therapeutic proteins are often found by strategically selecting a small range of solution conditions involving variation in temperature, pH, and ionic strength. Such formulations are typically based on quite limited information about the structure of the protein, and if problems arise during manufacturing or real-time stability studies, a more intensive study of the protein must be performed. An alternate, more thorough approach is based on the generation of a protein empirical phase diagram which can be used to define conditions where physical degradation occurs. These conditions are then used to develop high throughput assays that are used to screen libraries of potential stabilizers for formulation purposes. This approach currently employs static structural characteristics of the protein for the generation of the empirical phase diagram. Proteins, however, are dynamic molecules, and ideally a comprehensive phase diagram should be based on dynamic as well as static structural characteristics. The proposed research will extend the empirical phase diagram approach to include data related to dynamic aspects of a protein's structure. For the proposed work, techniques that will be used to characterize the dynamic aspects of a protein include hydrogen/deuterium exchange, fluorescent quenching, pressure perturbation differential scanning calorimetry, high resolution ultrasonic spectroscopy, red edge shift spectroscopy, and time correlated single photon counting.

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.

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Belief in a Mission...

The PhRMA Foundation is lastingly indebted to a cadre of PhRMA Board members who despite uncommon demands on their time through the nature of their jobs have given more than four decades of faithful and sagacious service.

2006 TREASURER'S REPORT

The PhRMA Foundation ended 2005 in sound financial shape and increased the reserve funds. Contributions were up 6% from the previous year, to $3.1 million. We awarded approximately $1.8 million in grants and held down non-grant program and administrative expenses. Total expenditures, at $2.3 million, were $495,000 below budget. Total net assets at December 31 were $10.3 million, a 12.6% increase from $9.2 million the prior year. Of this amount, $3.0 million represents funds authorized but not yet paid for the future years of grants already awarded. The increase in net assets is attributable to $372,000 in investment gains and interest income, actual contributions $375,000 more than budgeted, and actual grant awards $441,000 less than budgeted. We did not need to transfer funds from reserves (the Future Commitment Fund) to cover payment this year of awards granted in previous years. Financial details are shown in the accompanying Statement of Income and Expenditures.

For 2006, contributions were targeted to reach $3.2 million, as we entered the fifth full year of our new program. 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.

The Foundation's financial position as of December 31, 2005, has been audited by the Rosslyn, Virginia, accounting firm of Buchanan & Company. A full report can be obtained by contacting the Foundation.

Steven M. Paul, M.D.
Treasurer, PhRMA Foundation
and
Executive Vice President, Science and Technology
President, Lilly Research Laboratories
Eli Lilly and Company

Statement of Income and Expenditures For the Year Ended December 31, 2006

INCOME	
Contributions	$3,075,439
Interest and Dividends	257,729
(Realized and Unrealized) Gains in Securities	113,960
Other Income	37,421
Total Income	**$3,484,549**
EXPENDITURES	
Programs	
Awards in Excellence	23,290
Center of Excellence for Integration of Genomics and Informatics	175,000
Clinical Pharmacology Program	277,000
Health Outcomes Program	245,000
Informatics Program	330,000
Pharmaceutics Program	215,000
Pharmacology Programs	516,232
AFPE Fellowship Award	5,000
Other Grants	45,850
Subtotal–Grants	$1,832,372
Other	
Committee Meetings, Travel and Honoraria	68,562
Publications and Special Projects	82,748
Subtotal–Other	$151,310
Program Total	**$1,983,682**
Administrative	
Staff, Rent, Taxes Insurance, Depreciation	296,166
Professional Services and Investment Expenses	38,185
Office Expenses	9,107
Subtotal–Administrative	$343,458
TOTAL EXPENDITURES	**$2,327,140**

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The PhRMA Foundation owes its success to the pharmaceutical companies that have provided their generous support over the past 41 years. We thank all of you for continuing to invest in the future of pharmaceutical research and the scientists of tomorrow.

PhRMA Foundation Programs for 2007

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	$ 80,000 total $ 20,000 per award per year	October 1, 2006 December 15, 2006/January-August
Post Doctoral Fellowship in Health Outcomes (2002)	1 budgeted/ 2 years	$ 80,000 total $ 40,000 per award per year	October 1, 2006 December 15, 2006/January-December
Sabbatical Fellowship in Health Outcomes (2002)	1 budgeted/ 1 year	$ 40,000 total $ 40,000 per award per year	October 1, 2006 December 15, 2006/January-December
Research Starter Grants in Health Outcomes (2002)	3 budgeted/ 2 years	$180,000 total $ 30,000 per award per year	October 1, 2006 December 15, 2006/January 1, 2007
Informatics Advisory Committee			
Post Doctoral Fellowships in Informatics (2002)	2 budgeted/ 2 years	$160,000 total $ 40,000 per award per year	September 1, 2006 December 15, 2006/January-December
Sabbatical Fellowship in Informatics (2002)	1 budgeted/ 1 year	$ 40,000 total $ 40,000 per award per year	September 1, 2006 December 15, 2006/January-December
Research Starter Grants in Informatics (2002)	3 budgeted/ 2 years	$180,000 total $ 30,000 per award per year	September 1, 2006 December 15, 2006/January 1, 2007
Pharmacology Advisory Committees			
Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)	6 budgeted/ 2 years	$240,000 total $ 20,000 per award per year	September 1, 2006 December 15, 2006/January-August
Post Doctoral Fellowships in Pharmacology/Toxicology (2002)	2 budgeted/ 2 years	$160,000 total $ 40,000 per award per year	September 1, 2006 December 15, 2006/January-December
Sabbatical Fellowship in Pharmacology/Toxicology (2002)	1 budgeted/ 1 year	$ 40,000 total $ 40,000 per award per year	September 1, 2006 December 15, 2006/January-December
Research Starter Grants in Pharmacology/Toxicology (1972)	3 budgeted/ 2 years	$180,000 total $ 30,000 per award per year	September 1, 2006 December 15, 2006/January 1, 2007
Paul Calabresi Medical Student Research Fellowship (1974)	2 budgeted/ 6 months-2 years	$ 36,000 total $ 18,000 per award	September 1, 2006 December 15, 2006/January-August
Pharmaceutics Advisory Committee			
Pre Doctoral Fellowships in Pharmaceutics (1987)	2 budgeted/ 2 years	$ 80,000 total $ 20,000 per award per year	October 1, 2006 December 15, 2006/January-August
Post Doctoral Fellowship in Pharmaceutics (1992)	2 budgeted/ 2 years	$160,000 total $ 40,000 per award per year	October 1, 2006 December 15, 2006/January-December
Sabbatical Fellowship in Pharmaceutics (2002)	1 budgeted/ 1 year	$ 40,000 total $ 40,000 per award per year	October 1, 2006 December 15, 2006/January-December
Research Starter Grants in Pharmaceutics (1972)	2 budgeted/ 2 years	$120,000 total $ 30,000 per award per year	October 1, 2006 December 15, 2006/January 1, 2007

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

www.phrmafoundation.org

Visit the PhRMA Foundation website at www.phrmafoundation.org for detailed information.

This website describes the Foundation programs, special events and recent awards.

Brochures can be requested by writing or calling:

Ms. Eileen McCarron

Executive Director

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