2007 Annual Report

PHARMACEUTICAL RESEARCH
AND MANUFACTURERS
OF AMERICA FOUNDATION

PhRMA
FOUNDATION

Contents

Mission Statement

The mission of the PhRMA Foundation is to support young scientists in disciplines important to the pharmaceutical industry by awarding them competitive research fellowships and grants at a critical decision point at the outset of their careers. The aim is to encourage young scientists who will be the leaders of tomorrow to pursue careers in research and education related to drug discovery.

The program will help to build a larger pool of highly-trained, top-quality scientists to help meet the growing needs of scientific and academic institutions, government, and the research-intensive pharmaceutical industry.

The Foundation's program is of particular benefit to the pharmaceutical industry in serving its purpose of developing new life-saving, cost-effective medicines for patients all around the world.

Message *from the* Chairman

As the newly appointed Chairman of the PhRMA Foundation's Board of Directors, I am proud to reflect on a wonderfully successful year and look forward to expanding our efforts to support young scientists pursuing a career in pharmaceutical research.

Our mission and programs focus on expediting the careers of young scientists as they receive training and practical experience fundamental for their own research efforts. This support in no way obligates award recipients to the Foundation; on the contrary, it provides an opportunity for researchers to distinguish themselves as innovative and insightful scientists.

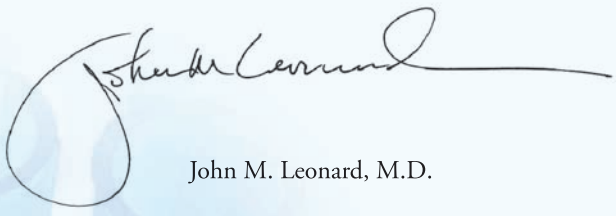
In 2006, we requested the participation of past award recipients in a brief survey to gauge how funding had impacted their careers. The results, summarized on page 6 of this report, indicate the remarkable number of active researchers who have proposed and validated drug targets in published works. Furthermore, several scientists who participated in the survey acknowledged that positive early experiences in the lab inspired them to become field leaders in academia, industry, and government.

Because sufficient funding enhances the postdoctoral experience for young researchers, we enthusiastically support universities throughout the United States. Many of our programs are geared toward postdoctoral fellows who depend on external funding to continue a project or pursue a promising new study.

We are also exploring educational opportunities that would support the efforts of government agencies such as the FDA. Initiatives to facilitate public outreach through research, training, and funding are among the Foundation's objectives for the coming year.

I would like to recognize our committee members, whose generous investment of time and effort is crucial to the success of the Foundation. In March 2007, Darryle D. Schoepp, Ph.D., joined Merck Research Laboratories (MRL) as Senior Vice President and Franchise Head for Neuroscience. Dr. Schoepp, a member of our Basic Pharmacology Advisory Committee, shares his past experiences as a young researcher pursuing funding on page 7 of this report.

We thank our benefactors and contributors who provide invaluable assistance to the PhRMA Foundation and to highly capable young scientists. By supporting our programs, you are investing in the future of scientific and medical research.



John M. Leonard, M.D.

Message *from the* President

Each year, the PhRMA Foundation explores new ways to disseminate its mission, improve its funding programs, and facilitate the careers of young scientists. Without our contributors, none of this would be possible. Your generosity has allowed the Foundation to support young researchers for more than four decades.

The responses to our 2006 Past Awardee Accomplishments survey demonstrated how funding received from the PhRMA Foundation factored into the incredible accomplishments and remarkable careers of so many of today's leading scientists.

Several award recipients from academia, industry, and government took the time to speak to us personally, reflecting upon invaluable experiences in the lab and classroom that enriched their early careers. Many of these individuals, whose contributions to science and medicine are unparalleled, believe their careers and lives could have been quite different had they not received initial funding from the PhRMA Foundation. Additionally:

- More than one-third of past award recipients have published a key concept that impacted drug discovery or development.
- 80 percent were awarded additional funding from major government agencies such as the NIH, FDA, and CDC after receiving a PhRMA grant or fellowship.
- Truly dedicated to promoting the importance of scientific research, more than 75 percent were willing to talk to legislators and others about their personal field experiences, while more than 80 percent of survey participants have referred a student fellow or new faculty member to the Foundation.

Just as strong as its commitment to scientists early in their careers is the Foundation's interaction with an active network of researchers and executives who wholly understand and support our mission. This includes our dedicated members, many of whom, while managing demanding work schedules, volunteer their time, knowledge, and efforts as Committee participants.

The extensive reviews of potential awardees conducted by Committee members have resulted in more than forty years of outstanding recipients. These recipients are also part of our network distinguished by their extraordinary scientific and academic contributions. This year, we were proud to recognize two such individuals, who specialize in pharmacology and toxicology and clinical pharmacology, with the Award in Excellence—a testimony that the assistance provided by our organization makes a difference, not only in the lives of researchers, but in the health and welfare of patients everywhere.

The PhRMA Foundation continues to support the cycle of teaching and learning in which scientific concepts, contexts, and techniques are first shared, and in due course, applied, within a government, academic, or industry setting.

We express our sincerest appreciation for your generosity and support of our mission and programs.

Del Persinger

AWARDS *in* EXCELLENCE

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 2007 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 out-standing achievements of all of our awardees and underscores the importance of continuing support to those who follow in their footsteps.

Dr. Stephen Spielberg, pictured with **Del Persinger** from the PhRMA Foundation, receiving the 2007 Award in Excellence in Clinical Pharmacology at the 2007 ASCPT Annual Meeting in Anaheim, California

2007 Award in Excellence in Clinical Pharmacology

Stephen P. Spielberg, M.D., Ph.D.

Dean, Dartmouth Medical School,
Vice President for Health Affairs, Dartmouth College, and
Professor of Pediatrics and of Pharmacology and Toxicology

Dr. Stephen P. Spielberg received an AB (Biology) from Princeton University, an M.D. and Ph.D. (Pharmacology) from the University of Chicago, did a pediatric internship and residency at Children's Hospital, Boston, and a post-doctoral fellowship in human biochemical genetics at the National Institute of Child Health and Human Development. He then joined the faculty of Johns Hopkins University School of Medicine as Assistant Professor of Pediatrics and Pharmacology, moving to the University of Toronto, Hospital for Sick Children where he was Professor of Pediatrics and Pharmacology, Director of the Division of Clinical Pharmacology and Toxicology, and Director of the Centre for Drug Safety Research. After 15 years in academic medicine, he moved to Merck Research Laboratories as Executive Director, Exploratory Biochemical Toxicology and of Clinical and Regulatory Development in 1992, and subsequently to Johnson & Johnson in 1998 to become Vice President for Pediatric Drug Development. He was Chair of the Pediatric Task Force for PhRMA, represented the pharmaceutical industry on the FDA Pediatric Advisory Subcommittee and on pediatric legislative initiatives in the US and EU, and was the Rapporteur for the Pediatric ICH Initiative (ICH E-11) to harmonize pediatric drug development regulations among Europe, Japan, and the US.

He has served as Associate Editor of Drug Metabolism and Disposition, Section Editor for Therapeutics and Toxicology for Current Opinion in Pediatrics, and on the editorial boards of Clinical Pharmacology and Therapeutics, Pharmacoepidemiology and Drug Safety, Therapeutic Drug Monitoring, and Pediatric Alert. He is on the External Review Board of the Elizabeth Glaser Pediatric Research Network, the Board of Directors of the Foundation for the National Institutes of Health, Chairs the Pediatric Pharmacology Unit Advisory Board for the NICHD, is on the Council of the Convention of United States Pharmacopeia, and is President of

the American Society for Clinical Pharmacology and Therapeutics (2006). His research interests include: mechanisms of idiosyncratic adverse drug reactions, human pharmacogenetics, and pediatric clinical pharmacology; he has published over 130 papers in these areas. He is the recipient of the Rawls-Palmer Award and Lectureship from the American Society of Clinical Pharmacology and Therapeutics (1992), the first recipient of the Werner Kalow Award in Pharmacogenetics and Drug Safety (1995), and the William B. Abrams Lectureship from FDA/ASCPT (2001).

Dr. Spielberg received a Faculty Development Award in Clinical Pharmacology in 1979 from the PhRMA Foundation.

2007 Award in Excellence in Pharmacology/Toxicology

Sue Piper Duckles, Ph.D.

Professor and Associate Dean in the College of Medicine, University of California, Irvine

Sue Piper Duckles, Ph.D. received her B.A. from University of California, Berkeley in 1968 and Ph.D. degree from the Department of Pharmacology at the University of California, San Francisco in 1973. Further postdoctoral training was with Dr. John Bevan in the Pharmacology Department at UCLA. With receipt of a Faculty Development Award from the Pharmaceutical Manufacturers Association Foundation, Inc in 1976, she was appointed Assistant Professor in Residence at UCLA. In 1979 she became Assistant Professor in the Dept. of Pharmacology, College of Medicine, University of Arizona and was promoted to Associate Professor in 1983. In 1985 she joined the Dept. of Pharmacology in the College of Medicine, University of California, Irvine and was promoted to Full Professor in 1988.

Dr. Duckles has devoted her research career to understanding the regulation of vascular function in the brain as well as in peripheral circulations. Her work has inherent importance for understanding the etiology and treatment of common diseases such as stroke and hypertension. Most recently, Dr. Duckles has elucidated mechanisms underlying the effects of gonadal steroids, including estrogen and testosterone, on the cerebral vasculature.

More than 10 years ago, Dr. Duckles recognized the dearth of research on male-female differences and sex hormone influences on vascular function, in spite of numerous clinical observations suggesting sex differences in incidence and severity of cardiovascular disease and stroke. Dr. Duckles helped bring the field together in 1996 by co-organizing the first symposium to focus on gonadal steroids and vascular function. She was among the first grant recipients of the NIH Women's Health Initiative for basic research, and her work on gonadal steroids continues to be funded by NIH. While the clinical results on hormone replacement therapy in postmenopausal women remain controversial, Dr. Duckles and her collaborators have made significant progress in establishing beneficial effects of estrogen on the endothelial lining of blood vessels and delineating the mechanisms. Dr. Duckles has taken an integrative approach by monitoring contractile function as well as underlying biochemical changes in blood vessels isolated from rodent models of hormone replacement therapy. Her work has demonstrated three significant, but distinct, effects of estrogen on cerebrovascular function. Acute estrogen increases NO production via the PI3 kinase/Akt pathway while long-term exposure acts via endothelial-dependent mechanisms to increase levels of eNOS, COX-1 and prostacyclin synthase, resulting in increased vasodilator production. Finally, chronic estrogen suppresses vascular inflammation. Her studies of testosterone demonstrate that, overall, testosterone treatment has the opposite effects. This multiplicity of effects of estrogen and testosterone indicates that gonadal steroids profoundly influence cerebrovascular function and suggest that manipulation of these pathways may have both advantageous and deleterious effects.

Dr. Sue Duckles following the award presentation at the 2007 Annual ASPET Meeting in Washington, DC, pictured with **Eileen Cannon** and **Dr. George Fuller**

Throughout her career, Dr. Duckles has been recognized as a leader, both at the University, nationally and internationally. In 1990 she was elected Chair of the Irvine Division of the Academic Senate, serving for two years. Since 1993, Dr. Duckles has served as Associate Dean for Faculty Development in the College of Medicine. She has strengthened faculty recruitment and established an effective new faculty orientation program. She also developed a novel program, Strategic Planning for Assistant Professors, to provide ongoing guidance and mentorship of junior faculty by experienced senior faculty.

Throughout her career Dr. Duckles has been a member of journal editorial boards and has participated in peer review for the National Institutes of Health and the American Heart Association. Dr. Duckles was elected President of the Western Pharmacology Society (1992), president of the American Society for Pharmacology and Experimental Therapeutics (ASPET) (1997-1998), and Vice President for Science Policy for the Federation of American Societies for Experimental Biology (FASEB) (2000-2001).

In 2001 Dr. Duckles was selected by the American Society for Pharmacology and Experimental Therapeutics to start a new scientific journal for the society. As chair of the Editorial Board Dr. Duckles recruited an outstanding Editorial Board and hired a full-time editor. The well-received journal, Molecular Interventions, is just completing its third year of publication. Molecular Interventions publishes brief reviews in key areas of the field, as well as topical features reflecting the breadth and depth of the discipline of Pharmacology.

In 2002 Dr. Duckles served as President of the 14th World Congress of Pharmacology held in San Francisco. In addition, she was selected to organize the 10th International Symposium on Vascular Neuroeffector Mechanisms (July, 2002). Dr. Duckles currently serves as President of the International Union of Pharmacology (IUPHAR).

Dr. Duckles received a Faculty Development Award in Pharmacology/Toxicology in 1976 from the PhRMA Foundation.

Survey Findings

The PhRMA Foundation is proud of the dedicated scientists that it has supported over the past 42 years. A survey was conducted in late 2006 in which the previous award recipients were asked for an update of their career path. It was sent to over 900 scientists and more than 700 responses were received. The overwhelming response in itself shows how indebted the award recipients are to the PhRMA Foundation for the assistance that was provided early in their career. The PhRMA Foundation is known for assisting to expedite the careers of young scientists in training, and in providing support for the research or salaries of young faculty members.

Some of the highlights from the survey results are as follows:

- Over 90% of the individuals who responded are still active in research
- More than 35% have published a key concept that had an impact on drug discovery or development
- 80% of the awardees received funding following their PhRMA Foundation funding. The funding came from substantial national sources including NIH, NSF, FDA and many other organizations
- The cumulative additional award total is approximately 2 Billion Dollars.

The following segment highlights four of our former award recipients who continue to have significant careers in pharmaceutical research. We are proud of their many accomplishments and that our funding helped to start their research careers.

FOSTERING *FRONTIER* PHARMA SCIENTISTS

There are times at the beginning of a young scientist's career when opportunities abound; when the importance of his or her discipline is so clear that no other profession seems feasible. This is a crucial realization—one that can determine future success, and more importantly, dedicate an individual to improving the health and lives of others through the field of pharmaceutical research.

So many of today's extraordinary scientists trace their achievements to early days in the lab; in part made possible by private funding. Since its inception in 1965, the PhRMA Foundation has helped launch the careers and facilitate the research of young scientists, bestowing more than 2,000 fellowships, awards, and grants. These individuals have become the educators, industry experts, and government leaders responsible for significant contributions to drug discovery and development.

Results from a 2006 survey completed by past award recipients revealed the impact of the PhRMA Foundation's support on their lives and careers. More than 90 percent of those who responded are active in research today and over one-third have published a key concept that influenced drug discovery or development. Many have transitioned from academia to industry to government. For these incredibly passionate and successful scientists, support received from the PhRMA Foundation was not simply a financial reward, but a professional affirmation of their true potential as scientists, innovators, and drug developers.

Whether the grant, fellowship, or award symbolized recognition for their early work in a highly competitive field, or established a solid foundation for future funding, the support allowed these scientists to fully dedicate themselves to their research, encouraged them to stay engaged and inspired during lengthy investigative projects, and afforded the time needed to define the personal interests, strengths, and skills that would shape their futures.

Darryle Schoepp, Ph.D.

Lisa Rider, M.D.

Darryle Schoepp, PhD, spent 20 years at Eli Lilly and Company, becoming vice president and global head of neuroscience research before joining the department of neuroscience at Merck Research Laboratories as senior vice president and franchise head. Dr. Schoepp oversees the neuroscience drug discovery and development process.

Having just left his first job as a postdoctoral research fellow at the University of Kansas, Dr. Schoepp joined the faculty at Marshall University School of Medicine as an assistant professor. "I was the third person to apply for a grant. There were some startups, but not many," he notes. "But the funding was key for my research at the time."

A relatively new area of neuroscience, signal transduction became the focus of Dr. Schoepp's research. His studies were published and, after receiving the grant, he continued to make significant progress, collecting more data and eventually applying for and receiving additional funding.

"The grant allowed me to put my new ideas down and got me started in a whole new line of research, carrying me to industry," says Dr. Schoepp. As in many professions, the course of Dr. Schoepp's career has been cyclical, returning once more to the topic that first connected him with the PhRMA Foundation. Among his career achievements is his notable research in Alzheimer's and Parkinson's diseases as well as several discoveries of novel pharmacological agents for neuro-degenerative disease management currently in clinical development. His most recently published research, which concerns glutamate regulation in psychiatric disorders and targets the discovery of receptor agonists and antagonists, proposes a breakthrough drug for schizophrenia.

Receiving a grant or award is a career and life-changing experience, but it is by no means an isolated event. In fact, an

award recipient's history can greatly affect his or her future funding opportunities.

Previous PhRMA Foundation award recipient G. William Rebeck, PhD, associate professor of neuroscience at Georgetown University Medical Center, is part of the University's research team that discovered a link between molecules active in disease development and the brain chemical that helps establish memory. He received a 1989 PhRMA Foundation Pre Doctoral Fellowship. In Dr. Rebeck's experience, this fellowship awarded by the PhRMA Foundation facilitated the support he received throughout his career. "What matters in your early years as a scientist is building a strong reputation. [A board] recognizes someone who has been funded as a good writer and a good scientist who knows what he's doing." For Dr. Rebeck, receiving the grant was a positive experience that extended beyond his personal research and affected his entire lab. "I was working with an assistant professor as her first student. This grant had a bigger impact on her life because it helped take care of the people in her lab. More students were awarded fellowships as a result."

As unfortunate as it may be, financial restrictions often interfere with or delay a critical research project, prohibiting a young scientist from pursuing an exciting new opportunity. Much more than an encumbrance, this decline in momentum can significantly impact a new scientist's career.

As a third-year student at Duke University School of Medicine, Lisa Rider, MD, was studying neutrophil and signal transduction. A fellowship from the PhRMA Foundation allowed Dr. Rider to continue her studies for a full year, during which time she authored two highly cited research papers. "This was the year that really piqued my interest in the lab. Without that time, I would not have had the full experience," says Dr. Rider.

G. William Rebeck, Ph.D.

David Nelson, Ph.D.

The accomplishments that followed have shaped her truly remarkable career. Now a pediatric rheumatologist and Deputy Chief of the Environmental Autoimmunity Group, Dr. Rider has led several collaborative studies developing novel measures to assess juvenile myositis and studies of immunogenetic risk factors and illness outcomes. In a previous position at the Food and Drug Administration, her dedication to regulatory issues for juvenile rheumatoid arthritis has initiated countless clinical trials and the approval of the first biologic therapies for treatment.

David Nelson, PhD, research fellow at Eli Lilly and Company, first learned of PhRMA's funding opportunities as an assistant professor at the University of Arizona College of Pharmacy. "As a new assistant professor starting a research program, getting the grant meant I could fund the lab, run preliminary experiments, and generate data." The support awarded by PhRMA was a significant factor in subsequent funding that Dr. Nelson received from the National Institutes of Health. His pivotal research has documented subtypes of serotonin receptors, many of which became drug targets.

The grants awarded by the PhRMA Foundation continue to be fundamental in the development and careers of young scientists. As funding becomes increasingly competitive, the PhRMA Foundation remains steadfastly dedicated to supporting innovative researchers as they shape the future of drug discovery and development.

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 Medical Student Research Fellowships 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

Post Doctoral Fellowships in Informatics

The PhRMA Foundation Post Doctoral program in Informatics provides stipend support for individuals engaged in a multidisciplinary research training program that will create or extend their credentials in informatics. The intent of this program is to support post doctoral career development activities of individuals preparing to engage in research that will bridge the gap between experimental and computational approaches in genomic and biochemical studies. It is anticipated that this research training will be accomplished in academic and/or industrial laboratory settings where multi-disciplinary teams are organized to address problems which span the range of biological complexity rather than focus on the application of single technologies.

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

2007 Post Doctoral Fellowship in Informatics

Barrett C. Foat, Ph.D.
Columbia University

"Discovering Structurally Defined Cis-Regulatory Elements Within mRNAs By Integrative Analysis Of Genomic Sequence And Functional Genomics Data"

When a cell functions properly, it tightly controls each step in the process of gene expression. Specific proteins execute this regulation by recognizing and binding to control elements on the DNA or mRNA coding for a gene. While there are several known regulatory elements within DNA and mRNAs, it is possible that these represent only a small fraction of those that actually exist. The known elements are recognized by regulatory proteins based on their nucleotide sequence alone. However, a mRNA molecule can stick to itself—looping back into knotted "structures" that, instead of nucleotide sequence, can be specifically recognized by regulatory proteins. Because RNA structure is difficult to measure directly, computational prediction is often required to study it. However, the existing computational methods for discovering structural regulatory elements are limited. Thus, to help us more fully understand the regulation of gene expression, this scientist will develop a computational approach to discover structurally defined regulatory elements in mRNA, while taking advantage of previously unused types of genomics data. He will follow up his computational results with corroborating genetics experiments. He expects to identify RNA structural elements involved in the regulation of mRNA stability, mRNA localization, and translation. He will perform this study using yeast, which is readily amenable to computation and experimentation. However, the tools and methods that he develops here will eventually be applicable to humans.

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.

2007 Research Starter Grants in Informatics

Hilary A. Coller, Ph.D.

Princeton University:

"Experimental and Computational Analysis of the Transition Between Proliferation and Quiescence"

Control of cell proliferation is a fundamental question in biology and physiology, yet, we have a poor understanding of how cells decide whether to divide and execute this decision. They have characterized the gene expression profiles that accompany cell cycle exit and reentry in human fibroblasts. Thousands of genes are regulated during this complex and carefully orchestrated process. With the availability of the human genome sequence, this laboratory now hopes to understand the underlying logic of the signaling pathways that control this transcriptional program. They have initiated this endeavor, identifying transcription factors and microRNAs likely to play a role. A systems biology approach has been proposed to define the quiescence regulatory network using experimental and computational approaches. The work is initiated by completing an analysis of the motifs and recognition sites likely to regulate cell cycle arrest. A quantitative model will then be developed to describe the contribution of these potential regulators to the gene expression changes observed. The predictions of the network will then be tested experimentally and the results will be incorporated into the quantitative model. Ultimately, it is expected that the studies will be beneficial for understanding pathologies of proliferation control, including cancer.

Uri Hershberg, Ph.D., Research Associate, Department of Pathology, Yale University, from Yale University School of Medicine received a Post Doctoral Fellowship in Informatics in 2005

Ilya Ioschikhes, Ph.D.

Davis Heart and Lung Research Institute, Ohio State University

"Micro-RNA Regulation in Ischemia"

Recently, it has been estimated that 30% of human genes may be regulated, in part, by a novel posttranscriptional mechanism involving microRNAs (miRNAs). MiRNAs are small RNA molecules that regulate gene expression primarily through translational repression. The functional importance of miRNAs is evidenced by the many biological processes in which they are implicated, including developmental timing, cell proliferation, apoptosis, metabolism, cell differentiation and morphogenesis. Medical significance of the miRNAs is conveyed through regulation of various genes related to cancer, cardiovascular function, etc. Precise knowledge of the miRNA binding sites (targets) is essential for understanding of specific mechanisms of the posttranscriptional regulation. Algorithm and software development for computational recognition of the miRNA targets is one of the hottest and rapidly expanding areas of bio-informatics. Yet, although the general miRNA phenomenon is quite well described, there is still a paucity of precise experimental data concerning specific miRNAs and their targets, since only a few miRNAs have experimentally defined functions and targets in vivo. Respectively, also the algorithm development per se is at its starting phase, often mechanistically adjusting for new needs mathematical apparatus and concepts from other areas of bioinformatics. Development of algorithms more specifically considering biophysical interaction between the miRNA and genomic/cDNA sequence is therefore the next necessary step in

this area. In our project, we are suggesting development of a novel miRNA target search algorithm, presumably more efficient than currently available algorithms. The algorithm uses strategy of sequence comparison specifically designed for miRNA/mRNA binding. We also will verify our program on the experimental data obtained in the course of this project. They hypothesize that miRNAs may play a vital role in mediating cardiovascular disease. Algorithm predictions will be verified on genes active in ischemia. This study will lead to new insights of the molecular mechanisms involved in ischemia and may result in new and novel treatments.

Sunduz Keles, Ph.D.

University of Wisconsin, Madison

"Statistical Methods For The Analysis Of Chip-Chip Data"

With the completion of many genome sequencing projects comes the great challenge to fully comprehend the information encoded in these sequences. Identifying interactions between DNA binding proteins, i.e., transcription factors and their DNA binding sites is an integral part of this challenge. These interactions control critical steps in cell functions and their dysfunction can significantly contribute to the progression of various diseases. ChIP-chip experiments, which couple chromatin immunoprecipitation (ChIP) with DNA microarray analysis (chip), have become powerful tools for the genome-wide identification of transcription factor DNA interactions. These experiments produce massive amounts of noisy data with small number of replicates. The nature of the data generated heavily relies on the actual designs of the chips.

Preliminary studies indicate that analysis methods that overlook the design considerations have high false positive rates in identifying the studied interactions. The proposed research aims to develop innovative, robust statistical methods that are powerful at small sample sizes and that can efficiently utilize all the characteristics of chip designs. More specifically, hierarchical mixture models that allow information sharing across the probes on the chip and probe specific binding affinities and incorporate the variable nature of the ChIP-chip peak structure will be developed.

These models are expected to be especially powerful for the common situation in which there are only a small number of replicates. In collaboration with several biological labs at the University of Wisconsin, Madison and the University of California, Berkeley, the developed methods will facilitate more sensitive and powerful analysis of DNA-protein interactions from fruit fly to humans. Furthermore, this study proposes empirical Bayes methods to integrate ChIP-chip data with other sources of genome-wide data such as gene expression and sequence data for a more comprehensive understanding of DNA-protein interactions.

Carlo C. Maley, Ph.D.

The Wistar Institute

"Tools for Measuring Evolution in Neoplasms"

Cells in tumors evolve by natural selection. A tumor is a mosaic of different mutant cells competing for resources and survival. This research adapts software tools from evolutionary biology to explore how cancer cells become malignant and how they respond to therapy. The rate at which normal tissue progresses to cancer depends on both the mutation rate and the number of evolving cells. Using serial biopsy samples from patients with Barrett's esophagus, a pre-malignant tumor that can progress to esophageal adenocarcinoma, the cancer whose incidence is increasing fastest in the western world, this project will develop software using coalescence theory to estimate mutation rates, stem cell population sizes, time since initiation of the tumor, and the ordering of mutational events during progression. These parameters can be used as biomarkers for identifying pre-malignant tumors with high risk of becoming cancerous and monitoring treatment effectiveness in malignant tumors. Moreover, once they can be measured, mutation rate and the number of stem cells may represent therapeutic targets for cancer and cancer prevention.

Fanyi Zeng, M.D., Ph.D., Professor & Associate Director, Institute of Medical Genetics Shanghai Jiaotong University, from the University of Pennsylvania School of Medicine, Department of Pharmacology is a recipient of a 2007 Post Doctoral Fellowship in Pharmacology and Toxicology

On May 22, 2007 the Health Outcomes award recipients received recognition at the ISPOR Annual Meeting in Arlington, Virginia. Pictured with **Del Persinger**, PhRMA Foundation, are **John Zeber**, Ph.D., University of Texas Health Science Center San Antonio, **Hong Song Hee**, Ph.D., from the University of Tennessee Health Science Center and **Jennifer L. Gatz**, Ph.D., University of Kentucky College of Pharmacy, Department of Pharmacy Practice & Science

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 funding may be used for incidentals directly associated with the preparation of the dissertation.

2007 Pre Doctoral Fellowship in Health Outcomes

Josh Carlson, MPH
Institute for Public Health Genetics, University of Washington

"Pharmacogenomic Drug Targeting In Non Small-Cell Lung Cancer: Evaluating the Evidence, Cost-Effectiveness, And Policy Options"

Increased understanding of the molecular mechanisms of cancer has led to the development of many new drugs that "target" specific cancer tumor characteristics. In this targeted paradigm, genomic differences in the drug target may influence the efficacy of the drug therapy. Erlotinib and gefitinib, two recently approved epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI's), have shown differential response and survival in non-small cell lung cancer (NSCLC) among subgroups defined by 3 types of genomic markers: 1) EGFR protein expression, 2) EGFR gene copy/amplification, and 3) mutations in the EGFR gene.1-5 Pharmacogenomic tests are commercially available to test these EGFR genomic markers, but pharmacogenomic testing is not routinely used in clinical practice. Despite mounting evidence, there is a lack of well designed prospective studies with sufficient data on EGFR status to demonstrate clinical utility. Without such evidence, uncertainty remains as to the potential impact and value of EGFR testing as well as the economic incentives for EGFR pharmacogenomic test development. The proposed research will provide an evidence-based evaluation of the presence and magnitude of effect of EGFR-TKI's in the treatment of NSCLC in genomic subgroups, incorporate these estimates into a cost-effectiveness model, and evaluate policy recommendations for promoting evidence-based pharmacogenomic test development. The findings of this study will help improve the integration of EGFR pharmacogenomics into clinical practice in an evidence-based and cost-effective manner.

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.

2007 Post Doctoral Fellowship in Health Outcomes

Jennifer L. Gatz, Ph.D.
University of Kentucky

"Predictors of Absconding from State Psychiatric Hospitals"

Absconding from psychiatric hospitals, also known as patients going "absent without leave," occurs when patients leave a hospital's care without permission. Patients who leave are at risk of self-harm, harm from others, and substance misuse. In addition, patients who do not return to the hospital after absconding may not transition appropriately to an outpatient setting and may miss doses of their psychiatric medications. The specific aims of this project are to identify key predictive demographic characteristics of absconders and to evaluate the effect of subtype of schizophrenia and frequency of admission on the likelihood that patients will abscond. This study will also use focus group interviews to determine psychiatric nurses' perceptions of the factors that influence absconding. Data collected from three public psychiatric hospitals in Kentucky from 2000 to 2006 will be used; as a group, these hospitals have nearly twice the U.S. rate of 2.1 absconding events per 10,000 patient days. Logistic regression modeling, which has traditionally been used to investigate absconding, depends on a normative distribution of the outcome variable and therefore may not be the best statistical technique to use for an event as rare as absconding. In this study, Poisson regression, which is often used to model rare events such as adverse drug events and mortality, will be the technique used to statistically model absconding events. The overall goal of this study is to provide a better understanding of the factors that influence absconding to aid healthcare providers in public psychiatric hospitals in preventing these undesirable events.

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.

2007 Research Starter Grants in Health Outcomes

Jeffrey Curtis, M.D., M.P.H.
University of Alabama at Birmingham

"The Extra-articular Benefits and Risks of Biologic Therapies in Patients with Inflammatory Diseases"

Recently, a number of high-quality reports have fueled controversies about the safety of Tumor Necrosis Factor (TNF)- antagonists, biologic response modifiers used to treat rheumatoid arthritis (RA) and other inflammatory diseases such as the spondyloarthropathies (SpA). Conflicting evidence about the risk of infections, heart failure (HF), and malignancies, and a possible protective benefit of these agents on the risk of ischemic vascular events (acute myocardial infarction [AMI] and stroke) remain topics of intense scrutiny but substantial uncertainty. In addition, new non TNF- antagonist biologic response modifiers (i.e. rituximab, abatacept) and new indications for TNF- antagonists have recently been FDA approved, raising additional questions about how these new drugs and diseases will affect the side effect profile of these biologic medications. These are also very high cost agents, ranging from $12,000-$15,000 per patient per year for a typical course of therapy. Thus, the combination of high cost, potentially serious yet poorly understood side effects, and wide use among patients with inflammatory diseases supports the timeliness and importance of this project.

The overall goals are to (1) generate new knowledge on the risk/benefit profile of TNF-antagonists and newer biologics by building on our previous work in this area; (2) advance methodology used to exploit observational data in health services research.

Hong, Song Hee, Ph.D.
University of Tennessee Health Science Center

"Preference Based Valuation of Resource Variation in Medication Therapy Management Services"

Medicare Modernization Act requires prescription drug plans to provide Medicare Therapy Management (MTM) services for Medicare beneficiaries with high risks of inappropriate use of prescription drugs. Adequate compensation for the MTM service is a vehicle of provider incentive programs to achieve desired levels of medication safety and effectiveness among Medicare beneficiaries. Recently, for the payment of MTM services, three Current Procedural Terminology (CPT) codes were added to the compendium. Pharmacists can now use these codes to bill Medicare and health plans for the services performed in a face-to-face encounter.

The addition of three CPT codes marks an important step toward the formal recognition of pharmacists as patient care providers. However, it raises some questions as to whether they adequately compensate for a full spectrum of MTM services that are different in resource requirement. The three CPT codes are created solely on the basis of amount of time taken to provide MTM services; they do not take into account other important resources that may be required to provide quality MTM services. Their simplicity shows a stark contrast with the complexity of RBRVS (Resource-Based Relative Value Scale) payment system for physician services.

This study uses a preference-based conjoint analysis to determine whether compensation for MTM services should vary not only with the time spent but also with other characteristics of MTM services that require different resource utilization. The alignment of provider compensation with the value placed on resource variations of the MTM service by Medicare beneficiaries encourages pharmacists to provide tailored MTM for medication safety and effectiveness.

John E. Zeber, PhD, MHA
University of Texas Health Science Center San Antonio

"Serious Mental Illness: Medication Adherence and Quality of Life Beliefs"

Patients with schizophrenia and bipolar disorder (serious mental illness, or SMI) represent a vulnerable population with substantial healthcare needs and treatment costs. Compounding this challenge is the fact that 40% are medication non-adherent, resulting in symptom exacerbation, other clinical consequences, and a significantly higher risk of relapse or hospitalization. Factors contributing to poor adherence are multidimensional, and may be viewed as a manifestation of health beliefs, treatment priorities, and perceived costs or benefits. Consequently, just as SMI patients differ in their health needs, preferences, and treatment requirements, their approaches to medication decisions also vary. Recent evidence questions the dominance of atypical over conventional antipsychotics, raising concerns over adverse events and efficacy versus tolerability issues. Gaining a more nuanced understanding of how patient sub-groups present unique clinical dimensions while understanding treatment preferences offers a significant opportunity for tailoring quality care while improving outcomes. Information regarding SMI health status perceptions (e.g., "utilities" where 0=death, 1=perfect health) is often considered suspect due to functional limitations. Obtaining primary data on such quality of life markers, frequently used in Pharmacoeconomics, health policy analyses and comparative studies of disease burden, is not a simple task. Therefore, little published information exists on SMI health utilities. Fortunately, a new methodology by Brazier et al. converts SF-36 scores directly onto preference-weight utilities. Taking advantage of extremely large VA datasets, this scientist seeks a creative integration of analytical and clinical insights extending health preferences into the adherence context. Objective and study design: Via administrative and survey data, explore multidimensional aspects of medication adherence in a national cohort of SMI veterans (approximately 115,000), including quality of life and health status outcomes. Research plan: 1) explore and statistically identify clinically-relevant adherence sub-groups; 2) compare these groups across multiple administrative data variables and SF-36 variables; 3) assess quality of life by mapping SF-36 values to utility scores. Other outcomes include associating adherence and treatment preferences to specific medications, health services utilization, and pharmacy costs. Findings from this study will help develop interventions to reconcile health beliefs and treatment preferences in order to improve adherence and clinical outcomes.

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 dissertations in pharmacology and toxicology.

The fellowship program provides a stipend of $20,000 annually for up to two years. Up to $500 a year of the funding may be used for incidentals directly associated with the preparation of the dissertation.

Three hundred and twenty seven fellowships have been awarded under this program since it began in 1978 including the ten fellows awarded in 2007.

The 2007 PhRMA Foundation Pharmacology/Toxicology award recipients were recognized during the 2007 ASPET Award Presentation in Washington, DC on April 28, 2007. They are accompanied by **Eileen Cannon**, PhRMA Foundation, and **Dr. George Fuller**, Chairman of the Basic Pharmacology Advisory Committee

2007 Pre Doctoral Fellowships in Pharmacology/Toxicology

Sonia K. Bhangoo
Northwestern University

"HIV-1 Related Peripheral Sensory Neuropathy"

Neuropathic pain associated with diseases such as AIDS has long been a debilitating affliction for which there is little treatment. Patients suffer from symptoms ranging from a loss of sensation to excessive and spontaneous pain. One area of research has focused on the role of the neuroinflammatory response to injury in the genesis and maintenance of neuropathic pain, more specifically, the role of chemokines in the mechanisms of pain. Chemokines are small chemotactic cytokines that mediate leukocyte migration, which is part of the inflammatory response associated with nociception. The project demonstrated that several rodent models of neuropathic pain are associated with the upregulation of chemokine signaling in the dorsal root ganglia (DRG) and peripheral nerve, where pain processing takes place. Additionally, when chemokines or their ligands are injected into rodents' paws, the result is hyperalgesia and allodynia. This project is concerned with understanding the role of chemokine signaling in the physiology of the DRG and its relationship to the genesis of HIV-1 related neuropathic pain. In particular, the project demonstrated that following the administration of Nucleoside Reverse Transcriptase Inhibitors (NRTIs), which are commonly used in the treatment of HIV-1 infection, rodents develop peripheral neuropathy. In association with this syndrome DRG cells upregulate the expression of the CXCR4 chemokine receptor and its ligand the chemokine SDF-1/CXCL12. The role of increased chemokine signaling in the genesis of NRTI induced painful neuropathy was demonstrated by the fact that the painful effects of NRTIs were inhibited by the CXCR4 antagonist, AMD3100. HIV-1 uses both the CCR5 and CXCR4 receptors to gain entry into target cells as well. It is still not known, however, how HIV-1 and NRTIs interact with respect to the development of neuropathic pain. They hope to determine if the upregulated expression of CXCR4 receptors in the DRG following NRTI treatment is responsible for the proalgesic effects, and also underlies the observed synergism between HIV-1 and NRTIs in the generation of painful neuropathies in HIV-1.

Namandjé N. Bumpus,
University of Michigan

"Investigation of the Effects of A Prevalent P450 2B6 Genetic Polymorphism On Catalytic Activity"

The cytochromes P450 (P450) are a superfamily of enzymes that play a major role in the oxidative metabolism of a number of exogenous and endogenous compounds including drugs, hormones and vitamins. Most P450-mediated reactions result in the

detoxification of exogenous compounds via the formation of hydrophilic metabolites that can be readily excreted from the body. Because metabolism by P450s leads to a decrease in plasma concentration of the parent drug, P450s play an important role in drug bioavailability. Poor bioavailability is a major reason why compounds generated in the discovery phase fail to make it to the market. Thus, there is considerable interest in better prediction of clinical outcomes by using in vitro approaches to understand P450-catalyzed reactions. P450 2B6 is a human polymorphic enzyme that is expressed in a number of tissues including the liver, kidney, heart and brain. P450 2B6 is primarily responsible for the oxidative metabolism of a growling list of clinically relevant drugs including efavirenz, used to treat HIV-1; and bupropion, an anti-depressant and smoking cessation aid. A number of single nucleotide polymorphisms have been found in the P450 2B6 gene. One of these variant alleles denoted as P450 2B6*4, which corresponds to a lysine 262 arginine mutation in the protein, has been shown in vivo and in vitro to exhibit differences in substrate metabolism. As a result, this mutation may be related to certain adverse drug reactions. This variant is prevalent across all ethnic groups tested, and has been reported to have a 5-9% allele frequency. In light of this, project will examine the effects of this mutation on the metabolism of P450 2B6 substrates and on the response to known modulators of P450 2B6 activity. In doing so, the project aims to elucidate the mechanism(s) underlying the differences observed in the activity of this enzyme.

In San Diego, CA on November 11, 2007, the recipients of the 2007 PhRMA Foundation Awards in Pharmaceutics received their awards. Pictured from left to right are **Darin Y. Furgeson**, Ph.D., of the University of Wisconsin - Madison, **Heidi M. Mansour**, Ph.D., R. Ph., The University of North Carolina at Chapel Hill, **Hugh D. C. Smyth**, B. Pharm., Ph.D., of the University of New Mexico, **Adora M. Padilla** of the University of Connecticut, and **Clare Aubrey-Medendorp** of the University of Kentucky

Gina Chun

The George Washington University

"The Role of Polo-like kinase 1 in Cell Cycle Progression after Genotoxic Insult: Consequences of Forced Checkpoint Bypass"

Exposure to carcinogens significantly increases the risk of developing cancer. Occupational and environmental exposure to genotoxic agents can lead to DNA damage and carcinogenesis. It is known that hexavalent chromium compounds [Cr(VI)] are occupational/environmental human respiratory carcinogens. Molecularly, Cr(VI) carcinogenesis involves dysregulation of cell cycle signaling resulting in cells that become death resistant and gain a survival phenotype. Alterations in regulators of cell cycle checkpoints that progress mitosis after DNA damage can compromise the genomic integrity of the cell. Recently, Polo-like kinase 1 (Plk1) has been shown to play a fundamental role in the DNA damage response. Overexpression of Plk1 has been shown to promote mitosis after DNA damage. Plk1 is overexpressed in a variety of tumors and its expression correlates with poor patient prognosis. Therefore, Plk1 has become a promising target for cancer therapy. Indeed, our preliminary data implicate Plk1 in the bypass of Cr(VI) induced G2/M cell cycle arrest. The overarching goal of this proposal is to investigate the role of Plk1 in the bypass of the DNA damage checkpoint after genotoxic exposure. The project proposes that the dysregulation of Plk1, which is a common event in tumor formation, is sufficient to promote mitotic progression of cells with damaged DNA. The consequences of overriding a critical checkpoint in the face of genotoxic insult can lead to cellular alterations, mutagenesis and neoplastic transformation. They will utilize both human lung fibroblasts and S. cerevisiae (yeast) to examine the role of Plk1 in promoting mitosis after DNA damage. Moreover, they will investigate if overexpression of Plk1 promotes error-prone repair of damaged DNA and increases mutagenesis. These studies will further elucidate the consequences of bypassing the DNA damage checkpoint and will enhance the understanding of Plk1 as a promising therapeutic target.

Sophie C. Desbiens

Boston University School of Medicine

"GABAB Receptor Regulation by CREB and Estrogen with Applications to Cocaine Addiction"

Cocaine abuse is an important problem: in the US alone it is estimated that nearly 34 million people age 12 and over have tried cocaine at least once in their lifetime. In this project, we will explore regulation of the GABAB receptor (GABABR) subunit genes by CREB and estrogen with applications to cocaine addiction. The GABABR mediates slow metabotropic inhibition, and expression of two subunits GABABR1 and GABABR2 is believed required for receptor function. GABABR agonist and modulators have been shown effective in reducing cocaine consumption and relapse in humans and/or animal models of addiction. In addition, baclofen, a GABABR agonist, is more effective at preventing acquisition of cocaine self-administration in female rats than in males. Studies have shown that chronic cocaine exposure leads to an increase in phosphorylated cAMP response element-binding protein (CREB). Interestingly, expression of the GABABR1 isoforms (R1a and R1b) is under the control of alternative promoters in the R1 gene and these promoters are differentially regulated by CREB family members. The studies proposed in this project will lay the foundation for regulation of the GABABR subunit genes in the nucleus accumbens, hippocampus and neocortex, which are important brain areas for addiction. The ability to control the specific expression of alternative GABABR subunits may also provide a novel treatment option for drug addiction.

Iram R. Hassan

New York Medical College

"Novel Docosahexaenoic Acid-Derived Lipid Mediators Are Protective In Ischemic Renal Injury"

Ischemic acute renal failure (ARF) is a clinical problem associated with high morbidity and mortality with inflammation being a major feature of its pathophysiology. Hence, endogenous pathways that can limit inflammation are of interest. -3 polyunsaturated fatty acids (PUFA) have a well established role in dampening inflammation as evidenced in clinical studies and animal experiments. Fish oil contains the essential -3 PUFA docosahexaenoic (DHA) acid which has been shown to exert anti-inflammatory effects and can ameliorate ARF in animal models. The molecular mechanisms of action for the protective properties of DHA have recently been attributed to the formation of novel DHA-derived lipid mediators (LM).15-lipoxygenase (LOX) is a key enzyme in the formation of a class of anti-inflammatory eicosanoids, namely lipoxin A4 (LXA4). Recent reports demonstrated that 15-LOX can also give rise to novel DHA-derived lipid autacoids neuroprotectin D1 (NPD1) and 17HDHA, which share the anti-inflammatory properties of LXA4. Strong preliminary data show that dietary DHA is protective against ischemic renal injury which correlates with endogenous formation of NPD1 and 17HDHA. More importantly, systemic treatment with NPD1 attenuates inflammation in the kidney and amplifies cytoprotective heme-oxygenase 1 (HO-1) expression. Based on these findings, we hypothesize that the protective actions of dietary DHA in ischemic renal injury are mediated by novel DHA-derived anti-inflammatory LM. To test this hypothesis, we propose the following Specific Aims: 1. Establish that dietary -3 PUFA trigger the formation of anti-inflammatory DHA-derived LM. 2. Demonstrate that the beneficial effects of dietary DHA are attributed to formation of NPD1 and 17HDHA. 3. Determine if the renoprotective effects of NPD1 and 17HDHA are mediated via amplification of HO-1. Results from this study may provide a molecular mechanism for the protective effect of dietary DHA in ischemic renal injury.

Michael P. Holt

University of Colorado at Denver and Health Sciences Center

"Role of Hepatic Macrophages in Drug-Induced Liver Injury"

The idiosyncratic nature, severity and poor prognosis of drug-induced liver injury (DILI) make these reactions a major safety issue during drug development, as well as the most common cause for the withdrawal of drugs from the pharmaceutical market. The key to predicting and preventing DILI is to understand the underlying mechanisms. There is growing evidence that initiation of hepatocyte injury, caused by a drug or a reactive metabolite of a drug, triggers cells of the innate immune system, including hepatic macrophages (M), which leads to further tissue damage and/or repair. Evidence suggests that hepatic M contribute to tissue damage by the production of a range of pro-inflammatory cytokines and mediators. However, studies also demonstrated that these cells play a key hepato- protective role through the production of mediators that counteract inflammatory events and promote liver regeneration. This dichotomy of hepatic M functions may be explained by the plasticity and/or the heterogeneity of these cells. Hepatic M consists of at least two populations: the resident M (Kupffer cells, KC) and the infiltrating M. Our capability to clearly distinguish these two populations in the liver of mice treated with acetaminophen (APAP)

allows us, for the first time, to separate infiltrating M from the resident KC, and to focus our study on the role of the former in DILI. The specific objective of the current proposal is to test the hypothesis that the infiltrating M play a critical role in ameliorating APAP-induced liver injury by the promotion of tissue repair and regeneration. The proposed study will investigate the mechanisms involved in the hepato-protective effect of the infiltrating M and their roles in three important liver repair processes, including phagocytosis of apoptotic inflammatory cells, hepatocyte regeneration and angiogenesis. These studies will contribute to the ultimate goal of understanding the molecular and cellular mechanisms of tissue damage and repair during DILI. Such understanding can help identify predisposing factors that determine susceptibility to DILI and may ultimately facilitate the development of strategies to predict and prevent DILI. Moreover, the expectation is that these results will significantly contribute to understanding the pathogenesis of other inflammatory diseases caused by viral infection, alcohol ingestion and autoimmune conditions.

Andrea Mountney
The Johns Hopkins School of Medicine

"Sialidase Treatment As A Therapy To Enhance Recovery From Spinal Cord Injury"

Spinal cord injuries typically result in paralysis with little functional recovery, for which there are no restorative pharmacological treatments. In the central nervous system (which includes the spinal cord), when the axons that carry signals are severed they fail to regenerate, even though the nerve cell bodies from which they arise remain intact and healthy. In the past, it was a widely held belief that mature central nervous system neurons were incapable of axon regeneration. Now, it is appreciated that axon regeneration failure is due, in large part, to specific "stop" signals that the injured axon receives from the surrounding milieu. These stop signals are in the form of axon regeneration inhibitors, molecules on residual myelin membranes and glial scar cells that accumulate and persist at the injury site. Reversing the action of these molecular inhibitors may allow enhanced axon regeneration with significant recovery of nervous system function after injury. One of the axon regeneration inhibitors found on residual myelin is myelin-associated glycoprotein (MAG), which exerts its inhibitory effect by first binding to specific receptors on injured axons. The receptors, gangliosides GD1a and GT1b, carry terminal sialic acid (saccharide) moieties essential to MAG binding. Treatment of axons with sialidase, a purified enzyme that cleaves terminal sialic acids, reverses MAG-mediated inhibition of axon outgrowth in vitro and in an animal model of brachial plexus nerve injury in vivo. Based on these positive results, the current fellowship will support research to test whether intrathecal delivery of sialidase after spinal cord contusion injury will improve axon regeneration and functional recovery in the rat. Since contusion is the most prevalent type of human spinal cord injury, this preclinical model is the most relevant to test the therapeutic potential of sialidase. Recombinantly expressed, highly purified sialidase was prepared and confirmed to cleave MAG receptors in vitro. Its ability to cleave sialoglycans in vivo without toxicity when delivered intrathecally to rat spinal cords was established. In pilot studies, sialidase delivery improved behavioral and neurophysiological recovery in rats that received a moderate contusion injury followed by intrathecal infusion of sialidase (compared to infusion of saline control). This proposal will extend and expand the pilot study by evaluating the anatomical, physiological and behavioral efficacy of sialidase delivery to the contused rat spinal cord. Sialidase treatment will also be combined with another mechanism-based therapy under preclinical evaluation, chondroitinase, which is believed to act on a distinct axon regeneration inhibitor, chondroitin sulfate proteoglycan. Proof of sialidase efficacy in this preclinical model, either alone or in combination with chondroitinase, would form the basis for its consideration as a therapy in human spinal cord injury.

Jeremy S. Paige
Weill Medical College

"Mechanism of Nitric Oxide-Mediated Axon Outgrowth In Animal Models Of Peripheral Nerve Injury"

Nitric oxide (NO) is an endogenously-produced signaling molecule with numerous effects on the cardiovascular, immune, and nervous system. Many medically-useful drugs function by either generating NO or by manipulating NO signaling in cells. An emerging concept is that NO promotes nerve regeneration following injury. Nerves are composed of long cellular filaments called axons, and these axons are destroyed in diseases that cause peripheral neuropathies such as diabetes. NO exerts its effects on cells by modifying proteins. However, the targets of NO that account for its nerve regeneration activity are unknown. To understand the mechanism by which NO regulates regeneration, a method was developed to identify new protein target of NO in nerves. Using this method, collapsin response mediator protein-2 (CRMP-2), a protein known to be required for proper neuronal development, was identified as a novel target of

NO. Thus, NO modification of CRMP-2 may mediate the effects of NO on nerve regeneration. The experiments seek to integrate the biochemical mechanism of NO action with the physiological effects of NO in intact laboratory animals. We hope that the identification of NO targets that mediate nerve regeneration will enable the development of small molecule NO donors that could lead to more efficient therapies for those who suffer from sensory neuropathies.

Rachel J. Roth
Yale University

"Regulation of Energy Expenditure and Lipid Metabolism by the Mitogen Activated Protein Kinase Phosphatase-1"

Obesity has become a worldwide epidemic, and is associated with the development of metabolic syndrome, or syndrome X. Metabolic syndrome is defined by multiple symptoms including insulin resistance, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD). Many details by which obesity leads to metabolic syndrome remain unknown. The stress-responsive mitogen-activated protein kinases (MAPKs), p38 MAPK and c-Jun NH2-terminal kinase (JNK), play important roles in metabolic homeostasis. This laboratory has shown that mice lacking expression of the MAPK phosphatase-1 (MKP-1), a dual-specificity phosphatase which inactivates the stress-responsive MAPKs by dephosphorylation, results in p38 MAPK and JNK hyper-activation in insulin-responsive tissues. MKP-1-deficient mice are resistant to diet-induced obesity, exhibit enhanced energy expenditure in skeletal muscles, and are resistant to the development of NAFLD. Thus, they hypothesize that MKP-1 is a critical negative regulator of metabolism. They will test this hypothesis by determining how MKP-1 regulates energy expenditure by investigating its role in regulation of PPARg co-activator-1 (PGC-1), a target of p38 MAPK that stimulates mitochondrial biogenesis and metabolism. The project will examine the tissue-specificity of MKP-1 signaling for metabolic homeostasis by ablating the expression of MKP-1 in skeletal muscle. Lastly, the project will determine the pathophysiological role of MKP-1 by investigating its involvement in the development of NAFLD by crossing mkp-1-/- mice with a mouse model that is prone to the development of hepatic steatosis. Together, these data will provide new insight into the physiological and pathophysiological contributions of the MAPKs in metabolism and may suggest new therapeutic avenues to combat obesity, NAFLD and other metabolic syndromes.

Jana Shirey
Vanderbilt University

"The Role of M4 mAChR in Modulating Hippocampal Neurotransmission"

Alzheimer's disease (AD) is a progressive, neurodegenerative disease characterized by abnormal changes in the brain that lead to amyloid plaques and neurofibrillary tangles. The severity of these pathologies correlates with severity of symptoms associated with AD. These symptoms include memory loss, language deterioration, and cognitive impairment, with disease progression eventually destroying the patient's cognition, personality, and ability to function. The risk of developing this devastating disorder doubles every 5 years beyond the age of 65. The hippocampus is a key cortical structure in the brain that plays an important role in a number of normal physiological processes including formation of short- and long-term memory and is a primary site of pathology in AD. One of the major neuromodulatory inputs to the hippocampus is a cholinergic projection from the basal forebrain which is critical for memory and attention mechanisms. Degeneration of this cholinergic projection is known to play a key role in the pathology of AD. Cholinergic transmission in the hippocampus is mediated primarily by muscarinic acetylcholine receptors (mAChRs), which are G protein-coupled receptors (GPCRs) that are further delineated into five subtypes (M1 - M5). Muscarinic agonists have a number of electrophysiological effects in the hippocampus including potentiation of glutamate-gated ion channel currents, reduction of both inhibitory and excitatory synaptic transmission, and direct excitatory effects on pyramidal cells. However, the specific mAChR subtypes involved in each of these actions are largely unknown. Determination of the specific roles of each of the mAChR subtypes in regulating hippocampal function will be critical for understanding the involvement of mAChR subtypes in both normal and pathological conditions. Until recently, it has not been possible to determine the mAChR subtypes involved in specific responses because of a lack of subtype-selective ligands. This laboratory and others have now made major advances in discovery of novel, highly selective pharmacological reagents that specifically activate M1 or M4, two of the major mAChR subtypes in the hippocampus. The focus of the present research project is to utilize these tools, combined with recently developed mAChR knockout mice, to rigorously determine the functions of these individual mAChR subtypes in hippocampal cells. Future work in the lab will focus on the use of these tools to examine the effects of specifically activating either M1 or M4 in animal models of cognitive impairment. Ultimately, these studies may lead to the development of novel treatments for memory disorders such as AD that could overcome many limitations of drugs that are currently available, such as tacrine.

Post Doctoral Fellowships in Pharmacology/Toxicology

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

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

2007 Post Doctoral Fellowships in Pharmacology/Toxicology

Jennifer Brightwell-Petta, Ph.D.

Tulane University Heath Sciences Center

"Amygdala, CREB, and Neuropathic Pain"

Chronic neuropathic pain afflicts millions of people in the United States. Currently available pain killers (e.g. opioids, NSAIDS, acetaminophen) do not adequately alleviate neuropathic pain, and often yield undesirable side effects including dependence. Peripheral neuropathic pain is a result of nerve injury and is associated with hyperexcitability of primary sensory neurons and spinal projection neurons. Plastic changes that occur in supraspinal regions may modulate such pain. The amygdala, most known for its role in regulating emotion as well as in opioid-mediated pain inhibition, has recently been linked to descending pain facilitation in a model of persistent inflammatory pain. Although inflammatory and neuropathic pain have different etiologic origins, supraspinal modulation may overlap. The preliminary study showed that disruption of neural activity in the amygdala reduces behavioral signs of neuropathic pain in the rat. The current proposal will investigate the cellular mechanisms responsible for this facilitation by testing the hypotheses that N-methyl-d-aspartate (NMDA)- and cAMP response element-binding (CREB) protein-dependent mechanisms in the amygdala contribute to chronic pain. To address the former question, the project will use the spared nerve injury (SNI) model of neuropathic pain and in vivo brain microdialysis to test the hypothesis that SNI enhances excitatory neurotransmission in the amygdala by measuring extracellular glutamate release. Second, she will examine if amygdalar NMDA receptor-blockade reduces pain behavior following SNI. She will address the latter hypothesis that CREB protein in the amygdala contributes to neuropathic pain by determining if behavioral signs of neuropathic pain are correlated with increased levels of phosphorylated CREB and finally, if blockade of CREB function using RNA interference reduces neuropathic pain. These experiments are timely and the results will aid in the development of novel drug targets for chronic pain.

Douglas J. Sheffler, Ph.D.

Vanderbilt University Medical Center

"Regulation of mGluR1 Function by Positive Allosteric Modulators"

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS) and is responsible for the generation of fast excitatory synaptic responses at the vast majority of CNS synapses. These fast excitatory synaptic responses at glutamatergic synapses are mediated by activation of the ionotropic glutamate receptors (iGluRs), which are glutamate-gated ion channels. Glutamate also activates metabotropic glutamate receptors (mGluRs), which are G protein-coupled receptors (GPCRs) that provide a mechanism by which glutamate can modulate activity at the same synapses at which it elicits fast synaptic responses via the iGluRs. Due to this modulatory function, subtype-specific mGluR activators have exciting potential for the development of novel treatment strategies for numerous psychiatric and neurological disorders. For example, selective activators of mGluR1 may have potential as cognition-enhancing agents and treatments for both Huntington's and Alzheimer's disease. However, in order to realize this potential, one must first overcome several obstacles, primarily the development of mGluR subtype-selective ligands. In GPCR nomenclature, the amino acids that form contacts to the endogenous ligand, which is glutamate for the mGluRs, comprise the orthosteric binding site. Unfortunately, it has proven difficult to develop mGluR subtype-

selective ligands to the orthosteric site due to high conservation of the glutamate binding domain among the mGluR subtypes. Alternatively, allosteric mGluR ligands, which bind to sites distinct from the highly conserved glutamate (orthosteric) binding site, display much greater subtype selectivity among the mGluR subtypes and provide a greater opportunity for mGluR drug discovery. These small molecules do not activate the mGluRs directly but act at allosteric sites on the receptor to either inhibit (allosteric antagonists) or increase (allosteric potentiators) glutamate-induced receptor activation. However, little is known about mGluR domains involved in the action of different classes of mGluR potentiators or the physiological impact of these compounds on mGluR signaling in native systems. Importantly, both orthosteric and allosteric ligands have been previously demonstrated to differentially activate distinct signaling pathways of a single GPCR in a phenomenon known as agonist-directed receptor trafficking. These studies imply that allosteric compounds could be developed which would potentially activate or inhibit specific signaling pathways. Differential effects of allosteric potentiators on coupling of mGluRs to diverse signaling pathways could have a tremendous impact on the in vivo actions and potential therapeutic utility of distinct classes of compounds. However, the effects of mGluR1 potentiators on coupling to different effector systems are not known. Defining the precise domains of the receptor required for the action of these compounds, the mechanisms involved in allosteric potentiation, and downstream mGluR signaling effects are essential for further development of this approach to mGluR activation. To date, three structural classes of mGluR1-selective positive allosteric ligands have been identified including (9H-xanthene-9-carbonyl)-carbamic acid butyl esters (RO-67-4853), (S)-2-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidines (RO-67-7476), and 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)-benzamide (CDPPB) analogs (VU-64). The focus of the present research project is to rigorously determine whether agonist-directed receptor trafficking occurs with different classes of positive allosteric potentiators of mGluR1, to characterize the binding site of these compounds, and to determine the effects of positive allosteric potentiators of mGluR1 on desensitization, resensitization, and downregulation of the receptor.

Diana Ye, Ph. D.
University of Pennsylvania

"The Role Of Tyrosine Phosphatase Of Liver Regeneration-1 (PRL-1) In Hepatocytes Proliferation During Liver Development And Regeneration"

Protein phosphorylation plays an essential role in regulation of many cellular processes including cell differentiation and proliferation. Protein dephosphorylation by protein tyrosine phosphatases (PTPases) can contribute both a positive and negative effect on cell proliferation and differentiation. PTPase of liver regeneration-1 (PRL-1) was initially identified as an immediate-early gene that was significantly induced during liver regeneration. Furthermore, it is the only PTPase that is upregulated during liver regeneration. PRL-1 expression is high during liver development, but low in normal adult liver. It is the only immediate-early gene expressed at a constitutively high level in several hepatoma cell lines. These data suggest that PRL-1 has a potential role in hepatic cell proliferation, but definite experimental proof that PRL-1 is required for this process has not been performed. The studies proposed herein will help to define the mechanisms of PRL-1 controlling of cell proliferation by conditional knockout of PRL-1 in hepatocytes. The cDNA microarray analysis will identify PRL-1 target proteins. Transfection studies will determine whether PRL-1 regulates the transcription of genes through its ability to dephosphorylate transcription factors. Understanding how PRL-1 controls hepatic cell proliferation may ultimately provide a useful drug target for the treatment of liver injuries and hepatocellular carcinoma.

During the 2006 ASPET Annual Meeting in San Francisco, CA, **Dr. Lee M. Graves**, from the University of North Carolina at Chapel Hill, received the 2006 Sabbatical Fellowship in Pharmacology and Toxicology. He is pictured here with **Eileen Cannon** and **Dr. George Fuller**.

Atul J. Butte, M.D., Ph.D., Assistant Professor, from Stanford University School of Medicine was awarded a 2006 Research Starter Grant in Informatics

Fanyi Zeng, M.D., Ph.D.
University of Pennsylvania

Identification and studies of glutamate receptor RNA binding proteins

Learning and memory are thought to be mediated by synapses and are accompanied by changes in the electrical activity of the brain, changes in second messenger molecules, modifications of existing synaptic proteins and synthesis of new proteins. Malfunctions of these processes will result in cognitive dysfunction and many CNS disorders. Glutamate is the major excitatory neurotransmitter in the mammalian CNS. Activation of glutamate receptors (GluR) is responsible for basal excitatory synaptic transmission and many forms of synaptic plasticity that are thought to underlie learning and memory. The translational control of GluR mRNA and other post-transcriptional events largely require interaction between RNA binding proteins (RBPs) and GluR mRNA. The use of pharmacological agents has enabled the study of the regulation of glutamate receptors. One of the ionotropic glutamate receptor subunits iGluR2 has been shown to be translated and inserted into the dendritic membrane in response to pharmacologic activation by DHPG in dendrites of neurons from primary cell cultures of rat hippocampi. This research proposal outlines the means to identify RBPs that interact with iGluR2 using the in vivo PAIR technique (peptide nucleic acid assisted identification of RNA binding proteins), investigate their binding properties, and characterize the role of RBPs in modulating protein synthesis of iGluRs under physiological as well as pharmacological conditions. The resulting work will augment studies of the regulatory mechanisms governing RBPs in CNS and their influence on post-synaptic activities. This research may also lead to potential targets for pharmacological treatment of cognitive dysfunction in CNS disorders such as Alzheimer's disease.

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 ten have been awarded, including the grants beginning on January 1, 2007.

2007 Research Starter Grants in Pharmacology/Toxicology

Changjian Feng, Ph.D.
University of New Mexico

"Mechanism of Intrinsic Regulation of Electron Transfer in Endothelial and Neuronal Nitric Oxide Synthases"

There is still much unknown about how nitric oxide (NO) production by nitric oxide synthase (NOS) is tightly regulated. This is remarkable because unregulated NO production by NOS has been implicated in an increasing number of diseases lacking effective treatments, including stroke, septic shock and cancer. Before logically designing an effective preventive and therapeutic strategy by targeting NOS/NO, one must understand the mechanism of NOS regulation at the molecular level. The long-term goal of this research is to gain a detailed understanding of the molecular mechanism of intrinsic NOS regulation through in-depth knowledge of catalytically significant interdomain electron transfer (IET) processes. The objective of this research is to investigate the mechanism of specific protein sequences in regulating the essential IET process between the flavin mononucleotide (FMN) and heme domains in NOS. We will focus on endothelial NOS (eNOS) and neuronal NOS (nNOS) because unlike inducible NOS (iNOS), eNOS and nNOS synthesize NO in a calcium/calmodulin (CaM)

dependent manner, thus presenting a unique therapeutic target site. Recent published studies from this laboratory provide the first direct observation that CaM controls the FMN-heme IET through facilitating FMN/heme interactions. Thus, it is proposed to further investigate molecular mechanism of CaM interacting with eNOS/nNOS, using mutants of NOS or CaM at the predicted binding/interacting sites.

This study will identify specific inter-domain interactions that are catalytically important in NO production by eNOS/nNOS. This new important mechanistic information has the potential of facilitating bio-rational design of direct and selective NOS inhibitors/activators through disrupting/enhancing the specific interactions, in order to provide better therapeutic interventions.

Sumei Liu, Ph.D.
The Ohio State University

"Role Of Enteric Corticotropin-Releasing Factor (CRF) In Stress-Related Gastrointestinal Dysfunctions"

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders characterized by cramping, abdominal pain, bloating, constipation, and diarrhea with no sign of structural or biochemical abnormalities. Previous clinical studies have shown that stressful life events and psychological conditions (anxiety and depression) are important risk factors for IBS and influence the onset and severity of symptoms. Endogenous corticotropin-releasing factor (CRF) in the brain plays a significant role in stress-evoked gastrointestinal functional abnormalities. Recent studies showed that peripheral administration of CRF also altered gut motility, intestinal mucosal function, and visceral sensation that mimicked the changes induced by stress. Peripheral administration of peptide CRF receptor antagonists with poor brain penetration alleviated stress-induced alterations of gut motility, secretion, and visceral sensation. These observations point out a peripheral CRF signaling pathway that might co-exist with the central CRF mechanisms and might also be involved in stress-related alterations of gut function. However, the site and mechanisms underlying this peripheral CRF signaling pathway are largely unknown. This project addresses the CRF signaling mechanisms in the gut by testing the hypothesis that CRF acts in the enteric nervous system (ENS) to mediate gut responses to stress. The ENS in humans and animals functions like an independent brain-in-the-gut and controls many gut functions such as motility, secretion, local blood flow, and visceral sensation. The ENS and CNS are linked bi-directionally by the sympathetic and parasympathetic pathways forming the brain-gut axis. Lack of direct information on the neurobiology of CRF in the ENS is a major gap in knowledge necessary for understanding how CRF works in the gut, how it is involved in disordered states and how selective CRF receptor antagonists might be useful in the therapeutics. The proposed studies on effects of stress and CRF on the neurobiology of ENS have significant potential for filling many of these gaps. Results of these studies will improve insight into the specific role of gut-derived CRF in stress-related functional bowel disorders at the molecular, cellular, and integrated system levels of organization. Understanding the CRF signaling pathway in the ENS will help in developing new strategies for management of functional bowel disorders.

Edward "Ted" M. Mills, Ph.D.
University of Texas at Austin

"Molecular Mechanisms of MDMA-induced Hyperthermia"

The electron transport chain in mitochondria is the central component through which mitochondria regulate much of cellular physiology. As fuels such as fatty acids and sugars are combusted, electrons are donated to the respiratory chain protein complexes. As electrons travel along the series of complexes, protons are extruded from the inner matrix to the outer side of the inner mitochondrial membrane, forming a large proton gradient across the membrane that is quantitatively expressed as the mitochondrial membrane potential. Proton flux back into the matrix through the ATP synthase liberates energy that is consumed for the purpose of ATP production – the major energy currency for the work in biological systems. Protons can also "leak" back into the matrix through uncoupling proteins, so named because they "uncouple" the proton gradient from ATP production. Proton leak has the capacity to release large amounts of energy, but since that energy is not readily consumed, it is released as heat. Recent findings from this laboratory have linked thermogenic uncoupling to the lethal hyperthermic effects of the widely abused amphetamine-type drugs "ecstasy" (MDMA) and "speed." Mice deficient in the skeletal muscle form of uncoupling protein are completely protected from hyperthermia and death induced by these agents. Uncoupling proteins are expressed in humans, but their physiologic functions have not been defined. Recent evidence has linked these thermogenic mediators to regulation of metabolic rate, obesity and diabetes – rampant diseases in modern society. Moreover, other recent findings suggest that uncoupling proteins regulate an expanding portfolio of functions

Dewey H. Barich, Ph.D., Consultant, Semiconductor Safety Association, from the University of Kansas received a PhRMA Foundation Post Doctoral Fellowship in Pharmaceutics in 2004

including cell growth, synaptic transmission, and reactive oxygen species production. The proposed studies will define the mechanisms by which uncoupling proteins are activated by amphetamines in genetically modified mice. The results obtained will illuminate their potential functions in physiology and disease, and eventually will guide efforts to exploit uncoupling proteins as targets for drug development in hyperthermia, diabetes, and obesity.

Michael J. Schell, Ph.D.

The Uniformed Services University of the Health Sciences

"PPAR-Targeted Regulation Of Peroxisomes and Mitochondria In Brain Cells"

Alzheimer's disease, high cholesterol, and diabetes occur with a high prevalence in Western societies, owing to changes in longevity, diet, and lifestyle. Such "diseases of prosperity" are the subject of intense research in the pharmaceutical industry, and better drugs and new drug targets for these diseases would be desirable for improving human health. The peroxisome proliferator-activated receptors (PPARs) are a class of nuclear receptors that modulate gene transcription in cells. Drugs that modulate PPARs have proven to be effective therapies for treating diabetes, high cholesterol, Alzheimer's disease, and stroke. PPARs regulate the expression of genes involved in energy metabolism and inflammation. Despite the utility of high-affinity drugs that selectively target PPAR subtypes, many of the efficacious properties of these drugs for treating brain diseases are not fully explained by our current understanding of their mode of action. The proposed studies aim to explore the effects of PPAR-targeted drugs on brain peroxisomes and mitochondria—and the metabolism within them—in cultured neurons and glia. The goal is to uncover new and previously unappreciated actions of this exciting class of drugs on brain organelles in order to facilitate the development of better therapies. Using live imaging of proteins, calcium, respiration, and free radical production in individual brain cells, we expect to uncover new modes of action for the PPAR drugs that will help explain their efficacy in brain. It is anticipated that this research will pave the way towards the development of PPAR-based drugs that are selectively targeted to the brain, and lead to better cures for the types of neurological diseases increasingly prevalent in our sedentary, ageing society.

R. Grace Zhai, Ph.D.

University of Miami

"Understanding the Mechanisms of Neurodegeneration and Establishing a Model to Isolate Neuroprotective Factors"

Following nerve injury, the distal axons and synaptic terminals undergo Wallerian degeneration within 48 hours. However, in the slow Wallerian degeneration (WldS) mouse, a naturally occurring mutant, this process is delayed by 3-4 weeks. This delay is caused by the overexpression of a chimeric gene Ube4b/Nmnat, which contains the entire coding sequence of NMNAT (nicotinamide mononucleotide adenylytransferase), an enzyme that produces NAD. Recently it was found that the loss of nmnat in Drosophila causes a rapid and severe neurodegeneration similar to Wallarian degeneration in vertebrates. Interestingly, overexpression of nmnat not only delays Wallerian-like degeneration but also has potent neuroprotective effects in several neurodegeneration conditions, suggesting that the function of NMNAT in nerve terminal maintenance and regeneration is evolutionarily conserved. However, the detailed mechanism under-lying the protective effect of NMNAT remains unclear. In this proposal, they will combine genetic and molecular approaches, taking advantage of Drosophila as a genetic model organism to (1) characterize the molecular mechanisms by which NMNAT protects neurons and delays neurodegeneration and (2) establish a model for drug screening to facilitate the isolation of small molecules that can mimic and/or enhance the protective function of NMNAT in the nervous system, which will greatly facilitate the design and screen of drugs for the treatment of neurodegenerative disorders.

Xiaobo Zhong, Ph.D.
The University of Kansas Medical Center

"Pharmacogenomics of P450 Oxidoreductase"

Genetic polymorphisms involved in microsomal cytochrome P450 mediated drug metabolism account for clinically significant differences in drug efficacy and toxicity within the general population. Microsomal P450 enzymes are heme-containing proteins that catalyze oxidation of more than 80% of prescription drugs. All microsomal P450 enzymes require a cofactor, P450 oxidoreductase (POR). It is the only flavoprotein that donates electrons to all microsomal P450 enzymes for their oxidation functions. Genetic polymorphisms in the POR gene may affect its function and subsequent P450 activities, but such polymorphisms have not been identified in the general population. In this project, they propose to perform a comprehensive study to correlate POR polymorphisms with POR gene expression, POR activity, and POR-assisted P450 activities using a set of human liver samples. The proposed studies will provide information how genetic polymorphisms in the POR gene cause inter-individual variations on P450 catalyzed drug metabolism. This information is important for further developing personalized medicine for many current prescribed drugs based on patient's POR genotypes.

Paul Calabresi Medical Student Fellowship

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

The minimum period of the fellowships is six months and the maximum is two years, with a maximum stipend of $18,000. One hundred and sixty six 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.

Jonathan E. Schmitz from the Rockefeller University received a 2007 Paul Calabresi Medical Student Research Fellowship. Pictured at the 2007 ASCPT Annual Meeting in Anaheim, CA with **Del Persinger**

2007 Paul Calabresi Medical Student Fellowships

Jonathan E. Schmitz
Rockefeller University

"Metagenonic Screening for Novel Bacteriophage Lysins"

A focus of the Laboratory of Bacterial Pathogenesis at Rockefeller University is the investigation of bacteriophage lytic enzymes (lysins) as potential therapeutic compounds.

Bacteriophages are a class of viruses that infect bacteria, and the lysins are a set of proteins they synthesize that specifically digest bacterial cell walls. In addition to the important role they play in bacteriophage biology, the lysins are receiving increased attention as potential pharmacological agents. For a particular class of pathogens known as the gram-positive bacteria, purified lysins have shown antibiotic activity in both liquid culture and in animal models. Their appeal lies in both their potency and in their high specificity for individual bacterial species; traits that could help prevent the emergence of resistant bacterial strains

The research project supported by the Paul Calabresi Fellowship involves the identification of novel lysins through a process known as metagenomic screening. In this approach, DNA is extracted in bulk from environmental samples (such as soil, manure, or water) without respect to the specific source organisms. The environmental genes are then expressed in an appropriate host, and the proteins for

which they encode are screened for particular functional properties. The potential advantage of metagenomic screening is that it may identify genes from species that are not readily culturable in the laboratory. For this research project, bacteriophages are isolated from the environmental samples prior to DNA extraction, and the specific functional property being screened for is the ability to inhibit the growth of other bacterial species. In particular, viral metagenomic screens will be conducted for lysins with activity against the gram-positive pathogens Staphylococcus aureus ("staph" infections), Bacillus anthracis (anthrax), and Clostridium difficile (antibiotic-associated diarrhea).

Brian J. Trummer
Roswell Park Cancer Institute

"Concentration and Exposure Dependent Mechanisms of Taxane Antitumor Action and the Tumor Resistance Response"

Significant advances in the treatment of cancer have been made with the introduction of the taxanes paclitaxel and docetaxel. Although the target of taxane action at the microtubule was defined in the 1970s, the secondary effects of the taxanes upon both tumor and normal cells continue to be investigated. Specifically, recent reports on the pro-apoptotic and anti-angiogenic activities at ultra-low concentrations raise interest in optimal modulation of drug concentration and exposure time. This laboratory plans to investigate the effects of taxane concentration and time exposure on the gene expression and phosphorylation states of key signaling proteins in pro-apoptotic and anti-angiogenic signaling pathways. They hypothesize that tumor and normal cell responses to the clinically important taxanes may vary with time and concentration to which the cells are exposed. They hypothesize that it may be possible to optimize dosing regimes to accentuate taxane antitumor effects without inducing tumor survival responses. This approach could offer more effective and less toxic taxane-based cancer therapies.

PHARMACEUTICS

Pre Doctoral Fellowship 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. Two fellowships were granted in 2007.

2007 Pre Doctoral Fellowships in Pharmaceutics

Clare Aubrey-Medendorp
University of Kentucky

"Surface Energy Evaluation Using Atomic Force Microscopy"

The majority of pharmaceutical materials are in the solid crystalline form. This includes the active pharmaceutical ingredient and excipients used in formulating the solid dosage form. The arrangement or packing of the molecules in a crystal determines its physical, chemical, and mechanical properties. Thus, controlling crystal polymorphism and growth morphology is crucial to drug performance. Currently, the ability to design crystals with desirable properties and to control crystallization based on structural understanding is limited. Therefore, investigation of growth conditions on crystal properties is pivotal. A better understanding of the growth factors can be provided through elucidation of interfacial properties, such as surface energy. Surface energy is the energy needed to create a new unit of area. For crystal growth, the surface energy between a crystal surface and a liquid environment not only determines the growth kinetics and growth morphology, but also plays a major role in controlling the internal structure or molecular packing motifs. This study aims to develop a method using atomic force microscopy (AFM) to determine the surface energy on crystalline solid surfaces in various solvents and additives. Specifically, in situ AFM will be used to 1) measure the force of adhesion of a model crystal surface upon introducing selected solvents or solutions of tailor-made additives, and 2) to

determine surface energetics based on the results from the force measurements. The overall goal is to apply the knowledge of solid-liquid surface energy to engineer and predict growth morphology and polymorphism.

Adora M. Padilla
University of Connecticut School of Pharmacy

"Phase Separation in Freeze-Dried Amorphous Solids: Implications for Product Quality"

With the biotechnology industry on the rise, the number of protein-based drug molecules reaching clinical trials, and ultimately market, has dramatically increased. There are many challenges to overcome in the development of such protein molecules as they are highly susceptible to physical and chemical degradation. For this reason, it is often necessary to stabilize them by conversion of the aqueous solution to a solid by freeze-drying. However, the process of freeze-drying introduces many physical stresses on a protein, as formation of ice requires low temperatures and high solute concentrations are produced during ice formation. There is much speculation in the literature over phase behavior of such protein-excipient systems, but the lack of a useful method of detection has limited understanding in this area. Currently, the two main techniques used for the study of amorphous phase separation are differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). Both techniques have limitations in the detection of multiple amorphous phases. Thus, the application of these techniques to phase separation problems does not always yield useful or meaningful data. The first aim of this research is to apply techniques from other fields of science to the detection of phase separation in freeze-dried systems. These techniques include Raman Microscopy, Thermally Stimulated Current Spectroscopy (TSC), and Small Angle X-Ray Scattering (SAXS). The techniques will first be validated by detection of phase separation in well-studied phase separating polymer-polymer systems. Additionally, process and formulation related factors are believed to play a role in the phase behavior of pharmaceutically relevant freeze-dried systems. It is the broader aim of this research to define the critical process and formulation parameters associated with phase separation in pharmaceutically relevant protein-stabilizer systems.

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.

2007 Post Doctoral Fellowships in Pharmacology/Toxicology

Heidi M. Mansour, Ph.D., R.Ph.
University of North Carolina-Chapel Hill

"Biomaterial Microparticulate and Nanoparticulate Self-Assemblies for Pulmonary Aerosol Delivery"

Inhaled aerosol therapy has attracted attention as a means of drug delivery by a non-invasive route for local and systemic action and for delivery of sensitive macromolecules and biological material. Aerosol therapeutic systems can also improve patient compliance to their drug regimen due to simplicity and ease of use and lead to better disease-state and drug therapy management. Engineered biomaterial colloidal particulate systems, such as liposomes, pegylated liposomes, microparticles, and nanoparticles, can play an important role in improving drug and needle-free vaccine delivery and impart enhanced immunogenicity. Needle-free local deposition of the vaccine formulation reduces systemic exposure, and hence, the incidence of potential side effects is reduced. Another significant advantage of pulmonary aerosol vaccination is that it is likely that lower doses of the antigen will be required for vaccination as a result of targeted pulmonary delivery. Liposomes have been shown to have the potential to produce both targeted and controlled delivery to the lung because they can be prepared with phospholipids endogenous to the lung and to lung surfactant. Liposomes are promising colloidal vehicles for pulmonary aerosol inhalation delivery owing to their capacity to target immune cells, such as alveolar macrophages as microparticles, and pulmonary dendritic cells as nanoparticles.

Novel aspects of these needle-free vaccine aerosol inhalation studies are immunological protection studies using select tuberculosis antigens and adjuvants in pegylated liposomes as microparticles and nanoparticles will illustrate the following: protective effects and the influence of extended-release behavior of these biomaterial particulate self-assemblies delivered as aerosolized colloidal aqueous dispersions and dry powder aerosols; using self-assembled biomaterials for probing local (host) effects using vaccine microparticles and nanoparticles to understand colloidal biomaterial particulate size effects on the nature of pulmonary immunity; provide a strategy for distinguishing TH1 from TH2 effects; and developing general inhaled aerosol needle-free vaccine delivery strategies for pulmonary infections that have a significant global impact, such tuberculosis, measles, bordetella pertussis, respiratory syncytial virus, severe acute respiratory distress syndrome, and influenza.

Research Starter Grants in Pharmaceutics

The purpose of 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.

2007 Research Starter Grants in Pharmaceutics

Darin Y. Furgeson, Ph.D.

The University of Wisconsin-Madison

"Multifunctional Recombinant Polymer Micelles for Intracellular Geldanamycin Delivery"

Statistics from the American Cancer Society show 14% of women will be diagnosed with breast cancer in their lifetime and breast cancer remains the second leading cancer killer in women. To treat breast cancer, oncologists commonly turn to chemotherapy in which patients typically endure large doses of a toxic drug due to the inability of the drug to preferentially accumulate at the tumor site. The objective of this project is to create a multi-targeted, polymer-drug conjugate containing genetically engineered, thermoresponsive elastin-like polypeptides (ELPs) for intravenous, thermally targeted delivery of geldanamycin (GA). Based upon human elastin, ELPs are highly biocompatible and capable of rapid thermosensitive transition at temperatures within clinical hyperthermic temperature ranges. GA is a highly potent, hydrophobic drug currently in clinical trials for inhibition of heat shock protein 90 (HSP90), a regulator of a large number of oncogenic signaling proteins including HER-2/ErbB2 and mutated p53. However, the sole clinical formulation of GA requires toxic excipients tao solubilize the drug for intravenous delivery. By conjugating GA to ELP copolymers through intracellular-sensitive bonds (ELP-GA), GA is not only solubilized but may now be targeted to tumors through multiple mechanisms including the putative enhanced permeability and retention (EPR) effect and by hyperthermia. The thermosensitivity of the ELP allows for active targeting by external heat sources of localized, subcutaneous breast tumors following intravenous administration. Initial cell viability studies with ester-linked ELP-GA conjugates have shown a 3-fold decrease in the IC50 values for MCF-7 cells (human breast carcinoma). Genetically engineered polymers represent the next step in macromolecular, targeted therapeutics due to the precise genetic control of structure, architecture, and biophysical characteristics. Research stemming from this study could present a new paradigm for multimodal, targeted drug delivery through hyperthermic targeting and passive accumulation in the tumor compartment through the EPR effect.

Hugh D.C. Smyth, B. Pharm., Ph.D.

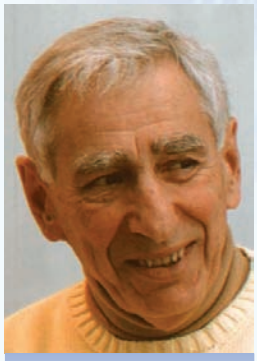
University of New Mexico.

"Active Biomaterials for Targeted and Controlled Release Aerosolized Chemotherapy"

Lung cancer is the leading cancer killer in both men and women. Despite new treatments and prevention efforts, annual deaths due to lung cancer continue to rise. Surgical intervention is often not possible and intensive chemotherapy is required with frequent serious side effects. Moreover, the rate of success of chemotherapy is low. It depends on the ability to deliver adequate concentrations of drug to the tumor and prevent cancer cell growth and repopulation while minimizing the severe and limiting systemic adverse effects. The long term goal of this research is to develop a targeted inhaled aerosol drug delivery system for chemotherapy agents and significantly increase their efficacy in lung cancer treatment. Through this research, they seek to achieve this goal by developing novel carrier particles made of biocompatible and biodegradable materials to facilitate targeted and controlled release of chemotherapy agents in the airways. Aerosol delivery will significantly improve the drug concentrations at the tumor and drug penetration into the tumor without significant systemic toxicity. Controlled release is necessary for maintaining high drug concentrations at the tumor target and for preventing tumor growth between treatment cycles.

IN MEMORIAM

Bernard L. Mirkin



Bernard L. Mirkin, PhD, MD, an accomplished scientist, professor, and philanthropist, passed away on August 13, 2007 at his family's summer home in Maine.

As the founding director of the Children's Memorial Institute for Education and Research (CMIER), Dr. Mirkin spent more than a decade uniting gifted scientists devoted to children's health. By building relationships with the members of his laboratory, Dr. Mirkin established a communicative and stimulating environment in which advancing cures for childhood diseases was the focus. Today, CMIER is one of the most esteemed pediatric research facilities in the nation.

Pursuing his passion for knowledge from an early age, Dr. Mirkin attended the Bronx High School of Science, earned his undergraduate degree from New York University, and his PhD in Pharmacology from Yale University. He continued his education at the University of Minnesota, where he received his MD before joining the Departments of Pediatrics and Pharmacology as a professor.

Intrigued by the fields of clinical and developmental pharmacology, Dr. Mirkin studied drug behavior in newborns and pediatric cancers such as neuroblastoma. Never defeated by the ever-changing nature of disease, his determination and ability to think outside the box were qualities that colleagues and aspiring scientists most admired. Dr. Mirkin facilitated the careers of many young scientists through his steadfast encouragement and guidance and in 2001, a research scholar position was established in his name.

Widely published in scholarly journals and books and frequently invited to present lectures in the United States and abroad, Dr. Mirkin was recognized as an extraordinary scientist and physician in biographical references such as Who's Who in Science, Who's Who in America, and The Best Doctors in America. He contributed to the boards and task forces of many professional organizations, including the PhRMA Foundation, where he served as a Committee member for 34 years.

Dr. Mirkin shared his time and talents generously and was deeply affected by the lack of sufficient health-care services in impoverished countries. A journey to Tanzania inspired Dr. Mirkin to establish "Nyansha Circle of Life," an organization that built a medical clinic in the village and developed programs to increase local awareness of AIDS, vaccines, and obstetrical disorders.

Bernard Mirkin was a kindhearted, thoughtful, and generous person who never lost sight of his dream to end childhood disease. His legacy inspires all who knew him and those who will trace his footsteps, improving the field of medicine while touching the lives of so many colleagues, students, family members, and friends.

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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 three decades of faithful and sagacious service. They have done so, plainly, because they believed in what the Foundation was doing, and they believed in its potential for even greater performance in an essential mission

TREASURER'S REPORT

The PhRMA Foundation ended 2006 in sound financial shape and increased the reserve funds. Contributions were up 12% from the previous year, to $3.5 million. We awarded approximately $1.86 million in grants and held down non-grant program and administrative expenses. Total expenditures, at $2.4 million, were $249,000 below budget primarily because a Center of Excellence was not awarded. Total net assets at December 31 were $12.6 million, a 22.3% increase from $10.3 million the prior year. Of this amount, $3.1 million represents funds authorized but not yet paid for the future years of grants already awarded. Most of the increase in net assets is attributable to nearly $1.3 million in investment gains and interest income. The remaining additions to net assets were two fold: 1) Actual contributions were $706,000 more than budgeted and 2) actual grant awards were $256,000 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 2007, contributions were targeted to reach $3.4 million, as we entered the sixth 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, 2006, has been audited by the Rosslyn, Virginia, accounting firm of Buchanan & Company. A full report can be obtained by contacting the Foundation.

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PhRMA Foundation Programs for 2008

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, 2007 December 15, 2007 January – August
Post Doctoral Fellowship in Health Outcomes (2002)	1 budgeted/ 2 years	$80,000 total $40,000 per award per year	October 1, 2007 December 15, 2007 January – December
Sabbatical Fellowship in Health Outcomes (2002)	1 budgeted/ 1 year	$40,000 total $40,000 per award per year	October 1, 2007 December 15, 2007 January – December
Research Starter Grants in Health Outcomes (2002)	3 budgeted/ 2 years	$180,000 total $30,000 per award per year	October 1, 2007 December 15, 2007 January 1, 2008
Informatics Advisory Committee			
Post Doctoral Fellowships in Informatics (2002)	2 budgeted/ 2 years	$160,000 total $40,000 per award per year	September 1, 2007 December 15, 2007 January – December
Sabbatical Fellowship in Informatics (2002)	1 budgeted/ 1 year	$40,000 total $40,000 per award per year	September 1, 2007 December 15, 2007 January – December
Research Starter Grants in Informatics (2002)	3 budgeted/ 2 years	$180,000 total $30,000 per award per year	September 1, 2007 December 15, 2007 January 1, 2008
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, 2007 December 15, 2007 January – August
Post Doctoral Fellowships in Pharmacology/Toxicology (2002)	2 budgeted/ 2 years	$160,000 total $40,000 per award per year	September 1, 2007 December 15, 2007 January – December
Sabbatical Fellowship in Pharmacology/Toxicology (2002)	1 budgeted/ 1 year	$40,000 total $40,000 per award per year	September 1, 2007 December 15, 2007 January – December
Research Starter Grants in Pharmacology/Toxicology (1972)	3 budgeted/ 2 years	$180,000 total $30,000 per award per year	September 1, 2007 December 15, 2007 January 1, 2008

Paul Calabresi Medical Student Research Fellowships (1974)	2 budgeted/ 6 months up to 2 years	$36,000 total $18,000 per award per year	September 1, 2007 December 15, 2007 July 1, 2008

Pharmaceutics Advisory Committee

Pre Doctoral Fellowships in Pharmaceutics (1987)	2 budgeted/ 2 years	$80,000 total $20,000 per award per year	October 1, 2007 December 15, 2007 January – August
Post Doctoral Fellowships in Pharmaceutics (1992)	2 budgeted/ 2 years	$160,000 total $40,000 per award per year	October 1, 2007 December 15, 2007 January – December
Sabbatical Fellowship in Pharmaceutics (2002)	1 budgeted/ 1 year	$40,000 total $40,000 per award per year	October 1, 2007 December 15, 2007 January – December
Research Starter Grants in Pharmaceutics (1972)	2 budgeted/ 2 years	$120,000 total $30,000 per award per year	October 1, 2007 December 15, 2007 January 1, 2008

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

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Associate

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Ethical Considerations

The Scientific Advisory Committee as well as the program advisory committees of the PhRMA Foundation are dedicated to ensuring the appropriate use of animals and humans in research.

In their deliberations, they consider all aspects of a proposal and may deny support for many reasons. Careful consideration is given to ensure the humane use and care of animal subjects. For human and animal research, the project review committee requires, in writing, a statement of adherence to prevailing standards of ethical research practices. Institutional Review Board approval is required before any research project may be initiated. In addition, informed consent is required before any person can participate in a research project.

PhRMA FOUNDATION

PHARMACEUTICAL RESEARCH
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