Visit the PhRMA Foundation website at www.phrmafoundation.org for detailed information. This website describes the Foundation programs, special events and recent awards. Brochures can be requested by writing or calling:

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

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

The Foundation’s program is of particular benefit to the pharmaceutical industry in serving its purpose of developing new life-saving, cost-effective medicines for patients all around the world.
This year, the PhRMA Foundation proudly celebrates its 40th anniversary. We celebrate not just because the Foundation has reached a significant milestone, but because over the past four decades we have provided fellowships and grants that have supported more than 2,000 innovative young scientists in their important work.

Looking to the years ahead, we are committed to expanding this support and to strengthening our efforts on behalf of the entire biomedical field.

One of the major strengths of the biomedical research enterprise in the U.S. is its long tradition of cooperation among academia, government agencies, the biopharmaceutical industry, and physicians and other healthcare providers. This cooperation has created an interdependent biomedical community where the well-being of each part affects the entire enterprise.

As we move forward in support of this vibrant field, the PhRMA Foundation will continue to:

- Work on the new Safe and Innovative Medicines Program, in conjunction with PhRMA's Science & Regulatory Division.
- Help counter the erosion of public trust in the biomedical enterprise through our close personal ties within the academic and scientific communities and by supporting strategic collaborations that will help translate ideas into the discovery and development of innovative new medicines.
Help create a vital medical curriculum that addresses both the discovery and development process for new therapeutics.

Bolster the public’s confidence in the biomedical enterprise by actively collaborating with PhRMA on its “Center for the Future of Medicine.” This is both a web- and community-based effort to create an accessible, inclusive and user-friendly venue that will create respectful, thought-provoking discussions among physicians, medical students, pharmacists, academic and government researchers, and biotechnology and pharmaceutical industry scientists. With such dialogue, we hope that these professionals recognize that their interdependence is essential to improving the public’s health and quality of life.

We pursue all these initiatives, and others, knowing that the discoveries of today will enable us to improve the medicines of tomorrow. We also know, on the other hand, that reductions in research funding to universities could deter innovation, and that any deterrent to private investment in biomedical R&JD will inhibit the flow of new and innovative medicines to patients in need.

That’s why it is critical for all parties to understand how important medicines are in the prevention and treatment of disease, in the reduction of other healthcare costs and in improving patient productivity and quality of life. In essence, more effective medicines are a key solution to better health and better healthcare.

With our 40-year record of service and support to draw on, the PhRMA Foundation looks forward to meeting these challenges in a spirit of collaboration with our many partners.

Peter B. Corr, Ph.D.
In our 40th year, we find that demand for our programs remains as high as ever. Applications for assistance increased over the previous year by almost 20% across the board. In all, our contributions rose in 2004 to nearly $2.9 million.

Our core commitment is to support innovative pharmaceutical research that shows promise for successful outcomes. We believe that the money spent on bright, talented young researchers is a worthwhile investment in the advancement of health care and the pharmaceutical industry. With more than three dozen awards each year, we are funding projects in many critical areas, including the following:

- HIV
- Cancer
- Stem cell with emphasis on Alzheimer’s and Parkinson’s diseases
- Toxicity issues and DNA damaging agents
- Renal toxicity
- Alzheimer’s Disease
- Drug metabolism
- Drug delivery issues affecting patients with cystic fibrosis and asthma
- Prevention of cervical cancer
- Tumor targeting/drug delivery
- Cost of illness studies/economic burden of cancer
- Osteoporosis Management
- Obesity/Metabolic Syndrome
The Foundation is actively integrating many of its activities with PhRMA. We see great value in a partnership that combines PhRMA’s expertise and the Foundation’s outstanding reputation within academia and national scientific societies. An important initiative is working to support and enhance the Safe and Innovative Medicine program being developed by PhRMA’s Science and Regulatory Division. The Foundation is uniquely positioned to accomplish this given the longstanding strong personal ties we have established with the leaders within academia and the scientific community and the good will we have built up with them through years of support.

Through our efforts we intend to help reestablish meaningful, respectful communications among the various stakeholders within the biomedical field. One element of our activities will be to work cooperatively with academia to increase the emphasis within medical education on the value of medicines. Another element is to expand our reach within the scientific community by taking advantage of new opportunities associated with our support and funding.

We are supporting a program for scholarship endowment for the FDA Alumni Association that is being established to celebrate the centennial of the original Food and Drug Act of 1906. We are also working with PhRMA to expand medical curriculums to explore drug discovery and development issues so that students have a greater understanding of the medicines they will be using to assist patients. We are excited about these new opportunities and believe that our involvement will make a difference.

One of our more rewarding programs is hosting networking receptions for current and former award recipients at the annual meetings of major national scientific organizations. These receptions, attended by PhRMA staff as well representatives of member companies, enable us to establish and maintain relationships with our researchers. They also give our scientists the opportunity to discuss their work with each other and at times form collaborations. These are important relationships that continue to benefit the world of pharmaceutical research.

None of these efforts would be possible without the tremendous support of the pharmaceutical companies, and we are grateful for that support. As stewards of our contributors’ money, we have been able to keep our inflation-adjusted administrative costs essentially flat, as we implement these stellar programs that have helped so many scientists pursue rewarding careers in pharmaceutical research.

Del Persinger
This year is the 40th anniversary of the PhRMA Foundation. Established by PhRMA (then the Pharmaceutical Manufacturers Association) in 1965 in the wake of the Thalidomide tragedies, the Foundation was given the mission of providing financial support and professional encouragement to universities to stimulate basic research and the training of investigators.

From the beginning, the Foundation spurred greater emphasis on drug studies in the medical curriculum. In addition, it called for intensified training in the disciplines associated with clinical testing and drug development.

A guiding principle was the belief that private groups could conduct and support programs that the government may have turned down in the face of other pressing demands. However, the PhRMA Foundation was not created to compete with public or private agencies in making grants. Instead, the money was intended to help promising young scientists get started in their careers and compete more favorably for national and other grants.

40th Anniversary
Even after 40 years, the Foundation remains committed to its founding principles. These include:

- Enhanced drug safety.
- Support for research into drug toxicity.
- Education in drug usage.
- Greater financial support for innovative research.
- Increased emphasis on drug studies in the medical curriculum.
- More effort to keep practicing physicians abreast of drug development.

True to its original intent, the Foundation’s awards are given to worthy individual scientists and are not targeted for a specific type of science, disease, or product line.

Our awards are based on merit alone and come with no strings or conditions. Even though many of our award recipients have gone on to make important discoveries, there is no ownership of these discoveries by the contributing companies.
The Foundation’s formula continues to be successful even after 40 years. Its ingredients remain the same.

- Tremendous support, in terms of financial assistance and volunteer time, from the PhRMA member companies.
- Clear purpose for and the integrity of the programs without any commercial overtones.
- Advisory committees made up of acknowledged scientific experts—drawn about equally from industry and academe—to create and administer programs and to advise staff.
- The extremely high caliber of the more than 2,000 awardees who continue to be the strongest asset of the PhRMA Foundation.

This legacy of success puts us in a strong position to undertake new programs designed to strengthen the pharmaceutical industry. For instance, we are working closely with PhRMA to support and enhance the Safe and Innovative Medicine program being developed by PhRMA’s Science and Regulatory Division. Our goal is to help turn around the erosion of public trust in our industry. In line with this goal, we are also working closely with PhRMA on its “Center for the Future of Medicine” to promote increased dialogue among all stakeholders within our industry.

After 40 years, the activities of the PhRMA Foundation appear more important than ever. We look forward with confidence to the years ahead.
The PhRMA Foundation’s primary mission is to encourage young scientists to pursue careers in research and education related to drug discovery by providing funding to university-based scientists, and educators for scientific and medical research. The Foundation’s current program includes a Center of Excellence—in Clinical Pharmacology. Pre Doctoral, Post Doctoral, and Sabbatical Fellowships are offered as well as Research Starter Grants. Fellowships and Research Starter Grants are offered in Health Outcomes, Informatics, Pharmaceutics, and Pharmacology, which includes Toxicology, and Clinical Pharmacology. The Foundation accepts applications in all program areas for research on drugs for rare diseases.

Informatics

Post Doctoral Fellowships in Informatics

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

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

Receiving the fellowships that began between January and December 2005 are:

Uri Hershberg, Ph.D., Yale University School of Medicine: “New Models of Germinal Center Dynamics: A Novel Interface of Experimental and Simulation Methods.”

The Germinal Center (GC) is one of the cornerstones of immune function. In the GC, through a process of rapid mutation, proliferation and selection, the immune system generates B cells with a high affinity of reaction to invading pathogens. This process enables the immune system to detect the pathogen, destroy it and retain its ‘image’ for further encounters. The dynamical nature of the GC is at the heart of its function. It is thus hard to decipher, by reductionist experimental means alone, the exact forces that contribute to the selection of high affinity mutants. The aim of this proposal is to use tools from computational biology and bioinformatics to build data driven models of the GC that will help guide further experimental research of the GC. A new form of cooperation between
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At the Annual Meeting of the American Association of Pharmaceutical Scientists on Sunday, November 7, 2004 Dr. Dewey Barich of the University of Kansas and Mrs. Sandra Goss of the University of Connecticut were recognized as award recipients in Pharmaceutics. Also pictured are Eileen McCarron and Del Persinger of the PhRMA Foundation.
Research Start Grants in Informatics

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

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

Receiving the grants that began in January 2005 are:

- Yan Cui, Ph.D., The University of Tennessee Health Science Center. "Genetical Genomics of Gene Networks." This research focuses on discovering gene modulatory networks with genetical genomics approaches. Gene expression programs strongly influence the development of organisms and their responses to external stimuli. These programs are executed via the networks of gene modulation. Many diseases are related to malfunctions of part of the gene modulatory network. The structure of gene modulatory networks of higher organisms remains largely unknown, except for a few intensively studied pathways. A better understanding of the structures of gene modulatory networks will improve the understanding of the complex processes involved in higher order biological functions and will profoundly affect research on many diseases. Genetical genomics is an emerging research field at the boundary of genetics and genomics.

- Michael A. Thomas, Ph.D., Idaho State University. "Bioinformatics and Genome-Scale Molecular Evolution." This research in this laboratory is largely focused on understanding the influence of natural selection on alternative splicing (AS) leading to gene function diversification and rapid evolutionary transitions in the human genome. Using a database of human full-length cDNAs representing nearly every human gene, they will extend the study of natural selection intensity from the single gene to the genome level. This investigation is centered on functionally divergent AS isoforms of human genes in the study of natural selection by examining conserved coding domains, individual human genes, and biologically significant classes of genes. The preliminary data indicates that there is wide variation among AS isoforms (from the same gene locus) with respect to the intensity of natural selection. By targeting AS isoforms, this lab will explore how so few genes can provide so much complexity in higher organisms and how rapid evolutionary change can follow relatively few mutational substitutions. These studies will provide a richer understanding of the evolutionary process by providing a new view of the role of alternative splicing in evolution, a concept previously understudied and underappreciated. The implications of this study will change the way researchers study and interpret rates of molecular evolutionary change—this will affect researchers in many fields. The proposed research is also a true post-genome project; they take advantage of readily and freely available genome resources, build upon international & interdisciplinary collaborations, and use computational resources in novel, exciting ways.

- Receiving the grants that began in January 2005 are:

  - Yan Cui, Ph.D., The University of Tennessee Health Science Center. "Genetical Genomics of Gene Networks." This research focuses on discovering gene modulatory networks with genetical genomics approaches. Gene expression programs strongly influence the development of organisms and their responses to external stimuli. These programs are executed via the networks of gene modulation. Many diseases are related to malfunctions of part of the gene modulatory network. The structure of gene modulatory networks of higher organisms remains largely unknown, except for a few intensively studied pathways. A better understanding of the structures of gene modulatory networks will improve the understanding of the complex processes involved in higher order biological functions and will profoundly affect research on many diseases. Genetical genomics is an emerging research field at the boundary of genetics and genomics.

It begins with treating genome-wide gene expression data as quantitative traits. Quantitative Trait Loci (QTL) mapping methods are used to identify the genomic regions regulating the variations in gene expression levels. The identified QTLs become entry points from which to explore gene modulatory networks. This study proposes to develop an integrated computational method based on QTL mapping, single nucleotide polymorphism (SNP) analysis, probabilistic graphical models and global optimization algorithms. It extends beyond mapping of regulatory loci to a systematic evaluation of possible gene modulation relations using genome-wide genotype, SNP and gene expression data. All data is obtained from a single genetic reference panel of BXD recombinant inbred (RI) strains. The QTL mapping result provides strong constraints on the possible structures of gene network. Tentative gene modulatory networks can be constructed based on QTL mapping result. The QTL-derived networks include all the genes in the QTL regions as potential modulator genes. The complexity of the QTL-derived networks can be greatly reduced by studying the SNPs that distinguish the two progenitor strains of the BXD mice (C57BL/6J and DBA/2J). This step filters out the genes without the SNPs that likely underlie the QTL effects. Bayesian network models will then be used to systematically evaluate the gene modulatory relations.
Health Outcomes

Pre Doctoral Fellowship in Health Outcomes

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

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

Receiving the fellowship that began in March 2005 is:

Joshua D. Epstein, University of Southern California: “Response Shift While Experiencing Prostate Cancer: How Patient and Caregiver Preferences for Health Change.” Response shift is defined as a change in an individual’s internalized standards, values, and/or concepts of health utility due to an adjustment from one health state to another. Not accounting for response shift when measuring a change in utility can give misleading health valuations and have the potential to alter cost-effective ratios as a result. In this prospective study, the change in utility over the course of therapy will be assessed for 90 newly diagnosed prostate cancer patients and their primary caregiver (i.e. spouse). Methods: Each subject's utility for the patient's health state and a hypothetical health state will be elicited before therapy (pre test) and 8 months after (post test) using a visual analogue scale, time trade off method, and the Health Utilities Index Mark 3. To account for a possible response shift, a retrospective assessment (then test) of baseline health status will be elicited at the same time as the post test. This study will determine if accounting for response shift (difference between then test and post test) when measuring utility change is significantly different from traditional pre-post differences. It will also allow an assessment of whether preferences for hypothetical health states are influenced by personally being affected or closely experiencing disease in a significant other. Insights here may lead to a change in how the experience of community members, when valuing health states in generic health utility measures, is considered. This research will affect the measurement of outcomes used in cost-effectiveness analyses.

Post Doctoral Fellowship in Health Outcomes

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

Recipient of the Post Doctoral Fellowship that began in September 2005 is:

Ebere Akobundu, Ph.D., University of Maryland, Baltimore County: “The Application of the Probabilistic Reduction Approach to Health Econometric Model Specification and Testing.” The objective of the proposed research project is to apply the Probabilistic Reduction (PR) approach to econometric model specification and testing to the area of applied pharmacoeconomics and outcomes research. Health economists employ models that account for certain characteristics of health expenditure (i.e. cost) data. However, prior literature has been relatively silent on the identification of misspecification tests that are appropriate for determining the extent to which there is data support for the assumptions that are built into the model. The misspecification tests derived within the context of the PR approach are internally consistent because they are derived from the assumptions used to reduce the joint distribution to the conditional distribution, from which the regression model is derived. The PR approach will be used in two separate applications to derive misspecification tests that are appropriate for assessing the...
validity of the models. In the first application, the PR approach is used to identify an alternative method for conceptualizing, estimating, and conducting diagnostic tests of a regression model when the dependent variable is drawn from a skewed distribution. In the second application, the PR approach is used to define a systematic method for interpreting the Logit model and conducting misspecification tests of this model prior to drawing any inference or to calculating the predicted probability. This application will focus on the case where the model’s dependent variable contains a significant number of zero values. The goal of this project is to illustrate the importance of misspecification testing when conducting applied research using cost data. The hope is that this research will generate interest in developing appropriate misspecification tests of other models currently used in applied pharmaeconomics and outcomes research.

Sabbatical Fellowship in Health Outcomes

The 2005 Sabbatical Fellowship is the first one awarded in the field of Health Outcomes. It provides stipend funding to enable faculty members at all levels with active research programs an opportunity to work at other institutions for periods of six months to one year to learn new skills or develop new collaborations that will enhance their research and research training activities in pharmacoology. The Sabbatical Fellowship provides up to $40,000 for one year of stipend funding.

Receiving the fellowship that began in September 2005 is:
Daniel C. Malone, Ph.D., The University of Arizona: “The Economic Consequences of Metabolic Syndrome.” Obesity contributes to numerous risk factors for CAD that is now called metabolic syndrome. Approximately 23% of the US population is estimated to have metabolic syndrome, comprised of a constellation of risk factors including abdominal obesity, hypertension, dyslipidemia, and impaired fasting glucose. This condition has been linked to a 2 to 6-fold increase in coronary heart disease. The health economics of specific diseases (dyslipidemia, diabetes, hypertension, obesity) that contribute to metabolic syndrome and their treatment that are components of metabolic syndrome has been studied. However, there currently exists very little information about the economics of metabolic syndrome. Because the condition is a composite of unhealthy findings, it is important to more fully understand the total impact of metabolic syndrome on health care organizations and government programs that pay for health care. The specific aims are to: evaluate the relative contribution of the risk factors for metabolic syndrome in terms of their prevalence and impact on health care costs; determine the overall direct medical care costs of patients with metabolic syndrome as compared to those members without the condition; and model the long-term consequences of metabolic syndrome using a multi-disease Markov model.

Research Starter Grants in Health Outcomes

The purpose of the PhRMA Foundation Research Starter Grants is to offer financial support to individuals beginning their independent research careers at the faculty level. The program provides a research grant of $30,000 per year for up to two years. This program supports individuals beginning independent research careers in academia who do not have other substantial sources of funding. The program is not offered as a means to augment an ongoing research effort.

Recipients of the Research Starter Grants that began in January 2005 are:
Benjamin M. Craig, Ph.D., The University of Arizona: “Economic Burden of Cancer borne by Patients, Medicare, and Other Payers, 1992-2001.” The primary objective of this cost-of-illness (COI) study is to produce results that better inform clinical decisions and health policy about the economic burden of cancer from the perspectives of the patient, Medicare, and other payers. Currently, COI evidence is necessary to help guide the expansion of Medicare to include outpatient prescription drug coverage,

The PhRMA Foundation presented the 2005 fellowships and grants in Health Outcomes at the 10th Annual Meeting of the International Society For Pharmaeco-economics and Outcomes Research (ISPOR) on May 17, 2005 in Washington, D.C. Pictured from left to right; Eileen McCarron, PhRMA Foundation, Dr. Euni Lee, Howard University, Dr. Eberechukwu Akobundu, University of Maryland, Baltimore, Joshua D. Epstein, University of Southern California, Dr. Jean Paul Gagnon, Chairman of the Health Outcomes Advisory Committee, Dr. Benjamin M. Craig, University of Arizona and Dr. Daniel C. Malone, University of Arizona.

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McCarron at the ISPOR Annual Meeting in May 2005. Health Outcomes from Jean Gagnon and Eileen California accepts the Pre Doctoral Fellowship in Joshua Epstein from the University of Southern ambulatory care settings (stand-alone vs. hospital-based (AOM) prescription in postmenopausal women in two physician practice patterns of anti-osteoporosis medication secondary data analysis is proposed to evaluate and compare WHI publication on HRT use, but it is not clear how the osteoporosis. Few studies described the impact of the breast cancer, stroke, and myocardial infarction even (HRT) had increased postmenopausal women’s risk of treatment with hormonal replacement therapy (WHI) study, a recent randomized controlled trial showed estrogen replacement therapy (ERT) was the most preva- lent form to prevent and/or treat osteoporosis in the U.S. economic burden borne by patients, Medicare, other payers, and society; and (3) analyze the distribution of economic outcomes over the period of time following diagnosis. To produce well-informed evidence-based policy, decision makers need to know the cost of cancer, who is bearing this economic burden, and when the payments are due. The three aims in this research will contribute information useful for making budgetary decisions, setting research funding priorities, developing Medicare policy, and measuring the economic outcomes of cancer prevention, treatment and control.

Eunmi Lee, Pharm.D., Ph.D., Howard University: “The Impact of Women’s Health Initiative Study on Osteoporosis Management.” Osteoporosis is a major public health problem affecting millions of people and takes an enormous medical and economic toll on an aging pop- ulation. A preliminary study done by the PI suggests that estrogen replacement therapy (ERT) was the most preva- lent form to prevent and/or treat osteoporosis in the U.S. ambulatory care setting. The Women’s Health Initiative (WHI) study, a recent randomized controlled trial showed that the treatment with hormonal replacement therapy (HRT) had increased postmenopausal women’s risk of breast cancer, stroke, and myocardial infarction even though the treatment provided beneficial outcomes on osteoporosis. Few studies described the impact of the WHI publication on HRT use, but it is not clear how the WHI study influenced osteoporosis medication use. A sec- ondary data analysis is proposed to evaluate and compare physician practice patterns of anti-osteoporosis medication (AOM) prescription in postmenopausal women in two ambulatory care settings (stand-alone vs. hospital-based outpatient clinic) using two national surveys; National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1997 to 2004. The use of AOM will be compared before and after the WHI publication to determine whether the publication has influenced utilization of AOM and to describe its impact on individual anti-resorptive agent. This project will provide annual prevalence of AOM use and describe predicting factors for AOM use after adjusting for visit characteristics, physician specialties, and medical conditions using a multivariate analysis. Based on the findings, the investigator will develop a strategy to educ- ate postmenopausal women and build a pharmacy-based prospective intervention study focusing on the women who were associated with suboptimal AOM therapy.

Rochelle E. Tractenberg, Ph.D., Georgetown University: “Modeling Changes in Cognitive, Functional and Behavioral Outcomes with Quality of Life in Alzheimer’s Disease” Alzheimer’s disease (AD) is a progressive neurodegenerative illness that is usually associated with cognitive decline, so studies of AD and its treatment tend to focus on cognitive change (loss). Impairments in activities of daily living and behavioral disturbances are two other types of symptoms in AD, but they tend to be considered, and analyzed, as resulting from cognitive decline. Statistical models of the natural history of AD have focused on cognitive decline and have depended on increasingly complex analytic methods. Motivated by recent evidence of independence in progression within these three symptom domains as reflected in key outcome measures, this project focuses instead on increasing the complexity of the symptoms modeled. Dr. Tractenberg will build analytic models based on multiple symptom outcomes. The PhRMA Foundation Research Starter grant will allow her to carry out analyses that will replicate earlier findings of independence of changes in symptoms within these three domains in two different patient cohorts, and assess the correlation between symptomatic changes and quality of life (QOL). The association between changes in these three symptom types and quality of life has never been assessed in this patient population. Although the symptoms reflect the objective disease progression and the QOL ratings are subjective, their combination can add an important dimension to the interpretation of both observed changes, and association between changes, in symptomatic domains. These findings would have imme- diate implications for the design and conduct of clinical trials in AD, namely, they would suggest that a simple cognitive endpoint may not be as appropriate an outcome for clinical trials in AD as some combination of cognitive, functional and behavioral measures. Additionally, deter- mining the association of changes in each domain and the patient’s quality of life (QOL) may help focus resources on therapies that might have the greatest impact, as well as facilitating the identification of truly meaningful changes in all three types of symptoms. The implications could easily pertain to other diseases as well.
Pharmacology

Pre Doctoral Fellowships in Pharmacology/Toxicology

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

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

Three hundred and seven fellowships have been awarded under this program since it began in 1978 including the six fellows awarded in 2005.

Those who received fellowships that began between January and August 2005 are:

Cynthia D. Andjelic, The University of Utah: “Determining the Mechanism of Papuamide a Inhibition of Human Immunodeficiency Virus (HIV) Fusion.” HIV remains a serious disease with limited treatment options. Due to problems such as toxicity and resistance, the search for new treatments and therapeutic targets is ongoing. Papuamide A is a cyclic depsipeptide isolated from two sponges, *Theonella mirabilis* and *Theonella swinhoei*, collected off the coast of Papua New Guinea. Papuamide A demonstrated potent anti-HIV activity but the molecular mechanism of action has not been determined. In this laboratory, preliminary papuamide A-HIV protein interaction studies indicated papuamide A binds strongly to a region of HIV glycoprotein 41’s (gp41) cytoplasmic tail. Since HIV gp41 is known to mediate the fusion of the virus and target cell membranes, a virus fusion assay was performed. Papuamide A inhibited gp41-mediated fusion in this assay. Therefore, the goal of this research is to determine if papuamide A inhibits HIV’s cytopathic effects by binding to gp41’s cytoplasmic tail, preventing gp41-mediated fusion of HIV with its target cell. The ability of papuamide A to inhibit HIV entry through interaction with gp41’s cytoplasmic tail would identify a novel site of action that could be used in the development of therapeutic treatments. Drugs inhibiting the early HIV life cycle event of fusion would prove to be beneficial addition to current treatments. Furthermore, these studies could lead to an increased understanding of the role HIV’s gp41 cytoplasmic tail plays in the fusion process.

Ashley Thuy Doan, University of Wisconsin at Madison: “Characterization of RACK1, a Regulator of Cell Adhesion and Migration.” Cancer is one of the primary causes of human morbidity and mortality, with 90% of all cancer deaths arising from tumor invasiveness and metastasis. Changes in the expression and function of cell-cell and cell-matrix adhesion molecules correlate with the transition of benign tumors to invasive, malignant tumors. RACK1 is an adaptor protein that has been shown to localize to both cell-cell and cell-ECM adhesions. The function of RACK1 at these sites still remains to be elucidated. Moreover, elevated levels of *rack1* mRNA have been demonstrated in non-small cell lung, colon, and breast carcinoma cells compared to normal tissue. Thus identification of the function of RACK1 and its regulation in normal and tumor cells appears to be essential to evaluate oncogenic or tumor-suppressor potential. This research hopes to evaluate the roles of paxillin as a potential downstream effector of RACK1 in the regulation of adhesions and cell migration. And subsequently elucidate the role of RACK1 in modulating cell-cell contact and metastasis in breast epithelial cells. The discovery of RACK1 affect on cell migration would make it a rational target for further drug development. These drugs might have a considerable impact on tumor invasion and the possible development of new therapeutic agents.

Melinda D. Hains, The University of North Carolina at Chapel Hill: “Identification of Novel Binding Partners of RGS12.” Intercellular communication via G protein-coupled receptor (GPCR) signaling pathways in the nervous system is crucial for normal brain function and the regulation of neural processes. Thus, delineating the factors that control GPCR signaling is important to the understanding of nervous system-related disorders. “Regulators of G-protein signaling” (RGS) proteins accelerate G-alpha-mediated
On April 2, 2005 the 2005 Pharmacology/Toxicology award recipients received recognition at the ASPET Annual Meeting in San Diego, California. Pictured with Eileen McCarnan, PhRMA Foundation and George C. Fuller, Ph.D., Chairman of the Basic Pharmacology Advisory Committee are (left to right) Joshua S. Krumenacker, Ph.D., Baylor College of Medicine, Rheem A. Totah, Ph.D., University of North Carolina at Chapel Hill, and Shawn B. Bratton, Ph.D., The University of Texas at Austin.

GTP hydrolysis, and thus can profoundly inhibit signaling by many GPCRs. However, contributions by RGS proteins to the physiological control of GPCR function are only now being elucidated. RGS12, a neurospecific member of the R12-RGS subfamily, is an example of an RGS protein with numerous signaling regulatory elements. This lab has found that the RGS12 PTB domain binds in a phosphorylcase-dependent manner to the SNARE-binding synaptic (‘synaptic protein interaction’) region of the Cav2.2 N-type calcium channel, and thereby desensitizes GABAB-receptor mediated inhibition of calcium current in dorsal root ganglia. Thus, the long term objectives are to identify proteins that interact with RGS12, to characterize these interactions, and to define the role RGS12 plays in mediating signaling pathways such as pain processing. In a yeast two-hybrid screen for RGS12 domain interactors, two members of the ERK mitogen-activated protein kinase (MAPK) signaling module were recently isolated. This proposal is directed toward understanding the interaction of RGS12 with these proteins, and to define the role of RGS12 as a potential scaffold for the extracellular-regulated kinase (ERK) MAPK signaling module.

Using fluorescence and electron paramagnetic resonance spectroscopy, the lab will use site-directed labeling to identify regions of the G protein subunit that undergo conformational changes upon interaction with an activated GPCR. Then, these biophysical techniques will be used to measure how the distances between several pairs of labeled amino acids within G and between G and the GPCR change upon interaction with the receptor. The group will then determine the functional role of these conformational changes in mediating G protein activation in a system where the G protein can bind to the GPCR, but cannot release GDP. These studies will provide an important model of receptor-mediated G protein activation, and aid in understanding the structure of the GPCR-G protein complex as well as the determinants of receptor-G protein binding, coupling, and specificity to take advantage of this interaction as a novel target for pharmaceutical intervention.

Margaret M. Panning, SUNY Upstate Medical University: “The Molecular Mechanism of Endoplasmic Reticulum Protein Degradation by the Ubiquitin-Proteasome Pathway, and the Consequences of Bortezomib-Induced Histone De-Ubiquitination.” The ubiquitin-proteasome pathway (UPP) is now recognized to be pivotal in maintaining cell integrity by both controlling the stability of key regulatory proteins and catalyzing the degradation of misfolded or unassembled endoplasmic reticulum (ER) proteins, a process termed ER-associated degradation (ERAD). As the relevance of the UPP to health and disease is becoming apparent, proteins involved in this pathway are emerging as therapeutic targets, with proteasome inhibitors such as bortezomib now being used in the clinic. The rate-limiting step of protein degradation by the UPP is the modification of targeted substrates by covalent attachment of polyubiquitin, a process governed by ubiquitin-protein ligases (E3s). The first aim of this study is to define the enzymes involved in degradation of the type 1 isostitol 1,4,5-triphosphate receptor (IP3R1), an ER mem-
brane calcium channel that becomes a UPP substrate in response to various extracellular stimuli. Identification of the E3(s) involved in IP3R1 ubiquitination will better define the role of these enzymes in UPP substrate recognition and their potential as drug targets. The second aim will compare the turnover rates of endogenous and exogenous membrane proteins to determine whether susceptibility of proteins to ERAD is dependent upon their expression level. Results from this research will help to clarify how cells handle aberrant proteins. The third aim will focus on characterizing the molecular mechanism by which the proteasome inhibitor bortezomib leads to cell death, particularly its role in de-ubiquitinating histones, furthering the understanding of the anti-cancer activity of this novel drug.

Michael J. Van Kanegan, The University of Iowa College of Medicine: “Regulation of TrkA Signaling by Protein Phosphatase 2A.” The goal of this research is to determine novel regulatory mechanisms of neurotrophin signaling mediated by protein phosphatase 2A (PP2A). PP2A is a ubiquitous Ser/Thr phosphatase that removes phosphates from proteins to toggle their activity on or off. The substrate specificity and subcellular localization of PP2A is determined by close to 20 regulatory subunits that associate with a core dimer of catalytic and scaffold subunits. Studying the function of PP2A is very challenging, since there are more than 48 possible heterotrimers. This lab has devised a clever strategy, using scaffold subunit knockdown and mutant replacement, to discern the function of specific families of regulatory subunits. With this approach, specific PP2A holoenzymes that modulate nerve growth factor (NGF) signaling pathways will be identified. Extensive studies have shown the prototypical neurotrophin, NGF, to be required for the survival and differentiation of sensory and sympathetic neurons. NGF has been implicated in many neurodegenerative diseases including Alzheimer’s disease, as well as in chronic states of inflammation and neuropathic pain. NGF elicits its biological effect by activating the TrkA receptor, which initiates several signaling cascades, including the MAP kinase pathway. Although PP2A has been shown to modulate the MAP kinase pathway at multiple levels, mechanistic details have yet to be defined. The preliminary data suggest that specific PP2A holoenzymes differentially regulate NGF signaling by positively regulating the TrkA receptor, while negatively regulating the downstream kinases, ERK1/2. Studying the mechanisms by which PP2A regulates TrkA receptor signaling may provide the basis for future therapies of not only diseases involving aberrant NGF receptor signaling, but also of diseases in which other growth factor signaling cascades are dysregulated, such as cancers.

Post Doctoral Fellowships in Pharmacology/Toxicology

The PhRMA Foundation Post Doctoral program in Pharmacology/Toxicology provides stipend support for individuals engaged in a multidisciplinary research training program that will create or extend their credentials in pharmacology or toxicology. The purpose (intent) of this program is to support post doctoral career development activities of individuals prepared (or preparing) to engage in research that integrates information on molecular or cellular mechanisms of action with information on the effect of an agent on the intact organism. Recent graduates from pharmacology Ph.D. programs interested in postdoctoral experience that integrates pharmacology with a morphological specialty (cell biology/anatomy/pathology) are also eligible to apply for this fellowship. It is anticipated that this research training will be accomplished in academic and/or industrial laboratory settings where multidisciplinary teams are organized to integrate informatics, molecular, cell, and systems biology with pharmacology/toxicology research.

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

Receiving the fellowships that began between January and December 2005 are:

Joshua S. Krumenacker, Ph.D., Baylor College of Medicine: “Role of Cell Death Pathways in the Phosphotyepicity of Embryonic Stem Cells.” New hope has recently emerged regarding the use of embryonic stem (ES) cells for future transplantation and regenerative therapies to treat debilitating neurodegenerative disorders.
such as Alzheimers and Parkinsons disease. Before optimal treatments of these diseases can involve ES cells, a careful understanding of the pluripotent nature of ES cells and what cellular signals determine ES cell differentiation will be necessary. The objective of this proposal is to examine the expression, function and downstream actions of cell death (apoptosis) signaling pathways in the proliferation and self-renewal of mouse and human ES cells. The requirement for caspase signaling in ES cell self-renewal will be defined and investigated by pharmacologically blocking the caspase family of enzymes. Overall, the work proposed in this application will elucidate the role of cell death pathways in the self-renewal and differentiation of mouse and human ES cells.

Aime V. Levesque, Ph.D., Dartmouth Medical School: “Visualization of Drug:Target Interactions In Transplantable Tumor Models.” In response to DNA damage, cells arrest their cell cycle progression in an attempt to repair the damage through the activity of cell cycle “checkpoints.” Once repair is complete, cells may recover and continue to proliferate, or, if the damage is excessive, cells may undergo cell death. One promising approach to cancer therapy is to inhibit the cell cycle checkpoints, thereby forcing cells to prematurely enter the next phase of the cell cycle with damaged DNA. This abrogation of cell cycle arrest is lethal and occurs preferentially in cells defective for the p53 tumor suppressor protein. Since more than 50% of tumors have defects in p53, the combination of DNA damaging agents and checkpoint inhibitors could significantly improve the outcome of cancer chemotherapy. This lab has generated isogenic cell lines that differ with respect to their p53 status to confirm that p53 protects cells from checkpoint abrogation mediated by the checkpoint inhibitor 7-hydroxystaurosporine (UCN-01). The therapeutic potential of drug combinations using DNA damaging agents such as cisplatin and checkpoint inhibitors such as UCN-01 has generated great excitement, and they, as well as many pharmaceutical companies, are attempting to synthesize better checkpoint inhibitors. A major problem arises in the design of clinical trials of novel inhibitors, as it is difficult to assess the optimum dose of drug to prescribe. The normal design of a Phase I clinical trial is to escalate the dose of drug until toxicity is seen, and then to use the drug at the maximum tolerated dose. However, checkpoint inhibitors are non-toxic to cells when used alone. Toxicity observed in animals and humans is due to off-target effects of these drugs. The long-term goal of this research program is to use non-invasive imaging to assess target-mediated activity and drug efficacy in cancer patients receiving therapy. Toward this goal, the lab proposes to develop cell-based assays and transplantable tumor models that can be used to assess on-target effects of checkpoint inhibitors. They propose to validate a cyclin B promoter-driven reporter as a means to monitor cell cycle arrest induced by DNA damaging agents in cell culture and in transplantable tumor models. The impact of p53 status on cell cycle arrest induced by DNA damaging agents in cell culture and in transplantable tumor models will then be assessed using fluorescent reporter constructs. Lastly, a model in which the activation state of Chk1, the target of UCN-01, can be directly visualized by its binding to other checkpoint regulatory proteins will be established.

Post Doctoral Fellowship in Pharmacology/Morphology including Cell Biology.

The goals of this post doctoral program are to increase understanding of the actions of drugs by direct study of their effects on cells and tissues, to correlate the morphological changes, and uncover associations observed with functional parameters of cells and tissues. This program provides a stipend of $40,000 annually for up to two years to well-trained graduates from Ph.D. programs who seek to further develop and refine their research skills through formal post doctoral training. This fellowship was first offered in 1968. One hundred and eleven awards have been made to date including the one awarded in 2004.

Receiving the fellowship that began in January 2005 is Erik I. Charych, Ph.D., Rutgers, The State University of New Jersey: “The Effects of PSD-95 Regulation by Cypin on Spine Formation and Maturation in Neuronal Dendrites.” The majority of excitatory synapses among neurons in the mammalian brain occur on dendritic spines, morphologically distinct protrusions of the dendritic shaft that are characterized by a high degree of morphological heterogeneity. PSD-95, a major component of the postsynaptic density (PSD) of excitatory synapses,
plays a key role in synapse formation and synaptic function, including the formation and/or maturation of dendritic spines. Cypin (cytoplasmic PSD-95 interactor) is an abundant brain protein that was isolated by virtue of its interaction with PSD-95. Several lines of evidence suggest that cypin negatively regulates the synaptic localization of PSD-95. Recent studies from this laboratory suggest that different types of apoptosome complexes may be formed during stress, some of which are not associated with apoptosis. Furthermore, other laboratories have suggested that apoptosome complexes are not essential for the induction of apoptosis. Thus, it is proposed to further analyze the function of various Apaf-1 apoptosome complexes and to determine their importance for drug-induced apoptosis in a variety of tissues. The proposed studies will significantly improve the basic understanding of apoptosome complexes and will provide insight as to how these complexes might be modulated for therapeutic purposes.

Research Starter Grants in Pharmacology/Toxicology

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

The first Research Starter Grant awards were made in 1972, and a total of six hundred and two have been awarded, including the grants beginning on January 1, 2005.

Recipients of the Research Starter Grants that began in January 2005 are:

Shawn B. Bratton, Ph.D., The University of Texas at Austin: “Role of Apaf-1 Apoptosome Complexes in Drug-Induced Cell Death.” Most chemotherapeutic drugs kill cells by triggering a form of cell suicide, known as apoptosis. Importantly, many of these drugs initiate death signals that eventually result in injury to mitochondria and consequently release of cytochrome c from the intermembrane space into the cytoplasm. Once in the cytoplasm, cytochrome c stimulates formation of a protein complex, known as the Apaf-1 apoptosome. This complex then activates a series of proteases (caspases), which are responsible for proteolytically dismantling the cell.

Recipients of the Research Starter Grants that began in January 2006 are:

David W. Grainger, Ph.D., Professor, Department of Chemistry, Colorado State University received the 2005 Award in Excellence in Pharmaceutics at the Annual Meeting of AAPS in Nashville, Tennessee on November 6, 2005.
Paul Calabresi Medical Student Fellowships in Clinical Pharmacology

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

The minimum period of the fellowship is three months and the maximum is two years, with a maximum stipend of $18,000. One hundred and sixty-four Medical Student Fellowships have been awarded since the program began in 1974. This fellowship has been named in honor of Dr. Paul Calabresi who served the PhRMA Foundation as a committee Chairman and member for 25 years.

The recipients of the Paul Calabresi Medical Student Fellowships that began in July 2005 are:

Kyle O. Arneson, Vanderbilt University School of Medicine: "Neurofurans: Novel Products Providing Insights into the Physiologic and Pathologic Roles of Oxygen in the Central Nervous System." Oxidative stress and free radicals have been implicated in the pathogenesis of many disease states including neurodegenerative diseases such as Parkinson’s, Huntington’s, and Alzheimer’s. One obstacle in studying these diseases is the lack of sensitive and specific biomarkers that correlate to disease presence and progression. This lab has discovered a unique class of compounds that form by the free radical attack of docosahexaenoic acid (DHA), the most abundant polyunsaturated fatty acid in neurons. These compounds have been termed neurofurans (NFs) because of their localization to neurons and due to their structure. The hypothesis is that NFs may be a sensitive and specific marker of oxidative stress and cellular dysfunction within the central nervous system. This proposal outlines studies to fully characterize the structure and mechanism of formation of the NFs. Also, the utility of NFs as a sensitive and specific biomarker of oxidative stress will be looked at in several environments and disease states, both in vivo and in vitro. Through these studies they hope not only to characterize and utilize this novel set of compounds, but to use this information to gain understanding into the physiologic role oxygen plays in the central nervous system as well as the pathologic role it plays in neurodegeneration.

Albert A. Davis, Emory University School of Medicine: "Muscarinic Acetylcholine Receptors and Alzheimer’s Disease." Alzheimer’s Disease (AD) is a progressive neurologic disease characterized by memory loss, cognitive dysfunction, and behavioral changes. The exact cause of AD is not completely understood, but it is known that a key chemical used by neurons to communicate with one another, acetylcholine (ACh), is lost in the brains of AD patients. Current therapy for AD relies on drugs called cholinesterase inhibitors, which enhance the levels of ACh, and these drugs have been moderately successful in preserving cognitive function. However, one significant disadvantage of cholinesterase inhibitors is that they indiscriminately activate all types of muscarinic acetylcholine receptors (mAChR). There are five distinct types of mAChRs (M1-M5), and a growing body of evidence supports the theory that selective activation of specific subtypes of receptors will have distinct effects on memory. In addition, these receptor subtypes may have distinct effects on the production and accumulation of amyloid-beta peptide (Aβ), a molecule which is believed to play an important role in the development and progression of AD. This project will take advantage of recent achievements in drug development and animal modeling to test the hypothesis that the M1 mAChR is pivotal in the pathophysiology and symptomatology of AD. Three specific aims will (1) characterize novel M1-selective drugs and their effects on receptor function; (2) test the hypothesis that selective M1 activation reduces the accumulation of Aβ; and (3) investigate the effects of Aβ accumulation on the expression and function of mAChRs.

Pharmaceutics

Pre Doctoral Fellowships in Pharmaceutics

This program has been in effect for 18 years. It assists awardees who have one or two years remaining in the pharmaceutics pre-doctoral training—the time during which they are engaged in dissertation research. We provide the funding during the doctoral program after course work has been completed and the remaining training activity is a student’s research project.
will ultimately fail during the development process. One solubility and, unless a solution can be identified, the API which provides adequate bioavailability in spite of the low translates into poor biological activity. It is then the technology have poor aqueous solubility which often entents (APIs) identified using high throughput screening libraries which can be screened for biological activity. Unfortunately, many of the active pharmaceutical ingredi- ents (APIs) identified using high throughput screening technology have poor aqueous solubility which often translates into poor biological activity. It is then the responsibility of the formulator to design a dosage form which provides adequate bioavailability in spite of the low solubility and, unless a solution can be identified, the API will ultimately fail during the development process. One approach is to formulate the API into a solid dispersion. Specifically, a carrier matrix, most often a polymer, may be used to stabilize APIs into an amorphous state which has a higher solubility than its crystalline counterpart. Some generalizations can be made about the characteristics of a stable solid dispersion including decreased molecular mobility of the API, low free volume, high glass transition temperature, and high configurational entropy of crystallization. These characteristics prohibit molecular rearrangement which must precede nucleation and growth of the crystalline phase. Upon mixing an API with a poly- mer, the relative strength of the cohesive interactions (drug-drug and polymer-polymer interactions) and adhe- sive interactions (drug-polymer interactions) will greatly influence these factors. However, little work has been done to understand this on a molecular level providing lit- tle insight into the mechanisms of stabilizing the amor- phous state. It is the broader aim of this project to under- stand, on a molecular level, the mechanisms of stabilizing drugs in solid dispersions through spectroscopic tech- niques so that poorly soluble APIs can make it to market.

Patrick J. Marsac, Purdue University: “Molecular Level Understanding of Polymer Induced Formation and Stabilization of Amorphous API.” Pharmaceutical compa- nies are increasingly taking advantage of combinatorial chemistry allowing them to produce larger chemical libraries which can be screened for biological activity. Specifically, a carrier matrix, most often a polymer, may be used to stabilize APIs into an amorphous state which has a higher solubility than its crystalline counterpart. Some generalizations can be made about the characteristics of a stable solid dispersion including decreased molecular mobility of the API, low free volume, high glass transition temperature, and high configurational entropy of crystallization. These characteristics prohibit molecular rearrangement which must precede nucleation and growth of the crystalline phase. Upon mixing an API with a poly- mer, the relative strength of the cohesive interactions (drug-drug and polymer-polymer interactions) and adhe- sive interactions (drug-polymer interactions) will greatly influence these factors. However, little work has been done to understand this on a molecular level providing lit- tle insight into the mechanisms of stabilizing the amor- phous state. It is the broader aim of this project to under- stand, on a molecular level, the mechanisms of stabilizing drugs in solid dispersions through spectroscopic tech- niques so that poorly soluble APIs can make it to market.

Aaron M. Mohs, The University of Utah: “PEGylated Biodegradable Macromolecular Contrast Agents for Blood Pool Magnetic Resonance Imaging.” Magnetic resonance imaging (MRI) can give great insight into the morphology and functionality of pathological tissues. Current Gd(III)-based clinical contrast agents to enhance tumor morphology and functionality are all low molecular weight agents, which result in transient blood pool retention time and rapid extravasation out of the vasculature. This shortens the contrast enhancement window and spatial resolution of image, respectively. Macromole- cular contrast agents have been developed because they possess superior characteristics for imaging and they are con- fined largely to the vasculature. These agents, however, are potentially toxic and their development has been limited...
due to slow elimination and consequential metabolic release of toxic Gd\(^{3+}\) ions. In response, the first goal of this project consists of designing and synthesizing PEGylated and biodegradable, through the disulfide bond, Gd\(^{3+}\)-chelate-based macromolecular blood pool contrast agents, PEG-g-poly(GdDTPA-o-L-cysteine), in an attempt to alleviate the toxicity concerns. With this type of contrast agent, a high molecular weight can be obtained to produce optimal agents allowing a more complete data analysis of the MR exams. To this end, in the second part of the proposal, these agents will be extensively tested in vivo for the detection and staging of neoplastic tissue using dynamic contrast-enhanced MRI. Imaging-based pharmacokinetic models will be used to draw correlations between the parameters and the cancer stage. PEGylated and biodegradable macromolecular blood pool contrast agents will be a safe and effective tool for contrast-enhanced MRI in order to noninvasively detect and stage cancers and tissues from P-gp knockout mice.

Beverly M. Morey, The University of North Carolina, Chapel Hill: "Influence of Efflux by P-Glycoprotein On Cytochrome P450-Mediated Drug Metabolism in the Intestine." Intestinal cytochrome P450 enzymes and efflux transporters represent two important barriers to effective drug absorption. Current literature suggests that these processes may function synergistically to reduce intestinal bioavailability; recent studies have indicated that intestinal efflux of drugs by the transporter P-glycoprotein (P-gp) enhances drug metabolism mediated by the cytochrome P450 family of enzymes (CYP3A) during absorption, but the mechanism by which this interaction occurs has not been unequivocally identified. An understanding of the functional relationships between a drug's intrinsic metabolic capacity, intrinsic efflux capacity and rate of passive diffusion is critical for the development of predictive models of intestinal bioavailability; however, these relationships have yet to be fully defined. Therefore, a set of hypotheses has been proposed, and experiments designed, to evaluate these relationships in order to critically assess the influence of P-gp efflux on CYP3A-mediated drug metabolism and to determine the impact of this interaction on intestinal absorption. The proposed following primary hypotheses will be explored: (1) at doses that produce saturate CYP3A-mediated drug metabolism, P-gp efflux will reduce the rate of CYP3A metabolism but will not alter the extraction ratio; (2) under linear conditions, P-gp efflux will not alter the extraction ratio of CYP3A metabolism. This study aims to dissect the interaction between P-gp and CYP3A4 in the intestine by studying efflux and metabolic processes separately and in concert. Experimental methods will rely primarily on in vivo models, including metabolically active Caco-2 cells and controls, and repeated application of viral vectors still has safety

Research Starter Grants in Pharmaceutics

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Receiving the grants that began in January 2005 are:

Cory J. Berkland, Ph.D., The University of Kansas: "Particle Design for Improved Delivery and Controlled Release of Inhaleable Pharmaceuticals" Inhalated aerosols are an effective means to treat diseases affecting the lung, including asthma and cystic fibrosis. The large surface area of the pulmonary system, ~140 m\(^2\), and ready access to the circulatory system offer potential for noninvasive delivery of therapeutics circumventing the need for injections. Whether treating the lung as a locus of disease or a route of systemic drug delivery, the common difficulty of efficiently administering aerosols in the deep lung remains. Researchers have discovered that ~1-3 µm particles deposit with high efficiency to the deep lung, avoiding deposition in the oropharyngial cavity common for larger particles (~3 µm) and exhalation before deposition common for submicron particles. Creating particles possessing such a narrow size distribution, however, is a difficult task and usually only a small percentage of dry powder dose reaches the deep lung. The goal of this lab is to create large porous particles wherein >90% of the particle population possess aerodynamic diameters of ~1.3 µm to improve deep lung deposition. They will fabricate the particles from poly(dilacti-co-glycolic) acid, controlling the particle size and density. Aerodynamic properties of particle batches and their ability to controllably release tobramycin will be evaluated.

Aliasger K. Salem, Ph.D., The University of Iowa: "Controlled release of Heat-Shock Protein-Antigen Genes for Sustained Protection and Prevention against Cervical Cancer" Heat Shock Protein (HSP) therapy has shown significant potential in generating a strong immune response for prevention of cervical cancer. HSP's taken up by antigen-presenting cells (APCs) are predominantly processed by the class I antigen-presenting pathway. The result is activated CD8+ T cells, effectors of the cellular immune system, which are necessary for defense against tumors. While injections of tumor-specific antigens in the past have elicited only very weak antibody responses, application of a gene delivery approach to HSP therapy has shown significant therapeutic potential for enhancing the response. However, such plasmids require repeat doses and remain susceptible to in vivo degradation. Prolonged and repeated application of viral vectors still has safety

The University of North Carolina, Chapel Hill: "Influence of Efflux by P-Glycoprotein On Cytochrome P450-Mediated Drug Metabolism in the Intestine." Intestinal cytochrome P450 enzymes and efflux transporters represent two important barriers to effective drug absorption. Current literature suggests that these processes may function synergistically to reduce intestinal bioavailability; recent studies have indicated that intestinal efflux of drugs by the transporter P-glycoprotein (P-gp) enhances drug metabolism mediated by the cytochrome P450 family of enzymes (CYP3A) during absorption, but the mechanism by which this interaction occurs has not been unequivocally identified. An understanding of the functional relationships between a drug's intrinsic metabolic capacity, intrinsic efflux capacity and rate of passive diffusion is critical for the development of predictive models of intestinal bioavailability; however, these relationships have yet to be fully defined. Therefore, a set of hypotheses has been proposed, and experiments designed, to evaluate these relationships in order to critically assess the influence of P-gp efflux on CYP3A-mediated drug metabolism and to determine the impact of this interaction on intestinal absorption. The proposed following primary hypotheses will be explored: (1) at doses that produce saturate CYP3A-mediated drug metabolism, P-gp efflux will reduce the rate of CYP3A metabolism but will not alter the extraction ratio; (2) under linear conditions, P-gp efflux will not alter the extraction ratio of CYP3A metabolism. This study aims to dissect the interaction between P-gp and CYP3A4 in the intestine by studying efflux and metabolic processes separately and in concert. Experimental methods will rely primarily on in vivo models, including metabolically active Caco-2 cells and controls, and repeated application of viral vectors still has safety

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concerns. The use of biodegradable particles for delivering plasmids has been shown to be an attractive approach for immunization. These particles can target specific cell types (with targeting ligand strategies), are non-toxic to cells, protect DNA from enzymatic degradation, enable preferential uptake by antigen presenting cells, and can provide sustained release of DNA, negating the requirement for repeat doses or boosters. This project will test the hypothesis that poly lactic acid-polyethylene glycol (PLA-PEG) particles encapsulating plasmids encoding HSP-antigen genes can generate a stronger more sustained immune response against HPV-16-induced cervical cancer than current approaches. This will be achieved by (1) Optimizing PLA-PEG HSP-E7 cDNA particles for genetic vaccination; and (2) Evaluating the immune response and anti-tumor effect from mice vaccinated with PLA-PEG HSP-E7 cDNA particles. It is anticipated that these studies will provide a long-term framework in which cancer therapies are approached by synergistically coalescing gene delivery, degradable particle technology, cell targeting strategies and heat shock protein therapy.

Duxin Sun, Ph.D., The Ohio State University: "Site-Specific Activation of Geldanamycin Prodrugs in Tumors." Tremendous effort has been extended to improve the efficacy of chemotherapy; however, a breakthrough has not yet been achieved. A delicate dose regimen is usually required to balance drug toxicity and resistance; therefore, a targeted drug delivery system to increase efficacy and decrease toxicity will be beneficial for cancer chemotherapy. Geldanamycin (GA) is a potent anticancer compound that inhibits molecular chaperone (Hsp90). However, clinical evaluation of GA has been terminated due to its toxicity and poor water solubility. 17-allylaminogeldanamycin (17-AAG) is a derivative of GA in clinical trials, but its hepatotoxicity and poor water solubility may again limit its development. This lab has successfully evaluated monoclonal antibodies directed against tumor-associated glycoprotein-72 (TAG-72) in clinical trials for tumor targeting. The GA was inactivated by glycosylation at C-17 position and re-activated by corresponding enzyme. The proposed study will employ anti-TAG-72 antibodies for targeted delivery an enzyme called galactosidase to colorectal cancer. This enzyme will site-specifically activate inactive GA prodrugs to active drugs to cause tumor destruction. This system may improve tumor eradication by increasing active drug concentration at the site of tumor while minimize systemic toxicities associated with GA.

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.
Belief in a Mission...

The PhRMA Foundation is lastingly indebted to a cadre of PhRMA Board members who despite uncommon demands on their time through the nature of their jobs have given more than three decades of faithful and sagacious service.
The PhRMA Foundation ended 2004 in sound financial shape and increased the reserve funds. Contributions were up 1% from the previous year, to $2.89 million. We awarded $2.1 million in grants and held down non-grant program and administrative expenses. Total expenditures, at $2.5 million, were $212,000 below budget. Total net assets at December 31 were up 10%, to $9.16 million. Of this amount, $2.8 million represents funds authorized but not yet paid for the future years of grants already awarded. Most of the increase in net assets is attributable to $720,000 in investment gains and interest income. We did not transfer funds from reserves (the Future Commitment Fund) to cover payment this year of awards granted in previous years. Financial details are shown in the accompanying Statement of Income and Expenditures.

For 2005, contributions were targeted to reach $2.7 million, as we entered the fourth full year of our new program. On behalf of the Board and staff, I give special thanks for the continuing support of our generous contributors, who are listed in this report.

The Foundation’s financial position as of December 31, 2004, has been audited by the Rosslyn, Virginia, accounting firm of Buchanan & Company. A full report can be obtained by contacting the Foundation.

Steven M. Paul, M.D.
Treasurer, PhRMA Foundation
and
Executive Vice President, Science and Technology
President, Lilly Research Laboratories
Eli Lilly and Company
## Statement of Income and Expenditures
### For the Year Ended December 31, 2004

### INCOME

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### EXPENDITURES

**Programs**

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awards in Excellence</td>
<td>15,295</td>
</tr>
<tr>
<td>Center of Excellence for Integration of Genomics and Informatics</td>
<td>350,000</td>
</tr>
<tr>
<td>Clinical Pharmacology Program</td>
<td>328,000</td>
</tr>
<tr>
<td>Health Outcomes Program</td>
<td>245,000</td>
</tr>
<tr>
<td>Informatics Program</td>
<td>320,000</td>
</tr>
<tr>
<td>Pharmacogenetics Program</td>
<td>230,239</td>
</tr>
<tr>
<td>Pharmacology Programs</td>
<td>605,829</td>
</tr>
<tr>
<td>AFPE Fellowship Award</td>
<td>5,000</td>
</tr>
<tr>
<td><strong>Subtotal—Grants</strong></td>
<td><strong>$2,099,363</strong></td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Committee Meetings, Travel and Honoraria</td>
<td>54,358</td>
</tr>
<tr>
<td>Publications and Special Projects</td>
<td>29,044</td>
</tr>
<tr>
<td><strong>Subtotal—Other</strong></td>
<td><strong>$83,402</strong></td>
</tr>
</tbody>
</table>

| **Program Total**                                                           | **$2,182,765** |

**Administrative**

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staff, Rent, Taxes Insurance, Depreciation</td>
<td>278,441</td>
</tr>
<tr>
<td>Professional Services and Investment Expenses</td>
<td>64,228</td>
</tr>
<tr>
<td>Office Expenses</td>
<td>8,052</td>
</tr>
<tr>
<td><strong>Subtotal—Administrative</strong></td>
<td><strong>$350,721</strong></td>
</tr>
</tbody>
</table>

**TOTAL EXPENDITURES**                                                       **$2,533,486**
Advisory Committees

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Benefactors

The PhRMA Foundation owes its success to the pharmaceutical companies that have provided their generous support over the past 40 years. We thank all of you for continuing to invest in the future of pharmaceutical research and the scientists of tomorrow.

Our 2005 Benefactors are:

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Schering-Plough Corporation
SCHWARZ PHARMA, INC.
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Wyeth
# PhRMA Foundation Programs for 2006

<table>
<thead>
<tr>
<th>Name of Program/Year of First Awards</th>
<th>Number of Awards</th>
<th>Budgeted Yearly</th>
<th>Deadline/Starting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health Outcomes Advisory Committee</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre Doctoral Fellowships in Health Outcomes (2002)</td>
<td>2 budgeted/2 years</td>
<td>$ 80,000 total $ 20,000 per award per year</td>
<td>October 1, 2005/January-August</td>
</tr>
<tr>
<td>Post Doctoral Fellowship in Health Outcomes (2002)</td>
<td>1 budgeted/2 years</td>
<td>$ 80,000 total $ 40,000 per award per year</td>
<td>October 1, 2005/January-December</td>
</tr>
<tr>
<td>Sabbatical Fellowship in Health Outcomes (2002)</td>
<td>1 budgeted/1 year</td>
<td>$ 40,000 total $ 40,000 per award per year</td>
<td>October 1, 2005/January-December</td>
</tr>
<tr>
<td>Research Starter Grants in Health Outcomes (2002)</td>
<td>3 budgeted/2 years</td>
<td>$180,000 total $ 30,000 per award per year</td>
<td>October 1, 2005/January-December</td>
</tr>
<tr>
<td><strong>Informatics Advisory Committee</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Doctoral Fellowships in Informatics (2002)</td>
<td>2 budgeted/2 years</td>
<td>$160,000 total $ 40,000 per award per year</td>
<td>September 1, 2005/January-December</td>
</tr>
<tr>
<td>Sabbatical Fellowship in Informatics (2002)</td>
<td>1 budgeted/1 year</td>
<td>$ 40,000 total $ 40,000 per award per year</td>
<td>September 1, 2005/January-December</td>
</tr>
<tr>
<td>Research Starter Grants in Informatics (2002)</td>
<td>3 budgeted/2 years</td>
<td>$180,000 total $ 30,000 per award per year</td>
<td>September 1, 2005/January-December</td>
</tr>
<tr>
<td><strong>Pharmacology Advisory Committees</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)</td>
<td>6 budgeted/2 years</td>
<td>$240,000 total $ 40,000 per award per year</td>
<td>September 1, 2005/January-August</td>
</tr>
<tr>
<td>Post Doctoral Fellowships in Pharmacology/Toxicology (2002)</td>
<td>2 budgeted/2 years</td>
<td>$160,000 total $ 40,000 per award per year</td>
<td>September 1, 2005/January-December</td>
</tr>
<tr>
<td>Sabbatical Fellowship in Pharmacology/Toxicology (2002)</td>
<td>1 budgeted/1 year</td>
<td>$ 40,000 total $ 40,000 per award per year</td>
<td>September 1, 2005/January-December</td>
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<tr>
<td>Research Starter Grants in Pharmacology/Toxicology (1972)</td>
<td>3 budgeted/2 years</td>
<td>$180,000 total $ 30,000 per award per year</td>
<td>September 1, 2005/January-December</td>
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<tr>
<td>Paul Calabresi Medical Student Research Fellowship (1974)</td>
<td>2 budgeted/1 year to 18 months</td>
<td>$ 36,000 total $ 18,000 per award per year</td>
<td>September 1, 2005/January-August</td>
</tr>
<tr>
<td><strong>Pharmaceutics Advisory Committee</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pre Doctoral Fellowships in Pharmaceutics (1987)</td>
<td>2 budgeted/2 years</td>
<td>$ 80,000 total $ 20,000 per award per year</td>
<td>October 1, 2005/January-August</td>
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<tr>
<td>Post Doctoral Fellowship in Pharmaceutics (1992)</td>
<td>2 budgeted/2 years</td>
<td>$160,000 total $ 40,000 per award per year</td>
<td>October 1, 2005/January-December</td>
</tr>
<tr>
<td>Sabbatical Fellowship in Pharmaceutics (2002)</td>
<td>1 budgeted/1 year</td>
<td>$ 40,000 total $ 40,000 per award per year</td>
<td>October 1, 2005/January-December</td>
</tr>
<tr>
<td>Research Starter Grants in Pharmaceutics (1972)</td>
<td>2 budgeted/2 years</td>
<td>$120,000 total $ 30,000 per award per year</td>
<td>October 1, 2005/January-December</td>
</tr>
</tbody>
</table>

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

www.phrmafoundation.org