

2003 ANNUAL REPORT







Pharmaceutical Research and Manufacturers of America Foundation

C O N T E N T S



Andrew T. Bender, 2001 Fellow for Pre Doctoral Training in Pharmacology/Toxicology, Vanderbilt University, Department of Pharmacology

Photographs throughout this year's Annual Report highlight some of the PhRMA Foundation past awardees.

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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.

CHAIRMAN'S MESSAGE



Tadataka Yamada, M.D.

FROM ITS INCEPTION 38 YEARS AGO, THE PhRMA FOUNDATION HAS

achieved both industry endorsement and academic recognition for its programs to encourage the pioneering efforts of young scientists in pharmacological research. The academic community views our awards as some of the most prestigious available to young scientists at the onset of their careers. In 2000, to keep pace with advances in the industry, we implemented a redesigned, revitalized program to concentrate focus on the cutting edge-scientific disciplines that would grow in importance in the 21st century.

The success of this program over the past three years has been tremendous. Applicants for our career-starting grants and fellowships are more qualified than ever and have increased across the board. In some disciplines—Health Outcomes, for example—increases of 200% have been seen. Most important, the generosity of our contributors has made it possible to grow our program substantially—by 50% over the past three years. These developments make it clear that, not only are we engendering greater industry support, we are accomplishing our primary mission of encouraging more scientists to specialize in the disciplines vital to the progress of research in this infant century.

As the next logical step in our revitalized efforts, we have established two significant goals that will expand the reach and potential of our programs. First, we want to enhance our core scientific program, while maintaining its commitment to excellence and its focus on the cutting edge of science. Second, building on the Foundation's programs and relationships, we will work to communicate to a broad audience the pharmaceutical industry's commitment to research and the development of new cures and treatments for patients.

As the first step toward achieving these goals, we have changed the composition of the Foundation Board. We have retained CEOs, but we also

have added corporate R&D heads to the mix. In addition to myself, six other R&D leaders now serve as Directors:

- Peter Corr of Pfizer Inc, Foundation Vice Chairman
- Frank Douglas of Aventis, Foundation Treasurer
- Steven Paul of Eli Lilly and Company
- Cecil Pickett of Schering-Plough Research Institute
- James Palmer of Bristol-Myers Squibb Company
- Bob Ruffolo of Wyeth

Since new science is proposed every year by the Foundation's award applicants, these Directors will get an insider's view of the research that is being conducted in the country's top-notch universities and can provide the Foundation with informed guidance and insight into the scientific disciplines we are promoting.

The second critical step is communicating to the broadest possible audience our industry's commitment to research and the importance of research. This commitment has been evidenced throughout our history of supporting young scientists and through initiatives such as academic centers of excellence. It is these programs that benefit young scientists and the academic community in general that we will leverage to convey the importance of research and the value of medicines to key audiences. Finally, we will continue to rely on our past award winners as ambassadors to carry news of what we are doing to the broader research community.

It is my pleasure to chair the Foundation Board and to preside over this exciting time in our continuing development. In 2003, with the successful programs outlined here, and with a staff in place to keep them all in motion, we were able to apply almost 90 percent of all Foundation contributions directly to our awards program. We remain indebted to the generosity, dedication, and goodwill of all of our contributors. We urge you to continue to support our outstanding organization that is an existing representation of the industry's commitment to pharmaceutical research and to the young scientists of today. Our goal is for 100% participation from our member companies. With full support, we can best accomplish our mission, ensure our commitment to excellence, generate increased visibility for our commitment to pharmacological research, and herald the success of the Foundation's programs well into the future.

Kristen Mitchell (right), 2000 Fellow for Advanced Pre Doctoral training in Pharmacology/Toxicology working with Dr. B. Paige Lawrence, Assistant Professor, College of Pharmacy, Washington State University



Thank you.

PRESIDENT'S MESSAGE



Del Persinger

AS EILEEN McCARRON, OUR DEVELOPMENT DIRECTOR, AND I HAVE

traveled around the country this past year to present the Foundation awards, we have met regularly with past awardees as well as the 22 academic leaders who serve on the award review committees. This is the third year we have presented the awards at the annual meetings of the scientific societies in disciplines we support—pharmacology/toxicology, clinical pharmacology, pharmaceutics, and health outcomes.

It has been both gratifying and enlightening to learn, as we speak with some of the 10,000+ scientists who attend the annual meetings, how well known the PhRMA Foundation awards have become and the high esteem in which they are held in academic circles around the country. We hear time and again that our awards are considered to be real career starters that open the door to major career funding.

We also held private receptions for past awardees at all these meetings, where we are continually told that our awards have been critical to their career development. We have hosted, among others, distinguished professors, department chairs, deans, chancellors, and vice presidents, all of whom have expressed their deep gratitude for our assistance. After 38 years of building relationships and trust, the Foundation has a deep reservoir of goodwill among our alumni, who come from all over the country and represent a broad range of disciplines and disease specialties.

In 2003, we surveyed our past awardees and garnered some statistics that support this view of our awards as career starters. Of the hundreds who responded to the survey, 85% stated they had received other funding after receiving our award. Respondents reported that they used PhRMA Foundation funding to organize and develop their research plans. National funding, usually provided by such major institutions as NIH and NSF, was a follow-up to the work funded by our grants and often supports these scientists throughout their careers. We are tremendously proud of the scientists we support and of their accomplishments. We also, however, must pay tribute to our advisory committee members whose assistance in helping us identify the best and the brightest recipients at such an early point in their careers is critical to the success of our awards program. The knowledge and dedication of these committee members have enabled the Foundation to make a lasting contribution to the development of young scientists, and we are indebted to them for their efforts, past, present, and future.

Many of the academic representatives on our review committees firmly believe in the importance of building stronger relationships with industry, and we are exploring new ways to promote these relationships. We will look to involve our new Board members, who are R&D leaders in the industry and stakeholders in the work of the Foundation, in this effort and in our other programs. We look forward to working closely with our new directors, and we believe they will bring a great deal of energy, enthusiasm and ideas that will provide immense benefit to the Foundation.

Looking to the future, the Foundation increasingly will emphasize the pharmaceutical industry's commitment to research and the importance of research in developing new cures and treatments. As always, we depend on the generosity of our member companies that are on the frontline in the neverending war against disease to support this work. We will continue to maintain and enhance a Foundation program that is highly visible, builds goodwill, fosters strong ties between the industry and the academic community, and remains a source of pride to our contributors and award recipients alike. We thank you and look forward to working with you in the coming year.

Jiping Tang, M.D. (right), 2001 Research Starter Grant recipient, Assistant Professor, Louisiana State University Health Sciences Center, School of Medicine



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AWARDS IN EXCELLENCE

THE ANNUAL PhRMA FOUNDATION AWARDS IN EXCELLENCE HONOR

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

The two awardees for 2003 exemplify the very best in their chosen fields of clinical pharmacology and pharmacology/toxicology. The Foundation is proud of their achievements and is gratified to have been of assistance to them at the beginning of their outstanding careers. Their successes typify the outstanding achievements of all of our awardees and underscore the importance of continuing support to those who follow in their footsteps.

The recipients of the PhRMA Foundation Awards in Excellence for 2003 are Richard M. Weinshilboum, M.D., and Edward Bresnick, Ph.D. Dr. Bresnick passed away on March 26, 2003, several months after the recipients were chosen, and his award was presented posthumously to his wife. Dr. Weinshilboum received his award on April 2, 2003, in Washington, DC at the Annual Meeting of American Society of Clinical Pharmacology and Therapeutics.

RICHARD M. WEINSHILBOUM, M.D.

2003 Award in Excellence in Clinical Pharmacology

Dr. Weinshilboum received B.A. and M.D. degrees from the University of Kansas, and completed his residency training in Internal Medicine at the Massachusetts General Hospital, a Harvard teaching hospital, in Boston. He was also a Pharmacology Research Associate at the National Institutes of Health in Bethesda, Maryland, in the laboratory of Nobel laureate Dr. Julius Axelrod. In 1972, Dr. Weinshilboum began his affiliation with the Mayo Medical School and Mayo Clinic in Rochester (MN), where he is presently Professor of Molecular Pharmacology and Experimental Therapeutics and Internal Medicine. Dr. Weinshilboum's research has focused on pharmacogenetics and pharmacogenomics, and he has authored more than 250 scientific manuscripts that address these topics. His major area of investigation has been the pharmacogenetics of drug metabolism, with a focus on methylation and sulfation.

Del Persinger speaking at the Annual Meeting for the American Society for Clinical Pharmacology and Therapeutics



Dr. Weinshilboum has been the recipient of many awards and honors including an Established Investigatorship of the American Heart Association, a Burroughs Wellcome Scholar Award in Clinical Pharmacology, the Oscar B. Hunter Award of the American Society for Clinical Pharmacology and Therapeutics, the Harry Gold Award of the American Society for Pharmacology and Experimental Therapeutics and the Catecholamine Club Julius Axelrod medal. In 1973, The PhRMA Foundation gave him the Faculty Development Award in Clinical Pharmacology.

EDWARD BRESNICK, PH.D.

2003 Award in Excellence in Pharmacology/Toxicology

Dr. Bresnick will be remembered as a scientist and educator who inspired those he mentored and who engendered strong mutual loyalties with those trained in his lab. During his career, he mentored 26 graduate students to degrees at six universities, as well as mentoring 38 postdoctoral fellows. Many of his postdoctoral fellows remained with him as faculty, and it is notable that he essentially retired so he could work in the lab of a former post doc, Alan Eastman, at Dartmouth.

Dr. Bresnick received his B.S. from St. Peters College and then moved to Fordham University where he received an M.S. in Chemistry in 1954 and a Ph.D. in Biochemistry in 1958. He began his early career as a Senior Biochemist with the Wellcome Research Laboratories but then moved into an academic track at Baylor College of Medicine, being promoted from Assistant Professor to Professor. Dr. Bresnick received a Research Starter Grant from the Foundation in 1971. He then took on several leadership roles, first as Professor and Chair of Cell and Molecular Biology at the Medical College of Georgia, then Professor and Chair of Biochemistry at the University of Vermont College of Medicine. He also served as Professor of Oncology and Director of the Eppley Institute for Research in Cancer and Allied Diseases; Professor and Chair, Department of Pharmacology and Toxicology at Dartmouth Medical School; Director of the Norris Cotton Cancer Center at Dartmouth; and Vice Chancellor for Research and Professor of Pharmacology and Medicine, at the University of Massachusetts Medical Center. He was a prominent member of many national committees and organizations, serving as President of the American Association for Cancer Research and a member of the ISSX Publications Committee. Dr. Bresnick served on the Editorial Boards or as an Associate Editor of numerous prominent journals, and also as Editor of Toxicology and Applied Pharmacology.

Dr. Bresnick was first and foremost an educator and was dedicated to training the next generation of scientists. His scientific contributions and his service to his beloved profession are themselves enormous, but his greatest legacy is the group of scientists he mentored into productive research careers. Through them, his influence will remain on the scientific landscape for decades to come.

Richard M. Weinshilboum, M.D. (left) of the Mayo Clinic is accepting the 2003 Award in Excellence in Clinical Pharmacology from Del Persinger at the ASCPT Annual Meeeting

On April 2, 2003 the **PhRMA Foundation presented** the 2003 Award in Excellence **Award in Clinical** Pharmacology to Richard M. Weinshilboum, M.D. during the **Annual Meeting for the American Society for Clinical Pharmacology and Therapeutics in** Washington, DC at the Marriott Wardman Park Hotel. We are grateful for this opportunity and we thank **ASCPT** for this special opportunity.



R&D LEADERS OF TODAY

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 grant that I received from the PhRMA Foundation allowed me to start my research career with enough support to set up my laboratory. Without that support I would not have been able to successfully climb the academic ladder".

Daniel Acosta, Jr., Dean, College of Pharmacy, University of Cincinnati

"The PhRMA award was pivotal in facilitating the development of my own academic career and in my current position I have seen how important these awards remain to current awardees"

Alastair J.J. Wood, M.D., Assistant Vice Chancellor, Professor of Medicine, Professor of Pharmacology, Vanderbilt University School of Medicine

"The Research Starter Grant program enabled me to rapidly pursue a very novel idea. With these funds I could generate the preliminary data needed for a successful federal grant application. It was a tremendous boost to my laboratory at a very critical juncture of my career."

Darryle D. Schoepp, Ph.D., Executive Director, Neuroscience Research, Lilly Research Laboratories,Eli Lilly and Company

"PhRMA Foundation funding of a grant early in my career was critical to jump-starting my academic research in drug metabolism, and has been equally important in helping several of our School's junior faculty."

Sid Nelson, Ph.D., Professor of Medicinal Chemistry and Dean, School of Pharmacy, University of Washington

"The encouragement and financial support of an award from the PhRMA Foundation was most important and timely in helping me establish an independent research career. I particularly enjoyed the opportunity to meet with other awardees and learn about their work."

> Sue Piper Duckles, Ph.D., Professor and Associate Dean, University of California, Irvine, Secretary-General, International Union of Pharmacology

"By coming earlier in my career, the research support from the PhRMA Foundation played a critical role in my ultimately obtaining federal funding. For nearly three decades I have turned to the PhRMA Foundation to help launch the careers of fellows and junior faculty. In all cases these grants have been of benefit in fostering training or establishing a laboratory. The returns on these investments have been enormous."

> Salvatore J. Enna, Ph.D., Professor and Chairman, University of Kansas Medical Center, Past President of ASPET

"The funding I received from the PhRMA Foundation early during my academic career allowed me to subsequently establish a productive research and training program which has produced a number of prominent scientists."

Mustaga F. Lokhandwala, Ph.D., Professor of Pharmacology, College of Pharmacy, University of Houston

"Support from the PhRMA Foundation came at a crucial time when I was starting my career in academia. It was a morale booster at a point when one was truly needed and the funding permitted me to generate key data that provided a basis for future successful grant applications. Thank you PhRMA Foundation!"

> Jay I. Goodman, Ph.D., Professor, Michigan State University, Past President of the Society of Toxicology

"The PhRMA Foundation support for careers in Clinical Pharmacology over the last 30 years has been vital to our discipline and to many individuals like myself that made a commitment to pursue this field of research. My sponsor and mentor was himself a PhRMA Foundation awardee, and I am pleased to see that one of my former fellows is currently a recipient of a PhRMA Foundation Faculty Development Award."

Juan J.L. Lertora, M.D., Ph.D., Head, Section of Clinical Pharmacology, Program Director, General Clinical Research Center, Tulane University Health Sciences Center

"Without the support from the PhRMA Foundation, my career path may not have turned out as well as it is today. Keep up the good work!"

> Sunny E. Ohia, Ph.D., Dean, Professor of Pharmacology, College of Pharmacy, University of Houston



David R. Linden, Ph.D., 2001 Fellow in Pharmacology/Morphology in his lab at the University of Vermont

FELLOWSHIPS AND GRANTS



My PhRMA Foundation Fellowship in Informatics has provided me with the resources to begin developing computational tools to analyze the colossal amount of genomic data to study proteins encoded in their genomes.

> Michael L. Goodson, Ph.D., 2002 Post Doctoral Fellowship in Informatics, University of California, Davis

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

INFORMATICS

Post Doctoral Fellowships in Informatics

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

The post doctoral award consists of a \$40,000 annual stipend for up to two years. The second year of this award is contingent upon a progress report approved by the Foundation and submission of a financial report. The award is intended solely as a stipend and may not be used otherwise. Receiving the fellowships that began between January and December 2003 are:

William G. Fairbrother, Ph.D.,

Massachusetts Institute of Technology: "Predictive Inhibition of Exonic Splicing Enhancers." Estimates of the total number of coding SNPs (cSNPS) in the human genome range between 250,000 and 400,000. Although most SNPS represent selectively neutral alleles that do not disrupt the function of the gene in which they reside, a great deal of interest has recently been focused on the possibility that some SNPs do have functional consequences. As approximately 10-15% of all possible base changes in human exons have been estimated to result in the disruption of an exonic splicing enhancer (ESE), ESEs represent a broad target for the disruption by SNPs. This proposal utilizes a combination of novel computational approaches and experimental validation to identify cases where SNPs disrupt ESEs. These cases would represent good candidates for association studies to determine the roles of these alleles in relatively common conditions like hypotension, type II diabetes, and schizophrenia. The first part of this proposal tests the hypotheses that the requirement of an exon to include ESEs accounts for the limited spectrum of synonymous substitutions observed. Dr. Fairbrother then proposes to use this information to identify uncharacterized sequence variants that may alter splicing phenotypes.

Sean G. Megason, Ph.D., California Institute of Technology: "Imageomics: High-through Acquisition of in vivo Data Using Imaging." Integrating the vast amounts of data that are being generated by genomics and other highthroughput technologies into a cohesive and useful body of knowledge is essential to reaping their benefits. There is currently a strong need to develop technologies for acquiring in vivo, cell-based data in a digitized, integratable format. The research proposed here seeks to develop methods for automatically identifying (segmenting) every single cell in confocal image sets of whole zebrafish embryos and digitizing this information into an integrated database. They will generate transgenic fish that contain a single, bright, well-resolved fluorescent spot in each nucleus using lacl-EGFP to integrated lacO sites. These spots will allow every cell in the embryo to be segmented. The shape of each cell will be determined using a membrane bound red fluorescent protein. This information will be stored in a database to allow for annotation of the data, reconstruction, and visualization. They will use this technology to first construct a cell-based, 3D, digital atlas of zebrafish development and to then determine the nearly complete 4D cell lineage of zebrafish. In future work, this approach will be used to scan in gene expression patterns and other types of *in vivo* data with cellular resolution into the database in high-throughput to enable systems biology based approaches to understanding molecular pathways.

Edith D. Wong, Ph.D., University of California, San Francisco: "Examination of Genome Instability in Plasmodium Falciparum Using Functional Genomics." Malaria is a deadly disease that annually infects 300 to 500 million people, killing 1.5 to 2.7 million people, typically young children. Most of these deaths result from infection by Plasmodium falciparum. Extended misuse of a small number of inexpensive anti-malarials has contributed to the emergence of resistant strains, rendering these drugs ineffective. Thus, a deeper biological knowledge of the organism, which will fuel the development of new anti-malarials, is greatly needed. Additionally, vaccine development has been significantly hindered by a high rate of antigenic variation. However, the extent to which the organism manipulates its genome to evade the host immune response is unknown. To further understand pathogenesis, this study proposes to use functional genomics to characterize the nature and extent of P. falciparum genome plasticity. It will utilize a whole genome P. falciparum microarray developed by the DeRisi laboratory to shed light on the organism's ability to manipulate its genome in response to environmental stimuli. The study will: (1) examine the extent of genomic variability in P. falciparum strains by using comparative genomic hybridization (CGH) to determine deletion and amplification sites in existing strains; (2) use CGH to study whether particular environmental conditions induce genome rearrangements; and (3) determine whether sites of genome rearrangements are regulated during meiosis by using the *P. falciparum* microarray to map potential hot spots and cold spots of meiotic recombination. These studies will elucidate fundamental aspects of genome instability in *P. falciparum*, leading to novel drug and vaccine targets.

Research Start Grants in Informatics

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

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

"starter" aspect of the program strives to assist those individuals who are establishing careers as independent investigators. The program is not offered as a means to augment an ongoing research effort.

Receiving the grants that began in January 2003 are:

Jessica C. Kissinger, Ph.D., University of Georgia: "Pattern Finding and Phylogenetic Restriction in the Trypanosoma Cruzi Genome." Trypanosoma cruzi, the causative agent of Chagas' disease is currently estimated to infect 16-18 million people in the Americas and it threatens the blood supply and organ donations in many countries, including the US. This proposal seeks to address issues relevant to the treatment and prevention of Chagas' disease using bioinformatics approaches. Computational tools will be extended and developed to permit the identification of genes that are unique, i.e. phylogenetically restricted to T. cruzi, which may serve as potential therapeutic targets. This comparison is possible because the genome sequences of two related kinetoplastid parasites are nearly complete and the genome sequence of T. cruzi is in progress. A second aspect of the research involves the identification of genes that are coordinately regulated during key developmental stages in the parasite lifecycle that may prove to be viable vaccine candidates. Post-transcriptional regulation appears to play a prominent role in T. cruzi. Similarity searches and de novo patternfinding algorithms will be applied to 3' UTR sequences to look for existing and novel regulatory regions. Candidate genes will be assessed in a high-throughput vaccine screen.

Christina S. Leslie, Ph.D., Columbia University: "Computational Learning from Complex Biological Data."This research focuses on two projects related to fundamental learning problems in computational biology: protein homology detection and inference of regulatory networks from gene expression data. For the first problem, the research plan is to continue development of their new and highly successful discriminative approach to protein classification based on support vector machine (SVM) classifiers with "string kernels" for biological sequences. This method achieves both powerful homology detection and fast prediction; therefore, it is scalable to very large datasets and complex multi-class problems. They will implement a robust online multi-class domain prediction system: given a multidomain protein sequence query, the system will predict both the location and family label of the domains in the guery sequence. This work will involve new algorithms for multi-class SVM classification and approaches for optimizing local predictions. It also incorporates new



David A. McClellan, Ph.D., Assistant Professor of Integrative Biology, Brigham Young University, 2002 Research Starter Grant in Informatics

The PhRMA Foundation would like to thank the International Society for Pharmacoeconomics and Outcomes Research for inviting us to present our 2003 Awards in Health Outcomes at ISPOR's eighth annual international meeting. This special presentation was held in Arlington, Virginia, on May 20, 2003. The PhRMA Foundation funding helped start a project that I received NIH funding to complete. It also enabled me to complete a project that will be submitted for publication.

Marc Lipsitch, D.Phil., 2002 Research Starter Grant in Health Outcomes, Assistant Professor, Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts



ideas for using unlabeled data-a large database of protein sequences without structural or functional annotations-to improve performance of their SVM-string kernel classifiers. For the second problem, they will develop a new approach to inferring gene regulatory networks from time series gene expression data based on dynamic Bayes net models. The goal is to learn the structure of interactions between sets of genes, such as activation, inhibition, and mediation, using methods that are robust to the sparse and irregularly sampled time series datasets currently available. This plan proposes a robust approach of first learning statistical spline models for sets of coexpressed genes and then computing mutual information scores based on these models to learn the structure of the regulatory network. This lab is working both with publicly available yeast datasets and with new human expression data from the lab of their biological collaborator, Dr. Erwin Bottinger at Albert Einstein Medical School. The human time series data comes from epithelial cells induced with transforming growth factor data (TGF-b), an important factor linked with human diseases processes such as cancer, making it a highly relevant system for computational study.

HEALTH OUTCOMES

Pre Doctoral Fellowships in Health Outcomes

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

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

Receiving the fellowships that began between January and August 2003 are:

Joette M. Gdovin, University of South Carolina: "Herpes Zoster (shingles) and Postherpetic Neuralgia: Incidence and Costs of Disease Among Medicare Beneficiaries 65 Years and Older." Herpes zoster (HZ) or shingles is a common cause of morbidity in the older adult population. Postherpetic neuralgia (PHN) is a severe, disabling complication of HZ. Yet there are no current population-based estimates on the incidence and costs of HZ or PHN. The research in this proposal will fill this gap in the literature. This research has three objectives: (1) Provide current population-based estimates on the incidence of HZ and PHN in Medicare beneficiaries ≥65 years; (2) Estimate the current medical costs associated with HZ disease and PHN in Medicare beneficiaries \geq 65 years; and (3) Gain knowledge through the development of research methods for cost-effectiveness analysis utilizing Medicare claims data. Methods: A five-percent beneficiary Standard Analytic File from the Centers for Medicare and Medicaid Services including data from January 1, 2000 through December 31, 2001 will be studied. Incidence rates and medical costs of HZ and PHN for Medicare beneficiaries \geq 65 years will be calculated. Estimates of associations among patient characteristics and risk of HZ and PHN will be modeled. Costs associated with HZ will be predicted. Measures necessary for applying Medicare claims data to cost-effectiveness, cost-of-illness, and burden of disease studies imperative to the health care marketplace will be developed.

Nina Oestreicher, University of Washington: "The Cost-effectiveness of Gene Expression Profiling in Women with Early Stage Breast Cancer."The current NIH criteria (NIHC) used to predict breast cancer recurrence and guide the use of adjuvant chemotherapy do not take into account genetic characteristics of a tumor and some women may receive unwarranted chemotherapy. Gene expression profiling (GEP) utilizes DNA microarrays, and may be able to predict more accurately the women whose tumors will metastasize than NIHC. This research proposes to evaluate the incremental clinical and economic outcomes associated with the use of GEP vs. NIHC in early stage breast cancer patients. They will develop a disease simulation computer model to evaluate the costeffectiveness of NIHC vs. GEP. The model will be informed by published data and by their analyses of patient-level data of GEP performance and treatment costs, unique to this study. Extensive sensitivity analyses will be conducted, including a multivariate analysis using Monte Carlo simulation. The results of this analysis will help guide the use of GEP to individualize drug therapy and the development of therapeutics directed at novel drug targets.

Post Doctoral Fellowship in Health Outcomes

The PhRMA Foundation Post Doctoral program in Health Outcomes provides stipend support for individuals engaged in a research training program that will create or extend their credentials in health outcomes. The purpose of this program is to support post doctoral career development activities of individuals prepared (or preparing) to engage in research that will strengthen representation of health outcomes in schools of pharmacy, medicine and public health. To accomplish these goals, support will be provided for a two-year period to selected individuals who are beginning careers in health outcomes research and who give promise of outstanding development as researchers. The award consists of a \$40,000 annual stipend for up to two years.

Recipient of the Post Doctoral Fellowship that began in January 2003 is:

Brian L. Erstad, Pharm. D., University of Arizona:"Proton Pump Inhibitor Therapy for Peptic Ulcer Bleeding." Of the estimated 300,000 hospital admissions each year in the U.S. due to upper gastrointestinal bleeding, approximately 5-10% of patients die as a result of bleeding-related complications. This mortality rate has remained relatively unchanged for at least 30 years, possibly due to the increasing number of patients with concomitant illnesses, and until relatively recently, the lack of effective of therapies. This study will be a cost-benefit analysis based upon a decision analytical model. The first source of information is published literature. Some of the applicable literature has already been extracted and reviewed with some of the more important publications cited in this submission. The literature lacks all of the information needed to construct the decision model in accordance with current clinical practice. Therefore, they expect to obtain information based upon past cases seen at a university medical center. Data from the financial services' office will be used to determine the number of patients admitted for various types of upper gastrointestinal bleeding based on coding procedures, as well as overall costs of hospital stay. Finally, a detail medical record review will be used to collect clinical and treatment data necessary for the model.

Research Starter Grants in Health Outcomes

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

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

Recipients of the Research Starter Grants that began in January 2003 are:

Tawny Bettinger, Pharm. D., University of Texas at Austin: "Depression and Diabetes: Improving Patient Outcomes in Primary Care." With a greater than 25% prevalence of depression in the diabetic population, the cooccurrence of diabetes and depression is of great concern to clinicians who treat these disorders. Although it is not clear what the exact relationship is between depression and poor glycemic control, research has shown that when diabetes and depression co-occur, there is poorer metabolic control, poorer diet and medication adherence, increased functional impairment, and higher health care costs. Because of the long term medical complications that can occur with poor glycemic control, as well as, the potential impact on a patient's quality of life, it is an extremely important issue to address. Patient adherence to medication, in general, is a major problem. Add to that a diagnosis of depression and the patient is three times more likely to be nonadherent with medications than a patient without depression. Studies evaluating interventions by physician extenders to increase adherence have resulted in improved patient outcomes. Additionally, studies evaluating the utilization of physician extenders to prompt physicians in the treatment of depression have also proven to enhance patient outcomes. Part 1 of the proposed study will be the development of the Treatment Adherence Program (TAP), with an advisory committee providing feedback and changes being made accordingly. In part 2 of the proposed study, a clinical pharmacist will provide the intervention group regular followup contact, extensive patient education on depression and medication management.

David K. Blough, Ph.D., University of Washington: "A Comparison of Imputation Techniques in the Estimation of the Cost Effectiveness Ratio."The primary objective of this research is to ascertain if there are important differences between methods for imputing missing data in cost effectiveness analyses. Missing data is often a problem in longitudinal clinical trials. These are trials in which subjects are measured repeatedly over time at a number of visits. In order to calculate a cost effectiveness ratio for the treatment under study, it is necessary to have unbiased estimates of both cumulative outcome and cumulative cost. Missing data can cause both of these measures to be underestimated. If the missing data can be assumed to be missing at random (that is, the loss of information is not associated with the outcomes or other covariates), it is possible to impute the missing data. However, to appropriately account for the uncertainty in the imputation, multiple imputation should be used. This is a method that imputes more than one value for each missing observation. The complete data sets are then analyzed (in this case the cost effectiveness ratio is estimated) and the results are combined to obtain an overall estimate of the parameter of concern. It is the purpose of this research to ascertain if the use of multiple imputation results in important differences in the cost effectiveness ratio relative to easier techniques for filling in missing

At the 2003 American Society for Pharmacology and **Experimental Therapeutics** awards ceremony during their annual meeting in San Diego, California on April 11, 2003, the **PhRMA Foundation presented** several important awards. These awards included the 2003 Award in Excellence Award, a 2003 Pre Doctoral Fellowship, two 2003 Post **Doctoral Fellowships and two** 2003 Research Starter Grants in Pharmacology/Toxicology. We would like to thank ASPET for this wonderful opportunity.



The predoctoral fellowship that I received from the PhRMA Foundation has allowed me to develop a strong background that will greatly contribute to my career in pharmaceutical research.

Amy Ulfers, Ph.D. Candidate, 2002 Pre Doctoral Fellowship in Pharmacology/Toxicology, BrownUniversity, Department of Molecular Pharmacology, Physiology and Biotechnology, Providence, Rhode Island data (last value carried forward, mean, hotdeck). The nonparametric bootstrap will be applied both to simulated data and to a real data set in order to obtain point estimates and confidence intervals for the cost effectiveness ratio under different imputation schemes. These will then be compared.

Amy Barton Pai, Pharm.D., University of New Mexico: "Impact of Clinical Pharmacy Services on Medication Cost and Hospitalization Rates in Hemodialysis Patients." Approximately 350,000 end-stage renal disease (ESRD) patients in the United States utilized over \$17.9 billion Medicare dollars in 1999. The ESRD population and cost is projected to double by 2010. ESRD patients have a mean of 5 comorbidities per patient and are prescribed a median of eight medications. The average monthly medication cost per patient is approximately \$1,200.00. For every dollar spent on medication an additional \$1.77 is spent on drug-related problems (DRPs). Dialysis patients are at high risk for DRPs. It is unknown if continued pharmacist intervention in hemodialysis patients will improve patient care, reduce medication utilization and cost, and prevent hospitalization as seen in other populations. The purpose of this study is to investigate the impact of continued pharmacist intervention in ambulatory hemodialysis patients. Methods: Patients at the largest dialysis unit in the state (n=150)under the same group of nephrologists will provide the necessary study population. Patients will be randomized to group A: Pharmaceutical Care; in depth monthly medication reviews conducted by a clinical pharmacist or Group B: Standard Care; medication reviews conducted by nursing staff. Patients randomized to Group A will be assigned to a clinical pharmacist who will review medication and medical records and perform a medication interview on a monthly basis. Group B will serve as controls. Medications will be classified into categories and average wholesale cost determined. Percentage of individual medication and medication class will be determined. DRPs will be classified, ranked, and recommendation outcomes will be determined. Quality of life (QoL) will be assessed using a renal-specific instrument at baseline, 6, and 12 months. Results will be compared between patient groups (Group A v. Group B).

Eve Wittenberg, Ph.D., Harvard Medical School/Massachusetts General Hospital: "The Effect of Age, Race and Gender on Economic Valuations of Health States." The proposed research will explore the relationship between individuals' age, race and gender on their preferences for health related quality of life. Evaluations of medical interventions, including pharmaceuticals and technologies, often rely on measures of quality of life to distinguish among outcomes. A complete understanding of the factors that affect preference-based quality of life measures is critical to assessing the validity of economic evaluations, and to appropriately designing and applying quality of life valuations. This research will explore whether the tradeoff between quality and length of life differs by these demographic characteristics. The investigator will conduct a pooled analysis of primary data and a meta-analysis of published studies to test for these relationships. The pooled analysis will combine existing data sets to maximize the statistical power to detect associations. The meta-analysis will include all published studies from 1976-2001 that include preference scores. The results of this research will inform the methods of cost-utility analysis and economic evaluation of medical interventions by improving understanding of the factors that affect preference-based measures of health related quality of life. It will also inform policy decisions that guide health care resource allocation to maximize preferences.

PHARMACOLOGY

Pre Doctoral Fellowships in Pharmacology/Toxicology

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

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

Two hundred and ninety-four fellowships have been awarded under this program including the eight awarded in 2003.

Those who received fellowships that began between January and August 2003 are:

Michelle Y. Cheng, University of California, Irvine: "Prokineticin 2 and Suprachiasmatic Output." Organization of physiology and behavior with recurring daily environmental conditions is an adaptation that occurs in essentially all living organisms. In mammals, the master pacemaker driving circadian rhythms resides in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. During the last few years, a clear view of molecular clock mechanisms within the SCN has emerged. This lab has recently shown that prokineticin 2 (PK2) functions as a specific SCN signaling molecule that transmits the behavioral circadian rhythm. The proposal is to further investigate the mechanisms of PK2 signaling in the output

pathway of the SCN circadian clock. One objective is to investigate the effect of chronic PK2 infusion on circadian clock-controlled behavioral rhythms such as the locomotor rhythm. A second objective is to investigate the direct effects of light on PK2 output from the SCN. Particularly, PK2 output from the SCN will be examined with a number of genetically modified mice. How the PK2 rhythmic output from the SCN responds to abrupt shifts of light/dark cycle will also be examined. These proposed studies will gain further insight into the role of PK2 signaling in mediating SCN circadian output, and should help validate receptor for PK2 as a novel target for treating circadian disorders such as jet-lag, shift work syndrome, and chronic insomnia.

Laura T. Donlin, Columbia University: "Negative Regulation of T Cell Receptor Signaling and T Cell Function by the Scaffolding Protein Sin."T cell development and activation, and therefore some autoimmune disorders, are controlled by a variety of factors including scaffolding proteins. This study aims to elucidate the function of the scaffolding protein Sin in T cell activation and autoimmunity. Preliminary results from this lab suggest that Sin is a negative regulator of T cell function and thus a potential regulator of autoimmunity. This hypothesis will be tested with these specific aims: (1) to characterize mice over expressing a Sin construct in T cells; (2) to generate and examine mice with a targeted disruption of the Sin loci; and (3) to determine the functional consequence of a recently identified interaction between Sin and Zap-70, a key T cell receptor (TCR) signaling molecule. The mouse models will serve as means to definitively classify Sin as a positive or negative regulator of T cell function, and may potentially serve as models for autoimmune disease. Determining the function of the Sin-Zap-70 interaction will further elucidate the role of Sin in T cells, while potentially identifying a new target for therapeutic intervention in T cell pathology.

Bradley J. Duffy, Duke University Medical School: "Characterization of a Novel Binding Partner and Potential Regulator of Vertebrate Weel." Entry into mitosis is a major regulatory event in the cell cycle. Without proper control of mitosis, a cell's genome will not be properly segregated after cell division. This failure will lead to genomic instability and greatly increases the risk of developing cancer. Entry into mitosis requires active Cdc2/cyclin B complexes. As would be expected, these complexes are tightly regulated in order to ensure that mitosis begins at the proper time. Inhibition of Cdc2 activity is maintained until mitosis to allow for the completion of DNA replication or repair of DNA damage. The kinase Wee1 catalyzes the inhibitory phosphorylation of Cdc2 and is further activated following DNA damage to

prevent entry into mitosis. Interestingly, Wee I protein levels are significantly lower than normal in colon carcinoma cells, while restoring BRCA1 activity in the breast cancer cell line HCC1937 increases Wee1 protein levels in response to ionizing radiation and restores the DNA damage checkpoint. These findings suggest that regulation of Weel protein levels may be important in tumorigenesis and further suggest that Weel and its regulators are promising targets for cancer drugs. One outstanding question that must be answered if WeeI mediated checkpoint pathways are to be exploited for cancer therapeutics is how Weel stability is controlled in vertebrates. In S. cerevisiae the stability of Swel, the S. cerevisiae homolog of Weel, is negatively regulated by the proteins Hsl1 and Hsl7. This study has identified a Xenopus homolog of the S. cerevisiae protein Hsl7 and has shown that both the S. cerevisiae Hsl7, and its Xenopus homolog can bind Xenopus Weel. Therefore, by using the powerful cell cycle reconstitution system provided by Xenopus egg extracts, the potential role Xenopus Hsl7 has in Wee1 regulation will be investigated. Since Wee1 and Hsl7 are both enzymes it may be possible in the long run to set up simple activity screens to identify compounds that are able to modulate cell cycle progression. Therefore, these proteins hold great potential as cancer therapeutic targets

Aaron N. Hata, Vanderbilt University School of Medicine: "Determination of the Structural Elements Governing Ligand Binding in mCRTH2." Prostaglandin D₂ (PGD₂), the predominant prostanoid produced by activated mast cells, has been implicated in allergic diseases such as allergic rhinitis, bronchial asthma, allergic conjunctivitis and atopic dermatitis. PGD₂ exerts its effects through two G-protein coupled receptors, DP and CRTH2. CRTH2 is expressed on eosinophils, basophils and Th2 cells and has been demonstrated to mediate chemotactic responses in these cells, suggesting that activation of CRTH2 may play a role in the During the American Association of Anatomists (AAA) Awards Banquet on April 14, 2003, in San Diego, California, the PhRMA Foundation recognized our 2003 Post Doctoral Fellow in Pharmacology/Morphology. We are grateful for the opportunity to present our award at this annual event.

Attendees at the ASPET Annual Meeting in San Diego April 2003. From the left, Aaron Hata, Phillip F. Pratt, Ph.D., David M. Bourdon, Ph.D., and Miller B. Jones, Ph.D.





Sumei Liu, Ph.D., from the Ohio State University receives the 2003 Post Doctoral Fellowship in Pharmacology/ Morphology from Eileen McCarron at the AAA Annual Awards Banquet in San Diego, April 2003

pathogenesis of allergic disease. This study proposes to characterize the pharmacology of the mouse CRTH2 ortholog and investigate the structure of the ligand binding pocket. By altering pharmacological properties through sitedirected mutagenesis, insight into the critical structural elements of the ligand-binding pocket that govern ligand binding and receptor activation will be gained. Molecular modeling studies of CRTH2 will generate receptor models that identify specific receptor-ligand interactions within the binding pocket. These will be validated using an iterative bi-directional approach coupling experimental results with molecular modeling. This work lays the groundwork for future development of small molecule inhibitors of CRTH2 which may be useful in the treatment of asthma and other allergic disease.

Einsley-Marie Janowski, Georgetown University: "Molecular Basis for Sex Differences in Drug-Induced Cardiac Arrhythmias." Cardiac arrhythmias are very common, causing more than 300,000 deaths a year in the US. The initiating factor for cardiac arrhythmias is often abnormal cardiac repolarization. Many drugs act as a catalyst to these arrhythmias because they block channels necessary for cardiac repolarization. Female gender is an independent risk factor for drug-induced cardiac arrhythmias; however, the reasons behind this gender-based susceptibility have not been fully elucidated. Research has shown that dihydrotestosterone (DHT) may be a significant factor in the apparent protection of men from cardiac arrhythmias. The focus of this project will be on the influence of DHT on cellular gene expression and potassium channel activity. Specifically, this researcher will determine if the expression of cardiac ion channel modulators KCNE1, KCNE2, and KCNE3 are influenced by DHT in vivo. Microarray analysis will be performed to search for global changes in gene expression upon exposure to DHT of rat cardiomyocytes modified via transfection with the genes for the androgen receptor and its known co-activator FHL2. Finally, the research will identify and characterize druginduced action potential and potassium current changes in cardiomyocytes before and after the androgen receptor activation described above. These experiments will elucidate the molecular mechanisms underlying DHT action in the myocardial cells.

Aleksandar Stojanovic, Dartmouth

Medical School: "Development of Novel Therapeutics to Target Rhodopsin Retinitis Pigmentosa Mutations." G Protein-Coupled Receptors (GPCRs) are an important group of transmembrane receptors that are targeted by approximately 60% of today's marketed drugs. Rhodopsin, the dim light-activated photoreceptor in the retina, is a prototypical GPCR for which we now have a crystal structure. Retinitis Pigmentosa (RP), a clinical problem associated with misfolded rhodopsin protein, is a disorder for which treatment is limited. The primary goal of this research is to establish the biochemical and structural bases for GPCR misfolding, using RP rhodopsin as a model. The experiments have suggested that, in diverse mutations, common principles at the molecular level may lead to the misfolding defect. The preliminary data shows that L¹²⁵R (TMIII) and A¹⁶⁴V (TMIV), both of which are in close proximity to the β ionone ring, may severely disturb a very important E¹²²-H²¹¹ salt bridge, thus interfering with the rhodopsin folding process. Based on rhodopsin's crystal structure, it has been observed that an analog of vitamin A may be useful in stabilizing the misfolded structures arising from this perturbed salt-bridge. These studies will be aimed at (1) determining the structural defects caused by specific RP mutations; and (2) determining which II-cis-retinal analogues may be able to stabilize the mutated rhodopsin protein and delay the disease process.

Amelia L. M. Sutton, Case Western Reserve University: "Vitamin D Stimulates Expression of Semaphorin 3B. a Tumor Suppressor that Potentially Mediates Vitamin D-induced Osteoblast Growth Inhibition and Differentiation."Vitamin D is critical for the proper development and maintenance of the skeleton. I,25-dihydroxyvitamin D₃ $(1,25(OH)_2D_3)$ is the bioactive metabolite of vitamin D that functions through the vitamin D receptor (VDR), a member of the nuclear hormone receptor family. The 1,25(OH)₂D₃-VDR complex acts on bone both indirectly, by regulating calcium and phosphate homeostasis, and directly by modulating osteoblast and osteoclast activity. In particular, vitamin D inhibits the proliferation and induces the differentiation of a variety of cell types, including osteoblasts. This property makes the VDR an attractive therapeutic target for a number of diseases, including cancer and osteoporosis. Despite the established actions of vitamin D on osteoblasts, relatively few transcriptional targets have been identified that mediate its effects. To characterize novel genes regulated by 1,25(OH)₂D₃ in MG-63 human osteoblastic cells, this study utilized gene expression array analysis. Using this approach, several genes that are highly induced following a 6-hour treatment with 10⁻⁸ M 1,25(OH)₂D₃, have been identified. One of these transcripts encodes semaphorin 3B (SEMA3B), a secreted adhesion molecule that appears to be inhibitory to both cell growth and migration. Furthermore, the SEMA3B gene is disrupted in some lung cancers and other tumors, indicating that it is a potential tumor suppressor. In agreement with the microarray data, Northern blot analysis shows a time- and dose-dependent induction

of SEMA3B expression by vitamin D treatment in MG-63 cells. Cycloheximide treatment abolishes the vitamin D induction, suggesting that this response is mediated through another factor induced by vitamin D. Additionally, SEMA3B is growth-inhibitory to osteoblasts as conditioned media from COS-7 cells transfected with a SEMA3B expression plasmid suppresses the proliferation of MG-63 cells. Based on these preliminary data, it is hypothesized that SEMA3B is required for vitamin D-mediated growth inhibition and stimulation of differentiation in osteoblasts. To test this hypothesis, the study proposes to (1) characterize the induction of SEMA3B by vitamin D and its synthetic analogues in primary murine osteoblasts; (2) examine the role of SEMA3B in vitamin Dmediated growth inhibition and cell cycle arrest; and (3) determine the in vivo effect of SEMA3B on osteoblast differentiation and in bone development and maintenance.

Diana Zi Ye, Michigan State University: "Role of Poly(ADP-ribose) Polymerase (PARP) in Regulating Pancreatic β -cell Phenotype." It has been estimated by the Juvenile Diabetes Research Foundation that 17 million Americans have diabetes mellitus. Insulin-dependent (IDDM) and non-insulin dependent (NIDDM) diabetes are the two major types of diabetes, and they are characterized by a reduction in insulin secretion and biosynthesis from pancreatic β -cells. Chronic hyperglycemia can cause changes in gene expression profile. For example, hyperglycemia can decrease the expression of β -cell specific genes while increase the expression of metabolic genes that are normally present at low abundance. Poly(ADP-ribose) polymerase (PARP) inhibitors have been shown to stimulate β -cell regeneration, differentiation, and insulin biosynthesis. The mechanisms whereby PARP regulates β -cell differentiation and insulin biosynthesis remain unknown. PARP has been shown to regulate gene transcription via poly(ADP-ribosyl)ation of nuclear proteins such as transcription factors, forming binding complexes with transcription factors and/or binding to DNA directly. This study's preliminary data show that in INS-1 cells (a rat insulinoma cell line), PARP inhibitors can induce insulin gene promoter activity and inhibit liver-isoform pyruvate kinase (L-PK) and fatty acid synthase (FAS) promoter activity, which were suppressed or activated by elevated glucose concentration, respectively. The hypothesis is that PARP may regulate transcription factors, which control transcription of genes important for metabolism and phenotype of β -cells. Understanding how PARP regulates β -cell phenotype may ultimately provide a useful therapeutic target for the treatment of diabetes mellitus.

Post Doctoral Fellowships in Pharmacology/Toxicology

This program provides stipend funding to welltrained 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 welltrained scientific investigators.

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

Receiving the fellowships that began between January and December 2003 are:

David M. Bourdon, Ph.D., University of North Carolina-Chapel Hill: "PLC-E: Mechanisms of PARI and G Protein Regulation." The $G\alpha_{12}$ family of heterotrimeric G proteins $(G\alpha_{12} \text{ and } G\alpha_{13})$ was identified in 1991 and has been associated with biological responses including cell growth and transformation. However, few G protein-coupled receptor (GPCR)/effector pathways linked to these G proteins have been firmly established. Preliminary data from this laboratory suggests that the protease-activated receptor-1 (PAR1) activates PLC- ε via activation of G α_{12} . To date, no laboratory has studied the direct coupling of a GPCR to $G\alpha_{12/13}$ leading to activation of PLC-E. This research plan proposes to purify PARI for the first time and to define PARI $G\alpha$ -subunit selectivity. In addition, purified PLC- ϵ will be examined to delineate G α and $G\beta\gamma$ activation domains that are key to its novel modes of regulation. Finally, PLC- ε will be examined for its ability to act as a GTPase accelerating protein (GAP) and this project aims to localize the regions of PLC- $\!\epsilon$ that mediate GAP activity. These studies will provide key molecular insight into the regulation and actions of an important new effector protein and a unique GPCR that initiates its activation. Moreover, the ubiquitous expression of PLC- ϵ together with its likely major role in cell growth and transformation and other physiological responses, make it a potentially important drug target. This protein may prove a key therapeutic target in a variety of pathophysiologies, most notably cancer, that have resisted rational drug design and application.

Miller B. Jones, Ph.D., University of North Carolina-Chapel Hill: "Structural Analysis of the Sorting Nexin RGS Domains." The research in this proposal outlines experiments to characterize the roles of the regulators of G protein signaling (RGS) domains of a new subclass of



Jennifer D. Bilyeu, 2002 Pre Doctoral Fellow in Pharmacology/Toxicology from The University of Tennessee Health Sciences Center, Department of Pharmacology

Award recipients are recognized at the 2002 AAPS Annual Meeting in Toronto, Ontario. From left to right, Carol S. Lim, Ph.D., The University of Utah, recipient of the Research Starter Grant in Pharmaceutics, and Carol E. Stotz, The University of Kansas, Carol F. Kirchhoff, University of Illinois at Chicago, Meagan E. Anderson, The University of Kansas recipients of Pre Doctoral Fellowships in Pharmaceutics



RGS proteins, sorting nexin 13 (SNX13; aka RGS-PX1), sorting nexin 14 (SNX14) and sorting nexin 25 (SNX25), in heterotrimeric G protein signaling and to identify structural determinants of selectivity of RGS domains for $G\alpha$ subunits. Currently, the RGS domain of SNX13 has been described to selectively bind and accelerate the GTPase activity of the stimulatory a subunit of heterotrimeric G proteins (Gas); the RGS domains of SNX14 and SNX25 remain uncharacterized. Using a combination of GST-pulldowns, co-immunoprecipitations, co-purification experiments and surface plasmon resonance the $G\alpha$ subunit(s) that binds to these RGS domains in a nucleotide dependent manner using purified recombinant proteins will be determined. Selectivity will be further determined by isolating specific $G\alpha$ subunits from crude brain lysates using purified recombinant affinity-tagged RGS boxes. The study will then determine the atomic resolution structure of these RGS domains with their $G\alpha$ binding partner(s). The final objective will be to ascertain the structural determinants of RGS domain selectivity for $G\alpha$ subunits using sequence data, structural data generated in this proposal and previously known structural data of other RGS domains.

Post Doctoral Fellowship in Pharmacology/Morphology

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

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

This fellowship was first offered in 1968. One hundred and ten awards have been made to date including the one awarded in 2003.

Receiving the fellowship that began July 2003:

Sumei Liu, Ph.D., The Ohio State University: "CRF and CRF Receptors in the Enteric Nervous System of Guinea Pig Colon." Studies to achieve the specific aims of this project are designed to test the general hypothesis that corticotropin releasing factor (CRF) is a messenger substance of importance in the enteric nervous system (ENS) of guinea-pigs experiencing stressful environmental conditions. Cellular neurophysiological methods of electrophysiological recording, intraneuronal marker injection, immunocytochemistry, and molecular biological techniques will be used in studies that test the hypothesis. Pilot/feasibility studies found that enteric neurons express immunore-

activity for CRF receptors and that exposure to CRF or urocortin in vitro preparations evoked a dramatic increase in neuronal excitability that mimicked slow synaptic excitation. The proposed studies are focused on CRF-evoked neurophysiological responses and functional expression of CRF receptor(s) in the ENS of guinea pig colon. The studies are designed to identify the CRF receptor subtype/s responsible for the excitatory action of CRF and to elucidate the cellular mechanisms underlying the excitatory action. Actions of CRF at the single neurona level are postulated to be transformed into output at the circuit level that may be reflected as alterations in colonic motility and mucosal secretion at the level of the integrated organ. Changes in motility and secretion are expected to underlie the marked disturbances of colonic function (e.g. abdominal discomfort, diarrhea and urgency of defecation) that are observed in animals exposed to environmental stressors. Aim 1 will identify the actions and mechanisms of action of CRF on morphologically and neurochemically identified enteric neurons in the myenteric and submucosal plexuses of guinea-pig colon. Aim 2 will study the functional expression of CRF₁ and/or CRF₂ receptor protein and mRNA in the ENS of guinea-pig colon. Aim 3 will test the hypothesis that stressevoked activation of enteric neurons is mediated by CRF. The overall goal of the study is to improve insight into the role of CRF in stressinduced alterations of gastrointestinal function.

Sabbatical Fellowship in Pharmacology

This is a relatively 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 pharmacology. The Sabbatical Fellowship provides up to \$40,000 for one year of stipend funding.

Receiving the fellowship that began January 2003 is:

Jose E. Manautou, Ph.D., University of Connecticut School of Pharmacy: "Hepatic Transport of APAP and its Metabolites: *In Vitro* Analysis." High doses of the popular analgesic and antipyretic acetaminophen (APAP) can produce fatal liver injury in humans and laboratory animals. This toxicity is highly dependent on the way in which APAP is metabolized by the liver. A significant portion of a given dose of APAP undergoes elimination from the liver into the bile. Previous studies from this laboratory show that biliary excretion of APAP decreases significantly when another chemical known as indocyanine green is co-administered with APAP. The lab has also demonstrated that indocyanine green competes with APAP for common biliary excretion pathways. It is hypothesized that competition for transport pathways between APAP and chemicals that are prominently excreted in bile changes susceptibility APAP toxicity. Follow-up in vivo studies are currently underway to address this. These in vivo studies, although necessary to understand the nature of this interaction, cannot identify specific transport proteins involved in the disposition of APAP from the liver. The goal of this study is to investigate the involvement of specific transporters in the disposition of APAP from the liver by conducting in vitro uptake studies using membrane vesicles generated form cell expression systems and livers from mutant and knockout animal models for transporter. These studies are significant because they are expected to increase understanding on substrate specificity for liver transporters and to provide new insights on hepatic disposition and potential for drug interactions.

Medical Student Research Fellowships in Clinical Pharmacology

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

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

Recipients of the Medical Student Research Fellowship that began in July 2003 are:

Jeffrey M. Craft, Northwestern University: "Ligand Modulation of Neuroinflammation in Animal Models of Alzheimer's Disease." Neuroinflammation involving chronically activated astrocytes and microglia in the brain has been implicated in the progression of several neurodegenerative disorders, including Alzheimer's disease (AD). Furthermore, a rapidly expanding body of evidence suggests that the discovery of small molecule ligand modulators of the intracellular signal cascades controlling glial activation is a promising, yet currently unexploited, avenue for therapeutic intervention. Recently, the description of a novel class of 3-amino-pyridazine compounds capable of attenuating glial activation in vitro has raised the possibility that these compounds may be efficacious in neurodegenerative disease. Through the use of an intracerebral amyloid beta infusion model and a newly described double mutant amyloid precursor protein transgenic mouse model, they intend to study the effect of these novel 3-amino-pyridazine compounds. The Morris water maze test will be implemented to measure any effect on the cognitive capabilities of the model organisms with and without treatment. In addition, histological and biochemical examination for AD-related pathology and cytokine upregulation will be performed to measure the effect of the compounds on these disease-relevant endpoints. The rapid turnaround time of these models, furthermore, will also enable the further refinement and development of this new class of potential therapeutics.

Rebecca W. Silbermann, Brown University School of Medicine: "Oral RNA Interference as a Novel Inflammatory Bowel Disease Therapy." Pharmacologic therapy for Inflammatory Bowel Disease (IBD) is currently centered on daily administration of high dose anti-inflammatory medications. Adverse effects of these drugs are a result of their systemic absorption throughout the entire small intestine and colon. These problems have been addressed in two ways: by identifying specific pro-inflammatory cytokines that are upregulated in IBD that may serve as local drug targets, and in improving the drug delivery systems themselves. This plan will study the effectiveness of locally delivered RNA interference as a therapy for IBD. RNA interference is the process by which the incorporation of multiple, double stranded, small interfering RNAs (siRNAs) into a cell inhibits expression of the homologous gene. They plan to develop siRNA constructs with homology to an inflammatory cytokine associated with IBD and to deliver these constructs to specific cell targets using commercially available nanoparticles. The plan will demonstrate that the nanoparticle delivery system allows the siRNAs to be adequately incorporated into the target cells, and prove that the siRNAs effectively inhibit their target cytokine. It will then establish whether these siRNA-coated nanoparticles can be concentrated in target cells in vivo, and whether this RNA interference results in relief of IBD symptoms. If successful, this project will form the basis of a novel, highly localized therapy for IBD.

Research Starter Grants in Pharmacology/Toxicology

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

The first Research Starter Grant awards were made in 1972; and a total of five hundred thirty four have been awarded, including the grants beginning on January 1, 2003.

Recipients of the Research Starter Grants that began in January 2003 are:

Janet L. Fisher, Ph.D., University of South Carolina School of Medicine: "Structural Basis for the Pharmacological Properties of the $GABA_{A}$ Receptor $\alpha 6$ Subunit."The $GABA_{A}$ receptor is responsible for most fast inhibitory neurotransmission in the central nervous system and is a target for many drugs commonly used as sedatives, anxiolytics and anti-epileptics. The sensitivity of the $GABA_A$ receptor to many of these drugs depends upon its subunit composition. The GABA_A receptor exhibits a great deal of structural heterogeneity, with seven different subunit families, and sixteen different subunit subtypes. The α family is the most diverse, with six different subtypes $(\alpha I - \alpha 6)$. This diversity raises the possibility that drugs selective for certain subunits may be developed that produce fewer side-effects than those currently available. The α 6 subunit exhibits unique functional and pharmacological properties compared to the other a subunits. The α 6 subunit is found only in cerebellar granule cells, and its expression has been linked to the motor effects of alcohol and anti-epileptic drugs. α 6-containing receptors have higher sensitivity to the agonists GABA and pentobarbital, and to the inhibitor amiloride. The proposed work will determine the structural basis

The PhRMA Foundation was honored to participate in the Annual Meeting of the American Association of Pharmaceutical Scientists on October 26, 2003 in Salt Lake City, Utah. We would like to thank AAPS for recognizing our 2003 award recipients in Pharmaceutics who were present at this prestigious event.

Pictured with George C. Fuller, Ph.D. and Eileen McCarron at the 2003 ASPET Annual Meeting in San Diego, are from left to right, Phillip F. Pratt, Ph.D., Medical College of Wisconsin and Janet L. Fisher, Ph.D., University of South Carolina School of Medicine recipients of the Research Starter Grant in Pharmacology/Toxicology; Aaron N. Hata, Vanderbilt University School of Medicine, recipient of the Pre Doctoral Fellowship in Pharmacology/Toxicology; and David M. Bourdon, Ph.D. and Miller B. Jones, Ph.D. from the University of North Carolina at Chapel Hill, recipients of Post Doctoral Fellowships in Pharmacology/Toxicology





The PhRMA Foundation has provided instrumental funding and support at key stages in my career development to establish a research path in pharmaceutics.

LaToya S. Jones, Ph.D., 2002 Post Doctoral Fellowship in Pharmaceutics, Postdoctoral Fellow, Department of Pharmaceutical Chemistry, University of Kansas

Joseph Turek, M.D., 2000 Medical Student Research Fellowship, PhD Student, University of Illinois at Chicago, Residency at Duke University, General Surgery, summer 2002 for these unique properties through sitedirected mutagenesis of the α 6 subunit. The pharmacological properties will be determined by patch-clamp recordings from mammalian cells transiently transfected with the wild-type or mutated subunits. The results of this work will provide a better understanding of the structures that underlie the functional variability of the GABA_A receptor subunits and may lead to the development of more specific drugs that target the GABA_A receptors.

Phillip F. Pratt, Jr., Ph.D., Medical College of Wisconsin: "Adenoviral Delivery of Dual-Specificity Phosphatases as Anti-Mitogenic Agents in Primary Rat Mesangial Cells." Glomerulonephritis (GN) is an inflammatory disease of the glomerulus resulting in glomerular expansion due to proliferation of resident cells, like mesangial cells (MC). Mesangial cells have contractile properties and may regulate glomerular filtration by contracting or relaxing. Hyperproliferation of MC results in glomerular expansion, perturbed glomerular function and impairment of renal function. Platelet-derived growth factor (PDGF) stimulates mitogen-activated protein kinases (MAPK), like extracellular-regulated kinase (ERK). ERK is phosphorylated, ERK can phosphorylate cytosolic and nuclear proteins. ERK activity is decreased by removal of phosphates from tyrosine or threonine. Dual-specificity phosphatases are becoming recognized as probable MAPK regulators since they remove phosphates from both tyrosine or threonine residues. Specifically, one family member, MKP-3, appears to be highly specific for ERK due to an N-terminal protein binding motif. The goal of this proposal is to test the hypothesis that MKP-3 dephosphorylates ERK in primary cultures of rat MC and is down-regulated in response to PDGF treatment. Additionally, adenoviral transfer of MKP-3 is hypothesized to inhibit the proliferative response to PDGF, making it a likely candidate for future therapeutic strategies to limit the proliferation of MCs in glomerulonephritis.



PHARMACEUTICS

Pre Doctoral Fellowships in Pharmaceutics

This program has been in effect for 15 years. It assists awardees who have one or two years remaining in their pharmaceutics pre doctoral training—the time during which they are engaged in dissertation research. We provide the funding during the doctoral program after course work has been completed and the remaining training activity is a student's research project.

The fellowship program provides a stipend and funds to cover costs incidental to the training for up to two years. The level of support is \$20,000 per year and up to \$500 a year may be used for incidentals directly associated with the preparation of the dissertation. Two awards were made in 2003.

Those who received fellowships that began between January and August 2003 are:

David L. Bourdet, University of North Carolina at Chapel Hill: "Molecular Characterization of H-2 Antagonist Saturable Transport in the Intestine"The H-2 antagonists, ranitidine and famotidine, are cationic, hydrophilic compounds which traditionally would not be predicted to have adequate oral bioavailibility. However, bioavailability for this class of compounds ranges from 40-70%. Mechanistic studies have indicated that saturable transport mechanisms exist in both the absorptive and secretory pathways across Caco-2 cell monolayers. Such mechanisms may be responsible for facilitating transport across the intestinal epithelium and thus improving oral absorption for these compounds. Importantly, these pathways may also lead to significant drug-drug interactions due to inhibition of intestinal absorption. The proposed research plan attempts to identify the cellular proteins or lipoproteins that mediate this transport using a photoaffinity labeling technique. Functional studies have indicated that these transport mechanisms are unlikely to be mediated by known transport proteins. Photoaffinity labeling therefore aims to directly identify the novel, unknown protein components through covalent attachment of a photoreactive probe to the protein of interest. The research plan aims to design an appropriate probe in order to isolate the protein(s) of interest and thus allow structural characterization of the proteins mediating both absorptive and secretory transport for this class of compounds in the intestine. A clear understanding of this molecular interaction between H-2 antagonists and transport proteins could provide a rational basis for the design of an entire class of drugs that have traditionally exhibited poor absorption properties—namely cationic hydrophilic molecules.

Laura M. Land, University of Kentucky: "An Investigation of the Physicochemical Mechanisms Underlying Enhanced Oral Bioavailability Following Administration of Hydrophobic Drugs Via Lipid-Based Delivery Systems." Nearly one half of all new chemical entities fit into the category of being poorly water-soluble. As a result, lipid-based dispersed systems have been developed as a means of enhancing the transport rate of hydrophobic compounds across the gastrointestinal membrane. Yet, it is still unclear which compounds will benefit from formulation in lipid-based drug delivery systems. The fundamental goal of this study has been to determine the physicochemical mechanism(s) by which oral bioavailability of poorly water-soluble compounds may be enhanced by delivery via a lipid-based delivery system. Specifically, the influence of microemulsion systems on transport properties of hydrophobic compounds will be evaluated. Two hypotheses have been formulated with respect to this issue: (1) The resistance to mass transport of the unstirred water layer is diminished in the presence of microemulsion droplets; and (2) The solubility of drug in lipidbased systems is a function of the composition and is super-saturated relative to the solubility in the individual components. The high thermodynamic driving force that accompanies supersaturated systems results in a faster rate of transport across a membrane. The general scheme of the research to be employed includes identification and characterization of suitable microemulsion systems, and evaluation of the transport properties of a variety of dispersed systems using side-by-side diffusion cell studies and pulsed gradient spin-echo Nuclear Magnetic Resonance spectroscopy.

Research Starter Grants 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 those individuals who are establishing careers as independent investigators. The program is not offered as a means to augment an ongoing research effort.

Receiving the grants that began in January 2003 are:

Tonglei Li, Ph.D., University of Kentucky: "Surface Energy Evaluation with Atomic Force Microscopy."The aim of this proposal is to investigate how the solvent and additive/impurity molecules affect the surface energy of pharmaceutical crystalline materials by using atomic force microscopy (AFM). It has been found that during the dissolution process the etching pattern is regular and solvent-dependent. The pattern can be affected also by structurally similar additives. It has been hypothesized that the adsorption of solvent or additive molecules on the crystal surface may trigger or stabilize the surface reconstruction of host molecules on the surface. What is proposed here is to test this hypothesis. The anticipated study is to use AFM to measure the surface energy in situ of a model crystal surface upon dissolving in selected solvents or tailor-made additives. Using AFM makes it possible to measure the adhesion force between a tip and a crystal surface, which can be related to the adhesion work that is a function of surface energies including the one of the crystalsolution interface. With the help of contactangle measurement, the surface energy of the crystal-solution interaction can be derived. The hypothesis may be proved by using a tailor-made additive solution on the model surface and monitoring the surface energy with the concentration varied.

Y. Bruce Yu, Ph.D., University of Utah: "Design, Synthesis and Characterization of a Peptide Ligand/Anti-Ligand Pair for Cancer Radiotherapy."The focus of this research project is to design a ligand/anti-ligand pair as docking anchor for pretargeted radioimmuno-therapy (PRIT) of cancer. The prototype of the ligand/ anti-ligand pair is the heterodimeric coiled-coil, a natural protein dimerization domain. To minimize the size of the peptides and enhance heterodimerization affinity and specificity, a set of strategies, based on the structural biology of coiled-coils and physicochemical principles, will be applied to the design of the peptide sequences. The designed peptides will be made using solid-phase synthesis and purified by HPLC. An assortment of biophysical and biochemical methodologies will be employed to assess the affinity and specificity of the peptide pairs. A few pairs of peptides with high affinity and specificity will be selected for further testing in the presence of the chelator and the metallic ion used in PRIT. The pair of peptides with the highest affinity and specificity in the presence of the chelator and the metallic ion will be the final candidate for the docking anchor for PRIT. The specific goals of the heterodimer design are: affinity: comparable to that of the biotin-streptavidin system (10^{13} M^{-1}) : specificity: a specificity constant of at least 10: and size: at least one chain of the heterodimer will be shorter than 21 amino acid residues.



George C. Fuller, Ph.D., Chairman of the Basic Pharmacology Advisory Committee, speaking at the ASPET Annual Meeting in San Diego, April 2003

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 RECOGNIZES THESE INDIVIDUALS FOR THEIR CONTRIBUTIONS



The PhRMA Foundation lost one of its most ardent supporters this year. Dr. Paul Calabresi died on October 25, 2003 in Providence, Rhode Island. Dr. Calabresi was a member of the PhRMA Foundation Clinical Pharmacology Advisory Committee since 1978. In 1989, he became the Chairman of this committee and remained in this position until the time of his death. He was a

Professor of Medicine and Chairman Emeritus of the Brown University Department of Medicine. Dr. Calabresi was also well known for his extensive work with many cancer research institutions spanning four decades. He served as president for several of the organizations that he represented.

Dr. Calabresi was a caring and warm individual who was generous with his time and enthusiasm. Through his leadership and guidance, over the past 25 years, the PhRMA Foundation has assisted many clinical pharmacologists with their career paths through our fellowships. We are indebted to Dr. Calabresi for all of his support throughout the years, and we will truly miss him.



The PhRMA Foundation would like to give tribute to Louis Lasagna, M.D., Sc.D. Dr. Lasagna passed away on August 6, 2003, following a long illness. In 1976, Dr. Lasagna founded the Tufts Center for the Study of Drug Development, an academic research group. He was Chairman of the Board and Adjunct Scholar at the Center, Dean of the Sackler School of Graduate Biomedical

Sciences, and Dean for Scientific Affairs at The Tufts University School of Medicine. He received a PhRMA Foundation award in Clinical Pharmacology in 1970 and our 2001 Award in Excellence in Clinical Pharmacology. He was highly regarded by his former students and former colleagues, and he will be greatly missed.

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BELIEF IN A MISSION...

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

T R E A S U R E R ' S R E P O R T



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

THE PhRMA FOUNDATION ENDED 2002 IN SOUND FINANCIAL SHAPE.

During 2002, most of the PhRMA member companies contributed according to our formula. Contributions were up slightly over the previous year, to \$2.76 million. More than \$1.76 million was awarded in grants, and total expenditures were \$2.2 million. Our new program was fully implemented in 2002. Total net assets at year-end were \$7.04 million. Of this amount, \$4.22 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 2003, contributions were targeted at the same level, as we entered the second full year of our new program. On behalf of the Board and staff, I give special thanks for the continuing support of our generous contributors, who are listed in this report.

The Foundation's financial position as of December 31, 2002, has been audited by the Rosslyn, Virginia, accounting firm of Buchanan & Company. A full report can be obtained by contacting the Foundation.

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

Statement of Income and Expenditures For the Year Ended December 31, 2002

INCOME	
Contributions	\$2,792,787
Interest and Dividends	165,246
(Realized and Unrealized) Loss in Securities	-539,679
Depreciation of Fixed Assets	-5,080
Other Income	55,439
Total Income	\$2,468,713

EXPENDITURES

Programs Awards in Excellence Center of Excellence for Integration of Genomics and Informatics Clinical Pharmacology Program Health Outcomes Program Informatics Program Pharmaceutics Program Pharmacology Programs AFPE Fellowship Award Subtotal–Grants	16,662 175,000 459,042 188,500 247,500 147,500 526,994 3,750 \$1,764,948
Other Committee Meetings, Travel and Honoraria Publications and Special Projects Subtotal–Other Program Total	67,506 82,445 \$149,951 \$1914,899
Administrative Staff, Rent, Taxes and Insurance Professional Services and Investment Expenses Office Expenses Subtotal–Administrative	252,446 34,350 9,391 \$296,187
TOTAL EXPENDITURES	\$2,211,086

ADVISORY COMMITTEES



William R. Darrow Foundation Chief Scientific Advisor

On October 20, 2003, the PhRMA Foundation honored Fred Radzialowski for his two decades of service at a special dinner in Washington, DC. Pictured here at the dinner are: (from left to right) Paul Guth, George Fuller, Del Persinger, Fred Radzialowski and Eileen McCarron

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Peter A. Schad, Ph.D.

Chief Scientific Officer Digital Infuzion Gaithersburg, Maryland

David B. Searls, Ph.D.

Senior Vice President Worldwide Bioinformatics GlaxoSmithKline King of Prussia, Pennsylvania



At the October meeting of the Basic Pharmacology Advisory Committee, the PhRMA Foundation recognized Frederick M. Radzialowski, Ph.D. for the two decades of service to the PhRMA Foundation. Fred became a member of the Basic Pharmacology Advisory Committee in 1984 and remained an active member of this committee up to and including the year 2003. Fred also served as Chairman of the Scientific Advisory Committee from 1989 through 1993. Dr. Radzialowski has had a very successful career as a Scientific Executive with G. D. Searle and *Company and as President of* FMR Research Associates since 1993. Fred is retiring and with his wife Eleanore, plans to travel extensively, enjoy grandchildren, and develop service activities to help others. His expertise has been invaluable and he has been instrumental in selecting the brightest and the very best scientists to receive our awards. *Thank you Fred for the many* years of dedication and support that you have given to the PhRMA Foundation.

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Eileen McCarron Director of Development

Elaine Dorsey Associate

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The PhRMA Foundation owes its success to the pharmaceutical companies that have provided their generous support over the past 38 years. We thank all of you for continuing to invest in the future of pharmaceutical research and the scientists of tomorrow.

Jo El J. Schultz, Ph.D., University of Cincinnati College of Medicine, recipient of the 2002 Research Starter Grant in Pharmacology/Toxicology

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PhRMA FOUNDATION PROGRAMS FOR 2004

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date/Starting Time			
Health Outcomes Advisory Committee						
Pre Doctoral Fellowships	2 budgeted/	\$ 80,000 total\$ 20,000 per award per year	October I, 2003			
in Health Outcomes (2002)	2 years		December I5, 2003/January-August			
Post Doctoral Fellowship	I budgeted/	\$ 80,000 total	October 1, 2003			
in Health Outcomes (2002)	2 years	\$ 40,000 per award per year	December 15, 2003/January-December			
Sabbatical Fellowship	l budgeted/	\$ 40,000 total	October I, 2003			
in Health Outcomes (2002)	I year	\$ 40,000 per award per year	December I5, 2003/January-December			
Research Starter Grants	3 budgeted/	\$180,000 total	October I, 2003			
in Health Outcomes (2002)	2 years	\$ 30,000 per award per year	December I5, 2003/January I, 2004			
Informatics Advisory Committee						
Post Doctoral Fellowships	2 budgeted/	\$160,000 total	September 2, 2003			
in Informatics (2002)	I to 2 years	\$ 40,000 per award per year	December 15, 2003/January-December			
Sabbatical Fellowship	l budgeted/	\$ 40,000 total	September 2, 2003			
in Informatics (2002)	I year	\$ 40,000 per award per year	December 15, 2003/January-December			
Research Starter Grants	3 budgeted/	\$180,000 total	September 2, 2003			
in Informatics (2002)	2 years	\$ 30,000 per award per year	December 15, 2003/January 1, 2004			
Pharmacology Advisory Committees						
Pre Doctoral Fellowships	6 budgeted/	\$240,000 total	September 2, 2003			
in Pharmacology/Toxicology (1978)	2 years	\$ 20,000 per award per year	December 15, 2003/January-August			
Post Doctoral Fellowships	2 budgeted/	\$160,000 total	September 2 2003			

in Pharmacology/Toxicology (2002) Post Doctoral Fellowship

in Pharmacology/Morphology (1968)

Sabbatical Fellowship in Pharmacology/Toxicology (2002)

Research Starter Grants in Pharmacology/Toxicology (1972)

Medical Student Fellowships (1974)

Center of Excellence in Clinical Pharmacology (2002) 2 years I budgeted/ 2 years I budgeted/ l year 2 budgeted/ 2 years I budgeted/ up to 2 years

2 budgeted/

\$ 36,000 total I year to 18 months \$ 18,000 per award per year

\$ 40,000 per award per year

\$ 40,000 per award per year

\$ 40,000 per award per year

\$ 30,000 per award per year

\$250,000 per award per year

\$ 80,000 total

\$ 40,000 total

\$120,000 total

\$500,000 total

December 15, 2003/January-December

September 2, 2003 December 15, 2003/January-December

September 2, 2003 December 15, 2003/January-December

September 2, 2003 December 15, 2003/January 1, 2004

October 1, 2003 December 15, 2003/July 1, 2004

September 2, 2003 December 15, 2003/January-August

Pharmaceutics Advisory Committee

Pre Doctoral Fellowships	3 budgeted/	\$120,000 total	October I, 2003
in Pharmaceutics (1987)	2 years	\$ 20,000 per award per year	December I5, 2003/January-August
Post Doctoral Fellowship	l budgeted/	\$ 80,000 total\$ 40,000 per award per year	October 1, 2003
in Pharmaceutics (1992)	2 years		December 15, 2003/January-December
Sabbatical Fellowship	l budgeted/	\$ 40,000 total\$ 40,000 per award per year	October 1, 2003
in Pharmaceutics (2002)	I year		December 15, 2003/January-December
Research Starter Grants	2 budgeted/	\$120,000 total	October I, 2003
in Pharmaceutics (1972)	2 years	\$ 30,000 per award per year	December I5, 2003/January I, 2004

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

www.phrmafoundation.org