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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.
Just as the pharmaceutical industry has expanded its horizons to encompass new knowledge and cutting-edge technologies, the PhRMA Foundation is charting a new and more ambitious course. Our newly redesigned program, inaugurated last year, has been a resounding success, thanks in large part to your generous support.

As you know, the new program stays true to our past mission of jump-starting the careers of top young scientists in disciplines key to the pharmaceutical industry. But we have expanded our sights to focus much more on strengthening academic centers that produce top scientists in such leading-edge fields as genomics, informatics and health outcomes.

With the tremendous reception of our new program in academia across the nation, we have implemented a major additional initiative—to greatly expand the visibility of the Foundation more broadly as a vital indication of our industry’s commitment to research. This initiative has many facets, including, for example, participation in major professional society meetings, interviews and donated advertising in major publications, and increasing involvement of our past awardees, many of whom are lending their enthusiasm and energy. We are in contact with more than 800 of our alumni, and you will see in this Report examples of their testimony to the unique and central role the Foundation has played in their careers. Many of these scientists, who believe passionately in the importance of research, are eager to help us convey this message.

Our past awardees are not only ambassadors of research, but also represent the impressive success of our program. Among these shining stars of the Foundation’s firmament are company R&D leaders such as Frank Douglas of Aventis, Gus Watanabe and Darryle Schoepf of Eli Lilly, Stephen Spielberg of Johnson & Johnson, and Clark Smith of Pharmacia; university executives such as Dean Daniel Acosta of the University of Cincinnati School of Pharmacy, Dean Craig Brater of Indiana University School of Medicine, Dean Mustafa Lohmandwala of the University of Houston School of Pharmacy, Dean Sidney Nelson of the University of Washington School of Pharmacy, Dr. Craig Schnell, Vice President for Academic
Affairs at North Dakota State University, Dr. Alastair Wood, Assistant Vice Chancellor for Research at Vanderbilt University School of Medicine, and Dr. Ray Woosley, Vice President for Health Sciences and Dean of the College of Medicine at the University of Arizona; past presidents of scientific societies such as, Dr. Sue Piper Duckles, Dr. David Eaton, Dr. Salvatore Enna, Dr. Jay Goodman, Past President of the Society of Toxicology, and Dr. Gabriel Plaa; outstanding scientific leaders such as Dr. Peter Isakson of Pharmacia, winner of the 2002 Discoverers Award for Celebres; Dr. Lou Lasagna, co-founder of the Tufts Center for the Study of Drug Development; and Dr. Craig Venter, who spearheaded the private-sector group that mapped the human genome; former FDA Commissioner Arthur Hull Hayes and Nobel Prize winner Dr. Louis Ignarro of UCLA School of Medicine.

I want to congratulate this illustrious group’s newest members—this year’s award winners, who are listed in these pages. They prove the value of our program, and they prove why it is worthy of the financial support of all PhRMA members. I am deeply grateful for your support, which creates new careers and publicly demonstrates the industry’s commitment to research. Especially in these challenging times, we need every company’s participation to accomplish our goals.

With your support, we will continue our unique role in helping develop the next generation of scientists, and, in turn, the next generation of medicines that help and heal.

Steve Danzer, Ph.D., 2000 Fellow in Pharmacology/Morphology from Duke University, School of Medicine
For the past 36 years, the PhRMA Foundation has been funding young scientists at the beginning of what have turned out to be many distinguished careers. Today, our nationally known and highly respected program is viewed within academia as one of the most prestigious awards available. Academic representatives cite as reasons that the awards are non-targeted, have been dependable for so many years, and—most important—represent the earliest funding opportunity for promising young scientists. Few other foundations—including PhRMA member company foundations—provide this type of funding at this point in careers. As a result, Foundation awards have helped launch the careers of hundreds of accomplished government, academic and industry leaders in R&D. Because of this track record and its unique mission, the Foundation provides great leverage for its contributors.

We are now in the second year of our new program that resulted from a complete, ground-up strategic review conducted in 2000. One of the most notable changes is a totally new program for Centers of Excellence, which awards $1 million over three years. The first of these awards—The Center of Excellence for Integration of Genomics and Informatics—was given to Harvard Medical School, Lipper Center for Computational Genetics, under the direction of Dr. George Church. The competition was stiff, with applications from 17 schools from across the nation.

As another new initiative, we now present most of our PhRMA Foundation awards at the annual meetings of the major professional societies for each of our disciplines. These presentations give us an audience of more than 10,000 scientists, who represent the entire national community. At the General Sessions, we honor our new awardees before their peers and tell large and influential audiences about our new program. At private receptions that we host, we meet individually with dozens of our past awardees, helping us maintain and grow our active network of more than 800 scientists.
In these and other ways, by combining the Foundation’s historic strengths with new, cutting-edge programs and initiatives, the Foundation provides substantial benefits to its contributors in terms of Pipeline, Partnerships and Publicity.

With our new and expanded leading-edge program, we are more effectively feeding the two pipelines that serve our two main purposes: to build academic centers and to provide candidates in hard-to-recruit disciplines.

We are placing major emphasis on building partnerships in completely new ways: helping to further both research itself and dissemination of the message about the importance of research.

- We are generating more top quality applications for grants and fellowships than we can fund, and these applications are shared—with the student’s permission—with the research divisions of our contributors.

- We are encouraging the directors of our new Centers of Excellence to partner with our contributing companies to host students in the second and third years of their fellowships.

- We are also partnering with our active network of more than 800 former awardees, many of whom are willing and highly capable research “ambassadors.” Through their career experiences and their intense commitment, they help convey the importance of pharmaceutical research in finding and developing new cures.

In short, while we have seen all across the country that our new program speaks for itself, we are adding many enthusiastic voices and generating considerable positive publicity and good will for our award winners, for our contributors and for their commitment to research.

I thank all who contribute for your strong and continued confidence and support. We can’t do it without you.
Every year, the PhRMA Foundation grants Awards in Excellence to past awardees who are dramatic, living proof that the Foundation program fills a need and makes a difference. These awards are given to scientists who received a Foundation grant at the outset of their careers in a discipline important to the research-based pharmaceutical industry when they were deciding on their area of specialization—and went on to distinguish themselves through their scientific and/or academic achievements.

This year’s two awardees have distinguished themselves in the areas of clinical pharmacology and pharmacology/toxicology. The Foundation is proud of their achievements and is proud to have been of assistance to them at the beginning of their outstanding careers. They exemplify the very best in their chosen fields. What they have achieved makes it easier to appreciate the importance of providing the same kind of support to those who are following in their footsteps.

The recipients of the PhRMA Foundation Awards in Excellence for 2002 are Arthur J. Atkinson, Jr., M.D., and Louis J. Ignarro, Ph.D.

**ARTHUR J. ATKINSON, JR., M.D.**

2002 Award in Excellence in Clinical Pharmacology

Arthur J. Atkinson, Jr., is a Senior Advisor in Clinical Pharmacology to the Director of the NIH Clinical Center. He has published more than 100 scientific articles, has been lead editor and contributor to two books, and has served on the editorial boards of a number of scientific journals.

Dr. Atkinson received his A.B. degree in Chemistry from Harvard College in 1959, his M.D. from Cornell University Medical College in 1963, and his post doctoral training in clinical pharmacology at the University of Cincinnati. Following internship and residency at the Massachusetts General Hospital, Dr. Atkinson joined the Laboratory of Clinical Investigation of the National Institute of Allergy and Infectious Diseases at NIH.

In 1970, Dr. Atkinson moved to Northwestern University Medical School, where he started a program in clinical pharmacology. To help initiate the program, the PhRMA Foundation awarded him a Faculty Development Award. At Northwestern, Dr. Atkinson set up the first U.S. laboratory devoted to general therapeutic drug monitoring and conducted important basic and clinical research.
George Fuller, Ph.D. (right) is accepting the 2002 Award in Excellence in Pharmacology/Toxicology from Del Persinger for Louis J. Ignarro, Ph.D. at the ASPET Annual Meeting in New Orleans, Louisiana

On April 20, 2002, the PhRMA Foundation presented the 2002 Award in Excellence in Pharmacology/Toxicology and a 2002 Research Starter Grant at the American Society for Pharmacology and Experimental Therapeutics awards ceremony during ASPET’s annual meeting in New Orleans. We are grateful for this opportunity and we thank ASPET for this special occasion.

LOUIS J. IGNARRO, Ph.D.

2002 Award in Excellence in Pharmacology/Toxicology

Louis J. Ignarro, Distinguished Professor of Pharmacology at the UCLA School of Medicine, received the Nobel Prize in Physiology or Medicine in 1998.

His research has included elucidation of the mechanism of action of nitroglycerin; discovery that nitric oxide relaxes smooth muscle and inhibits platelet function; introduction of S-nitrosothiols into biology; discovery that EDHF is nitric oxide; and discovery that nitric oxide is the neurotransmitter that promotes erectile function. The latter finding led to the development of the impotence drug Viagra.

Dr. Ignarro received a B.Sc. in Chemistry and Pharmacy from Columbia University in 1962, a Ph.D. in Pharmacology from the University of Minnesota in 1966, and post doctoral training at the Laboratory of Chemical Pharmacology at NIH during 1966-1998.

From 1968 to 1972, Dr. Ignarro held a research position with Ciba-Geigy. During 1973-1985, he was in the Department of Pharmacology at Tulane University School of Medicine, and he has been in the Department of Pharmacology at the UCLA School of Medicine for 17 years. He was awarded a PhRMA Foundation Research Starter Grant in 1973 while he was at Tulane University.

For most of his professional life, Dr. Ignarro has concentrated on signal transduction mechanisms involving cyclic GMP and nitric oxide. He has published more than 500 scientific articles and has trained numerous graduate students, post doctoral fellows, and clinical fellows.

In addition to the Nobel Prize, Dr. Ignarro has received many other awards and recognition for his groundbreaking research, including the Ciba Award for Hypertension Research, the Roussel Uclaf Prize, and the Basic Research Prize of The American Heart Association. He is a member of many professional societies, including the National Academy of Sciences and the American Academy of Arts and Sciences Institute of Medicine, and is on the editorial board of numerous scientific journals.
For three decades, the PhRMA Foundation has supported young scientists at the beginning of their careers to encourage them to pursue specialties in research and education that are important to the research-based pharmaceutical industry and, ultimately, to patients.

That's a fine general statement, but what has been the real impact of the Foundation's program?

The best testament comes from the words of the awardees themselves, some of whose comments follow and give a real flavor of the impact of the Foundation's program in specific human and scientific terms over the years.

“The PhRMA Foundation funding came at a very critical point in my career—when I was trying to establish myself in the scientific field and in my academic department. Without this funding, I would not have been able to prepare for further funding at the federal level. I was also able to attract students and fellows to my lab as a result of the funding and recognition provided to me by the PhRMA Foundation.”

G. Allen Nickols, Ph.D., Science Fellow, Pharmacia Corporation

“That's a fine general statement, but what has been the real impact of the Foundation's program? The best testament comes from the words of the awardees themselves, some of whose comments follow and give a real flavor of the impact of the Foundation's program in specific human and scientific terms over the years.

“Without initial support from the PhRMA Foundation, I would not likely have succeeded in academia nor would some of the young scholars I was privileged to mentor who received similar support.”

D. Craig Brater, M.D., Dean, Indiana University School of Medicine

“A PhRMA Foundation Research Starter Grant was the first extramural support I received as a new faculty member. The turnaround was fast from application to funding which gave the establishment of my research program a critical jump start. With the help of the funding from PhRMA Foundation, I was able to develop research which was subsequently funded by NIH and AHA.”

Carl A. Gruetter, Ph.D., Professor, Marshall University School of Medicine

“The PhRMA Foundation was absolutely essential in beginning my independent laboratory; without their support, I do not believe I would have progressed to the point I have. That early success in receiving a PhRMA Foundation Faculty and Research Starter Award made me believe that I could in fact participate in academic science—it gave me great hope.”

Stephanie W. Watts, Ph.D., Associate Professor, Michigan State University

“As a new Assistant Professor, the grant that I received from the PhRMA Foundation played a key role in allowing me to establish my research program and propel me into a successful career as an independent investigator.”

Neil M. Nathanson, Ph.D., Professor, University of Washington

“The awards I received from the foundation were critically important in the initial phases of my academic career. In later years, I also relied on this program to assist junior faculty in the department I chaired to assist them in developing their professional careers. Several students in our department received advanced pre-doctoral fellowship awards. The students benefited in numerous ways from this program, including the opportunity it provided them to write a research proposal, and the prestige associated with the award.”

Samuel J. Strada, Ph.D., Senior Associate Dean, University of South Alabama
“It is difficult to get NIH funding for research when you are first starting because you need the papers to show you are an independent researcher but you can’t get the papers without having the grant money. PhRMA Foundation money helped me to get the first papers and to get my foot in the door.”

Jean D. Deupree, Ph.D., Associate Professor, University of Nebraska Medical Center

“My first extramural funding came from the PhRMA Foundation (January 1996); I have been continuously funded by NIH ever since. Thank you for giving me my start!”

Lisa R. Merlin, M.D., Associate Professor, SUNY Downstate Medical Center

“My PhRMA Foundation Research Starter Grant was the first faculty grant I received. It provided me with the resources to get preliminary data for an NIH grant. My PhRMA Foundation grant played an integral role in getting my career started, and I am grateful to the Foundation for their support of junior faculty. Thank you, PhRMA Foundation!”

Kathryn M. Partin, Ph.D., Associate Professor, Colorado State University

“The PhRMA Foundation was instrumental in helping me understand the importance of corporate-based research programs and the valuable synergies and advances that arise from university-industry collaborations.”

Anita P. Hoffer, Ph.D., Consultant, Hypnion, Inc.

“The PhRMA Foundation provided me with the initial funding I needed to launch my research. The support given was essential in establishing my research efforts. Thank you for your support. You have a wonderful program.”

Marc W. Harrold, Ph.D., Professor, Duquesne University

“Without the PhRMA Foundation award, I would have likely ended up moving from academic medicine like so many others, and would never have had the chance to do the good work I’ve had the privilege to do over the last 15 years.”

William J. Elliott, M.D., Ph.D., Professor, Rush-Presbyterian-St. Luke’s Medical Center

“The PhRMA Foundation Research Starter Grant that I received was absolutely vital for the success I have had as a research scientist and educator. The money was not large, but the prestige was vital.”

Garold S. Yost, Ph.D., Professor, University of Utah

“I am extremely grateful for the start that the PhRMA Foundation gave me, to get funding so rapidly and early in my career enabled me to rapidly establish my lab and enhanced and accelerated my career.”

Anna Tate Riegel, Ph.D., Associate Professor, Georgetown University
We awarded the first Center of Excellence in Clinical Pharmacology in July 2002. 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 relatively new clinical pharmacology programs with potential 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 2002 Center of Excellence in Clinical Pharmacology was awarded to Indiana School of Medicine, under the direction of David A. Flockhart, M.D., Ph.D., Chief, Division of Clinical Pharmacology.

This Center proposal is designed to build upon a small Division of Clinical Pharmacology at the Indiana University School of Medicine. This Division was established and has been led for many years by Craig Brater with a single faculty member, Stephen Hall. With the arrival of David Flockhart as the new Division Director in August 2001, they now propose to build a stronger division. The small size of the Division and its relatively limited resources have not allowed it to forge links with other centers of strength in the School of Medicine. They propose a program to build strong recruitment, research and training relationships with the Departments of Pediatrics and Psychiatry and with the Cancer Center and the Center for Women’s Health. They have chosen these four relationships because (a) they represent important areas of clinical pharmacology critical to the maintenance of clinical pharmacology and to the future of the discipline; (b) they are well funded and have great academic strength at Indiana University; and (c) Dr. Flockhart and Dean Brater are aggressively committed to research and training relationships with the Division. This leadership team proposes to use these relationships as building blocks to form the firm and stable foundation of a strong Center for Excellence in Clinical Pharmacology that will provide outstanding training and conduct state of the art research.
In 2002, the PhRMA Foundation offered a new program to support Centers of Excellence in Research Training. This award provides $350,000 per year for up to three years. In July, the funding began in the first PhRMA Foundation Center of Excellence for Integration of Genomics and Informatics. The goal of this program is to help nurture and develop the next generation’s leaders in biomedical research, particularly as it relates to pharmaceutical discovery. This Center of Excellence program was created to address the increasingly complex and sophisticated technologies and skills required for computational exploitation of genome-related data, and the consequent need for multidisciplinary training and interdisciplinary research to build tomorrow’s careers in this field.

The intent is to promote the close integration of computational approaches with the results of bench research, rather than novel informatics technology for its own sake. The proposed training program had to be geared towards basic research necessary for the discovery and development of novel therapeutics and diagnostics.

The 2002 Center of Excellence for Integration of Genomics and Informatics was awarded to Harvard Medical School and the Massachusetts Institute of Technology, under the direction of Dr. George M. Church, Professor of Genetics and Health Science & Technology.

This award will leverage work being performed at the Lipper Center for Computational Genetics. Research already underway brings together the detailed biophysics of macromolecular interactions (3D structures and in vitro binding kinetics constants) with novel genomic tools and computational systems modeling and databases. These disciplines are further merged with problems of clinical and biotechnological impact for commercial and clinical technology transfer. They use quantitative whole genome and proteome measures to guide computational modeling of regulatory and enzymatic networks in microbial and mammalian cells. CEIGI post doctoral fellows are pursuing new methodologies in eight broad fields:

1. They are seeking causative mutations relevant to pharmacogenomics from full human genome sequencing technology using femtoliter-scale in situ reactions.
2. They apply similar engineering to in situ measures of RNA splicing and proteins.
3. They seek ways to connect RNA & protein measures mechanistically through combinations of motifs.
4. They are finding ways to quantitate interactions comprehensively in vitro and in vivo.
5. They are developing technologies to nudge (embryonic or adult) stem cells from any individual (human) to any tissue type in order to access the correct cells to measure toxicity and efficacy.
6. Alternatively, they will engineer sentinel cells that can home to the correct tissues and report.
7. For stem cells, cancer cells, or microbial cells, the effects of mutations in every regulatory and structural domain of every gene on replication will be assessed by a variation on a new array method.
8. They will take the above data into mechanistic (not merely statistical) models and look at the maximum outliers and non-optimizations. The CEIGI fellows will have significant independence in the context of the remarkable Boston computational genomics community and mentoring. Collaborations and consultations with pharmaceutical companies interested in genomics and systems models have already been established involving CEIGI fellows with significant mutual benefit.
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 in Clinical Pharmacology, Pre Doctoral, Post Doctoral, and Sabbatical Fellowships were offered as well as Research Starter Grants and the Centers of Excellence program. Fellowships and Research Starter Grants were offered in Health Outcomes, Informatics, Pharmacovigilance, 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 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 new 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 2002 are:

Nicholas Bergman, Ph.D., University of Michigan Medical School: “Identification of Strain-Specific Virulence Factors in Haemophilus influenzae.” Haemophilus influenzae is a phenotypically diverse pathogen of the human respiratory tract. They postulate that the different disease profiles among H. influenzae strains reflect diversity at the genomic level, yet a comprehensive search for regions that differ between two or more strains of H. influenzae has not yet been done. Here they propose to survey the entire genome of four representative strains of H. influenzae using a PCR-based procedure, and construct a detailed physical map of each. Regions that differ between different strains will be identified and characterized. From the resulting set of chromosomal regions they will construct murineized pools, which will be screened for strain-specific loci that determine a given strain’s ability to persist and/or colonize the host. Finally, they will assess the roles each gene plays in H. influenzae’s adaptations to its host. Performing the research described here furthers several goals. First, it will provide a deeper understanding of how H. influenzae interacts with its host, and how strain-specific genes play a role in the different phenotypes and diversity inherent in a given bacterial species. Finally, they will develop techniques that are generally applicable to other bacterial species for which only one genomic sequence is known and will facilitate other characterizations of interstrain differences without the expense and effort of resequencing each strain’s genome.

Michael L. Goodson, Ph.D., University of California, Davis: “Identification of SMRT and N-CoR isoforms through Analysis of EST and Genomic: A General Method for Identifying Alternative mRNA Splicing Events.” The Privilege laboratory studies transcriptional regulation by nuclear hormone receptors and the co-activators SMRT and N-CoR. In this research proposal, Dr. Goodson describes the use of data from the Expressed Sequence Tag (EST) database and the human genome sequence to validate and characterize a previously described alternative splicing event in SMRT. He proposes to develop a computer algorithm which will identify alternative splicing events from data in the EST database. Initially it will use this algorithm to search for additional isoforms of SMRT and N-CoR. This algorithm, which will be used to search for alternative splicing events in a large number of genes from Genbank.

Data from this large set of alternative splicing events will be useful in developing more accurate models to predict alternative mRNA splicing. He also describes methods for subsequent analysis of alternatively spliced isoforms of SMRT and N-CoR using methods that would be generally applicable to many splicing events.

Katharine Winans, Ph.D., Stanford University School of Medicine: “A Comparative Genomics Approach to Studying Vibrio Cholerae Subtype Population Dynamics.” Pathogenic Vibrio cholerae represents an historic human scourge. Responsible for seven or possibly eight worldwide pandemics since the first recorded in 1817, this microbe thrives in part because it is able to survive indefinitely in an external aquatic reservoir in between periods of human infection. These V. cholerae subtypes bear rotating responsibility for the observed pandemics; O1 El Tor drove the seventh pandemic; and O139 Bengal appears responsible for the possible eighth pandemic. They hypothesize that the successive supplanting of one pathogenic V. cholerae subtype by another is due at least in part to the superior environmental fitness of each successive subtype. They propose to use a comparative genomics approach to elucidate the genetic determinants of the enhanced environmental fitness of new subtypes. Their research capitalizes on the availability of full genome sequence for the O1 El Tor V. cholerae subtype. This research may be divided into the following objectives: (1) to identify differences in growth and survival phenotypes of the three subtypes in a laboratory setting; (2) to compare the genomes of the three subtypes using a DNA microarray derived from the O1 El Tor genome;
(3) to monitor the gene expression profiles of the three subtypes under culture conditions that discriminate among the three variants; (4) to confirm the participation of sentinel genes in growth and survival phenotypes; and (5) to probe environmental biofilm samples for the expression of sentinel genes. This proposal represents a novel application of genomic methods to the complex questions of microbial ecology and population dynamics. They suggest that the techniques they develop may prompt application of these methods to future population dynamics inquiries.

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.

Recipients of the Research Starter Grant that began in January 2002 are:

Sharon Browning, Ph.D., North Carolina State University, Department of Statistics: “Gene Mapping Plays an Important Role in Medical Genetics in Identifying the Genes Responsible for Controlling Susceptibility to Disease.” In order to map the genes involved in complex diseases such as diabetes, cancer and infectious illness, it will be necessary to increase the amount of information by collecting larger pedigrees and genotyping more genetic markers. As the spacing of genetic markers becomes increasingly dense, analysis of the data becomes increasingly sensitive to modeling assumptions concerning the dependencies between markers. Moreover current algorithms for analyzing genetic data are unable to work with simultaneously large pedigrees and large numbers of markers even though they employ sequential approximation models. Thus there is an urgent need for improved algorithms. They propose to address the problems of uncertainty in genetic map distances, incorporation of realistic models into the analysis, and efficient calculation with large numbers of markers on large pedigrees by developing new algorithms based on importance sampling Monte Carlo and Markov chain Monte Carlo.

Martha L. Bulyk, Ph.D., Brigham & Women’s Hospital and Harvard Medical School: “Identification of Transcription Factor Binding Site in Higher Eukaryotic Genomes.” The goal of this proposal is to perform comparative genomic analyses of the human and mouse genomes, in order to identify conserved DNA regulatory elements. Currently, the research for conserved regulatory elements is focused on genomic regions surrounding orthologous mouse and human gene pairs that display similar tissue-specific mRNA expression patterns, as these genes are most likely to be regulated transcriptionally by orthologous transcription factors (TFs). Concomitantly, the research will apply and further develop new microarray technologies for high-throughput characterization of the binding specificities and regulatory roles of TFs. Predicted regulatory elements from computational analyses will be verified using protein binding microarray experiments, in order to identify what TFs bind them. As with the current protein binding microarray technology, the research will identify the genomic locations of binding sites for specific TFs, and the genes they regulate. These experiments will provide much valuable data on cellular regulatory networks, and in combination with mRNA expression analysis, protein interactions databases, and prior genetic and biochemical data in the literature, will permit the construction of a more detailed connectivity map of regulatory networks within cells. These experiments will also provide the opportunity to devise more accurate algorithms for the computational prediction of DNA regulatory elements in the human genome.

David A. McClellan, Ph.D., Brigham Young University: “Software Development and Undergraduate Training Program in Proteomics.” They propose augmenting the present bioinformatics core research group by establishing a team within the core that will formally focus on the development of analytical software that will implement many of the principles associated with applied bioinformatics, primarily in conjunction with evolutionary proteomics, the study of the selective influences that affect the phenotypes of proteins such that they become more or less well optimized for a particular suite of micro-environmental and functional requirements over evolutionary time. Such a group will design and implement software that will allow them to identify the selective influences involved in the development of drug resistance in infectious diseases such as HIV and the influenza virus. The formal organization of this group also will allow us to establish a focused collaborative undergraduate and graduate student-training atmosphere in our laboratories, and assist them in attracting the brightest students of the university so they can properly train them in the newest molecular and analytical techniques, and utilize their emergent skills. These students will be prepared to meet the future needs of academic and industrial research.

The PhRMA Foundation funding allowed me to devote concentrated effort in the development of Bioinformatics. The award led to collaborative works in biocomplexity and bioinformatics to develop tools to study infectious diseases.

Keith Crandall, Ph.D. (left), 2001 Award in Bioinformatics, Thomas L. Martin Professor of Biology, Brigham Young University.
HEALTH OUTCOMES

Pre Doctoral Fellowships in Health Outcomes
This is a new program for the PhRMA Foundation. 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 between January and August 2002 is:

Denise M. Boudreau, University of Washington: “The Association between HMG-CoA Inhibitor Use and Breast Cancer: A Case-Control Study & A Comparison of Patient Interview Data and Pharmacy Records for Antihyperlipidemic, Lipid Lowering, and Antidepressant Medication Use Among Older Women. "HMG-CoA inhibitors (statins) make up a therapeutic class of agents that reduce plasma cholesterol levels by inhibiting hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase. While cholesterol lowering decreases risk of coronary heart disease (CHD), uncertainties remain about the long-term impact of statins on cancer incidence and mortality. This is troubling given the widespread long-term use of these medications, an expanding indication in primary prevention of coronary heart disease, and a possible move of these agents to OTC status. The overall goal of this study is to evaluate the association between statins and breast cancer among women aged 65-79 years using a population-based case-control design. Cases will be 975 women identified from the Surveillance, Epidemiology, and End Results (SEER) registry that were diagnosed with primary invasive breast cancer between July 1, 1997 through May 1999, whose names appeared on the Health Care Financing Administration (HCFA) tapes, and who resided in either King, Snohomish, or Pierce counties at the time of diagnosis. The control group will consist of 1007 comparable women without breast cancer identified through the HCFA tapes and matched to cases on age, and county residence. Both the cases and the controls have already been identified from the Puget Sound Area Breast Cancer Evaluation Study (PACE). Information regarding current and past medication use (20 years prior to reference date), medical and reproductive history, lifestyle factors, family history, and demographics was collected by patient interview in the PACE study. In case-control studies such as PACE that collect information retrospectively, there is concern about the possibility that self-reported histories of medication use may be inaccurate. Therefore, they propose to use pharmacy records from Group Health Cooperative (GHC) and two retail pharmacy chains to validate the self-report of medication exposures in the past 5 and 10 years for approximately 25% of our study sample. Self-report of exposure to the following therapeutic classes will be evaluated: antihypertensives, statins, and antidepressants.

Research Starter Grants in Health Outcomes
This is the first time that this program has been offered in Health Outcomes Research. 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 research. The program is not offered as a means to augment an ongoing research effort.

Recipients of the Research Starter Grants that began in January 2002 are:

Marc Lipsitch, D.Phil., Harvard University: “Develop Methods for Evaluating Antimicrobial Cycling and Other Interventions to Control Infections Resistant to Antibiotics in Hospitals.” Resistance to antimicrobial agents (antibiotics) is a growing problem in many infections, especially those acquired in hospitals. Antimicrobial
cycling or rotation, in which hospital or unit policy mandates preferential use of one antibiotic class for a period, and then switches to preferential use of an unrelated antibiotic class, is frequently cited as a measure for control of resistant, hospital-acquired infections. The grant is supporting research into the relative merits of cycling and other antibiotic use policies using deterministic and stochastic compartmental mathematical models of the transmission dynamics of resistant and sensitive infections in a single intensive care unit. The goal of the research is to define circumstances under which cycling is likely to be more effective than alternative approaches, such as use of multiple drug classes simultaneously in different patients. The use of mathematical models is not meant to replace clinical trials of these regimens, of course. However, due to the scale, logistical difficulties, time requirements, sample size requirements and expense of such trials, it is impractical to perform them under all circumstances (for example, units or hospitals of different sizes, different target pathogens, different antimicrobial classes) in which a particular intervention might be useful. Thus, models can serve as a basis for targeting the design of such trials to test interventions in the most promising settings; models can also provide a framework for assessing the generalizability of trial results. Additionally, the modeling process may help to identify alternative interventions that are as promising as (or more promising than) cycling for inclusion in future trials.

Lisa A. Prosser, Ph.D., Harvard Medical School: “Are Managed Care Decisions Consistent with Public Preferences?” Little research regarding the agreement of public preferences with managed care decision making exists. From a public policy perspective, understanding the extent to which managed care decisions are consistent with public preferences could have important implications for improving the decision-making process in managed care organizations. The research project described here proposes to use contingent valuation to measure public preferences regarding managed care decision making. The specific aims are: (1) to evaluate the feasibility of using willingness-to-pay values to proxy for public preferences regarding coverage decisions; (2) to describe the relative value of individual criteria important to respondents when valuing coverage for new and existing health interventions; and (3) to measure willingness-to-pay for specific coverage decisions previously undertaken by managed care organizations. A telephone survey and focus groups will be conducted to evaluate public preferences for coverage of new health interventions. Results will be analyzed using both qualitative and quantitative methods. The relative importance of specific decision criteria will be assessed. If shown to be feasible, the contingent valuation method developed in this project could be extended to compare preferences and the relevant importance of decision criteria between community members, managed care decision makers, and physician/other providers. If managed care decisions are not consistent with public preferences, this research can help identify what factors cause divergence. Future research in this area could improve the ability of managed care organizations to make decisions consistent with public preferences.

Judith A. Shinogle, Ph.D., M.Sc., University of South Carolina: “Effects of Patient Cost-Sharing on Utilization and Costs in a Managed Care Population.” The proposed research will examine the effects of an increase in prescription copayments within a three-tier system. Outcomes examined include: number of prescription drug claims, number of brand-name prescription drug claims, total cost of outpatient drug claims, cost per prescription drug claim, number of outpatient physician visits, total outpatient physician claim costs, cost per outpatient physician claim, and number of days the patient remains on chronic therapy. Currently, there is a paucity of information on the effects of copayment changes across different therapeutic categories as well as the effects on other services such as outpatient physician visits. This research will fill this void by using flexible functional forms to model the prescription drug and outpatient physician visit utilization and expenditures after an increase in prescription drug copayments in a threatened copayment plan. These models will be developed within therapeutic categories as well as with the entire data set and will be used to predict the effect of a price change on utilization of prescription drugs and physician visits. Policy makers, benefits managers, and pharmaceutical manufacturers will benefit from the outcomes of this research by improving their abilities to budget and plan health care benefits.

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. Upon $500 a year of the funding may be used for incidentals directly associated with the preparation of the dissertation.

Two hundred and eighty-six fellowships have been awarded under this program including the nine awarded in 2002.

Those who received fellowships that began between January and August 2002 are:

Jennifer Dawn Bilyeu (née Adams), The University of Tennessee Health Science Center: “Role of NF-κB in Chemoresistance to Anthracyclines.” Anthracyclines are antitumor drugs that are widely used in the treatment of various types of cancer. Doxorubicin (DOX) is one of the most extensively used and studied anthracyclines, yet the efficacy of DOX is limited by both acquired and induced resistance mechanisms. One putative mechanism of induced resistance to DOX and other anthrac-tyclines involves the activation of NF-κB. NF-κB is a transcription factor that has been implicated in the regulation of several genes involved in cell survival, such as the MDR1 gene encoding the ATP-binding cassette (ABC) transporter that is responsible for multidrug resistance.

In an attempt to characterize the mechanism of the induced chemoresistance to anthracyclines, the activation of NF-κB in response to DOX and AD 198 treatment of cells was investigated. Specifically, this project will involve the characterization of the kinases involved in the phosphorylation of NF-κB inhibitory protein IκB in response to DOX and AD 198 treatment and identifying the pro-sur-vival genes regulated by anthracycline-induced NF-κB activation. These studies will provide vital information on the regulation of NF-κB in response to anthracyclines and possibly constitute the basis for an adjunctive protocol in chemotherapy through NF-κB inhibition.

Stacy A. Blaine, University of Colorado Health Sciences Center, Department of Pharmacology: “Regulatory Mechanisms of Ras Mediated Induction of Cytosolic Phospholipase A2.” Mutations in ras genes are observed with high frequency in non-small cell lung cancer (NSCLC) and contribute to transformed growth of these cells. Their laboratory has reported that in a panel of NSCLC cell lines expression of oncogenic forms of Ras is associated with increased expression and activity of cytosolic phospholipase A2 (cPLA2) and cyclooxygenase-2 (COX-2), resulting in high constitutive levels of prostaglandin production. Expression of oncogenic Ha-Ras alone is sufficient to induce expression of these enzymes in nontransformed, normal lung epithelial cells. Numerous studies have linked increased COX-2 expres-sion and elevated levels of prostaglandins to both lung and colon cancers. It is reasonable to surmise that cPLA2, the rate-limiting enzyme in eicosanoid production, also plays an important role in transformation. Induction of cPLA2 by oncogenic Ha-Ras is mediated in part by transcriptional activation. The minimal region of the cPLA2 promoter required for this induction has been defined, and Ms. Blaine has identified three required regulatory ele-ments. She has shown that both the JNK and ERK MAP kinase pathways are necessary for cPLA2 promoter activity. Activation of NF-κB is required for cPLA2 transcriptional activity in both lung and colon cancer.

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Laurie B. Cook, University of Rochester: “An Analysis of Ubiquitinated TRH Receptors.” G protein-coupled receptors (GPCRs) are a large superfamily of transmembrane proteins. Only three GPCRs, rhodopsin, δ opioid receptor, and the gamma subunit of the gamma-aminobutyric acid (GABA)ergic receptor have been shown to be ubiquitinated. Ubiquitin, a highly conserved 76 amino acid protein, is covalently attached to lysine residues and is classically used to signal proteins for proteasomal degradation. They now know that in addition to acting as a proteasomal degradation signal, ubiquitin can also direct the ligand-induced internalization and lysosomal degradation of plasma mem-brane proteins, including the yeast alpha factor receptor. Their preliminary data provide evi-dence for the ubiquitination of the pharyngeal TRH receptor in cell culture. They showed that the C-terminus is not a major site for ubiquitin-ation. They investigated possible roles for ubiquitin in TRH receptor internalization and concluded that TRH receptor internalization was independent of ubiquitin conjugation. To investigate the regulatory role of TRH receptor ubiquitination and GPCR ubiquitination in gen-eral, they propose to: (1) determine where TRH receptors are ubiquitinated, and (2) determine the function of TRH receptor ubiquitination.

Christopher N. Davis, University of Florida, College of Medicine: “Development and Evaluation of a CX3CR1 Antagonist.” The CX3C1R1 receptor is a functional receptor on microglia that is critical for the chemotaxis of microglia in response to brain injury. The CX3C1R1 receptor is critical for microglia-mediated neuroprotection. Development of a CX3C1R1 antagonist could potentially be used for the treatment of a variety of neurological disorders. This project is aimed at the development of such a compound and its evaluation for potential beneficial effects in animal models of neurological diseases.

Pre Doctoral Fellowships in Pharmacology/Toxicology

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determining fundamental roles of the chemokine, fractalkine, and its receptor, CX3CR1, in CNS function and pathology. CX3CR1 and fractalkine are known to be upregulated in a variety of neuropathological disorders suggesting that these genes play a role in aspects of disease initiation, progression, and/or resolution. In the first specific aim, experiments are designed to determine structural features of fractalkine important for agonist binding and efficacy at CX3CR1. Non-selective CX3CR1 antagonists exist in the forms of cyclically encoded peptides. Therefore, cues provided by a non-selective CX3CR1 antagonist, VMP-4 (encoded by human herpes virus 8), will be used to modify fractalkine and VMP-4 to create selective antagonists to CX3CR1. The second aim is designed with the goal of determining the role of fractalkine and its receptor in an animal model of multiple sclerosis (MS), experimental allergic encephalomyelitis (EAE). The effects of novel CX3CR1 antagonists (developed in aim one) will be evaluated in a recognized animal model of CNS pathology, i.e., EAE. Development and evaluation of novel CX3CR1 antagonists will shed light on fractalkine/CX3CR1 functions in neuropathology and could prove useful in the treatment of MS.

Yong-Hsin Valerie Ng, University of California, San Francisco: “Regulation of Cytochrome P-450 Eicosanoid Formation by the Nuclear Receptor Peroxisome Proliferator-Activated Alpha (PPARα) in the Vasculature.” Cytochrome P-450 (CYP) eicosanoids are potent vasoactive compounds implicated in the regulation of blood pressure. Many studies have shown that their levels can be regulated in the liver and kidney by certain compounds known as peroxisome proliferators (PPs). These compounds include hypolipidemic drugs, pesticides, and plasticizers. Though the CYP eicosanoids exert potent vasodilatory and vasoconstrictive effects in the vasculature, the regulation of their formation at their site of action has not been characterized. The purpose of this study is to test the hypothesis that CYP eicosanoid formation in the vasculature is regulated by the nuclear receptor peroxisome proliferator-activated receptor-alpha (PPARα). The first specific aim will characterize, in vivo, the levels of CYP eicosanoids in response to PPs. PPs act via PPARα, which has recently been found to play an important beneficial role in vascular tone regulation. The second and third specific aims will determine the role of PPARα in mediating the effects of CYP eicosanoids. A more complete knowledge of CYP eicosanoid formation is essential for understanding their role in controlling blood pressure and will set the groundwork for designing therapeutic interventions to regulate blood pressure.

Blaine Robinson, University of Michigan: “Role of Mismatch Repair in Gemcitabine Cytotoxicity and Radiosensitization.” The proposed research involves the use of Gemcitabine, a clinically active drug that when used prior to irradiation, produces enhanced cell killing (radiosensitization). Mismatch repair proficient and deficient colorectal cancer cell lines will be employed to better understand the mechanism of action for Gemcitabine radiosensitization which is currently not well understood. Gemcitabine is able to deplete deoxyribonucleotide pools, in particular dATP by inhibiting ribonucleotide reductase during exposure to a 24-hr incubation immediately before ionizing radiation. A depletion in one of the deoxyribonucleotide pools may allow for DNA misincorporations to occur. These lesions in the DNA from Gemcitabine may be involved in producing the enhanced cell killing once ionizing radiation causes double strand DNA breaks. Using mismatch repair proficient and deficient cell lines will allow them to study how DNA misincorporations from Gemcitabine affect radiosensitization. A better understanding of which lesions are necessary for and which prevent radiosensitization will allow for the development of better clinical protocols using the drug and radiation in combination. The overall goal of this research is to determine the currently unknown mechanism of Gemcitabine radiosensitization.

Amy Ulfers, Brown University: “Characterization of the Binding Properties of Synapse Associated Proteins using NMR.” Synapse associated proteins (SAPs) are multi-domain modules which mediate receptor clustering on the postsynaptic membrane of excitatory synapses. SAPs function by binding to both receptor subunits and to other scaffolding or signaling molecules to form a multimeric complex in the neuronal membrane. This project will investigate the binding properties of SAPs by studying the structure and behavior of key SAP domains using nuclear magnetic resonance spectroscopy (NMR) and other spectroscopic techniques. This information can then be used to rationally design a lead compound that modifies glutamate receptor function by specifically binding to the SAPs that mediate receptor clustering. Such a compound would provide a novel manner to modulate neuronal excitation and could eventually be useful for treating conditions involving disruptions at excitatory synapses, such as epilepsy, memory loss, and drug addiction.

Christopher A. Wells, Medical University of South Carolina: “Homology Modeling G Protein Heterotrimers.” G proteins are heterotrimers that are involved in translating cellular signals from extracellular sources through G protein coupled receptors into the cell through a large variety of effectors. Based on sequence alone of known family members, there are a possible 1000 heterotrimers, even more exist due to modifications, cellular expressions, etc. The knowledge of which heterotrimers exist is very limited—only 60 of the
possible 1000. The goal of this work is to shed light on all of the possibilities using homology-modelling to predict interaction of subunit family members. Knowledge of distinct heterotrimeric will be useful in cellular signaling, drug targeting, and cell manipulation. The ability to model distinct heterotrimers could easily be expanded to work between G proteins and effectors or their regulators, or other protein-protein interactions.

Post Doctoral Fellowship in Pharmacology/Toxicology

This program provides stipend funding to well-trained graduates from Ph.D. programs who seek to further develop and refine their research skills through formal post doctoral training. The PhRMA Foundation and its Pharmacology/Toxicology 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 between January and December 2002 is:

James M. Corbitt, Ph.D., University of North Carolina at Chapel Hill: “Novel Mechanisms of RGS Protein Signaling.” Regulators of G-protein signaling (RGS) proteins function as GTPase-activating proteins (GAPs) for certain Gα subunits, increasing the rate at which Gα subunits hydrolyze bound GTP and return to the inactive state. Recently, a genetic model using Caenorhabditis elegans (C. elegans) has provided evidence of a novel interaction between two neuronal second messenger pathways, Gα and Gαq, along with the RGS proteins EGL-10 and EAT-16, regulate feeding and egg-laying behavior. Genetic data indicate that Gao and Gq, regulated signaling pathways inhibit and activate, respectively, the feeding and egg-laying behavior of the nematode. Inhibitory activity of Gao occurs at least in part at the level of Gao, and EAT-16 lies functionally between Gao and Gaoq. These observations suggest a novel form of regulation involving an RGS protein between two heterotrimeric G-proteins and establish whether this model is representative of mammalian signal transduction. They will use a proven method of protein expression and purification, and a well-defined assay system of phospholipid vesicles reconstituted with purified proteins will be used to determine GAPase activity. Results from this project should support the C. elegans genetic evidence in biochemical and molecular terms and likely will define a new aspect of signal transduction in mammals. The specific aims of the proposal are: (1) to express and purify C. elegans Gao and RGS proteins; (2) determine GAPase activity between C. elegans RGSs and Gα proteins; and (3) determine the relative potential of R7-RGS proteins to function as GAPs and Gβγ subunits for Gα proteins.

Post Doctoral Fellowships in Pharmacology/Pharmacogenomics

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.

We thank the association for this meaningful recognition.
Raogo Ouedraogo, Ph.D., SUNY Downstate Medical Center: “Orexin in the Energy Homeostasis: Case of the Enteric System.” Orexins (orexin A and B) are novel neuropeptides that appear to play a role in the regulation of energy balances. First described as produced in the perifornical and lateral (LHA) hypothalamus area, these peptides have been recently reported as synthesized in other tissues including the enteric nervous system (ENS) and endocrine cells in the stomach, gut and pancreas. Orexin A increases food intake in rodents and orexin-containing neurons in both the lateral hypothalamic area and enteric nervous system, are activated by feeding. The ENS contains glucosensitive neurons; however, it is not known whether they contain orexin. In addition, orexin A immunoreactivity has been shown in blood but the source of blood orexin A is not known. Furthermore, recent report has shown differential mRNA expression of orexin receptor subtypes in peripheral organs indicating discrete peripheral effects of orexins and the existence of a peripheral orexin system. They propose to determine whether orexin-containing submucosal neurons are glucosensitive and “sense” intraluminal glucose and whether the mechanism of excitation by mucosal glucose involves KATP channels. They also propose to define the role played by orexins in the endocrine cells, and whether the expression of orexins in the bowel is linked to nutritional state.

Medical Student Research Fellowship 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 this field. 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 forty-six Medical Student Fellowships have been awarded since the program began in 1974.

Recipient of the Medical Student Research Fellowship that began in July 2002 is:
Joshua Fessel, Vanderbilt University, Division of Clinical Pharmacology: “Pathogenesis of Hypoxia-Induced Lung Injury Using Novel Products Of Lipid Peroxidation (isofurans) that Are Mediated by Oxygen Tension.” This research proposal proposes to determine the subcellular biochemical events underlying hypoxia-induced lung injury, or oxygen toxicity. The injury is thought to involve an oxidative insult to the lung, but this has never been conclusively shown. Their efforts will focus upon analyses of novel products of lipid peroxidation (isofurans) that are uniquely sensitive to elevated oxygen concentrations. They will examine in vitro the biochemical and functional changes that occur in the mitochondria (the most likely site for the conversion of molecular oxygen to a free radical) as a result of hyperoxic injury, with an emphasis on oxidative damage to the mitochondrial membrane and functional changes due to loss of membrane integrity. Subsequent to these investigations, they will pursue investigations in animal models to determine the utility of isofurans as a biomarker for oxygen toxicity, a condition for which no biomarker currently exists. The proposed studies should provide insights into the basic mechanism of oxygen toxicity and provide a starting point for more rationally designed therapies for the treatment or prevention of oxygen toxicity.

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 stresses 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 have been awarded, including the grants beginning on January 1, 2002.

Recipients of the Research Starter Grants that began in January 2002 are:
Amy Lee, Ph.D., Emory University: “Molecular Regulation of Neuronal Ca2+ Channels by Car-Binding Proteins.” Ca2+ entry through pre synaptic Ca2+ 2.1 (P/Q-type) channels initiates neurotransmitter release at most central synapses. Because small fluctuations in intracellular Ca2+ concentrations can cause large changes in synaptic efficacy, regulation of pre synaptic Ca2+ 2.1 channels can powerfully influence processes of information transfer and storage in the brain. They have shown that two similar Ca2+ binding proteins, CalM and CalB1, interact with the pore-forming α1 subunit of Ca2+ 2.1 channels, but with surprisingly different modulation effects on the channel. The results imply that interactions of Ca2+ 2.1 with CalB1, CalM, and/or other Ca2+ binding proteins may fundamentally determine the nature of pre synaptic Ca2+ signals and the functional consequences of synaptic activity. The goal of this proposal is to characterize the molecular regulation of Ca2+ 2.1 by CalM and CalB1 using techniques in molecular biology, biochemistry, and electrophysiology.

Accomplishing this goal will broaden the understanding of how CalM and other Ca2+ binding proteins may differentially regulate their targets and may reveal alternative pharmacological strategies for treating neurological disorders linked to Ca2+ 2.1 defects such as migraine, spinocerebellar ataxia, and epilepsy.

Jo El J. Schultz, Ph.D., University of Cincinnati, College of Medicine, Department of Pharmacology and Cell Biophysics: “Role of Protein Kinases in Fibroblast Growth Factor-2-Induced Cardioprotection.” The overall objective of this proposal is to investigate the signaling mechanisms underlying the cardioprotective effect of fibroblast growth factor-2 (FGF2). The pathway(s) triggered by FGF2 to elicit protection in the heart during ischemia is unknown; however, evidence indicates that in many cell types, FGF2 can signal through protein kinase C (PKC) and mitogen-activated protein kinase (MAPK). Both of these pathways have also been shown to be important in cardioprotection. A broad multidisciplinary approach will be established that will combine diverse techniques and will integrate genetic information at the molecular level with physiological information at the whole animal level. To ascertain the molecular mechanism(s) for FGF2-mediated cardioprotection, we will assess the biochemical patterns in activity of protein kinases that are either known to mediate FGF2 signaling or have been implicated in the development of cardioprotection. This will be done by determining which of these pathways is markedly altered during ischemia in wildtype, FGF2 knockout and FGF2 transgenic mice and correlating these molecular/biochemical changes with postischemic recovery of cardiac function and myocardial infarction. The results from this proposal will provide important new insights into molecular and signaling mechanisms of FGF2-induced cardioprotection and should facilitate the development of novel pharmacological and/or gene therapeutic strategies that improve and enhance cardiac resistance to ischemia in susceptible cardiac patients.

Kristen Mitchell, 2000 Fellow for Advanced Pre Doctoral Training in Pharmacology/Toxicology, College of Pharmacy, Washington State University.
Pre Doctoral Fellowships in Pharmaceutics

This program has been in effect for 14 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 2002.

Those who received fellowships that began between January and August 2002 are:

Megan E. Anderson, University of Kansas, Department of Pharmaceutical Chemistry: “Characterization and Optimization of ICAM-1 Peptide Conjugated to MTX.” The objective of this project is to utilize ICAM-1 peptide (i.e., CBR) to target a drug to activate T-cells that express leukocyte function associated antigen-1 (LFA-1). A cyclic peptide, CBR (ICAM-1,2,3,4,5,6) was characterized for its ability to bind LFA-1 and deliver MTX into T-cells. The research has found that CBR can bind to and internalize by LFA-1 receptor of T-cells. To further prove the internalization of CBR peptide, this peptide was conjugated with methotrexate (MTX); this MTX-CBR conjugate is as active as MTX to induce T-cell apoptosis. This suggests that conjugation did not change peptide’s conformation and infinity for LFA-1 receptor of T-cells. Neither was the binding capacity of MTX to dihydrofolate reductase (DHFR) significantly modified by conjugation. Furthermore, the selectivity of this drug delivery system was determined using the ability of LFA-1 antibody to reduce the CBR-MTX toxicity; this suggests that the conjugate was internalized by LFA-1 receptor. In this project, the first aim is to further characterize the properties of this drug-peptide conjugate by determining the degree of transport via LFA-1 receptor or reduced folate carrier, which normally transports MTX. The leukemic cell line, CEM-MTX, which does not express RFC and is resistant to MTX, will be utilized. The second aim is to develop smaller cyclic peptides in order to optimize LFA-1 binding and internalization. By residue screening, the research has shown that the sequence PRGG contained within CBR is essential for peptide activity. Therefore, the plan is to synthesize a hexapeptide-MTX conjugate containing the PRGG sequence and evaluate its LFA-1 binding and drug delivery properties in the same manner as MTX-CBR. In the future, the binding and internalization properties of the cyclic hexapeptide will be optimized by mutation studies.

Carol F. Kirchhoff, University of Illinois at Chicago, Department of Biopharmaceutical Sciences: “Physical Stabilization of Model Proteins through Interaction with PEGylated Phospholipid Assemblies,” dissertation work in academia, industry, and biotechnology and genomics, proteins, and biotechnology are leading to increased numbers of proteins being discovered or identified for use as drugs. From a formulation perspective, protein therapeutics are in their infancy, and pose challenging stability issues. Proteins are complex macro-molecules, which may undergo chemical as well as physical degradation resulting in the loss of bioactivity. In order to produce protein products with a marketable shelf life, they must be stabilized against these physical and chemical degradations. Several approaches have been used to physically stabilize proteins; these include chemical mutagenesis, chemical attachment of polyethylene glycol, and the addition of excipients. However, these techniques may compromise protein activity and/or induce toxicity. Here, they are assessing the potential for the effect of non-toxic PEGylated phospholipids (methoxy-PEG-dioleoyl phosphatidylethanolamine 2000 and 5000 DSPE-PEG 2000 and DSPE-PEG 5000) to physically stabilize a model protein, myoglobin. The overall hypothesis they are testing is that PEGylated phospholipids stabilize therapeutic proteins and increase their shelf life without reducing the bioactivity of the drug. Recent studies from their laboratory have shown that vasoactive intestinal peptide changes conformation, and increases stability and activity after association with DSPE-PEG mixtures. The preliminary data demonstrated Interleukin-2 was stabilized after interaction with DSPE-PEG 5000. Physical stability is being assessed at the

The PhRMA Foundation assisted me with my research by funding my first project as a faculty member. This research has been instrumental in establishing faculty status.

Jiping Tang, M.D., (center above), 2001 Research Starter Grant Award, Assistant Professor, Louisiana State University Health Sciences Center, School of Medicine.
isoelectric point (pI) of the protein. At the pI, the protein is electrically neutral and chemically most, but physically least stable. Here, they propose to use media pH to influence the deamidation rate, as pH is known to significantly affect the stability of proteins. They have chosen to study the deamidation of a Type I’ β-turn model peptide, KKYTVSINGKKITVSI, as a model system. The proposed research investigates the relationship between deamidation rate and secondary structure using this model peptide. The four specific aims of the research are: (1) to develop a stability indicating assay for the model peptide; (2) to characterize the extent of deamidation; (3) to determine the chemical stability of the model peptide and its controls; and (4) to correlate the degree of peptide folding to the deamidation rate. In Specific Aim 1, an HPLC stability-indicating assay has been developed and is sufficient for detecting the deamidation components. In Specific Aim 2, the secondary structure of the model peptide will be characterized using CD and NMR. In Specific Aim 3, the rate of deamidation will be studied in solutions of varying organic content. Factoring out the structure-independent effects of the solvent on the rate, it will correlate the deamidation rate with the degree of peptide folding (Specific Aim 4).

Post Doctoral Fellowships in Pharmaceutics

This program was initiated to encourage more qualified graduates to obtain 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.

Those who received fellowships that began between January and December 2002 are: LaToya Shantel Jones, Ph.D., University of Kansas: “A Biophysical Approach to Improving the Thermal Stability of Virus-Based Vaccines.” Although vaccines offer the most promising approach for the eradication of infectious diseases, the intrinsic instability of many vaccines, especially virus-based vaccines, limits their current use. They believe that the solution to this critical pharmacoeconomics issue lies in the rational selection of excipients and appropriate formulation conditions, which can best be determined by understanding the origin of the instability of the vaccine entity. Therefore, they propose to take a biophysical approach to characterize the physical changes of adenovirus and aden-associated viruses (AAV), which serve as model vaccines for this study, occurring when the viruses are stressed. Characterization will be facilitated using spectroscopic, calorimetric, hydrodynamic and light scattering techniques. The results from these studies will then be used to develop high-throughput screening assays to determine the effectiveness of GRAS excipients and a number of doubly and singly charged peptide and PEG molecules as stabilizers for the model vaccines. Since some of the biophysical techniques (e.g., DSC) are not amendable to high-throughput screening assays, extensive characterization of Ad and AAV in the presence of excipients will be limited to those identified as potentially stabilizing. Finally, as a test of proof of concept of this approach, storage stability of Ad and AAV in the presence and absence of the potentially stabilizing excipients will be assessed.

Lisa Kueblitz, Ph.D., University of Colorado Health Sciences Center: “Investigation into Protein Aggregation: Predisposing Factors and Early Events.” Protein aggregation is a phenomenon of significant importance to both the pharmaceutical and medical fields, both for its involvement in disease pathology and its detrimental impact on pharmaceutical protein formulations. Although the field has been widely investigated, there are specific areas that need a more thorough treatment before they can fully begin to understand the processes of protein aggregation and how to effectively circumvent them. This project investigates the formation of aggregates by attempting to characterize aggregation prone intermediate states employing high-pressure methods. Using other biophysical methods, factors such as pH, temperature and excipients will be considered in regard to their effects on protein aggregation, and attempts will be made to predict the propensity for specific formulations to form aggregates. Finally, the effect of excipients and additives on the inhibition of aggregation will be studied. These studies will focus on two models: monoclonal antibodies have been chosen as the pharmaceutical model, based on their increasing prevalence in current disease treatments. Beta-microglobulin will serve as the pathological model, as it has been implicated in hemodialysis related amyloidosis, a condition affecting most diabetic patients who undergo long-term dialysis.
Sabbatical Fellowship in Pharmaceutics

This is a new program for the PhRMA Foundation. The program provides stipend funding to enable faculty members at all levels with active research programs an opportunity to work at other institutions for periods of six months to one year to learn new skills or develop new collaborations that will enhance their research and research training activities in pharmaceutics. The Sabbatical Fellowship provides up to $40,000 for one year of stipend funding.

Receiving the Fellowship that began between January and December 2002 is:

Jeffrey A. Hughes, Ph.D., University of Florida, Department of Pharmaceutics: “Chemical Strategies for Nucleic Acid Delivery.” The overall goal of this sabbatical fellowship is to educate/re-educate the candidate in classical thermodynamics and how these principles can be applied to drug delivery systems. During this leave, an important factor will be providing time for reflection over the efforts that have been made in the past few years and planning for the next ten. Even though education is an important parameter, Dr. Hughes is looking forward to being back in the laboratory in a more dedicated manner to continue investigations with novel non-viral delivery systems since hands-on work in the laboratory is an excellent learning situation. The research application will focus on the characterization of novel non-viral delivery systems using an AAV based plasmid in the supercoiled form to produce novel vectors that permit neuron and glial transfection in vivo. These studies include detailed methods of vector production along with methods to assay for particle size and polydispersity, transfection efficacy, and parenchymal toxicity. The proposed studies fit well into the suggested mentors (Dr. Behr) current research projects. Dr. Behr is a leader in the field of non-viral gene therapy. In specific, they will: (1) test the hypothesis that novel lipids based on disulfide bond permits non-viral transfection of multiple cell types in neurons and the adult rat septum for extended periods of time; and (2) test the hypothesis that reducing the Liposome/DNA complex size increases the spread and efficiency of gene transfer in novel systems and the rat septum, using a combination of in vivo measurements of gene expression and in vivo MRI analysis of particle spread.

Research Starter Grant in Pharmaceutics

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 these 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 2002 is:

Carol S. Lim, Ph.D., University of Utah: “Cellular Kinetics of the Delivery of Drug-Receptor Complexes to Nuclear Targets.” The major focus of this research is to investigate steroid hormone receptor action at a molecular level to study the real-time kinetics and delivery of drug ligand-receptor complexes to the nucleus at a molecular level. This will employ a model system that uses green fluorescent protein-tagged progesterone receptor in living cells to test the activity (and even potency) of steroid drugs, and to determine the subcellular compartmentalization and nuclear accumulation pattern of drug-occupied steroid receptors in living cells. Subcellular compartmentalization and nuclear accumulation are important parameters to measure in terms of drug accessibility to nuclear targets (genes). Additionally, receptor interactions with other critical protein factors (coactivators and corepressors) will be tested to determine drug agonist vs. antagonist specificity. This proposal will test the feasibility of measuring cellular kinetics of drug-receptor complexes. The human progesterone receptor B isofrom (PRB) will be used as a model receptor. The major focus of this project is: (1) to correlate the rate of import into the nucleus of drug-occupied PRB to the dose of drug and hence the transcriptional activity of the drug; (2) to correlate nuclear accumulation patterns of antagonist-occupied PRB with the mechanism of action of drug antagonists (DNA-binding or non-DNA binding antagonist drugs); and (3) to detect colocalization of PRB with other protein factors in the cell, such as coactivators or corepressors, after the addition of drug.

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.
The PhRMA Foundation ended 2001 in sound financial shape. During 2001, most of the PhRMA member companies contributed according to our new formula. Contributions were up 45% from the previous year, to $2.73 million. More than $1.3 million was awarded in grants, and total expenditures were $1.7 million. These grants were the last paid under the old program, and the higher level of contributions was necessary as an advance commitment so that the new program could be implemented in late 2001. Total net assets at year-end were $6.58 million. Of this amount, $4.21 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 2002, contributions are targeted at the same level, as we enter the second year of our new program. On behalf of the Board and staff, I give special thanks to the continuing support of our generous contributors, who are listed in this report.

The Foundation’s financial position as of December 31, 2001, has been audited by the Rosslyn, Virginia, accounting firm of Buchanan & Company. A full report can be obtained by contacting the Foundation.

Richard J. Markham
Treasurer, PhRMA Foundation
and Vice Chairman of the Management Board and Chief Operating Officer Aventis

The PhRMA Foundation would like to thank Irwin M. Weiner, M.D. for his twenty years of dedicated service and leadership. Ike served on the Basic Pharmacology Advisory Committee from 1981 through 2001, first as a committee member and then also as chairman of the committee. We are indebted to Ike for all of his efforts over the past two decades for the PhRMA Foundation.
## Statement of Income and Expenditures
For the Year Ended December 31, 2001

### INCOME

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<tr>
<th>Description</th>
<th>Amount</th>
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<tr>
<td>Contributions</td>
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<td>Interest and Dividends</td>
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<td>(Loss) on Disposition of Fixed Assets</td>
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<td>Other Income</td>
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<td><strong>Total Income</strong></td>
<td><strong>$2,489,544</strong></td>
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### EXPENDITURES

#### Programs

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<td>Awards in Excellence</td>
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<tr>
<td>Faculty Awards in Clinical Pharmacology</td>
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<tr>
<td>Faculty Development Awards in Basic Pharmacology</td>
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<tr>
<td>Fellowships for Careers in Clinical Pharmacology</td>
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<tr>
<td>Pre Doctoral Fellowships in Pharmacology/Toxicology</td>
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<tr>
<td>Pharmacology/Morphology Fellowships</td>
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<td>Medical Student Fellowships</td>
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<td>Research Starter Grants</td>
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<tr>
<td>Pre Doctoral Fellowships in Pharmaceutics</td>
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<td>Undergraduate Fellowships in Pharmaceutics</td>
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<tr>
<td>Post Doctoral Fellowships in Pharmaceutics</td>
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<tr>
<td>Faculty Development Awards in Pharmacoeconomics</td>
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<td>Faculty Development Award in Bioinformatics</td>
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<td>AFPE Fellowship Award</td>
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<td><strong>Subtotal--Grants</strong></td>
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#### Other

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<tr>
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<tr>
<td>Committee Meetings, Travel and Honoraria</td>
<td>90,036</td>
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<tr>
<td>Publications and Special Projects</td>
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<td><strong>Subtotal--Other</strong></td>
<td><strong>$121,887</strong></td>
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#### Program Total

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<tr>
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#### Administrative

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<tr>
<td>Staff, Rent, Taxes and Insurance</td>
<td>233,632</td>
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<tr>
<td>Professional Services and Investment Expenses</td>
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<td>Office Expenses</td>
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<td><strong>Subtotal--Administrative</strong></td>
<td><strong>$289,991</strong></td>
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### TOTAL EXPENDITURES

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
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</thead>
<tbody>
<tr>
<td><strong>TOTAL EXPENDITURES</strong></td>
<td><strong>$1,748,603</strong></td>
</tr>
</tbody>
</table>
Advisory Committees

The PhRMA Foundation would like to congratulate Darryle D. Schoepp, Ph.D. (1985 RSG) Executive Director, Neuroscience Research Division, Lilly Research Laboratories, for receiving the 2002 Pharmacia-ASPET Award in Experimental Therapeutics. Shown here receiving the award from Marlene Cohen, Ph.D., Lilly Research Fellow, ASPET President 2001-2002 at the ASPET Annual Meeting, April 2002, New Orleans, Louisiana
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Pharmaceutical Research Consulting
FMR Research Associates Inc.
Glenview, Illinois

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Eli Lilly and Company
Indianapolis, Indiana

Patricia Seymour, Ph.D.
Principal Research Investigator
Pfizer Global Research & Development
Groton, Connecticut

Stephanie W. Watts, Ph.D.
Associate Professor
Michigan State University
Department of Pharmacology and Toxicology
East Lansing, Michigan

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P H A R M A C O L O G Y

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Chief, Laboratory of Investigation Gerontology Research Center
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Clinical Center
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Clinical Pharmacology
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PhRMA FOUNDATION STAFF

Del Persinger President and Chief Executive Officer

Eileen McCarron Director of Development

Elaine Dorsey Associate
The PhRMA Foundation owes its success to the pharmaceutical companies that have provided their generous support over the past 37 years. We thank all of you for continuing to invest in the future of pharmaceutical research and the scientists of tomorrow.

Our 2002 Benefactors are:

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- Abbott Laboratories
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- Amgen, Inc.
- AstraZeneca LP
- Aventis Pharma AG
- Berlex Laboratories, Inc.
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Novartis Pharmaceuticals Corporation
- Organon Inc.
- Pfizer Inc
- Pharmacia Corporation
- PhRMA
- Reed Exhibition Companies
- The Procter & Gamble Company
- Sanofi-Synthelabo Inc.
- Schering-Plough Corporation
- Schwarz Pharma, Inc.
- Solvay Pharmaceuticals, Inc.
- Wyeth Pharmaceuticals
- Yamanouchi Pharma America, Inc.

Andrew T. Bender, 2001 Fellow for Pre Doctoral Training in Pharmacology/Toxicology, University of Washington, Department of Pharmacology
## PhRMA Foundation Programs for 2003

**PhRMA Foundation Programs for 2003**

<table>
<thead>
<tr>
<th>Name of Program/Year of First Awards</th>
<th>Number of Awards</th>
<th>Length of Award</th>
<th>Program Budget</th>
<th>Deadline Announcement Date/Starting Time</th>
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<tbody>
<tr>
<td><strong>Health Outcomes Advisory Committee</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre Doctoral Fellowships in Health Outcomes (2002)</td>
<td>2 budgeted/2 years</td>
<td>$80,000 total</td>
<td>$20,000 per award per year</td>
<td>October 1, 2002/January-August</td>
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<tr>
<td>Post Doctoral Fellowship in Health Outcomes (2002)</td>
<td>1 budgeted/2 years</td>
<td>$80,000 total</td>
<td>$40,000 per award per year</td>
<td>October 1, 2002/January-December</td>
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<tr>
<td>Sabbatical Fellowship in Health Outcomes (2002)</td>
<td>1 budgeted/1 year</td>
<td>$40,000 total</td>
<td>$40,000 per award per year</td>
<td>October 1, 2002/January-December</td>
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<tr>
<td>Research Starter Grants in Health Outcomes (2002)</td>
<td>3 budgeted/2 years</td>
<td>$180,000 total</td>
<td>$30,000 per award per year</td>
<td>October 1, 2002/January 1, 2003</td>
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<tr>
<td><strong>Informatics Advisory Committee</strong></td>
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<td></td>
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<tr>
<td>Post Doctoral Fellowships in Informatics (2002)</td>
<td>3 budgeted/1 to 2 years</td>
<td>$160,000 total</td>
<td>$40,000 per award per year</td>
<td>September 1, 2002/January-December</td>
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<td>Sabbatical Fellowship in Informatics (2002)</td>
<td>1 budgeted/1 year</td>
<td>$40,000 total</td>
<td>$40,000 per award per year</td>
<td>September 1, 2002/January-December</td>
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<tr>
<td>Research Starter Grants in Informatics (2002)</td>
<td>3 budgeted/2 years</td>
<td>$180,000 total</td>
<td>$30,000 per award per year</td>
<td>September 1, 2002/January 1, 2003</td>
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<tr>
<td><strong>Pharmacology Advisory Committees</strong></td>
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<tr>
<td>Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)</td>
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<tr>
<td>Post Doctoral Fellowships in Pharmacology/Toxicology (2002)</td>
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<td>Sabbatical Fellowship in Pharmacology/Toxicology (2002)</td>
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<td>Research Starter Grants in Pharmacology/Toxicology (1972)</td>
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<td>Medical Student Fellowships (1974)</td>
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<td>Pre Doctoral Fellowships in Pharmaceutics (1987)</td>
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All of the above programs will accept applications for research on drugs for rare diseases

[www.phrmafoundation.org](http://www.phrmafoundation.org)