

Annual Report

Supporting innovative science for 47 years

BENEFACTORS

The PhRMA Foundation owes its success to the pharmaceutical companies that have provided their generous support over the past 47 years. We thank all of you for continuing to invest in the future of pharmaceutical research and the scientists of tomorrow.

OUR 2012 BENEFACTORS ARE

Astellas US LLC
Bayer Corporation
Biogen Idec
Boehringer Ingelheim
Celgene Corporation
Daiichi Sanko, Inc.
Eli Lilly and Company
Endo Pharmaceuticals Inc.
GlaxoSmithKline
Johnson & Johnson
Lundbeck Inc.
Merck & Co., Inc.
Novartis
Pfizer
PhRMA
Sanofi

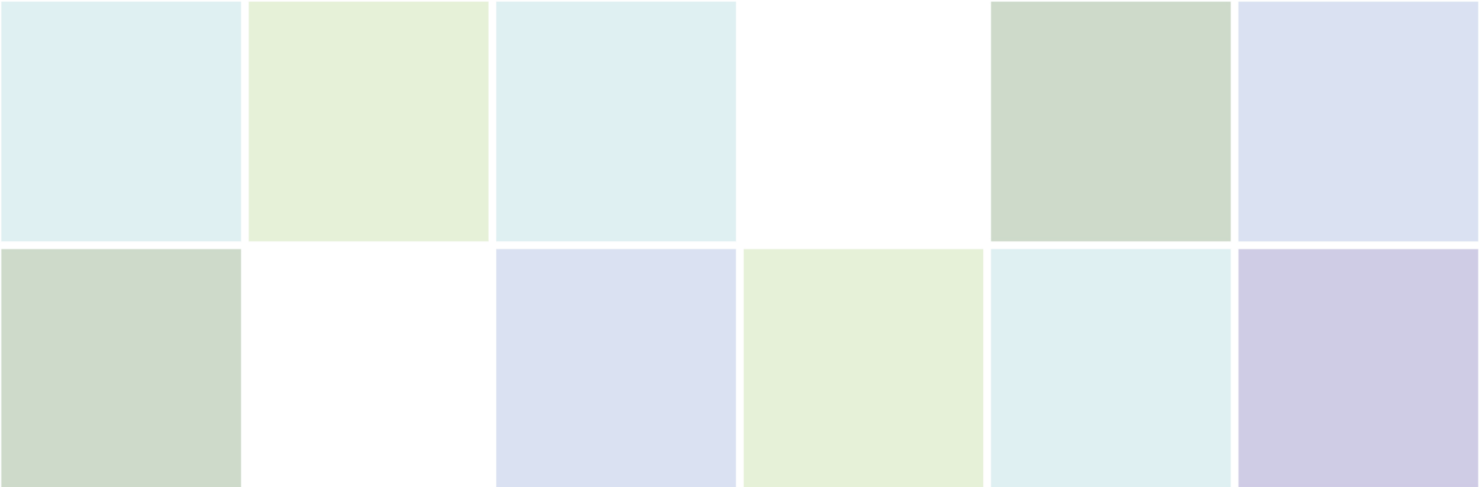


MISSION STATEMENT

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.







CONTENTS

iv	Message from the Chairman
v	Message from the President
1	Awards in Excellence
5	The Promise and Practice of Translational Medicine
7	Fellowships and Grants
7	Informatics
12	Pharmacology/Toxicology
22	Health Outcomes
26	Pharmaceutics
31	Clinical Pharmacology
38	Board of Directors
39	Treasurer's Report
40	Statement of Income and Expenditures
41	Advisory Committees
44	PhRMA Foundation Programs for 2013

MESSAGE FROM THE CHAIRMAN

I am pleased to chair the PhRMA Foundation Board of Directors as we head in new directions at this critical time for the biopharmaceutical industry. For 48 years, the Foundation has maintained a renowned program to start young scientists on teaching and research careers in key disciplines. But now, beyond that core program, the Foundation has taken on a new mission to have a direct impact in important areas such as comparative effectiveness research, translational medicine, prescribing and adherence. We are doing this by launching strategic partnerships that reach important organizations, such as NIH, Reagan-Udall Foundation, AHRQ, FDA and prestigious universities, medical schools, and research centers nationwide.

These partners and subject areas tie directly to the priorities of the PhRMA Board. It is no coincidence that I am becoming Foundation chair at the same time that I become chair of the new PhRMA Scientific Leadership Advisory Council (SLAC). Nor is it coincidence that the memberships of the SLAC and the Foundation Board overlap. Together, we can look ahead, provide advice to the PhRMA Board, and let that direction guide the programs of the Foundation. Already, the Foundation has been working closely with PhRMA's departments of Scientific and Regulatory Affairs, Policy and Communications to align objectives and focus. As a result, we have four exemplary programs, described below, with more to come.

In only two years, the Centers of Excellence for Comparative Effectiveness Research Education Program has achieved more than we thought possible, laying the



groundwork for a national conference that will bring educators, researchers, practitioners, policymakers, and other leaders together in 2014. Four prominent universities participate in the program, establishing Centers of Excellence throughout the country to support comparative effectiveness research and training.

The Foundation received an unprecedented number of applications for its new Translational Medicine and Therapeutics Program and awarded grants to five exceptional

scientists in the first year. Eventually, we will fund centers of excellence in this discipline. Our committee includes members from FDA, the Gates Foundation, NIH, universities and PhRMA member companies. The remarkable, widespread interest in this program gives us the opportunity to influence the birth and growth of a discipline that will be vital to patients and to our industry. We also have new and exciting initiatives focused on medication adherence and safe and effective prescribing.

As a PhRMA board member, you have a unique opportunity to shape the decisions and policies that will directly affect our member companies and the industry as a whole. I cannot overstate the importance of contributions from all board members. To ensure that we can maintain and grow the high impact we are achieving for science, for practitioners, for your companies and for patients, 100 percent participation is needed.

The Foundation's contributions to the scientific community and outstanding reputation have brought us this far, and we are now at a crossroads. Please help us continue in this exciting new direction.

A stylized, handwritten signature in black ink, consisting of a large, sweeping 'E' followed by a horizontal line and a large, circular flourish.

ELIAS A. ZERHOUNI, M.D.

MESSAGE FROM THE PRESIDENT

When our Scientific Advisory Committee met in 2011 to continue expanding the PhRMA Foundation's reach, they focused on a new grant program in translational medicine and therapeutics—a field that has the potential not only to improve medicine and health care on a global level, but also to support the cycle of knowledge and understanding from bench to bedside and back again. The ongoing communication and application of findings bridges basic, translational, and clinical science. Our 2012 Annual Report is dedicated to the study and practice of translational medicine.

Funding research fellows in translational medicine serves many purposes—two of which parallel the Foundation's goals to support young scientists and escalate the research, innovation, and pace at which treatments for chronic disease and illness are developed. The Translational Medicine and Therapeutics (TMT) Program differs from other Foundation initiatives through its core objective to change how scientific information and advances are shared. Understanding is compromised when the transfer of knowledge happens late—or not at all. Such a loss affects our efficiency and ability to bring safer, more effective drugs to market in a timely way.

Throughout the world, people are living longer and increasingly facing the complexities of advanced illness, expensive and sometimes ineffective treatments, and poor access to those treatments. With this in mind, we envision the expansion and widespread practice of translational medicine as an important step in the quest to treat disease and provide cost-effective, high-quality health care worldwide.

As the TMT Program was developed, we considered the current environment of biopharmaceutical research. Academia and industry have common goals in the realm of translational medicine, which seeks to connect existing knowledge with current and future practice. Whether targeting conventional



therapies or speeding the creation and availability of new treatments, translational medicine is well-positioned to address challenges in drug development.

The Foundation has always contributed to STEM education (science, technology, engineering, and mathematics), particularly as it relates to training and workforce development in the pharmaceutical and health sciences. In 2010, there were more than 550,000 graduates enrolled in science

and engineering fields (a historic peak), and our programs aim to support even more growth in these areas.

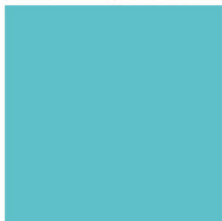
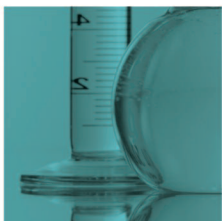
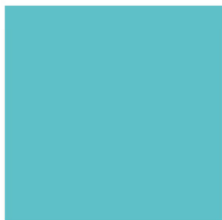
Another Foundation endeavor having an impact in the academic sector is our Centers of Excellence for Comparative Effectiveness Research (CER) Educational Program. Now in its second year, the initiative has been highly visible and successful in its mission to establish graduate-level programs that focus on CER principles and practices. Four eminent institutions are participating: Johns Hopkins University, University of Washington, University of Utah, and the Harvard School of Public Health. Like the TMT Program, the Centers of Excellence for CER Education initiative is rooted in the Foundation's efforts to improve health care delivery.

We have also developed a new award, the Center for Adherence Improvement Young Investigator Grant, to support and encourage adherence research. Proper use of medicine may improve clinical and economic health outcomes, but first we must help patients understand why closely following a prescribed dose and course of therapy can yield better results.

From conception to development, each of the Foundation's programs is vetted, discussed and reviewed by our committees to ensure it is aligned with our mission: to help foster discovery of lifesaving medicines for people throughout the world.

A handwritten signature in black ink, appearing to read 'Del Persinger'.

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 2012 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.

2012 Award in Excellence in Pharmacology/Toxicology

Margarita L. Dubocovich, Ph.D.

Professor and Chair

Department of Pharmacology and Toxicology

University at Buffalo, The State University of New York



Margarita L. Dubocovich

Dr. Dubocovich is known internationally for her work on melatonin receptors that has provided the tools and guidance for the discovery of melatonin receptor ligands and the development of analogues with therapeutic potential for the treatment of circadian disorders of sleep and depression. Dr. Dubocovich's

education, positions in academia and pharmaceutical companies, research accomplishments, awards and honors, as well as her service to scientific societies are summarized below.

Dr. Dubocovich became the first female Chair of Pharmacology and Toxicology at the School of Medicine and Biomedical Sciences at University at Buffalo (UB) on November 1, 2008. During these four years she has reengineered the educational, research, and service activities of the Department, having hired seven new faculty members who bring a broad range of expertise that includes state-of-the-art research in medicinal chemistry and molecular

modeling, human stem cell and glia progenitor cells, neuropharmacology of mood, mechanism of action of drugs of abuse, circadian rhythm disorders, and cardiovascular and cancer research.

In addition to her work as Professor and Chair at UB, Dr. Dubocovich is the Director of a professional development program called The Collaborative Learning and Integrated Mentoring in the Biosciences (CLIMB) Program at UB, which also supports CLIMB UP, a summer research program for undergraduates, and CLIMB Next Step that promotes the career advancement of postdoctoral fellows.

Dr. Dubocovich started her academic career at Northwestern University Feinberg School of Medicine (Chicago, Illinois, USA) (1982-2008). She moved through the ranks from Assistant Professor to Professor in the Department of Molecular Pharmacology and Biological Chemistry, with a joint appointment in the Department of Psychiatry and Behavioral Science (1990-2008). She retired from Northwestern University as Professor Emeritus in 2008 before moving to University at Buffalo to take the current position.

Before moving to Northwestern, Dr. Dubocovich spent

two years as Research Associate in the Department of Pharmacology in the School of Medicine at the University of Colorado (Denver, CO) (1980-1982) under the mentorship of the late Norman Weiner.

Dr. Dubocovich obtained her PhD in Pharmacology at Buenos Aires University in Argentina under the mentorship of Dr. Salomon X. Langer (1972-1976). She worked as a research fellow of the National Research Council of Argentina.

Upon completion of her PhD degree in 1976, she moved to Europe as part of a research team lead by Dr. S.X. Langer to first join the Department of Pharmacology at Wellcome Research Laboratories (later acquired by Glaxo) in the UK (1976-1977), and subsequently the Department of Biology at Synthelabo (now Sanofi) (Paris, France) (1977-1980). Research at these pharmaceutical companies provided experience in the discovery and development of new therapeutic agents for the treatment of psychiatric disorders.

Dr. Dubocovich's research ultimately aims to discover novel drugs with differential actions at the MT1 and MT2 receptors.

Dr. Dubocovich has authored over 150 articles including peer-reviewed articles, reviews, book chapters, and symposium proceedings in journals such as *Science*, *Nature*, *Trends in Pharmacological Science*, *Trends in Neuroscience*, *Pharmacological Reviews*, *Molecular Pharmacology*, and the *FASEB Journal*, among others.

Dr. Dubocovich has been continuously funded since the start of her academic career in 1982 by the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, The National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of General Medical Sciences.

Dr. Dubocovich established strong collaborations and worked together with scientists in biotechnology (Nelson Research, California, US) and pharmaceutical (Glaxo, UK; Takeda Pharmaceutical North America) companies towards discovering and developing novel melatonin ligands for the treatment of insomnia, circadian disorders as observed in mood, sleep, jet lag, blindness, cardiovascular disorders and cancer. Further, some of these novel melatonin ligands (eg, luzindole, 4P-PDOT, 5-MCANAT, GR 196429, GR 128107) are well characterized pharmacologically and are available to the scientific community for use in the characterization of melatonin receptors.

Dr. Dubocovich has collaborated with scientists at biotechnology and other major pharmaceutical companies. These collaborations have led to discoveries of novel molecules with therapeutic potential, several peer-reviewed publications and patents related to novel melatonin agonists and antagonists developed jointly with collaborators in academia or at pharmaceutical companies. Further she has also worked with law firms in patent litigation cases involving melatonin ligands.

Dr. Dubocovich has received numerous awards, including: The Award For Outstanding Scientific Contributions from the Latinoamerican Congress in Pharmacology, the 2011 Distinguished Postdoctoral Mentor Award from the UB Postdoctoral Association, the 2011 Aaron B. Lerner Pioneer Award in Recognition of Outstanding Contributions to Melatonin Research, and the 2011 Award to Hispanics in the Medical and Health Care Fields from City of Buffalo Mayor Byron W. Brown at the occasion of the Hispanic Heritage Month.

Dr. Dubocovich has served as a regular member of two separate NIH Study sections and in several NIH Ad Hoc study sections and other grant reviews committees. Dr. Dubocovich chairs the IUPHAR Subcommittee on Melatonin Receptor Nomenclature and Classification, where she was the driving force behind the establishment of the current melatonin receptor nomenclature and classification. She has also contributed to the current melatonin receptor classification and signaling databases published by IUPHAR Nomenclature Committee as well as that published by the *British Journal of Pharmacology*, *The Sigma and RBI Handbook of Receptor Classification and Signal Transduction*, and most recently by the *Alliance for Cellular Signaling*.

Dr. Dubocovich often serves as a media spokesperson for melatonin and melatonin receptors, an area of great public interest, and was quoted in newspapers, and on the radio and television worldwide. She is Associate Editor of the *Journal of Pineal Research*.

Dr. Dubocovich has dedicated much of her time training students of diverse backgrounds at all levels to pursue careers in pharmacology and toxicology. At UB she is currently the driving force of a movement designed to increase diversity at the graduate level and beyond. She is currently seeking funding from the National Institute of Health to support these activities. ●

2012 Award in Excellence in Clinical Pharmacology

Andre Terzic, MD, PhD, FAHA

Director

Mayo Clinic Center for Regenerative Medicine



Andre Terzic

Dr. Andre Terzic is Director, Mayo Clinic Center for Regenerative Medicine, and holds the Marriott Family Endowed Chair of Cardiovascular Research at Mayo Clinic, where he is Professor of Medicine and Pharmacology. He currently also serves as Director, J. Willard, Jr. and Donna Marriott Heart Disease Research Program;

Director, National Institutes of Health Program in “Cardio-vasology”; Chair, Discovery-Translation Scientific Advisory Board; and Theme Leader, Regenerative Medicine & Transplantation. During his tenure, Dr. Terzic has been appointed Mayo Clinic Associate Director for Research; Co-Director Mayo Clinic Center for Individualized Medicine; Associate Director, National Institutes of Health Training Program in “Clinical Pharmacology”; and Co-Director Robert and Arlene Kogod Program on Aging. He received medical and scientific education at the University of Paris, Belgrade and Illinois, followed by advanced fellowship training in clinical pharmacology and cardiovascular medicine at the French National Institutes of Health, Thomas Jefferson University and Mayo Clinic. Nationally, he has served in senior leadership roles, including as President, American Society for Clinical Pharmacology and Therapeutics (ASCPT) and as of 2012 Chair, Functional Genomics and Translational Biology Council, American Heart Association.

Elected to the American Society of Clinical Investigation (ASCI) membership and Fellow of the American Heart Association (FAHA), Dr. Terzic has pioneered multiple cardioprotective and cardioregenerative therapeutic modalities. He has authored over 380 scientific manuscripts, advancing the development of diagnostic and therapeutic strategies for heart disease. His works include reports on the discovery of causes and cures for human dilated cardiomyopathy and atrial fibrillation. Publications from his group in journals of high impact highlight the translation of discoveries, made at

the bench, to advancing disease management applications in cardiac surgery through safer cardioplegia, general medicine through improved pharmacotherapy in diabetic patients, and cardiology through individualized strategies for management of heart failure, ischemic heart disease and rhythm disturbances. His multidisciplinary program at Mayo Clinic is focused on deciphering molecular pathways of disease susceptibility, and the identification of genetic basis of maladaptation in human cardiovascular disease with the goal of identifying targets for improved diagnostics and safer therapy. Drawing from expertise in population sciences, genomics and proteomics, experimental and translational medicine, the program capitalizes on emerging technologies to transform therapies from palliative measures to definitive patient solutions. In particular, the ability to early detect for each individual the defining basis of disease risk and to personalize treatment by targeted drug- or stem cell-based repair advances the cardiovascular therapeutic armamentarium. Most recently, he led efforts in the discovery and development of next generation regenerative therapies applied to cardiovascular practice. He has served as lead investigator in the C-Cure international multicenter clinical trial, the first-in-man study using organ-specified stem cells for heart repair. His scientific papers have been cited over 8,300 times in the literature underscoring the impact of the work, and his research program has received continuous funding from the National Institutes of Health. He has served on independent Data and Safety Monitoring Boards pertinent to assessment of novel therapeutics, and has been nominated to the Food and Drug Administration Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. Moreover, he has served on a number of editorial boards, including recently Clinical Pharmacology and Therapeutics, Cardiovascular Diabetology, Current Cardiology Reviews, Gene Therapy and Molecular Biology, Biomarkers in Medicine, Clinical Translational Science, Journal of Cardiovascular Translational Medicine, Regenerative Medicine, and Personalized Medicine.

Dr. Terzic is the recipient of numerous national and international recognitions including the Medal of Merit from the International Society for Heart Research, the Leon I. Goldberg Award from the American Society for Clinical Pharmacology and Therapeutics, the Klaus Unna Award from the University of Illinois, the Established Investigatorship from the American Heart Association, and the Excellence in Teaching Award, Outstanding Cardiovascular Research Mentor Award, Landmark Contribution to the Literature Award and Outstanding Investigator Award from the Mayo Clinic. He was awarded the 2010 Martin E. Rehfuess Medal in Medicine, Thomas Jefferson University, and the 2011 Henry W. Elliott Distinguished Service Award, American

Society for Clinical Pharmacology and Experimental Therapeutics.

Of note, Dr. Terzic has had a two decade long contribution in mentoring, and has trained within the last ten years over 40 fellows, physician-scientists and students who have received more than 50 prestigious national and international awards and grants. These have included National Institutes of Health, American Heart Association, PhRMA Foundation and ASCPT funding, underlying the development of independent scholarly careers. In this way, Dr. Terzic has generated an environment poised to advance the next vanguard in clinical pharmacology. ●



The Promise and Practice of Translational Medicine

T With its focus on bringing scientific innovation and information to patients, translational medicine has the capacity to change public health. It seeks to broaden and apply a discovery's implications to patients and refine the meaning and real-time application of that finding throughout a process that parallels the course of drug development. The field's success is evident in therapeutic areas such as oncology, infectious disease, and cardiology and its ability to increase understanding of clinical variation among diseases, pathogenesis, and therapies could improve health care as a whole. Translational medicine goes beyond incorporating findings at the clinic—it fosters a full cycle of knowledge, understanding, and usability.

Although there isn't widespread agreement on one definition of translational medicine, there is consensus about its purpose: to improve human health. "The conventional definition of translational medicine has focused on the transfer of laboratory-based results into the clinic, but there has increasingly been a voice that addresses a more enlightened perspective," said Michael Liebman, PhD, Managing Director of Strategic Medicine, Inc., and Chair of the PhRMA Foundation's Translational Medicine and Therapeutics (TMT) Advisory Committee. "This evolving view embraces the idea that it is critical to first identify true clinical needs [and] move them to the laboratory—then the results can be more readily translated into clinical utility." Transforming discoveries into novel therapeutics and diagnostics makes findings usable and helpful for patients, which is the fundamental goal.

The PhRMA Foundation's TMT Program aims to expand the interpretation of translational medicine as a practice that goes beyond bench-to-bedside conventions. It strives to adapt scientific advances into patient-focused research, bring the research into practice, and take the knowledge of what did and didn't work back to the bench. The program, which has generated interest among prestigious universities

throughout the country, awards postdoctoral fellowships to graduate students to develop and refine their training in TMT and starter grants for faculty beginning independent research careers. More than 70 applications were received in 2013 and five postdoctoral fellowships and research starter grants totaling \$560,000 over two years have been awarded. As the program enters its second year, it will continue to build a cadre of trained TMT investigators.

"Because the Foundation's mission focuses on supporting the development of critical skills, knowledge, and resources to address gaps that limit improving patient outcomes and management, it is somewhat unique in its ability to focus on the multidisciplinary activities that can contribute to this goal," said Dr. Liebman. "The Foundation has enabled the adoption and refinement of the definition of translational medicine to drive its funding focus. Carefully selecting projects and individuals who adhere to its definition of translational medicine can significantly contribute to expanding this critical base of personnel and research productivity. TMT is focused on funding high-impact projects, and will additionally work to publicly discuss and support the design, implementation, and results of such projects, especially as they convert into clinical application."

Translational medicine takes a collaborative and iterative approach to drug discovery and development that has the potential to unite industry, academia, and government in the pursuit of better health outcomes—a priority that underlies the objectives of the entire biomedical field. Determining the clinical utility and capacity of a lab discovery is facilitated by sharing insight throughout all stages of medical research and clinical trials. "The gap between data and knowledge unfortunately continues to grow at an explosive rate because new technologies support data generation and knowledge generation lags far behind," said Dr. Liebman. "The biggest issue in any research is defining the actual question that needs to be answered. A physician may ask for a better drug for his pa-

tients, but the problem [may actually] require more accurate diagnosis and stratification of patients to know who should receive drugs that are already available, and to focus the research on the disease groups who are not being adequately treated.” Such knowledge can inform drug discovery and development and build a platform for pursuing more productive translational research, but only when vital information is properly collected, managed, and shared. Collaborative partnerships among research centers, institutions, universities, and hospitals are widening communication pathways to gather and share existing data on disease and heighten patient understanding.

As global health trends continue to show increases in life expectancy, the pervasiveness of chronic disease—coupled with more expensive and sometimes ineffective or inaccessible treatments—has led healthcare reformers to call for greater accountability from scientists and practitioners. Generating new ideas and rethinking concepts to contribute to and improve health outcomes requires a substantial commitment from everyone involved. According to Dr. Liebman, translational medicine seeks to understand and solve real-world health issues and address all components of care, including access, effectiveness, and cost. “The real issues that have held back translational/clinical research are

reflective of the need to educate, explore, debate, and discuss how to change the system, and not discrete points in the process. Resources and appropriate funding are critical, but we need to recognize that these are elements of the system, and it is the system that must evolve...not just these individual elements independent of one another.”

A major obstacle in the development of effective therapies is a lack of understanding about what causes diseases and how those diseases manifest in different people. “To overcome potential barriers to translating new knowledge into practice, it is critical to train both researchers and clinicians in more systems-based reasoning and to encourage its application in both,” said Dr. Liebman. “This extends to regulatory processes, education, and marketing in terms of how we move from treating the symptoms of a disease to understanding and managing the interaction between the disease process and the patient.”

The objectives of biomedical science cannot be achieved without an application to the patient—an outcome that drives all of the Foundation’s grant and fellowship programs. As valuable realizations result in more effective treatments and ultimately better health, translational medicine will continue to produce clinically meaningful information—bridging research, discovery, and practice. •



Fellowships and Grants

INFORMATICS

Pre Doctoral Fellowships 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 \$1,000 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.

2012 Pre Doctoral Fellowship in Informatics

Mark Hallen

Duke University

“Antibiotic Design Using a New Drug Design Algorithm That Models Protein Backbone Flexibility”



Mark Hallen

In recent years, the frequency of bacterial resistance to antibiotics has grown faster than the arsenal of antibiotics available. This threat calls for new drug discovery approaches. Computational drug design is an emerging strategy in drug discovery that is quite promising for this purpose. By screening potential drugs

computationally, it allows cheap evaluation of many compounds for potential use as antibiotics. The approach is particularly attractive when the compounds are chemically diverse or otherwise hard to synthesize. At the same time, it can be used to identify compounds that are particularly susceptible to resistance, or to evaluate possible side effects. However, current approaches in computational drug design have relatively high false-positive and false-negative rates, especially when evaluating compounds differing significantly

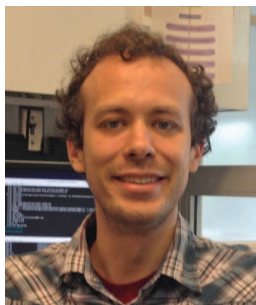
from previous drugs. Thus, new algorithms to model drug function accurately while maintaining computational efficiency would be very useful at this time. Most antibiotics function, like many other drugs, act by binding to proteins. Thus, this research aims for more realistic modeling of protein-drug binding. It builds on the Dead-End Elimination (DEE)/A* algorithm, a method that predicts changes in protein structure due to changes in chemistry such as drug binding or mutations. The algorithm can search the space of favorable chemical changes at the same time, allowing for greater search efficiency. DEE/A* searches a predefined space of possible changes in protein structure, and using some protocol for estimation of the energies for different structures (an “energy function”), it is guaranteed to find the lowest-energy structure from the given space of structures according to the given energy function. Thus, in order to improve the results of DEE/A*, this work will focus on increasing the search space and speeding up the energy function without incurring intractable computational cost. This

research has begun by developing a version of DEE/A*, Dead-End Elimination with Perturbations (DEEPer), that searches over a greater range of structural changes for each residue in a drug binding site or other region of a protein. Current and future work includes development of more efficient ways to search this space of structures, expanding the space further. It also includes work on a more accurate energy function, aiming to reproduce the accuracy of physical modeling techniques that are more realistic but are currently too computationally expensive to use extensively in drugs design. Additionally, DEEPer will be used to search for possible drugs targeting three essential bacterial enzymes: LpxA, LpxC, and bacterial dihydrofolate reductase. Furthermore, since DEE/A* efficiently picks mutations for a specified function, mutants of gramicidin S synthetase, an enzyme that produces the broad-spectrum but rather toxic antibiotic gramicidin S, will be searched for as well. The mutant enzymes may produce novel antibiotics similar to but less toxic and more effective than gramicidin S. •

Sam DeLuca

Vanderbilt University

“Development of RosettaQSAR: A Novel High Throughput Computational Ligand Docking System Incorporating QSAR Derived Constraints”



Sam DeLuca

Currently, QSAR and computational ligand docking studies are valuable but independently used tools for drug design. Data from Pharmacophore maps produced by tools such as COMFA are typically compared to docking simulations by hand in a qualitative manner. ROSETTALigand has been previously successful at predicting binding poses with high resolution (Kaufmann, et. al, Proteins, 2009). We are developing ROSETTAHTS, an extension to ROSETTALigand which will integrate these two methods using information from QSAR derived pharmacophore maps to guide low resolution ligand docking. Pharmacophore maps are generated using BCL::PharmMap (unpublished), and contain information about hydrogen bonding, steric bulk, and polarizability. Discrete cartesian grids describing chemical features of the binding site are overlaid on the protein structure and score initial placement of the ligand prior to fine grained docking. As the scoring grids are precomputed, sampling of the binding site is rapid. Rapid initial sampling, increases the practicality of structure based virtual High Throughput Screening (vHTS). The integration of structure and ligand based vHTS techniques allows the full range of pharmacological information to be considered at once. This technique can be used to rapidly develop small focused libraries for HTS, decreasing the number of compounds that need to be purchased for testing. •

Post Doctoral Fellowships in Informatics

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

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

2012 Post Doctoral Fellowship in Informatics

Chirag J. Patel, Ph.D.

Stanford University

“Comprehensive and Systematic Screen for Environmental Factors Associated with Cardiovascular-related Diseases”



Chirag J. Patel, Ph.D.

Cardiovascular diseases are a top cause of mortality worldwide. Notable risk factors for cardiovascular disease include blood lipids, including HDL-cholesterol, LDL-cholesterol, and triglycerides. Both genetic and environmental factors contribute to individual differences in levels of lipids. Our knowledge regarding the comprehensive genetic contribution to lipid levels is advancing rapidly through what is known as genome-wide association studies (GWAS), a study in which entire human genomes are compared in disease and healthy individuals. On the other hand, knowledge of the contribution of environmental factors on cardiovascular disease has not kept up with this pace. There are lack of data-driven methods—like GWAS—to search for, and discover, novel environmental factors associated with disease. To address this shortcoming, a new way of conducting data-driven study to connect the

environment with disease, called an “Environment-wide Association Study” (EWAS), will be executed. Specifically, over 200 environmental factors measured in individuals’ body tissue (e.g., hair, urine, and blood), will be analytically connected with serum lipid levels. Examples of these exposures include markers of air pollution, pesticides, nutrients (e.g. vitamins and minerals), and infectious agents (e.g., bacteria and viruses). To conduct such a study, six independent and large cohorts representative of the United States population have been attained. Such an informatics framework may allow for the discovery of modifiable factors associated with serum lipids with robust statistical evidence. Furthermore, factors found through such a study might be novel targets for therapeutic-based intervention. ●

Research Starter Grant in Informatics

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 \$60,000 for one year. 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.

2012 Research Starter Grant in Informatics

Bartek Rajwa, Ph.D.

Purdue University

“Algorithms for Automated Detection of Sample Signature Changes in High-Throughput Cytometry-Based Drug-Discovery Assays”



Bartek Rajwa, Ph.D.

Cell-based assays and phenotypic screening techniques are becoming increasingly important tools for drug discovery. It has been rightly argued that they reflect the complexity of the studied biological systems in a more faithful fashion than simple biochemical assays. In fact, in the last decade, the majority of the first-in-class small-molecule

drugs approved by the US Food and Drug Administration were discovered using phenotypic screening. Cell-based approaches also allow studying the heterogeneity of cellular populations, providing a toolkit to analyze the possible role of heterogeneity and its functional significance. Flow cytometry (FC) is one of the premiere techniques for functional single-cell analysis. Despite its popularity it has not typically been employed for screening—the majority of FC instruments do not support integration with high-throughput (HT) pipelines, and FC data analysis is performed in an exploratory and interactive fashion that is not amenable to automation. Although recent FC auto-sampler devices allow utilization of cytometry in a high-throughput context, the development of algorithms for robust and operator-independent processing of experimental results still lags far behind. This study addresses the issue of automated quantification and mining of FC results, providing an interface to the HT experimental format. To achieve this goal, a departure from established exploratory techniques is proposed and the use of signal processing and multispectral classification algorithms is advocated. The study proposes implementation and dissemination pathways as well. •

Michelle Meyer, Ph.D.

Boston College

“Tools for Non-Coding RNA Discovery in the Human Microbiome”



Michelle Meyer, Ph.D.

Bacteria known to cause disease are only a small subset of the bacteria that live on and within the human body. Most human associated bacteria reside in the gastrointestinal tract where they provide many benefits such as producing nutrients and vitamins that the human body cannot make for itself, and preventing invasion by pathogenic bacteria. Historically, it has been difficult to study these bacteria because they cannot be grown under laboratory conditions. However, advances in DNA sequencing technology have allowed researchers to study them by sequencing their collective genomes, the microbiome. Changes in the microbiome are correlated with chronic conditions such as psoriasis, obesity, and inflammatory bowel disease. Most studies of the microbiome to date have focused on microbial diversity and protein coding genes, largely ignoring how these genes might be controlled. In the last decade, researchers have discovered that non-coding RNAs are important controllers of bacterial growth, metabolism, and virulence. They also are diverse across different types of bacteria, and are thus good potential targets for new antibiotics targeted to specific subsets of bacteria. Yet the process for computational non-coding RNA discovery is time consuming and generates many false-positives. The proposed research seeks to develop new tools for ncRNA discovery that allow efficient analysis of large human microbiome datasets, and minimize the number of false-positive RNAs identified. These tools will significantly accelerate the discovery of potential therapeutic targets that are selective for bacteria associated with chronic disease rather than beneficial bacteria. •

Victor Jin, Ph.D.

The Ohio State University

“Deciphering Transcriptional Regulatory Code
in the Human Genome”



Victor Jin, Ph.D.

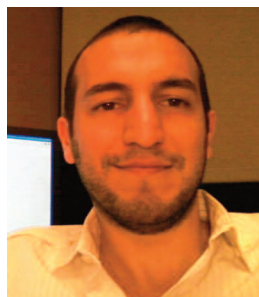
This project plans to use systems biology approaches which integrate computational modeling and experimental validation to decipher transcriptional regulatory code in the human genome. Many studies suggest that the inappropriate expression of certain TFs has been linked to human diseases such as cancers and neurological

and developmental disorders. The preliminary data showed that ER α interacts with different co-TFs to regulate distinct subset of genes in MCF7. This project will thus use ER α before and after estrogen (E2)-treatment and four ER α + breast cancer cell types (MCF7, T-47D, BT474, and ZR-75-I) as a model system to test two central hypotheses: 1) a given seq-TF regulates a distinct subset of genes in each cell type and may interact with different TF partners to instruct cell-specific gene regulatory networks; 2) a certain group of TFs form different transcriptional chromatin hubs and co-regulate cell-specific interactomes. Next generation sequencing techniques will be employed to generate different 'omics data and bioinformatics analyses will be developed to cope with the innate complexities of high-dimensional datasets. Successful completion of this application will provide new insights into the molecular basis of cell-specific gene expression. The integrated 'omics approach will become a novel paradigm to study transcriptional regulatory mechanism. ●

Ali Torkamani, Ph.D.

Scripps Translational Science Institute

“Targeting Chromatin Modification in Cancer”



Ali Torkamani, Ph.D.

Recent evidence from tumor genome sequencing studies has revealed that mutations in genes (“chromatin modification genes”) that influence the structural organization of the genome are commonly mutated in a number of cancers. In certain cancers, such as renal cell carcinoma, these mutations are observed in approx-

imately 40% of cases. The elevated frequency of these mutations in renal cancer suggests that a therapeutic designed to specifically combat the effects of these mutations would be extremely useful in a large proportion of cancer patients. However, the nature of the mutations in these chromatin modification genes does not lend itself to a straightforward therapeutic strategy. In other words, targeting these mutated genes directly would not be effective. Therefore, the research supported by the PhRMA Foundation is directed towards identifying tumorigenic mechanisms that co-operate with mutations in chromatin modifying genes, in order to identify drug targets that may selectively affect cells with these mutations while leaving normal cells unharmed. ●

PHARMACOLOGY/TOXICOLOGY

Pre Doctoral Fellowships 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 \$1,000 a year of the funding may be used for incidentals directly associated with the preparation of the dissertation.

Three hundred and seventy fellowships have been awarded under this program since it began in 1978 including the ten fellows awarded in 2012.

2012 Pre Doctoral Fellowships in Pharmacology/Toxicology

Lyndsey Anderson

Vanderbilt University

“Elucidating the Basis for Pharmacoresistant Epilepsy”



Lyndsey Anderson

Epilepsy is a common neurological disorder that is most commonly treated with anti-epileptic drugs (AEDs). Unfortunately, approximately one-third of persons with epilepsy do not achieve adequate seizure control with the currently available AEDs. This phenomenon is called pharmacoresistant epilepsy and research into causes of this medical problem is needed in order to develop strategies to prevent its emergence. Various animal models of provoked seizures have been employed to study pharmacoresistant epilepsy, but there are no reliable *in vivo* models of spontaneous pharmacoresistant epilepsy. This project will study a genetically engineered mouse model of epilepsy (*Scn2a*-Q54 mice) that exhibits spontaneous, pharmacoresistant epilepsy. Neurons from the hippocampal region *Scn2a*-Q54 mouse brains exhibit hyperexcitability caused by abnormal sodium currents. Preliminary studies demonstrated that acute administration

of ranolazine, an FDA approved drug which acts by suppressing sodium current, significantly reduced seizure frequency in 4½ week old male but not female *Scn2a*-Q54 mice. However, acute ranolazine treatment did significantly reduce seizure frequency in younger females. The goal of this project is to exploit this novel animal model of pharmacoresistant epilepsy in an effort to understand the basis for drug resistance. This project will test the hypothesis that pharmacoresistance in *Scn2a*-Q54 mice occurs when secondary epileptogenic mechanisms (e.g. hippocampal scarring, neuron loss), which develop as a consequence of chronic seizures, become responsible for seizure susceptibility rather than the genetically engineered mutation. This project will investigate the contribution of age and sex hormones to the development of ranolazine resistance in *Scn2a*-Q54 mice, and determine whether hippocampal changes correlate with emergence of pharmacoresistance. Results from these studies will contribute new clues about the mechanisms of pharmacoresistant epilepsy and could inspire new treatment strategies for its prevention. •

Steven Grinnell

Weill-Cornell Medical College

“Truncated Opioid Receptor Splice Variants: New Targets for Powerful Pain Relief with Minimal Side Effects”



Steven Grinnell

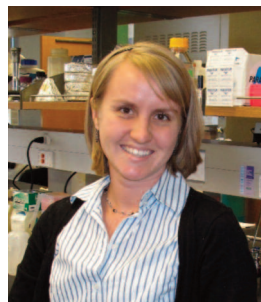
Pain remains a pervasive problem throughout medicine, transcending all specialty boundaries. Despite the extraordinary insights into pain and its mechanisms over the past few decades, few advances have been made with analgesics. Most pain remains treated by opiates, which have significant side effects that limit their utility.

A newly synthesized drug, IBNtxA, was found to be a potent analgesic lacking the traditional side effects associated with classical opiates including respiratory depression, constipation, physical dependence and, perhaps most important, rewarding behavior associated with abuse and addiction liability. This agent appears to act through a truncated, six transmembrane variant of the mu opioid receptor. While truncated splice variants have been reported for a number of G protein coupled receptors (GPCRs), their functional relevance has been unclear. This evidence suggests that truncated variants are physiologically important and can comprise new therapeutic targets through direct physical interaction with other GPCRs. The goal of this study is to characterize the newly identified opioid receptor, both in an artificial system to explore the range of possible receptor partners, as well as in a human neuroblastoma cell line which natively expresses this target. These approaches will offer significant insights into opioid pharmacology and the phenomenon of GPCR heterodimerization—with far-reaching implications for the treatment of pain clinically and the development of a new generation of painkillers with minimal side effects. •

Sara Nowinski

University of Texas at Austin

“Mitochondrial Uncoupling as a Bioenergetic Strategy for Skin Cancer Prevention and Treatment”



Sara Nowinski

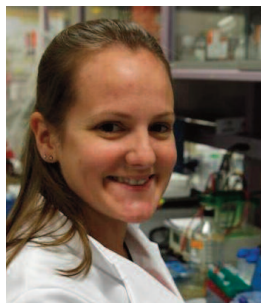
Almost eight decades ago, Otto Warburg discovered that compared to normal tissues, nearly all malignant tumors exhibit increased glycolysis and decreased oxygen consumption. This general property is so pervasive that it is now used clinically to image malignancies by [F^{18}] fluoro-deoxyglucose positron emission

tomography (FDG-PET). In opposition to this malignant phenotype, mitochondrial uncoupling proteins dissipate the electrochemical proton gradient across the inner mitochondrial membrane. This increases oxygen consumption by driving futile respiration that is uncoupled from ATP synthesis. Our lab previously generated hemizygous mice that express a keratin 5 – uncoupling protein 3 (K5-UCP3) transgene in the basal epidermis, and are completely protected from the formation of skin carcinomas in response to a chemical carcinogenesis regimen. In order to provide insight into the mechanism of UCP3-induced cancer resistance, we inter-bred K5-UCP3 animals with “pre-initiated” Tg.AC mice that express an oncogenic Ras gene, producing bigenic K5-UCP3/Tg.AC mice. While wild type Tg.AC mice form tumors in response to treatment with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) alone, K5-UCP3/Tg.AC animals are protected from TPA induced tumorigenesis, indicating that UCP3 likely inhibits tumor promotion. Preliminary data suggest that UCP3 causes this effect through two primary mechanisms: by promoting the differentiation of stem cell and basal keratinocytes, and by decreasing the signaling pathway response to the tumor promoter TPA. K5-UCP3 epidermis does not display a proliferative response to TPA treatment, and excitingly, this lack of proliferation coincides with decreased activation of Akt (PKB), a major driver of tumor development in many types of cancer. Ongoing research will further examine the cellular and molecular mechanisms underlying UCP3 driven chemo-prevention, and explore the role of endogenous UCP3 as a putative tumor suppressor. •

Lindsay M. Garvin

The George Washington University

“Mechanistic Study of the Repression of MUC5AC and MUC5B Gene Expression by the Delta 9-11 Compound, VBP15, in Human Lung Epithelial Cells”



Lindsay M. Garvin

Glucocorticoids are commonly used steroid drugs for a variety of airway diseases including asthma. Because many adverse side effects are observed in patients on long-term gluco-corticoid treatment, alternative drugs are currently being designed and tested. An example of glucocorticoid alter-

natives are the $\Delta 9, 11$ compounds, also known as the VBP compounds, which are thought to function by repressing cytoplasmic signaling of the inflammatory transcription factor NF κ B rather than through the classical pathway of glucocorticoid transcriptional regulation. The overproduction of mucus, made up of mucins, is a major problem in lung diseases. MUC5AC and MUC5B are the primary mucins found in the lung. Preliminary data demonstrated that VBPI5 reduces MUC5AC mucin gene expression in A549 lung epithelial cells in a dose- and time-dependent manner. This study also demonstrated that VBPI5 induced nuclear translocation of the Glucocorticoid Receptor (GR), and used a GR antagonist to determine that GR is necessary for the VBPI5-induced repression of MUC5AC. Further experiments are necessary to complete these experiments and to determine if GR is also necessary for MUC5B mucin repression by VBPI5. Mechanistic studies to determine how this novel drug VBPI5 mediates mucin gene repression will be carried out. VBPI5 may be a useful drug for treatment of lung diseases if it's potential to reduce mucin production in the lungs of patients with asthma or other airway diseases without the harmful side effects observed in long-term glucocorticoid treatment is fulfilled. •

Jennifer Lamberts

University of Michigan

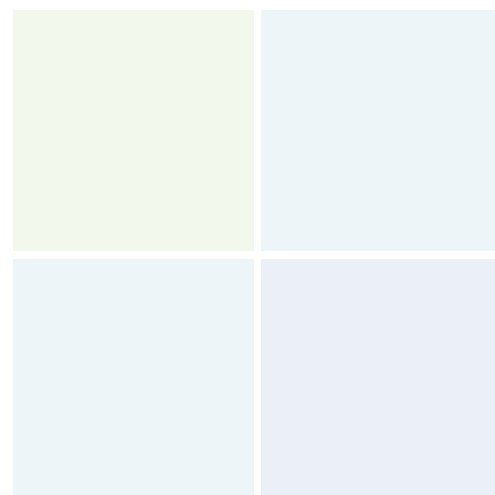
“Examination of the Role of G α_o Protein in Addiction Liability: Focus on Opioid Receptors”



Jennifer Lamberts

Although many drugs known to be useful for the treatment of neurological diseases have been shown to display abuse liability, including prescription opioids for pain (e.g. Oxycontin®) and stimulants for attention deficit hyperactivity disorder (e.g. Ritalin®), the development of safer central nervous system pharmaceuticals

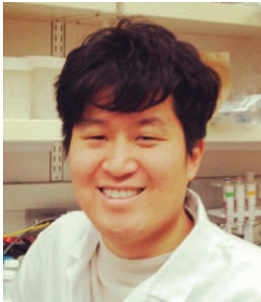
is hindered by the lack of mechanistic knowledge regarding the addictive process. Many drugs of abuse elicit both their desired and rewarding effects through direct or indirect activation of G protein-coupled receptors linked to G proteins of the G α_i/o family. However, it is currently not well understood how these G α subtypes contribute to addictive behaviors. The goal of this project is to probe the role of the specific G α isoform G α_o in the action of opioid drugs. To study this, mice lacking G α_o protein are being evaluated for differences in several behaviors associated with opioid administration. This research will contribute new knowledge toward advancing our current understanding of the complex behavior(s) underlying opioid use and abuse. Furthermore, the identification of a role for specific intracellular proteins in the addictive process could provide new avenues for the development of non-addictive medications to treat neurological disorders. •



John Park

University of California, Irvine

“Molecular Dissection of Thrombospondin-4 Domains in Pain Processing”



John Park

Chronic pain is a common clinical problem affecting millions of people in the United States. Chronic pain, specifically neuropathic pain, or pain caused by injuries in the peripheral or central nervous systems, is difficult to manage since existing drugs only provide partial pain relief in a subset of patients, and their long-term

use is limited by their side effect profiles. Thus, the development of new medications for better pain management relies on our better understanding of chronic pain mechanisms. This study has shown that nerve injury induces elevated levels of the thrombospondin-4 (TSP4) and calcium channel $\alpha_2\delta_1$ subunit ($\text{Ca}_v\alpha_2\delta_1$) in the spinal cord and dorsal root ganglia, which are important organs for sensory information processing. This correlates with recent findings showing $\text{Ca}_v\alpha_2\delta_1$ as the neuronal thrombospondin receptor in synapse formation in the brain. Based on these findings, we hypothesize a novel chronic pain mechanism in which $\text{Ca}_v\alpha_2\delta_1$ and TSP4 interact to induce neuronal hyper-excitability in the spinal cord that leads to neuropathic pain states. The project will address this hypothesis by identifying the molecular domain(s) of TSP4 responsible for causing pain sensations and determining whether its interaction with $\text{Ca}_v\alpha_2\delta_1$ is required to mediate pain states. Successful completion of the proposed studies will help to identify the functional roles of these protein interactions in pain processing, and may lead to better understanding of neuropathic pain mechanisms and development of target specific, safe medications for neuropathic pain management. •

Craig Ulrich

University of Nevada, Reno

“New Therapeutic Targets for the Treatment of Preterm Labor”



Craig Ulrich

The Myometrial Function Group in Nevada headed by Dr. Buxton is committed to developing an entirely new understanding of preterm labor in women in order to contribute new therapeutic targets for the prevention of this devastating problem. The project goal is to map the human uterine smooth muscle proteome during pregnancy as well as the induction of labor and pre-term labor because the molecular mechanisms involved in uterine quiescence during gestation and the induction of labor at term in women is still unknown. Identifying proteins that are disparately regulated during labor and pre-term labor will give us and others a high confidence list of target protein networks in which to explore hypothesis driven approaches to prevent preterm labor. Preterm delivery is a global problem. The Buxton group in Nevada is working to understand the genetic, proteomic and post-translational regulatory distinctions among term pregnancy, labor and spontaneous preterm labor in women in order to develop an effective treatment for preterm labor that allows a fetus to remain in the mother’s womb until term. Predicting which mothers are at highest risk for preterm labor and discovering new therapeutic drug targets to prevent preterm labor is the goal of this project. •

Celeste Greer

Yale University

“Transcriptional Elongation Blockade as a Mechanism of Transcriptional Repression and Anti-Cancer Activities of Histone Deacetylase Inhibitors”



Celeste Greer

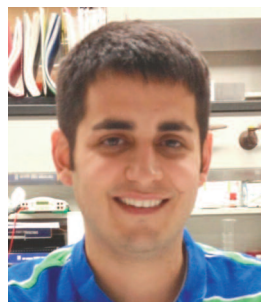
Histone deacetylase (HDAC) inhibitors are used clinically in cancer therapy to induce cell cycle arrest and apoptosis in cancer cells, while not harming normal tissues. On a molecular level, these drugs block the deacetylation of lysine residues, which causes an increase in the acetylation of histone tails and other

proteins. This acetylation is usually associated with an escalation in the transcriptional level of genes. However, HDAC inhibitors can repress the transcription of essential oncogenes that many cancer cells of different types overexpress in order to promote their growth and survival. The mechanism for the transcriptional repression induced by HDAC inhibitors is poorly understood, and this project focuses on understanding this mechanism. This research has found that HDAC inhibition decreases the rate at which polymerase reaches the end of genes to produce full-length mRNA transcripts. Genome-wide experiments that detect and quantify the RNA products of RNA polymerase II (RNAP) that emerge as it transcribes genes have shown that HDAC inhibitors cause an increase in RNA products from near transcription start sites, while decreasing those seen along the gene body of repressed genes. This suggests that HDAC-mediated transcriptional repression is not due to a reduction in transcriptional initiation, but rather a blockade of elongation. Looking at the change in the positioning of total RNAP and phosphorylated RNAP in response to HDAC inhibitor treatment genome-wide will validate this idea. Synergistic lethality has been reported for HDAC inhibitors and flavopiridol, which inhibits a protein that helps overcome elongation blocks, and their combined effect on the repression of transcriptional elongation of oncogenes will be tested. These studies will also test the involvement of other known positive and negative regulators of transcriptional elongation in the repression induced by HDAC inhibitors. The identified factors represent potential new targets for cancer therapy development that could be targeted alone or in combination with HDAC inhibitors. •

Jacob Junco

University of Texas Health Science

“Mechanism of Resveratrol and Ursolic Acid to Synergistically Inhibit Nfkb and Skin Cancer Development”

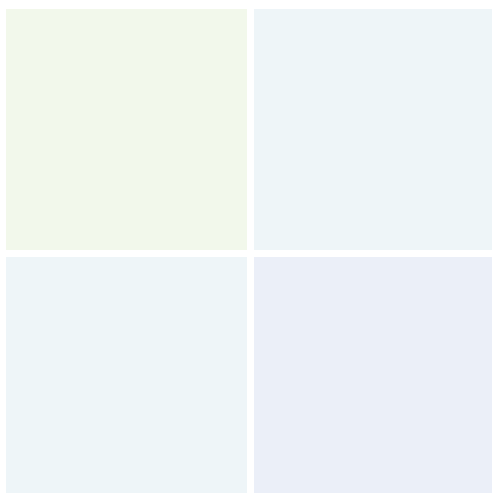


Jacob Junco

There are over one million new cases of skin cancer in the United States annually, and skin cancer increases the risk of developing other cancer types by 15-30%. Much of current skin cancer research focuses on the use of natural phytochemical compounds to prevent or treat these diseases. Certain combinations of phytochemicals have been shown to “synergize”,

resulting in stronger than expected inhibition of cancer cell growth and full cancer development. Resveratrol (RES), a polyphenol found in grapes and Ursolic Acid (UA), a triterpene found in apples, are phytochemicals that suppress skin cancer development and the tumor-promoting inflammatory nuclear factor kappaB (NFκB) pathway in mice. Preliminary experiments using a mouse model of chemically-induced skin tumor promotion showed that a RES and UA combination synergistically inhibited epidermal proliferation and NFκB activation, and synergistically activated 5' adenosine monophosphate-activated protein kinase (AMPK). AMPK is known for its energy sensing and anti-diabetic properties, however recent evidence has implicated AMPK as a potential cancer suppressor. In preliminary studies in a human skin cell line, RES and UA also synergistically suppressed NFκB and activated AMPK. In addition, both RES and UA induced death of various skin cancer cell lines. For this project, various strategies will be employed to determine if the anti-inflammatory or anti-skin cancer effects of the RES and UA combination depend on its ability to synergistically activate AMPK. A chemically-induced skin cancer model in mice will be used to test if RES and UA can synergistically prevent full skin cancer development. In addition, RNA interference and specific chemical inhibitors will be used to determine if RES, UA, or the combination kill cancer cells via AMPK. Depending on these results, AMPK-deficient mice or AMPK-deficient skin cancer cell lines injected into immunodeficient mice will be analyzed to reveal if the anti-skin cancer effects of RES, UA,

or the combination depend on AMPK. Finally, little is known about the proximal target or receptor of UA. Preliminary studies for this project indicated that UA may modulate glucocorticoid receptor (GR) function in a ligand binding-independent fashion. Experiments using RNA interference will determine if GR is necessary for the anti-inflammatory and anti-cancer effects of UA in various cell lines. Overall, these studies may inspire the development of the RES and UA combination or mechanistically similar synergistic drug combinations as potent preventers of skin cancers or other cancer types. •



Chantell Evans

University of Wisconsin-Madison

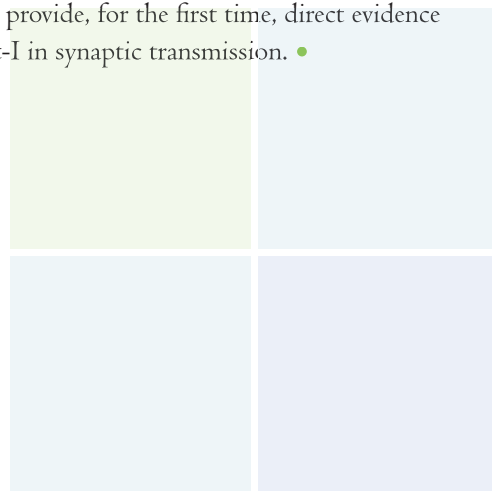
“Direct Implication of the Functional Role of Synaptotagmin-I In Synaptic Transmission”



Chantell Evans

For over 50 years it has been known that the rapid influx of calcium (Ca^{2+}) triggers fusion of synaptic vesicles with the plasma membrane releasing neurotransmitters, thereby mediating neuronal communication. In nerve terminals, the SNARE (soluble [N-ethyl-maleimide-sensitive factor] attachment protein receptor) protein

family is the minimal fusion machinery required for synaptic vesicle fusion. Synaptotagmin (syt)-I is suggested to be the Ca^{2+} sensor that regulates SNARE-mediated fusion. Electrophysiology studies using various divalent cations, in place of Ca^{2+} , revealed strontium (Sr^{2+}), a non-physiological metal, can facilitate synaptic transmission, albeit with altered release kinetics. In addition, *in vitro* assays demonstrated that Sr^{2+} facilitates syt-I binding to its effectors, but fails to stimulate membrane fusion. Interestingly, other syt isoforms can trigger membrane fusion in response to Sr^{2+} *in vitro*. To directly demonstrate syt-I as the sensor for fast synaptic transmission, this study will utilize a novel chemical genetic approach where the metal binding loops of a Sr^{2+} activated syt isoform will be grafted onto syt-I. Thereby, making the syt-I chimera able to transduce Sr^{2+} to fast fusion *in vitro* and to fast synaptic transmission in syt-I knockout neurons. These results will provide, for the first time, direct evidence for the role of syt-I in synaptic transmission. •



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 intent of this program is to support post doctoral career development activities of individuals 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.

2012 Post Doctoral Fellowship in Pharmacology/Toxicology

Lauren Holden, Ph.D.

University of California, San Diego

“Structural Characterization of the Pro-Inflammatory Chemokine Receptor CCR1”



Lauren Holden, Ph.D.

Chemokines and their receptors are critical mediators of cell migration during development, routine immune surveillance, and inflammation. Under normal physiological conditions, chemokines function by binding G-protein coupled receptors (GPCRs). Ligand binding causes specific conformational changes in the

receptor that trigger equally specific intracellular signaling pathways involved in cell movement and receptor activation. Inappropriate expression of chemokines or signaling through their receptors contributes to the pathology of many autoimmune diseases, as well as numerous cancers. CCRI, in particular, is a chemokine receptor that has generated a lot of interest because of its involvement in the development of many inflammatory diseases, including multiple sclerosis and rheumatoid arthritis. The aim of this proposal is to solve the structure of the chemokine receptor CCRI in complex with small molecule antagonists. The data from this study will provide valuable insight into structural mechanisms for inhibiting the function of CCRI, which can be used to

aid the future development of drugs targeting CCRI. The results will also provide a springboard for determining structures of other chemokine receptors involved in inflammatory and other diseases. ●

Uyen Chu, Ph.D.

University of Wisconsin-Madison

“Peri-harvest ERK5 Transactivation by Pitavastatin for Cardiac Preservation”



Uyen Chu, Ph.D.

Heart transplantation remains the best therapeutic option for patients with end-stage cardiac failure. However, one of the major challenges limiting short- and long-term survival of recipients is graft failure stemming from insults associated with ischemia reperfusion (I/R) injury and depletion of energy stores in the

transplant tissue. Thus, there is a continual need for improvements to the current transplantation technology especially organ preservation post-harvest and *en route* to implantation into the patient. Previously, it was shown that transgenic mice expressing the cardiac-specific constitutively active kinase MEK5alpha, protected the heart from I/R injury. MEK5alpha is the upstream MAPK-kinase responsible for the activation of the terminal MAPK ERK5, indicating a

therapeutic potential of ERK5 activation in cardiac protection. Using a one-hybrid system measuring ERK5 transcriptional activation, the commonly prescribed anti-hyperlipidemic drug pitavastatin (Livalo) was identified as a lead compound that activates ERK5. Further research has uncovered that other members of the statin family agents (simvastatin or Zocor®) can also activate ERK5. The

current research project is aimed to (1) explore the mechanism underlying the cytoprotective effect of ERK5 transactivation by pitavastatin in cultured human ventricular myocytes and (2) to determine the efficacy of donor pre-treatment by pitavastatin on post-harvest ischemic tolerance and cardiac function in rats using the Langendorff model. ●

Sabbatical Fellowship in Pharmacology/Toxicology

This program provides stipend funding to enable faculty members at all levels with active research programs an opportunity to work at other institutions for periods of six months to one year to learn new skills or develop new collaborations that will enhance their research and research training activities in pharmacology. The Sabbatical Fellowship provides up to \$40,000 for one year of stipend funding.

2012 Sabbatical Fellowship in Pharmacology and Toxicology

Jean-Christophe Rochet, Ph.D.

Purdue University

“Role of Age-Related Autophagy Impairment
in Parkinson’s Disease Pathogenesis”



Jean-Christophe Rochet, Ph.D.

Parkinson’s disease (PD) is a debilitating disorder of the central nervous system that disrupts the lives of ~5 million people worldwide. The disease involves the death of neurons in a region of the brain called the *substantia nigra*, and surviving neurons often contain aggregated (entangled) forms of the protein α -synuclein. The risk of PD

increases with aging and with a variety of ‘PD stresses,’ including (i) genetic features that cause an increase in α -synuclein levels, and (ii) exposure to pesticides and herbicides commonly used in rural areas. Current therapies only temporarily relieve symptoms without slowing the underlying neuronal loss. Thus, there is a critical need for drugs that prevent the death of neurons in the brains of PD patients. The overall objective of the research supported by the

Sabbatical Fellowship is to determine whether PD stresses such as those outlined above have an enhanced toxic effect in aged cells or mice. The central hypothesis of this project is that aging renders neurons in the *substantia nigra* more vulnerable to PD stresses via a mechanism involving disruption of autophagy, a cellular ‘waste disposal’ system involving the destruction of harmful, aggregated proteins. This hypothesis will be tested by determining the amount of cell death caused by rotenone or α -synuclein in a cell culture model under conditions of normal or accelerated aging. A second approach will be to monitor movement abnormalities and neuron death caused by α -synuclein in normal versus rapidly aging mice. Both the cellular and animal models will be examined for evidence of defects in autophagy. The results of these studies will improve our understanding of how aging increases the risk of PD, and they will stimulate the development of new ways to treat this devastating syndrome. ●

Research Starter Grant in Pharmacology/Toxicology

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 \$60,000 for one year. 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.

2012 Research Starter Grant in Pharmacology and Toxicology

Travis Salisbury, Ph.D.

Marshall University School of Medicine

“The Aryl Hydrocarbon Receptor Mediates Adipose-Breast Cancer Cell Interactions”



Travis Salisbury, Ph.D.

The present high rates of obesity in the United States have raised concerns regarding the influence of obesity on several human diseases including cardiovascular disease, diabetes, and cancer. Epidemiological reports indicate that obesity increases the risk for multiple types of cancers including: liver, endometrial, colon and

breast cancer in postmenopausal women. Adipose tissue is known to secrete a multitude of bioactive signaling molecules such as adipokines, growth factors, proinflammatory proteins and hormones that are capable of stimulating tumor angiogenesis, metastasis and growth. Therefore, obesity associated increases in cancer risk could in part be attributed to increased levels of adipocyte derived signaling factors within the circulation or tumor microenvironment that have tumor promoting capability. The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor. This receptor is known to mediate the toxic effects of environmental toxicants as well as the cancer chemopreventive effects of compounds found in cruciferous vegetables. The objectives of this proposed work are based on findings suggesting that adipocytes secrete signaling molecules that stimulate the growth of breast cancer cells through AHR dependent mechanisms. Gene expression profiling experiments have identified that the expression of E2F4 in human breast cancer cells is dependent on the AHR. Given these novel findings, the objectives of this proposed project are to investigate whether adipocyte secreted growth factors

stimulate tumor growth by stimulating the expression of E2F4 through an AHR dependent mechanism. The hypothesis that chemopreventive AHR ligands inhibit breast cancer cell growth by reducing the expression of E2F4 will also be investigated. The findings of this work will provide greater insights into how adipocytes stimulate cancer growth, and will lead to novel cancer therapies involving the AHR. •

Patrick T. Ronaldson, Ph.D.

University of Arizona

“Blood-to-CNS Delivery of Neuroprotective Drugs during Hypoxia/Reoxygenation”



Patrick T. Ronaldson, Ph.D.

Stroke is the third most common cause of death in the United States and is the number one cause of long-term morbidity. Of all strokes, 86% are ischemic and are demarcated by restricted blood flow and oxygen supply to part of the brain. Ischemic stroke causes an irreversibly damaged ischemic core and salvageable surrounding tissue known as the penumbra. The primary goal of drug therapy for acute ischemic stroke is to salvage the penumbra as much as possible and as early as possible. There is only one therapeutic agent approved by the FDA for acute ischemic stroke treatment, recombinant tissue plasminogen activator (r-tPA). The objective of r-tPA therapy is to restore blood flow and oxygen supply to ischemic brain tissue; however, considerable cellular damage to the brain occurs

when cerebral perfusion is re-established, a critical “component” of ischemic stroke known as hypoxia and reoxygenation (H/R) injury. Therefore, there is a critical need in stroke therapy for neuroprotective and/or antioxidant drugs that can be delivered to the brain for “rescue” of salvageable neural tissue. The laboratory is particularly intrigued by recent evidence demonstrating that 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (i.e., statins) exhibit neuroprotective and antioxidant properties in the central nervous system (CNS) independent of effects on cholesterol biosynthesis. A critical limiting factor in use of statins as neuroprotective/antioxidant drugs in management of stroke is the fact that brain delivery of such therapeutics is highly restricted by the blood-brain barrier (BBB). An alternative approach to optimize CNS drug delivery is to target endogenous BBB transporters such as organic anion transporting polypeptide 1a4 (Oatp1a4) that are involved in blood-to-CNS transport of statins. Oatp1a4 functional expression at the BBB is regulated by transforming growth factor- β (TGF- β) signaling mediated by activin receptor-like kinase (ALK)-5. Pharmacological targeting of TGF- β /ALK5 provides a novel approach for controlling Oatp1a4 expression/activity for optimization of CNS drug delivery in the context of ischemic stroke. Studies supported by this PhRMA Foundation Research Starter Grant in Pharmacology/Toxicology will investigate effects of H/R (using a well established *in vivo* rodent model) on Oatp1a4 mediated transport of statins at the BBB. These studies will also establish how TGF- β /ALK5 signaling modulates CNS statin delivery via regulation of Oatp1a4 at the BBB. This work is clinically significant because it will point to endogenous transporter targets that can be exploited for optimization of CNS drug delivery. Such studies will elucidate approaches that will provide novel therapeutic options and, therefore, improve overall health for stroke patients. •

Seena Ajit, Ph.D.

Drexel University College of Medicine

“The Role of Methylation in Pain”



Seena Ajit, Ph.D.

According to American Academy of Pain Medicine, pain affects more Americans than diabetes, heart disease and cancer combined. Pain and analgesia cannot be attributed to genetics alone because only a modest percentage of the trait variance is accounted for by the associated genes. Epigenetics has been predicted to play a key

role in pain and analgesia both in terms of influencing pro- and antinociceptive gene expression and in modulating pharmacodynamic or pharmacokinetic properties of analgesics.

Epigenetic modification resulting from DNA methylation plays a critical role in cellular differentiation, development and disease. The epigenome is variable in different tissues and is constantly changing in response to cues from internal and external environments. Determining the methylome of spinal cord (SC) in a rodent model of inflammatory pain will help us determine the epigenetic changes in pain state. The proposed study will investigate changes in DNA methylation in SC from a mouse model of inflammatory pain using reduced representation bisulfite sequencing, a technique recommended as a viable compromise between breadth and depth of sequencing.

In somatic cells epigenomic changes are heritable but could potentially be reversed with drug treatments. Several inhibitors targeting enzymes responsible for epigenetic modifications, such as histone deacetylase and DNA methyl transferase inhibitors have been either approved or are in clinical trials for treating cancer. There is increased interest in exploring the utility of inhibitors targeting enzymes responsible for inducing epigenetic changes beyond oncology. DNA methyl transferase inhibitors will be used as pharmacological tools to assess if methylation changes can alter pain sensitivity in rodent models. This project will also assess alterations in gene expression of key epigenetic regulators to understand the molecular changes underlying pain. A multipronged approach combining next generation sequencing to characterize the epigenome of SC along with pharmacological and behavioral studies will help elucidate the role of methylation in pain. Results from these studies can provide a new context in the quest for understanding complex disease etiologies. •

HEALTH OUTCOMES

Pre Doctoral Fellowships in Health Outcomes

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

The fellowship program provides a stipend of \$25,000 annually for up to two years. Up to \$1,000 a year of the funding may be used for incidentals directly associated with the preparation of the dissertation.

2012 Pre Doctoral Fellowship in Health Outcomes

Emily Reese

University of Maryland

“The Need to Conduct Future Research on the Benefit of the Prostate Specific Antigen Screening Test Using the Value of Information Framework”



Emily Reese

The National Cancer Institute estimated that in 2011 approximately 240,000 new prostate cancer (PC) cases were diagnosed and was responsible for over 33,000 deaths. As with other forms of cancer, early detection of PC through screening can increase survival. The main screening test for PC is the prostate specific antigen (PSA) test which measures the level of PSA in a man's blood. Though PSA screening has resulted in high numbers of early stage PC diagnosis, the test has a very high false positive rate. Experts have voiced concerns regarding the test's usefulness in the clinical setting and randomized clinical trials report conflicting results with the PSA screening test's ability to reduce death associated with PC. Practice recommendations and clinical guidelines from professional organizations are also mixed regarding the appropriateness of PSA screening for PC and its ability to reduce PC mortality. The lack of consensus regarding the use of PSA creates a challenge to both healthcare providers and patients when trying to make informed treatment decisions about PC. This study seeks to establish the value of PSA screening research and to determine whether future research should be focused on specific populations (i.e. African Americans, men aged

greater than 65 years of age), through use of the value of information framework. Value of information provides a framework for estimating the expected benefits of clinical research by focusing on uncertainty in a decision. First, this study will estimate the expected value of information from PSA screening based on findings from published randomized controlled trials. With this estimate, the population-level expected value of information will be established for male Medicare beneficiaries. Finally, the expected value of perfect information, or the most the US government should spend to resolve uncertainty in the use of the PSA screening test for the male Medicare population, will be estimated. Though commonly used to prioritize research in Europe, this study will be among the first in the US to use a value of information framework to establish the value of pursuing future PSA research and what groups of male Medicare beneficiaries benefit most from this research. •

Melea Ward

University of North Carolina at Chapel Hill

“A Comparative Effectiveness Analysis of Patients Newly Initiating Tyrosine Kinase Inhibitor Therapy for Chronic Myeloid Leukemia”

Chronic myeloid leukemia (CML) accounts for 15% of adult leukemias. There are currently three oral oncology agents known as tyrosine kinase inhibitors (TKIs) approved

for the first-line treatment of CML, imatinib, dasatinib, and nilotinib. Historically, imatinib was the only TKI approved for first-line treatment of CML and the second-generation TKIs, dasatinib and nilotinib, were approved as second-line treatment for CML patients who were resistant or intolerant to imatinib. During the middle of 2010, both dasatinib and nilotinib received FDA approval as first-line treatment options for CML. No study has directly compared imatinib and second-generation TKIs for patients newly initiating therapy using observational data. The proposed research is a

secondary data analysis of commercial fully-insured and Medicare adult patients newly initiating TKI therapy following first-line approval of the second-generation TKI therapies. The results from the proposed study will be used to inform payers and clinicians through a comparative effectiveness analysis. •



Melea Ward

Post Doctoral Fellowships 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 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 \$55,000 annual stipend for up to two years.

2012 Post Doctoral Fellowship in Health Outcomes

Dominique Comer, PharmD

Thomas Jefferson University

“A New Frontier: Using Linked Pharmacy Data to Understand Primary Nonadherence and Therapeutic Inertia in Hypertension”



Dominique Comer, PharmD

Optimal hypertension management requires the cooperation of both the patient and the provider. However, medication nonadherence and therapeutic inertia are common in clinical practice and contribute to poor long-term blood pressure control. The adoption of electronic prescribing systems, in which prescriptions

are directly linked to pharmacy claims, creates an opportunity to understand the association of adherence and inertia in practice and to use this knowledge to develop targeted interventions to measure and improve blood pressure control in routine care. In addition, this proposal demonstrates the

breadth of data that will be available in a state-wide health information exchange database and how researchers will be able to use such data in the future. The aims of this proposal are to identify patients at high risk of primary nonadherence and to determine the impact of primary nonadherence on therapeutic inertia in clinical practice. Multi-payer pharmacy data gathered through the electronic prescribing network will be merged with clinical records available in the electronic health record. A retrospective cohort study of patients prescribed a new antihypertensive medication will be conducted. Following the completion of these aims, predictions will be drawn for primary non-adherence in clinical practice using readily available demographic and clinical data to understand the implications of nonadherence on measures of therapeutic inertia. •

Heidi S. Wirtz, MS, PharmD

University of Washington

“Comparative Effectiveness Research in Colorectal Cancer”



Heidi S. Wirtz, MS, PharmD

Each year in the United States approximately 140,000 people are diagnosed with colorectal cancer (CRC), and currently there are more than 1.1 million CRC survivors. CRC survivors face an increased risk of local recurrence and second primary cancer. Finding effective ways to prevent CRC recurrence and improve survivorship care is

therefore a critical public health goal. One important consideration for CRC survivors is the effect of medications on recurrence risk. Although common medications have been linked to primary CRC risk, little is known about how these common medications affect CRC recurrence. Surveillance is also a principal part of long-term CRC follow-up care, yet many CRC survivors do not undergo surveillance colonoscopy. Previous studies that have

examined variation in the use of surveillance among CRC survivors are limited to only the first one to two years post-treatment, and have not examined determinants of CRC surveillance over time. Comparative effectiveness research (CER) methods can be used to address these important questions. The overall goal of this research project is to design and conduct CER studies that will inform decision-making in CRC treatment and survivorship care. The objectives of the research plan are threefold:

1) To evaluate the association between common medication exposure and CRC recurrence; 2) To conduct a value of information analysis to determine the impact of clinical trial evidence in evaluating the use of commonly used medications as adjuvant therapy in CRC treatment; and 3) To evaluate factors associated with surveillance utilization among CRC survivors. The research will assess the complex implications of survivorship care and its influence on CRC recurrence as well as inform policy decisions about CRC research priorities. •

Research Starter Grants 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 \$60,000 for one year. 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.

2012 Research Starter Grant in Health Outcomes

Vahram Ghushchyan, Ph.D.

University of Colorado

“Theoretical and Applied Contributions
to the EQ5D Health Utility Index”



Vahram Ghushchyan, Ph.D.

Health outcomes researchers pioneer quantitative approaches to allocative efficiency of health care resources in order to improve population health. Allocative efficiencies can take the form of maximizing health gains given a fixed budget. Health technology assessment agencies like the National Institute of Health and Clinical Excellence (NICE) define health gains in terms of quality-adjusted life years (QALYs) and use QALYs in cost-effectiveness analyses. Likewise, US payers who care about value-based pricing also seek evidence on efficiency and effectiveness. In order to calculate QALYs, researchers combine survival projections with utility scores over survival intervals. Thus, understanding the pathogenesis of utilities

and how they are associated with various health states is a significant part of health outcomes research worldwide.

Many health utility measures are censored from the top by construction; that is, perfect health takes a value of one. EQ5D is a commonly used patient reported outcome that is mapped to utility scores for various populations. There is a gap, however, in defining the optimal regression method for estimating population average utility scores from the EQ5D Index for health states. Current research will fill this gap in the literature on robust regression methods for utilities by bridging statistical and simulation methods to determine a robust estimation technique for researchers constructing QALYs. An optimal modeling approach will be derived and using this new approach a registry of preference-based QALYs based on the EQ5D will be developed in the Medical Expenditure Panel Survey (MEPS), a large-scale nationally representative federally-funded data. •

PHARMACEUTICS

Pre Doctoral Fellowships in Pharmaceuticals

This program has been in effect for 24 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 \$1,000 a year may be used for incidentals directly associated with the preparation of the dissertation. Seven fellowships were granted in 2012.

2012 Pre Doctoral Fellowships in Pharmaceuticals

Sweta Modi

University of Kentucky

“Mechanism Based Liposome Loading Strategies and Predictive Release Kinetics of Hydrophobic and Hydrophilic Anticancer Agents”



Sweta Modi

The greatest challenge in cancer chemotherapy is reducing drug toxicity to normal cells. One potential way of accomplishing this is through the design of drug delivery systems that more efficiently target cytotoxic drugs to tumors. Drug-loaded nanoparticles such as liposomes are of great interest for treating solid

tumors because the poorly developed microvasculature in rapidly growing tumor tissue enables nanosized particles in the blood circulation to infiltrate tumor tissue and accumulate. For nanoparticles to be optimally effective, reliable methods are needed to achieve maximum drug loading, retention of the drug prior to nanoparticle accumulation in the tumor, and controllable drug release rates in the tumor tissue. The main objective of the current project is to truly enable quality by design in the formulation of liposomal delivery systems by developing comprehensive, mechanism-based mathematical models to describe drug loading and

release kinetics, taking into account not only the therapeutic requirement but the physicochemical properties of the drug, the liposome, the intraliposomal microenvironment, and the local environments that the liposomes may encounter *in vivo*. Strategies to maximize loading of poorly soluble drugs into liposomes are of particular interest due to the low aqueous solubility of many anticancer agents. Both loading and release kinetics will be examined using liposomes varying in phospholipid composition and model drugs having different physico-chemical properties. Mathematical models will be developed and tested against the experimental results for their ability to accurately predict the extent of drug loading and release kinetics. The mechanism-based models to be developed, if successful, will be useful tools in designing liposomal drug delivery systems with tailored release profiles that can be modified depending on the therapeutic requirement (type of tumor, tumor size and growth rate, etc.). Better understanding of the physicochemical factors governing drug loading of nanoparticles and drug release kinetics should facilitate the clinical application of nanotechnology for treating cancer patients. •

Poonam Sheth

University of Arizona

“Understanding Aerodynamic Particle Size Distributions from Pressurized Metered-Dose Inhalers by Design”



Poonam Sheth

There is a fundamental gap in understanding and predicting how device, formulation and drug substance variables affect the overall product performance of combination pressurized metered-dose inhalers (pMDIs), where at least one of the two drugs is in suspension. It is hypothesized that a computational model, based on statistics and physical chemistry, can predict the aerodynamic particle size distribution (APSD) of combination pMDI formulations. Guided by strong preliminary data, this hypothesis will be evaluated through two specific aims: model and validation of APSD prediction for pMDIs with 1) one drug in suspension and one in solution and 2) both drugs in suspension. Under the first aim, an already proven pMDI model for one suspended drug will be modified to include a drug in solution. To achieve the second aim, with the input of the size distribution of two suspended drugs, the particles per unit volume and the Poisson distribution of the model will be modified to account for two drugs with different size distributions. The project will provide computational algorithms (supported by experimental data) that will improve the understanding of critical parameters on product performance minimizing the need for burdensome testing and affording the development of pMDIs through quality by design. •

Jonathan Sockolosky

University of California, San Francisco

“Engineering FcRn-mediated Recycling and Transcytosis in Recombinant Proteins to Improve Pharmacokinetics and Delivery”



Jonathan Sockolosky

Over the last two decades a variety of highly successful, FDA approved protein-based therapies have been devised by the biotechnology industry, and the interest in developing protein-based drugs continues to grow. However, a number of challenges impede the more widespread use of proteins as drugs including: their rapid elimination from circulation, the need to dose proteins via injection, and costly protein manufacturing. Strategies that overcome these limitations could decrease dosing frequency and cost of therapy as well as improve patient convenience and compliance. The focus of this research is to design more convenient protein therapeutics by enabling non-invasive administration and increasing their duration of activity through prolonged circulation. One clinically successful tactic to improve both protein circulation and delivery is to fuse the Fc-domain of immunoglobulin G (IgG) to therapeutic proteins so that the resulting fusion proteins interact with the human neonatal Fc receptor (FcRn), which enables transport of proteins across epithelial barriers and protection from intracellular degradation. Although successful, Fc-fusion proteins significantly increase molecular weight thereby restricting tissue penetration, decrease protein function, and are mainly limited to mammalian expression systems. As an alternative to grafting the high molecular weight Fc-domain to therapeutic proteins, we have modified their N- and/or C-terminus with a short peptide sequence that interacts with FcRn, termed “FcBP fusion.” The small size and simple structure of the FcRn binding peptide (FcBP) allows for expression of FcBP fusion proteins in *E. coli* and results in their pH-dependent binding to FcRn with an affinity comparable to that of IgG. The FcBP fusion proteins are internalized, recycled and transcytosed across cell monolayers that express FcRn. This strategy has the potential to improve protein transport across epithelial barriers, which could lead to non-invasive administration, and also enable longer half-lives of therapeutic proteins. •

Regina Bis

University of Colorado at Denver

“Mechanisms of Therapeutic Protein Aggregation Induced by Antimicrobial Preservatives”



Regina Bis

All multi-dose pharmaceutical formulations contain at least one preservative in order to combat the growth of bacteria. However, these preservatives can lead to protein instability and aggregation, decreasing the efficacy of the therapeutic as well as leading to toxic immunogenic responses in patients. In order

to create more stable and effective protein drugs, further aggregation studies are needed in the presence of critical additives found in formulations. Based on preliminary data, the hypothesis for this work is that the unfolding of the least stable regions in a protein initiate aggregation, and that these regions can be stabilized to prevent AP-induced aggregation. Specifically, preservatives perturb the equilibrium distribution of structural states available to the protein, causing a shift to a partially unfolded, aggregation-prone state. Previous work with cytochrome c (cyt c) demonstrated that a local region of the protein was destabilized while global stability remained unchanged in the presence of both benzyl alcohol and m-cresol. This work also showed that stabilizing this particular region attenuated aggregation. Similar effects using other preservatives have also been shown with cyt c. This protein is an ideal model system due to its well-characterized biophysics and solution behavior. Cyt c also offers unique optical probes arising from its iron heme. Most pharmaceutically relevant proteins are not well understood in their biophysics and solution behavior; hence the use of model proteins. However, these models may complicate the data. Experimentation on pharmaceutically relevant systems is necessary to obtain meaningful data on protein stability in therapeutic formulations. In this work, a pharmaceutically relevant protein, interferon α -2a, will be studied in the presence of antimicrobial preservatives. This protein has been marketed as Roferon[®], and the AP benzyl alcohol is used in its formulation. Interferon α -2a has been shown to aggregate and the immunogenic effect of these aggregates has been demonstrated. For studying aggregation, various biophysical techniques will be utilized that include

denaturant melts to probe protein stability changes, isothermal kinetics to monitor aggregation, and heteronuclear 2D NMR to monitor the effect of APs on protein structure. The final aim is to identify the local region that initiates aggregation and stabilize it with site-specific mutations to create an aggregation-resistant interferon α -2a. •

Tanya Clapp

University of Colorado at Denver

“Novel Approaches to Address the Instability of Vaccines with Aluminum-Containing Adjuvants”



Tanya Clapp

Aluminum-containing adjuvants have been formulated in vaccines to enhance the immune response against killed, inactivated and subunit antigens for decades. These adjuvants are in FDA-approved vaccines for half of the pathogens against which the CDC recommends all children be vaccinated, such as hepatitis B

(HBsAg), diphtheria, tetanus, and acellular pertussis (DTaP), Haemophilus influenzae type B (HiB), and human papillomavirus (HPV) vaccines. However, fundamental questions regarding stability and stability-related efficacy remain. It is widely accepted that formulations with aluminum-containing adjuvants results in vaccines efficacy losses if frozen. The potential for inadvertent exposure to freezing temperatures is unfortunately a real threat to vaccine products in both high and low resource countries. This project is designed to close the knowledge gap regarding the importance of general parameters of vaccine formulation to increase vaccine stability, with a focus on freeze-thaw exposure. Freeze-thaw agglomeration of the vaccine adjuvant particles has been blamed for loss of vaccine efficacy. This is regardless of the thermal stability of the antigen; though, some antigens are sensitive to freeze-thaw stress. Formulation strategies have been used to address particle agglomeration, although these required high concentrations of excipients. One aim of this research is to investigate the feasibility of engineering this class of adjuvant to have enhanced inherent stability against freezing induced agglomeration. The effect that this has on the adjuvant's ability to enhance the immune response will be evaluated. A second aim has its basis in the long-held theory that

formulating a vaccine to maximize antigen adsorption onto the adjuvant is best to elicit the most robust immune response. Several studies have suggested that tight interactions between the antigen and adjuvant can alter antigen conformation and stability. This project, therefore, investigates to what extent these interactions affect vaccine efficacy, especially following exposure to subzero temperatures. Data from particle size analyses, spectroscopic studies, and in vivo tests will be used to investigate both aims. The results have the potential to impact the current design of human vaccines with far reaching implications on a global scale. •

Matthew Herpin

University of Texas at Austin

“Aerosol Formulations for Ocular Drug Delivery”



Matthew Herpin

Currently, the majority of ophthalmic medications are delivered topically to the eye in the form of liquid droplets. There are several significant problems associated with patient self-administered eye drops. Firstly, the amount of liquid dispensed is very large compared to the actual capacity of the eye. This causes an

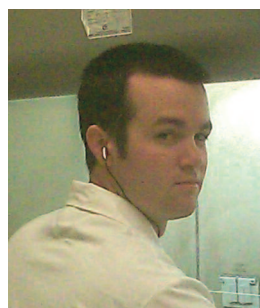
unpredictable amount of retention, overflow and potential systemic absorption. When this occurs, it is difficult to determine how much of the medicine actually is delivered to the site of action. In addition to drop overflow, the eyes are sensitive to the amount of liquid present. This helps regulate and control tear production and clearance of foreign material. When a droplet size volume of liquid is added to the eye, tear production is stimulated and the eye begins to wash away the material and reducing the amount available for action. Therefore, minimizing the volume of liquid administered, increasing the reproducibility of delivered dose, and minimizing off-target drug absorption are of utmost importance in this field. This project is focused on the development of a formulation and method for precise and accurate delivery of medicine to surface of the eye via a novel aerosol delivery system. The characteristics of the aerosol can be finely tuned so that an accurate dose can be emitted and deposited comfortably on the eye surface. Furthermore, because the medication is in an aerosolized

form; it does not carry the excessive liquid which would promote tear production and clearance. A major effort will be put forth in determining the essential parameters that will affect ophthalmic dosing and deposition for improved therapy. By precisely and accurately controlling drug administration, the negative effects of over and under-dosing can be eliminated thus improving safety and efficacy for existing approved drugs. In addition, compounds that were previously assumed too risky for this route due their narrow therapeutic window may now be considered and may open new doors and alternatives for current treatment of the myriad of ophthalmic conditions. •

Robert Price

University of Utah

“Nanofabrication of Genetically Engineered Polymers for Delivery to Solid Tumors”



Robert Price

The research proposed research focuses on the development of a system to fabricate non self-assembled nanoparticles from protein based polymers for use in drug and gene delivery. The use of recombinant DNA technology has lead to the ability to use cells to synthesize protein polymers of precise sequence and

length that have been used for a number of applications. Despite this fine control, these polymers have yet to be exploited for use as non self-assembled nanoparticles for delivery of gene or drug products to tumors. As a result of this control, the ability to tune the release characteristics of these particles by selectively altering the amino acid sequence of the polymers from which they are formed is afforded. The direct control over the amino acid sequence of the polymers being used also allows for the possible incorporation of targeting, environmentally responsive, or other functionalities at a later time. This proposal aims to use Silk-Elastinlike Protein Polymers (SELPs) to form these nanoparticles. It is believed that the ability to tune the properties of the nanoparticles formed will lead to a system able to carry a wide range of bioactive agents and allow for the particle properties to be optimized for each application. •

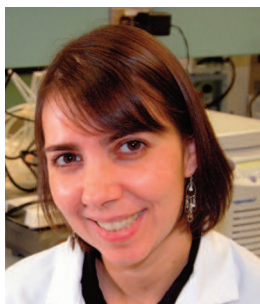
Research Starter Grants in Pharmaceuticals

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 \$60,000 for one year. 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.

2012 Research Starter Grant in Pharmaceuticals

Luciana Lopes, Ph.D.

Albany College of Pharmacy and Health Sciences
“Microstructured Systems for Topical Delivery of Anticancer Agents”



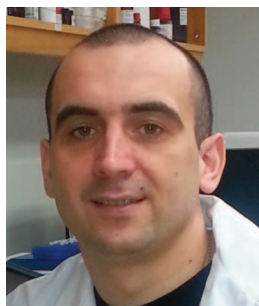
Luciana Lopes, Ph.D.

Paclitaxel is a highly efficacious drug against multiple tumors, including those that affect the skin. However, the usefulness of paclitaxel for treatment of skin tumors is limited by the serious adverse effects associated with the systemic administration of the drug, which include hypersensitivity reactions and

neutropenia. To enable the use of paclitaxel in cutaneous disorders, this project proposes the development of topical delivery systems that can localize the drug within skin lesions while reducing its systemic distribution. Considering that paclitaxel is a large non-polar molecule that does not cross efficiently the stratum corneum (the outermost skin layer responsible for the tissue barrier function), its penetration into viable deeper layers where tumors develop requires the use of penetration-enhancing strategies. Cationic microemulsions containing protein transduction domains will be developed to promote paclitaxel delivery into viable cutaneous layers. More specifically, this project aims at evaluating whether and how formulation composition, internal structure and the type of protein transduction domain affect skin permeability, drug delivery to the cutaneous tissue, and formulation safety. Additionally, the efficacy of a selected, optimized formulation against an artificial model of skin cancer will be determined. Upon completion, this project will increase the body of knowledge regarding formulation approaches to promote targeted skin delivery, and bring us closer to a new, safe and effective self-administered treatment strategy for skin disorders. •

Oleh Taratula, Ph.D.

Oregon State University
“Development of Multifunctional Nanomedicine Platform for Combinatorial Treatment of Advanced Prostate Cancer”



Oleh Taratula, Ph.D.

Prostate cancer is a leading cause of cancer deaths among men in the United States. One of the main reasons for the poor survival rate is the absence of an effective therapy for hormone refractory prostate cancer. Therefore, the main objective of the proposed research is an application of a novel combinatorial therapeutic

modality based on synergetic effect of chemotherapy associated with hyperthermia and enhanced by the suppression of cancer cellular resistance to chemotherapeutic agents and heat shock. The proposed approach provides a possibility for the targeted co-delivery of anticancer drugs and nanoheaters specifically to the tumor, local stimulated drug release and mitigation of cancer cell resistance through the development and in vivo evaluation of a novel drug delivery system which contains six main components: (1) superparamagnetic iron oxide nanoparticles (SPION) as the carriers of active ingredients, intratumoral nanoheaters, and drug release stimulator; (2) anticancer drugs; (3) suppressor of pump resistance; (4) suppressor of nonpump resistance (5) suppressor of thermotolerance, and (6) targeting moiety to the prostate cancer cells. This strategy will allow the application of lower concentration of the toxic anticancer agents, decreasing their adverse side effects on healthy tissue and organs. The proposed drug delivery system can lead to direct killing of the tumor tissue quickly, specifically and homogeneously. •

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 five 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.

2012 Paul Calabresi Medical Student Fellowship

Robert Freilich

Boston University School of Medicine

“miR-155 Suppresses Neurogenic Processes
During Inflammation”



Robert Freilich

Neurogenic processes in the Sub-Granular Zone (SGZ) demonstrate incredible responsiveness to the experiences of the individual, such that rewarding experiences enhance and detrimental experiences suppress neurogenesis. Either peripheral inflammation or direct CNS inflammatory challenges are both

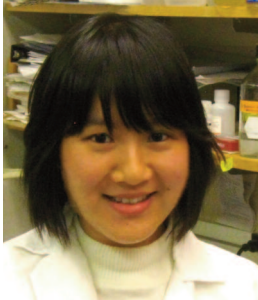
highly detrimental and both have demonstrated the ability to suppress neurogenesis. The project recently identified miR-155 and Interlukin-6 (IL-6) as the most up-regulated miRNA and mRNA respectively, during pro-inflammatory states in microglia, the resident immune cell of the CNS. IL-6 is known to provide swift inhibition of neurogenesis in the SGZ, which we have demonstrated a 50% reduction in IL-6 levels during an inflammatory challenge when miR-155 is inhibited. Further we demonstrate that blockade of IL-6 during inflammation reduced neuronal to astocytic differentiation by greater than 50%. To determine if miR-155

also has the ability to regulate the observed suppression of neurogenesis during inflammatory challenges, miR-155-/- deficient mice were given an MI-skewing challenge, lipo-polysaccharide, Intracerebroventricularly combined with BrdU injections that label newly divided cells. Surprisingly, a deficiency of miR-155 completely ablated the suppression of neurogenic processes of both proliferation and differentiation during inflammation in vivo. Proliferation was reduced by 20% in total BrdU+ cell counts and 31% along the SGZ under WT inflammatory condition, which were restored to control levels under similar inflammatory conditions in miR-155-/- mice. Differentiation, as measured with Doublecortin (DCX) intensity levels, along the SGZ, was also reduced 29% under WT inflammatory challenge, which was restored to control levels under similar inflammatory challenge in miR-155-/- mice. Therefore, this work demonstrates miR-155 has the ability to mediate the suppression observed in neurogenesis during inflammation. ●

Yixi Zhang

Harvard Medical School

“STAT3 Inhibitors in the Targeted Therapy of Ovarian Cancer”



Yixi Zhang

“Ovarian cancer, like many other cancers, is associated with dysregulated cellular signaling pathways. Current therapeutic approaches targeting specific pathways may result in activation of compensatory processes that promote survival and render these therapies less effective. Therefore, understanding the correlations

between several important pro-survival pathways is crucial in the development of targeted ovarian cancer treatment. This research project is focused not only on understanding the STAT3 pathway, which is constitutively activated and indispensable in ovarian cancer cells, but also on other potentially compensatory pathways such as the NFκB pathway. More specifically, the study aims to investigate the mechanisms by which some of the new STAT3 inhibitors work to treat ovarian cancer. Additionally, the project will evaluate the synergistic effects with combinations of inhibitors that would target multiple pro-survival pathways—a more effective chemotherapy. It is anticipated that the results could provide preliminary data for further clinical trials with these STAT3 inhibitors in treating ovarian cancer.” •

Jessica Wilson

University of Illinois, Chicago

“Intersectin1 Links Amyloidogenic Processes in Down Syndrome and Alzheimer’s Disease”



Jessica Wilson

Late-life manifestations of Down Syndrome (DS) are of increasing importance, as DS patients now survive well into middle age. By the age of 35, all DS patients exhibit Alzheimer’s Disease (AD)-like neuropathology and twenty percent are affected clinically. This comorbidity is likely attributed to trisomy of AD-related genes

within the Down Syndrome Critical Region (DSCR) of chromosome 21. Despite its prominent role in AD-pathogenesis, triplication of Amyloid Precursor Protein (APP), a DSCR protein, produces a restricted phenotype compared to the AD-like phenotype produced by triplication of the entire DSCR. This suggests that additional chromosome 21 genes are required for AD development yielding the hypothesis that Intersection1 (ITSNI), a scaffold protein encoded on the DSCR of chromosome 21, contributes to AD pathogenesis. ITSNI is the most highly induced transcript in non-DS cases of AD. Furthermore, ITSNI is overexpressed in DS and differentially expressed in the brains of DS patients with and without AD. Preliminary work in the lab suggests that ITSNI overexpression is sufficient to reduce levels of full length APP and alter the production of specific APP cleavage products, suggesting that ITSNI overexpression may mechanistically enhance APP processing. Conversely, knockdown of ITSNI leads to increased levels of both full-length APP and neuroprotective APP fragments relative to control shRNA. The effect of ITSNI knockdown is paralleled in the brains of ITSNI-null mice, suggesting that ITSNI is an important regulator of in vivo APP processing or trafficking. Based on these data, it is hypothesized that ITSNI overexpression, in DS and AD, increases the processing of APP into neurotoxic cleavage products through JNK pathways and its role in endocytosis. Ongoing experiments will elucidate whether ITSNI’s effect on APP levels and APP cleavage is due to ITSNI’s modulation of pathogenic JNK signaling pathways or ITSNI’s role in endocytosis and protein trafficking. •

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.

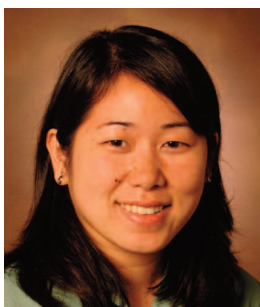
This program was established by the PhRMA Foundation in 1966 in recognition of the many problems involved in evaluating therapeutic agents. Drug investigation is a demanding task. As in nearly every aspect of the health field, manpower needs are acute. This program is intended to meet some of these workforce 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.

2012 Faculty Development Award

Cyndya A. Shibao, M.D.

Vanderbilt University

“Phosphodiesterase-5 Inhibition and
Glucose Metabolism”



Cyndya A. Shibao, M.D.

Each year cardiovascular disease causes the deaths of approximately 54,000 African American women in the United States. Obesity, hypertension and insulin resistance are more prevalent among African American women as compared to men and Caucasians. These conditions put them at increased risk for the development of

diabetes mellitus and cardiovascular disease. Studies in animal models have reported that nitric oxide in addition to its vascular actions modulates insulin metabolic function including glucose uptake in muscle tissue. Mice with disruption of the gene encoding endothelial and neuronal nitric oxide develop insulin resistance. Insulin stimulated

glucose uptake is impaired in animals treated with nitric oxide-synthase inhibitors. In this context, chronic treatment with phosphodiesterase-5 inhibitor which potentiate nitric oxide function, improves insulin resistance in high fat-fed mice. In humans, impaired nitric oxide function has been associated with insulin resistance states. In this regard, African American women are more insulin resistant than Caucasians despite comparable fitness and body fat levels and previous studies have reported impaired nitric oxide function in the vasculature. The overall goal of this research is to determine if prolonged PDE-5 inhibition improves insulin resistance in obese African American women and to understand the molecular mechanism underlying this effect with particular emphasis on insulin signaling in skeletal muscle. •

Comparative Effectiveness Research

The purpose of this program is to provide funding to a U.S. educational institution to develop or expand a degree-granting program in Comparative Effectiveness Research (CER). Each grant will be for \$250,000 to be distributed over three years. The formation of degree-granting programs to expand and improve training in CER methods and application is timely given the passage of Congressional legislation starting a Patient Centered Outcome Related Institution (PCORI), which will increase demand for CER in both the public and private sectors and the shortage of well-trained experts for conducting commonly applied methods, ranging from technology assessments to prospective observational studies and large-scale randomized comparator trials.

Two Center of Excellence for Comparative Effectiveness Research Education awards were given in 2012.

Comparative Effectiveness Research Centers of Excellence

Jodi B. Segal, M.D., MPH

The Johns Hopkins University



Jodi B. Segal, M.D., MPH

The Johns Hopkins University Center of Excellence for Comparative Effectiveness Research (CER) Education continues to work towards establishing a Certificate in Comparative Effectiveness Research. During the past year of funding, the center produced and offered an online course called

An Introduction to Comparative Effectiveness Research. This 3-credit course is offered to enrolled students of the Johns Hopkins University Bloomberg School of Public Health. Most of the lectures were recorded jointly by Dr. Jodi Segal and Dr. Albert Wu, the co-instructor; others were recorded by guests including Dr. Patricia Deverka from the Center for Medical Technology and Policy, and Danielle Whicher from the Berman Bioethics Institute. The course was offered during the first term of the 2012–2013 academic year and was well-received. Next year it will also be available to the students enrolled in the Science of Clinical Investigation certificate program. The second online course that will be supported by the Center of Excellence is now being prepared—this will be a course about the evaluation of healthcare delivery that is currently under development by Dr. Jill Marsteller, a health services researcher. Through these courses, we are able to reach our distance learning students

and to accommodate the diverse learning needs of our on-campus learners. A seminar series was developed in collaboration with the Center for Health Services and Outcomes Research by which they educate the faculty, fellows, and graduate students in our Hopkins community. This seminar series continues and involves presentations from faculty and guests on topics relevant to CER. The seminars that they recently hosted included: Patient Centered Benefit Risk Assessment—Challenges and Opportunities (Sonal Singh M.D., M.PH); The Role of The Patient in Patient-Centered Outcomes Research (John F P Bridges and Chris Carswell, Editors, *The Patient – Patient-Centered Outcomes Research*); Analytical Challenges While Investigating the Association between Physician Unconscious Preference and Clinical Decision Making (Adil H. Haider, MD, MPH); Developing eHealth Applications for Shared Decision-Making in Ambulatory Care (J. B. Jones, Ph.D., MBA, Center for Health Research Geisinger Health System); and Multi-Criteria Decision Analysis: Analytical Hierarchy Process (James G. Dolan, MD, University of Rochester). Finally, in collaboration with researchers from the University of Washington PhRMA Center of Excellence, a proposal was submitted to the Agency for Healthcare Research and Quality to support a conference with the aim of advancing CER curricula nationwide; they look forward to delivering this conference in late 2013 or early 2014. •

Louis P. Garrison, Jr., Ph.D.

The University of Washington



Louis P. Garrison, Jr., Ph.D.

In Fall 2011, working in concert with the UW Graduate School, the members of the Leadership Team for the UW Graduate Certificate in CER (Drs. Lou Garrison, Beth Devine and Anirban Basu), created the new Certificate. The proposal was submitted to the Graduate School on November 28, 2011, and

approved by the UW Board of Regents on January 12, 2012. The CER Certificate is comprised of 19 (Pharmaceutical Outcomes Research & Policy Program) or 17 (Health Services) credit hours of coursework including a capstone project, and varies according to the core curricular requirements for each program. (Table 1) The CER curriculum enhances the current PhD programs in the Pharmaceutical Outcomes and Health Services MS and PhD graduate programs by augmenting the core course requirements in each department, and building on the already solid foundation in epidemiology, biostatistics, health economics and policy for which the UW Schools of Pharmacy and Public Health are noted. The certificate is also available to students in epidemiology, biostatistics, nursing, medicine, economics, and other health-related graduate programs. A noted feature of the CER Certificate curriculum is that the faculty are developing two advanced methods courses that will be offered for the first time in the 2013-2014 academic year as part of the Certificate: 1) Bayesian Statistics for the Health Sciences; and 2) Advanced Methods in CER.

With support provided by the PhRMA Foundation, two awards were created to support graduate students in developing expertise in CER: (1) PhRMA Foundation Pre-Doctoral Fellowship in CER—this fellowship is intended for second or third year PhD students who intend to both complete the CER Certificate and plan to complete a CER-related dissertation. (2) PhRMA Foundation Dissertation Fellowship Program in CER—this fellowship is intended for fourth or fifth year PhD students whose CER-related dissertation is underway, and who need extra support

to purchase a needed dataset or for travel to present CER-related work at national meetings.

As of September 2012, five students had registered and are in the process of completing the coursework for the CER Certificate. Three are PhD students in the Pharmaceutical Outcomes Program (one a PharmD), one a PhD student in Health Services, and one an MPH student in Health Services (a MD). John Dickerson, a PhD student from Health Services applied for and was awarded the fellowship. His dissertation is focused on medication adherence. He is also registered for the CER Certificate.

Members of their Center for Excellence Leadership Team, along with colleague Dr. Jodi Segal from Johns Hopkins University, submitted a Conference Grant to AHRQ to conduct a 100-person “CER Curricular Conference” in October 2013. The specific aims of the conference are five: (1) Review existing competencies that have been proposed for practitioners and users of CER, (2) Describe existing curricula and other approaches that aim to achieve these competencies, (3) Learn about workforce needs for CER-trained researchers, (4) Identify curricular enhancements that can be made to existing CER curricula, and (5) Discuss unique methodological issues of CER unaddressed by related disciplines. Invited attendees will include leaders from academia; pharmaceutical, device and diagnostic industries; key employees of governmental organizations (Centers for Medicare and Medicaid Services, Food and Drug Administration, AHRQ, National Institutes of Health/National Center for Advancing Translational Sciences); accreditation bodies for academic institutions; health plans; health systems; professional organizations; and PhRMA-sponsored pre- and post-doctoral fellows.

The CER Certificate is housed in the UW Centers for Comparative and Health-System Effectiveness (CHASE) Alliance, where resources are consolidated and economies of scale are leveraged for the good of students and faculty alike. The CHASE Alliance brings together successful UW research groups and community partners with a common mission to undertake multidisciplinary, high impact comparative and health systems effectiveness research and implementation. Community partnership institutions include the Fred Hutchinson Cancer Research Center, Group Health Research Institute, and the VA Puget Sound Health Care System. •



The Foundation was honored to present its 2012 awards at distinguished scientific annual meetings throughout the country.

Our thanks to the following organizations:

The American Association of Pharmaceutical Scientists (AAPS)

Chicago, Illinois presented on October 14, 2012

by David Y. Mitchell, Ph.D., AAPS President

The American Society for Clinical Pharmacology and Therapeutics (ASCPT)

National Harbor, Washington, D.C. presented on March 14, 2012

by Darrell R. Abernethy, M.D., Ph.D., Chairman of the Clinical Pharmacology Advisory Committee

The American Society for Pharmacology and Experimental Therapeutics (ASPET)

San Diego, California presented on April 21, 2012

by Terry L. Bowlin, Ph.D., Chairman of the Basic Pharmacology Advisory Committee

The International Conference on Intelligent Systems for Molecular Biology (ISMB)

Long Beach, California presented on July 17, 2012

by Michael N. Liebman, Ph.D., Chairman of the Informatics Advisory Committee

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

Washington, DC presented on June 5, 2012

by Jean Paul Gagnon, Ph.D., Chairman of the Health Outcomes Advisory Committee



BOARD OF DIRECTORS



CHAIRMAN
Elias Zerhouni, M.D.
 President, Global
 Research & Development
 Sanofi
 Paris, France



Mikael Dolsten, M.D., Ph.D.
 President, Worldwide
 Research & Development,
 Executive Vice President,
 Pfizer Inc
 New York, NY



Ivan Gergel, M.D.
 Executive Vice President,
 Chief Scientific Officer,
 R & D
 Endo Health Solutions
 Chadds Ford, PA



Glenn J. Gormley, M.D., Ph.D.
 Global Head, R&D
 and Senior Executive Officer,
 Daiichi Sankyo
 President, Daiichi Sankyo
 Pharma Development
 Edison, NJ



Howard G. Hutchinson, M.D.
 Chief Medical Officer,
 AstraZeneca Pharmaceuticals LP
 Wilmington, DE



Peter S. Kim, Ph.D.
 President,
 Merck Research Laboratories,
 Merck & Co., Inc.
 North Wales, PA



John M. Leonard, M.D.
 Senior Vice President,
 Chief Scientific Office
 AbbVie
 North Chicago, IL



Jan M. Lundberg, Ph.D.
 Executive Vice President,
 Science and Technology,
 President, Lilly Research Laboratories,
 Eli Lilly and Co.
 Indianapolis, IN



John Orloff, M.D.
 Senior Vice President,
 Chief Medical Officer
 Global Development
 Novartis Pharmaceuticals
 East Hanover, NJ



Moncef Slaoui, Ph.D.
 Chairman, Research
 & Development,
 GlaxoSmithKline
 King of Prussia, PA



John Castellani
 President and CEO,
 Ex Officio,
 PhRMA
 Washington, D.C.

TREASURER'S REPORT

The PhRMA Foundation ended 2012 in solid financial shape despite a financially challenging year. Contributions were down 9% from the previous year, to \$2.77 million, including \$200,000 from PhRMA to fund the Young Investigators Adherence Improvement program.

We awarded over \$2.26 million in grants and held down non-grant program and administrative expenses. Total expenditures were \$2.8 million. Net assets at December 31 were \$18.5 million, a 9.7% increase from \$16.9 million the prior year. For the 14th 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.



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 truly appreciate the substantial 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, 2012, has been audited by the accounting firm of Tate and Tryon of Washington, D.C. A full report can be obtained by contacting the Foundation.

A handwritten signature in dark ink that reads "Mikael Dolsten". The signature is written in a cursive, flowing style.

MIKAEL DOLSTEN, M.D., PH.D.

STATEMENT OF INCOME AND EXPENDITURES¹

INCOME	
Contributions (I)	\$ 2,773,205
Contributions – in kind from PhRMA	\$ 35,426
Interest and Dividends	\$ 400,832
(Realized and Unrealized) Gains in Securities	\$ 1,348,498
Other Income	\$ 23,790
TOTAL INCOME	\$4,581,751
EXPENDITURES	
Programs	
Awards in Excellence	\$ 17,005
Clinical Pharmacology Program	\$ 286,500
Health Outcomes Program	\$ 224,000
Informatics Program	\$ 430,000
Pharmaceutics Program	\$ 390,000
Pharmacology Program	\$ 725,000
Comparative Effectiveness Program	\$ 124,998
AFPE Fellowship Award	\$ 7,500
Other Grants	\$ 60,007
Subtotal – Grants	\$2,265,010
Other	
Committee Meetings, Travel and Honoraria	\$ 108,641
Publications and Special Projects	\$ 19,774
Subtotal – Other	\$ 128,415
PROGRAM TOTAL	\$2,393,425
Administrative	
Staff, Taxes, Depreciation & Insurance	\$ 323,492
Rent & PhRMA Accounting Services ²	\$ 35,426
Professional Services and Investment Expenses	\$ 82,137
Office Expenses	\$ 3,047
Subtotal – Administrative	\$ 444,102
TOTAL EXPENDITURES	\$2,837,527

¹ Includes one 2012 contribution received in December 2011

² Rent and Accounting Services are donated by PhRMA

ADVISORY COMMITTEES

SCIENTIFIC ADVISORY COMMITTEE

Darrell R. Abernethy, M.D., Ph.D.

Associate Director for Drug Safety
Office of Clinical Pharmacology
Food and Drug Administration
Silver Spring, Maryland

Terry L. Bowlin, Ph.D.

Chief Executive Officer
Microbiotix, Inc.
Worcester, Massachusetts

Michael J. Hageman, Ph.D.

Group Director
Bristol-Myers Squibb Company
Princeton, New Jersey

Jean Paul Gagnon, Ph.D.

Former Senior Director, Public Policy
sanofi-aventis U.S.
Pittstown, New Jersey

Michael N. Liebman, Ph.D.

Managing Director
Strategic Medicine, Inc.
Kennett Square, Pennsylvania

BASIC PHARMACOLOGY ADVISORY COMMITTEE

Terry L. Bowlin, Ph.D. (Chairman)

Chief Executive Officer
Microbiotix, Inc.
Worcester, Massachusetts

Daniel Acosta, Jr., Ph.D.

Professor of Pharmacology
and Toxicology
College of Pharmacy
University of Cincinnati
Cincinnati, Ohio

Michael D. Ehlers, M.D., Ph.D.

Senior Vice President
Chief Scientific Officer, Neuroscience
Pfizer, Inc.
Cambridge, Massachusetts

Salvatore J. Enna, Ph.D.

Associate Dean for Research &
Graduate Education
Professor, Department of Molecular
and Integrative Physiology
Professor, Department of Pharmacology,
Toxicology and Therapeutics
University of Kansas Medical Center
Kansas City, Kansas

Jeffrey S. Fedan, Ph.D.

Team Leader/Research Physiologist
Pathology and Physiology
Research Branch
National Institute for Occupational
Safety and Health
Centers for Disease Control
and Prevention
Adjunct Professor
West Virginia University
Morgantown, West Virginia

Robert A. Kramer, Ph.D.

Vice President/Head of
Discovery for Oncology
Ortho Biotech Oncology R&D
Johnson & Johnson
Radnor, Pennsylvania

Jerome A. Langer, Ph.D.

Associate Professor
Department of Pharmacology
UMDNJ-Robert Wood Johnson
Medical School
Piscataway, New Jersey

Steven M. Lanier, Ph.D.

Associate Provost for Research
Professor of Pharmacology
Medical University of South Carolina
Charleston, South Carolina

George R. Lenz, Ph.D. MBA

GRLEN R&D Associates
Andover, Massachusetts

Harry LeVine, III, Ph.D.

Associate Professor
Center on Aging, Department of
Molecular & Cellular Biochemistry
University of Kentucky
Lexington, Kentucky

Nancy Pryer, Ph.D.

Director, Oncology Research
Novartis Institutes for
Biomedical Research
Emeryville, California

Gary O. Rankin, Ph.D.

Professor & Chair
Department of Pharmacology,
Physiology & Toxicology
Joan C. Edwards School of Medicine
Marshall University
Huntington, West Virginia

Darryle D. Schoepp, Ph.D.

Senior Vice President & Franchise Head
Neuroscience & Ophthalmology
Merck
North Wales, Pennsylvania

Patricia A. Seymour, Ph.D.

PAS Psychopharmacology Consulting
Westerly, Rhode Island

James J. Starling, Ph.D.

CSO-Oncology-Biology
Eli Lilly and Company
Indianapolis, Indiana

Stephanie W. Watts, Ph.D.

Professor, Pharmacology & Toxicology
Assistant Dean, The Graduate School
Michigan State University
East Lansing, Michigan

Megan Yao, Ph.D.

Vice President Oncology
Translational Medicine
ImClone Systems, a wholly owned
subsidiary of Eli Lilly & Company
New York, New York

Frank D. Yocca, Ph.D.

Vice President, Strategy and
Externalization
AstraZeneca Neuroscience
Cambridge, Massachusetts

**CLINICAL PHARMACOLOGY
ADVISORY COMMITTEE**

**Darrell R. Abernethy, M.D., Ph.D.
(Chairman)**

Associate Director for Drug Safety
Office of Clinical Pharmacology
Food and Drug Administration
Silver Spring, Maryland

Arthur J. Atkinson, Jr., M.D.

Adjunct Professor
Department of Molecular
Pharmacology and Biochemistry
Northwestern University
Chicago, Illinois

Terrence F. Blaschke, M.D.

Professor of Medicine and Molecular
Pharmacology (Active Emeritus)
Medical Student Academic
Advising Dean
Division of Clinical Pharmacology
Stanford University, School of Medicine
Stanford, California

Perry V. Halushka, M.D., Ph.D.

Professor of Pharmacology
and Medicine
Dean, College of Graduate Studies
Medical University of South Carolina
Charleston, South Carolina

Steven Ryder, M.D., FACP

President
Astellas Pharma Global Development
Deerfield, Illinois

**COMPARATIVE
EFFECTIVENESS RESEARCH
ADVISORY COMMITTEE**

Jean Paul Gagnon, Ph.D. (Chairman)

Former Senior Director, Public Policy
sanofi-aventis US
Pittstown, New Jersey

Jesse A. Berlin, ScD

Vice President, Epidemiology
Johnson & Johnson
Titusville, New Jersey

Beth Devine, PharmD, MBA, Ph.D.

Associate Professor
Pharmaceutical Outcomes Research
& Policy Program
University of Washington
Seattle, Washington

Daniel C. Malone, Ph.D., R.Ph.

Professor
Pharmacy Practice and Science
University of Arizona College
of Pharmacy
Tucson, Arizona

Martin D. Marciniak, M.P.P., Ph.D.

Vice President, U.S. Health Outcomes
GlaxoSmithKline
Research Triangle Park, North Carolina

C. Daniel Mullins, Ph.D.

Professor
Pharmaceutical Health Services
Research Department
Associate Director, Center on Drugs
and Public Policy
University of Maryland School
of Pharmacy
Baltimore, Maryland

Michael D. Murray, PharmD, MPH

Distinguished Professor and Endowed
Chair for Medication Safety,
Purdue University
Executive Director, Regenstrief Center
for Healthcare Effectiveness Research
Indianapolis, Indiana

**Nancy C. Santanello, M.D., MS,
FISPE**

Vice President, Epidemiology
Merck Research Laboratories
North Wales, Pennsylvania

**HEALTH OUTCOMES
ADVISORY COMMITTEE**

Jean Paul Gagnon, Ph.D. (Chairman)

Former Senior Director, Public Policy
sanofi-aventis US
Pittstown, New Jersey

J. Lyle Bootman, Ph.D., Sc.D.

Senior Vice President for Health
Sciences
Dean, College of Pharmacy
Professor of Pharmacy, Medicine
and Public Health;
Founding Executive Director
Center for Health Outcomes and
PharmacoEconomic (HOPE)
Research
Arizona Health Sciences Center
The University of Arizona
Tucson, Arizona

Geoff Makinson, Ph.D.

Senior Director, Global Market Access
Pfizer Inc
New York, New York

C. Daniel Mullins, Ph.D.

Professor
Pharmaceutical Health Services
Research Department
Associate Director, Center on Drugs
and Public Policy
University of Maryland School
of Pharmacy
Baltimore, Maryland

**Nancy C. Santanello, M.D., MS,
FISPE**

Vice President, Epidemiology
Merck Research Laboratories
North Wales, Pennsylvania

Sean D. Sullivan, Ph.D.

Professor of Pharmacy and
Public Health
Director, Pharmaceutical Outcomes
Research and Policy Program
Associate Dean for Research
School of Pharmacy
University of Washington
Seattle, Washington

**INFORMATICS ADVISORY
COMMITTEE**

**Michael N. Liebman, Ph.D.
(Chairman)**

Managing Director
Strategic Medicine, Inc.
Kennett Square, Pennsylvania

Ansu Bagchi, Ph.D.

Director, Applied Mathematics and
Modeling Informatics IT
Merck Research Lab IT
Rahway, New Jersey

Michael J. Becich, M.D., Ph.D.

Chair & Professor
Department of Biomedical Informatics
University of Pittsburgh School
of Medicine
Pittsburgh, Pennsylvania

Mark Burfoot, MBA, D.Phil.

Executive Director Global Head of
the Knowledge Office
Novartis Institutes for BioMedical
Research
Cambridge, Massachusetts

George R. Lenz, Ph.D. MBA

GRLEN R&D Associates
Andover, Massachusetts

Robert N. McBurney, Ph.D.

CEO, Accelerated Cure Project for
Multiple Sclerosis
Board Member, Optimal Medicine Ltd.
Chairman of the Board, Differential
Proteomics, Inc.
Newton, Massachusetts

Peter A. Schad, Ph.D.

Chief Scientific Officer
Digital Infuzion Inc.
Gaithersburg, MD
Helix BioConsulting LLC
Fuquay-Varina, NC

David B. Searls, Ph.D.

Independent Consultant
North Wales, Pennsylvania

**PHARMACEUTICS ADVISORY
COMMITTEE**

Michael J. Hageman, Ph.D.

Executive Director
Bristol-Myers Squibb Company
Princeton, New Jersey

Bradley D. Anderson, Ph.D.

H.B. Kostenbauder Professor
College of Pharmacy
University of Kentucky
Lexington, Kentucky

Bruno Hancock, Ph.D.

Senior Research Fellow
Pfizer Inc.
Groton, Connecticut

Patrick J. Sinko, Ph.D., RPh.

Associate Vice President for Research
Professor II (Pharmaceutics) &
Parke-Davis Chair Professor
Ernest Mario School of Pharmacy
Rutgers, the State University
of New Jersey
Piscataway, New Jersey

David B. Volkin, Ph.D.

Takeru and Aya Higuchi
Distinguished Professor
Co-Director, Macromolecule and
Vaccine Stabilization Center
Department of Pharmaceutical
Chemistry
University of Kansas
Lawrence, Kansas

PhRMA FOUNDATION

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Translational Medicine			
Pre Doctoral Fellowships in Translational Medicine (2013)	3 awarded/ 2 years	\$360,000 total \$60,000 per award per year	February I, 2013 April 15, 2013 July – December
Research Starter Grants in Translational Medicine (2013)	2 awarded/ 1 year	\$200,000 total \$100,000 per award per year	February I, 2013 April 15, 2013 July – December
Adherence Improvement			
Post Doctoral Fellowships in Adherence Improvement (2013)	2 awarded/ 1 year	\$100,000 total \$50,000 per award per year	October 30, 2012 March I, 2013 April I, 2013
Research Starter Grants in Adherence Improvement (2013)	1 awarded/ 1 year	\$50,000 total \$50,000 per award per year	October 30, 2012 March I, 2013 April I, 2013
Comparative Effectiveness			
Center of Excellence Award (2011) for Comparative Effectiveness Education	2 awarded/ 3 years	\$500,000 total \$83,333 per award per year	September 15, 2012 December 15, 2012 January I, 2013
Health Outcomes Advisory Committee			
Pre Doctoral Fellowships in Health Outcomes (2002)	2 awarded/ 2 years	\$100,000 total \$25,000 per award per year	February I, 2013 April 15, 2013 July – December
Post Doctoral Fellowship in Health Outcomes (2002)	1 awarded/ 2 years	\$110,000 total \$55,000 per award per year	February I, 2013 April 15, 2013 July – December
Research Starter Grants in Health Outcomes (2002)	2 awarded/ 1 year	\$120,000 total \$60,000 per award per year	February I, 2013 April 15, 2013 July I, 2013

PROGRAMS FOR 2013

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Informatics Advisory Committee			
Pre Doctoral Fellowships in Informatics (2009)	2 awarded/ 2 years	\$80,000 total \$20,000 per award per year	September 1, 2012 December 15, 2012 January – August
Post Doctoral Fellowships in Informatics (2002)	2 awarded/ 2 years	\$160,000 total \$40,000 per award per year	September 1, 2012 December 15, 2012 January – December
Research Starter Grants in Informatics (2002)	3 awarded/ 1 year	\$180,000 total \$60,000 per award per year	September 1, 2012 December 15, 2012 January 1, 2013
Basic Pharmacology Advisory Committee			
Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)	9 awarded/ 2 years	\$360,000 total \$20,000 per award per year	September 1, 2012 December 15, 2012 January – August
Post Doctoral Fellowships in Pharmacology/Toxicology (2002)	3 awarded/ 2 years	\$240,000 total \$40,000 per award per year	September 1, 2012 December 15, 2012 January – December
Research Starter Grants in Pharmacology/Toxicology (1972)	2 awarded/ 1 year	\$120,000 total \$60,000 per award per year	September 1, 2012 December 15, 2012 January 1, 2012
Clinical Pharmacology Advisory Committee			
Paul Calabresi Medical Student Research Fellowships (1974)	2 awarded/ 6 months up to 2 years	\$36,000 total \$18,000 per award	February 1, 2013 April 15, 2013 July 1, 2013
Faculty Development Award in Clinical Pharmacology (1966)	1 awarded/ 2 years	\$240,000 total \$120,000 per award per year	February 1, 2013 April 15, 2013 July 1, 2013

PROGRAMS FOR 2013 *(continued)*

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Pharmaceutics Advisory Committee			
Pre Doctoral Fellowships in Pharmaceutics (1987)	5 awarded/ 2 years	\$200,000 total \$20,000 per award per year	September 1, 2012 December 15, 2012 January – August
Post Doctoral Fellowships in Pharmaceutics	0 awarded 2 years	\$0 total \$40,000 per award per year	September 1, 2012 December 15, 2012 January – December
Research Starter Grants in Pharmaceutics (1972)	1 awarded/ 1 year	\$60,000 total \$60,000 per award per year	September 1, 2012 December 15, 2012 January 1, 2013

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

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.

PhRMA FOUNDATION STAFF



Del Persinger
President and CEO



Eileen Cannon
Executive Director



Charlotte Lillard
Associate



950 F Street NW, Suite 300, Washington DC 20004
P 202.572.7756 F 202.572.7799 foundation@phrma.org