PhRMA
FOUNDATION

ANNUAL REPORT

The PhRMA Foundation was pleased to have two full-page advertisements in Newsweek *in 2001, made possible by the generous contribution of the PhRMA Education Communication Program.*

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

THROUGH ITS FELLOWSHIPS AND GRANTS to young scientists, the PhRMA Foundation helps to fuel the creativity, knowledge and energy needed to pioneer pharmaceutical innovation. Throughout its history, the Foundation has helped companies achieve their research goals by jump-starting the careers of promising scientists in a variety of disciplines. Now, as the industry faces the challenges and embraces the opportunities of the genomic era, the Foundation is focusing on the cutting-edge talents that will help companies discover and develop the break-throughs of the future. I want to take this opportunity to thank all of you for your generous help in getting this re-designed program off the ground, and I am happy to report that the program is now up and running.

Regarding our new 2002 program, we have just completed our first round of application reviews and I am delighted to report that the number of applications received as well as the caliber of the applicants has been phenomenal. In our oldest program, Basic Pharmacology, we received twice the number of top quality applications for our new program than we could fund. In the Clinical Pharmacology program, we established a completely new approach, the Center of Excellence in Clinical Pharmacology. We received eleven meritorious applications for our one award. In the newer, cutting edge areas;

- Pharmaceutics—the award funding has increased by 50%

- Health Outcomes—there has been a 40% increase in award funding and more than a 50% greater number of applicants
- Informatics—has a 5 fold increase in funding and we went from one applicant last year to 20 applicants this year

The response to our announcement to the new Center of Excellence for Integration of Genomics and Informatics has been outstanding. We firmly believe that we will identify more than one new center that warrants the million dollars of funding allocated for this program.

The new program builds on the strengths of the program the Foundation has run for the past 36 years. Since its inception, the Foundation has supported more than 2,000 young scientists at critical junctures in their careers. In 2001, we awarded grants to 44 researchers. Please join me in congratulating them and wishing them every success in their important work. Details regarding their proposed research focus is listed in detail in this report. Their research will enrich their careers and, ultimately, benefit the patients we serve. Their endeavors may lead, one day, to a cure for cancer, a medicine to prevent Alzheimer's, a vaccine for AIDS or some other breakthrough that will transform the prospects for humankind.

Our program has been proven to work. Alumni of the PhRMA Foundation are serving in key posts throughout the industry and academia, and our ongoing programs will create a pool of potential employees prepared to push the frontiers of science even further. I believe that the ability of the Foundation to identify promising scientists and help prepare them for careers in the pharmaceutical industry is highly valuable. Our history and our stellar reputation make the Foundation uniquely capable of carrying out this crucial mission on behalf of the industry.

Let me close by reiterating my strong belief in the value of pharmaceutical research and the role these scientists of tomorrow will play in developing the next generation of medicines that help and heal. Let me also express my profound gratitude for your generosity in funding the work of the PhRMA Foundation.

PRESIDENT'S MESSAGE

Del Persinger

THE NEW PhRMA FOUNDATION PROGRAM is up and running with great success, due to the support of our Board of Directors, the generosity of our contributors, and the hard work of our committees and staff. Our new, streamlined program emphasizes disciplines in which there is a shortage of talent and operates at the leading edge of science in the areas of Pharmacology, Pharmaceutics, Informatics, and Health Outcomes Research. Also, we are building for the future through our entirely new award program—the Center of Excellence for Integration of Genomics and Informatics.

Our Foundation Advisory Committees are the backbone of our operation. These committees represent a blue chip roster of national science and R&D leadership in academia and industry. As part of implementing our new program, we have added members to our existing committees and created new ones, making our roster of volunteers even more impressive.

Eileen McCarron, our Director of Development, and I have been on the road this year, presenting our awards at professional society annual meetings for the disciplines we represent. Through our travels, we are meeting those who benefit from our program, including the heads of academic departments, our current awardees, and dozens of awardees from years past. We have heard over and over again personal testimony that our program really works—that the Foundation is instrumental in jump-starting careers in research and teaching.

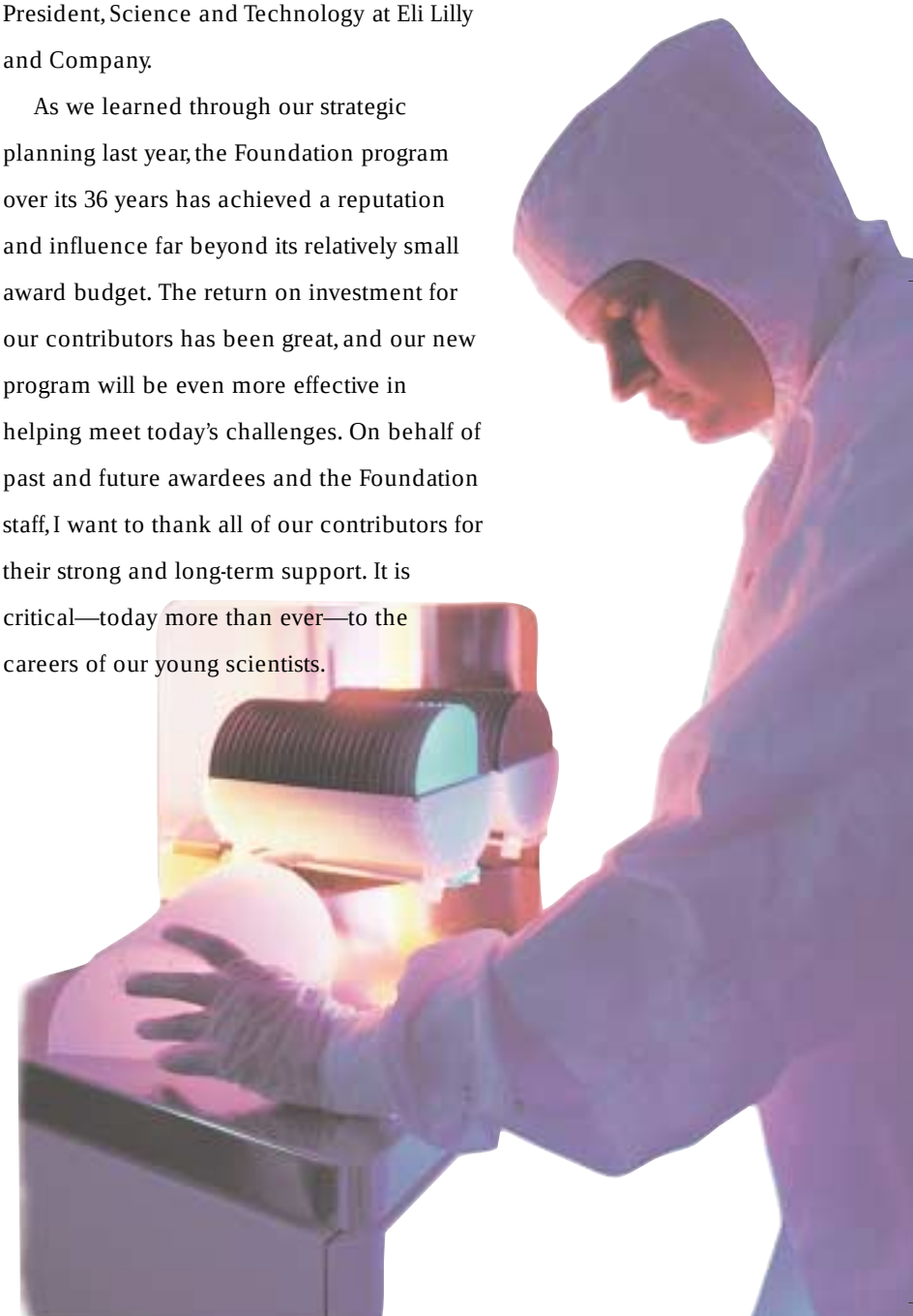
For example, Stephanie Watts is a highly talented double-award winner who received our Research Starter Grant in Basic Pharmacology and, later, a Faculty Development Award. Now Associate Professor of Pharmacology at Michigan State University,

she displays boundless enthusiasm for her profession and gives great credit to the Foundation. Stephanie told me: "Your awards have been absolutely critical in the development of my career—without you, I don't know that I would be here. My laboratory has published continuously because of PhRMA Foundation funding, obtained national grants from NIH and AHA, graduated PhD students, been active in scientific meetings, and been recognized as experts in serotonergic pharmacology and hypertension. I hope the Foundation will continue to support people in the way you have me." Stephanie has now joined our advisory committee and has served as a national spokesperson for our program and for the importance of the work our industry is doing.

Gary Rankin, who chairs the Department of Pharmacology at the Joan C. Edwards School of Medicine at Marshall University, is extending the frontiers of research, training a continuing stream of new researchers and serving as another enthusiastic advocate of our program. He told me at one of our receptions: "As a young scientist at a new medical school with little internal support, the receipt of a Foundation Research Starter Grant was the key step in starting my career. Several other faculty members in our Department have also received Research Starter Grants at critical times in their young careers. In each case, their Foundation support was the basis for NIH funding and the beginning of their important contributions to the knowledge base in pharmacology and toxicology. For this support we are extremely grateful." Gary's award covered 1979-80, and he told me that our award led to 17 straight years of follow-on funding from NIH that has totaled $2 million.

Many, many others told us similar stories. And we have plenty of representation in industry as well. Our past awardees include people such as Frank Douglas, Executive Vice President, Drug Innovation & Approval and Chief Scientific Officer at Aventis Pharma AG, and August (Gus) Watanabe, Executive Vice President, Science and Technology at Eli Lilly and Company.

As we learned through our strategic planning last year, the Foundation program over its 36 years has achieved a reputation and influence far beyond its relatively small award budget. The return on investment for our contributors has been great, and our new program will be even more effective in helping meet today's challenges. On behalf of past and future awardees and the Foundation staff, I want to thank all of our contributors for their strong and long-term support. It is critical—today more than ever—to the careers of our young scientists.



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 four awardees have distinguished themselves in the areas of pharmaceutics, clinical pharmacology, pharmacology/toxicology, 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 to those who follow in their footsteps.

The recipients of the PhRMA Foundation Awards in Excellence for 2001 are:

Kim L. R. Brouwer, Pharm.D., Ph.D.
Dr. Brouwer is Professor, Division of Drug Delivery and Disposition, School of Pharmacy, and Curriculum in Toxicology, School of Medicine, University of North Carolina. Her research program is designed to answer mechanistic and practical questions by integrating basic science and clinical research methodologies in pharmacokinetic, pharmacodynamic, and drug metabolism studies. She has published more than 200 research papers, abstracts, and book chapters.

Dr. Brouwer received her B.S. in Pharmacy from Oregon State University. She completed a Pharm.D. and three-year ASHP-accredited residency, combined with a Ph.D. in Pharmaceutical Sciences/Pharmacokinetics, at the University of Kentucky. She was awarded a PhRMA Foundation Research Starter Grant in 1987 to study mechanisms of inhibition of hepatobiliary transport systems.

Dr. Brouwer has been active in numerous professional organizations, is a member of the editorial advisory boards of several journals, and is a Fellow of the American Association of Pharmaceutical Scientists.

Cheryl F. Dreyfus, Ph.D.
Dr. Dreyfus has been Professor in the Department of Neuroscience and Cell Biology, UMDNJ/Robert Wood Johnson Medical School, New Jersey, since 1997. She received her Ph.D. from Cornell Graduate School of Medical Sciences in 1976 and received postdoctoral training at Einstein Medical College and Columbia College of Physicians and Surgeons. Her award from the PhRMA Foundation was a 1976 Pharmacology/ Morphology Fellowship.

Dr. Dreyfus has worked and written extensively in the areas of neurotrophins, neuronal plasticity, and, most recently, in glial cell biology. She has published almost 100 papers and has presented her work throughout the U.S. and the world.

Dr. Dreyfus is highly regarded as a teacher of Histology and Neuroscience. In recognition of her teaching, she has won the Andrew W. Mellon Teacher Scientist Award, was the Robert Wood Johnson Medical School Nominee for the University of Medicine and Dentistry Award for Distinguished Service in Education, 1998, and was awarded the Excellence in Teaching Award from the UMDNJ Foundation in 1996.

Louis Lasagna, M.D., Sc.D.
Dr. Lasagna is Chairman of the Board and Adjunct Scholar at The Tufts Center for the Study of Drug Development, Dean of the Sackler School of Graduate Biomedical Sciences, and Dean for Scientific Affairs at The Tufts University School of Medicine. He received his M.D. from Columbia University and honorary Sc.D. degrees from Hahnemann Medical School and Rutgers University. He also received an honorary doctoral degree from the University of Alcala in Spain.

Dr. Lasagna has worked and written extensively in the areas of clinical trial methodology, analgesics, hypnotics, medical ethics, and the placebo effect. He serves on a number of editorial boards and has been a consultant to several of the National Institutes of Health as well as the Food and Drug Administration.

In 1990, Dr. Lasagna was appointed to Secretary Sullivan's "Blue Ribbon Panel" which was commissioned to examine the Food and Drug Administration. In 1995, Dr. Lasagna served with three former FDA Commissioners on the so-called "Rogers Group" to prepare an agenda for legislative reform of the drug regulatory process, and in 1996 he testified before Congress on this topic.

Two Chairs have been created to honor Dr. Lasagna, one in Experimental Therapeutics at the University of Rochester and the other in Pharmacology and Experimental Therapeutics at Tufts University. Dr. Lasagna was awarded a PhRMA Foundation award in Clinical Pharmacology in 1970.

Gabriel L. Plaa, Ph.D.
Dr. Plaa is a pioneer in the use of dose-effect relationships to quantitatively compare hepatotoxicants, using both biochemical and morphological indices of liver injury. He has published more than 225 research articles, edited five books, written 35 chapters in other books, and authored 10 major scientific review articles.

At the time of his retirement in 1995, Dr. Plaa was Director of the Interuniversity Center for Research in Toxicology at the Universite de Montreal. A year later, he was named Professor Emeritus for his outstanding contributions to the institution and his scientific discipline during his academic career. He received a starter grant from the Foundation when he first moved to Canada in 1968 that enabled him to initiate his research activities in that country.

Dr. Plaa has served on many national scientific and expert committees in Canada and the U.S. He has received 14 major awards for his achievements, including the Merit Award of the Society of Toxicology in the U.S. and the Award of Distinction of the Society of Toxicology of Canada.

R&D LEADERS OF TODAY

FOR THREE DECADES, THE PhRMA Foundation has supported young scientists at the beginning of their careers to encourage them to pursue specialties in research and education that are important to the research-based pharmaceutical industry and, ultimately, to patients.

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

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

"The PhRMA Foundation provided that important first grant. This not only got my lab and clinical research off to a productive start, but facilitated collaboration with the pharmaceutical industry, where much to my surprise, the quality of science was outstanding. The decision to join the PhRMA industry has turned out to be scientifically and personally rewarding."

On behalf of Frank L. Douglas, Ph.D., M.D.
Executive Vice President, Drug Innovation & Approval
and Chief Scientific Officer, Aventis Pharma AG

"Funding by the Foundation helped to establish my career in pediatric clinical pharmacology. It was vital to my early work as a junior faculty member at Johns Hopkins, which led to my position as head of Pediatric Clinical Pharmacology at the Hospital for Sick Children in Toronto for 11 years. After that, I returned to the U.S., first at Merck and then to my current post as Vice President of Pediatric Drug Development at Johnson & Johnson. The Foundation's career development awards remain crucial to provide for the next generation of clinical pharmacologists."

Stephen P. Spielberg, M.D., Ph.D.
Vice President of Pediatric Drug Development
Johnson & Johnson

"The PhRMA Foundation funding jump-started my research career. It allowed me to begin my research and make sufficient progress to eventually receive an NIH grant to continue my work."

Clark W. Smith, Ph.D.
Global Head of Research Operations,
The Pharmacia Corporation

"The PhRMA Foundation award was my first grant—a training fellowship—and thus was the foundation of my career in research. It allowed me to have time and funds to develop the skills necessary to become a clinical researcher in ALS."

Merit E. Cudkowicz, M.D.
Assistant Professor of Neurology,
Harvard Medical School

"The PhRMA Foundation award allowed my institution to release me from clinical service for a year to concentrate on developing a research program. It showed my department and school that toxicologic pathology is important and is a marketable discipline."

Dennis W. Wilson, DVM, Ph.D.
Professor of Pathology and Director of the Environmental Pathology Training Program at the University of California, Davis

"I've been funded continuously by NIH for more than 20 years. But it was only because of the PhRMA Foundation fellowship that I was able to pursue a career in academic research because neither my first or second applications was funded."

R. Adron Harris, Ph.D.
Professor of Neurobiology & Pharmacology and Director of Waggoner Center for Alcohol & Addiction Research at the University of Texas, Austin

"My PhRMA Foundation award provided support at a time when, as a new postdoctoral fellow, establishing my own research path was extremely important. The award actively encouraged the cross-disciplinary approach that has been of such help in my research throughout my career. The Foundation programs are particularly beneficial in the way they foster a cooperative relationship between academia and the pharmaceutical industry."

Peter G. Smith, Ph.D.
Professor of Molecular and Integrative Physiology at the University of Kansas Medical Center

"The PhRMA Foundation award not only was key in launching my research program, but it also enabled me to receive the recognition needed for faculty placement. These awards are extremely important to promising young investigators at the critical early stages of their careers."

Haian Fu, Ph.D.
Associate Professor at Emory University School of Medicine

"When I started, the PhRMA Foundation Grant was a major source of my laboratory funding. It was the "extra" I needed to get my work going. And I received my first NIH grant—now in its 21st year—using preliminary data developed as a result of the PhRMA Foundation grant."

Gavril W. Pasternak, M.D., Ph.D.
Head of the Laboratory of Molecular Neuropharmacology at Memorial Sloan-Kettering Cancer Center and Professor of Neurology & Neuroscience, Pharmacology and Psychiatry at Weill Medical College of Cornell University

"The Foundation award played an important role at the beginning of my academic career, both in terms of enabling me to do research and in showing my department that I was worthy of support."

Brian B. Hoffman, M.D.
Professor of Medicine and Molecular Pharmacology at Stanford University

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. In 2001, Foundation goals in education and research were 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 seventh year and has made two awards for 2001.

Beginning their awards in July 2001:

Jennifer H. Lofland, Pharm.D., Project Director, Department of Health Policy & Clinical Outcomes, Thomas Jefferson University: "Patient-Focused Outcomes: Quality of Life and Lost Productivity." Jennifer Lofland, PharmD and David Nash, MD, MBA from TJU, and Donald M. Steinwachs, Ph.D. from John Hopkins School of Hygiene and Public Health, propose a collaborative study for the Faculty Development Awards in Pharmacoeconomics. Dr. Lofland teaches a 14-week, masters-level pharmacoeconomics course in which she discusses various topics such as health-related quality of life (HRQoL), cost effectiveness analyses, and pharmacoeconomics methodologies. This is the only course at TJU providing instruction in pharmacoeconomics or health related services. With didactic and experiential components, this career development plan will provide Dr. Lofland with the skills necessary to meet her long-term objectives to be an independent pharmacoeconomic and health services researcher. The didactic component will be completed at JSHPH. The experiential component will measure and evaluate patient-focused outcomes: HRQoL and lost productivity. The research objectives are to (1) validate a primary headache questionnaire, (2) determine methodologies for valuing lost productivity, (3) determine patient outcomes using the questionnaire; and (4) develop a predictive model to determine the variables associated with decreased HRQoL and increased lost productivity for primary headache patients.

David L. Veenstra, Pharm.D., Ph.D., Assistant Professor, University of Washington, School of Pharmacy: "The Role of Pharmacoeconomics in the Genomics Revolution." There are three primary objectives of the proposed development plan: (1) Pharmacoeconomic training: Provide significant commitment to the training of our graduate students in the Pharmaceutical Outcomes Research and Policy Program (PORPP) at the University of Washington. (2) Cost-effectiveness of pharmacogenomics: Evaluate the cost-effectiveness of pharmacogenomics-based therapies, and the impact of pharmacogenomics on drug development, reimbursement, and delivery. The project will use warfarin and P450 genotype as a case study, and develop a framework to identify the factors that influence the cost-effectiveness of pharmacogenomic-based drug therapies. (3) Pharmacoeconomics modeling and health care decision-making: Study the influences of pharmacoeconomics data derived from cost-effectiveness models on decisions made by health care payors. The project will quantitatively evaluate the impact of cost-effectiveness models using a randomized trial design.

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 2001 is:

Keith A. Crandall, PhD., Assistant Professor, Department of Zoology, Brigham Young University: "Undergraduate Training in Bioinformatics: Research Experience in Molecular Phylogenetics and Computational Biochemistry and Biophysics." Summer support has been granted to Dr. Crandall to develop an undergraduate curriculum in Bioinformatics at Brigham Young University. Central to this curriculum will be a research training experience with a core member of the Bioinformatics Program. These core members work in one of two research focal groups: molecular phylogenetics or computational biochemistry and biophysics. Both groups involve collaborative research among physical scientists (from Departments of Computer Science, Statistics, Chemistry, and Physics) and biologists (from Departments of Zoology and Microbiology) and offer training in both disciplines for undergraduate, graduate, and postdoctoral researchers. These research groups have been formalized at Brigham Young University with the contribution of more than $200,000 from the university's administration (University, Colleges, and Departments) to support undergraduate research, graduate training, and a 3-year seminar series in Bioinformatics. This award will allow Dr. Crandall to devote energy and skill to the development of a Bioinformatics undergraduate curriculum to train exceptional undergraduates interested in combining strong interests in biology and computer science into a single degree program. These students will be well trained to enter the job market in biotech companies and pharmaceutical companies, as well as further training at top graduate programs in Bioinformatics in the country.

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. Nine awards were made for 2001, bringing the total number of awards to 106.

Faculty and their undergraduate students who received fellowships that began between January and July 2001 are:

Mansoor M. Amiji, Ph.D., Associate Professor of Pharmaceutics, Department of Pharmaceutical Sciences, Northeastern University
Student: Erica J. Waugh "Long-Circulating Biodegradable Nanoparticle Formulation For Tumor-Selective Delivery." About 70% of all malignant cancers are solid tumors. Many solid tumors are associated with poor prognosis due to inadequate drug concentrations and the development of multiple drug resistance. Delivery of anti-cancer drugs in the center of a solid tumor remains a formidable challenge due to poor circulation, hypoxia, and positive interstitial pressure in the tumor mass. It is proposed to formulate and examine the *in vivo* tumor-selective uptake potential of poly(ethylene glycol) (PEG)-grafted gelatin nanoparticle formulation containing paclitaxel (Taxol) as a model drug. The specific aims of the proposed study are: (1) to develop and characterize control and PEGylated gelatin nanoparticles by ethanol precipitation method; (2) to examine the paclitaxel loading and release *in vitro* at 37C; (3) to develop a tumor model of Lewis lung cell carcinoma in C57BL/6J mice; and (4) to examine plasma and tumor concentrations of the drug over a 24 hour time period after intravenous administration in the control and nanoparticle formulations. The dose of paclitaxel administered will be 20 mg/kg. This study is expected to provide significant insight in the use of long-circulating biodegradable nanoparticle formulations for tumor-selective delivery.

Kim L. R. Brower, Pharm.D., Ph.D., Professor, Division of Drug Delivery and Disposition, University of North Carolina at Chapel Hill
Student: Maciej Jan Zamek-Gliszczynski "Hepatic Transport Mechanisms and Drug Interactions." Altered hepatic disposition of drugs may influence systemic concentrations, thereby affecting therapeutic efficacy/toxicity. Rapid hepatic uptake of drugs may occur by passive or carrier-mediated processes. Once inside the hepatocyte, drugs and metabolites may be excreted into bile via ATP-dependent export pumps located on the canalicular membrane, or may undergo basolateral efflux into sinusoidal blood. Sandwich-cultured (SC) hepatocytes, a novel *in vitro* model that re-establishes polarized excretion of xenobiotics, is a useful tool to study mechanisms of hepatobiliary drug transport and drug interactions. The studies outlined will determine the mechanisms of hepatic uptake and basolateral efflux of the model organic anion, 5 (and 6)-carboxy-2' 7'-dichlorofluoroscein (CDF). Traditionally, the nonfluorescent diacetate prodrug of CDF is administered, based on the assumption that this more lipophilic form diffuses through plasma membranes (CDF is a trivalent anion); intracellular esterases rapidly hydrolyze the diacetrate to yield fluorescent CDF, which is excreted extensively in bile by Mrp2. The utility of this model substrate to investigate mechanisms of hepatobiliary drug transport and drug interactions will be explored in rat hepatocytes and transfected Sf9 cells in the proposed studies.

Alekha K. Dash, Ph.D., Associate Professor, Department of Pharmaceutical & Administrative Science, Creighton University
Student: Adanze Ndubuisi
"A Novel Drug Delivery System for the Targeted Local Delivery of Doxorubicin." Doxorubicin (Adriamycin) has the widest antineoplastic spectrum and usefulness of the anticancer drugs. It is highly effective in the treatment of soft tissue and bone sarcoma. Since the drug °has a poor oral absorption, it is administered intravenously. The problems associated with this mode of administration in case of bone cancer for example are: (1) systemic toxicity of the drug, (2) drug concentration at cancerous site (bone) is likely to be low because bones are moderately perfused organs; and (3) narrow therapeutic range of the drug does not permit substantial increases in the dose to be administered. The aim of this investigation is to develop a sustained release novel crosslinked doxorubicin conjugated delivery system for the targeted local delivery of doxorubicin. The delivery system will be designed so that it can be surgically placed within or adjacent to the tumor. The sustained release of doxorubicin will result in

the desired drug concentration at and around the site of cancer while the systemic drug concentration will be negligible. The successful completion of this project will provide a novel approach to target anti-cancer drugs for bone cancer or any type of cancer treatment where local delivery is the best choice.

Maureen D. Donovan, Ph.D., Associate Professor, College of Pharmacy Division of Pharmaceutics, University of Iowa
Student: Joanne Reiland "Improved *In Vitro* Drug Release Testing Methods for Dosage Forms Administered to Limited Volume Sites." Drug release testing is a standard practice in both dosage form development and quality assurance. Frequently, release testing methodologies need to be significantly modified from compendial standards in order to obtain good correlation to *in vivo* drug release. For anatomical sites that have limited volumes of fluid for drug dissolution and release (nasal, vaginal, rectal ophthalmic), the typical large volumes of dissolution media provide little information about *in vivo* dosage form performance. The research hypothesizes that drug release into a small volume, potentially physiological relevant, solution will better characterize drug release and lead to better IVIVC's for dosage forms administered to alternative delivery sites. This work proposes to develop and validate a small volume dissolution cell capable of providing data about drug dissolution and release into a limited volume of dissolution media.

Anthony J. Hickey (Dennis Williams), Ph.D., Professor, School of Pharmacy, University of North Carolina at Chapel Hill
Student: Elizabeth Ann Mejia-Millan "The Influence of Vapor Pressure on Performance of Propellant Driven Metered Dose Inhalers." Chlorofluorocarbon propellants are being eliminated from metered dose inhaler products. New asthma drugs, such as β2-adrenergic agonists, and corticosteriods are being reformulated in alternative propellants. It is clear that alternative propellants have unique physico-chemical properties that influence lung deposition and efficacy. A systematic study of the impact of key parameters, such as vapor pressure, have not been conducted. It is proposed that an *in-vitro* study of formulation variables on emitted dose and droplet size be conducted. This study will be integrated into a normal human subject lung deposition study. It is intended that a knowledge of aerosol performance as a function of vapor pressure can be used to interpret literature studies of reformulated product, and also to aid in future formulation development strategies. The proposed study takes advantage of Ms. Mejia-Millan's unique qualifications, and forges a strong link between pharmaceutical and clinical sciences.

Russell J. Mumper, Ph.D., Assistant Professor of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky
Student: William M. Fountain, IV "NanoTemplate Engineering and Film-Composites for Transmucosal Drug Delivery." The NanoTemplate Engineering project relates to a novel method to pharmaceutically engineer solid nanoparticles in the size range of 5 to 50 nm containing plasmid DNA for non-viral gene therapy applications. Novel microemulsions are used as precursors (or "NanoTemplates") to form solid nanoparticles containing plasmid DNA. The NanoTemplate precursor method results in the formation of well-defined and uniform solid nanoparticles without the use of expensive or potentially damaging techniques involving high-torque mechanical mixing, microfluidization, homogenization, or milling. The Film-Composites for Trans-Mucosal Drug Delivery project relates to the development and use of novel films for the delivery of small molecules and peptides transmucosally through the buccal tissue into the systemic circulation. Mr. Fountain will continue the research on transmucosal delivery of hirudin (a 6 kDa peptide) as well as on the transmucosal delivery of midazolam (a benzodiazepine used for pre-operative sedation). He will assess the stability of each drug in the optimized film-composite, modifying and predicting the release rate of the drugs, and determining the bioavailibility of the drugs after buccal delivery in rabbits.

Steven L. Nail, Ph.D., Professor, Department of Industrial & Physical Pharmacy, Purdue University
Student: Teresa Schuman "The Effect of Thermal History of Freezing on Activity of Model Proteins After Freeze-Drying." The broad objective of the proposed research is to better understand the effects of seemingly subtle differences in freeze-drying processing conditions on the activity of model proteins. More specifically, it is to test the hypothesis that, with respect to shelf freezing of protein formulations, "slow is fast and fast is slow." That is, if the shelf temperature is decreased very slowly, as would be done when trying to effect slow freezing, there is promoted supercooling and uniform temperature within the supercooled liquid such that, once ice crystals nucleate, the effective rate of freezing is fast. If, however, vials are placed on shelves that have been pre-cooled to perhaps –45ºC, ice forms quickly in the liquid that is in contact with the bottom of the vial, perhaps before liquid in the bulk of the container has cooled to below the equilibrium freezing temperature. The effect of this "fast" freezing would be to seed the system with ice crystals, thus preventing supercooling and resulting, in effect, in slow freezing. The major practical benefit of the proposed research is more rational process validation, particularly in identification of critical processing variables.

Teruna J. Siahaan, Ph.D., Associate Professor, Department of Pharmaceutical Chemistry, The University of Kansas
Student: Phuong Nguyen
"Production and Purification of EC12-domain Protein of E-cadherin." The long-term objective of this project is to understand how to modulate tight intercellular junctions by regulating E-cadherin-E-cadherin interactions in the adheren junctions. The short-term goal of this project is to produce and purify EC12-domain protein of E-cadherin. The research has shown that HAV-peptides derived from the E-cadherin sequence can modulate the intercellular junction porosity. This is due to the binding of HAV-petides to E-cadherin, resulting in the inhibition of E-cadherin-E-cadherin interactions. To understand the mechanisms of HAV-peptide interaction with E-cadherin, the research will study the binding properties of the HAV-peptides to EC12-domain of E-cadherin using equilibrium dialysis and spectroscopic methods (NMR, CD, and fluorescence). The structural properties of EC12-domain protein will also be determined by NMR, CD, and molecular modeling. In this proposal, the undergraduate student will produce and purify sufficient amount of EC12-domain protein using *E. coli* expression system for structural and binding studies. The necessary ^{15}N-labeled EC12-domain protein will also be produced for structural studies.

Jagdish Singh, Ph.D., Associate Professor, Department of Pharmaceutical Sciences, North Dakota State University
Student: Roger Yan "Changes in Skin Due to Iontophoretic Current". The long-term objective of the proposed research is to understand the mechanism of alteration in skin barrier properties by iontophoresis in order to develop transdermal drug delivery systems for macromolecules including peptide and protein drugs. Initiation of current flow across the skin causes a rapid decrease in resistance of the membrane to achieve a new lower value. Voltage-induced effects, which decrease the electrical resistance and proportionally increase the flux of both ionic

permeants and polar, non-ionic solutes, suggest that these effects are primarily electric field induced pore formation. The overall hypothesis to be evaluated is that skin resistance changes are due to ions in the media changing the number of ions in the skin. To test the hypothesis, it is proposed to determine the effect of a constant D.C. voltage (200-10,000 mV), concentration and type of electrolytes on the resistance (conductivity) of the HSC. The belief is that the proposed research will significantly enhance our basic understanding about alterations in skin by iontophoresis in order to non-invasively deliver macromolecules including peptide and protein drugs.

Fellowships for Advanced Predoctoral Training in Pharmaceutics

In effect for 13 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 2001, bringing the total number of awards to 79.

Those who received fellowships that began between January and August 2001 are:

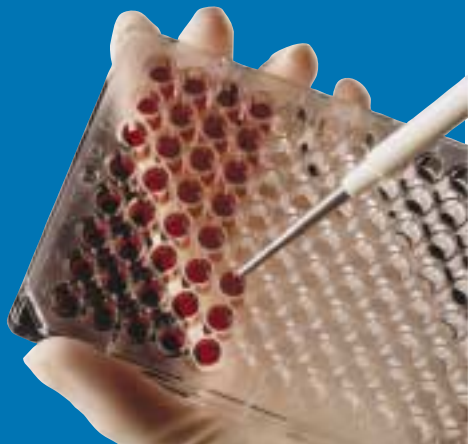
Monica Tijerina, Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah: "Effects of Subcellular Trafficking and Localization of Macromolecular Photosensitizing Agents on Anticancer Activity." Treatment of human ovarian carcinoma is a persisting problem in the US. Because a majority of cases are diagnosed in advanced stages of the disease, a distressing number of deaths occur each year. Here, HPMA copolymer-Mce$_6$ conjugates are proposed as novel chemotherapeutic agents for the treatment of ovarian cancer. The success of HPMA copolymer-Mce$_6$ conjugates for the treatment of human ovarian carcinomas has been demonstrated in animal studies, but further studies need to be performed to optimize this delivery system. The effect of subcellular uptake and localization will be examined and correlated to anticancer activity. Human ovarian cells will be chronically exposed to free or HPMA copolymer-Mce6 to determine if the conjugate can circumvent MDR. A detailed study correlating subcellular internalization and localization to anticancer activity will be performed. Uptake, subcellular trafficking and localization will be quantitatively assessed and analyzed utilizing a kinetic model describing adsorptive endocytosis of conjugates. These studies will provide invaluable information and allow the design of second-generation HPMA copolymer-Mce$_6$ delivery systems to be chemically tailored for optimum efficacy and biological activity.

Peter D. Ward, School of Pharmacy, University of North Carolina at Chapel Hill: "Phospholipase C Inhibitors as Potent and Selective Enhancers of Paracellular Permeability Across Intestinal Epithelium." Absorption enhancers can increase the permeability of the intestinal epithelium to hydrophilic drugs (e.g. peptides) by disrupting the tight junctions that constitute the major barrier to paracellular transport. Most absorption enhancers, however, have been found to be effective at high concentrations (high micromolar to low millimolar range); consequently, they also produce toxicity. This lab has identified at least two alkylphosphocholines as enhancers of paracellular permeability in *in vitro* epithelial models. Interestingly, these compounds are also inhibitors of phospholliace C (PLC). Furthermore, the research has found that U73122, an aminosteroid and a selective PLC inhibitor, is also a potent enhancer of paracellular permeability across MDCK cell monolayers. PLC inhibitors will be utilized as probes to investigate the involvement of this enzyme in the regulation of paracellular permeability across epithelial cells. To accomplish this goal, the correlation between increase of paracellular permeability and inhibition PLC caused by these compounds will be investigated. These compounds will also be utilized to investigate whether safety of paracellular enhancement is increased when enhancers alter paracellular permeability via modulation of a biochemical mechanism (i.e., PLC inhibition) associated with structure/function of tight junctions.

Lisa Kueltzo, Department of Pharmaceutical Chemistry, University of Kansas: "Structural Characterization and Membrane Interaction Studies of Small, Conformationally Labile Proteins." This project involves the investigation of a group of proteins that show unexpected conformational flexibility as a result of physical and chemical perturbation in spite of their small size (15-20 kDa). These proteins [VP22, acidic Fibroblast Growth Factor (FGF-1), bovine Granulocyte Colony Stimulating Factor (bGCSF), Keratinocyte Growth Factor 2 (FGF-10)] also possess varying degrees of interaction with lipid bilayers, which in some cases (VP22, aFGF) may be related to previously exhibited non-classical transport activity. This project involves characterization of the structures of these proteins under various conditions (e.g. temperature, pH, ionic strength), as well as an investigation of the extent of interaction of the exhibited conformational states with lipid bilayers and the

Dr. Albert Dreisbach, Assistant Professor, Tulane University School of Medicine receives his award with his mentor, Dr. Juan Lertora, a 1978 PhRMA Foundation Awardee, present to congratulate him.

top: *Del Persinger presents Kathleen Butler, M.D. from Thomas Jefferson University an award for a Fellowship for Careers in Clinical Pharmacology.*
bottom left: *Lewis J. Radonovich, M.D., from Johns Hopkins University receives his award, a 2001 Fellowship for Careers in Clinical Pharmacology.*
bottom right: *Dr. Arthur Atkinson, a member of our Clinical Pharmacology Advisory Committee and a former Foundation awardee.*



effect, if any, on transport activity. Initial data demonstrated that a truncated form of VP22 (VP22.C1: residues 159-301) possesses extensive conformational lability under physiological conditions and interacts with model lipids in a temperature dependent manner (Kueltzo, Normand, O'Hare and Middaugh, *J. Biol. Chem*. 2000). This research postulates that VP22.C1 may enter a molten globule like state under physiological conditions which may induce lipid bilayer interactions. This project is a collaboration with Dr. Peter O'Hare of the Marie Curie Research Institute, United Kingdom, Phogen, Pfizer, Merck and Human Genome Sciences.

John J. Schwegman, School of Pharmacy, Purdue University: "Measuring Protein Denaturation at the Ice/freeze Concentrate Interface Using Freeze-dry Microscopy Coupled with Microscopic FTIR/Raman Spectroscopy." The broad objective of the proposed research is a better understanding of the mechanism of loss of integrity of therapeutic proteins during freezing and freeze-drying. The specific aims of the study are: (1) to interface a specifically designed microscope stage to a microscope accessory on both a Fourier transform infrared (FTIR) and Raman spectrometer; (2) choose model proteins that are subject to loss of activity during freezing and freeze-drying and record the IR and Raman spectrum *in-situ* during controlled freezing and freeze-drying at specific locations relative to ice crystals; and (3) measure both relative concentration and secondary structure in the amide I region in order to test the hypothesis that loss of secondary structure during freezing is an interfacial phenomenon, where the protein partially denatures following adsorption at the ice/freeze concentrate interface. The research that is proposed is new, and if successful will end the speculation concerning the location of protein denaturation in the frozen mixture during freezing and freeze-drying. This is the first time that freeze dry microscopy equipment and FTIR/Raman microscopy equipment have been combined for *in-situ* measurements of spatially resolved spectra during freezing and freeze-drying.

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 2001.

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. 119 individuals have been supported under this program since 1967.

Recipients of the awards that began July 2001:

Albert W. Dreisbach, III, M.D., Assistant Professor, Tulane University School of Medicine: "The Effect of Endstage Kidney Disease on Phenotypic Expression of Cytochrome P450 CYP2C9." Cytochrome P450 CYP2C9 exhibits genetic polymorphisms and is responsible for the metabolism of such low therapeutic index drugs as warfarin and phenytoin. Approximately 20% of the population are heterozygous for mutant alleles that represent a high-risk population for serious bleeding with warfarin, particularly in patients undergoing hemodialysis. Both the prevalence of the known genotypes for CYP2C9 in endstage renal disease (ESRD) and the effect of ESRD on CYP2C9 phenotype have not been previously investigated. Many hepatic cytochrome P450 (CYP) isozymes are downregulated in ESRD by as much as 70%, with important implications for the dosing of drugs with predominantly hepatic clearance. Also, several CYP isozymes have been shown to be expressed in peripheral lymphocytes and the level of protein and mRNA expression correlates with hepatic CYP activity as measured by isozyme specific phenotypic probe drugs. The preliminary data demonstrates expression of CYP2C9 mRNA in peripheral blood mononuclear cells (PBMCs). In summary, the project proposes to investigate genotypic prevalence of CYP2C9 in ESRD, the effect of ESRD on CYP2C9 phenotype, and determine whether PBMCs are markers for hepatic CYP2C9 activity using warfarin as a phenotypic probe.

James V. Gainer, M.D., Assistant Professor, Department of Medicine, Vanderbilt University: "Aldosterone: Genetic Regulation and Vascular Reactivity." Genetic variation in the renin-angiotensin-aldosterone system (RAAS) contributes to the development of hypertension and cardiovascular and renal morbidity, complications more prevalent in African Americans than other ethnic groups. Accumulating data suggest that aldosterone plays a role in vascular toxicity independent of angiotensin (Ang) II. CYP11B2, also known as aldosterone synthase, is a focal point of aldosterone regulation. A common diallelic (C/T) polymorphism at position -344 in the promoter of CYP11B2 has been associated with increased basal and ACTH-stimulated aldosterone synthesis and hypertension in studies done in Caucasians. Independent of Ang II, increased plasma aldosterone has been associated with decreased vascular reactivity. The significance of CYP11B2 genetic variation in African Americans is not know. The central hypothesis of this proposal is that genetic variation in CYP11B2 is associated with increased aldosterone synthesis, which contributes to, altered vascular reactivity, endothelial dysfunction and hypertension in African Americans and Caucasians. To test this hypothesis, studies are proposed in humans to determine the effect of genetic variation in CYP11B2 on (1) the increase in aldosterone synthesis in response to Ang II and potassium, and (2) vascular responsiveness to vasodilation. Establishing CYP11B2-344C/T as a genetic susceptibility factor can lead to targeted therapies to reduce the incidence of hypertension and its morbidity.

Christopher J. Sweeney, MBBS, Indiana University School of Medicine: "A Phase I Trial of Feverfew in Patients with Cancer and A Phase I Trial of Weekly Paclitaxel and Interferon alfa2b in Patients with Refractory Malignancies." During the three years of the award, Dr. Sweeney will have the responsibility of conducting two phase I dose escalation clinical trials with pharmacokinetic and pharmacodynamic endpoints. Mentorship for these trials will be through Hematology/Oncology. The chromatographic assays and analysis of the PK/PD data will occur under the tutelage of the Division of Clinical Pharmacology. Dr. Sweeney has designed and written both clinical trials that have been approved by the Indiana University Institutional Review Board and IU Comprehensive Cancer Center Scientific Review Committee. The first study will be a dose escalation study of parthenolide. This is the active ingredient in the herbal remedy of feverfew. Dr. Sweeney has been actively involved in defining the *in vitro* anti-neoplastic activity of this sesquiterpene lactone that inhibits the transcription factor, Nuclear Factor kappa B (NFkB). This study, entitled, "A Phase I trial of feverfew in patients with cancer"; will define the pharmacokinetics and assess the ability of this compound to inhibit transcription of factors under control of NFkB. The second, entitled, "A Phase I trial of weekly paclitaxel and interferon alfa2b in patients with refractory malignancies", evaluates the pharmacokinetics and toxicities of increasing doses of weekly paclitaxel given with a fixed dose of interferon. The antiangiogenic activity of this combination will be assessed by measuring angiogenic factors in the blood and the presence of tumor responses.

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 2001 may request that the fellowship begin in July 2002, 2003, or 2004.

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, 72 fellowships have been awarded, including the two awarded in 2001. The program provides up to $24,000 per award per year.

Recipients who began their award in July 2001:

Kathleen A. Butler, M.D., Division of Clinical Pharmacology, Thomas Jefferson University: "Guanylyl Cyclase C as a Vaccine for Colorectal Cancer." The goal of this proposal is to determine the utility of a novel biomarker, guanylyl cyclase C (GCC) as a vaccine for colorectal cancer. Extensive data support that expression of GCC is specific to the intestinal epithelia, and expression is consistently maintained in metastatic colorectal cancer. The project will develop a panel of recombinant vaccinia viruses that express GCC, purified GCC protein, and naked DNA encoding GCC that will be used to vaccinate mice to determine whether an immune response can be mounted against

GCC. The specific aims are: (1) immunizing with protein that is tissue specific may trigger an inflammatory response in normal tissue, however unique characteristics of GCC that may moderate this response include residence in an anatomical site regulated by the mucosal immune system and possible existence of peripheral tolerance; (2) this research may also implicate GCC as a biomarker for inflammatory bowel disease and in the second phase of the research; and (3) the group will study whether the vaccine candidates that were developed in Aim 1 are able to mount an anti-tumor response in a murine colorectal cancer model. If successful, these studies will translate into human clinical trials as strategies to treat patients with colorectal cancer.

Lewis J. Radonovich, M.D., Johns Hopkins University, School of Medicine: "Improving the Antiviral Effect of Interferon-α for Hepatitis C." Approximately 1% of the world's population is Hepatitis C Virus (HCV) positive, yet only about 30% of patients with Hepatitis C achieve sustained response to interferon therapy. Despite meaningful medical progress with interferon-α, significant room for improvement remains in the area of Hepatitis C treatment. This study aims to address this serious public health issue by directing attention to the pharmacology of interferon. Since its discovery, interferon has been recognized as an antiviral protein. Yet, despite a broad range of antiviral activity *in vitro*, clinical use of interferon has been limited due to drug-induced toxicity primarily exhibited as a flu-like syndrome. Non-steroidal anti-inflammatory drugs (NSAIDs) have been used for years to decrease side-effects of interferon, but recently laboratory and clinical evidence has been produced which suggests NSAIDs may enhance interferon's antiviral effects. Although laboratory data have looked promising, clinical studies have been inconclusive for several reasons including use of different NSAIDs at different doses, lack of controlled circumstances and dissimilar patient populations, outcome measures, and exclusion criteria. This group has previously demonstrated an enhanced antiviral effect of acetaminophen-interferon combination similar in magnitude to ketoprofen-interferon described by others. Although other NSAIDs have been investigated, no further attention has been directed to

acetaminophen. The plan is to further pursue this agent, among others, in the proposed studies. The investigation will include pharmacologic evaluation of the effect of ketoprofen and acetaminophen in healthy human subjects. Specifically, in Study I, assays will be performed to assess antiviral action associated with the study drugs at maximal doses (study Ia) and in a dose-escalation, phase I trial fashion (study Ib). Ketoconazole, an inhibitor of EPO will be given as a negative control. In study II, combination therapy will be evaluated. Study III and IV are planned as Phase III trials involving HCV interferon non-responders and interferon-naïve cohorts respectively.

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 one year 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 one year. 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-five awards have been made since 1974, including the four awarded in 2001.

Individuals whose awards began July 2001 are:

Gene Hwang, Duke University School of Medicine:"Effects of Glioblastoma Multiforme Epidermal Growth Factor Receptor Variability on ZD-1839 Activity." Malignant gliomas (i.e. glioblastoma multiforme (GBM), etc.) and other central nervous system (CNS) tumors pose difficult problems, with median survival time 8–12 months after diagnosis. Both surgical and radiotherapeutic strategies remain unable to control these tumors, leaving chemotherapy as an essential component in the treatment algorithm. However, chemotherapeutic resistance/failure demands research into newer drugs, including ZD-1839 (4-(3-Chloro-4-fluorophenylamino)-7-emthoxy-6-(3-(4-morpholinyl)propoxy)quinazoline), which acts by blocking epidermal growth factor receptor (EGFR) (TGFα/EGF receptor) tyrosine kinase (TK) activity. EGFR activity is associated with tumor progression and poor prognosis (1, 3, 5, 9) and is over expressed in >50% of high-grade gliomas. ZD-1839 inhibits EGFR's TK and has been shown to have good activity against many EGFR expressing tumors. However, EGFR expression in gliomas varies among wild-type, wild-type amplified, and mutant-amplified with past studies showing differing activity associated with different receptor types (1). This project proposes to correlate the activity of ZD-1839 with EGFR type/amount expression of receptor. ZD-1839, which has been found to have a primarily cytostatic effect on multiple tumor types, will also be combined with temozolomide, a new methylating agent that has been shown to have minimal toxicity and good effect on GBMs. Scheduling, dosing, and toxicity will be examined. This will potentially allow identification of tumors likely to respond to ZD-1839 and more rational use of anti-EGFR agents as well as temozolomide + ZD-1839 combinations, with possible immediate implications for GBM management.

Susan I. McGovern, Northwestern University School of Medicine:"Non-Specific Inhibition of Enzymes: A General Mechanism?" High-throughput screening, both experimental and computational, is often used to discover novel leads for drug design. Unfortunately, many screening hits bind non-specifically, and differentiating specific from non-specific binding has become an area of intense study. Most efforts have focused on discarding non-specific inhibitors from screening databases, but this has been only partly successful because the bases of non-specific inhibition are poorly understood. To address this problem, this research will focus on compounds that are nonselective enzyme inhibitors. These dissimilar compounds were initially found in screens against different targets. In addition to their original targets, they typically also inhibit α-chymotrypsin, β-galactosidase, DHFR, and AmpC β-lactamase. These compounds have several peculiar properties. First, inhibition is time-dependent. Second, inhibition is reversible by incubation and then dilution, but not by dialysis. Third, decreasing the molar ratio of inhibitor to enzyme from 10,000:1 to 1,000:1 eliminates inhibition. Fourth, increasing ionic strength decreases inhibition by five to over 100-fold. The research proposes a model in which inhibitor molecules form vesicle-like aggregates that adsorb or absorb the enzyme and inhibit its function along with a series of enzyme assays, dynamic light scattering experiments, and electron microscopy experiments.

Franklin M. Mullins, Department of Anesthesiology and Pharmacology, Vanderbilt University:" An Investigation of the Effects of Na^+ on HERG Currents."The human cardiac delayed rectifier K^+ current I_{Kr} is carried by HERG, a channel encoded by the human ether-a-go-go related gene. Suppression of I_{Kr} can have anti-arrhythmic or proarrhythmic effects. I_{Kr} and HERG inwardly rectify at depolarized potentials via rapid, voltage dependent inactivation. The conformational change associated with HERG inactivation involves the outer pore. Raising extracellular $[K^+]$ ($[K^+]_o$) within the physiological range augments outward HERG current, and raising serum $[K^+]$ normalizes QT interval in patients with genetic or drug-induced suppression of I_{Kr} .This laboratory has recently shown that modest increases in $[K^+]_o$ can relieve inhibition of outward HERG currents by extracellular Na^+ (Na^+_o). Na^+_o inhibits outward HERG current at depolarized potentials, but Na^+_o can increase HERG current at hyperpolarized potentials when K^+_o is present. The research will test the hypothesis that Na^+ competes with K^+ for both external and internal pore sites by recording whole cell HERG currents from transiently transfected CHO-K1 cells. Specifically, it will test a model in which Na^+ occupancy of an external site destabilizes the inactivated state and Na^+ occupancy of a more internal site stabilizes the inactivated state.

Jeremy Van Buren, Southern Illinois University School of Medicine:"Potentiation of Calcium Currents by Cocaine". Cocaine use is a major health problem because of the dependence it causes and the generation of life threatening cardiac arrhythmias following overdose. In western countries, cardiovascular complications from cocaine abuse now account for the majority of drug-related emergency room visits and deaths. There are several studies suggesting that voltage-gated calcium channel blockers can prevent cocaine-induced cardiovascular events (including lethal ventricular fibrillation), and they have been suggested as an antidote to treat cardiac symptoms during cocaine intoxication. However, the specific role of voltage-gated calcium channels in cocaine-induced responses is not fully

understood. In preliminary experiments, this research has demonstrated for the first time that cocaine selectively and potently enhances voltage-gated calcium currents in ventricular myocytes. The hypothesis of this research is that a direct enhancement of calcium flow through voltage-gated calcium channels by cocaine is a major source of calcium overload. Findings from this study will provide a better understanding of cocaine action that may help in identifying cocaine-induced changes in cardiovascular parameters, leading to newer therapeutic strategies to deal with cocaine abuse and intoxication.

BASIC PHARMACOLOGY

Faculty Development Awards in Basic Pharmacology and Toxicology

In effect for 28 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 varies, and is aimed at keeping within the existing salary and fringe benefits structure of the applicant university. To date, 78 awards have been made, including two in 2001. The program provides up to $30,000 per award per year.

Recipients of the 2001 Faculty Development Awards in Pharmacology which began July 2001 are:

Charles L. Cox, Ph.D., Assistant Professor, Department of Pharmacology, College of Medicine, University of Illinois, Urbana-Champaign: "Modulatory Regulation of Thalamocortical Circuits by Neuropeptides." Activities within thalamocortical circuits play a critical role in sensory processing, alterations in behavioral states, and in certain pathophysiological conditions such as absence epilepsy. The excitability of neurons within this circuit is regulated by intrinsic properties of the neurons, modulatory inputs from external sources such as various brainstem nuclei, and intrathalamic synaptic connectivity. The proposed experiments will focus on the regulation of thalamic activity by a class of putative neuromodulators: neuropeptides. The thalamus receives a rich peptidergic innervation from brainstem, neocortical, and thalamic neurons, and it is likely the case that certain neuropeptides are colocalized with other classical neurotransmitters. Although an escalating number of neuropeptides are localized throughout the central nervous system, there is relatively little unknown regarding their functional role in synaptic transmission and modulation of neuronal excitability. This is especially true with regards to thalamocortical circuits. The functional role of neuropeptides is of great interest because it has been suggested that their release may be activity dependent, and their actions long-lasting. The proposed experiments involve a combined anatomical, physiological, and pharmacological approach to investigate the functional role of neuropeptides in thalamocortical circuits. The cellular mechanisms by which different neuropeptides alter the excitability of individual neurons, influence synaptic transmission, and thus their subsequent effect on network activities in thalamocortical circuits shall be determined. The findings should provide new insight on the functional role of neuropeptides and could have potentially important clinical ramifications regarding the regulation of certain behavioral states and pathophysiological conditions.

Theresa M. Filtz, Ph.D., Department of Pharmaceutical Sciences, Oregon State University, "Function and Interactions of Phospholipase C-β3 Subdomains." Stimulation of phospholipid hydrolysis by most extracellular signaling molecules is mediated by G protein-coupled receptors and membrane-bound G protein subunits activating phospholipase C-β (PLC-β) isoenzymes. PLC-β isoenzymes hydrolyze membrane inositol phospholipids into two second messengers which, in turn, activate a wide array of intracellular processes. However, PLC-β isoenzymes are not integral to the plasma membrane, but seem to be loosely associated with cellular particulate fractions, and access to the membrane site of G protein activators and substrate lipids will regulate PLC-β activity. The subdomains of PLC-β that are involved in membrane association for efficient signal transduction are unknown. This laboratory's long-term goal is to accurately describe the kinds and means of regulation of PLC- β isoenzymes. To this end, this proposal has two specific aims: first, to test the hypothesis that regions of PLC-β with homology to lipid binding domains facilitate PLC-β binding to the plasma membrane; and second, to test the hypothesis that mammalian proteins, other than G proteins, exist which regulate PLC-β3 activity. Successful execution of these aims will provide a more complete map of the modulators of PLC-β3 enzyme activity and modulation of G protein-regulated signaling in general.

On March 6, 2001 in Orlando, the PhRMA Foundation presented several 2001 Faculty Awards and Fellowships for Careers in Clinical Pharmacology at the Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics. We are grateful to ASCPT for this opportunity and extend a special thank you to Sharon Swan, Executive Director for this opportunity.

The PhRMA Foundation was honored to be invited to present the Awards in Pharmacoeconomics at the 6th Annual Meeting for the International Society for Pharmacoeconomics and Outcomes Research in Arlington, Virginia on May 22, 2001. We thank you Dr. Marilyn Dix Smith, Executive Director and the Board of ISPOR for this opportunity to highlight our scientists.

The PhRMA Foundation was honored to participate in the opening session of the 2001 Annual Meeting of the American Association of Pharmaceutical Scientists on October 21, 2001, in Denver, Colorado. We thank AAPS for the privilege of presenting our Awards in Pharmaceutics at this exclusive event.

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 seventy-seven fellowships have been awarded under this program, including the nine awarded in 2001. The program is in its 24th year.

Those who have been awarded fellowships that began between January and August 2001 are:

Andrew T. Bender, Department of Pharmacology, University of Michigan, "Cellular Regulation of Nitric Oxide Synthase in Response to Chemical Agents." The aim of this project is to understand how the ubiquitin-proteasome system and heat shock proteins affect drug action or toxicity. nNOS will be used as a model for these studies since recent discoveries show that drug mediated inactivation of the enzyme leads to its proteasomal degradation, moreover it has been found that nNOS exists in a complex with hsp90. Understanding regulation of NOS is important as it plays a role in key physiological functions such as neurotransmission, regulation of blood pressure and clotting, and aids in the defense against invading parasites and microbes. Recent work from this laboratory has identified xenobiotics and drugs such as guanabenz, a clinically used antihypertensive, which are suicide inactivators of NOS and inhibit NO synthesis by covalently altering the enzyme. Although the research has shown that covalent alternation of the enzyme enhances its degradation, it is not known what structural features target the enzyme for degradation or if the damaged enzyme can be repaired by heat shock proteins. Further elucidation in these areas will provide a means for predicting the effect a compound will have on NOS *in vivo*. This may not only aid in predicting drug toxicity, but also assist in the design of safer and more efficacious NOS inhibitors.

John B. Biggins, Department of Molecular Pharmacology & Therapeutics, Sloan-Kettering Institute: "Mechanism of Self-Resistance in *Micromonospora* to the Antitumor Antibiotic Calicheamicinγ_1^I."

Calicheamicinγ_1^I is the most prominent member of the enediyne family of antibiotics, and its unprecedented molecular architecture in conjunction with its superb biological activity and therapeutic value brand this molecule an excellent target for the study of natural product biosyntheses and self-resistance. Enediene antibiotics have demonstrated their usefulness as anti-neoplastic agents, as their potency far exceeds those of present therapeutic agents in clinical use. Calicheamicinγ_1^I has displayed potencies >8000-fold higher than that of adriamycin through its action of double-stand DNA scission. Despite this high toxicity profile, this molecule is a natural product of a species of *Micromonospora* bacteria, and there must be a resistance mechanism to protect the microbe from its own toxic metabolite. Through the efforts involved in cloning the gene cluster responsible for calicheamicin biosynthesis, a gene encoding for a protein that mediates cell survival in the presence of calicheamicinγ_1^I has been isolated. The specific focus is to explore the mechanism of action of this protein. Given the unprecedented structure and mechanism of action of this molecule, this work should clearly provide novel discoveries in the detoxification mechanisms and regulation of enediyene antibiotic producing organisms.

Stehen P. Bruinsma, Department of Molecular Biology & Pharmacology, Washington University: "Novel Modulators of Signal Transduction by G Protein-Coupled Receptors." G protein-coupled receptors mediate signals via a multitude of hormones and sensory stimuli. The receptors represent a major drug target—more than half of all currently prescribed drugs act on these receptors. The potential for new therapies acting on these receptors is great; an estimated 3% of the human genome encodes G protein-coupled receptors. Moreover, proteins that mediate the specificity and efficiency of the signal transduction via these receptors represent novel targets for drug interactions. The research uses engineered yeast to apply the power of genetics to the study of signaling by human G protein-coupled receptors. As part of the overall effort to understand how G protein-coupled receptors act as "on/off" switches to transduce signals, this research plan proposes to use a "gene mining" strategy to identify proteins that increase the efficiency of G protein-mediated signaling. Candidate proteins identified by the screen will be characterized for their potential as signal transduction modulators by two methods in yeast: epistasis studies to identify where in the MAP-Kinase pathway they act and DNA microarray analysis to create a signal transduction profile that can be compared to the pathways.

Jessica Holden, Department of Physiology, University of Wisconsin-Madison: "Mapping the GABA Binding Site on the $GABA_A$ Receptor: Effects of Allosteric Modulators on Binding Site Structure." The $GABA_A$ receptor is the major inhibitory neurotransmitter receptor in the mammalian central nervous system. Several classes of drugs including the benzodiazepines, barbiturates, neurosteroids, and volatile anaesthetics bind to the $GABA_A$ receptor. Defects in GABA mediated synaptic transmission have been implicated in disorders related to anxiety, wakefulness, and epilepsy. Thus, understanding the structure and function of the $GABA_A$ receptor will be important for developing new therapeutic treatments for these disorders. A high resolution structure of the $GABA_A$ is not available. The main goal of the proposed research is to identify amino acid residues that form part of the GABA binding site and to determine the secondary protein structures that contribute to forming this site. In addition, the research will examine how allosteric modulators, like benzodiazepines and barbiturates enhance $GABA_A$ receptor function. Substituted cysteine accessibility method and two-electrode voltage clamping will be used to meet these goals.

Dhruv Kaushal, Department of Pharmacology, University of California, San Diego: "Lysophosphatidic Acid Regulation of Nuclear Migration, Cell Death, and Cell Division in the Developing Cerebral Cortex." Lysophosphatidic acid (LPA) is a bioactive lysophospholipid that acts via a family of high-affinity G protein-coupled receptors in vertebrates. LPA modulates murine cerebral cortical neuroblast proliferation and morphology *in vitro* by acting on the LP_{A1} receptor. A spontaneous mouse mutation, *vacillans*, maps to the lp_{A1} locus. *Vacillans* mice show muscle weakness, tremor, and poor muscle control, suggesting that deficiencies in LPA signaling may contribute to some neuropathologies. A contribution of derangements in LPA signaling to the etiology of some human neuropathologies is also suggested by the neurological complications observed in patients with lipid storage diseases. This study will focus on the effects of normal and abnormal LPA signaling on the development of the cerebral cortex. The specific aims are (1) assess the role of LPA signaling and the effect of exogenous LPA on nuclear migration in the germinal layer of the cerebral cortex; (2) assess the role of LPA signaling and the effect of exogenous LPA on programmed cell death in the germinal layer of the cerebral cortex; and (3) assess the role of LPA signaling and the effect of exogenous LPA on cell-cycle dynamics in the germinal layer of the cerebral cortex.

Susan E. Ownby, Department of Pharmacology, University of Iowa: "Farnesol and Geranylgeraniol: Substrates for a Novel Isoprenoid Shunt." Lovastatin, a hydroxymethylglutaryl Coenzyme A reductase inhibitor, blocks the production of isoprenoid intermediates, which are used to modify small guanosine triphosphate binding proteins, including RAS, Rap1A and Rho family members. Isoprenylation is required to localize them to membranes where they interact with their activators and effectors. Lovastatin inhibits this localization and therefore their function. The research has shown that farnesol (FOH) and geranylgeraniol (GGOH) restore cellular functions altered by lovastatin. Evidence exists of enzymes that may convert FOH to farnesyl pyrophosphate in rat liver microsomes. The exact enzymes have not been identified in humans. The hypothesis is that a novel metabolic pathway, the "Isoprenoid Shunt," can utilize FOH and GGOH as metabolic precursors for isoprenoids depleted by lovastatin. The objective is to characterize this Isoprenoid Shunt by determining the exact fate of FOH and GGOH and how these isoprenoids affect the cholesterol biosynthetic pathway. The project aims are to: (1) determine if farnesyl protein transferase and/or geranylgeranyl protein transferase are required for FOH and GGOH utilization by the Isoprenoid Shunt; (2) define the protein and chemical targets of the metabolic precursors arising from FOH and GGOH as a result of processing by the Isoprenoid Shunt; (3) determine whether FOR/GGOH analogues restore cellular function after mevalonic acid-depletion; and (4) explore the existence of a farnesol kinase and/or farnesyl phosphate kinase in a crude bovine brain FPTase preparation and human-derived hepatocytes. The characterization of this Isoprenoid Shunt will lead to the development of new pharmaceutical agents useful for treating hypercholesterolemia and possibly cancers in which RAS mutations play a causative role.

Julie M. Radeff, Department of Molecular Pharmacology, Biology & Chemistry, Northwestern University: "Parathyroid Hormone Stimulation of PKC Isozymes in Osteoblasts." Parathyroid hormone (PTH) is an important modulator of bone homeostasis. Alteration of the regulation of bone remodeling leads to disease states such as osteoporosis. The goal of this research is to understand the molecular events stimulated by PTH in order to identify potential targets for the treatment and prevention of bone disorders. PTH has multiple effects on bone, modulating both tone resorption and bone formation through the same receptors on osteoblasts. While much attention has been focused on PTH activation of anabolic pathways involving PKA and cAMP, the pathways that lead to bone resorption are less understood, although there is evidence that protein kinase C activation is involved. The goal of this proposal is to delineate these pathways. The hypothesis of this research is two fold, (1) that PTH activates specific PKC isozymes through a phosphatidlycholine (PC)-specific phospholipase D (PLD) and that this occurs via the activation of the small G proteins RhoA and ARF in osteoblasts; and (2) that the activation of PKC isozymes by PTH through this pathway increases IL-6, a pro-resorptive cytokine, which ultimately leads to increased bone resorption. Understanding the effects of PTH on bone resorption is clearly important in developing better therapies for the treatment of bone disease.

Shine Samuel Tu, Department of Molecular Medicine, Cornell University: Regulation of Apoptosis by Cdc42." Epidermal growth factor (EGF) receptor has the ability to protect cells against programmed cell death. Although much is known about how the EGF receptor regulates malignant cell growth, little is known about its role in mediating cell survival. Downstream targets of this receptor, such as Cdc42, have been shown to regulate apoptosis. Therefore, this research proposes to investigate the role of Cdc42, and its downstream effectors, on EGF mediated cell survival. In Aim I of this proposal, the plan is to characterize EGF-stimulated activation of Cdc42 with a particular emphasis being the delineation of the underlying mechanisms responsible for this activation event. The overall goal will be to link EGF-mediated activation of Cdc42 to cell survival. Aim II will focus on understanding how Cdc42 activation is translated into a survival signal and the relationship between Cdc42-mediated survival and malignant transformation. The research first will examine the ability of caspase-insensitive Cdc42 mutants to cause malignant transformation and next to investigate the role of PAK, a key Cdc42 downstream target, on cell survival. These studies will provide information on the mechanism by which EGF regulates cell survival in the face of apoptotic signals.

Jack M. Webster, State University of New York, Upstate Medical University: "Identification of the Enzymes that Mediate Inositol 1,4,5-Triphosphate Receptor Ubiquitination and Investigation of its Physiological Significance in Mammalian Brain." Inositol 1,4,5-triphosphate ($InsP_3$) receptors are proteins that form tetrameric ion channels in endoplasmic reticulum (ER) membranes. Upon ligand ($InsP_3$) binding, these ion channels open and Ca^{2+} stored in the ER flows into the cytosol. Therefore, $InsP_3$ receptors play a key role in mediating the effects of cell surface receptors that generate $InsP_3$. Remarkably, $InsP_3$ receptors are degraded by the ubiquitin-proteasome pathway after persistent hormone or neurotransmitter stimulation of certain cell surface receptors, causing a reduction in $InsP_3$ receptor levels within the cell and thus desensitization of the Ca^{2+} signaling pathway. The first step in this degradation pathway is ubiquitination: the covalent attachment of a chain of ubiquitin molecules to the substrate destined for degradation. Two specific aims are proposed. (1) Identification of the ubiquitin-conjugating enzymes that mediate $InsP_3$ receptor ubiquitination; and (2) Characterization of $InsP_3$ receptor ubiquitination in rat brain. These studies should define the enzymology of $InsP_3$ receptor ubiquitination and provide information on the pharmacology, biological significance and potential clinical relevance of $InsP_3$ receptor ubiquitination in mammalian brain.

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 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 seven awards have been made to date, including the two awarded in 2001. The program provides up to $21,500 per year for two years.

Receiving the fellowship beginning July 2001:

Mi-Sook Chang, D.D.S., Ph.D., Department of Pathology, Columbia University: "Role of Caspases in the p25/Cdk5 Kinase-mediated Neuronal Apoptosis Following Oxidative Stress." Delineating possible mechanisms involved in the p25/Cdk5 kinase-mediated neuronal apoptosis will help us to develop more specific pharmacological intervention for neurodegernerative diseases. This study will test the hypothesis that the induction of neuronal apoptosis by p25/Cdk5 kinase in response to oxidative stress is dependent, at least in part, on the activation of caspases. Previous studies have demonstrated the cytotoxic effects of oxidative stress on the induction of neuronal apoptosis in neurodegernerative diseases. Caspase activation is involved in neuronal apoptosis. In addition, the mislocalization and constitutive activation of Cdk5 by p25, a truncated fragment of p35, induces neuronal apoptosis in cell culture. The p25 fragment also accumulates in neurons undergoing cell death in the brain. Furthermore, calpain, which directly cleaves p35 to p25, is activated in response to oxidative stress. Therefore, it has been suggested that deregulation of Cdk5 caused by the accumulation of p25 in response to oxidative stress may be involved in the pathogenesis of neurodegenerative diseases. This interaction between caspases and p25/Cdk5 kinase has not been previously examined. The specific aims are: (1) To determine which caspases are activated and play important roles in neuronal apoptosis mediated by the p25/Cdk5 kinase following oxidative stress; and (2) To determine whether IAPs (endogenous inhibitors of apoptosis) can suppress the neuronal apoptosis mediated by following oxidative stress-induced p25/Cdk5 kinase.

David R. Linden, Ph.D., Department of Anatomy and Neurobiology, University of Vermont: "Effects of Colitis on Myenteric Neuron Excitability." The motor disturbances that are present during inflammation of the bowel reflect a significant interaction between inflammatory mediators and the enteric nervous system. The neural mechanisms of inflammation-induced dysmotility are currently unknown. Using a guinea pig model of experimental colitis, the specific aims of this proposal are to test the hypothesis that inflammation causes increased excitability in intrinsic primary afferent neurons, which leads to an imbalance in the peristaltic reflex circuit. This hypothesis will be explored by addressing two questions: (1) Do the electrical or synaptic properties of functionally identified myenteric neurons change during experimental colitis? (2) Is the neurogenic propulsive motor activity of the intact guinea pig colon altered during inflammation? In conducting these studies, Dr. Linden will implement integrated combinations of techniques, including intracellular recording and labeling of neurons, retrograde axonal tracing, immunohistochemistry, motility assays, and analysis of drug actions. These results will advance the understanding of the mechanisms of neuro-immune integration and motility disturbances associated with inflammatory bowel disease and functional bowel disorders.

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 2001, supported six Research Starter Grants at $25,000 for one year. The first awards were made in 1972; and a total of 525 grants have been made, including the six awards beginning on January 1, 2001.

Recipients of the Research Starter Grant that began January 2001:

Gregory T. Knipp, Ph.D., Assistant Professor, Department of Pharmaceutics, Rutgers University: "Molecular and Functional Characterization of the Novel Human Peptide/Histidine Transporter." The existence and preliminary human digestive tract cell expression pattern of a new human peptide/histidine transporter 1 (PHT1) has recently been determined by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) analysis. PHT1 appears to be expressed in the human GI tract and is also expressed in Caco-2 cell monolayers.

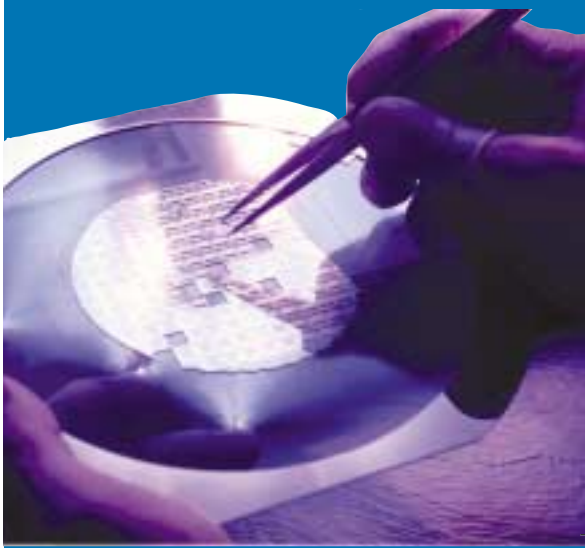
Presently, considerable emphasis on understanding the mechanisms responsible for peptide transport across the GI tract are focused on PepT1, which our preliminary data suggest is primarily localized in the human duodenum. A more comprehensive understanding of PHT1 expression and function in other regions of the human GI tract could dramatically change the current knowledge of active intestinal peptide transport. Given the large and growing number of peptide-based pharmaceuticals, PHT1 could play a significant role in the rational design and development of new drug products with improved bioavailability and therapeutic characteristics. This proposal outlines a strategy to determine the functional significance of PHT1 in regulating peptide absorption. In addition, the regional characterization of PHT1 will be completed to properly put into perspective the functional significance of PHT1. The results of these studies will drastically increase our current understanding of peptide and peptide-based pharmaceutical intestinal permeation.

Daniel L. Minor, Jr., Ph.D., Assistant Professor, Department of Biochemistry and Biophysics, University of California, San Francisco: "Molecular Evolution of Ion Channel Modulators." Ion channel proteins comprise a large family of molecules that play a central role in the generation and propagation of electrical signals in excitable and non-excitable cells. Specific compounds that inhibit ion channel function like the high affinity protein toxins from snake, insect, and marine snail venom are widely used in basic research. While these molecules are powerful tools for the study of channel structure and function, a limited number are well characterized and entire families of ion channels exist for which there are few or no specific inhibitors. The research outlined in this proposal is directed at establishing a general system for the rapid production of specific and selective ion channel activators and inhibitors from the scaffolds of small proteins of known structure through the use of molecular evolution and selection methods. A particular advantage of the strategies outlined in this study is that modulators can be developed that exploit the natural channel gating machinery from either the external or internal sides of the membrane. These molecules should provide new tools for studying the physiological roles of channel types for which there are currently no high affinity inhibitors and may provide a starting point for new channel specific drugs.

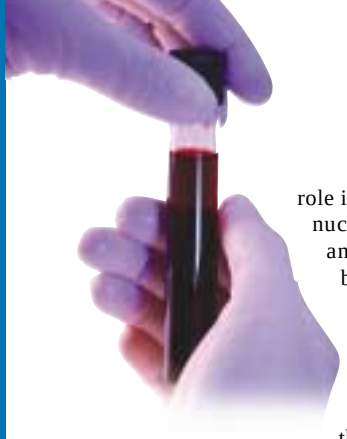
Jiping Tang, M.D., Assistant Professor, Department of Physiology and Biophysics, University of Mississippi Medical Center: "RhoA/Rho-Kinase Pathway in Cardiac Dysfunction in Diabetic Rats." This project is designed to test the hypothesis that RhoA, a small GTPase, may contribute to the development of heart failure in diabetes. Diabetic cardiomyopathy is a special heart problem and is one of the major causes of death in diabetic patients. The pathogenesis of diabetic cardiomyopathy is unclear. There is evidence that RhoA might be important in diabetic cardiomyopathy. RhoA activates Rho-kinase, which regulates myofibril formation and organization in neonatal rat ventricular myocytes. Transgenic mice overexpressing active-form of RhoA in heart die in a few weeks from heart failure. The cardiomyopathy in RhoA transgenic mice is similar to the cardiomyopathy in streptozotocin-induced diabetic rats. However, the role of RhoA in diabetic cardiac function has not been reported. The hypothesis in this research is that RhoA/Rho-kinase plays a central role in the abnormality of cardiac function in diabetes. The specific aims are: (1) to examine whether the transcription and activation of RhoA/Rho-kinase are enhanced in the heart of diabetic rats; (2) to investigate whether control of diabetes with insulin treatment inhibits the transcription and activation of RhoA/Rho-kinase in the heart of diabetic rats; and (3) to determine whether a Rho-kinase inhibitor attenuates cardiac dysfunction in diabetic rats. The long-term goal of this study is to determine the role of RhoA/Rho-kinase in cardiac dysfunction in diabetes and the possibility of using Rho-kinase inhibitor as a new treatment of diabetic heart disease.

Joanne (Juan) Wang, Ph.D., Assistant Professor, Department of Pharmaceutics, School of Pharmacy, University of Washington: "Molecular Characterization of Nucleobase Transporters in the Choroid Plexus." Nucleobase transporters play important physiological and pharmacological roles in mammalian cells. Transporters in the choroid plexus may play a critical role in targeting therapeutic nucleobase analogs to the brain. Although several nucleobase transport systems have been functionally characterized in mammalian tissues and cell lines, the underlying transporters have not been cloned. The major obstacle to cloning these transporters has been the lack of a heterologous expression system deficient in endogenous nucleobase transport activity. In the proposed studies, engineered yeast strains lacking endogenous nucleobase transporters will be developed and used for cloning and molecular characterization of mammalian nucleobase transporters. Specifically, endogenous yeast nucleobase transporter genes will be deleted; the resulting strain will be used to clone nucleobase transporters from rabbit choroid plexus using a functional complementation strategy. In addition, equilibrative nucleoside transporters in the choroid plexus might play a

Del Persinger and Eileen McCarron present the 2001 Pharmacology-Morphology awards to Dr. Mi-Sook Chang from Columbia University and Dr. David Linden, from the University of Vermont at the 9th Annual Awards Banquet for the American Association of Anatomists held in Orlando, Florida in April 2001.



In April 2001, the PhRMA Foundation hosted a special reception for the former and current awardees of the Foundation at the Annual Meeting for the American Society for Biochemistry and Molecular Biology & The American Society for Pharmacology and Experimental Therapeutics in Orlando, Florida. We are grateful to ASPET for this opportunity.



role in targeting nucleobase analogs to the brain. The project will express these transporters in the engineered yeast and determine whether they are *bona fide* transporters for nucleobases and nucleobase analogs. These studies will provide a fundamental understanding of the specific genes involved in nucleobase transport in the choroid plexus. Such information will eventually insure the ability to make predictions of *in-vivo* organ-specific drug transport and will pave the way for rational nucleobase drug targeting to the brain.

Kevin D. Wickman, Ph.D., Assistant Professor, Department of Pharmacology, University of Minnesota: "Opioid Regulation of G Protein-gated K^+ Channels." Many hormones and neurotransmitters bind to cell surface receptors leading to the modulation of several enzymes and ion channels via signal transducers termed G proteins. G protein-mediated signaling is ubiquitous, with different agents, receptors, and downstream targets impacting organ functions ranging from heart rate regulation to sensory perception. Clinicians frequently use drugs to adjust the output of G protein-mediated signaling pathways in the treatment of pain, seizures, arrythmias, and psychological disorders. Unfortunately, unwanted side effects often accompany the beneficial effects of many drugs. The majority of drugs in use today target relevant receptors. Since activated receptors control the function of several downstream enzymes and ion channels, it is conceivable that the desirable and undesirable effects of drugs are mediated by distinct branches of the signaling pathway. The long-term goal of this research is to understand how individual components of signal transduction pathways impact the establishment or modification of complex behaviors such as pain perception and addiction. This proposal seeks to determine the contribution of G protein-gated potassium channels to the physiological effects of opiate administration. This research may facilitate the design of a new generation of selective pharmacological agents which will be more effective in managing pain.

Jonathan J. Wilker, Ph.D., Assistant Professor, Department of Chemistry, Purdue University: "Metal-linked Nucleic Acids: A New Class of Compounds for Antisense Therapy." This proposal presents metal-linked nucleic acids as a new class of oligonucleotides for antisense therapy. Metal-linked nucleic acids are comprised of oligodeoxyribonucleotide analogs in which the phosphate linkage has been replaced by an inorganic metal-ligand complex. By bringing the breadth of inorganic chemistry to nucleic acids, an array of new compounds becomes apparent. In addition to the high specificity for target gene binding from the antisense approach and nuclease resistance, these complexes are expected to enable control of drug charge, structure, assembly, target affinity, and cellular uptake properties. Further roles for these oligonucleotides will include oncogene cleavage by iron EDTA analogs as well as cellular transport and localization studies with fluorescing terbium and europium derivatives. Experiments described below include synthesis, target binding, and cellular uptake studies of these antisense oligonucleotides. Metal-linked nucleic acids are presented to play a significant role in combating disease at the genetic level.

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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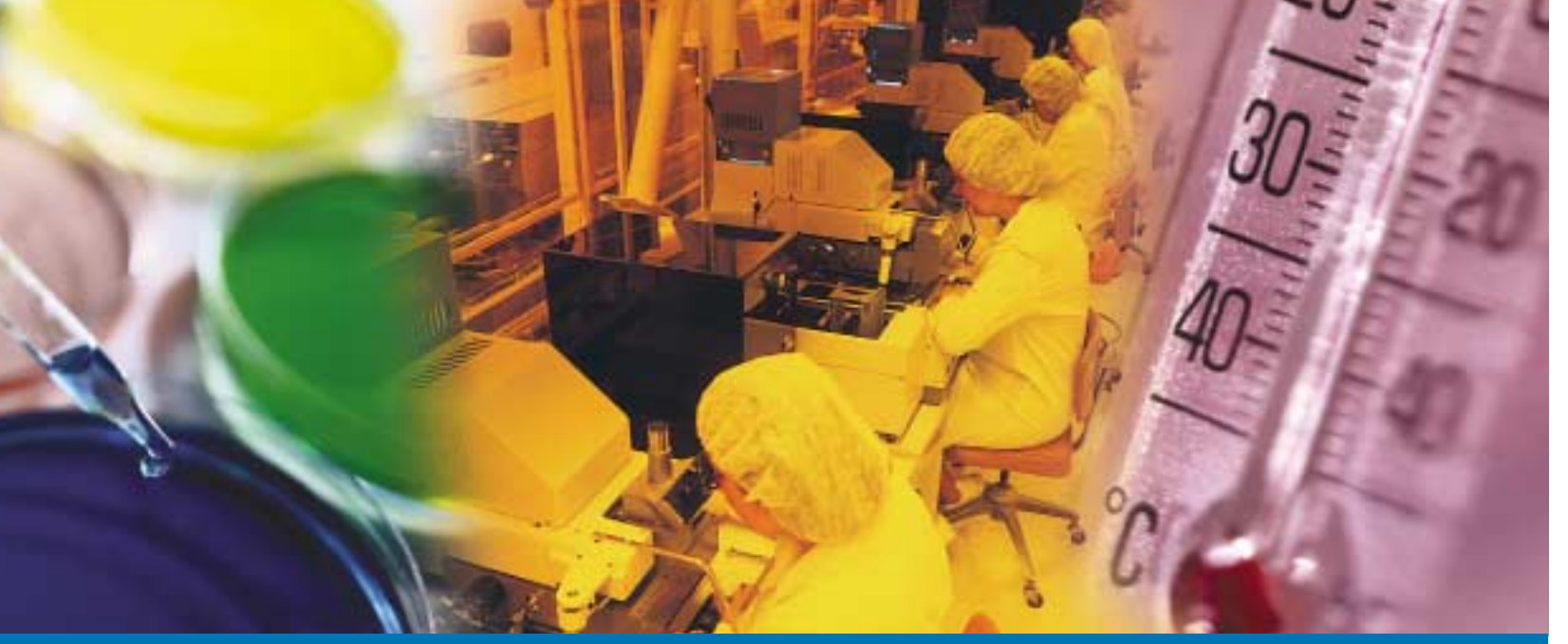


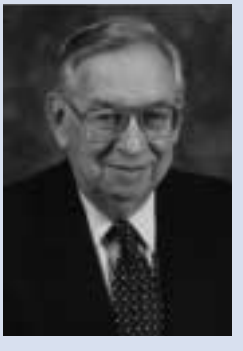
FINANCIAL REPORT

THE PhRMA FOUNDATION ENDED 2000 IN sound financial shape and laid the groundwork for significant improvements in 2001 and beyond. During 2000, the Foundation Board implemented a formula for contributions, and our benefactors responded well. Contributions were up 18% from the previous year, to $1.9 million. More than $1.4 million was awarded in grants, and total expenditures were $1.8 million. Total net assets at year-end were $5.86 million. Of this amount, $2.75 million represents funds authorized but not yet paid for the future years of grants already awarded. Financial details are shown in the accompanying Statement of Income and Expenditures.

Contributions are increasing significantly again for 2001 as we implement our new program. On behalf of the Board and staff, I give special thanks to the continuing support of our generous contributors, who are listed in this report.

The Foundation's financial position as of December 31, 2000, has been audited by the Rosslyn, Virginia, accounting firm of Buchanan & Company.

Del Persinger
President and Chief Executive Officer
PhRMA Foundation



The PhRMA Foundation would like to recognize Ted Brody after 29 years of service to the PhRMA Foundation as a committee member. Ted became a member of the Basic Pharmacology Advisory Committee in December of 1973. He has been an active member of the committee through the year 2000. Prior to his retirement, Ted was a Professor and Former Chairman of the Department of Pharmacology and Toxicology at Michigan State University in East Lansing, Michigan. Through his many years of dedicated service to the Foundation, he has helped to identify numerous young scientists who have gone on to successful careers in pharmaceutical research. Thank you Ted for your incredible support.

Statement of Income and Expenditures
For the Year Ended December 31, 2000

INCOME	
Contributions	$1,897,583
Interest and Dividends	477,365
Realized Gains on Sale of Securities	6,889
Unrealized (Losses) on Sale of Securities	-692,870
Other Income	60,922
Total Income	$1,749,889
EXPENDITURES	
Programs	
Awards in Excellence	22,500
Faculty Awards in Clinical Pharmacology	277,000
Faculty Development Awards in Basic Pharmacology	150,000
Fellowships for Careers in Clinical Pharmacology	54,668
Predoctoral Fellowships in Pharmacology/Toxocology	251,250
Pharmacology-Morphology Fellowships	66,000
Medical Student Fellowships	36,000
Research Starter Grants	225,000
Predoctoral Fellowships in Pharmaceutics	130,000
Undergraduate Fellowships in Pharmaceutics	25,000
Postdoctoral Fellowships in Pharmaceutics	25,000
Faculty Development Awards in Pharmacoeconomics	119,019
Faculty Development Award in Bioinformatics	45,000
Subtotal–Grants	$1,426,437
Other	
Annual Awardee Meeting	8,279
Committee Meetings, Travel and Honoraria	68,424
Publications and Special Projects	55,901
Subtotal–Other	$132,604
Program Total	$1,559,041
Administrative	
Staff, Rent, Taxes and Insurance	185,181
Professional Services and Investment Expenses	18,233
Office Expenses	33,182
Subtotal–Administrative	$236,596
TOTAL EXPENDITURES	$1,795,637

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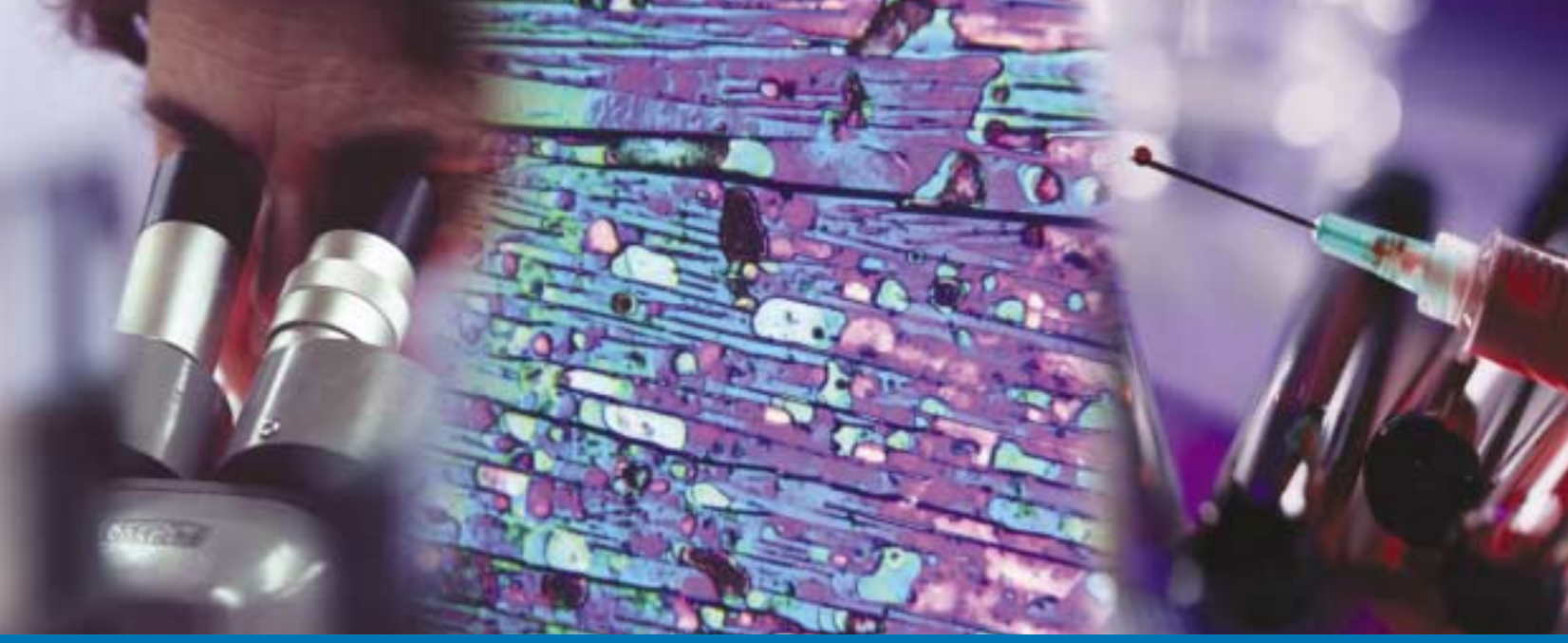

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