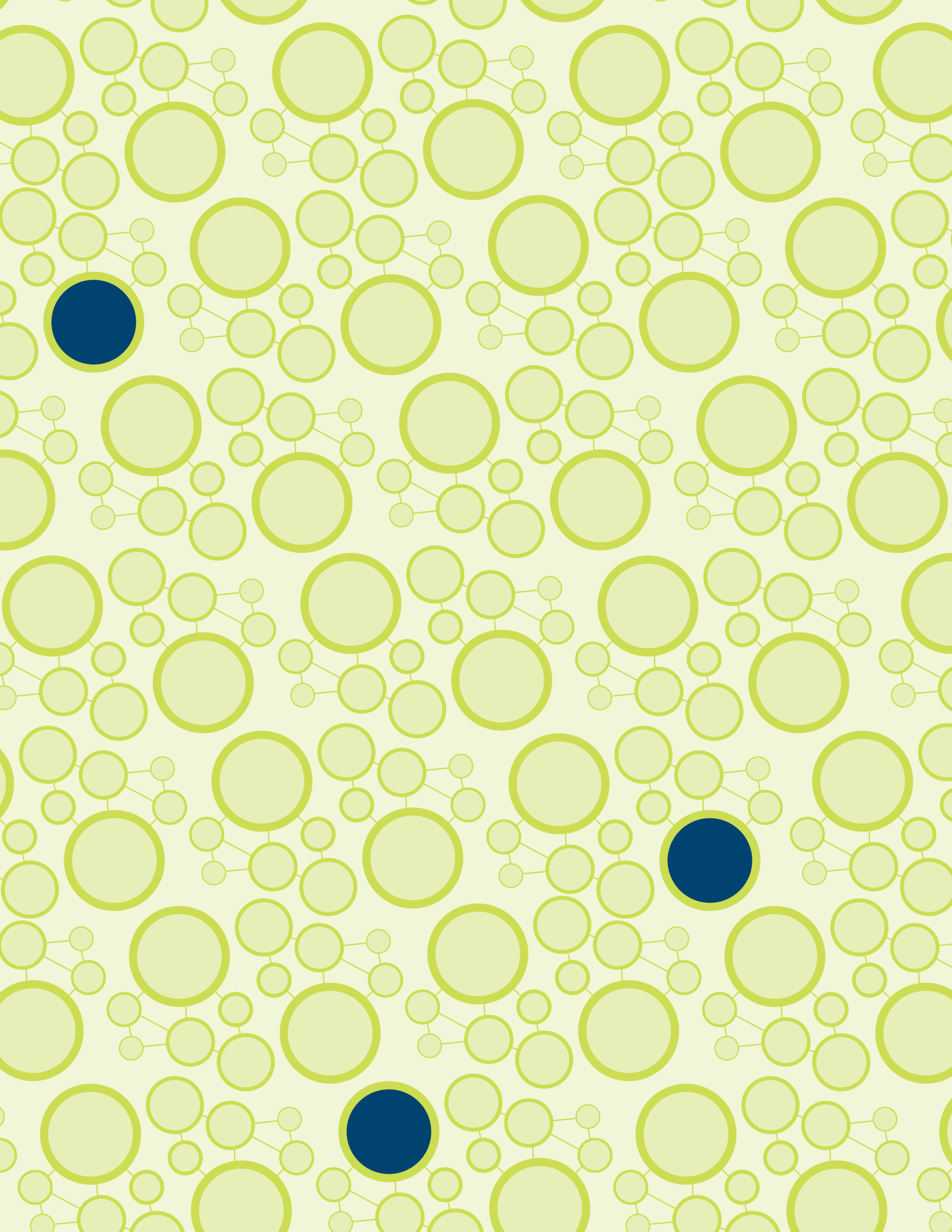


Pharmaceutical Research and Manufacturers of America Foundation



2009

Annual Report



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MISSION STATEMENT

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.

MESSAGE *from the* CHAIRMAN



The PhRMA Foundation is pursuing strategic partnerships that will leverage the nationwide visibility and reputation of the Foundation to advance training and education in critically important areas. Our most advanced initiative involves development of a comparative effectiveness research (CER) curriculum initiative to promote the field through education and training.

Comparative effectiveness may be a relatively new term, but many in the health care community believe the assessment and comparison of evidence-based information has the potential—if done wisely—to optimize disease prevention and treatment, greatly improving the quality of health care.

A critical component of patient care, comparative effectiveness bridges the gap between available medical data and treatment. If successfully integrated, CER training institutes could provide ongoing and valuable information about drug effectiveness and risk management. This type of research is not only crucial to the biopharmaceutical companies, it is essential for delivering higher quality treatments and greater value to patients.

The CER educational initiative is a planned effort to shape and support this emergent field from its beginnings. We have called upon experts from academic institutions, companies, and federal health agencies to build a program framework that teaches CER principles to scientists pursuing advanced degrees. A panel of experts including policy makers and representatives from the Agency for Healthcare Research and Quality (AHRQ), Association of American Medical Colleges (AAMC), and American Association of Colleges of Pharmacy

(AACP), as well as academic and biopharmaceutical company representatives, is working to identify the program's critical components, including specific areas of study.

One of the panel's objectives is to develop an overview of the skills, knowledge, and abilities a CER specialist should possess. Once finalized, the findings and suggestions will be published and distributed to academic institutions to use as a template for building graduate programs on comparative effectiveness. The PhRMA Foundation will support scientists entering this promising new field with pre-doctoral fellowships at participating universities.

Another educational initiative that will take priority this year focuses on the principles of safe and effective prescribing. We will partner with professional scientific organizations including the American Society for Clinical Pharmacology and Therapeutics and AAMC to determine effective ways for promoting a core curriculum that prepares medical students to be knowledgeable, safe, and effective prescribers.

We are enthusiastic about these initiatives and confident that our efforts to promote and improve medical education will have an increasingly positive impact on the future of therapeutics. These initiatives are possible thanks to the PhRMA Foundation's member companies, who continue to support our strong core programs and help us maintain a reputation that is recognized and respected throughout the field of health care.

A handwritten signature in black ink, reading "John M. Leonard". The signature is fluid and cursive, with a long horizontal line extending to the right.

JOHN M. LEONARD, M.D.

MESSAGE *from the* PRESIDENT



Every year I am approached at the annual meetings of scientific organizations such as ASCPT, ASPET, and AAPS by association leaders who received a PhRMA Foundation award at the beginning of their careers. I am continually impressed at how grateful they remain after all these years, because our award was so timely and so instrumental in helping them get their start.

For these leaders of the medical community, a PhRMA Foundation grant or fellowship was the springboard for major national funding, and an early milestone in long, successful careers. They have since mentored students who themselves have won PhRMA Foundation awards. We have in many cases a second generation, and in some cases even a third.

Our programs have cultivated professors, assisted industry leaders, and filled pivotal roles at government agencies. The path to becoming a scientist may be circuitous, but those supported by the scientific community are part of a cooperative cycle that facilitates research and innovation, where the potential to impact the field of drug discovery is virtually limitless.

At the beginning of this cycle, and crucial to its continuation, is the availability of support—from educators, mentors, and organizations like the PhRMA Foundation, whose programs fund the research of young scientists. Eventually these scientists become facilitators of this extraordinary cycle of scientific

progress. Giving back to the scientific community is seen as an opportunity, not an obligation, as demonstrated by so many of our past award recipients, who continually offer their time, talents and efforts.

In the dynamic biopharmaceutical companies, our award recipients have become innovators and decision makers, leading the field of drug discovery and development. Two such recipients are Joan Heller Brown, Ph.D., and Brian B. Hoffman, M.D., the 2009 Award in Excellence recipients profiled on page 1. Even in newer disciplines like Health Outcomes and Informatics, our former fellows are the authoritative voices—the spokespeople for advancing new research and the experts who will educate and guide the next generation of scientists.

The strength and promotion of our core programs have made 2009 another successful year. We are proud of our impact on the scientific community and grateful to the biopharmaceutical companies who continue to support our organization. Your contributions make it possible to develop new initiatives for advancing the education and research that are paramount to the health and wellbeing of patients. Our accomplishments and our legacy are a testament to your continued generosity.

A handwritten signature in dark ink, appearing to read 'Del Persinger', with a stylized flourish at the end.

DEL PERSINGER

AWARDS *in* EXCELLENCE

THE ANNUAL PhRMA FOUNDATION AWARDS IN EXCELLENCE honor past awardees who have gone on to distinguish themselves through their scientific and/or academic achievements. At the outset of their careers, when they were deciding on their area of specialization, these scientists received PhRMA Foundation grants in a discipline important to the research-based Pharmaceutical industry. These awardees are dramatic proof that our foundation program fills a critical need in the career development of young researchers and makes a substantial difference in their ability to succeed.

The two awardees for 2009 exemplify the very best in their chosen fields of clinical pharmacology and pharmacology/toxicology. The PhRMA Foundation is proud of their achievements and is gratified to have been of assistance to them at the beginning of their outstanding careers. Their successes typify the outstanding achievements of all of our awardees and underscores the importance of continuing support to those who follow in their footsteps.

2009 Award in Excellence in Clinical Pharmacology

Brian B. Hoffman, M.D.
Professor of Medicine
Harvard Medical School

Dr. Hoffman was born in Canada, he received a BSc (Biophysics) and MD from McGill University. After residency in Medicine at Stanford University, he returned to McGill to train in Clinical Pharmacology, and was subsequently a research fellow in molecular pharmacology at Duke University. He was then on the faculty at Stanford University School of Medicine in Clinical Pharmacology for more than 20 years. He moved to Boston, becoming Chief of Medicine at the VA Boston Health Care System, a major teaching affiliate of Harvard Medical School and Boston University School of Medicine.

Brian Hoffman's research has focused primarily on signal transduction mechanisms of drugs that activate G protein coupled receptors. In addition, he has remained active in clinical research, initially with investigations of novel assessments of drug effects in humans and more recently in the development of decision support software to help primary care physicians implement national guidelines for the drug treatment of hypertension. He has published more than 180 original papers and many review articles in these areas. Numerous post-doctoral fellows from his laboratory have gone on to highly successful careers in clinical pharmacology around the world, in academia and in industry.

Dr. Hoffman is passionate about teaching clinical pharmacology. In Palo Alto, he established a hypertension clinic in order to teach medical students, residents and fellows about



At the 2009 Annual Meeting of The American Society for Clinical Pharmacology and Therapeutics (ASCPT) at The Gaylord National Resort, Del Persinger (right) of the PhRMA Foundation presented Brian B. Hoffman, M.D. (left) with the 2009 Award in Excellence in Clinical Pharmacology.

rational therapeutics. As an Attending Physician on Medicine wards, he emphasizes teaching of principles of pharmacology and clinical pharmacology at the bedside. He has taken on a leadership role at Harvard in the 4th year medical student Clinical Pharmacology course. He views contributing to textbooks of pharmacology and clinical pharmacology as an important extension of his teaching. He has edited textbooks of pharmacology and of clinical pharmacology. Moreover, he has been an author of important chapters in other major textbooks of pharmacology for many years.

Dr. Hoffman is the representative for VA Boston to the Center for Integration of Medicine & Innovative Technology.

This organization is a non-profit consortium of Boston teaching hospitals and Engineering schools that fosters interdisciplinary collaboration among experts in medicine, science and engineering, in concert with industry and government, to improve patient care. He has also been an active, valued consultant and scientific advisory board member in biotechnology where he has the capacity to provide broad perspective ranging from molecular pharmacology through to assessment of drug effects in patients.

Dr. Hoffman has been in numerous leadership roles throughout his career including hospital administration, education, and research. He received the Leon I. Goldberg Award from the American Society of Clinical Pharmacology and Therapeutics, an Established Investigator Award from

the American Heart Association, and the Kaiser Foundation Award for Outstanding and Innovative Contributions to Medical Education from Stanford. He has seen extensive service on journal editorial boards, NIH study sections, as well as in positions concerned with excellence in education, research and clinical care.

Dr. Hoffman is dedicated to his family. He greatly enjoys fly fishing and is currently writing a history of the importance of the discovery of adrenaline for the development of pharmacology in the 20th century.

Dr. Hoffman received a 1982 Faculty Award in Clinical Pharmacology from the PhRMA Foundation.

2009 Award in Excellence in Pharmacology/Toxicology

Joan Heller Brown, Ph.D.

Professor and Chair

Department of Pharmacology

University of California, San Diego (UCSD)

A Phi Beta Kappa graduate of Cornell University, where she earned her B.A. degree in neurobiology, Heller Brown received her Ph.D. in pharmacology at Albert Einstein College of Medicine. Her postdoctoral studies were completed at the University of Colorado. A member of the UCSD faculty since 1975, Heller Brown has served as chair of UCSD's Biomedical Sciences Graduate Program, and as a member of the Faculty Council, the Faculty of Basic Biomedical Sciences Council, and the dean's Space Advisory Committee. She has served as interim chair of the pharmacology department since November 2002.

She was the recipient of an Established Investigator Award from the American Heart Association (AHA) and has been appointed as Fellow of the AHA, as well as of the International Society for Heart Research. She has served on the Scientific Advisory Board for a number of biotechnology and pharmaceutical companies and on the editorial and

advisory boards of numerous journals including the Journal of Biological Chemistry, Cellular Signaling, Circulation Research, Molecular Interventions and Nature Reviews Drug Discovery. She is an active member of the American Society for Experimental Therapeutics and served as editor of their flagship journal, *Molecular Pharmacology*.

Dr. Joan Heller Brown was selected in 2005 following a national search to replace former chair Palmer Taylor, Ph.D., who was named founding dean of the new UCSD School of Pharmacy and Pharmaceutical Sciences in 2002.

Commenting on her appointment Edward W. Holmes, M.D., UCSD vice chancellor of health sciences and dean of the UCSD School of Medicine stated "A preeminent leader in American pharmacology, Dr. Heller Brown is an outstanding administrator, excellent teacher, and an innovative researcher. We are fortunate to have her leadership for our top-ranked pharmacology department."

Paul Insel, M.D., UCSD professor of pharmacology, noted that "Joan is first-rate in all that she undertakes. Her research, teaching, mentoring of students and post-doctoral fellows, editorial duties and service to both UCSD and the broader scientific community are consistently of very high caliber. Her contributions in research, in particular with respect to signal transduction mechanisms in the cardiovascular system, are



*Dr. Joan Heller Brown (left) received the 2009 Award in Excellence in Pharmacology/Toxicology at the 2009 Annual Meeting of The American Society for Pharmacology and Experimental Therapeutics (ASPET) meeting in New Orleans, Louisiana. Dr. Brown is pictured here with **Eileen Cannon** of the PhRMA Foundation.*

widely recognized. In addition, Joan's positive interactions with colleagues at UCSD and elsewhere add to her effectiveness and the high esteem in which she is regarded."

Dr. Heller Brown's research focuses on how neurotransmitters and other chemical mediators affect various signaling pathways, causing altered cell growth or survival. Her studies

examine various molecular messengers formed within cells that ultimately regulate cellular activity involved in cardiovascular diseases such as cardiac hypertrophy, hypertension and heart failure, and responses of the brain to disease and injury.

She has published more than 180 papers and reviews in top ranked journals and contributed chapters to the textbooks Basic Neurochemistry, Goodman and Gilman's Pharmacological Basis of Therapeutics and Braunwald's Molecular Basis of Cardiovascular Disease, a companion to Braunwald's Heart Disease.

The Department of Pharmacology, ranked first among the nation's academic pharmacology departments in research grant awards from the National Institutes of Health (NIH), became the first basic science department in the UCSD School of Medicine in 1987. Among the department's 27 full-time and 17 adjunct faculty are three Howard Hughes Medical Institute Investigators and seven members of the National Academy of Science.

The department's research directions include computational and molecular science, catalyzed by the department's close affiliation with the San Diego Supercomputer Center, and structure-based drug design and bioinformatics. Cross campus efforts in environmental health sciences and pharmacogenomics have been launched through major NIH funded project grants. Additional affiliations with adjunct faculty at the Salk Institute, the Scripps Research Institute, the Burnham Institute, and the appointment of adjunct faculty from the local biotechnology and pharmaceutical industry create a natural bond for cross fertilization and communication, bridging the department's basic science efforts, and the goal of improving efforts in drug discovery.

Dr. Heller Brown received a Faculty Development Award in Pharmacology/Toxicology from the PhRMA Foundation in 1979.

RARE DISEASE RESEARCH

what it takes to make a difference

The fight against rare disease is fraught with adversity. But in a discipline where hope and research go hand in hand, little can deter those devoted to this rewarding field. Nearly 30 million people in the U.S. have been diagnosed with a rare disease, many of which result in severe, chronic pain and disability. According to the Food and Drug Administration (FDA), more than 350 products have been approved for rare disorders since the Orphan Drug Act was initiated in 1983. This remarkable progress is due in part to organizations like the PhRMA Foundation. With the generous support of its member companies, the Foundation has advanced the education, training and research of scientists who are developing new treatments for rare diseases.

Improving patient care starts with research—every discovery in the lab is a potential breakthrough for those afflicted with rare and chronic illnesses. For 45 years, the PhRMA Foundation has facilitated programs to develop life-saving, cost-effective medicines. By studying the genetic components of rare diseases, the Foundation's award recipients have helped link specific genes to a number of rare illnesses. As a result, they are better able to predict the course of these diseases and identify more effective, personalized treatments.

THE RESEARCHERS

The quest to understand and cure a rare disease requires remarkable perseverance and deep dedication—it is a commitment to demanding and complex work that may ultimately benefit only a few. Known and unexpected challenges can hinder research, sometimes substantially enough to turn a career in a different direction.

Funding, clinical trial participation, public awareness and personnel present significant hardships for small research teams. Despite these difficulties, great advances are being made to improve rare disease research, and many scientists agree that no shortage of staff or financial support will deter that progress.

Ninety percent of more than 2,000 scientists supported by the PhRMA Foundation are active in research today, and over one-third of past award recipients have published a key concept regarding drug discovery. Many have dedicated their careers to improving the lives of patients with rare disorders. These researchers have been instrumental in the development of new treatments, and some are shifting their focus to eliminate rare diseases entirely.

Merit Cudkowicz, MD, MSc, is a Professor of Neurology at Harvard Medical School and Co-Director of the Neurology Clinical Trial Unit (NCTU) at Massachusetts General Hospital.



Merit Cudkowicz, MD, MSc

Few of the patients she connected with as a resident had viable therapeutic options. Following her interests, Dr. Cudkowicz began researching Amyotrophic lateral sclerosis (ALS) and Huntington's disease in pursuit of potential treatments. Through support from the PhRMA Foundation, she was able to initiate several studies that

eventually gained federal funding. In 1994, she co-founded NCTU to conduct clinical research on ALS, Huntington's disease and other neurodegenerative disorders.

Much has changed in the field of ALS research over the past 15 years. According to Dr. Cudkowicz, it's not unusual today to imagine more effective treatments or even a cure. "More people want to study ALS," she says, and notes the increased interest is a key to better understanding. "Even if a drug doesn't work, we have a network of people to see and share the study data."

Researchers are also more hopeful about preventative treatments. "With a disease like Huntington's, we will

determine who's carrying the gene to treat people that have no symptoms and possibly delay the disease," says Dr. Cudkowicz. "The goal is to eventually prevent it altogether."

The administrative process for securing funding can slow a study considerably, but Dr. Cudkowicz says it's not enough to stop a promising idea from moving forward. She envisions a bright future for ALS and Huntington's



Peter Saltonstall

patients. "All rare disease researchers have built knowledge about what works and what doesn't, and we'll start seeing more drugs that are really working. We'll have a lot of options for helping people."

Thinking about a rare disease in a broader context can give researchers insight into common illnesses as well.

"There have been some wonderful advances in knowledge through research on rare diseases in recent years," says **Peter Saltonstall**, President and CEO of the National Organization for Rare Disorders (NORD). NORD is an association of volunteers and patient groups that advocate for the rare disease community and promote research efforts.

In 2005, University of Pennsylvania researchers identified the gene associated with fibrodysplasia ossificans progressiva (FOP), a disabling disorder that causes soft tissue to transform permanently into bone. "The amazing thing," says Saltonstall, "is that there is nothing wrong with this 'bone.' It simply grows in the wrong places. Therefore, studying FOP could actually help us do a better job of fixing broken bones."

Although cystic fibrosis (CF) is classified as a rare disease, it is one of the most widespread genetic disorders in the U.S.,



Bruce Stanton, PhD

affecting some 30,000 people. Sixty years ago, children diagnosed with CF rarely survived to adolescence. Today, people are living with the disease well into adulthood. The Cystic Fibrosis Foundation (CFF) supports a development pipeline of more than 30 drugs, most of which are in clinical trial testing. Their support facilitated the development of

a Lung Biology Center at Dartmouth Medical School and funds the studies of researchers like **Bruce Stanton, PhD**, Professor of Physiology.

Dr. Stanton began researching CF in 1992. Having received a PhRMA Foundation award at a time when many investigators could not secure funding, he was able to build a lab and hire staff. He now directs a prominent group of researchers and clinicians seeking better therapies for CF.

Few obstacles have hindered the progress of Dr. Stanton's research and he credits CFF for paving the way. "CFF has played a unique role in supporting basic scientific research as well as funding clinical trials, partnerships between biotechs and the academic community. Relatively speaking, we are very fortunate."

Steven B. Mizel, PhD, and **Heidi Mansour, PhD**, are also CF researchers and former PhRMA Foundation award recipients. Dr. Mizel is a Professor in the Department of Microbiology and Immunology at Wake Forest University School of Medicine. His research team is searching for a CF vaccine. Dr. Mansour's lab focuses on CF in pediatric and young adult populations at the University of Kentucky College of Pharmacy. An Assistant Professor in the Department of Pharmaceutical Sciences, two of her studies were funded by the PhRMA Foundation. She also received Pharmaceuticals awards from the Foundation in 2000 and 2007.

William Atchison, PhD, is a Professor of Pharmacology and Toxicology at Michigan State University. Dr. Atchison has devoted 25 years to researching Lambert-Eaton Myasthenic



William Atchison, PhD

Syndrome (LEMS), a rare autoimmune disease characterized primarily by acute muscle weakness.

Dr. Atchison's lab has made remarkable progress as the first to show LEMS could disrupt calcium channels at the nerve ending. Though obtaining sufficient resources for future tests could prove difficult,

Dr. Atchison is optimistic that LEMS research will continue to evolve. "My hope is that as we learn more about the 'compensatory response,' this will permit newer molecular approaches to be considered as therapeutic."

ADVOCACY AND AWARENESS

Pursuing new partnerships with academic institutions and non-profit organizations, the PhRMA Foundation continues to foster research-and-development-based educational programs, propose new training grants and expand public awareness campaigns that advance PhRMA's Safe and Innovative Medicines Program.

The Foundation has expanded its presence among the academic and scientific communities, and with the support of past award recipients is better able to promote drug discovery and development throughout academia and industry.

"One of our continuing themes is that everyone deserves hope, and without research there is no hope for a better future for people with rare diseases," says Saltonstall. His organization sponsors Rare Disease Day, an annual event that spreads awareness about progressive, degenerative and life-threatening diseases. The forum connects patients and researchers, whose combined knowledge and experiences create a powerful tool for discovery. A patient's insight and family history are invaluable to scientists striving to uncover the individual patterns of a disease.

In 2009, NORD hosted the Partners in Progress Summit attended by more than 300 representatives of the regulatory, research and development and patient communities. "One interesting issue that emerged was something one speaker called the 'trailblazing factor,'" says Saltonstall. "Specifically, once a drug 'blazes the trail' by becoming approved for a certain disease, researchers seem more interested in developing other products for that condition. The result is that there are several rare diseases with more than one approved drug, while many have no treatment at all. One of our challenges at this time is to find ways to accelerate and de-risk the process of new drug development so that even more orphan drugs can be brought to market. As we see more companies becoming interested in rare diseases, we're looking for innovative ways to encourage and support the development of the new treatments that patients so desperately need."

Bringing new drugs to market is an expensive process, and developing treatments for rare diseases can be even more costly. "There are many other factors needed to move research forward," says Saltonstall, "including whether a disease has an active, effective patient organization that is able to facilitate clinical trials and possibly even help in the process of developing a natural history and/or patient registry to provide basic information."

Virginia Ladd, RT, is the Founder, President and Executive Director of the American Autoimmune Related Diseases Association (AARDA). When she was diagnosed with lupus, autoimmune diseases were largely unheard of, and there was little collaboration among health agencies to support research and awareness. Ladd's personal struggle and frustration with a dire lack of understanding about lupus inspired her work as a patient advocate. Now 20 years after she began crusading for lupus, autoimmunity is a common part of the medical community's vernacular, and patients are getting more of the attention they deserve.

Engaging researchers from varied disciplines to study autoimmune disorders allows AARDA to maximize a broad range of experience and skills for better understanding of disease pathology. The organization initiated a study of blood registry at the National Institutes of Health, which led to a link between autoimmune diseases and a common genetic background. "Before the studies that came out of this effort, people really didn't know that these diseases had genetic commonalities," says Ladd.

Biomarkers could also become a valuable tool for the prediction, diagnosis and treatment of disease. These indicators, found in blood, body fluids and tissues, can signal abnormalities and gauge the body's response to certain treatments. "We feel strongly that research will eventually focus on biomarkers," says Ladd. "Along with studies on the basic core of what's driving autoimmune diseases, this type of research is the wave of the future."

FUNDING OPPORTUNITIES



Timothy Coté, MD, MPH

How extensively rare disease research will progress over the coming years depends largely on funding. Proper education and training are crucial, but without sufficient financial support, research can be delayed or halted entirely, especially for studies of lesser known diseases. Medical schools and teaching hospitals often rely on external funding to support pharmaceutical research projects, without which the access to life-saving treatments would be extremely limited.

Adequate funding not only provides opportunities for young scientists to realize their potential in the field of drug discovery and development, it allows many to establish cutting-edge programs, achieve additional financial support and open new research centers. Field leaders who received an award from the PhRMA Foundation 30 and 40 years ago still recognize the Foundation for contributing to their success.

The Foundation provides more than 3 dozen awards in five disciplines in the form of starter grants, pre- and post-doctoral fellowships, faculty development awards and sabbatical fellowships. This support can alleviate the high

costs of training in areas such as informatics, health outcomes, pharmacology and pharmaceuticals, while helping scientists develop and hone essential skills.

“You can’t do it without funding,” says **Timothy Coté, MD, MPH**, Director of FDA’s Office of Orphan Products Development, “but it’s incredible how much progress can be made with even shoestring funding if you have an investigator with fire in his belly.”

Public awareness often leads to more funding opportunities and new avenues for diagnosis and treatment. The more widely recognized and understood a disease, the better chance it has to garner the attention of researchers and sponsors. By definition, a rare disease may affect only a small percentage of the population, but these individuals, along with their families, friends and neighbors, can have a profound impact. Lack of interest in a disease that affects a small number of people can make finding researchers and study participants for clinical trials extremely difficult.

“Rare diseases come with their own special trials,” says Dr. Coté. “When you have very few patients, it’s hard to get enough participants in your studies. And finding experts to do the research is hard.” Nonetheless, Dr. Coté believes rare disease research and the regulation of rare diseases will continue to expand and improve.

PATIENT PERSPECTIVE

In recent years, new medications have become accessible to patients with rare metabolic, autoimmune, neurodegenerative and muscle diseases, as well as some cancers. Still, for more than half of Americans suffering from a rare disease, no approved treatment exists. Because a disease is only considered rare if it affects fewer than 200,000 people, advocacy, research efforts and available treatments are often lacking.

Patrick Skeldon, who was diagnosed with ALS in 2004, now relies much on his wife Deb to communicate. The disease has affected his speech and he finds it difficult to type.

Home modifications have helped Patrick cope with daily life; the couple has installed a ramped entry, elevator and

roll-in shower. He uses an internal Baclofen pump to control spasms and a variety of medicines, including Rilutek® (Riluzole), the only FDA-approved treatment for ALS.

For more than four years, Patrick has been involved in a clinical study administering high doses of Pramipexole, a treatment for early-stage Parkinson’s disease, and believes the drug has slowed the progression of his illness. He says the discussion of treatment options with his physician is always open and feels the future for ALS patients will continually improve. “I have been fortunate to have the best available medical, logistical and support groups at my disposal,” says Patrick.

When **Jennifer Dills** was diagnosed with ALS only two years ago, she was not completely surprised. She had read

about the disease online after noticing a slight limp in her walk.

Jennifer's physician recommended a multi-tiered regimen: prescription medication, vitamins and physical therapy. Her doctor later provided treatment for emotional lability, which she says has significantly alleviated her symptoms. With the help of her medical team, Jennifer implemented home modifications and acquired exercise and adaptive equipment, including a power wheelchair. Other options have been suggested to further improve her quality of life.

In January 2009, Jennifer began a year-long, double-blind trial for Talampanel, a medication thought to delay muscle weakening and functional deterioration associated with ALS. Currently this medication has not been approved however

when tested in a small group, Talampanel showed a more positive trend in ALS functioning than placebo. She also participated in a quality-of-life survey at Johns Hopkins and has enrolled in a study on the relationship of ALS and frontotemporal dementia.

Jennifer is active in the ALS community and has attended meetings at a local chapter of the ALS Association. She has also joined an online support group and recently began blogging about life with ALS, which she says has become a great source of support.

"When so much is unknown about a disease, I feel a responsibility to contribute in some way," says Jennifer. "Even if the research won't help me personally, maybe it will help others with ALS in the future."

HOPE FOR TOMORROW

Great progress is being made as scientists continue to decipher disorders that have mystified researchers for centuries. Their findings have improved diagnosis and treatment for thousands of rare illnesses and will one day provide the cures.

The PhRMA Foundation is hopeful that funding the training and studies of innovative scientists will continue to advance the field of rare disease research and ultimately enhance patient care.

"We feel that the entire rare disease community is on the precipice of a whole new world, and we are looking forward to some exciting times ahead as we seek ways to identify promising new avenues of study," says Saltonstall.

Patients like Patrick Skeldon and Jennifer Dills are also confident about the future. "I believe that a breakthrough in this disease is coming soon," says Jennifer. "That hope, along with the support of my family and friends, keeps me going."



FELLOWSHIPS *and* GRANTS

INFORMATICS

Pre Doctoral Fellowship in Informatics

THE PhRMA FOUNDATION PRE DOCTORAL PROGRAMS aim at supporting promising students during their thesis research by providing assistance in the form of stipend and funds to cover costs incidental to the training. This 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.

The goal of this fellowship is to increase the number of well-trained investigators in pharmaceutical research that incorporates Informatics.

2009 Pre Doctoral Fellowships in Informatics

Eugene Bolotin

University of California Riverside

“Revealing Nuclear Receptor/DNA Interactions Through Protein Binding Microarray Technology”

Errors in regulation of gene expression have been linked to susceptibility to and progression of several diseases such as diabetes, cancer and hemophilia. These errors can be caused by mutations in the response elements (REs) in the promoters of crucial genes. Transcription factors (TFs) regulate gene expression by binding to their corresponding REs in promoter regions of genes. However, relatively little is known about the REs for most TFs. One exception is hepatocyte nuclear factor 4 alpha (HNF4 α), a member of the nuclear receptor superfamily of ligand dependent TFs. Many HNF4 α target genes have been identified, including those involved in glucose, lipid and xenobiotic and drug metabolism. Through them, HNF4 α has been directly linked to several human diseases including diabetes, hepatitis, hemophilia, atherosclerosis and cancer.

However, even for a well studied TF such as HNF4 α , the total number and relative binding affinities of its REs is not known. To address this, we have developed a high-throughput assay using a protein binding microarray (PBM) with which the HNF4 α DNA binding specificity for ~4000 unique DNA sequences can be visualized in a single experiment. This system will allow exploration of various factors that can play

a role in TF binding to specific REs such as: the isoform of the TF, competitions between TFs for a single RE, and the co-activator/TF interaction. This project proposes to further develop the PBM system to compare the DNA binding specificity of HNF4 α isoforms and related nuclear receptor superfamily members, as well as to investigate the effects of co-activator interactions on target gene specificity. Using the data obtained from the PBM the project will develop novel computational and statistical tools to analyze transcription regulation, with the ultimate goal of elucidating the causes of some of the misregulation events.

Daniel J. Mandell

University of California, San Francisco

“Computational Design of High-Affinity Protein Biosensors”



Daniel J. Mandell

Predictive methods for computational design of protein interactions have important applications in creating potent biotherapeutics and biosensors. Proteins are capable of forming interfaces with extremely high affinity and specificity. Despite some seminal success in designing proteins with predetermined conformations, the accurate modeling

of protein interfaces remains extremely challenging, particularly in regions lacking secondary structure. This project combines methods recently implemented for modeling regions of proteins lacking secondary structure with

established protein sequence design tools, yielding a novel protocol that “molds” tight and selective protein interfaces from existing lower-affinity complexes. The designed interfaces are intended to be sufficiently high in affinity and specificity to serve as protein biosensors for real-time in vivo monitoring of an important class of signaling proteins, the guanine nucleotide exchange factors (GEFs). These regulators of guanine triphosphatases (GTPases) play key roles in cancer tumorigenesis and metastasis, as well as growth defects. Spatiotemporal targeting of activated GEFs in normal and transformed cells by these biosensors will help characterize GEF participation in disease progression. More broadly, the methodology developed will advance the state of automated design of protein sequences to be used as high affinity biotherapeutics.

Christopher L. McClendon
University of California at San Francisco

“Computational Models for Allosteric Inhibition”

Drugs targeting a protein’s active site can have numerous side effects because they often target other similar proteins as well. Allosteric inhibitors are those that target alternative protein sites or stabilize nonfunctional protein shapes. As such, they are underexplored but promising avenues for drug discovery against difficult drug targets. Furthermore, allosteric inhibitors often cause fewer side effects because they are more selective for their targets than active-site inhibitors. For a site to be suitable for allosteric inhibitor design, it must be both (1) allosteric, causing shape or flexibility changes at other sites, and (2) druggable, having the right shape and hydrophobicity for drug-like small molecules. To identify potential allosteric sites on proteins, this scientist will use molecular dynamics simulations and information theory to quantify correlated motions that could couple the active sites to other, novel sites. Then, he will use virtual fragment screening to predict the druggability of allosteric sites, as it has been shown that a site’s “druggability” correlates with the number of small molecule fragments that bind to the site. The results from the virtual fragment screen will be used to identify purchasable compounds that might bind to the target of interest, which can be tested in the lab using surface plasmon resonance.

Robert Yang
Washington University in St. Louis School of Medicine

“Attacking EGFR Dimerization: Computer-Aided Discovery and Design of Novel Inhibitors”

Epidermal growth factor receptor (EGFR) is a membrane receptor tyrosine kinase that plays important roles in regulating cell fate through a complex signaling cascade. Not surprisingly, perturbation of these receptors leads to a variety of tumors in organs including breast, brain, lung, ovary, and prostate. In particular, misregulation of the receptors have been linked to 70–80% of metaplastic breast carcinomas, 40–80% of non-small cell lung cancers, and approximately 60% pancreatic cancers. Despite initial clinical success with existing drugs, challenges such as acquired resistance emphasize the need for developing novel therapeutics. Towards this goal, the project proposes to adopt approaches that contrast the traditional strategies of developing antibody- and tyrosine kinase-based inhibitors. More specifically, the project will employ a cost- and time-effective protocol that focuses on *in silico* predictions and the subsequent testing of the predictions using cell-based bioassays. Based on recently discovered structural and mechanistic insights of the EGFR, the proposal outlines the utilization of virtual high-throughput screening (vHTS) and computer-aided structure-based peptidomimetic design as two strategies for developing new classes of EGFR inhibitors. Significant progress has already been made in the development, validation and application of the vHTS protocol. Insights gained from the progress has led to an additional aim that focuses on improving the efficiency of the vHTS protocol by integrating distributed grid-computing resources in the form of idle CPUs. Currently, two lead inhibitors are being pursued and are expected to serve as proof-of-principal for a novel class of small-molecule EGFR inhibitors. Furthermore, the binding sites of these lead inhibitors also present great potentials for investigating the feasibility of designing peptidomimetics by computational modeling. Peptidomimetics are synthetic chemicals engineered to mimic the structural components of natural receptors that are necessary for activation. The strategy is to create resembling small molecules that competes for the recognition sites to prevent the binding of malignant protein counterparts. This project will lead to novel EGFR drugs that should offer clinical benefits either by themselves or in combination with existing cancer therapies. Furthermore, the computational protocols developed in the project are highly generalizable and will serve as useful prototypes available to the scientific community.

Research Starter Grant in Informatics

THIS PROGRAM SUPPORTS INDIVIDUALS beginning independent research careers in academia. Applicants must be appointed to an entry-level tenure-track or equivalent permanent position in a department or unit responsible for Informatics activities as part of its core mission.

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

2009 Research Starter Grants in Informatics

Kun Huang, Ph.D.
The Ohio State University

“Multi-Resolution Analysis and Visualization of ChIP-seq Data in Genome-Wide Study on the Roles of Estrogen Receptor in Breast Cancer”

Estrogen receptor (ER) plays a key role in the transcriptional regulation of breast cancer. Selective estrogen receptor modulators such as tamoxifen have been widely used in preventing and treating breast cancers. A whole genome characterization of the ER target genes using ChIP-seq technology will allow researchers to obtain deep insight into the role of ER in breast cancer. ChIP-seq is a new technology which combines massively parallel DNA sequencing with the chromatin immunoprecipitations (ChIP) technique. It allows researchers to directly study the binding sites for proteins such as ER over the entire genome. However, each ChIP-seq experiment usually generates millions or even tens of millions of short DNA sequence tags and the ChIP-seq data are complex and bewildering to the experimental biologist. This project will develop an informatics framework composed of data analysis, methods and visualization software tools for accelerating and interpreting the genomic analysis with applications in understanding the role of ER and the mechanism of tamoxifen resistance in breast cancer. The research will identify genes that are responsive to estrogen in regular breast cancer cells and tamoxifen resistant breast cancer cells respectively and compare the functions of these genes. Experimental validation will be carried out for selected genes of interest. The findings will help to identify new drug targets for breast cancer and develop potential new avenues for treatment.

John Karro, Ph.D.
Miami University

“Development of Novel Sphingosine Kinase Inhibitors as a Targeted Therapeutic in Estrogen Receptor Mediated Breast Cancer”

The genome of any higher-ordered organism is littered with *transposable elements (TEs)*—genomic segments that have managed to insert multiple copies of themselves across the genome as a whole. The identification of these elements is a vital step in understanding genomic structure: they cover more than 45% of the human genome, can be the source of certain genetic ailments, and act as a record of genomic development that helps us to better understand how the species has evolved at the molecular level. However, identification of these segments can be difficult: there is a considerable amount of data to process, and many TEs have undergone a significant number of mutations—hence making them difficult to recognize. Using a combination of several existing computational methods and our own innovations, we hope to be able to produce a software tool that will take a sequenced genome and quickly identify all members of a specified TE family (i.e. all TEs originating from one, probably unknown, source).

Andre Rodin, Ph.D.
University of Texas-Health Science Center at Houston

“Multivariate Analysis of Candidate Blood Pressure Response Genes in Hypertensives”

The primary goal of this project is to reverse-engineer the interplay of gene variation (in candidate genes influencing renal tubular sodium transport and involved in renin-angiotensin-aldosterone system) and other variables contributing to the interindividual differences in blood pressure (BP) response to a thiazide diuretic. “Pathway,” or



Andre Rodin, Ph.D.

“systems biology,” data analysis methods will be applied to the association study of BP response to a hydrochlorothiazide in 585 hypertensive individuals.

Previously, they have been genotyped for genetic variation in 16 candidate genes, and measured for a number of intermediate phenotypes and other variables.

A series of univariate analyses

have been carried out, and a small number of statistically significant predictors of blood pressure response (and certain other intermediate phenotypes of interest) have been identified. However, the scope of these analyses was very limited. A follow up with the multivariate analysis will be used in order to gain the systemic understanding of the dataset and the underlying biological pathways. The project will apply innovative multivariate analysis methods, predominantly Bayesian Network (BN) modeling and boosted classifiers/clusters, to the data. Such data mining methods have been very successful when applied to the similar datasets in other domains. This dataset will be used to confirm, in the context of genetic epidemiology, the practical utility of BN modeling with respect to sensitivity and robustness. Various technical aspects of BN reconstruction will be investigated, as they apply to the genetic data.

Anastasia Maria Zimmerman, Ph.D.
College of Charleston

“Computational Motif Scanning to Evaluate Germline Repositories for Immunoglobulin Diversity in Emerging Genome Sequences”

Generation of immunoglobulin (Ig) diversity is critical to health by providing a mechanism to elicit immunological responses against the myriad of pathogenic microorganisms that inhabit the world in which we live. The capacity to stimulate B cells that bear specificity to an antigen to differentiate into memory B cells is central to vaccine development. As secreted antibodies are the product of rearranged Ig gene segments, it is of value to gain a genomic understanding of the genetic loci that contribute to Ig diversity among vertebrates. We have developed a novel computational method to scan emerging genomes for Ig gene segments. This approach does not rely upon homology to known genes meaning highly divergent Ig may be found. The project will utilize this motif based scanning approach as a basis to find Ig in three genomes which are considerably diverged from traditionally studied human and mouse models. It is anticipated this work will provide a basis in which both synteny and novelty of Ig between disparate genomes can be explored. A comparative genomics approach also has the potential to reveal novel Ig isotypes which may ultimately prove useful in generating synthetic Ig with binding sites to targeted antigens.

Sabbatical Fellowship in Informatics

THIS PROGRAM PROVIDES STIPEND FUNDING of \$40,000 annually to enable faculty members at all levels with active research programs an opportunity to work at the same or other institutions for periods of six months to one year in order to learn new skills or develop new collaborations that will enhance their research and research training activities in informatics.

2009 Sabbatical Fellowship in Informatics

Michael Thomas, Ph.D.
Idaho State University

“Creating the FishMine database as a resource for enhancing ecotoxicogenomics research”

This project will result in the creation of computational resources for ecotoxicogenomics, the systemic study of



Michael Thomas, Ph.D.

genes, biochemical pathways and networks perturbed by the presence of environmental toxins. Chronic exposure of a model organism, fathead minnow (*Pimephales promelas*), will be examined to trace pharmaceuticals in streamwater. Developing resources for toxicogenomics research related to trace pharmaceuticals is timely

and relevant; recent PhRMA Foundation-funded studies have identified trace pharmaceutical ingredients in the environment. Pharmaceuticals administered to patients may not be completely metabolized; unmetabolized portions are generally excreted and find their way into wastewater treatment systems not designed to remove pharmaceutical residues. Low concentrations may pass through treatment plants and be discharged into the environment; these have been measured in wastewater, surface water (rivers and streams) and drinking water. Adverse effects on aquatic organisms have been observed for specific compounds such as synthetic hormones.

The proposed sabbatical research project will create FishMine, an integrated genome resource, to facilitate transformative ecotoxicogenomics research: supporting discovery by providing researchers with a fuller, systemic perspective integrating results of fathead gene expression experiments with other genomes, transcriptome and proteome data from multiple organisms. FishMine will be based on a new, highly integrative framework for model organism comparative databases, allowing researchers to place the results of their work

into the context of other research by the ecotoxicogenomics community. This will provide a more predictive research system for a fuller interpretation of experimental results from multiple experiments and a basis for selecting the next experiment. These resources will be used by the investigative team to examine the effects of chronic exposure to trace pharmaceuticals in aquatic ecosystems, focusing on neuro-genomic implications of these compounds.

Current toxicology studies using fathead involve the transcriptional response of the fish to environmental toxins, including methylmercury, a neurotoxin, estradiol, a sex hormone, and fadrozole, an aromatase inhibitor that has been introduced in Japan for the treatment of breast cancer. *P. promelas* is important as a biological model in aquatic toxicology because of its relative hardiness, large number of offspring, native distribution and complex reproductive behavior. EPA guidelines outline its use for evaluation of acute and chronic toxicity of environmental samples or chemical species in vertebrate animals and there is substantial research record regarding the toxicity of organic contaminants to *P. promelas*.

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.

2009 Pre Doctoral Fellowships in Health Outcomes

Deidre V. Washington
University of North Carolina at Chapel Hill

"The Effect of Patient's Race on Communication with Pediatric Asthma Patients"

Asthma is one of the most common chronic diseases affecting children in the U.S. The National Asthma Education and Prevention Program has provided guidelines to help health care providers with the diagnoses and treatment of persistent

childhood asthma. These guidelines emphasize the importance of effective communication between physicians, parents and patients during medical visits to help the patients achieve optimal asthma control. In particular, asthma symptom assessment, pulmonary function monitoring, and adherence to long-term control medications are among the topics that should be discussed thoroughly to ensure that the patient's asthma is being well-controlled. Unfortunately, in spite of widespread dissemination of these guidelines, asthma health outcomes in pediatric patients are generally less than optimal. Furthermore, children belonging to racial and ethnic minority groups continue to experience poorer health outcomes, such as increased hospitalizations

and emergency room visits, compared to white children. These disparities persist even when controlling for differences in disease prevalence. Differences in communication patterns between physicians, parents and patients may be contributing to these observed disparities. To explore this hypothesis, communication between physicians, parents, and children with asthma will be examined according to the patient's race. This proposed research, conducted across several pediatric offices in North Carolina, includes obtaining audiotapes of the encounter between the participants in the examination room, transcribing the audiotapes, and coding the transcripts to further examine communication concerning symptoms, pulmonary function monitoring, and medication adherence. The findings from this research will help to inform future interventions designed to improve communication and health outcomes for pediatric asthma patients, and especially for children who identify as racial and/or ethnic minorities.

Annesha White
University of Florida

“Comparing Medicare Part D and the FEHBP Prescription Drug Plans: Addressing the Anticipated Needs of Older Persons”

By the year 2030, the United States will be comprised of 71 million persons over the age of 65. Policymakers and health care professionals are interested in recommendations that address the need to control rising Medicare costs while maintaining beneficiary choice among plans. One suggestion is that Medicare be transformed into a program similar to the Federal Employees Health Benefits Program (FEHBP). The FEHBP has successfully held down costs while offering a wide range of benefits and types of plans. The proposed research will assess the prescription coverage provided by Medicare Part D plans as compared to FEHBP prescription drug plans. The analysis will focus on the consumer perspective by comparing differences in coverage and cost sharing between drug formularies. Many projections indicate that Medicare will not be able to deliver promised benefits to the next generation of retirees without making changes in the

program. To avoid extreme increases in payroll taxes and other revenues or major cutbacks in services we must explore ways to change the economics of the health care system to achieve better value for money. Findings will benefit policymakers, health care professionals and consumers by suggesting whether the FEHB program is a good model for Medicare reform of prescription drug coverage.

Tifini Preliou Williams, M.S.
Purdue University

“Effect of Body Image Satisfaction on Readiness to Change for Diet, Exercise, and Medication Adherence in Patients with Type 2 Diabetes”



Tifini Preliou Williams, M.S.

Satisfaction with body image, or the way that individuals picture their bodies in their minds, has been linked to psychological (depression and self-esteem), individual (weight loss attempts, race and size, and SES), and environmental (media images, social influence, opposite sex preferences) factors. Treatment options for type 2 diabetes

(medication therapy, diet and exercise) can cause a change in individual's physical appearance and consequently impact body image satisfaction. Therefore, body image satisfaction can affect readiness to adhere to such treatments. Using the Transtheoretical Model, the impact of body image satisfaction and readiness to adhere to diet, exercise and medication regimens will be assessed. No previous research has been conducted to examine the effect of body image on adherence using the Transtheoretical Model. Findings about the psychological, individual, and environmental factors associated with body image satisfaction level and its impact on readiness to change can provide important information for clinical practice. The findings also will aid the market segmenting and targeting of patients with type 2 diabetes.

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.

2009 Post Doctoral Fellowships in Health Outcomes

Jason T. Hurwitz, Ph.D.
University of Arizona

“Outcomes and Prevention of End Organ Damage Associated with Overdoses of Over-The-Counter Cough and Cold/Pain and Fever Medications”

Active agents in many over-the-counter (OTC) drugs used to treat cough and cold/pain and fever (CCPF) have been available for decades despite safety concerns. Multiple studies have established that OTC-CCPF overdoses are common, but the reasons for unintentional overdoses are not completely known. The U.S. Food and Drug Administration recognize these safety risks, and recently began reviewing policy concerning cough and cold medications indicated for children. Despite publicized concerns about the safety of OTC-CCPF, the outcomes of resulting policy or legislation are unclear. The proposed research comprises a two-part study to address these gaps in the current literature and to evaluate interventions concerning OTC-CCPF safety. The first study



Jason T. Hurwitz, Ph.D.

examines the number and nature of overdoses associated with OTC-CCPF products, and consequent outcomes (e.g., organ damage and impairment, treatment responses, economic costs, and populations most at risk). This first study will use hospital and emergency care data from a large national database. The second study

involves collecting new data to evaluate what consumers know about the risks of using OTC-CCPF products, appropriate dosing, and other OTC drugs containing active ingredients found in CCPF products. This second study will also evaluate various methods of helping consumers to better determine and measure appropriate doses (e.g., label changes, consumer awareness brochures). Better information on the occurrences of unintentional overdoses from OTC-CCPF agents will help in designing interventions that increase patient safety by preventing overdoses or providing appropriate care following an overdose.

Research Starter Grant in Health Outcomes

THE PURPOSE OF THE PhRMA FOUNDATION Research Starter Grant 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.

2009 Research Starter Grants in Health Outcomes

Eswar Krishnan, M.D., M.Phil.
Stanford University School of Medicine

“Frailty and Drug Toxicity”

Chronic diseases need long-term treatment with medications. While some patients seem to develop numerous adverse effects with such therapy, some others do not have any such problem. The PhRMA starter grant is being used to discover why this is so and what can be done to prevent adverse effects to medications overall. The hypothesis is that there is a measurable trait—frailty—that represents the sum total of patient related factors that is a major determinant of adverse effects from medications. In the settings of medical care, the term frailty denotes a state of reduced functional reserve in all the major organ systems. When exposed to disease or injury, these individuals have poor health outcomes such as disability and death. People in the opposite end of the spectrum, the robust ones, weather the effect of disease and injury and quickly reclaim the premorbid status. By the same logic, it is very likely that frail individuals are at greater risk of suffering adverse health outcomes when exposed to medications. This theory will be examined using glucocorticoid steroid treatments for rheumatoid arthritis as a model. We will use patient-reported health outcomes data from a longitudinal cohort study of 9,240 older individuals (age >65 years) with RA followed semi-annually for up to 20 years by validated health assessment questionnaires will be used. The PhRMA Starter grant will enable the project to develop a frailty index for patients with arthritis, and to study the relationship between this metric and treatment choices and health outcomes. This study will ultimately lead to a tool that will enable physicians to better assess the risk for long-term toxicity in individual patients.

Junling Wang, Ph.D.
University of Tennessee

“Disparity Implications of Utilization-Based Eligibility Criteria For Medication Therapy Management Services”



Junling Wang, Ph.D.

Since January 1, 2006, the U.S. Centers for Medicare and Medicaid Services (CMS) have required prescription drug plans to establish medication therapy management services (MTMS) for Medicare Part D beneficiaries meeting three criteria: having multiple chronic conditions, using multiple covered drugs, and/or being likely to incur over

\$4,000 (in 2006 dollars) in annual Part D drug costs. The first criterion is based on the need for health services, and the other two are based on drug utilization. Currently, health plans other than those for Medicare Part D have also implemented MTMS.

Racial and ethnic minorities may be less likely to qualify for MTMS than their majority counterparts according to CMS rules because they tend to use fewer drugs and incur lower drug costs. Thus, CMS may have institutionalized systems that inadvertently produce differential access to MTMS. This research project tests corollaries of the **organizing hypothesis** that the predominantly utilization-based CMS rules may lead to racial and ethnic disparities in eligibility fulfillment. The study sample is adults from an existing database, the Medical Expenditure Panel Survey (1996–2005), a federal survey nationally representative of non-institutionalized civilians in the United States. By retrospectively analyzing historical data, our study will provide early warning against the disparity implications of MTMS eligibility criteria.

PHARMACOLOGY/TOXICOLOGY

Pre Doctoral Fellowship in Pharmacology/Toxicology

THE GOAL OF THIS PROGRAM IS TO INCREASE the number of well-trained investigators in pharmaceutical 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 forty one fellowships have been awarded under this program since it began in 1978 including the seven fellows awarded in 2009.

2009 Pre Doctoral Fellowships in Pharmacology/Toxicology

Stacy E. Dixon

Indiana University School of Medicine

*“Elucidating the role of TgGCN5-B histone acetyltransferase in *Toxoplasma gondii*”*



Stacy E. Dixon

Toxoplasma gondii is an obligate intracellular parasite that can infect nucleated cells in virtually all vertebrates. It is estimated that 30–90% of humans are seropositive for *Toxoplasma*. Infection is usually considered benign in normal, healthy individuals, but can be life threatening in immunocompromised patients. Acute infection

(tachyzoites) is controlled by a healthy immune response, but the parasite differentiates into a cyst form (bradyzoite) leading to permanent infection. Acute parasite infection can re-emerge when the immune system is compromised by diseases such as AIDS. Current therapies are effective only against tachyzoites and are highly toxic to the patient, highlighting the urgent need for novel therapeutics. The project outlined in the proposal focuses on a group of molecules involved in the regulation of gene expression in *Toxoplasma* that could provide potential candidates for drug development. Changes in gene expression are essential to both pathogenesis and cyst formation of the parasites.

In particular, the proposed studies will focus on histone acetylation within *Toxoplasma*. Histone acetyltransferases (HATs) activate gene expression by chemically modifying histone proteins that are intimately associated with DNA. We are investigating the role of a GCN5-family histone acetyltransferase in *Toxoplasma* termed TgGCN5-B. This project proposes to evaluate the role this HAT plays in *Toxoplasma* physiology as well as examine the efficacy of this protein as a novel therapeutic target.

Austin Dulak

University of Pittsburgh

“Mechanistic Rationale for Combination Targeting of c-Met and EGFR in NSCLC”

Lung cancer has an alarming incidence of 78.5 cases per 100,000 people per year with an expected 215,020 new cases in 2008 and is the leading cause of cancer-related death in both men and women. There are two major classifications of lung carcinomas, small cell (SCLC) and non-small cell (NSCLC), which accounts for nearly 80% of cases. Despite the high prevalence of lung cancer, few effective therapeutic options exist. Surgical resection is available for early-stage disease and for advanced cases treatment options include radiation, targeted therapies, and other chemotherapy regimens. Much research has been dedicated to identifying target-specific agents or drugs that will block dysregulated “cellular machinery” specifically in cancer cells. There was much hope for one class of these agents, the Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib; unfortunately, clinical outcome did not match preclinical expectations. Now, efforts have turned

to identifying new targets as well as improving therapeutic efficacy by combining targeted therapies to prevent resistance and compensatory signaling. One target currently being explored by Dr. Jill Siegfried's laboratory is the Hepatocyte Growth Factor (HGF)/c-Met pathway. Similar to EGFR, c-Met is a receptor tyrosine kinase expressed on the cell surface of tumor cells and is directly activated by its ligand, HGF. HGF/c-Met dysregulated signaling has been implicated in many human cancers including NSCLC. Disruption of this pathway through HGF and c-Met-directed therapeutics has been shown to decrease tumorigenic potential. Based on these studies, there have been strong efforts to develop therapies to block this pathway in many human cancers. When stimulated by their respective ligands, EGFR and c-Met initiate similar programs in lung cancer cells to promote growth, motility, and angiogenesis. Initially, these pathways were believed to be autonomous from one another. However, recently, our laboratory observed that EGFR communicates with c-Met in absence of HGF, the c-Met ligand. The question arises as to whether EGFR is acting alone to promote lung cancer growth or whether it relies, in part, on cross-communication with c-Met to mediate some of its downstream effects. The work presented in this proposal will aim to first understand the mechanism or "how" EGFR activates c-Met and what intermediates are involved in this process. The second portion of this proposal will focus on preclinical mouse experimentation to determine whether combining c-Met with EGFR TKIs will provide enhanced inhibition of lung tumor growth in contrast to each individual therapy. By utilizing EGFR TKIs such as gefitinib to augment c-Met targeted therapies, one would be able to subvert all c-Met signaling either directly through c-Met by HGF and indirectly through cross-talk from EGFR in NSCLC. With the five-year average survival for lung cancer patients at only 15%, investigations such as these are highly critical in order to identify novel targets and drug combinations to battle this devastating disease.

Gregory C. Hadlock
University of Utah

"Functional Consequences and Underlying Mechanisms of Methamphetamine-Induced Dopamine Transporter Complex Formation"

Methamphetamine (METH) abuse is a serious public health concern with devastating physical and psychological consequences. Among other effects, METH greatly increases the



Gregory C. Hadlock

release of the neurotransmitter dopamine (DA), which contributes to its rewarding and addictive properties. DA is involved in diverse central nervous system functions such as movement, cognition, emotion, and motivated behaviors. After the release of DA by neurons, the DA signal is terminated by the reuptake of DA from the synapse

back into the neuron by the DA transporter (DAT). Consequently, the DAT is a key regulator of DA signaling within the brain. Even after periods of abstinence, some METH abusers have decreased levels of DA transporter (DAT) within the striatum. Although there are multiple contributing factors, the mechanisms underlying this persistent decrease in DAT levels have not been completely elucidated. In rats administered METH in a dosing paradigm designed to mimic "bingeing" by METH-abusers, DAT activity is rapidly decreased (within 1 h) and there are similar persistent decreases in DAT levels. It has recently been discovered that this binge paradigm also causes the formation of higher molecular weight DAT complexes concurrent with decreased DAT activity. Relatively little is known about these complexes. Thus, the goal of this project is to investigate the relationship between DAT complex formation and METH-toxicity by determining the composition of the DAT complexes, their localization within neurons, their effect on DAT function, and the mechanisms underlying their formation. Accomplishing these goals will provide insight into the mechanism of action of METH, its effects on the DAT, and the pathophysiology of disorders associated with aberrant DA disposition including Parkinson's disease, attention deficit hyperactivity disorder, and drug abuse.

Erin Harleton
Columbia University

"TASK-1 Inhibition in Inflammation and Arrhythmias"

Cardiac arrhythmias result in high levels of morbidity and mortality. Ventricular arrhythmias are the leading cause of sudden cardiac death. Atrial arrhythmias are the most common sustained cardiac arrhythmia and, while not immediately fatal, they can lead to serious complications such as stroke and pulmonary embolism. Inflammation has been linked to the development of some cardiac arrhythmias in animal models and in human patients. For example,



Erin Harleton

peri-operative atrial fibrillation (AF) occurs in up to 60% of patients undergoing cardio-thoracic surgery and is thought to occur in part as a response to the inflammation associated with the surgery. Similarly, ventricular arrhythmias often occur after blockage of blood flow to sections of the heart and can be exacerbated after removal

of the blockage allows reperfusion accompanied by an influx of white blood cells, including neutrophils. This research has focused on the role of the neutrophil-derived mediator of inflammation known as platelet-activating factor (PAF). It has shown that PAF causes functional changes in isolated heart cells that mimic the changes thought to occur in an intact heart during arrhythmia. PAF works by activating its cell surface receptor which initiates the activation of an intracellular kinase that targets and phosphorylates an ion channel, TASK-1, that specifically allows potassium to cross the cell membrane. These studies have shown that the phosphorylation of the channel results in loss of current flowing through it, and that this is associated with both canine peri-operative AF and chronic AF in humans. A series of experiments is proposed that will elucidate the link between TASK-1 phosphorylation and inhibition, inflammation, and the *initiation* of AF in our canine peri-operative AF model. This project will also determine the extent of inflammation and TASK-1 inhibition in various stages of human AF, in order to elucidate their role in the *maintenance and progression* of AF. It has also been demonstrated that compensation for this loss of TASK-1 current, by activating a similar background potassium channel TREK-1, reverses the arrhythmogenic effects of TASK-1 inhibition *in vitro*. Therefore, *in vivo* experiments investigating the antiarrhythmic and cardioprotective potential of TREK-1 activation in a rat ischemia-reperfusion model will also be performed.

Carrie House
The George Washington University

“Contribution of Voltage-gated Na⁺ Channels to the Metastatic Potential of Colon Cancer Cells”

Cancer remains a leading cause of death worldwide and colorectal cancers, in particular, account for about 20 percent

of all cancer deaths in the United States. Critical to improving survival and quality of life for patients suffering with this disease, is exploration into novel biomarkers and drug targets that will improve early detection and offer a more targeted approach to cancer therapy. Voltage-gated sodium channels (VGSCs), most abundant in excitable cells where they are responsible for the depolarization phase of the action potential, have recently been implicated in the progression of several human cancers, including breast, prostate, and lung. The current project has shown that these channels, specifically the SCN5A isoform, may also contribute to metastasis in colon cancer. The mechanism by which these



Carrie House

channels confer an oncogenic advantage is still unclear, however it is possible that increased Na⁺ influx into the cell can disrupt intracellular pH, Ca²⁺ concentration, as well as the expression and activation of downstream kinases responsible for oncogenesis. The project will assess the differences in Na⁺ channel expression and meta-

static potential of two colon carcinoma cell lines not previously shown to functionally express VGSCs, SW480 and SW620, which were obtained from the primary tumor and lymph node metastasis of the same patient, respectively. Using pharmacological manipulation as well as siRNA-mediated knockdown of the SCN5A transcript, this project will assess the effects of channel activity on Na⁺ current, invasive capacity, and activation of downstream signaling molecules. Furthermore, it will clarify whether increased expression of SCN5A is necessary for oncogenic potential and/or if mutations in key regions of the gene further contribute to this phenotype. Finally, the project studies will assess whether depolarization leads to activation of downstream oncogenic signaling molecules and enhanced metastatic potential. The proposed studies will further our understanding of alternative pathways of metastasis involving gene products, such as VGSCs, not previously considered to be involved in the cancer phenotype. With a fuller understanding of the specific VGSCs involved, whether they harbor mutations, and which subsequent pathways they activate, these studies will highlight novel drug targets for cancer therapy.

Marina Khrapunovich
Albert Einstein College of Medicine

***“Mechanisms of Microtubule Stabilization
by New Natural Products”***

The microtubule cytoskeleton has proven to be an effective target for cancer therapeutics. A number of drugs that interfere with microtubule dynamics are useful antitumor agents. One class of drugs, known as microtubule stabilizing agents (MSAs), binds to microtubule polymers and stabilizes them against depolymerization. The prototype of this group of drugs, Taxol, is an effective chemotherapeutic agent used extensively in the treatment of human breast, ovarian, and small cell lung carcinomas. Since the discovery of its microtubule-stabilizing effects, many investigations have been done with Taxol to elucidate its mechanism of action.

Although electron crystallography and photoaffinity labeling determined that the binding site for Taxol is in a hydrophobic pocket in β -tubulin, little was known about the effects of this drug on the conformation of the entire microtubule. A recent study from our laboratory utilizing hydrogen/deuterium exchange (HDX) in concert with various mass spectral (MS) techniques has provided new information on the structure of the microtubule upon Taxol binding. The goal is to apply this powerful technique with new natural products, MSAs other than Taxol, to define the conformational changes occurring in tubulin upon their interaction with microtubules and to determine their possible binding sites. One such drug, discodermolide, has previously been shown to bind to β -tubulin at a site close to but distinct from the Taxol binding site. Thus far, project results confirm this overlapping binding site. Furthermore, while the conformational effects of the two drugs are very similar in β -tubulin, discodermolide imparts additional stability to the microtubule by stabilizing inter- and intra-dimer interactions via the β -tubulin subunit. Lateral inter-protofilament interactions are also enhanced by discodermolide via stabilization of the H3 helix in β -tubulin. Molecular modeling and docking experiments based on the obtained HDX data will provide further details on the precise binding site of discodermolide and on its conformational effects on microtubules. Additionally, analysis of HDX data obtained with four other MSAs, epothilone B, ixabepilone, laulimalide, and peloruside A, will not only provide structural information specific to the effects of each drug, but will also allow development of a HDX signature that can be used to select for effective chemotherapeutic agents, which may help to reduce the need for lengthy and expensive testing *in vivo*.

Michael A. Valentino
Thomas Jefferson University

***“The Novel Role of Guanylyl Cyclase C Signaling
in Appetite Suppression and Body Weight Regulation”***



Michael A. Valentino

We live amidst a global obesity pandemic with far-reaching health and economic consequences, underscored by the absence of FDA-approved therapies that produce safe, durable weight loss. Guanylyl cyclase C (GCC), an intestine-specific transmembrane receptor, is one of a family of homologous signaling proteins synthesizing cyclic GMP as their proximal effector. GCC is the receptor for the endogenous paracrine hormones guanylin and uroguanylin which regulate epithelial cell dynamics contributing to the spatiotemporal organization of the crypt-villus axis. Unexpectedly, GCC has emerged as an important intermediary in signaling programs controlling appetite and body weight. C57/Bl6 mice in which GCC signaling was eliminated exhibited excess body weight, which was amplified by a high-fat/high-calorie diet. This excess body weight was associated with adipocyte hypertrophy, an increase in subcutaneous and visceral adipose mass, and several obesity-related co-morbidities including cardiac hypertrophy, hepatic steatosis, hyperinsulinemia, and glucose intolerance. Interestingly, elimination of GCC signaling produced obesity in the absence of differences in intestinal lipid absorption efficiency, activity levels and caloric expenditure/basal metabolic rate. However, GCC-deficient mice were hyperphagic when fed standard, high-fat, or high-carbohydrate chow. Further, the excess weight gain in GCC-deficient mice was eliminated by restricting daily food intake to levels consumed by wild-type mice. Moreover, the hyperphagia in GCC-deficient mice was exacerbated by fasting, suggesting a defect in mechanisms contributing to the gut-neural axis which regulates hunger. Beyond nutrient digestion and absorption, the intestine plays an important role in energy homeostasis by regulating appetite circuits within the hypothalamus, mediated by enteroendocrine cells which secrete anorexigenic hormones following food intake and luminal nutrient stimulation. In that context, acute nutrient-stimulated satiety responses, mediated by enteroendocrine cell hormone secretion, were absent in GCC-deficient

mice. This defect in pathways regulating food intake was associated with a ~50% reduction in the enteroendocrine satiety hormones cholecystokinin (CCK) and glucagon-like peptide (GLP-1) in the jejunum and ileum, respectively. Importantly, this defect in enteroendocrine cell function was rescued by oral replacement of the downstream effector of GCC, cGMP, which returned expression of those hormones to normal levels in GCC-deficient mice. These observations

demonstrate a previously unrecognized role for GCC signaling in regulating appetite and body weight by modulating the function of enteroendocrine cells. This highlights a novel therapeutic paradigm in which oral hormone supplementation with GCC ligands could enhance enteroendocrine hormone levels and amplify nutrient satiety responses, thereby restricting appetite and defending against obesity.

Post Doctoral Fellowship in Pharmacology/Toxicology

THE PhRMA FOUNDATION POST DOCTORAL PROGRAM in Pharmacology/Toxicology provides 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 the effect of an agent in the intact organism. Recent graduates from pharmacology Ph.D. programs interested in post-doctoral experience that integrates pharmacology with a morphologic 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 in which 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.

2009 Post Doctoral Fellowships in Pharmacology/Toxicology

Crissy Dudgeon, Ph.D.
University of Pittsburgh School of Medicine

“p53-independent PUMA induction in anti-cancer therapies”

Colon cancer is the second leading cause of cancer-related death in the United States. Chemotherapy treatment of colorectal cancer is often ineffective because colon cancer cells can escape the suicidal or programmed cell death mechanism that is activated by chemotherapeutic drugs. One of the most important proteins that mediates this mechanism is p53, a tumor suppressor protein. p53 activates a number of other proteins to induce cancer cell death after chemotherapy treatment, such as the BH3-only protein PUMA. Unfortunately, p53 is not functional in over fifty percent of colon cancers, making cancer cells unable to activate PUMA and therefore insensitive to chemotherapy



Crissy Dudgeon, Ph.D.

treatment. The goal of this proposal is to find new alternative ways of inducing PUMA to reactivate cell death in colon cancer regardless of whether p53 is present or not. Recent studies from our laboratory have suggested that non-genotoxic agents, such as the kinase inhibitors staurosporine and UCN-01, induce PUMA through

the transcription factor FoxO3a. This study will test the hypothesis that FoxO3a-mediated PUMA induction can be used to restore apoptosis regulation in p53-deficient human cancer cells. The role of FoxO3a and the PI3K/Akt pathway in PUMA induction and apoptosis following kinase inhibitor treatment will first be investigated. Next, the dependency of PUMA will be analyzed for the chemosensitization effect of UCN-01, and to determine if PUMA mediates the anti-tumor effect of UCN-01 *in vivo* by promoting apoptosis. Lastly, a

high-throughput screening assay will be developed for identifying novel agents that activate PUMA in p53-deficient human cancer cells. The proposed studies will provide new insights into the mechanisms underlying chemotherapy treatment. These results may provide a rational basis for using combinations of anti-cancer agents that are dependent on PUMA to induce cell death. Furthermore, the results of these studies will be essential for developing PUMA-based anti-cancer therapies, for using PUMA as a biomarker for predicting therapeutic response, and for tailoring therapeutic regimen based on genetic profiles. In conclusion, restoring apoptosis in human cancer cells by activating PUMA may result in improved therapeutic strategies and agents.

Emily Oestreich, Ph.D.

University of North Carolina at Chapel Hill

“Cell-and chemical-biology investigations of RGS12 as a MAPK scaffold in muscle development and disease”



Emily Oestreich, Ph.D.

The growth of skeletal muscle is an intricate process requiring myoblast proliferation, differentiation, and cell-to-cell fusion to form myofibers, the basic contractile unit of a mature skeletal muscle. Following development, adult skeletal muscle has a remarkable regenerative capacity, both for general maintenance of contractile function and for repair following injury, given its retention of a specialized population of myoblasts called satellite cells.

The growth of skeletal muscle is an intricate process requiring myoblast proliferation, differentiation, and cell-to-cell fusion to form myofibers, the basic contractile unit of a mature skeletal muscle. Following development, adult skeletal muscle has a remarkable regenerative capacity, both for general maintenance of contractile

Skeletal muscle development and repair require a complex array of cell signals and transcriptional events, some of which are relayed by the sequential activation of mitogen-activated protein kinases (MAPKs). Multiple extracellular signals are capable of triggering MAPK activation. Therefore, mechanisms must be in place to ensure specific cellular actions. Scaffold proteins can fulfill this role by spatially and temporally organizing individual components of MAPK cascades into cell-signaling complexes. RGS12, a member of the “regulator of G-protein signaling” (RGS) protein family is one such scaffolding protein. RGS12 has a multi-domain architecture that is known to assemble a complete MAPK cascade in PC12 cells, a neuron-like cell model that culminates in extracellular-signal regulated kinase (ERK) activation and stimulation of neuronal differentiation. Because RGS12 is also expressed in skeletal muscle during mouse development, this protein may play a similar scaffolding role in developing and damaged skeletal muscle where ERK/MAPK signaling promotes myoblast and satellite cell proliferation and inhibits early stages of differentiation. The current project’s efforts in identifying proteins that control the proliferation of satellite cells, as may be the case for RGS12, should reveal novel therapeutic strategies for muscle trauma and sarcopenia, the degenerative loss of skeletal muscle mass that occurs with aging. Additionally, aberrant proliferation of satellite cell populations leads to rhabdomyosarcoma, the most common soft-tissue sarcoma in children. This disease has been causally linked to increased ERK/MAPK activity. Therefore, the pursuit of small molecules that interfere with the ERK/MAPK scaffolding function of RGS12 or otherwise disrupt its subcellular localization may prove beneficial in the treatment of this deadly childhood cancer.



Del Persinger, President and Chief Executive Officer, presented the 2009 Awards in Clinical Pharmacology at the ASCPT Annual Meeting in National Harbor, Maryland. The PhRMA Foundation is appreciative of this opportunity to highlight our new award recipients.

Research Starter Grant 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 sixteen have been awarded, including the grants beginning on January 1, 2009.

2009 Research Starter Grants in Pharmacology/Toxicology

Julie A. Gosse, Ph.D.
University of Maine

“Arsenic Perturbation of Allergy/Asthma Signal Transduction”



Julie A. Gosse, Ph.D.

Millions of people worldwide are drinking water containing high levels of arsenic, including millions of United States citizens who obtain their water from unregulated, contaminated, private wells. Additionally, high levels of arsenic contaminate many foods as well as industrial and mining waste sites. Recent epidemiological studies suggest

that arsenic exposure elevates asthma incidence, but the underlying molecular and cellular mechanism(s) of action are unknown. The most common form of asthma is allergic asthma, and mast cells are major effector cells in allergy and asthma. Additionally, mast cells are important immune defense cells in the body, charged with fighting parasitic infections. Arsenic is a known endocrine disruptor, and it was recently shown that endocrine disruptors can exacerbate mast cell degranulation (histamine and other-mediator release), thereby potentiating the allergic and asthmatic response. Also, arsenic can affect phosphorylation cascades and other components of signaling pathways similar to those comprising the pathway leading to mast cell degranulation. If arsenic potentiates the allergic and asthmatic response in mast cells, this effect may be a mechanism by which arsenic elevates asthma incidence. If arsenic inhibits mast cell signaling processes, this effect may reflect a type of immune suppression caused by arsenic exposure. These

studies will determine whether arsenic affects the function of mast cells, using a variety of biochemical, molecular, and cellular techniques. Also, this project will seek to determine the underlying molecular mechanisms of these effects.

David W. Koh, Ph.D.
Washington State University

“Targeting Poly(ADP-ribose) for Improved Cancer Therapy”



David W. Koh, Ph.D.

Cancer is the second most common cause of death in the United States. Problems associated with cancer treatment are the escaping cancer cells or the devastating side effects. Poly(ADP-ribose) (PAR), an essential polymer synthesized in the cell in response to DNA damage, has been identified as a target in chemotherapy.

Prolonging its existence by restraining the actions of PAR glycohydrolase (PARG) leads to massive cell death in response to low doses of DNA-damaging agents. Thus, combination drug therapy of a PARG inhibitor and a DNA-damaging anti-cancer agent is expected to lead to improved cancer cell death. Alternatively, this combination therapy is expected to lead to lower effective doses of anti-cancer agents, which will lead to a decrease in the fatal side effects associated with these agents. Therefore, it is proposed here to further investigate the mechanism of cell death resulting from this combination therapy. More specifically, the effect of restraining PARG action on DNA will be investigated. Further, a new method of restraining PARG function will be investigated to assist in discovering new drugs to target PARG for cancer treatment. When completed, this proposal will provide insight into the cancer therapeutic value of targeting PARG to improve the chemotherapeutic treatment of cancer.

Shasta L. Sabo, Ph.D.

Case Western Reserve University

“Fundamental Mechanisms of Synapse and Circuit Formation and Regulation by Serotonin and SSRIs”

The neural circuits that govern perception and behavior are composed of networks of neurons that communicate with one another via synapses. Abnormal cortical synaptic connectivity has been linked to diseases as diverse as autism, mental retardation, amblyopia, epilepsy, anxiety, depression and schizophrenia. The overall goal of this research is to understand how cerebral cortical neurons form synapses with one another and how perturbations in synapse formation, especially those related to developmental and psychiatric disorders, affect the composition and function of cortical circuits. For the proposed study, toward that goal, three hypotheses will be tested. For the first part of the proposed research, the fundamental mechanisms of synapse assembly will be studied by exploring whether axons of presynaptic partners release secreted cues that specifically attract dendritic filopodia of postsynaptic partners to sites of synapse formation. In the second part of the study, it is hypothesized that serotonergic signaling links synapse development to disorders such as autism, anxiety and depression. To begin to test this, whether and how serotonergic signaling alters synapse formation between cortical neurons

will be examined. Finally, it is not known how impaired or enhanced synapse formation affects a neuron's role within a cortical microcircuit. Altered synapse formation could impact circuit development by altering either (i) the strength and/or reliability of connectivity between neurons that would normally be part of a microcircuit without changing circuit size or (ii) synaptic specificity, recruiting new neurons into a circuit or reducing the number or types of neurons that comprise a circuit. In the third part of this proposal, the study proposes to determine how development of synaptic connectivity within cortical microcircuits is affected by perturbations in neuronal communication and exposure to altered serotonin signaling and antidepressant/anxiolytic drugs. To test these hypotheses, live, time-lapse fluorescence confocal imaging of postnatal rodent cortical neurons complemented with molecular genetic, pharmacological and electrophysiological manipulations will be used. It is expected that results of the proposed research will have an important positive impact because they are expected to provide new targets for therapeutic intervention in developmental neurologic and psychiatric diseases. In addition, the results of this study are likely to fundamentally advance the understanding of synaptic mechanisms that give rise to neocortical circuit structure and function.



On November 9, 2009 at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting in Los Angeles, California, the PhRMA Foundation Pharmaceuticals Awards were presented. Pictured from left are **Matthew Palombo**, Rutgers University; **Elizabeth Vasievich**, University of North Carolina at Chapel Hill; **Eileen Cannon**; **Kaitlin Lemke, Ph.D.**, University of Iowa, and **Krista Shipley, Ph.D.**, University of Kansas.

CLINICAL PHARMACOLOGY

Paul Calabresi Medical Student Fellowship

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 fellowships is six months and the maximum is two years, with a maximum stipend of \$18,000. One hundred and seventy 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.

2009 Paul Calabresi Medical Student Fellowships

Jennifer Dwyer

University of California, Irvine

“Mechanisms Underlying Age Differences in Dopaminergic Drug Sensitivity”



Jennifer Dwyer

Neuropsychiatric disorders are developmental in nature, with adolescence being a period of unique vulnerability for the emergence or change in symptomatology of psychiatric symptoms. The brain continues to develop during adolescence, with particularly striking maturation in neural circuits that are modulated by dopamine (DA),

which are also thought to be dysfunctional in a multitude of mental disorders. As a result of this maturation, adolescents respond uniquely to the therapeutic drugs that target these systems, with human and rodent adolescents showing a blunted behavioral response to indirect dopaminergic stimulation (e.g. amphetamines) and an exaggerated response to dopaminergic antagonism (e.g. antipsychotics). Recent work using rodent models suggests that the behavioral sensitivity of individual D1- and D2-like DA receptors changes with age, with D2-like receptors playing an augmented role in adolescent hyperlocomotion and repetitive behaviors. The current project will use specific

antagonists to determine which member of the D2-like family mediates the enhanced behavioral efficacy of D2-like agonists in adolescence. This project will also assess the neural circuitry underlying the behavioral effects of D1- and D2-like stimulation, both alone and in combination. The behavioral interactions of D1 and D2 receptors will be compared using direct agonists coupled to specific second messenger cascades in adolescent and adult animals. The behavioral data resulting from these experiments will be correlated with patterns of neuronal activation as determined by in situ hybridization for the immediate early genes c-fos and arc. Together these studies will improve our basic understanding of the functional development of DA systems during adolescence and how these changes relate to behaviors observed in neuropsychiatric disorders. Furthermore, they will provide a more complete understanding of how dopaminergic therapeutics activate the adolescent brain, promoting the successful application of current pharmacotherapies, as well as a framework for the development of novel therapies that are safe and effective in this unique clinical population.

James Antoon

Tulane University

“Effect of Novel Sphingosine Kinase Inhibitors on Estrogen Receptor Medicated Breast Cancer Proliferation”

Breast cancer is the most commonly diagnosed cancer in women, with almost 1 in 8 women diagnosed within her lifetime. It is also the second leading cause of cancer deaths in women, with a mortality rate of approximately 15% and 184,450 new cases in 2008. With resistance to first line



James Antoon

ceramide-S1P pathway plays a significant role in cellular regulation of apoptosis and proliferation. The concept of the ceramide-S1P rheostat states that the relative amount of ceramide compared to its metabolite, S1P, is critical in maintaining proper cell function. The enzyme sphingosine kinase regulates the conversion of ceramide (proapoptotic) into S1P

treatments targeting the estrogen receptor on the rise, the development of novel therapeutics targeting the estrogen signaling pathway are of growing importance. Recent research has shown aberrant sphingolipid signaling to be an important mechanism of breast cancer tumorigenesis and progression to endocrine resistance. The

(proliferative, prosurvival). Therefore, sphingosine kinase is viewed as a potential “switch” for cells in an anti-proliferative state to transition to cells in a pro-survival and proliferative on. An imbalance in the ceramide-S1P rheostat has been demonstrated in various cancers, including a two fold increase in sphingosine kinase in human breast cancer. As a result, efforts to target the conversion of ceramide to S1P as a potential therapeutic have intensified over the past several years. This research project supported by the PhRMA Foundation proposes that the novel sphingosine kinase inhibitors, SKI-II and ABC294640, block estrogen receptor activation in order to exert their effect on breast cancer. The long-term objective of this research is to elucidate the role of sphingosine kinase in estrogen-receptor mediated proliferation and determine the potential of the SKI-II and ABC294640 as a treatment for breast cancer.



The 2009 PhRMA Foundation Health Outcomes award recipients were recognized at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting in Orlando, Florida. Pictured from left to right are: Chris L. Pashos, Ph.D., 2008 ISPOR President; Jean Paul Gagnon, Ph.D., PhRMA Foundation Health Outcomes Advisory Committee Chairman; Eileen Cannon, Executive Director, PhRMA Foundation; Eswar Krishnan, M.D., M. Phil., Stanford University School of Medicine; Junling Wang, Ph.D., University of Tennessee; Jason Hurwitz, Ph.D., University of Arizona; Annesha White, University of Florida; Tifini Preliou Williams, Purdue University, and Michael Barry, M.D., Ph.D., FRCPI, 2009 ISPOR President.

Faculty Development Award in Clinical Pharmacology

THROUGH THIS PROGRAM, ANNUAL AWARDS are made to medical schools for support for full-time junior faculty members in the field of human clinical pharmacology. The level of support is variable, and is aimed at keeping within the existing salary and fringe benefit structure of the applicant university. The award is for two years. Individuals at the associate professor or professor level should not apply for this award.

This program was established by the PhRMA Foundation in 1966 in recognition of the many problems involved in evaluating therapeutic agents. Drug investigation is a demanding task. As in nearly every aspect of the health field, manpower needs are acute. This program is intended to meet some of these workforce needs in the field of clinical pharmacology. The ultimate aim of the awards program is to stimulate teaching, training, and research in clinical pharmacology. It is aimed at providing an opportunity for the development of the research potential of clinical pharmacologists during the years immediately following their formal training programs.

2009 Faculty Development Awards in Clinical Pharmacology

Mara Becker, M.D.M.S.C.E.
Children's Mercy Hospital

"Sources of Variability in Methotrexate Polyglutamation in Children with Juvenile Idiopathic Arthritis"

Methotrexate (MTX) is the most common second-line therapeutic agent used to treat Juvenile Idiopathic Arthritis (JIA) worldwide; however, there is significant variability in response and toxicity to this medication in both adults and children. MTX is known to inhibit several enzymes within the folate pathway ultimately affecting purine and pyrimidine synthesis and leading to the accumulation of the anti-inflammatory agent adenosine. Preliminary adult data suggest that MTX polyglutamation and folate gene polymorphisms may be useful for guiding therapy. There is currently no published data on intracellular MTX polyglutamate concentrations in children. Our aims in this project are to characterize the population variability in total intracellular MTX (MTXglutot) concentrations and patterns of intracellular MTX polyglutamate subtypes (MTXglu 1-7) in JIA patients receiving a stable dose of MTX. Once characterized, the project will identify clinical and genetic contributors to this observed variability, and further associations with outcomes, such as clinical response and gastrointestinal side effects. The ultimate goal of this research project will be to dose the appropriate JIA patients with the appropriate dose of MTX while limiting toxicity and enhancing clinical effectiveness.

Myaing N. Nyunt, M.D., Ph.D.
Johns Hopkins University

"Clinical pharmacokinetics, safety and efficacy of antimalarial drugs in pregnant women living with HIV"

The primary goal of my academic research career is to optimize antimalarial drug treatment in pregnant women. The proposed research plan consists of two components: 1) to access antimalarial and antiretroviral drug interaction in healthy volunteers, and 2) to evaluate the relative contribution of pregnancy, HIV and drug interaction on antimalarial treatment response in HIV-infected pregnant women living in malaria-endemic Mali, West Africa. A clinical study of healthy volunteers to assess the impact of chronic administration of HIV drugs (lopinavir-ritonavir) on the disposition of quinine, an antimalarial drug commonly used in pregnant women, and related toxicity has been completed. Data analysis is currently ongoing. The study results are expected to provide the quality and quantity of interaction between the two study drugs and to serve as preliminary data for the second component of my proposed plan for which a NIH clinical trial planning grant (R34) has been recently submitted. In this study, the efficacy and safety of artemether-lumefantrine, a fixed-dose combination of antimalarial drugs which is increasingly used in pregnant women, will be evaluated in three study cohorts: HIV-infected pregnant, HIV-negative pregnant, and HIV-infected non-pregnant. Treatment outcomes in the three cohorts will be compared and contrasted to distinguish the contribution of pregnancy- and HIV-related immune suppression, pregnancy-related changes in drug disposition, and drug interaction with HIV therapy in the success and failure of treatment response.

PHARMACEUTICS

Pre Doctoral Fellowship in Pharmaceutics

This program has been in effect for 19 years. It assists awardees who have one or two years remaining in the pharmaceuticals pre doctoral training—the time during which they are engaged in dissertation research. We provide the funding during the doctoral program after course work has been completed and the remaining training activity is a student's research project.

The fellowship program provides a stipend and funds to cover costs incidental to the training for up to two years. The level of support is \$20,000 per year and up to \$500 a year may be used for incidentals directly associated with the preparation of the dissertation. Two fellowships were granted in 2009.

2009 Pre Doctoral Fellowships in Pharmaceutics

Matthew Palombo

Rutgers, The State University of New Jersey

“CXCR4-targeting nanocarriers for treating HIV and cancer”

The chemokine receptor CXCR4 is a significant molecular target for both cancer, where it is overexpressed in over 23 types, and HIV where it acts as a coreceptor for viral entry into susceptible cells. This project will propose the development of flexible targeted anticancer or anti-HIV drug delivery nanocarrier system that will increase specificity for cells expressing CXCR4. The nanocarrier is particularly useful for drugs with poor water solubility. Preliminary results suggest that it is possible to synthesize a high drug load nanocarrier that is able to impart superior water solubility characteristics over neat drug. The nanocarrier design incorporates: a targeting element, an endosomal escaping agent, a novel polymeric scaffold, and the ability to attach a high level of drug cargo. The targeting element consists of a peptide that effectively binds to the CXCR4 receptor, thereby increasing the specificity for CXCR4+ cells especially CD4+ T-cells in HIV and multiple types of cancer. By including multiple copies of targeting peptide to the scaffold our lab has developed, multivalent nanocarriers can be created with enhanced uptake. The use of R.I. TATg facilitates the endosomal escape of the proapoptotic peptide BH3 or doxorubicin in the cancer application and ritonavir for the HIV application. A protease resistant peptide-based PEG polymer provides the scaffold to which the other elements are conjugated.

This system will be tested in vitro for anti-HIV properties as well as for apoptosis promotion in cancer cells in vitro as well as in a rodent breast cancer model.

Elizabeth A. Vasievich

University of North Carolina at Chapel Hill

“Elucidation of immunostimulatory properties of a simple vaccine for cervical cancer, combination of the vaccine with gene therapy and application of the adjuvant in the development of a vaccine for melanoma”

A simple vaccine consisting of a liposome and peptide has been developed in our group to treat a murine cervical cancer model. Not only has the vaccine been shown to be preventative of tumor development, but also able to act as a therapeutic vaccine to treat existing tumors. With the vaccine showing great promise with specific immune stimulation and tumor regression in vivo, this project will outline several expansions to this treatment. First, how the vaccine facilitates the proper immune activation will be investigated, using the enantiomeric lipids of the developed vaccine. Second, the vaccine will be combined with gene therapy to provide direct stimulation of dendritic cells (DC) by inducing tumor apoptosis and recruitment of DC to the tumor interstitium. Finally, the vaccine will be tested in an additional tumor model (with the appropriate tumor-associated peptide), to expand the application of our liposome and peptide vaccine formulation.

Post Doctoral Fellowship in Pharmaceutics

THIS PROGRAM WAS INITIATED to encourage more qualified graduates to obtain the post doctoral research training so vitally needed in the area of Pharmaceutics. The PhRMA Foundation and its Pharmaceutics Advisory Committee recognize the critical need for such well-trained scientific investigators. The post doctoral award consists of a \$40,000 annual stipend for up to two years. The second year of this award is contingent upon a progress report approved by the Foundation and submission of a financial report. The award is intended solely as a stipend and may not be used otherwise.

2009 Post Doctoral Fellowships in Pharmaceutics

Timothy Brenza, Ph.D.
University of Iowa

*"Tailoring Partical Surface Chemistry
for Enhanced Pulmonary Delivery"*



Timothy Brenza, Ph.D.

Pulmonary delivery is of increasing interest as a method for localized respiratory delivery of therapeutics and systemic delivery of biosensitive compounds. A major obstacle impeding the development of pulmonary therapeutic delivery is the innate defenses of the respiratory system to foreign particles. This has not dissuaded the development of

delivery vectors which target pulmonary tissues. In particular, the role which mucosal and cellular *chemical* interactions play in determining nanoparticle fate in the respiratory tract has largely been ignored. Therefore, the goal of this proposal is to optimize the physical properties and surface chemistry of nanoparticle vectors to limit mucosal and macrophage binding, while retaining lung epithelial uptake in physiologically-relevant environments. This problem will be tackled by (1) determining key physicochemical properties that control the adsorption of mucosal components on nanoparticle surfaces, and (2) determining key nanomaterial physicochemical properties that predict local lung fate under physiologically-relevant conditions. New knowledge gained from this research will be used in the smart design of aerosolized nanoscale materials for applications where targeting of the lung tissues is desired.

Caitlin D. Lemke, Ph.D.
University of Iowa

"Development of microparticle-based vaccines"



Caitlin D. Lemke

The goal of vaccination strategies is to produce a protective immune response in the vaccine recipient with minimal negative side effects. Effective antigen presentation and stimulation of the proper immune cells are crucial for mounting this protective immune response. Current vaccine protocols rely on the use of adjuvants, such as Freund's

and alum, which suffer from toxicity issues or limited efficacy respectively. New vaccine strategies that can maximize immune stimulation while minimizing health risks are desirable. The use of biodegradable microparticles as vehicles to deliver antigen in conjunction with immunostimulatory agents has shown significant potential for achieving this. The current project has shown that this approach is both safe and effective at stimulating antigen-specific immune responses. Furthermore, including various Toll-like receptor (TLR) ligands in the microparticle formulations can augment responses to an even greater degree. This strategy results in the co-delivery of antigen and immunostimulatory molecules to the same target cell, which is known to more effectively stimulate the immune system. This project is optimizing the microparticle formulations with the most effective cocktail of antigens and immunostimulatory TLR ligands to generate the strongest antigen-specific immune responses to date.

Krista Shipley, Ph.D.
University of Kansas

“Development of biomolecular NMR techniques to monitor and quantify deamidation in pharmaceutical proteins”

Protein stability and degradation is a continuing challenge in the development of protein-based drugs. The current project’s long-term goal is to understand both the processes that lead to protein instability and the mechanisms by which

stabilizers affect those processes. There is specific focus on a common form of chemical modification, deamidation, in calmodulin, a well-characterized protein that is vulnerable to this modification. The research will use biomolecular Nuclear Magnetic Resonance (NMR), which can study proteins at the atomic level, to identify specific sites of deamidation in the protein and follow the degradation process over time, as well as resulting changes in other parts of the protein that may lead to overall instability.

Research Starter Grant in Pharmaceuticals

THE PURPOSE OF 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.

2009 Research Starter Grant in Pharmaceuticals

Adah Almutairi, Ph.D.
University of California, San Diego

“Stimuli responsive functional materials”

Although therapeutics and diagnostics have demonstrated their potential to detect, prevent and cure diseases, their success hinges upon their ability to cross complex barriers in the body and reach their target intact. Rapid advances in macromolecular engineering have enabled more sophisticated tools to bear on such biomedical challenges. This research project applies cutting edge macromolecular engineering techniques and more broadly Nanotechnology to advance both in vivo molecular imaging and the delivery of drugs and biopharmaceuticals.

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TREASURERS REPORT



December 31 were \$12.2 million, a healthy level despite a 15.9% decrease from \$14.5 million the prior year. The decrease in net assets is attributable to nearly \$3.4 million (23.6%) in investment losses during the financial crisis. \$2.7 million of net assets represents funds authorized but not yet paid for the future years of grants already awarded. However, for the 10th year in a row, we did not need to transfer net assets to cover payment this year of awards granted in previous years. Financial details are shown in the accompanying Statement of Income and Expenditures.

The PhRMA Foundation ended 2008 in solid financial shape despite a financially challenging year. Contributions were down 16% from the previous year, to \$2.7 million. We awarded approximately \$1.8 million in grants and held down non-grant program and administrative expenses. Total expenditures, at \$2.5 million, were on target with budget. Total net assets at

I can also report that our financial situation improved during 2009. Contributions were nearly level, at an estimated \$2.65 million. And our net assets recovered strongly to an estimated \$13.9 million. 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. We need the support of all member companies during these challenging financial times. Our programs represent our industry's commitment to innovation in today's research as well as to the young investigators of tomorrow.

The Foundation's financial position as of December 31, 2008, has been audited by the Rosslyn, Virginia, accounting firm of Buchanan & Company. A full report can be obtained by contacting the Foundation.

A handwritten signature in black ink, appearing to read 'Garry A. Neil', written over a light blue background.

GARRY A. NEIL, M.D.

STATEMENT OF INCOME *and* EXPENDITURES

for the year ended december 31, 2008

INCOME	
Contributions	\$ 2,708,691
Contributions – in kind from PhRMA	\$ 303,336
Interest and Dividends	\$ 440,179
(Realized and Unrealized) Gains in Securities	– \$ 3,410,499
Other Income	\$ 85,901
TOTAL INCOME	\$ 127,608

EXPENDITURES	
<i>Programs</i>	
Awards in Excellence	\$ 15,328
Clinical Pharmacology Program	\$ 161,000
Health Outcomes Program	\$ 295,000
Informatics Program	\$ 342,500
Pharmaceutics Program	\$ 265,000
Pharmacology Programs	\$ 667,500
AFPE Fellowship Award	\$ 7,500
Other Grants	\$ 30,087
Subtotal – Grants	\$ 1,783,915
<i>Other</i>	
Committee Meetings, Travel and Honoraria	\$ 72,126
Publications and Special Projects	\$ 33,356
Subtotal – Other	\$ 105,482
PROGRAM TOTAL	\$ 1,889,397
<i>Administrative</i>	
Staff, Taxes, Depreciation & Insurance:	\$ 253,575
Rent & PhRMA Accounting Services ¹	\$ 303,336
Professional Services and Investment Expenses:	\$ 70,091
Office Expenses	\$ 9,082
Subtotal – Administrative	\$ 636,084
TOTAL EXPENDITURES	\$ 2,525,481

¹ Rent and Accounting Services are donated by PhRMA

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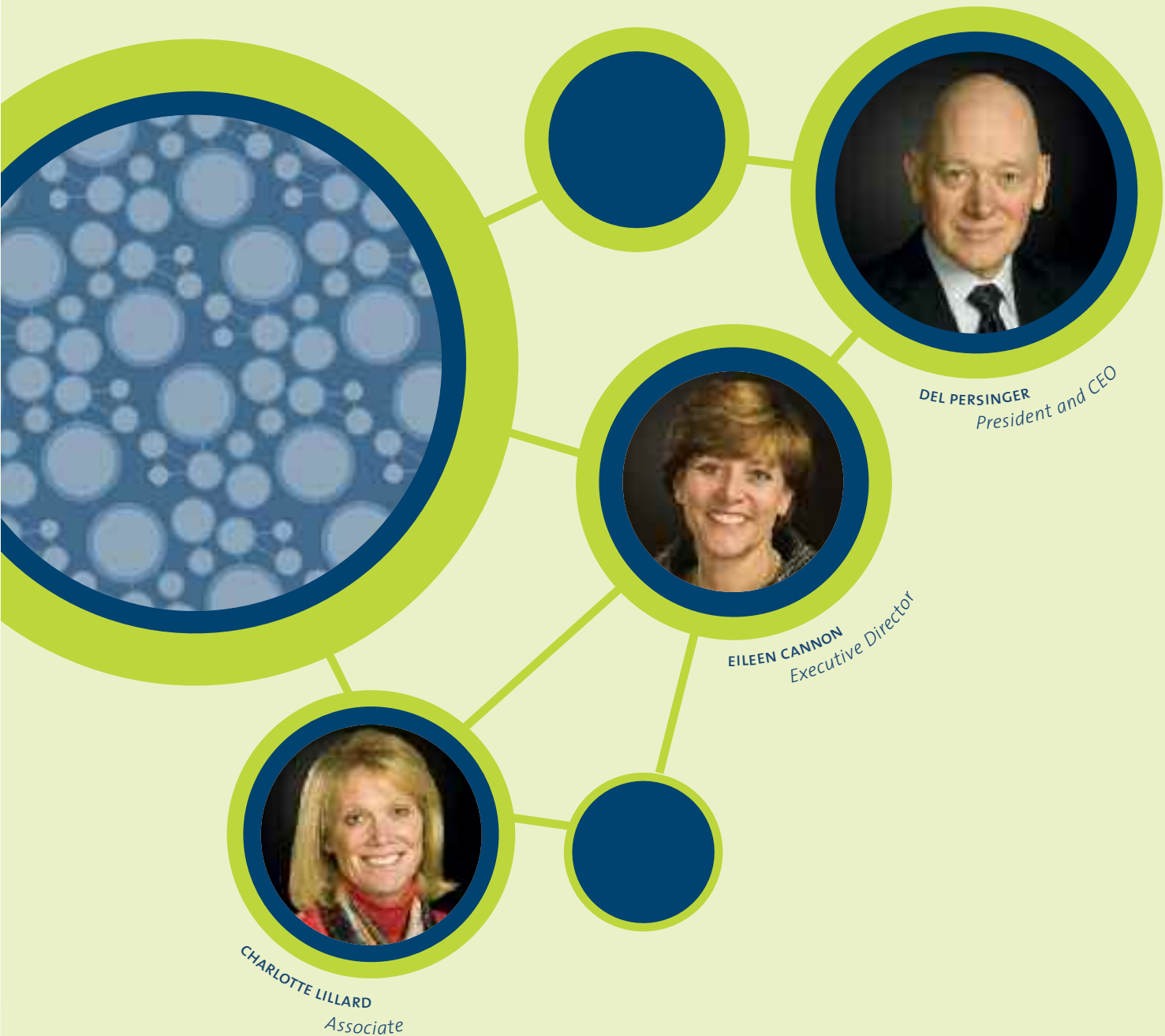
PhRMA FOUNDATION PROGRAMS *for* 2010

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
HEALTH OUTCOMES ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Health Outcomes (2002)	2 budgeted/ 2 years	\$100,000 total \$25,000 per award per year	October 1, 2009 December 15, 2009 January–August
Post Doctoral Fellowship in Health Outcomes (2002)	1 budgeted/ 2 years	\$110,000 total \$55,000 per award per year	October 1, 2009 December 15, 2009 January–December
Sabbatical Fellowship in Health Outcomes (2002)	1 budgeted/ 1 year	\$40,000 total \$40,000 per award per year	October 1, 2009 December 15, 2009 January–December
Research Starter Grants in Health Outcomes (2002)	2 budgeted/ 1 year	\$120,000 total \$60,000 per award per year	October 1, 2009 December 15, 2009 January 1, 2010
INFORMATICS ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Informatics (2009)	3 budgeted/ 2 years	\$120,000 total \$20,000 per award per year	September 1, 2009 December 15, 2009 January–August
Post Doctoral Fellowships in Informatics (2002)	1 budgeted/ 2 years	\$80,000 total \$40,000 per award per year	September 1, 2009 December 15, 2009 January–December
Sabbatical Fellowship in Informatics (2002)	1 budgeted/ 1 year	\$40,000 total \$40,000 per award per year	September 1, 2009 December 15, 2009 January–December
Research Starter Grants in Informatics (2002)	2 budgeted/ 1 year	\$120,000 total \$60,000 per award per year	September 1, 2009 December 15, 2009 January 1, 2010

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
BASIC PHARMACOLOGY ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)	9 budgeted/ 2 years	\$360,000 total \$20,000 per award per year	September 1, 2009 December 15, 2009 January–August
Post Doctoral Fellowships in Pharmacology/Toxicology (2002)	2 budgeted/ 2 years	\$160,000 total \$40,000 per award per year	September 1, 2009 December 15, 2009 January–December
Sabbatical Fellowship in Pharmacology/Toxicology (2002)	1 budgeted/ 1 year	\$40,000 total \$40,000 per award per year	September 1, 2009 December 15, 2009 January–December
Research Starter Grants in Pharmacology/Toxicology (1972)	3 budgeted/ 1 year	\$180,000 total \$60,000 per award per year	September 1, 2009 December 15, 2009 January 1, 2010
CLINICAL PHARMACOLOGY ADVISORY COMMITTEE			
Paul Calabresi Medical Student Research Fellowships (1974)	2 budgeted/ 6 months up to 2 years	\$36,000 total \$18,000 per award per year	October 1, 2009 December 15, 2009 January–August
Faculty Development Award in Clinical Pharmacology (1966)	1 budgeted/ 2 years	\$240,000 total \$120,000 per award per year	October 1, 2009 December 15, 2009 January–December
PHARMACEUTICS ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Pharmaceutics (1987)	2 budgeted/ 2 years	\$80,000 total \$20,000 per award per year	September 1, 2009 December 15, 2008 January–August
Post Doctoral Fellowships in Pharmaceutics (1992)	2 budgeted/ 2 years	\$160,000 total \$40,000 per award per year	September 1, 2009 December 15, 2009 January–December
Sabbatical Fellowship in Pharmaceutics (2002)	1 budgeted/ 1 year	\$40,000 total \$40,000 per award per year	September 1, 2009 December 15, 2009 January–December
Research Starter Grants in Pharmaceutics (1972)	2 budgeted/ 1 year	\$120,000 total \$60,000 per award per year	September 1, 2008 December 15, 2008 January 1, 2010

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

PhRMA FOUNDATION STAFF



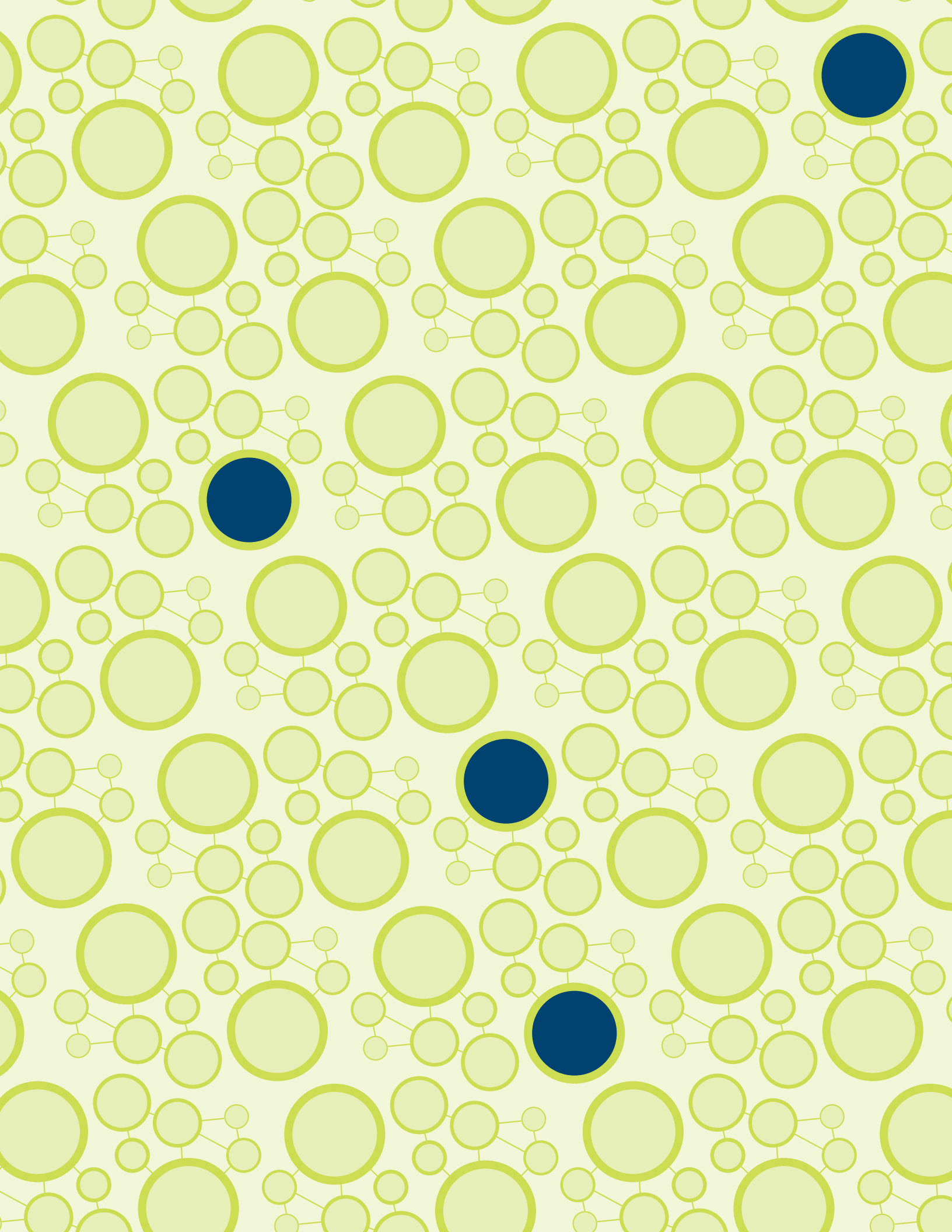
BENEFACTORS

The PhRMA Foundation owes its success to the pharmaceutical companies that have provided their generous support over the past 44 years. We thank all of you for continuing to invest in the future of pharmaceutical research and the scientists of tomorrow.

OUR 2009 BENEFACTORS ARE

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Endo Pharmaceuticals
GlaxoSmithKline
Johnson & Johnson
Merck & Co., Inc.
Novartis Pharmaceuticals Corporation
Pfizer Inc
PhRMA
Schering-Plough Corporation
Wyeth

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.





PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA FOUNDATION

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