PhRMA FOUNDATION

PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA FOUNDATION

2004 Annual Report

Contents

Del Persinger, President and CEO of the PhRMA Foundation, and George C. Fuller, Ph.D., Chairman of the Basic Pharmacology Advisory Committee, are pictured with the 2004 Research Starter Grant recipients (from left to right) John D. Robertson, Ph.D., University of Kansas Medical Center, Jessica A. Mong, Ph.D., University of Maryland School of Medicine, and Bryan L. Copple, Ph.D., University of Kansas Medical Center during the ASPET Annual Meeting in Washington, D.C.

Photographs throughout this year's Annual Report highlight some of the current and former PhRMA Foundation award recipients.

PhRMA FOUNDATION

The mission of the PhRMA Foundation

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

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

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

Chairman's Message

Tadataka Yamada, M.D.

The PhRMA Foundation has been in existence for almost 40 years, and it has been funded in full by the industry. Over 2,000 scientists have benefited from this generosity. In turn, the industry has gained from advances in science over four decades of cutting-edge PhRMA Foundation programs.

We have a tradition of supporting young researchers who display the kind of ingenuity that puts the United States in the forefront of drug discovery. These are principled, high-quality young scientists who spend lifetimes finding cures and improving others' lives. Their spirit, creativity and drive inspire the pharmaceutical companies. The potential of these nascent scientists is what the PhRMA Foundation cultivates through its fellowships and grants.

Our current 2004 award recipients are researching a broad spectrum of human diseases and conditions (described in this report) that include:

- a focus on neurodegenerative conditions, including Parkinson's and Alzheimer's diseases, as well as schizophrenia, attention deficit disorder, and tobacco dependence

- substantial initiative on cancer research, including therapies for prostate cancer, arsenic toxicity and the carcinogenic actions, and pharmaco-genomic treatment strategies

- research that uses informatics to develop integrated computational algorithms and experimental protocols that enable rapid analysis of the genetic networks underlying antibiotic resistance. Ultimately, the hope is to apply the methods to accelerate the discovery of effective antibiotic compounds.

- a focus on adherence issues for the users of asthma medication, with an attempt to validate the utility of a clinical tool by identifying patients who would benefit from intervention to enhance adherence.

Today's award recipients will become tomorrow's leaders, brightening our future. Already, many of our formerly funded scientists head research institutions and are playing critical roles in advancing drug discovery.

These scientists are our industry's greatest asset. Their success brings our industry important advancements as well as the respect and gratitude of the scientific community and gratitude of the members.

That's why we should support the PhRMA Foundation and leverage the foundation's success.

We thank you for your continued support.

Darrell R. Abernethy, M.D., Ph.D., Chairman of the Clinical Pharmacology Advisory Committee, at the 2004 ASCPT Annual Meeting, presenting Erik S. Musiek, from Vanderbilt University School of Medicine, with the 2004 Medical Student Fellowship

President's Message

Del Persinger

The PhRMA Foundation is viable because America's pharmaceutical companies are committed to it. Financial contributions and generous donations of time and knowledge make our mission possible.

On the PhRMA Foundation advisory committees, 24 of the 46 members are from the industry. Committee members give their time to share expertise in the review process, assessing the merits of research proposals and discussing the caliber of applicants. Throughout the foundation's four decades, advisory committee members have consistently selected exceptional awardees who have gone on to remarkable careers. These scientists, in turn, mentor future generations of pharmaceutical researchers.

This year, we welcome three new members to the advisory committees Dr. Janet Kerr, Senior Investigator, Merck & Co.; Dr. Glenn Gormley, Vice President, Clinical Development, AstraZeneca; and Dr. Robert Kramer, Vice President, Oncology & Immunology Drug Discovery, Bristol-Myers Squib Company.

The PhRMA-Foundation has a tradition of great leadership at many levels. People like the Board's Bob Ingram (Vice Chairman, Pharmaceuticals, GlaxoSmithKline) and the Basic Pharmacology Advisory Committee's Bernard Mirkin (Ph.D., M.D., Distinguished Chair and Director of Research at the Children's Memorial Institute and Professor of Pediatrics and Pharmacology at Northwestern University Medical School), carve out time to help several good causes. Bob serves the American Cancer Society Foundation, Arthur Ashe Institute for Urban Health, and many other organizations. Bernie has been a dedicated member of our committee since 1973. He has been the personal motivating force for an extensive initiative in Tanzania that is designed to be a comprehensive approach to address the HIV/AIDS epidemic, as well as other public health and educational concerns. The overall scope of the proposed programs will provide diagnostic and immunization services, public health education, family planning, and educational facilities in the rural village of Nyansha, which is located on the border of Burundi. His initial goal is to build a clinic and laboratory facility called The Nyansha Circle of Life. The broad perspective that our committee members' experiences bring to the foundation helps in assessing research for both its scientific and societal value.

Broad perspectives enhance our success. So do mind-expanding ideas. Award recipients—past and present—stretch our notions of what is possible. This report highlights one of those present recipients—Dr. George Church, director of the PhRMA Foundation Center of Excellence for Integration of Genomics and Informatics at Harvard Medical School and the Massachusetts Institute of Technology. We are proud of his accomplishments and those of the many other creative researchers described in this report.

Among our other past awardees is a scientist who is exploring the toxicity of cyanide and antidotes for it, a highly relevant subject in this era of chemical terrorism. Another scientist is running a 40-center clinical trial for a compound to treat amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease; one has founded the Center for Women's Health at the Columbia University Medical Center; and another has written the national guidelines for diagnosing and managing asthma. One former awardee traveled for Amnesty International to medically evaluate individuals who have been tortured, and another has taught a malaria bioinformatics workshop for the College of Medicine in Nigeria. The examples go on and on.

Almost 80 percent of PhRMA members contribute to the PhRMA Foundation annually, and we are confident that the excellent track record our volunteers have produced will bump that percentage even higher.

Thank you for your continued support.

Thomas G. Roberts, M.D., MSocSci, from Harvard Medical School, receiving a 2004 Research Starter Grant from Del Persinger at the ISPOR Annual Meeting

Notable Humanitarian Efforts

We are proud of the numerous accomplishments of our award recipients, including:

John Atkinson, M.D.	Chairs the Arthritis Foundation Board of Directors
Steve Baskin, Pharm.D., Ph.D.	Found the toxicity of cyanide and is currently working on an antidote, which is timely in this era of chemical terrorism.
Merit Cudkowicz, M.D.	Led three multi-center clinical trials in Amyotrophic Lateral Sclerorosis (ALS) and one in Huntington's Disease (HD). Recently awarded a large RO1to run a 40-center clinical trial for a compound to treat ALS.
Anna Drakontides, Ph.D.	Teaches medical and graduate students.
David Flockhart, M.D., Ph.D.	Active for many years in Amnesty International, traveling to various parts of the world to medically evaluate individuals who have been tortured.
Elsa-Grace V. Giardina, M.D.	Founded and directs the Center for Women's Health at the Columbia University Medical Center.
Jessica Kissinger, Ph.D.	Taught a malaria bioinformatics workshop in Nigeria for the College of Medicine.
Steven Patierno, Ph.D.	Founding Executive Director of The George Washington University Cancer Institute, an urban oncology center.
Gary Rankin, Ph.D.	Instrumental in chemical safety programs for safe use of garden chemicals for the general public.
Stanley Szefler, M.D.	Responsible for writing national guidelines on the diagnosis and management of asthma.
John Wilson, M.D.	Instrumental in creation of guidelines that promote safe and effective pediatric medicines, through work with the American Academy of Pediatrics.

Our Funding Does Make a Difference
A PhRMA Foundation Success Story

Rick G. Schnellmann, Ph.D.

While the world and I have changed significantly since 1986, memories of those early years as an assistant professor at the University of Georgia remain permanently etched in my mind. With a great deal of enthusiasm, and more confidence than justified, I began to develop my research program. Having heard of the PhRMA Foundation as a graduate student, I sought out their research funding programs for young investigators and immediately applied for a both a Research Starter Grant and a Faculty Development Award. I was very fortunate to receive both of these awards in January of 1987. These awards removed at least one critical level of my fear as a young investigator, securing initial funding to advance my research program. In addition, the competitive nature of the PhRMA Foundation Awards suggested that I could truly compete as an independent scientist. Finally, the awards ignited my productivity: I was no longer merely starting out, rather I was up and running, a critical beginning to my career goals, both scientific and professional.

As a mentor, I have trained numerous graduate students and postdoctoral fellows, and I strongly encouraged each to seek independent funding for their training. Many of my students and have received support from PhRMA and subsequently enjoyed fruitful research careers. Thus, I am convinced that early independence in one's training/career, such as that fostered by PhRMA, contributes to the development of successful scientists.

Rick G. Schnellmann, PhD received his doctoral degree from the University of Arizona in 1984. After a postdoctoral fellowship at Duke University, he joined the faculty at the University of Georgia. Rising through the academic ranks, he joined the University of Arkansas for Medical Sciences in 1994 and the Medical University of South Carolina in 2001. He is currently Professor and Chair of the Department of Pharmaceutical Sciences and recently accepted the position of Editor-in-Chief of the *Journal of Pharmacology and Experimental Therapeutics* (January 2004). His research interests are cell injury, death and regeneration.

Dr. Rick Schnellmann (far right) seated with his fellows; (from left to right) Bert Kinsey, Eric Williamson, Kyle Rasback, David Arrington and Mark Hallman (seated in center)

Broadening Perspectives, Expanding Minds

The Center of Excellence for Integration of Genomics and Informatics

Since July 2002, the Center of Excellence for Integration of Genomics and Informatics at Harvard University's School of Medicine has been exploring the sophisticated technologies and skills needed to computationally exploit genome-related data. The field of bioinformatics has exploded because finally there are massive amounts of biological data on which to work. No human mind can piece it together. Math and computer-science techniques are needed to understand these masses of biological data.

The center, headed by the visionary Dr. George Church, is on the leading edge of pharmaceutical research. Advances in genetics are making it possible to know from birth a person's genetic predisposition for a disease and to use that information to tailor treatment. Together with the research community, the pharmaceutical industry is riding a transition from genomic research to drug development. The prospects are exhilarating, and the implications reach far beyond science into ethics and business modeling. Dr. Church began building this lab in 1997, and the PhRMA Foundation funded the Center beginning in 2002.

Dr. Church's team is at the center of that transition from genomic research to drug development. His center is closing in on a way to bring the cost of sequencing a human genome down from $100 million to a price affordable for personal genomics ($1,000). Recently, the center's integration of computation and new wet-lab technology catalyzed the arrival of a new method called Polony sequencing, which received a Genome Technology Award this year. The center has trained several commercial and academic labs in this new technology already, and various aspects of this technology are being commercialized in four different companies.

The center also recently developed a new class of drug-like molecules that can drag any specified protein to destruction in a normal part of the cell (the proteasome), and the lab has developed new proteomics methods and applied them to stem cells and synthetic genes.

Dr. Church has achieved this by assembling an unusual and exceptionally talented team. They include scientists such as Dr. John Aach, a remarkable researcher who dips into his background in philosophy to be able to think in new ways (see page 10) about such subjects as the effects of RNAi-treatments on cellular phenotypes. Dr. Xiaxia Lin combines training in chemical engineering with computer science and technology to understand the way cells talk to each other and to look for ways to optimize biological systems. Dr. Kun Zhang uses his

versatile background in both computing and biomedical research to investigate uniform amplification of single chromosome molecules. Dr. Jun Zhu, who works on RNA splicing in cancer, did a co-major Ph.D. in both statistics and genetics. These are but four of the center's 22 talented and creative Fellows.

Like a conductor at the head of a first-rate orchestra, Dr. Church directs his virtuoso researchers (below) with respect and high expectations. His vision stands behind the lab's integration of computer science, philosophy, chemical engineering, economics and biology. And his high expectations drive the center's future plans. Dr. Church insists that integrating genomics and informatics be more than just cross-referencing different data types or raw understanding. It should, he emphasizes, include translation to clinical goals. Integration needs to be more than reactive to new technologies: It should include pro-active development as needed for modeling, he says. The center will be focused on integrating proteomics, polony sequencing and gene/genome/cell constructions to create a pipeline toward personalized molecular medicine.

Dr. Church and his team at the Center for Integration of Genomics and Informatics at the Harvard Medical School in Boston are a truly amazing community dedicated to the new themes of systems biology and synthetic biology as they apply to personalized molecular medicine. The PhRMA Foundation is proud to have played so fundamental a role in nurturing such creative researchers and in pushing forward the frontiers of science.

Two of the fellows in Dr. Church's Lab, Jay Shendure and Greg Porreca shown with the polony automation prototype that they co-developed

Meet the Mind Expanders

Dr. George Church, Director, CEIGI

"I had a very good math teacher in high school who recognized I was bored with class but not with math. In the ninth grade, he let me have part of the year off, gave me a book on linear programming (used at the time in business for optimizing resources) and said, "See if you can understand something. Then see if you can get the school computer to compute optimal solutions to problems without having to do it by hand." In the 11th grade he gave me time off to figure out how to program calculus into the computer. He himself didn't know anything about computers. But he pointed me in the right direction and gave me time to explore.

Later on, in college, my mentors also didn't force me into what they themselves were keen on. They looked at the talents I could bring to bear on a given problem, gave me resources, let me go, and steered me clear of hazards. This is the power of laizes faire in management.
Of course, it doesn't work with everyone.

I look for people accomplished in multiple fields. Ideally, they are sociable and good at communicating, enthusiastic, and willing over long periods of time to do things that don't work. Developing technology involves a lot of failures, so you have to be able to bounce right back.

Some people work forwards. I don't.

In our lab, we don't first create a widget and then ask, "What can we do with it?" I look for people who ask, "What it is the ultimate goal we want to achieve?" and then work backwards (like engineers do) to develop the technology needed to achieve that goal.

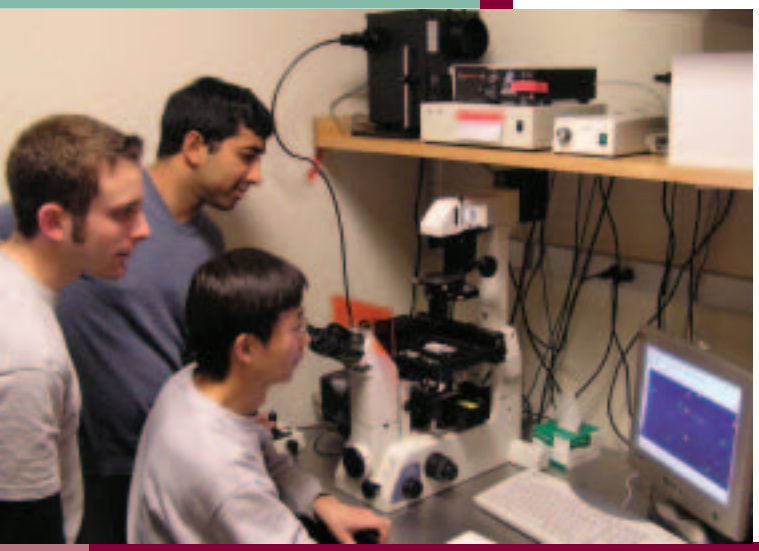
Some people see one way to the goal. I see 10 ways to the goal. I don't follow all those 10 paths. But I see them quickly, and this helps to be an integrative scientist.

The lab typically has a lot of things cooking in parallel. We do rapid prototyping. For example, to develop technology for automating the sequencing method, one of the post-docs quickly put together, for $250, a rough prototype of the basic concept using a bicycle wheel and items from the local hardware store. Then we made an $8,000 version of it. Now we have one that's fully integrated with a microscope. And part of that technology is already licensed to companies. So the lab came up with an idea for a technology, prototyped it, and then bridged to the production of it.

Twice a week, everyone gets together. I try to have the whole lab act like an artists' colony of inventors. Typically, there are about 35 people in the room. One person presents. Everyone brainstorms. I do the same as everyone else in the room. Obviously, as director, I'm responsible for raising money for the center, setting long-term directions, and recruiting people. But we all participate in generating ideas. And we all have to "sell" our idea to each other in the meetings. It's the free-market system for ideas.

Why do some people say my lab is unusual? There's a real focus on invention. Our group is more willing than a straight biomedical group to work on developing technology. We're equally good at experiments and theory, we share with each other, and there always seem to be a lot of fresh ideas around. Sometimes I blur the distinction between myself and my group. We are extensions of each other."

Fellows Jay Shendure, Greg Porreca and Kun Zhang pictured at the polony microscopy station in the lab



Dr. John Aach, CEIGI Fellow in Bioinformatics

"The world exists on clear distinctions and crisp categories. Yet I've mixed a bunch of fields together. My intellect has always motivated me to go anywhere. That's the way I am. Lucky I ended up where I did.

I always had a science and math bent. My father was a painter and versed in the arts. I really loved music—though I wasn't very talented in it—and at Princeton I majored in music, with a specialty in piano, as an undergraduate. I was doing what I loved.

But I couldn't stamp out the critical thinker in me. At that time at Princeton, music theory emphasized a modern 12-tone

system. Teachers would play, say, a series of 12-tone intervals and say, "That really fits." But it didn't to my ear. The whole thing didn't make sense to me. So in my undergraduate thesis I asked, "What is 'fitting?' What makes something sound 'good'?" I built a theory—integrating Skinnerian concepts of behavior— that if music has the right predictability (such as cadences) you're going to like it. It will sound "fitting." If it doesn't, you won't.

They gave me a C on the thesis. They didn't like it one bit.

I started thinking, "Well, that was music. What about other things? What clicks? Science? Our understanding of the truth?" I found an interdisciplinary graduate program at Boston University and stumbled onto a mixture of philosophy and psychology.

Philosophy teaches you that you can think about things systematically in areas that are very hard to quantify. I'm aware of that now when I look at science, where it's not uncommon to encounter the attitude that if you can't answer a question with an equation or an experiment, the question shouldn't be asked. Equations and experiments are important for driving science forward, but it impresses me how many important questions there are that can't be addressed that way. Philosophy can take a stab at dealing with complex, amorphous but critically important questions not with equations or experiments, but by working it over in your mind, being perceptive about where things don't fit, and getting a unified concept in your own mind about how they do.

So how does this relate to the way I deal with science? Here [in this lab], I'm sitting at the feet of the masters. They are perfectly capable of carrying on without me. So I ask myself, "Given my background, what can I bring?"

I strive for the broadest possible view. As in any field, there are specialists. Constitutionally, I'm not. I can go as deep as anyone into nuances. But I try to stake out the high ground, get the broadest picture, and be as much of a generalist as possible.

Computational biology is a rapidly developing field. There are hundreds of people looking at problems from all different perspectives, and devising a number of ways to respond. You can take one of those roads and make your career on it. People spend entire lives looking at one road, and this is absolutely critical. It's just not my way. My way is to follow as many roads as I can, touching the foundations and then building up a vision.

Like others in the lab, one of the things I've learned is that in cutting-edge science you have to get used to a high failure rate. Not everyone is cut out for that. It takes discipline to withstand it. But it's the only way to get it done.

There's a huge amount of human ingenuity unfolding here in the lab every day. It's been very exciting to be at the cutting edge of a fast-developing and important field, and it's been a privilege to work with George [Church] and with the center's many talented and brilliant students and researchers."

Darrell R. Abernethy, M.D., Ph.D., Chairman of the Clinical Pharmacology Advisory Committee presents Julio Licinio, M.D., Director of the New Center of Excellence in Clinical Pharmacology at UCLA, with the award at the 2004 ASCPT Annual Meeting in Miami Beach, Florida

Center of Excellence In Clinical Pharmacology

We awarded our second Center of Excellence in Clinical Pharmacology in July 2004. This new program will provide $250,000 of funding per year for up to two years.

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

The 2004 Center of Excellence in Clinical Pharmacology was awarded to The University of California, Los Angeles—David Geffen School of Medicine, under the direction of Julio Licinio, M.D., Professor of Psychiatry and Medicine/ Endocrinology, Neuropsychiatric Institute

Research Description:

The Center's mission is to develop innovative teaching, training, research, and service programs in clinical pharmacology. The PhRMA Foundation support will enable the Center to develop a clinical pharmacology teaching faculty and administrative infrastructure to develop an outstanding and highly competitive Clinical Pharmacology Program. The Center is the recipient of the NCRR/NIH K12 award in Clinical Pharmacology, the UCLA Mentored Clinical Pharmacology Research Scholars Program. This unique award provides funding to recruit superb trainees. The NIH-funded research focuses on pharmacogenomics and special populations. UCLA is the seventh largest recipient of NIH funds and the hospital is ranked third best in medical care nationwide. The Center plan aims to build on the extraordinary resource base that exists at UCLA to develop

a new interdepartmental clinical pharmacology center. It is currently a small unit which admitted its first trainees in 2002. The Center has taken advantage of the depth of teaching, service, research, and training at UCLA to bring together a cross-disciplinary group of experts who are highly supportive of the efforts in clinical pharmacology. The Center's faculty members are complementary and well-funded. The Center has two principle goals: (1) to utilize the depth of research conducted at UCLA and the support provided by NCRR/NIH-funded UCLA Mentored Clinical Pharmacology Research Scholars Program to launch individuals in careers in clinical pharmacology. With particular interest in fostering the transition from residency to successful, independently funded academic careers in clinical pharmacology; and (2) to advance clinical pharmacology and the attendant improved therapeutics in special populations, including pregnant women, children, the elderly and under-represented minorities. Importantly, in the teaching and training components of the Center the plan is to make a special effort to foster career development in members of under-represented groups. In this regard, the efforts are conducted jointly with Charles Drew University of Medicine and Science, the only one of four historically black medical colleges located west of the Mississippi. The Center works closely with the UCLA Center for Educational Research and Development to evaluate the program in order to ensure continuous improvement.

Dr. George Zografi has been a member of our Pharmaceutics Advisory Committee for 18 years and this was his final review season with us. Dr. Zografi is retiring from our committee as well as from his position as Professor, Pharmaceutical Sciences Division in the School of Pharmacy at the University of Wisconsin, Madison.

Dr. Zografi became a member of the Wisconsin faculty in 1972 and he served as Dean of the School of Pharmacy from 1975 to 1980. He received the Distinguished Pharmaceutical Scientist Award from the American Association of Pharmaceutical Scientists in 1995 and, in 1996, the Volwiler Research Achievement Award from the American Association of Colleges of Pharmacy.

His expertise has been invaluable to our committee over the years. With his direction and guidance, many young scientists have received our support in the field of pharmaceutical research. He has a genuine interest in the scientists whom he has guided over the years and he will be missed in both academia and within our advisory committee.

Thank you, George, for the many years of dedication and support that you have given to the PhRMA Foundation.

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 2004 exemplify the very best in their chosen fields of clinical pharmacology and pharmacology/toxicology. The PhRMA Foundation is proud of their achievements and is gratified to have been of assistance to them at the beginning of their outstanding careers. Their successes typify the outstanding achievements of all of our awardees and underscore the importance of continuing support to those who follow in their footsteps.

The recipients of the PhRMA Foundation Awards in Excellence for 2004 are Garret A. FitzGerald, M.D. and Susan B. Horwitz, Ph.D.

Garret A. FitzGerald, M.D.

2004 Award in Excellence of Clinical Pharmacology

Garret A. FitzGerald, M.D. (right) of the University of Pennsylvania accepting the 2004 Award in Excellence in Clinical Pharmacology from Darrell R. Abernethy, M.D., Ph.D. at the ASCPT Annual Meeting

Dr. FitzGerald is the chair of the Department of Pharmacology at the University of Pennsylvania. He received a M.B., B. Ch. and a M.D. degree from University College, in Dublin, Ireland. His residency training was in St. Vincent's and Mater Hospitals in Dublin. In 1983, Dr. FitzGerald was awarded a PhRMA Foundation Faculty Development Award. He was at the Division of Clinical Pharmacology at Vanderbilt for several years, serving as professor and director when John Oates became Chair of Medicine there. In the early 1990's he was a professor and chairman at University College in Dublin. He returned to the United States in 1994 to become Professor of Medicine and Pharmacology, University of Pennsylvania, where he remains today.

Dr. FitzGerald is a distinguished scientist and pharmacologist. His work with circulating prostaglandin and other arachadonic acid metabolites in the 1980s has provided fundamental understanding about the role in inflammation in athero-sclerosis. He and others worked out the effects of aspirin on platelet function with respect to pathway selective inhibition of prostacyclins vs thromboxanes, and that is the scientific basis for low-dose aspirin for the secondary (and probably primary) prevention of coronary thrombosis. More recently he has been working on the tissue selectivity of the

cyclooxygenase isoforms COX-1 and COX-2 and has developed hypotheses of why COX-2 inhibitors may not afford the clinical cardioprotection that would be expected. The fundamental importance of this last area is not yet clear (work done in the past two years). The fundamental importance of the first two areas is proven and has changed how we practice medicine and develop drugs.

Dr. FitzGerald has received many awards throughout his distinguished career including the Established Investigator, American Heart Association award from 1985 -1990.

Susan B. Horwitz, Ph.D.

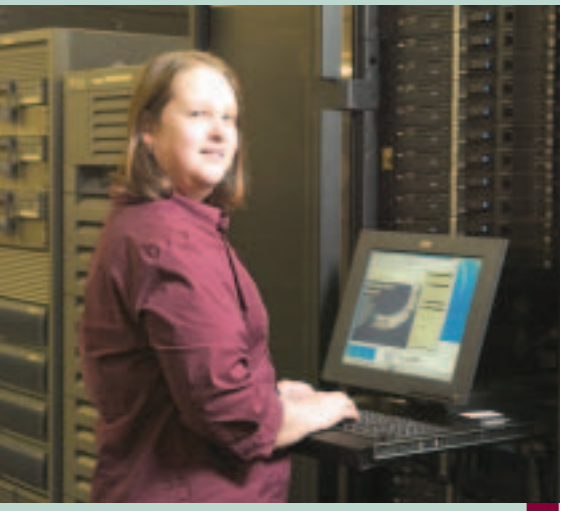
2004 Award in Excellence of Pharmacology/Toxicology

Dr. Horwitz graduated from Bryn Mawr College and went on to receive her Ph.D. from Brandeis University in 1963. She is presently the Falkenstein Professor of Cancer Research at the Albert Einstein College of Medicine in New York. Dr. Horwitz is the Associate Director for Experimental Therapeutics at the Albert Einstein Cancer Center and Co-Chair, Department of Molecular Pharmacology. She is the recipient of many awards including, in 1994, the ASPET Award for Experimental Therapeutics. She was elected a fellow in the American Academy of Arts and Sciences in 1994, and in 1996 she received the C. Chester Stock Award from the Memorial Sloan-Kettering Cancer Center. Dr. Horwitz served as president of the American Association for Cancer Research (2002-2003). Dr. Horwitz received a 1972 Research Starter Grant in Pharmacology/ Toxicology from the PhRMA Foundation (formerly PMA Foundation).

Susan B. Horwitz, Ph.D., Professor and Co-chair of the Department of Molecular Pharmacology at the Albert Einstein College of Medicine of Yeshiva University

An internationally recognized pharmacologist, Dr. Horwitz has been a pioneer in understanding, at the molecular level, the mechanisms of action and of resistance to antitumor drugs. Her contributions span several decades of research and encompass agents which have served as prototypes for some of our most important antitumor drugs that are currently in clinical use. She made major contributions to our understanding of the mechanisms of action of camptothecin, the epipodo-phyllotoxins and bleomycin. Her most seminal research contributions have been in the development of Taxol®, a drug that has been the major focus of her research program. She and her co-workers demonstrated that Taxol's anti-mitotic effects were due to a novel interaction between the drug and micro-tubules, the latter being essential for the intracellular movement of organelles and the pairing and segregation of chromosomes during mitosis. Her perceptive analysis identified Taxol® as a prototype for a new class of antitumor drugs. By defining its unique mechanism of action, she encouraged the National Cancer Institute to move forward to support basic studies and then clinical trials with Taxol®. The drug was the most important antineoplastic agent developed in the 1990's. It has substantial activity against common solid tumors such as ovarian, breast and lung.

Fellowships and Grants



PhRMA Foundation funding allowed me to set up my bioinformatics research program and begin searching the genomes of parasites for new therapeutic targets.

Jessica C. Kissinger, Ph.D.,
2003 Research Starter Grant in Informatics, Center for Tropical & Emerging Global Diseases & Development of Genetics
University of Georgia

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 two Centers of Excellence—in Genomics and Informatics, and 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, Morphology, 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 biomedical studies. It is anticipated that this research training will be accomplished in academic and/or industrial laboratory settings where multidisciplinary teams are organized to address problems which span the range of biological complexity rather than focus on the application of single technologies.

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

Receiving the fellowships that began between January and December 2004 are:

Suman Ganguli, Ph.D., University of Michigan: "Informatics-driven in Silico Biological Models: the Functional Unit Representation Method." There is a growing need to develop computational simulation models of complex biological systems which could be used for biopharmaceutical experimentation. Such in silico models could potentially supplement and inform experimentation with existing in vitro and *in vivo* models. They are engaged in developing a new class of such computational models, using the techniques of object-oriented programming and agent-based modeling. The biological systems they are modeling using this methodology include multicellular tumor spheroids and immune cell trafficking. These models are being constructed so as to map naturally to the biological system, to closely mimic observed behavior of the biological system, and to facilitate useful experimentation in a biopharmaceutical context. For example, an in silico model of multicellular tumor spheroids will be used to investigate the effects and transport of therapeutic agents under various conditions. An in silico model of lymphocyte recruitment and migration will be designed to mimic and subsequently to study the effects of immunosuppressive compounds used in organ transplantation.

Margaret E. Glasner, Ph.D., University of California, San Francisco: "Enzyme Evolution and Design: The Generalist Hypothesis." Enzymes catalyze a stunning array of reactions, yet they are constructed from a limited number of folds. This raises two questions: How difficult is it to re-engineer proteins to catalyze different reactions? And what is the nature of intermediates that arise during evolution? One hypothesis regarding the last question is that proteins evolve

through intermediate "generalist" forms, which are not optimized for specific activities, but have broad substrate and chemical specificities. To test the generalist hypothesis, they are using a combination of bioinformatic and experimental methods. First, they will use bioinformatic methods to determine the evolutionary relationships among divergent proteins and to deduce the probable ancestral sequences of enzymes which are related but have different functions. The predicted ancestral sequences will then be synthesized and tested to determine if they are "generalists" with multiple activities. In addition, they will use directed or "test-tube" evolution to engineer proteins to perform the reactions catalyzed by distant relatives identified in the bioinformatic analysis, and intermediates in this evolution experiment will be tested for multiple activities. Investigating the generalist hypothesis will provide insight into the mechanism of protein evolution, which is vital for understanding how to re-engineer enzymes to synthesize biomedically useful products.

Ian J. Laurenzi, Ph.D., Yale University: "Functional Classification of Transcription Factors form Microarray Data." The main goal of this project is to enhance current data-mining techniques of identifying transcriptional regulators and their regulatory functions from the results of large-scale microarray assays. Inclusion of chemical and mechanistic information in these statistical analyses should elucidate unforeseen relationships between expression profiles improve the robustness of conclusions about regulatory networks from microarray expression data. Furthermore, it is proposed that simulation techniques can be used to both test and augment such data mining techniques, to deconvolute specific regulatory mechanisms such as interactions between activators, repressors and their targets. The methods will be applied to expression data sets of Gerstein group collaborators, expression data sets publicly available in the Yale- and Stanford Microarray databases, and other sources, to reconstruct extensive regulation networks in *S cerevisiae,* and compare these results with known mechanisms of transcriptional regulation in databases including the YPD, TRANSFAC, and SCPD, as well as in-house databases. Although the methods developed in this study will be applied to *S cerevisiae*, they will be amenable to the deduction of transcriptional regulation networks from microarray expression assays for other eukaryotes, such as humans.

Sunil Ojha, Ph.D., University of California, San Francisco: "Evolutionary Relationships among Flavin-dependent Enzymes." The number of unique structural folds is considerably smaller than the number of unique protein sequences, suggested that structural folds have co-opted for a number of different functions.Exploiting this fact, superfamily analysis, where the term superfamily is defined as a group of homologous enzymes that catalyze the same chemical reaction with differing substrate specificities or different overall reactions that share common mechanistic attributes, has expedited the functional annotation of uncharacterized proteins. This research focuses on clustering all of the flavoproteins into fold classes, and, within each fold class, into superfamilies. This clustering will allow them to identify the partial reaction or catalytic strategy common to each superfamily, along with the conserved active site residues responsible for the common chemistry.The particular focus will be to understand the details about how flavin co-factors are involved in common chemistry.They will use this knowledge to predict the use of flavin co-factors in new ORFs by searching sequence databases using probabilistic models of each flavoprotein superfamily and searching modeled structure databases with 3-D structural templates designed for each flavoprotein superfamily.

Research Start Grants in Informatics

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

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

Receiving the grant that began in January 2004 is:

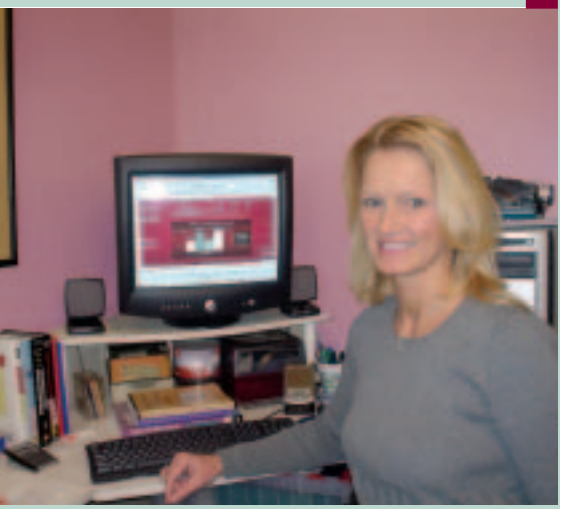
Timothy S. Gardner, Ph.D., Boston University: "Systematic Inference of Genetic Network Structure and Function." Resistance among microorganisms to antibiotic drugs is a serious and growing problem in both developing and developed nations. For example, 20% of enterococci isolated from hospital patients in

Amy Barton Pai, Pharm.D. 2003 Research Starter Grant recipient in Health Outcomes from the University of New Mexico

The PhRMA Foundation was honored to participate in the opening session of the 2004 Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics on March 24, 2004 in Miami Beach, Florida. They had a record number of people there with almost 1200 people in attendance. Thank you ASCPT for the privilege of presenting our Clinical Pharmacology Awards at this exclusive event.

PhRMA Foundation pre doctoral fellowship is an essential resource that provides students, like myself, with an important stepping block to build the foundation of our education and research in health outcomes.

Joette M. Gdovin, M.P.A.
2003 Pre Doctoral Fellow in Health Outcomes
University of South Carolina
Department of Health Services Policy and Management



1997 were resistant to vancomycin, a drug previously used as a "last resort" when all other antibiotics fail. Only nine years earlier, enterococcal resistance to vancomycin was zero. But despite recent technological advances and enormous investments in antibiotic development, few new drugs have been introduced in the past decade—the arsenal of effective antibiotics is shrinking. In part, this decline in productivity is due to the complexity and robustness of networks of genes, proteins and metabolites that protect microorganisms from stress. Early phases of drug discovery often fail to account for the physiological consequences of such complex networks.The aim of this project is to develop integrated computational algorithms and experimental protocols that enable rapid analysis of the genetic networks underlying antibiotic resistance. In preliminary studies, this lab has shown the effectiveness of such an approach and its potential value in certain stages of antibiotic development. In this work, they will integrate techniques from statistics, control engineering, computer science, molecular biology and microbiology to enhance the accuracy and broaden the utility of the network analysis methods. Ultimately, they hope to apply the methods to accelerate the discovery of effective antibiotic compounds.

Health Outcomes

Pre Doctoral Fellowships in Health Outcomes

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

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

Receiving the fellowship that began in May 2004 is:

Thy P. Do, University of Washington: "Discontinuation of Post-Acute Myocardial Infarction β-Blocker Therapy: Methods, Application, and Policy Implication." Randomized clinical trials have demonstrated the efficacy of β-blocker therapy in reducing mortality and cardiac events after an acute myocardial infarction (AMI). Consequently, practice guidelines recommend post-AMI patients without a contraindication to continue on β-blocker therapy indefinitely. Discontinuation of this therapy may not only affect patient outcomes, but may also influence the interpretation of a quality of care measure.
The first objective of this research is to assess the degree of long-term β-blocker therapy discontinuation in an outpatient setting. They will use failure-time analyses to estimate the yearly cumulative incidence of discontinuation (as well as subsequent reinitiation) among all patients discharged on β-blocker therapy. The second objective is to assess whether discontinuation could put patients at higher risk for recurrent events. They will conduct a cohort study analysis to estimate the rate ratio of recurrent coronary events in relation to the timing of b-blocker therapy discontinuation. The last objective is to discuss the interpretation of a HEDIS Effectiveness of Care measure (i.e., β-Blocker Treatment after a Heart Attack) in light of β-blocker therapy discontinuation seen in our study population. Such cross-sectional quality of care measures could present a very misleading impression of disease management if a high proportion of patients do not continue β-blocker therapy once initiated.

Research Starter Grants in Health Outcomes

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

The program provides a research grant of $30,000 per year for up to two years. This program supports individuals beginning independent research careers in academia who do not have other substantial sources of funding. The program is not offered as a means to augment an ongoing research effort.

Recipients of the Research Starter Grants that began in January 2004 are:

Christopher R. Flowers, M.D., M.S., Emory University, Winship Cancer Institute: "Examining The Cost-Utility of Pharmacogenomic Treatment Strategies For Cancer Patients." Pharmacogenetics and pharmacogenomics have emerged as fields aimed at identifying inherited factors that may predict when individuals will have a different response to a medication. For patients with cancer these have become areas of intense research aimed at developing and using drugs in ways that maximize their benefits and minimize toxic effects on the patient. In contrast to most drugs, anticancer drugs typically are dosed based on individual patient characteristics, such as a patient's weight, liver or kidney function, and age. Despite this individualized dosing, patients' can have a wide variety of responses to chemotherapy. Often drug dosages and regimens require adjustment after therapy has begun based on the severity of ensuing drug toxicities.This arises in part because standard methods of prescribing chemo-therapy indiscriminately treat patients as large populations, ignoring the potential for genetic differences in drug response.One particularly promising application of pharmacogenomics is to use genetic testing to identify patients at risk for severe drug toxicity and then to pre-emptively modify the chemotherapy regimen to avoid toxic effects.Three prominent examples of pharmacogenomic applications that may reduce drug toxicity in cancer patients are: genotyping for thiopurine methyltransferase deficiency (TPMT) in children treated with 6-mercaptopurine (6-MP), testing for dihydropyrimidine dehydrogenase (DPD) deficiency in patients treated with 5-fluorouracil (5-FU), and evaluating UGT1A1 genotype in patients treated with irinotecan.Through this grant they will be examining the cost-effectiveness of pharmacogenomic-guided therapy versus standard clinical practice, and developing tools for performing future cost-effectiveness analyses of pharmacogenomics.

Suzi Levens, M.D., M.S., The Pennsylvania State University: "Use of Large Data Sets to Inform Intervention Development: Benzodiazepine Use as a Target." Despite persistent safety concerns about the use of benzodiazepines in older adults and the availability of alternative treatments for anxiety disorders and effective withdrawal strategies in the elderly, benzodiazepine use among older patients remains common. The objective of this study is to use a public access data set to identify trends in benzodiazepine prescribing from 1992 to 2000 and to characterize residual use.They will use data from the Medicare Current Beneficiary Survey (MCBS) and Medicare claims data for aged survey respondents.They will estimate the proportion of older benzodiazepine users and characterize this population and their benzodiazepine use and evaluate how these have changed since selective serotonin reuptake inhibitors (SSRI's) and related medications became available.The anticipated results of this study will inform the design and targeting of clinical and educational interventions to reduce inappropriate benzodiazepine use and thus prevent adverse drug effects in older adults including falls, fractures, motor vehicle accidents, and cognitive impairment.

Thomas G. Roberts, M.D., MSocSci, Massachusetts General Hospital (MGH): "Design, Outcomes, Ethics, and Costs of Developmental Cancer Trials in the Era of Modern Targeted Therapies." This research focuses on evaluating the economic implications of targeted cancer therapies as well as improving the efficiency of cancer drug development. There are several important reasons to support this area of research. First, there are more patients receiving experimental cancer drugs than ever before; in fact, cancer drugs in development now outnumber those in any other therapeutic drug class. Second, although the ethics and outcomes of Phase I cancer trials have historically attracted much inquiry, almost all of research was performed in the era of cytotoxic drugs. This older research may not inform the field today when more than 75% of cancer drug in development are targeted agents that have vastly different therapeutic effects, side effect profiles, and costs of development when compared to the older cytotoxic agents.Third, it has become clear that classic designs of developmental cancer trials are poorly suited for evaluation of newer targeted cancer drugs. Some experts have proposed changes to the designs of phase I trials, emphasizing alternative end points and new statistical designs; while others have argued for the application of new imaging and molecular technologies to evaluate response. To date, however, there has been no systematic evaluation of the outcomes, designs, or costs of modern Phase cancer trials.

The PhRMA Foundation was honored to participate in the 9th Annual Meeting of the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) on May 18, 2004 in Arlington, Virginia. We would to thanks ISPOR for recognizing our 2004 award recipients in Health Outcomes who were present at this prestigious event.

Diana Zi Ye, 2003 Pre Doctoral Fellow in Pharmacology/ Toxicology from Michigan State University

The PhRMA Post Doctoral Fellowship in Pharmacology has provided me with the flexibility and resources to pursue my scientific interests.

David M. Bourdon, Ph.D.,
2003 Post Doctoral Fellow in Pharmacology/Toxicology, Post Doctoral Fellow,
Harden Laboratory
University of North Carolina
Department of Pharmacology

Angela Wisniewski, Pharm.D., State University of New York at Buffalo: "Cross-Sectional Study of Asthma Medication Adherence." It is currently estimated that there are over 20 million Americans with asthma. The annual cost is approximately $13 billion, including $4.6 billion in indirect costs from lost days of work or school. Asthma is more prevalent among minority populations and is associated with disproportionately higher morbidity and mortality. Medications that effectively treat both the acute and chronic manifestations of the disease are available. The cornerstone of management to treat the underlying chronic inflammatory process in patients with persistent asthma is use of anti-inflammatory medications, as recommended by the National Asthma Education Prevention Program (NAEPP). Patient adherence to these medications is low, ranging from 20-60%, and is often found to be associated with race, ethnicity, socioeconomic status, and level of education. There is a general lack of available information regarding effective strategies to improve adherence to asthma pharmacotherapy, particularly among minority populations. A sample of minority patients with asthma (African American/Black, Hispanic/Latino, and low socioeconomic status regardless of race or ethnicity) will be utilized for this study. Quantitative (survey) and qualitative (interviews, focus groups sessions) research methodologies will be employed to (1) characterize the factors associated with low adherence to anti-inflammatory asthma medications; (2) identify actual or perceived barriers to adherence; and (3) have patients integrally involved in the process of identifying and formulating patient-acceptable and feasible intervention strategies to improve adherence. The results from this study will be used to develop and test the efficacy of intervention strategies to improve adherence to anti-inflammatory asthma medications.

Nataliya Zelikovsky, Ph.D., The Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine:" Medical Adherence Measure: Validation of a Semi-Structured Interview" Non-adherence with medical regimens is known to be problematic among adolescents and can have serious consequences, including increased utilization of services, morbidity, and mortality. Children with chronic illnesses have to follow complex schedules of medication regimens, dietary restrictions, and clinic attendance. These tasks can become burdensome, both physically and emotionally, taking a toll on the patient and family. Although non-adherence has been identified as common, it has been difficult to estimate rates of non-adherence accurately and consistently, given the paucity of appropriate measurement tools.The present study proposes to assess the validity and reliability of a newly developed clinical interview, Medical Adherence Measure (MAM), with 50 adolescents (ages 11-18) with chronic renal failure. The MAM examines the patient's knowledge of the regimen, self-reported adherence, and obstacles to optimal adherence in the areas of medication, diet, and clinic attendance.To establish the test retest reliability, the MAM will be administered to participants three times: at recruitment, two weeks later, and three months after recruitment. To examine the validity of self-reported adherence obtained on the MAM, information will be compared to objective indicators in each area of the prescribed regimen at recruitment and three months later. Specifically, patient reported medication adherence will be compared to physician rated Biomedical Marker Score and pill counts using MEMS technology. Patient reported adherence with prescribed renal diets will be compared to adherence ratings based on 3-day diet recalls conducted by dieticians. Reported attendance at clinic will be compared to medical records. The goal of this proposed study is to validate the utility of this clinical tool in identifying patients who are not adherent and would benefit from intervention to enhance adherence.

Pharmacology

Pre Doctoral Fellowships in Pharmacology/Toxicology

The goal of this program is to increase the number of well-trained investigators in pharmacological 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 fellowships have been awarded under this program since it began in 1978 including the six fellows awarded in 2004.

Those who received fellowships that began between January and August 2004 are:

Alexander J. Finn, Duke University Medical Center: "Prokineticin 2 and Suprachiasmatic Output Regulation of the Neuromuscular Junction by Abl Tyrosine Kinases." The goal of this research is to define the mechanisms by which Abl tyrosine kinases regulate the neuromuscular junction (NMJ), a cholinergic synapse at sites of nerve-muscle contact. High density clustering of postsynaptic acetylcholine receptors (AChRs) at the NMJ is essential for neural control of muscle contraction. This clustering occurs early in development when the presynaptic nerve secretes the glycoprotein agrin, which, in turn, activates the muscle-specific receptor tyrosine kinase (MuSK). Although this event has served as the paradigm of synapse induction for over a decade, little is known regarding the signaling network that links agrin-induced activation of MuSK to AChR clustering. In this lab, they have recently identified the Abl family of nonreceptor tyrosine kinases, Abl and Arg, as critical mediators of postsynaptic assembly downstream of agrin and MuSK. They showed that Abl kinases localize to the postsynaptic membrane of the NMJ in vivo and that Abl kinase activity is required for agrin-induced AChR clustering and enhancement of MuSK tyrosine phosphorylation in myotube culture. Further, agrin stimulation of cultured myotubes increases endogenous Abl kinase activity and induces formation of a MuSK-Abl complex conducive to reciprocal tyrosine phosphorylation. Based on their novel findings, they hypothesize that Abl family kinases are required for the formation and stabilization of the NMJ and provide the developing synapse both the tyrosine kinase activity required for signal amplification and the cytoskeletal regulatory activity required for assembly and remodeling. To test this hypothesis, they propose the following specific aims: (1) perform a detailed characterization of Abl kinase-induced tyrosine phosphorylation of MuSK; (2) determine the role of Abl kinases in postnatal synaptic maintenance; and (3) identify additional components of the postsynaptic MuSK-Abl signaling complex. Their results will provide a mechanistic understanding of the role of nonreceptor tyrosine kinases in the formation and stability of the NMJ. Moreover, they may illuminate the signaling cascades affected in diseases stemming from aberrant NMJ function, such as the congenital myasthenic syndromes and myasthenia gravis, and may have broad implications for central synapse formation and intercellular communication, in general.

Ryan E. Hibbs, University of California, San Diego: "Elucidation of Ligand Binding and Induced Conformational Changes in the Acetylcholine Binding Protein, a Nicotinic Receptor Surrogate." The nicotinic acetylcholine receptor (nAChR) is the prototypic member in the superfamily of ligand-gated ion channels (LGIC), a prevalent target of drug action. nAChR subtypes mediate fast neurotransmission via cation flux both centrally as well as in the periphery. For approximately 40 years, structure and function of nAChRs have been under rigorous study; however these transmembrane proteins have resisted crystallization, precluding a high-resolution structure. Research into these receptors is important therapeutically in the treatment of degenerative disorders such as Parkinson's and Alzheimer's diseases, schizophrenia, attention deficit disorder, and tobacco dependence. The proposed studies describe a fluorescence-based approach, using cysteine labeling mutagenesis, to map binding sites for different classes of ligands in the acetylcholine binding protein, a nicotinic receptor surrogate. After determining sites of ligand binding, time-resolved fluorescence methods will be employed to determine ligand-induced changes in receptor flexibility and conformation. Preliminary data from several cysteine mutants demonstrate a proof of principle in the application of this method to nAChR study. These studies should lead to a clearer understanding of receptor function, the importance of structural fluctuations in solution governing ligand specificity, and a template for rational design of receptor subtype selective therapeutic agents.

PhRMA Foundation award recipients in Pharmaceutics at the 2003 AAPS Annual Meeting in Salt Lake City, Utah. Pictured with Del Persinger and Eileen McCarron are Y. Bruce Yu, Ph.D., University of Utah, Laura M. Land, University of Kentucky, Tonglei Li, Ph.D., University of Kentucky, and David L. Bourdet, University of North Carolina at Chapel Hill

Janet L. Fisher, Ph.D., Assistant Professor, University of South Carolina School of Medicine, recipient of a 2002 Research Starter Grant in Pharmacology/Toxicology

Leah K. Lyons, University of Miami School of Medicine: "Vav3 a Novel AR "Coactivator" Promotes Androgen Independent Prostate Cancer Progression." Prostate cancer which relapses in androgen ablated patients is termed androgen independent (AI) and marks the stage that is poorly responsive to available therapies. The past decade of prostate cancer research has provided strong evidence that in AI disease, androgen receptor (AR) signaling pathways remain functional despite the presence of low levels of androgen. Previous work in this lab aimed at identifying factors involved in the progression to androgen independence found the expression of the Vav3 gene to be upregulated in androgen independent cell lines as compared to an androgen dependent cell line. Preliminary studies show that Vav3 enhances the transcriptional activity of AR. The proposed research focuses on investigating the mechanisms of the effects of Vav3 on AR activity and determining the significance of Vav3 upregulation to androgen independent tumor formation.They will create alterations in Vav3 to determine what Vav3 functions are required for the effects on AR signaling. These studies seek to establish Vav3 and associated proteins as novel drug targets for androgen independent prostate cancer. To identify the importance of Vav3 upregulation to AI disease, they will decrease activity or levels of Vav3 in an androgen independent prostate cancer cell line, and monitor tumor formation. They expect that if Vav3 is necessary for androgen independent tumor formation, mice receiving cells in which Vav3 levels or activity have been reduced should exhibit decreased tumor formation as compared to the parental lines in which Vav3 has not been manipulated.

Geniece P. McCollum, University of Rochester: "Mechanisms of Arsenic-Induced G1 Growth Arrest and Differentiation in a Myeloid Leukemia Cell Line."Arsenic is worthy of much attention as a toxicant and carcinogen, because every human population is exposed to some form of it. Arsenic toxicity manifests itself in a variety of ways. Ingestion of arsenic-tainted drinking water has been associated with cancers of the skin, liver, bladder, kidney and lung, as well as with cardiovascular and neurological effects. On the other hand, although arsenic can be very toxic, it has been an active ingredient in folk remedies for more than 2400 years. In the 1970's, investigators in China confirmed that arsenic trioxide had therapeutic value for the treatment of malignancies, especially acute promyelocytic leukemia (APL). Clinical studies were initiated in the United States, and the U.S. FDA approved arsenic trioxide for the treatment of relapsed or refractory APL in 2000. Despite long-standing knowledge of arsenic's effects on humans, its mechanisms of action: toxic, carcinogenic and chemotherapeutic, remain unknown. This lab studies arsenic-induced growth inhibition of a myeloid leukemia cell line in order to increase understanding of arsenic's chemotherapeutic mechanisms. They have used flow cytometric analyses of cell cycle distribution in synchronous and asynchronous populations to measure arsenic's effects on cell cycle progression. Cells in different phases of the cell cycle respond to arsenic in different ways. When treated with arsenic, mitotic cells are particularly susceptible to caspase-dependent apoptosis, whereas cells in earlier stages of the cell cycle experience growth delay and become resistant to cell death through differentiation. This lab is currently using ribonuclease protection assays and immunoblots to identify arsenic-induced gene products associated with sensitivity and resistance to arsenic-induced cell death. It is useful in chemotherapy to inhibit the growth of cancer cells, but if normal cells are changed in such a way that they become resistant to death, they may be more prone to malignant transformation. Although it may sound paradoxical, it is conceivable that arsenic's ability to inhibit the growth of cancer cells is closely related to its ability to induce carcinogenesis. Therefore, their goal is to increase understanding of arsenic's chemotherapeutic mechanism and, in turn, add considerably to the understanding of arsenic's carcinogenic actions.

Jennifer M. Sasser, Medical College of Georgia: "Increased Angiotensin II and Endothelin-1 Signaling in Insulin-Dependent Diabetes Mellitus Increase the Superoxide: Nitric Oxide Balance and Contribute to Injury in the Renal Cortex." Diabetic nephropathy is the leading cause of end stage renal disease in this country; however the mechanisms by which diabetes mellitus alters renal function are not completely understood. Two factors which may contribute to the development of renal injury in diabetes are angiotensin II and endothelin-1, molecules that regulate blood pressure and cellular growth and proliferation. Both angiotensin II and endothelin-1 also increase the production of reactive oxygen substances, which may

be detrimental in the pathogenesis of diabetes. This research predicts that inhibition of either angiotensin or endothelin receptor activation or antioxidant treatment will reduce renal injury and improve renal function in an animal model of diabetes. These studies will provide insight into the mechanisms involved in the development of diabetic nephropathy and investigate therapeutic targets which may slow or prevent the progression of renal injury.

Rebecca M. Steinberg, University of Texas at Austin: "The Effects of Prenatal PCB Exposure on Reproduction: From Molecules to Behavior." Environmental toxicants often act as Endocrine-Disrupting Chemicals (EDCs) through their actions on steroid hormone receptors.The developing female brain is particularly vulnerable to EDCs, as the normal female ontogeny of the nervous system requires the near-absence of gonadal hormones.Thus, the presence of exogenous EDCs is interpreted by the brain as an apparent increase in circulating hormones, which may cause masculinization of reproductive physiology, brain morphology, and sexual behavior. This laboratory and others have previously demonstrated persistent effects of fetal exposure to EDCs on neural protein expression and on adult social behaviors. This present study is unique in providing a broad picture of the effects of EDC exposure by revealing molecular, cellular, and behavioral endpoints. In this research, ecologically relevant doses of polychlorinated biphenyls (PCBs), an EDC persistent in the environment and commonly detected in human and animal tissues, are administered to study the toxicological effects of EDC exposure. The research program is divided into two specific aims. In Aim 1, they will document and quantify molecular and cellular changes in the brain of exposed individuals. The research will focus on gene and protein expression of gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus, the brain region that initiates and maintains the body's hormonal environment. GnRH cells regulate reproductive cyclicity and sexual development in the female, and work from this lab has shown that these cells are targeted by EDCs. Using immunohistochemistry and real-time PCR, they will also examine expression of other key endocrine and nuclear receptors that regulate GnRH neurons in hypothalamic tissue. In Aim 2, they will record the physical and sexual development, reproductive behaviors, and fecundity of female rats given prenatal exposure to PCBs. Additionally, the second generation, the offspring of exposed individuals, will also be monitored for birth or developmental abnormalities. The data provided by this research will offer a unique comprehensive view of how common exposure levels of environmental contaminants may be exerting long-term effects on female reproductive abilities.

Post Doctoral Fellowship in Pharmacology/Toxicology

The goal of this program is to increase the number of well-trained investigators in pharmacological 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.

Receiving the fellowship that began February 2004:

Hong Sun, M.D., Ph.D., University of California, San Francisco:"Elucidating the Mechanisms of Metabolic Changes in Renal Failure." The overall goal of this research project is to characterize and understand the underlying mechanisms of reduced hepatic clearance of drugs that are primarily metabolized by the liver in renal failure patients. They hypothesize that renal failure affects the hepatic clearance of drugs in some cases by reducing the metabolic activity of enzymes in the liver, but more frequently by reducing the hepatic uptake that is mediated by transporters. Uremic toxins that accumulate in the plasma of end stage renal disease (ESRD) patients are most likely the "evil humors" that cause functional and quantity changes of uptake transporters in the liver. Using erythromycin as a model compound, they plan to determine whether impaired function of liver uptake transporters causes the reduced hepatic clearance of erythromycin in renal failure patients. To achieve the overall goal, the proposed studies are designed to: (1) determine the inhibitory effects of circulating uremic toxins on uptake of erythromycin by hepatocytes; (2) evaluate whether the inhibitory effects of uremic toxins would affect the hepatic clearance of

During the 12th Annual Awards Banquet and Reception of the American Association of Anatomists, the PhRMA Foundation presented our Post Doctoral Fellowship in Pharmacology/Morphology. This special event was held on April 20, 2004 in Washington, DC. We were honored to be included.

Del Persering presenting at the ASPET Annual Meeting in April 2004

erythromycin in isolated perfused rat livers (IPRL); (3) identify what uptake transporters are affected by the uremic toxins; and (4) evaluate whether the uptake transporters are down-regulated in chronic renal failure rats. They believe that elucidating the mechanisms for reduced hepatic clearance in renal failure would be an important guide to dose adjustment in renal failure patients.

Post Doctoral Fellowship in Pharmacology/Morphology including Cell Biology

The goals of this post doctoral program are to increase understanding of the actions of drugs by direct study of their effects on cells and tissues; to correlate the morphological changes, and uncover associations observed with functional parameters of cells and tissues.

This program provides a stipend of $40,000 annually for up to two years to well-trained graduates from Ph.D. programs who seek to further develop and refine their research skills through formal post doctoral training.

This fellowship was first offered in 1968. One hundred and eleven awards have been made to date including the one awarded in 2004.

Receiving the fellowship that began between January and December 2004 is:

Bradley A. States, Ph.D., The Burnham Institute: Center for Neurosciences & Aging. "The Role of NR3A in the Development and Plasticity of Glutamalergic Synapses in the CNS." Dendritic spines represent the principal sites of excitatory synaptic contact for many neuronal cell types in the central nervous system (CNS). Importantly, the molecular constituents of dendritic spines, such as neurotransmitter receptors, as well as the number of spines themselves, can be modified by synaptic activity, resulting in long-lasting changes in neuronal excitability which under lie several experimental paradigms of learning and memory. A principal effector of such modifications is the NMDA receptor which gates calcium in response to coincident synaptic activity between pre- and postsynaptic neurons. The goal of this proposal is to elucidate the function of the NR3A subunit of the NMDA receptor in the development and plasticity of glutamatergic synapses in the CNS. They hypothesize that the NR3A subunit plays an important role in the development and plasticity of glutamatergic synapses in vivo based on several lines of experimental evidence. NR3A is highly expressed in brain regions which exhibit extensive plasticity and remodeling capabilities. The developmental time course of maximal NR3A expression closely parallels synaptogenesis *in vivo*. Genetic deletion of NR3A in mice results in an approximate 3 to 4 fold increase in the density of dendritic spines in primary somatosensory cortex, where NR3A is highly expressed, compared with wild-type littermates, thus potentially increasing the number of synaptic contacts in these cells by the same number. Studies in this proposal will investigate the electrophysiological and pharmacological mechanisms by which the NR3A subunit influences spine density by reproducing the increased spine density phenotype in primary neuronal cultures from NR3A knockout animals, which will permit fine structural analysis and pharmacological manipulation. Key characteristics of these putative additional sites of synaptic contact, such as the ratio of silent (containing NMDA receptors only) to active (containing AMPA and NMDA receptors) synapses will be investigated electrophysiologically in acute cortical and hippocampal slices, and by molecular techniques in primary neuronal cultures. The influence of altered spine density on synaptic plasticity in NR3A knockout mice will also be investigated by comparing long-term potentiation in acute slices and in primary neuronal cultures from NR3A knockout and wildtype mice. Electrophysiolgical findings will be correlated with molecular and morphological observations of receptor localization and spine density. It is expected such studies will yield clues as to how the NR3A NMDA receptor subunit influences neuronal morphology, and how this in turn impacts synaptic transmission and plasticity. These investigations may additionally provide further insights into mechanisms of action and/or treatment strategies for the myriad cerebral pathologies in which the NMDA receptor is implicated.

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 five hundred thirty-eight have been awarded, including the grants beginning on January 1, 2004.

Recipients of the Research Starter Grants that began in January 2004 are:

Bryan L. Copple, Ph.D., University of Kansas Medical Center: "Modulation of Macrophages by Hypoxia during Fibrosis." Hepatic veno-occlusive disease (HVOD) is a type of liver fibrosis that occurs in humans exposed to pyrrolizidine alkaloid (PA) plant toxins and in patients who receive high-dose chemotherapy for bone marrow transplantation. Currently there is no medical treatment for this disease and the molecular events that promote its pathogenesis are poorly understood. During early stages of HVOD, PAs and chemotherapeutic drugs damage endothelial cells in the liver, which promotes inflammation and extensive hepatocyte death (i.e., early HVOD). At later stages (i.e., late HVOD), fibrosis occurs which leads to liver failure. Preliminary results suggest that hypoxia (i.e., low intracellular pO2) occurs in damaged regions of the liver in an animal model of HVOD. Furthermore, monocytes and macrophages (i.e., MPs) accumulate in these damaged regions of the liver, become hypoxic and express the hypoxia-regulated transcription factor, Egr-1 (early growth response factor-1). Interestingly, several studies have shown that Egr-1 regulates the expression of numerous genes involved in the pathogenesis of liver fibrosis. Based upon these observations, the following hypothesis is proposed. Damage to endothelial cells in the liver during early HVOD causes extensive vascular disruption and hypoxia. MPs migrate into these injured regions of the liver, become hypoxic and express Egr-1, which upregulates genes involved in liver fibrosis. These early events lead to the deposition of extracellular matrix (i.e., fibrosis, late HVOD).

Jessica A. Mong, Ph.D., University of Maryland School of Medicine: "Hormonal Modulation of Lipocalin-type Prostaglandin D Synthase: Potential Roles in Sleep." Quality sleep is imperative for the maintenance of good health. Persons suffering from sleep disturbances are not only fatigued but have impaired memory and learning, increased stress and anxiety and decreased quality of daily life. In America,

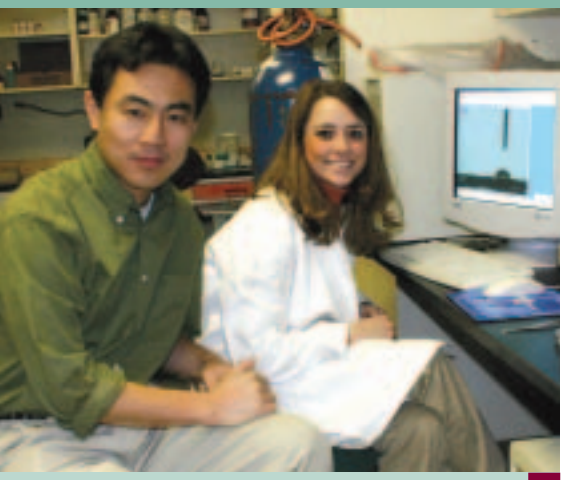
between 31% and 50% of middle-aged people report having sleep problems and sleep disturbances are twice as common among women compared to men. In fact, complaints by women of insomnia, disturbed sleep, difficulty returning to sleep and fatigue rise sharply during their perimenopausal and menopausal years when estrogen levels decrease markedly. Studies from a number of different species, including humans, suggest that sex hormones (estrogens, progestins and androgens) influence the physiology and pathology of sleep. However, the molecular and cellular mechanisms by which hormones act to influence sleep behavior are unknown. This proposal seeks to investigate potential molecular pathways through which hormones influence sleep. Prostaglandin D2 (PGD2) is a sleep promoting substance found in the mammalian brain. Lipocalin-type Prostaglandin D Synthase (L-PGDS) is an enzyme that is the sole producer of PGD2 in the brain. Recently, this research revealed that estrogen dramatically affects the expression of the L-PGDS gene in ventrolateral preoptic area (VLPO), a putative sleep center in the brain. Thus, it is hypothesized that the affect of sex steroids on sleep patterns is mediated by steroid-induced changes in the expression of L-PGDS in the VLPO and the consequent change in the ability of the VLPO sleep active neurons to be come activated. The overall goal of these projects is to continue to investigate the roles of L-PGDS and estrogen in the cellular and molecular mechanisms of sleep/wake patterns. The rat serves as a valuable model in this regard because of the extensive knowledge on general sleep patterns already gained. To gain a better understanding of the potential significance of steroid mediated changes in L-PGDS transcript expression as it relates to sleep the first aim of the project is to investigate (1) the effects of gonadal steroids on L-PGDS protein expression; (2) the cell types that make the L-PGDS enzyme; and (3) whether or not these cells are directly responsive to Estrogen, Progesterone and/or Testosterone. Secondly, this study proposes to examine the changes in the functionality of the sleep-promoting neurons in VLPO under various hormonal states and pharmacological applications. The potential findings of this research will advance the understanding of steroid associated control of sleep and may present an opportunity for the pharmaceutical industry to find alternative non-sedating compounds to hormonal replacement therapy for the alleviation of sleep disturbances in menopausal women.

John D. Robertson, Ph.D., University of Kansas Medical Center: "DNA-Damaging Agents, Caspase-2, and Apoptosis." Damage to DNA caused by exposure to environmental chemicals can result in toxicity or carcinogenicity. Although the underlying biochemical and molecular mechanisms for these effects are in some cases at least partially understood, in many other instances they remain unclear. The broad objective of this research proposal is to understand how DNA damage leads to the engagement of cell death pathways by activating a family of enzymes known as caspases. In general, seven or so of these enzymes provide the biochemical basis for gene-regulated forms of cell death called receptor- and mitochondria-mediated apoptosis. Of particular interest for this research proposal is whether caspase-2 is required for cell death to occur in response to DNA-damaging anti-cancer drugs and whether this necessarily proceeds via mitochondria-mediated apoptosis. Further, additional information will be obtained by investigating whether caspase-2 plays a role in cancer prevention by helping to eliminate cells with DNA lesions in a mouse model of skin carcinogenesis. The hypothesis to be tested is that caspase-2 activation is required for the engagement of the mitochondrial apoptotic pathway in response to DNA-damaging agents. Completion of this research will provide critical new information about the biochemical and molecular mechanisms whereby DNA-damaging chemicals activate cell death pathways.

Ning Zheng, Ph.D., University of Washington: "Crystallographic Studies of the Keap1-Nrf2 Complex, a Molecular Switch Regulating Phase II Enzyme Expression."Most small molecule drugs and organic chemicals with pharmacological potentials are xenobiotics, compounds that are foreign to the human body and frequently toxic. The transcription factor

The PhRMA Foundation would like to thank the American Society for Pharmacology and Experimental Therapeutics for inviting us to present our 2004 Awards in Pharmacology/ Toxicology at the ASPET Award Ceremony on Saturday, April 17, 2004 during Experimental Biology 2004 in Washington, DC.

Pictured with George C. Fuller, Ph.D., Del Persinger and Eileen McCarron are the award recipients who were recognized at the 2004 ASPET Awards Ceremony in Washington, DC. From left to right, Jennifer M. Sasser, Medical College of Georgia, John D. Robertson, Ph.D., University of Kansas Medical Center, Jessica A. Mong, Ph.D., University of Maryland School of Medicine, Bryan L. Copple, Ph.D., University of Kansas Medical Center, and Ryan E. Hibbs, University of California, San Diego



The PhRMA Foundation has jump-started my academic career. The Research Starter Grant allows me to do top-notch studies, recruit and train some of the best graduate students in pharmaceutics.

Tonglei Li, Ph.D.
2003 Research Starter Grant in Pharmaceutics.
Assistant Professor
College of Pharmacy,
University of Kentucky
and
Clare Aubrey
Graduate Student

Nrf2 plays a pivotal role in activating the expression of genes encoding Phase II drug detoxifying enzymes and antioxidant enzymes in response to xenobiotics and electrophilic compounds.Under normal conditions, the cellular protein Keap1 negatively regulates Nrf2 by both sequestering it in the cytoplasm and promoting its rapid degradation by the ubiquitin-dependent proteolytic pathway. Upon exposure to electrophilic agents, Nrf2 dissociates from Keap1 and translocates into nucleus, transactivating drug detoxifying and antioxidant genes. It has been postulated that the Keap1-Nrf2 complex serves as the cellular "redox switch" that responds to xenobiotic insults. In this proposal, they plan to initiate biochemical and crystallographic studies of the Keap1-Nrf2 complex. Their final goal is to determine the atomic structure of the complex by X-ray protein crystallography. These studies aim to reveal the detailed structural basis of the Keap1-Nrf2 interactions, which is crucial for understanding not only how Keap1 negatively regulates Nrf2 but also the nature of the molecular event that triggers Nrf2 dissociation from Keap1, the hallmark of Nrf2 activation. One immediate application of these studies is to develop better cancer chemopreventive agents that can modulate the Keap1-Nrf2 system to enhance the expression of the Phase II and antioxidant enzymes.

Medical Student Research Fellowships in Clinical Pharmacology

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 investigative projects at a point when career choices are still relatively flexible, they will eventually choose research careers in clinical pharmacology.

The minimum period of the fellowship is three months and the maximum is two years, with a maximum stipend of $18,000. One hundred and sixty-nine Medical Student Fellowships have been awarded since the program began in 1974.

Recipient of the Medical Student Research Fellowship that began in July 2004 is:

Erik S. Musiek, Vanderbilt University School of Medicine: "Biochemical Pharmacology of Cyclopentenone Neuroprostanes."Oxidative stress has been implicated in the pathogenesis of several neurodegenerative conditions, including Parkinson's and Alzheimer's diseases. Membrane bound polyunsaturated fatty acids (PUFAs) are particularly susceptible to free radical-mediated damage, and docosahexaenoic acid (DHA) is the most abundant PUFA in neurons. Increased levels of neuroprostanes (NPs), prostaglandin-like molecules derived from free radical-initiated peroxidation of DHA, can be measured in brain tissue in settings of oxidant injury, and one type of NPs, the A4/J4-NPs, are extremely abundant in oxidatively damaged brain tissue. A4/J4-NPs, also known as cyclopentenone NPs, contain a highly reactive unsaturated carbonyl prostane ring, and can form adducts with relevant thiol-containing molecules such as proteins and glutathione. The overall goal of this project is to examine the formation, metabolism, and bioactivity of cyclopentenone neuroprostanes (A4/J4-NPs), the most abundant class of NPs formed in the brain, and elucidate their contribution to the pathogenesis of Parkinson's disease (PD). This lab will explore the hypothesis that A4/J4-NPs exert potent biological activity and contribute to the pathological sequelae of oxidative stress in PD and other neurodegenerative diseases. They will first determine factors that influence the formation of A4/J4-NPs in the central nervous system, and then examine factors influencing the metabolism of A4/J4-NPs. Third, they will assess the neurotoxicity of A4/J4-NPs, focusing on the molecular mechanisms of neuronal death. Finally, they will examine the formation of A4/J4-NPs in brain tissue from humans with PD. These studies will provide insight into the role of oxidized lipid mediators, in particular A4/J4-NPs, in PD and other neurodegenerative diseases.

Pharmaceutics

Pre Doctoral Fellowships in Pharmaceutics

This program has been in effect for 16 years. It assists awardees who have one or two years remaining in the pharmaceutics pre doctoral training—the time during which they are engaged in dissertation research. We provide the funding during the doctoral program after course work has been completed and the remaining training activity is a student's research project.

The fellowship program provides a stipend and funds to cover costs incidental to the training for up to two years. The level of support is $20,000 per year and up to $500 a year may be used for incidentals directly associated with the preparation of the dissertation. Three awards were made for 2004.

Sandra L. Goss, University of Connecticut: "The Role of Gastric pH and Bicarbonate Secretion in Calcium Absorption." Intestinal absorption of calcium from supplements is generally low and variable (20-40%). Unfortunately, increasing the solubility of the calcium salt does not give a comparable increase in absorption, even though calcium is primarily absorbed passively, since active transporters are quickly saturated with the large doses. They hypothesize that much of the ingested calcium from a calcium supplement precipitates as calcium carbonate (CaCO3) due to intestinal secretion of bicarbonate (a source of carbonate) and the low solubility product of CaCO3 (~10-8). An in vitro system was developed to simulate certain aspects of the human GI tract. The apparatus was used to determine the effects of pH, pCO2 and time to neutralization on the amount of calcium that remains available for intestinal absorption. Experiments showed that the presence of another species, CaHCO3+, along with CaCO3, influenced the concentration of soluble calcium. To further investigate the significance of CaHCO3+, calcium absorption in Caco-2 cells is being determined at varying pH and pCO2, thereby altering the amount of HCO3+ available to associate with calcium. An in vivo study will be conducted to determine the effect of altering gastric pH, and therefore, bicarbonate secretion, on calcium absorption in humans. If increasing gastric pH significantly increases calcium absorption from an administered solution, then the physicochemical mechanism of calcium precipitation may, in part, explain the difficulties associated with calcium absorption.

Thomas J. Urban, University of California, San Francisco: "OCTN1 and OCTN2, Members of the Novel Organic Cation/Carnitine Transporter Family, Contribute to Intestinal Absorption, CNS Exposure, and Active Renal Secretion of Cationic Drugs." The genes of the novel organic cation transporter (OCTN) family, OCTN1 and OCTN2, encode plasma membrane transporters that are bifunctional, facilitating the pH-dependent transport of organic cations and the sodium-dependent transport of small zwitterions across cell membranes. Both OCTN1 and OCTN2 are highly expressed in kidney function, where they are implicated in both active secretion of organic cations. OCTNs have been shown to facilitate uptake of carnitine and organic cations in a cell culture model of human intestine, suggesting that OCTNs also contribute to absorption of drugs administered orally. Furthermore, the presence of OCTN transporters at the blood-brain barrier (BBB) or in brain parenchyma has been shown to control the uptake of carnitine into the central nervous system (CNS), and a similar effect may be expected with other substrates of these transporters, suggesting a novel mechanism for oral and CNS drug delivery. They propose to elucidate the importance of OCTN transporters to drug delivery and drug disposition by investigating their distinct functional characteristics, structure-activity relationships, and physiological significance in cellular models and in vivo. The overall goal of the proposed studies is to better define the significance of OCTN1 and OCTN2 to xenobiotic disposition, with an emphasis on the role of these transporters in intestinal absorption and CNS penetration of drugs. Functional analysis of these transporters and identification of isoform-specific inhibitors will provide useful tools for high-throughput drug development and rational drug design, may improve oral drug delivery, and may provide a novel mechanism for targeted drug delivery to the CNS.

Ryan E. Hibbs, University of California, San Diego and Jennifer M. Sasser, Medical College of Georgia, recipients of the 2004 Pre Doctoral Fellowships in Pharmacology/Toxicology, are pictured with Del Persinger and Dr. George Fuller at the ASPET Annual Meeting

The PhRMA Foundation is grateful to the American Association of Pharmaceutical Scientists for recognizing the Post Doctoral and Pre Doctoral Fellows at the 2004 AAPS Annual Meeting and Exposition on November 7, 2004 in Baltimore, Maryland. Thank you for this wonderful opportunity.

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.

Amy Ulfers, 2002 Pre Doctoral Fellow from Brown University, Department of Molecular Pharmacology, Physiology and Biotechnology

Stephanie L. Winslow, University of Kansas: "Characterization and Deamidation of Model Cyclic ß-turn Peptides and their Linear Analogs."Recent advances in biotechnology have made peptides and proteins available as pharmaceuticals. For example, tissue plasminogen activator, human growth hormone, and erythropoietin are now available as therapeutic agents. Peptides and proteins are inherently unstable and deamidation is a leading pathway for peptide and protein chemical degradation. As a result of this and other instabilities, peptides and proteins are often formulated in the solid state to limit degradation. Previous research has explored the mechanisms of deamidation in solution and has shown that secondary structure generally slows the rate of degradation. Little is known, however, regarding the role that secondary structure plays in the deamidation of peptides and proteins incorporated into solid polymer matrices. The overall goal for this project is to understand the effects of secondary structure on peptide degradation in polymer matrices. Cyclic b-turn peptides and their linear analogs will be used as models of Asn residues in structured and unstructured domains. The model peptides will be co-lyophilized with poly (vinyl pyrrolidone) (PVP) and subjected to accelerated stability testing while varying relative humidity. Peptide structure will be evaluated in solution using 2D NMR and circular dichroism (CD) and in the solid state using Fourier transform infrared (FTIR) spectroscopy and solid state NMR. Energy minimizations and molecular dynamics simulations will also be performed. The results are expected to help in better understanding peptide and protein formulations and the factors important in stabilizing them. Advances in this area will lead to improved pharmaceutical products. In addition, the results are expected to increase the fundamental understanding of chemical reactions in amorphous solids.

Post Doctoral Fellowship in Pharmaceutics

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

Receiving the fellowship that began in March 2004 is:

Dewey H. Barich, Ph.D., University of Kansas: "Characterization of Pharmaceutical Formulations."The successful administration of a drug requires that the active product ingredient (API) in the formulated product remains soluble and physically/chemically stable. Stability and solubility are both dramatically affected by the drug's physicochemical properties. For example, small amounts of amorphous or highly reactive drug forms may negatively impact stability studies by promoting physical form change or chemical degradation. The identification of these highly reactive components is particularly difficult after a drug has been formulated into tablets because the tablet's other components often interfere with the signals from the API. Thus, the ability to identify, quantify, and determine physicochemical properties of different drug forms within a formulation remains a daunting task. The goal of this proposal is to develop new analytical methods to better understand the physicochemical environment of an API within a formulation.The primary analytical technique to be used for drug form characterization is solid-state NMR spectroscopy (SSNMR).The SSNMR results will be compared with results from more traditional analytical techniques for characterizing forms in the solid state, including powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), water vapor sorption, and Raman spectroscopy.

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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.

Treasurer's Report

Frank L. Douglas, Ph.D., M.D.

The PhRMA Foundation ended 2003 in sound financial shape.
During 2003, most of the PhRMA member companies contributed according to our formula. Contributions were up slightly over the previous year, to $2.87 million. More than $2.26 million was awarded in grants, and total expenditures were $2.7 million.This was the second year of our new program. Total net assets at year-end were $8.28 million. Of this amount, $3.54 million represents funds authorized but not yet paid for the future years of grants already awarded. Financial details are shown in the accompanying Statement of Income and Expenditures.

For 2004, contributions were targeted at the same level, as we entered the third 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, 2003, has been audited by the Rosslyn, Virginia, accounting firm of Buchanan & Company. A full report can be obtained by contacting the Foundation.

Frank L. Douglas, Ph.D., M.D.
Treasurer, PhRMA Foundation
and
Former Member of the Management Board
and
Executive Vice President for Drug
Innovation and Approval
Aventis

Statement of Income and Expenditures
For the Year Ended December 31, 2003

INCOME

Contributions	$2,871,687
Interest and Dividends	130,136
(Realized and Unrealized) Gains in Securities	865,325
Other Income	49,860
Total Income	$3,917,008

EXPENDITURES

Programs	
Awards in Excellence	15,295
Center of Excellence for Integration of Genomics and Informatics	350,000
Clinical Pharmacology Program	466,000
Health Outcomes Program	288,500
Informatics Program	265,000
Pharmaceutics Program	260,000
Pharmacology Programs	617,125
AFPE Fellowship Award	3,750
Subtotal–Grants	$2,265,670
Other	
Committee Meetings, Travel and Honoraria	59,528
Publications and Special Projects	55,723
Subtotal–Other	$115,251
Program Total	$2,380,921
Administrative	
Staff, Rent, Taxes and Insurance	269,084
Professional Services and Investment Expenses	42,583
Office Expenses	10,954
Subtotal–Administrative	$322,621
TOTAL EXPENDITURES	$2,703,542

Advisory Committees

William R. Darrow Foundation Chief Scientific Advisor

The Pharmaceutics Advisory Committee pictured with Eileen McCarron and Del Persinger. Pictured from left to right are; Brad Anderson (2004 Adhoc Member), Bill Curatolo, Russ Middaugh, George Zografi and Jim Swarbrick. Dr. Bill Higuchi is not present in the picture.

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In Memory

James B.D. Palmer, MD, FRCP

James B.D. Palmer, MD, FRCP, Chief Scientific Officer and President of the Bristol-Myers Squibb Pharmaceutical Research Institute and a member of the PhRMA Foundation Board of Directors passed away recently in New York at the age of 51.

Dr. Palmer was a physician by training. He began his training in clinical medicine, followed by pulmonary medicine, and in 1983 was appointed a medical research fellow in pulmonary medicine at the Royal Post-graduate Medical School in London.His lab research focused on neuropeptides in the lung. This background paved the way to a career in the pharmaceutical industry where he led teams that developed many novel and important medications. Dr. Palmer holds the patent forAdvair.

Dr. Palmer joined the pharmaceutical industry in 1985 with Glaxo, a predecessor of GlaxoSmithKline. From 1985 until 2002, Dr. Palmer held increa-singly important roles with GlaxoSmithKline, culminating in his appointment as senior vice president of New Product Development with global responsibility for Medical, Regulatory and Product Strategy. In this role, he was a member of the GlaxoSmithKline Corporate Executive Team.

In 2002, Dr. Palmer joined Bristol-Myers Squibb to become chief scientific officer and president of the company's Pharmaceutical Research Institute. In this role, Dr. Palmer was responsible for Bristol-Myers Squibb's worldwide R&D efforts. He led the institute through one of the most productive and successful periods in its history. Under his leadership, important new medicines for HIV, schizophrenia and cancer were approved by regulatory bodies worldwide and several other medicines for the treatment of Hepatitis B, diabetes and rheumatoid arthritis are reaching their final stages of development.

He was highly regarded by his colleagues and the PhRMA Foundation benefited through his guidance and support. Dr. Palmer was the devoted husband to Dr. Susan Davidson and father of three children.

Peter A. Schad, Ph.D.
Chief Scientific Officer
Digital Infuzion
Gaithersburg, Maryland

David B. Searls, Ph.D.
Senior Vice President
Worldwide Bioinformatics
GlaxoSmithKline
King of Prussia, Pennsylvania

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PhRMA Foundation Programs for 2005

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, 2004 December 15, 2004/January-August
Post Doctoral Fellowship in Health Outcomes (2002)	1 budgeted/ 2 years	$ 80,000 total $ 40,000 per award per year	October 1, 2004 December 15, 2004/January-December
Sabbatical Fellowship in Health Outcomes (2002)	1 budgeted/ 1 year	$ 40,000 total $ 40,000 per award per year	October 1, 2004 December 15, 2004/January-December
Research Starter Grants in Health Outcomes (2002)	3 budgeted/ 2 years	$180,000 total $ 30,000 per award per year	October 1, 2004 December 15, 2004/January 1, 2005
Informatics Advisory Committee			
Post Doctoral Fellowships in Informatics (2002)	2 budgeted/ 1 to 2 years	$160,000 total $ 40,000 per award per year	September 1, 2004 December 15, 2004/January-December
Sabbatical Fellowship in Informatics (2002)	1 budgeted/ 1 year	$ 40,000 total $ 40,000 per award per year	September 1, 2004 December 15, 2004/January-December
Research Starter Grants in Informatics (2002)	3 budgeted/ 2 years	$180,000 total $ 30,000 per award per year	September 1, 2004 December 15, 2004/January 1, 2005
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, 2004 December 15, 2004/January-August
Post Doctoral Fellowships in Pharmacology/Toxicology (2002)	2 budgeted/ 2 years	$160,000 total $ 40,000 per award per year	September 1, 2004 December 15, 2004/January-December
Post Doctoral Fellowship in Pharmacology/Morphology (1968)	1 budgeted/ 2 years	$ 80,000 total $ 40,000 per award per year	September 1, 2004 December 15, 2004/January-December
Sabbatical Fellowship in Pharmacology/Toxicology (2002)	1 budgeted/ 1 year	$ 40,000 total $ 40,000 per award per year	September 1, 2004 December 15, 2004/January-December
Research Starter Grants in Pharmacology/Toxicology (1972)	2 budgeted/ 2 years	$120,000 total $ 30,000 per award per year	September 1, 2004 December 15, 2004/January 1, 2005
Paul Calabresi Medical Student Research Fellowship (1974)	2 budgeted/ 1 year to 18 months	$ 36,000 total $ 18,000 per award per year	September 1, 2004 December 15, 2005/January-August
Pharmaceutics Advisory Committee			
Pre Doctoral Fellowships in Pharmaceutics (1987)	3 budgeted/ 2 years	$120,000 total $ 20,000 per award per year	October 1, 2004 December 15, 2004/January-August
Post Doctoral Fellowship in Pharmaceutics (1992)	1 budgeted/ 2 years	$ 80,000 total $ 40,000 per award per year	October 1, 2004 December 15, 2004/January-December
Sabbatical Fellowship in Pharmaceutics (2002)	1 budgeted/ 1 year	$ 40,000 total $ 40,000 per award per year	October 1, 2004 December 15, 2004/January-December
Research Starter Grants in Pharmaceutics (1972)	2 budgeted/ 2 years	$120,000 total $ 30,000 per award per year	October 1, 2004 December 15, 2004/January 1, 2005

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

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