PhRMA

FOUNDATION

annual report

mission

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

Robert A. Ingram

The dawn of a new millennium signals a new beginning for the PhRMA Foundation. We have designed a program that builds on the successes of the past while adapting to meet the needs of the future.

Our tradition of providing financial support to young scientists continues as one of our top priorities. Our support will help them jump-start careers in disciplines important to research-intensive industries. The unconditional support we provide reinforces the pharmaceutical industry's commitment to research. Since its inception, the Foundation has supported more than 2,000 young scientists at the outset of their careers. Our support is important to these scientists.

This year, the Foundation awarded grants to 41 young scientists. Please join me in congratulating them and wishing them success in their endeavors. Their research will advance their careers, contribute to our industry, and, ultimately, benefit the patients we serve.

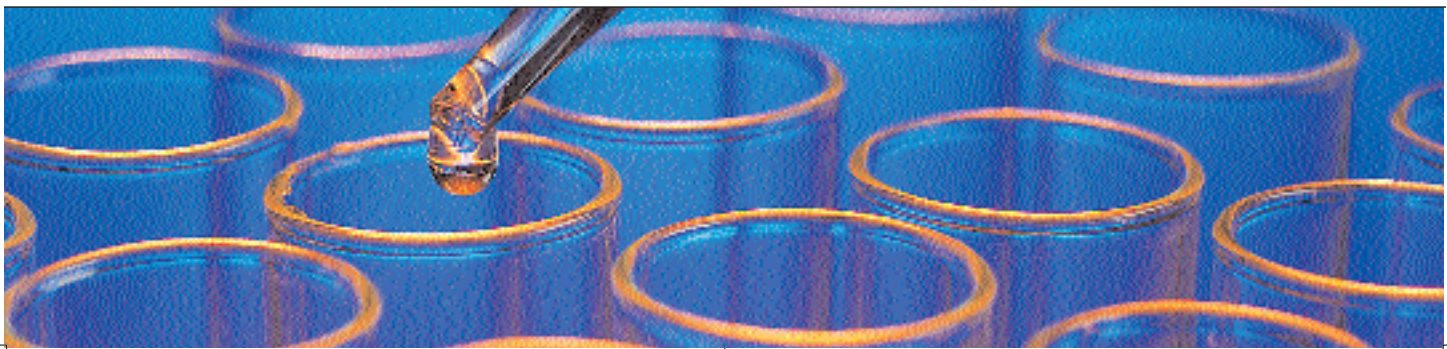
I also want to recognize Foundation Board and Advisory Committee members who have guided our program and selected these award recipients. Their support, expert advice, and valuable assistance during the past year have helped us chart a new course for the Foundation. These individuals have served with dedication and distinction, and their efforts reflect a belief in the Foundation's mission. Many of our members have served for 10 years, 20 years, and even longer. I also extend my special thanks to my immediate predecessor, Jan Leschly, who brought his trademark energy and ability to his responsibilities as Chairman. We are indebted to him for his leadership and service.

Because of the accelerating advances being made in biomedical science and technology, the Board recently conducted a comprehensive strategic review. This process was undertaken to ensure that our resources are being used efficiently and effectively.

Our review convinced us that the Foundation's focus on scientific disciplines and the careers of young scientists serves a unique purpose that must be preserved and strengthened. We help fledgling scientists when they need it most–at a critical stage in their lives when they are deciding on a career. Our committees have established a remarkable track record in identifying, encouraging, and helping scientists who have gone on to distinguish themselves in research and teaching careers. The pages of this report are full of examples.

Special recognition goes to the three scientists who received our 2000 Award in Excellence–Dr. D. Craig Brater, Dr. Thomas E. Ellenberger, and Dr. Kenneth P. Minneman. They received Foundation grants years ago, and eventually became leaders in their fields. Their success vividly demonstrates the value of the Foundation's underlying approach.

Few other foundations serve the same purpose as the PhRMA Foundation. Our focus on careers and disciplines, rather than a specific disease, product, or other more targeted goal, serves a special role in finding and training tomorrow's leaders. Already we see shortages of talent in key disciplines–like informatics and genomics–that cross traditional disciplinary boundaries. It is essential–for scientists, our industry, and society–that the Foundation continue its work.



Following its strategic review, the Board has rededicated the Foundation to its mission of helping young scientists at critical points in their careers. Our goal is to encourage a focus on cutting-edge fields that promote innovation and develop new methods of delivering research training. This approach–which we will implement next year–will accomplish two critical goals identified by the Board: to strengthen academic centers and to increase the number of scientists in disciplines essential to our industry's efforts to develop new medicines that help and heal patients.

To help develop this approach, we convened a senior advisory panel of industry R&D leaders. On behalf of the Board, I thank them and recognize four leaders–the late Robert I. Levy, M.D., Senior Vice President, Science & Technology, American Home Products Corporation; Lee E. Babiss, Ph.D., Vice President of Preclinical Research & Development, Hoffmann-La Roche Inc.; Frank L. Douglas, Ph.D., M.D., Executive Vice President, Aventis Pharmaceuticals Inc., and Robert J. Dinerstein, M.D., Ph.D., Senior Research Scientist, Aventis Pharmaceuticals Inc.

The strategic changes made by the Board renew the Foundation's sense of purpose. We are confident that, with its redesigned programs, the PhRMA Foundation will be better able to help the pharmaceutical industry meet the scientific challenges of the 21st century and the needs of the patients it so proudly serves.

president's message

Del Persinger

Over the past 35 years, the PhRMA Foundation has established an outstanding record of achievement and a national reputation as a highly prestigious program. Much of the credit is due to my two immediate predecessors, Morry Bectel and Donna Moore, who served over a period of 14 years and were deeply committed to the Foundation's mission. I want to thank both of them for their dedication in preserving and strengthening this valuable organization.

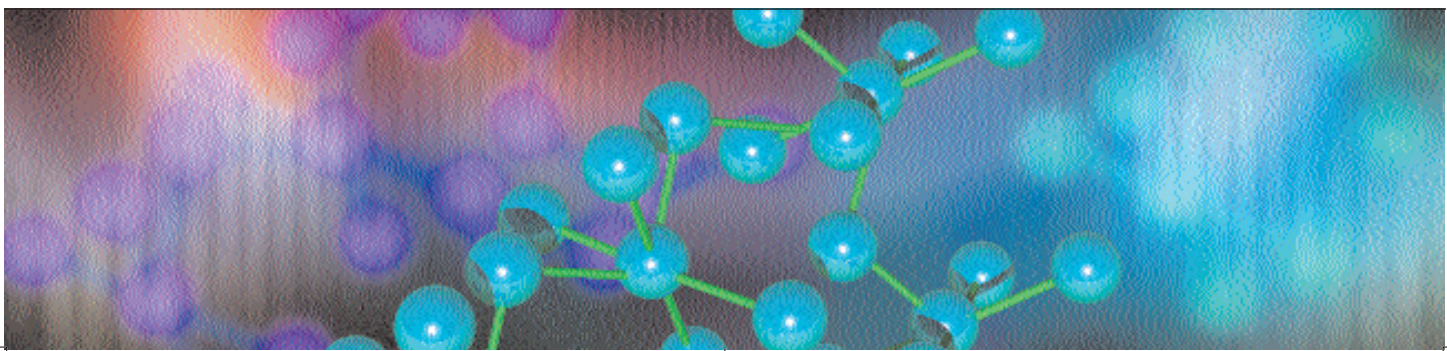
The 41 awards made this year reflect our continuing commitment to helping young scientists in key disciplines at the outset of their careers. These awardees–in the areas of basic pharmacology, clinical pharmacology, pharmacology-morphology, pharmaceutics, pharmacoeconomics, and bioinformatics–and the three recipients of our Awards in Excellence are described in the following pages. This year, I met a number of our current and past awardees at our Foundation events, heard some inspiring personal stories, and received first-hand confirmation of the key role the Foundation plays.

Looking ahead, under the Board's guidance, the Foundation has developed a comprehensive new strategic plan that builds on our achievements. The plan has been carefully crafted with the help of the Foundation's scientific committees, prominent academic and industry scientists, heads of company foundations, and past awardees. The new program, which we will implement in 2001, incorporates two major changes: We will streamline and reorganize existing award programs; and we will establish a new program for academic Centers of Excellence in Research Training–interdisciplinary "incubators" focused on breakthrough science.

The reorganization will consolidate the six existing program areas into four–pharmacology, pharmaceutics, informatics, and health-outcomes research–and concentrate within those areas on cutting-edge subjects. We will emphasize fellowships and research starter grants, increase the size of some awards to make them more competitive, and provide more flexibility to meet changing industry needs.

The new Centers of Excellence will differ from the traditional Foundation programs in size, scope, and process. The Center concept recognizes the industry's and Foundation's role in helping to develop the next generation of leaders in biomedical research; the need for increasingly complex and sophisticated skills and technologies; and the multidisciplinary nature of the training required for careers in pharmaceutical research. The approach is to leverage Foundation resources by partnering with an existing expert research center that has a senior mentor. We will gain access to state-of-the-art expertise and resources; the Center will gain additional resources to recruit and train scientists in disciplines important to our industry–with the first Center focusing on informatics and genomics. In this way, we will build important bridges between industry and academia and provide a model research environment for training future pharmaceutical research leaders. Assuming our first Center is successful after two years of experience, we plan to start a second Center devoted to health outcomes research or predictive technologies.

The backbone of all this work–both our continuing program and our strategic planning for the future–is the membership of the Foundation's scientific committees. Our committees comprise an extraordinary



group of highly distinguished and accomplished scientists who have shown enormous dedication and an uncanny ability to identify top talent in our universities. The vast majority of Foundation awardees–after the Foundation's initial help–remain in research, obtain major follow-up funding for continued training, and truly distinguish themselves in their subsequent careers, as the examples in these pages show. The Foundation could not have established this record of success without the long-term dedication of our committee members. It is a true honor and pleasure to work with this group, and I give special thanks to each and every one: to Bill Darrow, our Chief Scientific Advisor, our committee chairmen, and all the members, who are mentioned later in this report.

Also, my thanks to Eileen McCarron, who joined the Foundation a year ago as Director of Development, for her great work in carrying through the current Foundation program while helping to create the new one.

Along with our Board and our committees, Eileen and I firmly believe that our new program will strengthen our tradition and take us to a new level in serving the needs of young scientists, academic centers, the pharmaceutical industry, and most of all, patients.

With great sadness and sense of loss, we note the death of Dr. Robert I. Levy as this *Annual Report* was going to press. Dr. Levy was a stong believer in the Foundation's mission and was instrumental in the development of our new program. We are grateful for his support and will long remember his contributions.

awards in excellence

Every year, the PhRMA Foundation grants Awards in Excellence to past awardees who are dramatic, living proof that the Foundation program works and makes a difference. These awards are given to scientists who received a Foundation grant at the outset of their careers in a discipline important to the research-based pharmaceutical industry when they were deciding on their area of specialization–and went on to distinguish themselves through their scientific and/or academic achievements.

This year's three awardees have distinguished themselves in the areas of clinical pharmacology, pharmacology, and pharmacology-morphology. The Foundation is proud of their achievements and is proud to have been of assistance to them at the beginning of their outstanding careers. They exemplify the very best in their chosen fields. What they have achieved makes it easier to appreciate the importance of providing the same kind of support for those who will follow in their footsteps.

The awardees were honored at a reception sponsored by Reed Exhibition Companies. The reception featured remarks by Boomer Esiason, of NFL fame, who praised the pharmaceutical industry for developing new treatments for cystic fibrosis that have greatly helped his son, and by Dr. Bruce Stanton, Professor of Physiology at Dartmouth Medical Center and a former Foundation awardee, who discussed the new treatments for cystic fibrosis and the outlook for future advances.

The recipients of the PhRMA Foundation Awards in Excellence for 2000 are:

D. Craig Brater, M.D.

Craig Brater, M.D., who is Dean of the Indiana University School of Medicine, the author of many important publications, and the recipient of many awards and honors, received a PhRMA Foundation Research Starter Grant early in his distinguished career in teaching and research.

Dr. Brater is the author or co-author of 117 research publications, 54 book chapters, 33 reviews, and 32 symposia. The primary focus of his research has been on the experimental aspects of the pharmacology and toxicity of aminoglycosides, loop diuretics, and non-steroidal anti-inflammatory agents.

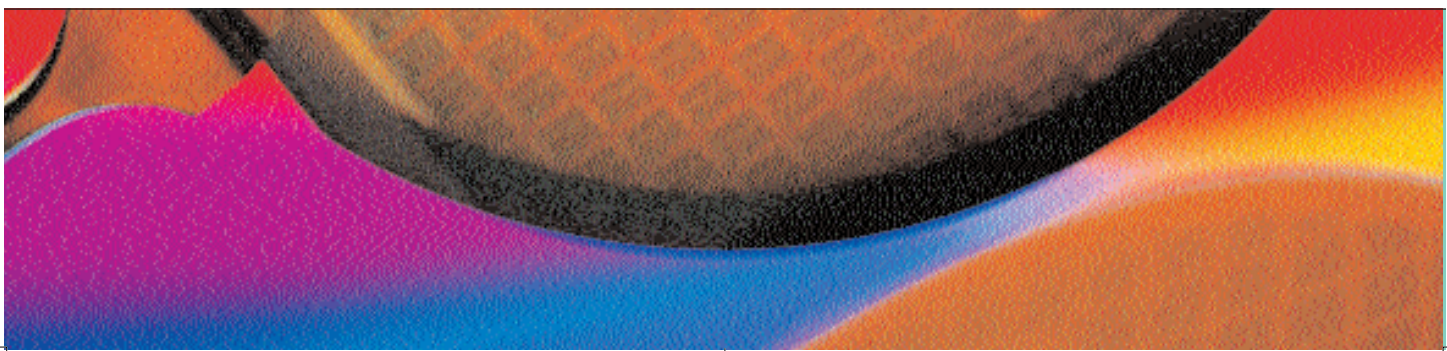
Dr. Brater has held academic appointments at three medical schools, has been a professor of Medicine and Pharmacology at Indiana University for the past 14 years, and was Chairman of the Department of Medicine for 10 years until his recent appointment as Dean of the School of Medicine. He is the principal investigator on two individual investigator grants and one training grant from the NIH and is co-investigator on another grant. In addition, he is principal investigator on an FDA Clinical Pharmacology Award.

Dr. Brater received his BA in Chemistry and a Doctorate of Medicine from Duke University. His many awards include a Research Career Development Award from the NIH, the Rawls Palmer Progress in Medicine Award of the American Society for Clinical Pharmacology and Therapeutics, and the Duke University Distinguished Alumnus Award.

Thomas E. Ellenberger, D.V.M., Ph.D.

Thomas E. Ellenberger, D.V.M., Ph.D., a leading structural biologist, received a PhRMA Foundation Fellowship for Advanced Predoctoral Training in Pharmacology/Toxicology in 1987 while studying gene amplification in multidrug resistant strains of the human parasite *Leishmania major*. Early in his career, he realized that the future of pharmacological research would depend on detailed structural analysis of the protein targets for drugs.

An Associate Professor at Harvard Medical School, Dr. Ellenberger has conducted a series of breakthrough research projects. In 1996, he published a paper that provided a structural foundation for studying excision repair of alkylation-damaged DNA.



Two years later, his research on human alkylabase-DNA repair enzyme complexed to DNA clearly demonstrated the mechanism of nucleotide flipping that exposes damaged bases in DNA for excision by DNA N-glycosylases.

In 1998, Dr. Ellenberger also published a paper that was a landmark step in the structural biology of DNA replication, showing a replicative polymerase complexed to DNA and nucleotide substrates. This work provided direct evidence for two metals that catalyze DNA synthesis, and it revealed an induced fit mechanism for selecting the correct nucleotide for incorporation opposite a DNA template.

Dr. Ellenberger's recently published structure of the DNA-interacting domain of a hexameric DNA helicase is a significant breakthrough in another part of the DNA replication story. This new structure established a foundation for building pharmacological approaches to targeting replicative helicases for antimicrobial treatments. Dr. Ellenberger's ultimate goal is to use X-ray crystallography to create a three-dimensional picture of a complete replicative fork at atomic resolution.

After obtaining his D.V.M. degree from Iowa State University in 1983, Dr. Ellenberger obtained his Ph.D. in Pharmacology from Harvard Medical School in 1989. He then received training in X-ray crystallography during postdoctoral studies at Harvard University before joining the faculty of Harvard Medical School in 1993.

Kenneth P. Minneman, Ph.D.

Kenneth P. Minneman, Ph.D., who is Professor of Pharmacology at Emory University School of Medicine, received a Faculty Development Award from the PhRMA Foundation in 1981. His teaching and research have focused on adrenergic receptor pharmacology and signaling.

At Emory, Dr. Minneman supervises the research of undergraduates, graduate students, and postdoctoral research associates, and teaches medical and graduate pharmacology and neuroscience courses. He is the co-editor of a medical textbook, *Medical Pharmacology: Molecular to Clinical.*

Dr. Minneman attended the Massachusetts Institute of Technology, where he received a B.S. after formulating his own major in interdisciplinary biological sciences with a focus on psychology, neuroscience, and physiology. He received a Ph.D. in Pharmacology from the University of Cambridge in England. His postdoctoral training was at the University of Colorado Medical Center.

Dr. Minneman has been at Emory University for 20 years. He has participated in seminars at many universities, organized and participated in numerous conferences in the U.S. and abroad, and served as a consultant to pharmaceutical companies on various aspects of drug development.

The PhRMA Foundation is indebted to the generous support of Reed Exhibition Companies, which sponsored the Foundation's special reception for the 2000 Awards in Excellence and made a contribution to the Foundation. A special thanks is extended to Kevin Richards, Industry Vice President, and Michael Critser, Director, Industry Development, who made this event a success.

left to right: Kenneth Minneman, Thomas Ellenberger, Boomer Esiason, Bruce Stanton, and D. Craig Brater

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 the best indication of the value of the Foundation's program comes from the words of the awardees themselves. Some of their comments follow:

◆ *"The first grant I ever received was from the PhRMA Foundation. That helped launch my research career and I was subsequently funded by NIH."*

That's from August M. Watanabe, Executive Vice President of Science and Technology and Member of the Board of Directors, Eli Lilly and Company. Prior to joining Lilly in 1990, Dr. Watanabe spent 18 years at Indiana University School of Medicine, where he served as Professor of Medicine and Chairman of the Department of Medicine.

◆ *"PhRMA Foundation support has been crucial in my career. I first received a Postdoctoral Fellowship in Clinical Pharmacology and then a Faculty Development Award. Without this support, my career in clinical pharmacology could not have begun. When I moved to the Mayo Clinic, I also received a New Program Award. That award helped start the successful building of the program here at Mayo. The fact that PhRMA Foundation funding is specifically directed toward clinical pharmacology is crucial for the ongoing viability of this important field. It is doubtful whether I would have entered the field of clinical pharmacology without the generous support from the PhRMA Foundation."*

So says James J. Lipsky, M.D., Director of Clinical Pharmacology at the Mayo Clinic and Professor of Pharmacology and Medicine at the Mayo Medical School.

◆ *"The PhRMA Foundation funding was for my early faculty career at Vanderbilt University in Pharmacology and Medicine (Clinical Pharmacology). At Vanderbilt, we were required to obtain funding to support our salary and our laboratory. Part of this support was by the PhRMA Foundation and was critical in allowing me the time to establish a laboratory as well as to teach."*

That's from Alan S. Nies, Sr., M.D., Senior Vice President, Clinical Sciences, Merck Research Laboratories.

◆ *"The PhRMA Foundation Fellowship in Clinical Pharmacology supported my core training in clinical pharmacology during 1977-79. It provided the opportunity to obtain training in conducting clinical research, laboratory analysis, and pediatric pharmacokinetics, as well as experience in designing clinical trials in pediatric pharmacotherapy in childhood asthma and other childhood disorders. It also gave me the unique opportunity to meet leaders in the field of clinical pharmacology, with many serving as role models for my own career development."*

So says Stanley J. Szefler, M.D., who holds the Helen Wohlberg & Herman Lambert Chair in Pharmacokinetics at the National Jewish Medical and Research Center, is Director of the Pediatric Clinical Trials Center, and is a Professor of Pediatrics and Pharmacology at the University of Colorado Health Sciences Center.

◆ *"The Faculty Development Award was particularly useful in helping to establish a research program in clinical pharmacology of antithrombotic agents, and the Developmental Award for Clinical Pharmacology Units was instrumental in establishing balanced basic and clinical research programs in the Division of Clinical Pharmacology at Jefferson."*

That's the experience of Thorir D. Bjornsson, M.D., Ph.D., who is Vice President, Clinical Pharmacology, Worldwide Clinical Research & Development for Bristol Myers Squibb. Dr. Bjornsson is also an active member of our Clinical Pharmacology Advisory Committee.

◆ *"My postdoctoral training support from the PhRMA Foundation was a Pharmacology-Morphology Award. This award enabled me to advance my training in the field of Serotonin Receptor Pharmacology. My work during this term of support provided the foundation of my early scientific career. It also positioned me to be a significant founding scientist at Synaptic Pharmaceutical Corporation. Synaptic's first research projects were directed at the cloning and elucidation of Serotonin Receptor function. The awards of the PhRMA Foundation provide research support to scientists at pivotal points in their research careers. My case was no exception!"*

So says Theresa A. Branchek, Ph.D., Vice President for Research at Synaptic Pharmaceutical Corporation, who is responsible for setting the research directions and scientific strategy at her company.

◆ *"The training afforded me by the receipt of the PhRMA Foundation grant permitted me to gain basic pharmacological skills and meld them with my clinical and basic endocrinology skills. My entire career has been an affirmation of that combined training."*

That's the report from Alan D. Rogol, M.D., Ph.D., who spent 25 years at the University of Virginia, the last 15 as Professor of Pediatrics and Chief of the Division of Endocrinology, and is now Principal Clinical Scientist at Insmed Incorporated.

◆ *"The PhRMA Foundation, awarding me a research starter grant and career development award in Clinical Pharmacology in my first year in the United States, facilitated my career by jump-starting my cardiovascular research program, supporting my career development in Clinical Pharmacology, and introducing me to many friends and colleagues in the pharmaceutical industry."*

That's from Michael J. Jamieson, M.D., Regional Medical Research Specialist with Pfizer Inc. He directs Pfizer-sponsored cardiovascular clinical trials and oversees investigator-initiated research (at all levels, from molecular through clinical and outcomes) for nine southwestern states.

◆ *"I received a fellowship award from the PhRMA Foundation that supported clinical and laboratory research in oncology at the Dana-Farber Cancer Institute in Boston and at the Yale School of Medicine. This funding allowed me to pursue independent laboratory studies on the mechanism of cancer cell resistance to certain critical cancer chemotherapy drugs and sparked a lifelong interest in the translation of laboratory discoveries to the clinical arena in an attempt to improve the therapeutic options for patients with cancer and immune diseases."*

That statement is from Susan L. Kelley, M.D., Executive Director, Oncology Clinical Research at Bristol-Myers Squibb Pharmaceutical Research Institute. She has worked in clinical research in the pharmaceutical industry for 13 years with a focus on oncologic and immunologic drug development.

◆ *"The faculty development award granted to me in 1987 provided funding in my academic career, but–equally important–through annual awardee meetings gave me important networking opportunities."*

Those are the words of Ullrich Schwertschlag, M.D., Ph.D., Senior Director, Wyeth/Genetics Institute.

fellowships and grants

The PhRMA Foundation's primary mission is to improve public health through scientific and medical research by providing funding to university-based scientists, researchers and educators. Foundation goals in education and research are accomplished through its twelve funding programs–one in pharmacoeconomics, one in bioinformatics, three in pharmaceutics, three in clinical pharmacology, two in basic pharmacology, and one in the combined field of pharmacology-morphology. The Research Starter Grant provides starter funds in pharmacology, clinical pharmacology, drug toxicology and pharmaceutics. The Foundation also accepts applications in all program areas for research on drugs for rare diseases.

PHARMACOECONOMICS

Faculty Development Awards in Pharmacoeconomics

There is widespread concern about rising health care expenditures as well as increasing interest in understanding the impact of new therapies on patient-focused outcomes such as mortality, functional status, and quality of life. Because of these new perspectives, choices about new drugs are now based not only on traditional safety and efficacy measures, but also on patient-assessed efficacy and economic value measures. A drug development program needs to include all of the outcome measures so that the information needs of the different decision makers can be met. Taking this into consideration, the PhRMA Foundation, recognizing the need for human resources to perform these outcome analyses, has implemented its Faculty Development Awards in Pharmacoeconomics program. Each award offers $40,000 annually for two years. The program is now in its sixth year and has made two awards for 2000.

Beginning their awards in July 2000:

Denise R. Globe, Ph.D., Assistant Professor of Pharmaceutical Economics and Policy, University of Southern California, School of Pharmacy: "Cross-Cultural Adaptations of Methods to Measure Patient Preferences For Health States: A Tool For Pharmacoeconomic Analyses." This project will assess the cultural appropriateness of quality of life (QOL) measurements and the current algorithms used to translate these measures into patient preferences. Ultimately through this research, a cross-culturally validated tool for pharmacoeconomic research, the utility index, will be developed. Additionally, Dr. Globe will be designing a pilot study to assess outcomes of care and cost effectiveness for the pediatric and adult patients with hemophilia, which will be included in a proposal for a pharmacoeconomic analysis expected to be submitted for federal grant support.

David A. Holdford, Ph.D., Assistant Professor, Department of Pharmacy, Virginia Commonwealth University: "Development of a nationally recognized graduate and post graduate program in pharmaceutical outcomes research at VCU." Key elements of this plan include developing a reliable source of research funds, recruiting top students to participate and assist with research, and enhancing a reputation for scholarly research and publications. Dr. Holdford will develop a model for patient satisfaction with pharmaceutical therapy and examine the link between satisfaction and patient behavior (e.g., medication compliance).

BIOINFORMATICS

Faculty Development Awards in Bioinformatics

Begun in 1997, the Faculty Development Award in Bioinformatics seeks to help develop a core of experts in the new science of Bioinformatics. The aim of this discipline is to couple computer technology with the enormous amount of information currently stored in biological databases. It is a process whereby genomic sequence data is turned into molecular biology information for the purpose of benefiting mankind through drug discovery. Because of the shortage of trained scientists and faculty, the PhRMA Foundation is pleased to offer this program. The Faculty award offers $30,000 per year for two years.

Beginning his award in 2000 is:

William N. Grundy, Ph.D., Assistant Professor, Department of Computer Science, Columbia University: "Data-driven Computational Gene Finding and Functional Annotation." A biologist with access to a collection of genomic data wants to answer two primary questions. First, where are the genes within the complete genomic sequence and how are the genes structured? Second, what are the functions of the corresponding proteins? The work proposed here is accordingly divided into two phases. First, to develop and apply a gene finding system. This system is designed to be scaleable and flexible with respect to the gene features it models, the machine learning algorithms it employs, and the range of experimental data from which it learns. The system will be trained to recognize genes in *C. elegans* and human DNA. In the second phase, the gene finding software will be generalized to model families of function-

ally related proteins. Initially, the models will be sequence-based. In order to learn from non-sequential data, functional classification techniques will be developed using a discriminative learning method called support vector machines. This method will take as input the statistics calculated by the sequence-based modeling system, as well as features derived from DNA microarray experiments, the upstream promoter region of each gene, similarity scores to known protein families, and three-dimensional structural information. The resulting discriminative classification system will provide excellent protein recognition capabilities.

PHARMACEUTICS

Undergraduate Research Fellowships in Pharmaceutics

The Undergraduate Research Fellowship program began in 1990 and is designed to encourage undergraduate students in pharmacy, chemistry, biology or a related discipline to pursue an advanced degree in pharmaceutics, thereby increasing the number of well-trained investigators in this important discipline. The Foundation's plan to accomplish this goal is to provide support for undergraduate students to participate in meaningful research projects with motivated, inspiring, and research-active pharmaceutics faculty members.

The pharmaceutics faculty member must apply for the award and, once selected, is provided with a one-year, $5,000 fellowship that the faculty member can provide to a qualified undergraduate of his or her choosing. Five awards were made for 2000, bringing the total number of awards to 97.

Faculty and their undergraduate students who received fellowships between January and July 2000 are:

Kim L. R. Brouwer, Pharm.D., Ph.D., Professor, Division of Drug Delivery and Disposition, University of North Carolina at Chapel Hill
Student: Mitesh G. Prajapati
"Mechanism(s) of Induction of Brain P-glycoprotein." The purpose of the proposed study is to evaluate the time course, dose-dependency, gender specificity and cellular mechanism(s) of P-gp induction by morphine. Male rats will receive different doses of morphine or saline for 5 days. Rats will be sacrificed by decapitation at specified times, and P-gp in brain tissue will be detected by Western blot analysis. To determine if morphine-induced increases in P-gp expression are due to increased mRNA, tissue samples will be subjected to Northern blotting. Results of these experiments will allow assessment of the dose- and/or time-dependency of P-gp induction. Gender differences in P-gp induction will be determined in separate studies. The morphine brain-to-serum concentration ratio will be quantitated and examined as a function of P-gp expression to evaluate the potential pharmacodynamic impact of P-gp induction.

Nandita G. Das, Ph.D., Assistant Professor of Pharmaceutics and **Supid K. Das, Ph.D.,** Associate Professor of Pharmaceutics, Department of Pharmaceutical Sciences, Idaho State University
Student: Jerry T. Holland
"Nanoemulsion Delivery System for Poorly Soluble Antineoplastic Agents." Major drawbacks of many currently marketed antineoplastic drugs include poor aqueous solubility and toxicity to host tissue such as the bone marrow and gastrointestinal tract. This study proposes the formulation of lipid based nanoemulsion delivery systems (average droplet diameter <500 nm) administered orally or parenterally, which would enhance the bioavailability of an antineoplastic drug and improve its efficacy by reducing dosage size and frequency and thus reduce toxicity. Tamoxifen citrate, a drug of choice in breast cancer therapy but with limited aqueous solubility, will be the model drug for this project.

Teruna J. Siahaan, Ph.D., Associate Professor, Department of Pharmaceutical Chemistry, University of Kansas
Student: Jennifer Page "Modulation of Intercellular Junctions of HAV-peptides." The long-term objective of this project is to understand how to modulate tight intercellular junctions by regulating protein interactions that mediate the intercellular junctions for improving drug delivery. Tight intercellular junctions are mediated, at least in part, by cell surface proteins called E-cadherins. Cadherin-mediated cell-cell adhesion is produced by homophilic interactions in which E-cadherin molecules from one cell interact with other E-cadherin molecules from another cell. The hypothesis is that peptide sequences similar to those found in the binding region of cadherin-cadherin interactions can be used to modulate E-cadherin-mediated cell adhesion in an equilibrium fashion; thus, they can be used to identify the mechanisms of intercellular junction formation by E-cadherins. Here, the undergraduate student will use cadherin peptides to modulate intercellular junction for improving paracellular delivery of marker molecules using *in vitro* cell culture models.

Philip C. Smith, Ph.D., Associate Professor, Division of Drug Delivery and Disposition, University of North Carolina at Chapel Hill

Del Persinger, President and CEO of the PhRMA Foundation, presented the Foundation's 2000 Faculty Awards in Pharmacoeconomics at the 5th Annual Meeting for the International Society for Pharmacoeconomics and Outcomes Research in Arlington, Virginia on May 23, 2000. The Foundation is grateful to ISPOR for this opportunity to highlight its scientists.

left to right: Del Persinger, Denise Globe, from the University of Southern California and David Holdford, from the Virginia Commonwealth University.

Student: Melanie Tallman
"Disposition of Omeprazole in CF-Knockout Mice." This laboratory has preliminary data indicating that the CF-knockout mouse model manifests similar increased clearance for a wide range of drugs as seen in humans with CF. Omeprazole is a proton pump inhibitor widely used in children, especially CF children, for gastric esophageal reflux disease (GERD). Children with GERD are often refractory to drug therapy, progressing to surgical intervention to remedy the problem. The proposed research effort will perform pharmacokinetics studies of omeprazole disposition in CF-knockout mice (-/-) relative to heterozygous non-CF (+/-) littermates and wild-type mice (+/+) to determine if increased clearance of omeprazole or poor bioavailability may occur in humans with CF. With the ability to perform intravenous and oral studies in the CF mouse model, the experiments will be able to discern if possible reduced AUC in CF is due to altered bioavailability or systemic clearance of omeprazole. If these studies document altered AUC for omeprazole in CF, they will be used as preliminary data to justify further clinical studies of omeprazole in children with CF.

Robert M. Straubinger, Ph.D.,
Associate Professor, Department of Pharmaceutics, State University of New York at Buffalo
Student: Geraldine Colella
"Molecular Markers of Liposome-Mediated Cancer Drug Delivery." This research program is focused on defining the mechanism by which liposomal association of taxol (paclitaxel) reduces toxicity in animal models. To date, pharmacokinetics indicates very subtle differences between liposomal paclitaxel and the clinical formulation Taxol®,which is given in Cremophor EL and ethanol. However, these results are consistent with a delay in exit of the liposome-delivered drug from the central to the peripheral compartment. However, information on the biological response to drug deposition in the various tissues is lacking. The undergraduate candidate will investigate several biological effect endpoints as tissue markers of paclitaxel disposition. Formulation characteristics will be varied, and magnitude of the biological responses will be quantified. Markers of apoptosis, such as Caspase 3, will be investigated initially. Subsequently, drug-responsive gene expression endpoints will be investigated, once an intense, ongoing effort within the laboratory yields opportunities for participation suitable for an undergraduate research project in the area of biopharmaceutics.

Fellowships for Advanced Predoctoral Training in Pharmaceutics

In effect for 12 years, this program assists awardees who have one or two years remaining in their pharmaceutics predoctoral training–the time during which they are engaged in dissertation research.

The fellowship program provides a stipend of $12,000 a year for two years and $500 a year for incidentals directly associated with the preparation of the dissertation. Four awards were made for 2000, bringing the total number of awards to 75.

Those who received fellowships that began between January and August 2000 are:

Jeremy A. Bartlett, School of Pharmacy, University of Wisconsin at Madison: "Chemical Aspects of Mitochondrial Targeting in Photodynamic Therapy." The objective of this research project is to develop a reliable model to guide the design of new photosensitizers specifically tailored to promote selective destruction of carcinoma cells via mitochondrial targeting. Since cell and mitochondrial membrane potentials are negative inside, extensively conjugated cationic compounds displaying appropriate structural features are electrophoretically driven through these membranes and tend to accumulate into the cytosol and within cell mitochondria. The preferential uptake and retention of some of these cationic species by tumor cells, as compared to normal cells, have motivated the examination of mitochondrial targeting as a therapeutic strategy of relevance for both chemotherapy and photochemotherapy of neoplastic diseases. Mr. Bartlett proposes to investigate how molecular structure controls the subcellular site(s) of accumulation of extensively conjugated cationic dyes using a comprehensive series of closely related molecules. By imposing sequential, monotonous, variations in the structure of these model dyes he will explore in detail how the lipophilic/hydrophilic character, molecular size, and other structural features modulate carcinoma cell mitochondrial accumulation.

Heidi Mansour, School of Pharmacy, University of Wisconsin at Madison: "Phase Behavior and Spreading of Phospholipids at The Air-Water Interface." This study is primarily concerned with the factors that influence the spreading of phospholipids from a bilayer state to a monolayer state at the air-water interface, and, in particular, the interrelationships between bilayer and monolayer phase behavior for binary systems. Such interrelationships are particularly important in the areas of lung surfactant replacement therapy and pulmonary drug delivery where the air-water interface plays a major role, in the stability of pharmaceuti-

The PhRMA Foundation is grateful to the American Association of Pharmaceutical Scientists for recognizing the Awardees of the 2000 Advanced Predoctoral Fellowships in Pharmaceutics at its Annual Meeting in Indianapolis on October 29, 2000.

cal dispersions, and in lipid-based drug delivery. To optimize bilayered phospholipid systems, a highly ordered and tightly packed saturated phospholipid that is capable of lowering the surface tension of water will be mixed with another type of phospholipid that is more disordered, fluid, and capable of promoting bilayer spreading and membrane fusion phenomena. Bilayer phase behavior, spreading behavior from a bilayer to a monolayer, and the surface phase behavior of the monolayer formed at various temperatures and phospholipid compositions will be systematically examined. Based on the mixing tendencies of the components in the bilayer, Ms. Mansour hopes to be able to predict the surface phase behavior in the monolayer, and vice versa.

Matthew D. Troutman, School of Pharmacy, University of North Carolina at Chapel Hill: "The Relationship of Membrane Diffusion and Partition Parameters to the Barrier Functions of P-glycoprotein and Cytochrome P450 3A4 in Limiting Intestinal Absorption." Two of the most formidable barriers to intestinal absorption have been identified a P-glycoprotein (P-gp), the apically directed efflux pump, and Cytochrome P450 3A4 (CYP3A4), a major phase I oxidative enzyme. Both proteins have a broad overlapping substrate specificity that includes a diverse set of lipophilic compounds. The current *in vitro* techniques used to study the extent of P-gp and CYP3A4 activity on reducing the absorption their substrates have shown a poor ability to predict the actions of these proteins actually seen in the intestine. A reason for this discrepancy could involve a lack of understanding of the role of the physicochemical properties of drug molecules that determine passive diffusion across cell membranes and how these properties act to modulate the activities of P-gp and CYP3A4. A better understanding of how these substrate properties influence the results of *in vitro* activity assays will allow a refinement of these assays leading to a better correlation with *in vivo* intestinal absorprion.

Kevin S. Warner, Department of Pharmaceutics, University of Utah: "Structure-function Relationships of Chemical Skin Permeation Enhancers." Mr. Warner proposes to gain a mechanistic understanding of chemical permeation enhancement for the lipoidal pathway of hairless mouse skin (HMS) stratum corneum (SC). The studies will include the following specific aims: (1) examining the structure-function relationships of various homologous series of amphiphilic enhancers; (2) determining the effects of the enhancers used in (1) on the partitioning of model permeants into the transport rate-limiting lipid domains of HMS SC.

Specific Aim 1: Flux enhancement for the lipoidal pathway of HMS SC will be systematically determined using various homologous series of amphiphilic, nonionic, and ionic enhancers with model lipophilic permeants. Specific Aim 2: It is proposed to assess directly the effects of chemical permeation enhancers at isoenhancement concentrations (determined from the transport studies described in aim 1) on the partitioning of a lipophilic permeant into the lipid domains of HMS SC. These results should reveal the extent to which increases in permeant partitioning induced by the enhancers may contribute to the permeation enhancement.

Postdoctoral Research Fellowships in Pharmaceutics

Complementing the other two pharmaceutics programs offered by the Foundation, the Postdoctoral Research Fellowships in Pharmaceutics was initiated to encourage more qualified graduates to obtain the postdoctoral research training so vitally needed in the area of pharmaceutics. The PhRMA Foundation and its Pharmaceutics Advisory Committee recognize the critical need for such well-trained scientific investigators. The postdoctoral award provides $25,000 per year for two years. Since its inception, 11 awards have been given.

This award was not granted in 2000.

CLINICAL PHARMACOLOGY

The clinical pharmacology program provides funding at three levels–student, postdoc, and faculty.

Faculty Awards in Clinical Pharmacology

The Foundation Faculty Development Awards in Clinical Pharmacology program makes three-year awards to medical schools for salary and fringe benefit support of full-time junior faculty members. A ceiling of $40,000 has been set for Foundation support for any candidate in this area. 116 individuals have been supported under this program since 1967.

Recipients of the awards that began July 2000:

Bjoern C. Knollmann, M.D., Instructor, Georgetown University School of Medicine: "Modifiers of Cardiac Calcium Signaling and Their Role in the Treatment of Heart Failure." Ca^{2+} signaling between the cardiac Ca^{2+} channel and the sarcoplasmic Ca^{2+} release channel (ryanodine receptor) is an integral step in cardiac excitation-contraction coupling. A defect in this process may contribute to the impaired cardiac contractility found in humans with end-stage heart fail-

ure. Such defective signaling between the Ca^{2+} channel and the ryanodine receptor has been found in several animal models of heart failure, including transgenic mice overexpressing calsequestrin, a sarcoplasmic Ca^{2+} binding protein. In the proposed research, Dr. Knollmann will use this transgenic mouse model to investigate the mechanism of action of modifiers of cardiac Ca^{2+} signaling. By linking cellular Ca^{2+} signaling with functional studies *in vivo*, the proposed research will provide data on whether modifications of Ca^{2+} signaling will result in a therapeutic benefit.

Brendan F. McAdam, M.D., Assistant Professor, Division of Cardiology, Vanderbilt University School of Medicine: "Role of COX-2 in Vascular Prostacyclin Generation in Conditions Associated with Platelet Activation *In Vivo*." Prostaglandins (PGs) are formed by the catalytic activity of the cyclooxygenase enzymes (COX). There are two forms of this enzyme called COX-1 and COX-2: COX-1 is constitutively expressed and forms prostaglandins that mediate physiological responses whereas the inducible COX-2 is thought to be the isoform responsible for PG generation in inflammation. Two new drugs that are selective for the COX-2 isoform, Celecoxib and Rofecoxib, have recently been approved. Although COX-2 has traditionally been viewed as playing a negligible role in vascular prostacyclin (PGI_2) production, recent data suggest that COX-2 is constitutively expressed in endothelium and contributes to the formation of prostacyclin under physiological conditions. Endothelial (PGI_2) in part counteracts the activity of thromboxane (TxA_2), a potent platelet agonist and vasoconstrictor. Cigarette smoking, hypercholesterolemia, and diabetes mellitus are conditions associated with activation of platelets with increased formation of thromboxane A_2. The present studies will examine the contribution of COX-2 to the formation of PGI_2 in these clinical settings, to address the hypothesis that selective inhibition of COX-2 may result in an isolated reduction in prostacyclin leading to a relative shift in the balance of these prostanoids towards the unopposed prothrombotic effects of TxA_2.

Patrick Murray, M.D., Assistant Professor of Medicine, Anesthesia and Patient Care, University of Chicago Medical Center, University of Chicago: "The Effects of Vasoactive Drugs on Regional and Systemic Perfusion in Human Septic Shock." The term sepsis refers to the systemic inflammatory response to infection. Sepsis may lead to refractory hypotension (septic shock) and multiple organ system failure (MOSF). Unlike hypovolemic or cardiogenic shock, septic shock is associated with impaired vasoconstriction and elevated cardiac output. Despite increased cardiac output and oxygen delivery, death often ensues from refractory hypotension or subsequent MOSF. In addition, although overall systemic vascular resistance is diminished, regional vasoconstriction is also found in septic shock, notably in the renal, pulmonary, mesenteric circulations.

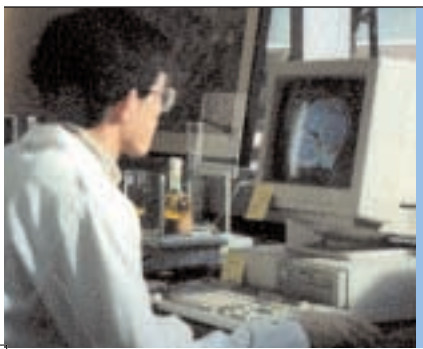
This application seeks to determine the regional circulatory effects of restoring vascular contractility with standard exogenous catecholamines and the novel use of exogenous vasopressin, alone or in combination, in septic humans, focusing on renal perfusion and function. Dr. Murray will also examine the systemic and regional effects of targeted vasodilator therapy with fenoldopam (a novel dopaminergic agonist) in septic humans, alone or in combination with the aforementioned vasoconstrictors. The aim of these experiments is to develop rational pharmacologic regimens and strategies for hemodynamic support in septic shock, focusing on prevention and management of septic acute renal failure, as a surrogate endpoint used to optimize systemic perfusion in hyperdynamic septic shock.

Fellowships for Careers in Clinical Pharmacology

The second award the clinical pharmacology program provides is postdoctoral Fellowships for Careers in Clinical Pharmacology. These fellowships offer clinicians an opportunity for intensive study in any of the basic sciences that fall within the general field of pharmacology. The program is open to physicians, dentists, and veterinarians who are well into their clinical training and wish to pursue careers in clinical pharmacology. With the year or two of support offered by this fellowship, depending on the particulars of the undertaking, a recipient can pursue full-time study in the basic pharmacologic sciences needed to complement clinical skills.

The program allows an awardee to apply for a fellowship three years in advance of the activation date of the award. For example, those applying for a fellowship in the fall of 2000 may request that the fellowship begin in July 2001, 2002, or 2003.

Although the level of support varies, it should be within existing stipend levels for equivalent postdoctoral fellows. First awards under this program were made in 1973. Since that time, 70 fellowships have been awarded, including the three awarded in 2000. The program provides up to $24,000 per award per year.



The PhRMA Foundation was honored to participate in the opening session of the 2000 Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics on March 14, 2000, in Los Angeles, California. We thank ASCPT for the privilege of presenting our Clinical Pharmacology Awards at this exclusive event.

Recipients who began their award in July 2000:

Andrew P. Beelan, M.D., Department of Medicine, Dartmouth Medical School: "A Clinical, Pharmacokinetic and Pharmacodynamic Study of the Combination of Cisplatin and UCN-01 in Cancer Patients." This a phase-I study of the combination of cisplatin, a non-phase specific DNA strand alkylator, and UCN-01, a protein kinase C inhibitor, in patients with advanced stage solid tumors. The specific aims of the project are: (i) to establish the maximum tolerated dose (MTD) of the combination of cisplatin followed by UCN-01 in patients with advanced solid tumors; (ii) to determine the pharmacokinetics of free cisplatin and total and free UCN-01 when cisplatin is administered 24 h prior to UCN-01, and (iii) to determine tumor p53 status at baseline, and proliferating cell nuclear antigen (PCNA) and Cyclin B1 levels at baseline, post cisplatin and post UCN-01 therapy.

Amos Bodner, M.D., MBA, University of Chicago School of Medicine: "The Elucidation of HIV-Induced Neurotoxicity." AIDS dementia caused by the HIV is characterized histologically by neuronal apoptosis despite evidence that the virus does not infect neurons. gp120, *in vitro* and *in vivo*, causes neuronal apoptosis by mechanisms only partially deduced. Proposed studies, in acutely isolated and cultured rat neurons and a human neuronal cell line, will determine: 1) the relative roles of the JNK pathway, mitochondrial membrane potential changes, and free radical production in HIV-induced neuronal apoptosis; 2) the relative efficacy of chemokines in neuronal rescue, and 3) potential therapeutic targets for the prevention of HIV dementia.

Iole Ribizzi, M.D., Brown University School of Medicine: "Amifostine Cytotoxicity in a Human Myelodysplastic Cell Line." Myelodysplastic syndromes are a group of heterogeneous hematological disorders characterized by ineffective hematopoiesis and peripheral blood cytopenias. Amifostine (AMF), a phosphorylated aminothiol, is currently used with selected cancer chemotherapeutic agents to provide broad-spectrum protection of various normal tissues. It also has been used to treat myelodysplastic syndromes (MDS), where it produces a stimulatory effect on hematopoiesis with a single or multilineage hematological response in 83% of patients. In this regard its mechanism of action is unknown. Dr. Ribizzi's findings have led her to hypothesize that exposure to AMF induces apoptosis in MDS cells. To test this hypothesis, three specific aims are proposed. First, to complete the evaluation of the cytotoxicity of AMF in MDS cells. This study will optimize and refine the exposure and the concentration of AMF. Second, to determine the relation between AMF-induced cytotoxicity and DNA fragmentation utilizing flow cytometry and gel electrophoresis techniques. Third, to assess the effect of AMF exposure in the expression of proteins involved in the induction of apoptosis including p53, Poly ADP ribose polymerase and caspase III and IX. It is anticipated that the results of this study can be rapidly translated into novel therapies for the treatment of MDS.

Medical Student Research Fellowships

The third program is the Medical Student Research Fellowships. This program, which began in 1974, offers students an opportunity to spend up to two years full-time conducting an investigative project in pharmacology-clinical pharmacology. The minimum period of the $12,000 award is three months and the maximum is two years. It is hoped that by having students become involved in investigative projects at a point when career choices are still relatively flexible, they will eventually choose research careers in clinical pharmacology. One hundred and forty-one awards have been made since 1974, including the three awarded in 2000.

Individuals whose awards began in 2000 are:

Joseph Y. Choi, State University of New York Health Science Center at Syracuse; "Calcium Mediated Inositol 1, 4, 5-trisphosphate Receptor Expression in Cerebellar Granule Cells." The mobilization of calcium (Ca^{2+}) from the extracellular and intracellular compartments increase cytoslic Ca^{2+}, which is a critical second messenger in cellular homeostasis. In cerebellar granule cells, Ca^{2+} enters from the extracellular environment through voltage-sensitive Ca^{2+} channels (VSCC), or NMDA receptor-channels. Sequestered stores of intracellular Ca^{2+} are released by the binding of IP_3 to its receptor, designated as the type 1 IP_3R (IP_3R1) in neurons. Dysfunction of these receptors has been linked to neuronal abnormalities such as ataxia and seizures in the mouse model. Understanding the basic mechanisms leading to these abnormalities in a rodent model would allow investigators to focus on the mechanism of IP_3R1 expression. The proposed questions are: 1) Is the IP_3R1 S1+ splice variant expressed in a developmentally, and anatomically specific, manner in the rat brain? 2) What is the functional significance of IP_3R1 S1+ isoform in granule cells? Mr. Choi plans to answer these questions using molecular

Amos Bodner, from University of Chicago receives his award from Darrell R. Abernethy, M.D., Ph.D., PhRMA Foundation Clinical Pharmacology Advisory Committee Member.

Bjoern C. Knollmann, from Georgetown University Medical Center

and calcium imaging techniques. The results from the proposed experiments will contribute to further understanding of IP_3 receptor function in the nervous system.

Bernard Hsiao, University of Miami School of Medicine: "Do Rapsyn-like Proteins Cluster Neuronal Nicotinic Receptors?" Receptor clustering is a key event in synaptogenesis. Aggregating receptors into a limited area vastly improves the efficiency of neurotransmitter signaling. The proteins involved in cluster formation are also important in organizing protein complexes vital to transmembrane signal transmission.

A three-pronged approach will be utilized to investigate this possibility. First, polymerase chain reaction using degenerate primers based on rapsyn will be used to screen nervous system cDNA. Second, database searches of genomic libraries for proteins homologous to rapsyn will be done. Third, a yeast two hybrid screen will be used if the previous homology based isolation techniques are unsuccessful. Candidate proteins will be tested for receptor clustering ability through co-expression of neuronal nAChRs and the protein in *Xenopus* oocytes.

Joseph W. Turek, University of Illinois School of Medicine: "Characterization of the Thromboxane A_2 Receptor Ligand-Binding Domain." It is well known that the arachidonic acid metablolite, thromboxane A_2 (TXA_2), interacts with a G-protein-coupled seven-transmembrane receptor to cause platelet aggregation and vascular smooth muscle contraction. Furthermore, evidence has accumulated that this biological activity is linked to both homeostasis and the genesis of certain thromboembolic disorders, including myocardial infarction and stroke. Based on these considerations, substantial interest has focused on the development of specific TXA_2 receptor antagonists to modulate TXA_2-mediated biological effects. However, despite these research efforts, attempts at rational drug design aimed at developing a specific TXA_2 receptor antagonist have been hampered by a lack of information concerning the TXA_2 receptor ligand-binding domain. The aim of this research project is to characterize the ligand-binding pocket of the TXA_2 receptor by utilizing two independent approaches, namely, photoaffinity labeling and site-directed mutagenesis. In these studies, amino acids involved in ligand-binding should alter the binding pocket, thus preventing appropriate receptor-ligand interactions.

BASIC PHARMACOLOGY

Faculty Development Awards in Basic Pharmacology and Toxicology

In effect for 27 years, the Faculty Development Awards in the Pharmacology program aims to strengthen basic pharmacology by providing support to promising young teachers in this field. To fulfill this goal, support has been provided, on a nationally competitive basis, to full-time junior faculty members who show the potential for outstanding accomplishments.

The program provides stipend and fringe benefits for two years. The level of support is varies, and is aimed at keeping within the existing salary and fringe benefits structure of the applicant university. To date, 76 awards have been made, including two in 2000. The program provides up to $30,000 per award per year.

Recipients of the 2000 Faculty Development Awards in Pharmacology which began July 2000 are:

Randy A. Hall, Ph.D., Assistant Professor of Pharmacology, Emory University School of Medicine: "$\beta_2$2-adrenergic Receptor Signaling: New Ideas and Novel Mechanisms." Stimulation of the β_2-adrenergic receptor (β_2AR) by adrenaline or noradrenaline leads to alterations in the metabolism, excitability, differentiation and growth of many cell types. This project aims to elucidate the molecular mechanisms by which the β_2AR can regulate Na+/ H+ exchange via association with NHERF, and also aims to find out whether the β_2AR can regulate physiological processes other than Na+/ H+ exchange in a NHERF-mediated fashion. Since NHERF seems to act as either an allosteric regulatory protein or adaptor protein, the ability of the β_2AR to regulate the set of intracellular proteins bound by NHERF will be examined. The ability of the β_2AR to regulate the activity of another NHERF binding partner, the platelet-derived growth factor receptor, will also be studied, as will the capacity of NHERF to alter cell growth and proliferation in a β_2AR regulated fashion. The phosphorylation of NHERF by G protein-coupled receptor kinase 6A, and possibly by other kinases, will also be examined, since an understanding of the regulation of NHERF by phosphorylation may be required for an understanding of NHERF-mediated signaling by the β_2AR. These studies will provide insight into novel signaling pathways by the β_2AR, a receptor that is a common target for therapeutics used in the treatment of hypertension, heart disease and other disorders.

Raymond R. Mattingly, Ph.D., Assistant Professor of Pharmacology, Wayne State University School of Medicine: "Regulation of Ras Through the Ras-GRF Exchange Factor." The long-term objectives of Dr. Mattingly's studies are to identify new mitogenic signaling pathways and so identify novel therapeutic targets. Ras is a promising candidate for drug action since it frequently plays a primary role in both the development and maintenance of human tumors. It is his hypothesis that the inappropriate expression and regulation of an exchange factor, such a Ras-GRF, that activates Ras may also contribute to tumorigenesis.

Dr. Mattingly has shown that the exchange factor activity of Ras-GRF is increased by stimulation of G protein-coupled receptors that act to increase the serine phosphorylation state of Ras-GRF. Thus his first two specific aims are: Aim 1–Mapping of the regulatory phosphorylation sites of Ras-GRF. Aim 2–Characterization of the role of the phosphorylation sites of Ras-GRF. Regulation of Ras-GRF activity is complex since it can also be controlled by calcium/calmodulin. Thus his third aim: Aim 3–Integration of the control of Ras-GRF by its multiple regulatory factors. These studies will greatly increase our knowledge of the control mechanisms for Ras and may identify new pharmacological approaches to human cancer.

Fellowships for Advanced Predoctoral Training in Pharmacology and Toxicology

One of the most popular of the Foundation's awards is the Advanced Predoctoral Training in Pharmacology and Toxicology fellowship program. The goal 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.

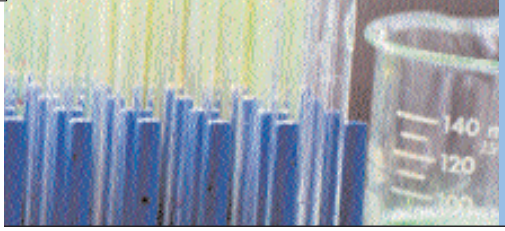
This fellowship provides a stipend of $12,000 annually for up to two years, and $500 a year for incidentals directly associated with preparation of the dissertation.

Two hundred and sixty-eight fellowships have been awarded under this program, including the eight awarded in 2000. The program is in its 23rd year.

Those who have been awarded 2000 fellowships that began between January and August are:

Deanna Grace Adams, College of Pharmacy, University of Arizona: "Caspase-Dependent Cleavage of Bcl-x_L: Interaction with MEKK3." The focus of this research is to identify signaling proteins that regulate apoptosis in response to the anticancer drug, etoposide. Since the Jun kinase pathway has been implicated in apoptosis signal transduction, Ms. Adams has focused her studies on MEKK3, Mitogen-Activated Protein (MAP) Kinase/Extracellular Signal-Regulated Kinase (ERK) Kinase Kinase)(1) which is a protein kinase that activates Jun kinase. The proteins that regulate MEKK3 are not known and so the yeast two hybrid system is used to identify such proteins. Ms. Adams isolated two proteins, 14-3-3ε and Bcl-x_L, that interact with MEKK3 in the yeast two hybrid system. Subsequent experiments have shown that only the caspase-cleaved form of Bcl-x_L interacts with MEKK3. One of the functions of Bcl-x_L and 14-3-3ε proteins is to maintain cell survival or inhibit apoptosis. An interaction between MEKK3 and these proteins suggests that MEKK3 regulates the apoptotic process. Recently, the proteolytic cleavage of Bcl-x_L by caspase-3 has been demonstrated in cells treated with apoptotic stimuli such as etoposide or IL-2 deprivation. The hypothesis of this study is that caspase-dependent cleavage of Bcl-x_L produces a protein, Δ61 Bcl-x_L, that functions as an intracellular activator of MEKK3 kinase activity.

Jay S. Degrosellier, Department of Medicine and Pharmacology, Vanderbilt University: "Role of Type I TGFβ Receptors in Signaling Atrioventricular Cushion Transformation." This project is testing the hypothesis that TGFβ2 signals through a unique receptor complex that includes TBRIII and is responsible for AV cushion transformation. Current models of TGFβ signaling presupposes a Type I receptor (TBRI) in all functional receptor complexes. Initial experiments will determine if the ALK2 or ALK5 TBRI is required for transformation by misexpression of either constitutively active or antisense ALK2 and ALK5. Data from the laboratory suggests a role for both TBRIII and ALK2 in transformation. Therefore the hypothesis that ALK2 directly associates with TBRIII by immunoprecipitation of the receptor complex will be tested. Cell surface ALK2 and TBRIII will be immunolocalize to determine whether they associate in response to TGFβ. An ALK2/re-porter receptor construct will be generated to test whether this interaction is functional. To test the hypothesis that specific Smads are necessary for AV cushion transformation dominant negative and constitutively active Smad constructs will be used. These experiments are part of a concerted strategy to determine whether TBRIII requires a TBRI and downstream Smad signaling.



Selena R. Knight, University of Miami School of Medicine: "Role of Androgen/Androgen Receptor in the Antiproliferative Effects of Vitamin D_3 in Prostate Cancer Cells." Prostate cancer cell proliferation is inhibited by the active metabolite of vitamin D, 1α,25-dihydroxyvitamin D_3 (1,25D); however, the magnitude of growth inhibition varies greatly among human cancer cell lines. The androgen sensitive, androgen receptor (AR) positive cell line LNCaP exhibits the most profound growth inhibition in response to 1,25D whereas androgen independent, AR negative prostate cancer cells such as ALVA31 are comparatively insensitive to this 1,25D-mediated inhibition despite the presence of functional 1,25D receptors (VDR). This proposal will directly test the hypothesis that, in addition to VDR, the AR is required for the antiproliferative effects of 1,25D. The studies will examine whether decreasing AR expression in LNCaP cells renders the cell insensitive to 1,25D antiproliferative actions and whether introducing AR into the AR-negative ALVA31 results in 1,25D sensitivity. The long term goal is to identify essential proteins and signaling pathways required for 1,25D-mediated antiproliferative effects on prostate cancer cells so that predictions of responsiveness to vitamin D-based therapies can be made for individual patients.

Dan F. McCune, Department of Pharmacology, University of Kentucky: "Regulation of the Cellular Localization and Signaling Properties of the Alpha$_1$-Adrenoceptor Subtypes in Rat Vascular Smooth Muscle Cells." The α_1-adrenoceptors (ARs) are G-protein coupled receptors (GPCRs) that maintain vascular tone and systematic blood pressure. Three genes encode three unique subtypes, the α_{1A}-, α_{1B}-, and the α_{1D}-ARs. Previous work indicates that all three receptor subtypes are expressed in peripheral vascular arteries; however, only a single subtype mediates the contractile response in a particular artery. The α_1-ARs also induce vascular hypertrophy. Preliminary evidence indicates that the α_1-ARs differ in their ability to activate hypertrophic growth responses as well. In this proposal, the hypothesis that there are differences in the ability of the α_1-ARs to stimulate hypertrophic responses and activate mitogen activated protein kinase (MAPK) cascades will be tested. The cellular distribution of the α_1-ARs will be characterized, and their co-localization with proteins involved in signaling and receptor trafficking determined. Recent evidence has shown that arrestin-mediated receptor internalization is required for GPCRs to activate the MAPK cascade. Thus, the hypothesis that arrestin-mediated α_1-AR internalization is a prerequisite for the activation of MAPKs will also be tested.

Kristen A. Mitchell, College of Pharmacy, Washington State University: "Immunotoxic Effects of TCDD on Antigen-Specific T Cell Responses." Host resistance to infection with influenza virus is the most sensitive adverse effect reported to date for toxicity resulting from exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a prevalent and extremely toxic environmental contaminant. TCDD-mediated immunotoxicity has been attributed, in part, to the perturbation of T cell-dependent immune responses; however, the precise mechanism underlying TCDD-mediated immunosuppression has not been determined. It has been difficult to define the mechanisms by which exposure to TCDD affects T cells due to the low frequency of antigen-specific T cells that respond to stimulation with antigen. The proposed research will utilize a transgenic model system in which the majority of T cells express receptors specific for influenza virus, thus increasing the number of antigen-specific T cells that respond during infection. The mechanisms by which exposure to TCDD suppresses T cell function will be determined by tracking antigen-specific T cells during influenza infection in TCDD-treated mice. Specifically, experiments are designed to address the hypothesis that exposure to TCDD suppresses the *expansion, differentiation*, and *activation* of T cells during infection with influenza virus.

Henry N. Nguyen, Department of Pharmacology, The George Washington University: "Prevention of Ischemic Neuronal Damage by Inhibition of Calcium Store Depletion." Although many people survive cerebral ischemia caused by stroke or cardiac arrest, most of these patients develop neuronal damage leading to neurological impairment. This dissertation research will test the hypothesis that neuronal damage following cerebral ischemia is caused in part by depletion of Ca^{2+} stores from the endoplasmic reticulum (ER). Mr. Nguyen will use a novel *in vitro* model: oxygen-glucose deprivation (OGD) in human neuronal cell line, SH-SY5Y. The first aim is to test for the protective effect of drugs and drug combinations that selectively regulate cellular Ca^{2+}, and in particular that inhibit ER Ca^{2+} depletion. Secondly to employ digital calcium imaging techniques to measure the effect of OGD on the Ca^{2+} levels in neuronal cells, and the effect of drugs on these levels. Finally, Mr. Nguyen will test OGD-treated cells for activation of signaling mechanisms associated with ER Ca^{2+} depletion, including down-regulation of the anti-apoptosis protein bcl-2, induction of the ER molecular chaperone GRP/BiP, activation of the transcription factor NFκB, and

The PhRMA Foundation extends a special thank you to the American Association of Anatomists for allowing us to present our 2000 Pharmacology-Morphology awards at its 8th Annual Awards Banquet. This distinguished event was held in conjunction with the Experimental Biology 2000 convention April 15-18 in San Diego, California.

phosphorylation of the protein initiation factor eIF-2α. He hopes to elucidate the mechanisms of ischemic neuronal damage and demonstrate drugs or drug combinations that can be used to alleviate such damage.

David S. Thiriot, School of Pharmacy, University of Wisconsin at Madison: "Engineering the Vesicle Monoamine Transporter to Study Structure and Functions: Studies on the role of VMAT native cysteines, sensitivity of VMAT to MTS reagents, and high-affinity dopamine binding domains in human VMAT2 and *C.elegans* VMAT." Reuptake of monoamine neurotransmitter from the synapse is a two-step process involving both plasma membrane reuptake transporters and the synaptic vesicle monoamine transporter.

Mr. Thiriot proposes to study the structure, function and drug binding sites of VMAT by two approaches. The first focuses on the role of cysteines in VMAT, chosen because cysteines are sites of unique chemical reactivity within a protein. This involves using site-directed mutagenesis to remove native cysteines or engineer new cysteines, and sulfhydryl-reactive methanethiosulfonate reagents to derivatize cysteines. Transporters are expressed in COS cells and assayed for ligand binding and uptake. This will provide information on locations of drug binding sites and lead to the generation of a functional cysteine-less or reduced-cysteine transporter, suitable for studies by scanning cysteine mutagenesis or intramolecular cysteine cross linking. The second approach involves the construction of a series of human VMAT2 /*C. elegans* VMAT chimeras and takes advantage of the 20-fold difference in dopamine affinity between these transporters to search for protein domains which contribute to high-affinity dopamine binding. Successful completion of this research will also generate tools that may be useful in future structural studies of VMAT.

Tonya G. Thomas, School of Medical Sciences, Indiana University: "The Role of Gamma-Glutamyl Transferase, Glutathione Peroxidase, and Glutathione Reductase in Diabetic Retinopathy." Prolonged hyperglycemia resulting from diabetes mellitus or experimental galactosemia may induce disorders in the microvascular structures of the body (kidney, nerves and retina), including retinopathy. Alternatively, retinopathy may be triggered by a metabolic abnormality. A lethal -glutamyl transferase (GGT)-deficiency causes mice to develop cataracts within one week of birth. Glutathione peroxidase (GPx) and glutathione reductase (GRx) (antioxidant enzymes, which act on glutathione) and GGT, which plays an important role in both the synthesis and degradation of glutathione, have been found within the neural retina as well as the retinal pigment epithelium (RPE). Activities of these enzymes are known to be influenced by hyperglycemia. In addition, hepatic GGT mRNA levels do not change with alterations in enzyme activity in diabetic rats, suggesting that activity in liver must be controlled by another mechanism, such as glycation or glycosylation. Therefore, the global hypothesis is that any disease state or chemical treatment that depletes retinal GGT activity (whether by decreased mRNA transcription or by protein modification) will lead to retinopathy.

Laura A. Volpicelli, Emory University School of Medicine: "Intracellular Trafficking of Muscarinic Acetylcholine Receptors in PC12 Cells." Muscarinic acetylcholine receptors (mAChR) play a role in learning and memory and are targets for the treatment of Alzheimer's Disease. Recent evidence indicates that intracellular trafficking of G protein-coupled receptors (GPRC) is fundamental for regulation of signal transduction. For example, activation of MAPK cascades may be mediated by GPCR internalization. Following endocytosis, GPCR traffic either to lysosomes for degradation or to endosomes that may facilitate receptor resensitization and recycling. This research project will include a series of experiments to characterize the endosomal compartments that mediate intracellular trafficking and resensitization of endogenously expressed mAChR. Furthermore, GPRC trafficking may be impaired in Alzheimer's Disease (AD), a neurologic disorder involving perturbed cholinergic transmission and decreased mAChR signaling. Many studies demonstrate disrupted trafficking of cell surface proteins in AD brains. Ms. Volpicelli will further test whether pathogenic mechanisms involved in the development of AD disrupt mAChR trafficking and impair signaling.

PHARMACOLOGY-MORPHOLOGY

Fellowship Awards in Pharmacology-Morphology including Cell Biology

The goals of this postdoctoral 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.

To be eligible for an award, a candidate must possess formal training in a morphologic specialty or in pharmacology. However, subsequent training in the complementary discipline, during the period of the fellowship, may be informal. On

left to right: Steve Danzer, from Duke University, Richard M. Nass, from Vanderbilt University, Mei Sun, from Children's Hospital in Boston, and Michael Gershon, M.D., Chairman of the Foundation's Pharmacology/Morphology Advisory Committee.

completion of the program, a fellow should be able to use the tools and concepts of both disciplines.

The awards are for two years. The level of support varies and is to be consistant with existing stipends for similarly trained individuals at an applicant university. The fellowship was first offered in 1968. One hundred and five awards have been made to date, including the three awarded in 2000. The program provides up to $21,500 per year for two years.

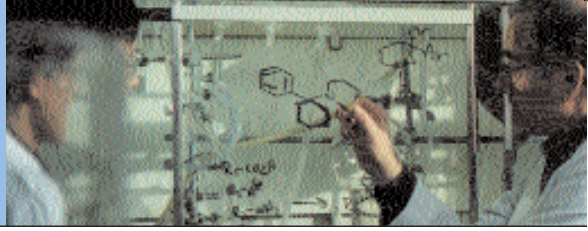
Receiving the fellowship beginning July 2000:

Steve Danzer, Ph.D., Department of Medicine, Neurobiology, Pharmacology and Cancer Biology, Duke University: "Regulation of Dentate Granule Cell Morphology by Neurotrophins and Neurotrophin-Blocking Drugs." Limbic epilepsy is the most common and most devastating form of human epilepsy. The hippocampal dentate gyrus is likely to play a prominent role in the development of this disease. In particular, dentate granule cells normally act as a filter, limiting excitatory input into the hippocampus. Loss of this filtering ability is likely due to the formation of recurrent excitatory synapses among the granule cells as shown by cellular electrophysiological studies. Morphological modifications observed in granule cells during epileptogenesis–sprouting of the mossy fiber axons of the granule cells and/or formation of basilar dendrites–underlie formation of these recurrent excitatory synapses. The molecular determinants of these morphological changes are unknown. Multiple lines of evidence lead us to hypothesize that a neurotrophin, BDNF, causes these morphological modifications. To test this hypothesis, individual granule cells in organotypic slice cultures will be simultaneously transfected by one plasmid expressing green fluorescent protein and another expressing a neurotrophin or a dominant negative of a neurotrophin receptor using biolistic technology. The complete morphology of these neurons will be examined. The ability of neurotrophin-blocking drugs to prevent epileptic changes in an *in-vitro* model will also be tested. This approach combining morphometry with altered expression of identified genes in individual neurons will provide a powerful tool for molecular pharmacological analysis of neuronal structure in health and disease.

Richard M. Nass, Ph.D., Department of Pharmacology, Vanderbilt University: "Pharmacogenetic Analysis and Neuronal Expression of the Dopamine Transporter." The dopamine transporter (DAT) constitutes the primary mechanism for the inactivation of dopamine (DA) neurotransmission in the brain. DAT proteins are high affinity targets for many important addictive and therapeutic drugs including cocaine, amphetamine, and methyphenidate (Ritalin), as well as providing a portal through which the exogenous neurotoxins 6-OHDA, MPP+, and methamphetamine enter the cell. Despite intensive analysis of DATs for more than two decades, little is known on how DATs mediate substrate transport, how antagonist recognition impedes substrate translocation, and how DATs are regulated. In the present application, Dr. Nass will advance a novel preparation for the isolation of DAT mutant, the delineation of DAT trafficking and functional regulators, and the exploration of molecular determinants of neurotoxin sensitivity. We seek to exploit the presence of DA neurons and DAT proteins in the nematode *Caenorhabditis elegans* to identify functionally critical DAT residues, delineate mechanisms of DAT-dependent toxin sensitivity and psychostimulant action, and to identify regulators of DAT expression. Dr. Nass will utilize the finding that DA neurons are sensitive to 6-OHDA in a CeDAT –dependent manner, and the ability to track CeDAT::GFP expression in DA processes, to establish visible screens for mutant CeDATs and CeDAT regulators.

Mei Sun, Ph.D., Department of Endocrinology, Children's Hospital/HMS: "Gene Therapy for Parkinson's Disease." It has previously been shown that HSV-1 vectors that express tyrosine hydroxylase (TH) can support long-term biochemical and behavioral correction of the 6-hydroxydopamine (6-OHDA) rat model of Parkinson's disease (PD). This study has a number of limitations including the use of a helper virus packaging system, limited stability of long-term expression, and expression of only TH. To address these issues, the laboratory in which Dr. Sun works developed a helper virus-free packaging system. Recently, the lab has improved the titers of the helper virus-free vector system, developed a modified neuronal-specific promoter that supports long-term expression, and developed large vectors that can coexpress multiple genes. This fellowship proposes to use the improved vector system to 1. Optimize production of dopamine and correction of the rat model of PD by coexpressing multiple dopamine biosynthetic genes (TH, aromatic amino acid decarboxylase, GTP cyclohydrolase) and a vesicular monoamine transporter; and 2. Optimize protection of nigrostriatal neurons by coexpressing the two neurotrophic factors (GDNF and BDNF) that are known to protect nigrostriatal neurons. These approaches will be tested in the rat models of PD.

On June 5, 2000 in Boston, the PhRMA Foundation presented several 2000 Advanced Predoctoral Fellowships in Pharmacology and Toxicology and Faculty Awards in Basic Pharmacology and Toxicology at the Annual Meeting for the American Society for Biochemistry and Molecular Biology & The American Society for Pharmacology and Experimental Therapeutics. We are grateful to ASPET for this opportunity and extend a special thank you to Christine K. Carrico, Ph.D. for her support at this presentation. E. Leong Way, Ph.D. presented the awards to the Foundation scientists.



RESEARCH STARTER GRANTS

Research Starter Grants are intended to provide financial support to scientists beginning their independent research careers at the faculty level. Grants are made in basic and clinical pharmacology, pharmaceutics, and drug toxicology. The program, in 2000, supported six Research Starter Grants at $25,000 for one year. The first awards were made in 1972; and a total of 519 grants have been made, including the six awards beginning on January 1, 2000.

Recipients of the Research Starter Grant that began January 2000:

Anton M. Bennett, Ph.D., Assistant Professor of Pharmacology, Yale University School of Medicine: "Identification of Substrates for Protein Tyrosine Phosphatases." The control of intracellular signaling cascades that are regulated by protein tyrosyl phosphorylation is dictated by the intrinsic and opposing activities of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). Much has been learned about how PTKs participate in cell growth. However, little is known about the role that PTPs play. The goal of this proposal is to elucidate how the Src homology 2 domain-containing PTP (SHP-2) functions in normal and oncogenic cell growth. A substantial body of evidence indicates that the phosphatase activity of SHP-2 is required for positive signaling downstream of several growth factor receptors. The specific aims of this proposal are two-fold: (1) develop a molecular-screening based approach for the identification of PTP substrates and (2) utilize this methodology to identify the substrate(s) for SHP-2 growth factor signal transduction. Identification of the substrate for SHP-2 will form the basis for elucidating the mechanistic contribution of this enzyme in normal and oncogenic cell growth. This information can be harnessed to reveal potentially new targets for drug design in cancer chemotherapeutics.

Margaret E. Black, Ph.D., Assistant Professor, Department of Pharmaceutical Sciences, Washington State University: "Mechanism of Resistance to Cancer Chemotherapeutic Agents by Guanylate Kinase." An underlying principle in cancer chemotherapy is the exploitation of biochemical and cellular differences that occur between normal and tumor cells by using drugs that target and kill tumor cells. The propensity of cancer cells to develop resistance to antineoplastic agents frequently results in treatment failure. Mutations that result in resistance often occur in key genes such as those that encode enzymes responsible for drug metabolism or are the drug targets themselves. One enzyme, guanylate kinase, is important in the activation of the anticancer drugs, 6-thioguanine and 8-azaguanine, as well as the antiherpetic drugs, acyclovir and ganciclovir that are currently used in gene therapy of cancer with Herpes Simplex Virus type 1 (HSV-1) thymidine kinase (TK).

Dr. Black seeks to randomly introduce mutations into the guanylate kinase cDNA and to select for drug resistant clones by genetic complementation in *E. coli.* Identification of these mutations will reveal changes that can lead to drug resistance as well as amino acid residues that are virtually non-mutable. Understanding the molecular mechanism of drug resistance will be useful for the design of new drugs that evade development of drug resistance and for creating guanylate kinase variants that are recalcitrant to developing resistance for use with HSV-1 TK in gene therapy for cancer.

Roy J. Duhé, Ph.D., Assistant Professor, Department of Pharmacology and Toxicology, University of Mississippi Medical Center: "Molecular Mechanisms of JAK2 Activation." Members of the Janus family of protein-tyrosine kinases (JAKs) are essential early mediators of cytokine-initiated signal transduction. Hyper-activation of the JAK2 has been causally linked to specific leukemias and may be an etiologic agent of other cancers. JAK2 contains an apparent autoinhibitory domain and defects in, or loss of, this domain contributes to JAK2 hyperactivation. Dr. Duhé proposes to use recombinant JAK2 expression vectors to determine whether the loss of the autoinhibitory domain directly induces JAK2 activation or whether this loss merely makes the JAK2 a better substrate for trans-activating protein tyrosine kinases (PTKs) in the cell. This data will provide essential insights into drug design based on the JAK2 autoinhibitory domain. Not only will this promote the development of JAK-suppressive drugs for the treatment of certain leukemias, but it may also provide insight into the development of JAK-enhancing drugs that may be useful in the treatment of immunosuppressive disorders.

Giovanni M. Pauletti, Ph.D., Assistant Professor of Biopharmaceutics/Pharmacokinetics, College of Pharmacy, University of Cincinnati Medical Center: "Rational Prodrug Design to Overcome Drug Resistance." Increasing resistance of tumor cells to cytotoxic agents impairs successful treatment of cancer patients undergoing chemotherapy. Various mech-

left to right: Anton M. Bennett, from Yale University, E. Leong Way, Ph.D., and Margaret E. Black, from Washington State University, Gionvanni M. Pauletti, from the University of Cincinnati Medical Center, and Roy J. Duhé, from the University of Mississippi Medical Center.

anisms have been identified to contribute to drug resistance of cancer cells, including reduced intracellular accumulation of cytotoxic drug molecules due to increased expression of specific membrane efflux systems. The therapeutic challenge of the future, therefore, is to design new approaches that improve delivery of antineoplastic drugs into drug-resistant tumor cells and/or to evaluate alternative drug strategies that minimize development of drug-resistant tumor cells. The objective of this application is to evaluate a novel prodrug strategy that is designed to increase intracellular accumulation of substrates for membrane efflux systems in drug-resistant tumor cells. The central hypothesis to be tested is that prodrugs of rhodamine 123 prepared with a unique folate/peptide promoiety exhibit decreased substrate activity for membrane efflux systems and reproducibly increase intracellular accumulation of the parent molecule in drug-resistant tumor cells.

Katherine L. Perkins, Ph.D., Assistant Professor, Department of Physiology and Pharmacology, State University of New York Health Science Center: "GABA-mediated Excitation of Interneurons in Adult Guinea Pig Hippocampus." *y*-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain, but it might also function as an excitatory transmitter among some interneurons. The objective of this application is to determine the mechanism whereby GABA application leads to the excitation of certain hippocampal CA3 interneurons. Interneurons in hippocampal slices of adult guinea pig hippocampus will be located using an upright compound microscope equipped with infrared/differential interference contrast technology, and the response of the interneurons to GABA application will be recorded intracellularly using microelectrode current-clamp recordings and whole cell voltage-clamp recordings. The central hypothesis to be tested is that GABA excites certain hippocampal CA3 interneurons by acting directly on HCO_3-permeable GABA receptor-channels on those interneurons.

Nephi Stella, Ph.D., Assistant Professor, Department of Pharmacology, University of Washington: "Cannabinoids and Cytokines in Microglial Cell Activation." Several pathologies, such as multiple sclerosis and Alzheimer's disease, are associated with an inflammation of the CNS. Microglial cells, the immune cells of the CNS, are invariably activated in these pathologies and participate in lesion propagation. A current line of research in molecular pharmacology is to investigate the mechanisms underlying microglial cell activation in order to discover novel pharmaceutical targets with anti-inflammatory properties.

The active component of marijuana, Δ9-tetrahydrocannabinol, is immunosuppressive. The signaling pathway linked to these biological effects (the cannabinoid signaling pathway) has been recently described. Neurons and peripheral macrophages express cannabinoid receptors, produce endocannabinoids (the substances that normally engage these receptors), and have the mechanisms responsible for the biological inactivation of these endocannabinoids.

The overall goal of this proposal is to determine if microglial cells express a functional cannabinoid signaling pathway under their quiescent state or during cytokine-induced activation.

Ethical Considerations

The Scientific Advisory Committee as well as the program advisory committees of the PhRMA Foundation are dedicated to ensuring the appropriate use of animals and humans in research. In their deliberations, they consider all aspects of a proposal and may deny support for many reasons. Careful consideration is given to ensure the humane use and care of animal subjects. For human and animal research, the project review committee requires, in writing, a statement of adherence to prevailing standards of ethical research practices. Institutional Review Board approval is required before any research project may be initiated. In addition, informed consent is required before any person can participate in a research project.

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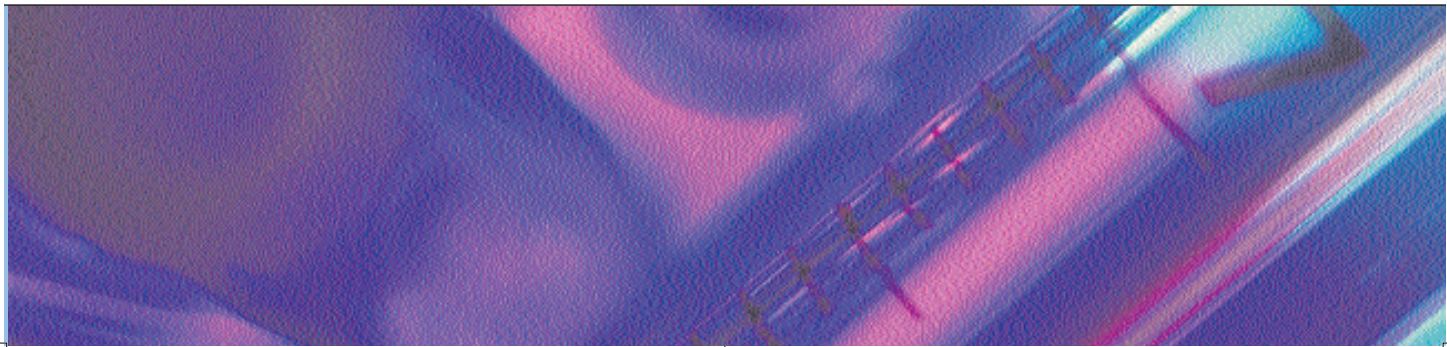


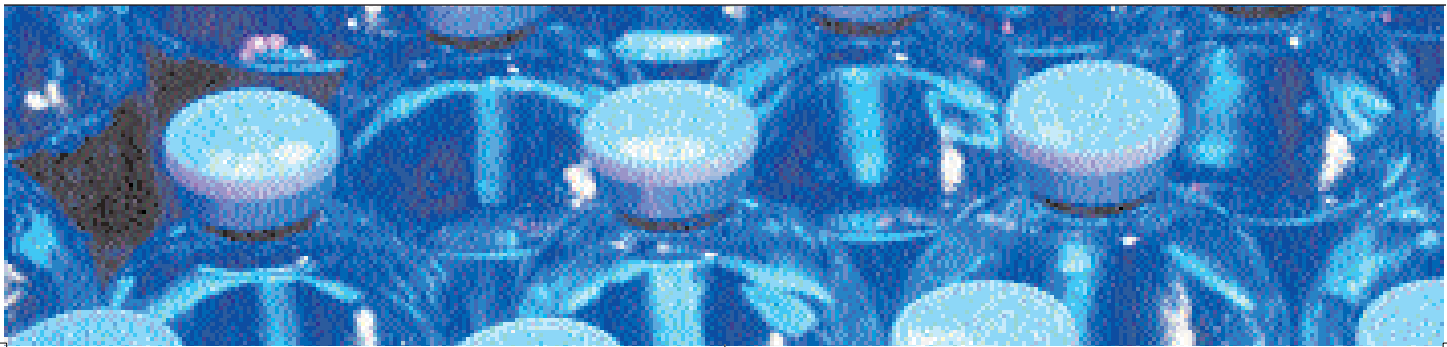
treasurer's report

Patrick J. Zenner

The PhRMA Foundation ended 1999 in sound financial shape and is laying the groundwork for significant improvements this year and beyond. For 1999, contributions were up 3% from the previous year, to $1.6 million, and total income was $2.3 million. More than $1.3 million was awarded in grants, and total expenditures were $1.8 million. Total net assets at year end were $5.9 million. Of this amount, $2.7 million represents funds tentatively 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.

During 2000, the Foundation Board implemented a formula for contributions, and our benefactors are responding well. We expect contributions to increase significantly this year, as we look ahead to the new program described in this report. On behalf of the Board and staff, I give special thanks for the continuing support of our generous benefactors, who are listed in this report.

The Foundation's financial position as of December 31, 1999, has been audited by the Rosslyn, Virginia accounting firm of Buchanan & Company.



Statement of Income and Expenditures
For the Year Ended December 31, 1999

Income:

Contributions	$1,605,084
Interest and Dividends	434,537
Realized Gains on Sale of Securities	89,076
Unrealized Gains on Sale of Securities	150,815
Miscellaneous Income	54,876
Total Income	$2,334,388

Expenditures:

Programs:	
Grants	
Awards in Excellence	16,000
Faculty Awards in Clinical Pharmacology	270,000
Faculty Awards in Basic Pharmacology	135,000
Fellowships for Careers in Clinical Pharmacology	75,000
Advanced Predoctoral Fellowships in Pharmacology-Toxicology	213,000
Pharmacology-Morphology Fellowships	77,336
Medical Student Fellowships	60,000
Research Starter Grants	125,000
Advanced Predoctoral Fellowships in Pharmaceutics	131,000
Undergraduate Fellowships in Pharmaceutics	30,000
Postdoctoral Fellowships in Pharmaceutics	18,750
Faculty Award in Pharmacoeconomics	120,000
Faculty Award in Bioinformatics	75,000
Subtotal - Grants	$1,346,086
Annual Awardee Meeting	61,184
Program Total	$1,407,270
Management and General:	
Committee Meetings, Travel and Honoraria:	51,297
Publications and Videos:	60,149
Professional Services and Investment Expenses:	56,849
Administrative and Staff Expenses:	198,446
Subtotal – M&G	$366,741
TOTAL EXPENDITURES	$1,774,011

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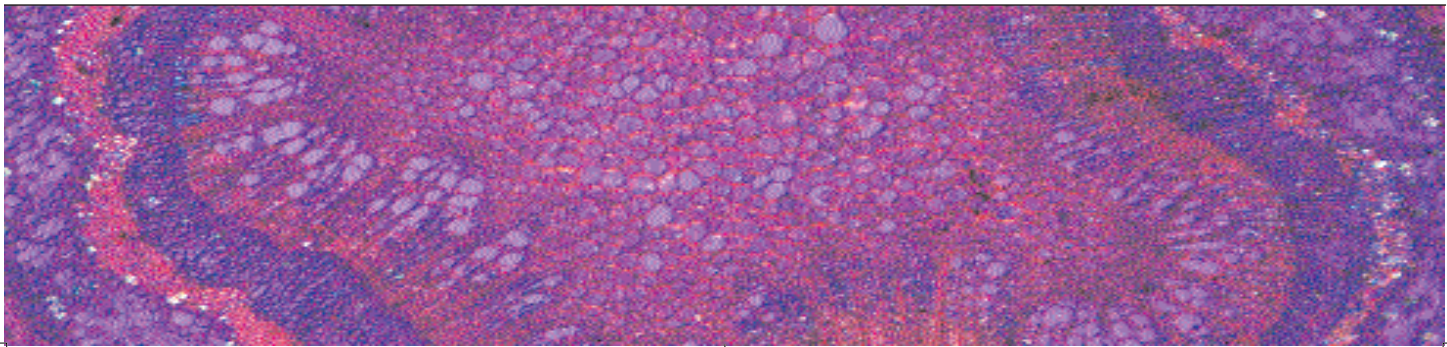

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The PhRMA Foundation warmly recognizes E. Leong Way, Ph.D., for his outstanding contributions to the Foundation for more than 30 years. Eddie was a member of the Foundation's Scientific Advisory Committee from 1968 through 1992 and a member of the Basic Pharmacology Advisory Committee from 1973 until he stepped down this year. He served with tremendous insight and spirit. The success of the Foundation's program is due to the collective knowledge, dedication, and generosity of its committee members. Thanks, Eddie, for sharing so many years with us. You will truly be missed.

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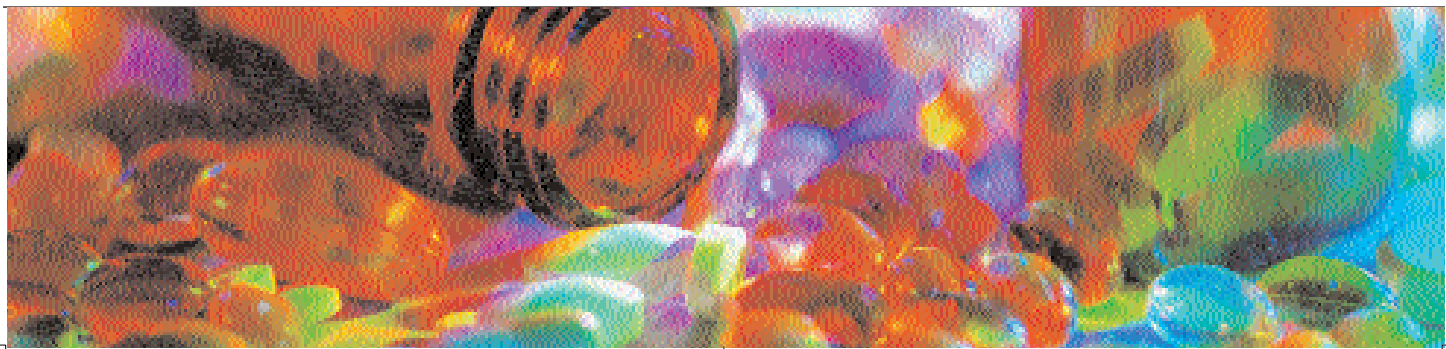

PhRMA Foundation Programs for 2001

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Clinical Pharmacology Advisory Committee			
(1) Faculty Awards in Clinical Pharmacology (1967)	3 budgeted/ 3 years	$360,000 total $ 40,000 per award per year	October 1 December 15 July 1
(2) Fellowships for Careers in Clinical Pharmacology (1973)	2 budgeted/ 2 years	$96,000 total $ 24,000 per award per year	October 1 December 15 July 1
(3) Medical Student Research Fellowships (1974-Amended 1982)	4 budgeted/ 3 months up to 24 months	$ 48,000 total $ 1,000 per month maximum $ 12,000	October 1 December 15 July 1
Basic Pharmacology Advisory Committee			
(4) Faculty Awards in Basic Pharmacology/Toxicology (1973)	2 budgeted/ 2 years	$120,000 total $ 30,000 per award per year	September 15 December 15 July 1
(5) Research Starter Grants (1972)	6 budgeted/ 1 year	$150,000 total $ 25,000 per award	September 1 December 15 January 1
(6) Advanced Predoctoral Fellowships in Pharmacology/Toxicology (1978)	9 budgeted/ 1 or 2 years	$225,000 total $ 12,500 per award per year	September 15 December 15 January-August
(7) Award in BioInformatics (1997)	1 budgeted/ 2 years	$ 60,000 total $ 30,000 per award per year	September 1 December 15 July 1
Pharmacology-Morphology Advisory Committee			
(8) Fellowships in Pharmacology-Morphology including Cell Biology (1968)	3 budgeted/ 2 years	$129,000 total $ 21,500 per award per year	January 15 March 15 July 1
Pharmaceutics Advisory Committee			
(9) Advanced Predoctoral Fellowships in Pharmaceutics (1987)	5 budgeted/ 1 or 2 years	$125,000 total 12,500 per award per year	October 1 December 15 January-August
(10) Undergraduate Research Fellowships in Pharmaceutics (1990)	7 budgeted/ 1 year	$35,000 total $ 5,000 per award	October 1 December 15 January-July
(11) Postdoctoral Fellowships in Pharmaceutics (1992)	1 budgeted/ 1 or 2 years	$50,000 total $25,000 per award per year	October 1 December 15 January-December
Pharmacoeconomics Advisory Committee			
(12) Faculty Awards in Pharmacoeconomics (1995)	2 budgeted/ 2 years	$160,000 total $40,000 per award per year	September 1 December 15 July 1

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

www.phrmafoundation.org