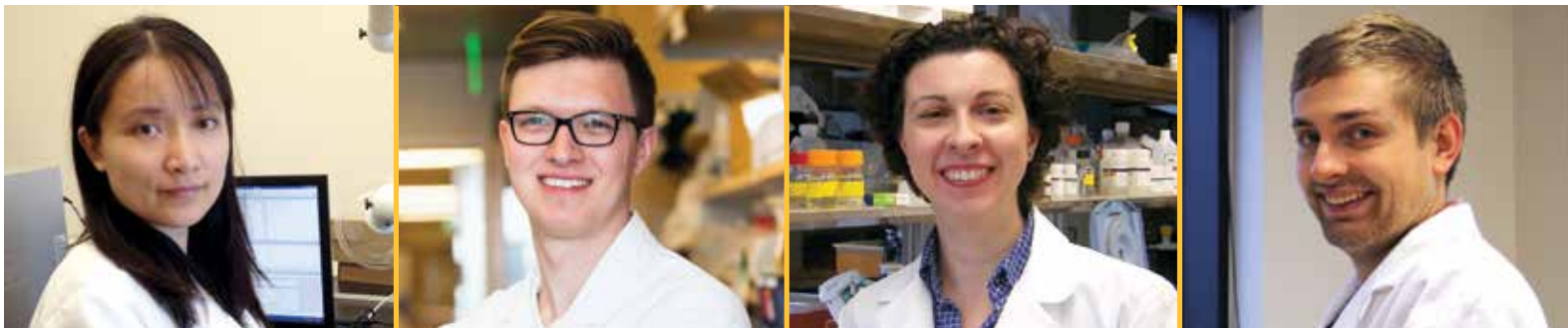


A large, stylized graphic of a laboratory flask, resembling an Erlenmeyer flask, is centered on the page. The flask is filled with a blue, glowing molecular structure composed of interconnected nodes and lines, representing a network or a complex chemical structure. The flask is set against a solid yellow background.

2014 Annual Report

SUPPORTING INNOVATIVE SCIENCE FOR 49 YEARS



Pharmaceutical Research and Manufacturers of America Foundation

The PhRMA Foundation owes its success to the pharmaceutical companies that have provided their generous support over the past 49 years.

We thank all of you for continuing to invest in the future of pharmaceutical research and the scientists of tomorrow.

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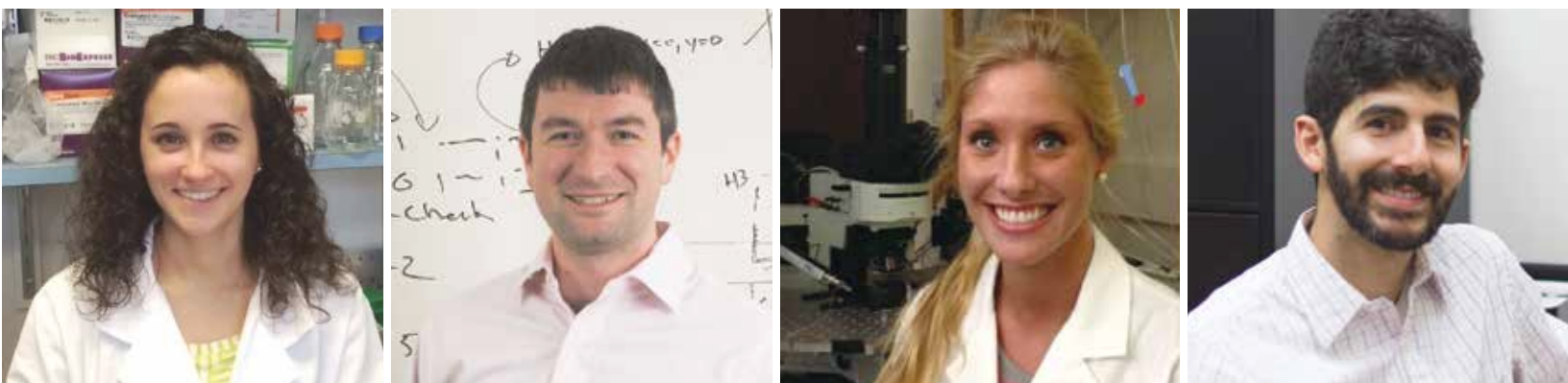
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Mission Statement

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

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

The Foundation's program is of particular benefit to the pharmaceutical industry in serving its purpose of developing new life-saving, cost-effective medicines for patients all around the world.



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Message from the Chairman



As our knowledge and understanding of disease biology grows, it is critically important that we focus on the disciplines that help ensure the effective and efficient development and delivery of new medicines to the patients who need them. To this end, it is ever more important that we create opportunities for the growth and development of the skilled and talented young scientists who will play a vital role in these disciplines.

The PhRMA Foundation has, therefore, focused its energies in five of these critical areas – regulatory science, comparative effectiveness, translational medicine, safe and effective prescribing, and medication adherence – to establish and expand programs supporting biomedical research and training.

Last September, the Foundation moved forward with our newest initiative to expand regulatory science education. We hosted a panel of experts from the FDA and NIH, with representatives from our member companies, the Association of American Medical Colleges, the Critical Path Institute, and the Reagan-Udall Foundation with the goal of creating guidelines for academic programs in regulatory science.

Another Foundation priority is comparative effectiveness research (CER). We launched our CER education program in 2009, and over the past six years have built a framework for CER training and certification. Through a competitive review and selection process, five prestigious universities were awarded grants to establish CER Centers of Excellence. Last January, we organized the first national meeting on CER education, with more than 120 people in attendance.

Regarding translational medicine and therapeutics, our joint grant program enjoys a robust network of support, with guidance from the FDA, NIH, PhRMA members, the Gates Foundation and nine U.S. universities. While still early in its development, this effort has garnered widespread interest, generating more than 70 applications in its first year.

The Foundation is also shedding light on the importance of safe and effective prescribing through a multi-level partnership with NIH and specialists from academia and industry. Together we are shaping course modules that will teach the principles of competent prescribing. This curriculum will better prepare medical students to maximize efficacy and minimize toxicity by focusing on topics like maternal and pediatric care, adverse drug reactions, pharmacogenomics and geriatric prescribing.

Finally, the Foundation's medication adherence program is off to a great start. The first grants were awarded in 2014 and provide stipend support for career development activities for individuals interested in conducting research on new and better approaches to improving medication adherence. We believe this initiative is the conduit to groundbreaking procedures, interventions, and tools that will improve the way patients take their medicines.

All of these programs share a common element: partnership. We believe that developing the skilled and educated workforce that is needed to ensure we remain at the forefront of translating research and development into real and sustained healthcare improvements is best accomplished through multidisciplinary collaboration. Our programs are based on both collaboration and a dedication to common goals.

Our award recipients, over 2,200 scientists over our 50 years of existence, have found their footing as biomedical investigators through their support from the PhRMA Foundation. We support them early in their training and a huge percentage of them go on to have successful careers in pharmaceutical research as researchers, educators or leaders in industry. Ten, twenty, and even forty years later, our grantees are telling us the same thing – that the Foundation had an integral role in their success. The Foundation, and the young people whose careers we will help launch, are counting on your continued support.

A handwritten signature in black ink, appearing to read 'Elias A. Zerhouni'.

Elias A. Zerhouni, MD

Message from the President



As I leave to begin the “retirement” phase of my life, the Foundation is celebrating its 50th year. When Eileen Cannon and I came to the Foundation 16 years ago, I was continually amazed at the respect and reputation we encountered wherever we went. At that time, we were a \$1.5 million a year organization – relatively miniscule in the world of major foundations. As we traveled and talked with members of the Foundation’s extensive network in universities and biopharmaceutical companies, we learned that much of the Foundation’s strong nationwide reputation comes from its consistent presence, mission and excellence over half a century. Our committees have done an amazing job of finding the most promising young talent, and those award winners have made us proud with their subsequent careers and accomplishments in research, teaching and leadership.

Beyond that consistent core program, we have seen a great deal of exciting change. It started at our first board meeting just two months into our tenure, when the pharma company CEO’s upset our carefully planned agenda with a simple question: “Why should the PhRMA Foundation exist? After all, our companies have our own much larger foundations.” We set about answering that question and discovered the uniqueness of the PhRMA Foundation. Essentially, we fund earlier in careers than virtually anyone else – in fact, we help start careers. We fund in key disciplines, with no strings attached. And, of course, we have the consistency and track record established over many years. When our board members saw the analysis at our next meeting, they not only agreed on the value of our foundation, they pledged additional support. Within three years, that support nearly doubled our contributions.

Later, our board – now composed of corporate heads of research – led us through a strategic look at how to use our increased resources to expand into new areas that would add value. An evolution began that has taken us to the frontiers of science with new programs and new partners. Over the past 16 years, our programs in basic and clinical pharmacology and

pharmaceutics have emphasized cutting-edge science. Our Pharmacoeconomics program evolved into the crucial discipline of Health Outcomes. Informatics grew from a start-up to a mature program with PhD alumni all over the nation. We started and grew new programs in Comparative Effectiveness Research and Translational Medicine. And most recently, we began an initiative in Regulatory Science Education. We are working with partners including the NIH and its foundation, FDA, PCORI, AHRQ and the Reagan-Udall Foundation, plus our traditional partners in the scientific professional societies, universities and biopharmaceutical companies.

It’s been a fascinating 16 years – some of the best of my entire career. And what has been best about it is the people who’ve made it happen. Our board members, who have been deeply engaged at a strategic level; our committee members, who volunteer large amounts of valuable time and stay with us for many years – some for 20 years or more; our awardees, who’ve achieved so much – and still express gratitude for what our awards have done for them, even when those awards were decades ago; and our contributors and partners. It is all of you who make the PhRMA Foundation what it is, and I will miss all of you. So goodbye, my friends. Thank you for your wonderful service, and keep doing what you do to bring longer, healthier lives to the patients (and retirees) who need you.

A handwritten signature in black ink, appearing to read 'Del Persinger', with a stylized, flowing script.

Del Persinger

Awards in Excellence

The PhRMA Foundation's annual Awards in Excellence honors past grant recipients whose academic and scientific achievements distinguish them as leaders in the field. As young scientists deciding on areas of specialization, each honoree received a PhRMA Foundation grant in a discipline important to the research based biopharmaceutical industry. Today, these honorees exemplify the difference that PhRMA Foundation grants are making in filling critical scientific needs and by providing timely support to young researchers to support and advance their careers.

The PhRMA Foundation's 2014 Awards in Excellence honor three leading academics and biopharmaceutical researchers for their research, their contribution to advancing our understanding of science and health, their dedication to students and mentoring and their commitment to the future. Each honoree embodies the very best in their chosen fields of Pharmacology/Toxicology, Pharmaceutics, and Clinical Pharmacology.

2014 Award in Excellence in Pharmacology/Toxicology:



Nancy R. Zahniser, Ph.D.

Dr. Nancy Zahniser is a pharmacology professor at the University of Colorado (CU) School of Medicine. Highly regarded for her achievements as an educator and mentor, Dr. Zahniser has helped many young scientists obtain funding and launch independent careers in biopharmaceutical research.

In 1977, Dr. Zahniser received her Ph.D. in pharmacology from the University of Pittsburgh's School of Pharmacy. As a graduate student, she worked with Dr. Israel Hanin, studying drugs with the potential to improve cognitive function by increasing acetylcholine levels in the brain. She completed postdoctoral training in receptor pharmacology at CU, receiving the PhRMA Foundation Faculty Award in Pharmacology/Toxicology in 1984, and rising through the academic ranks as professor, vice and acting chair, and associate dean for research education.

Dr. Zahniser's studies seek to understand how brain dopamine (DA) transporters (DATs) are dynamically regulated, as well as their role in drug addiction. She was the first to demonstrate the influence of guanine nucleotides on DA receptor binding, and showed that release-regulating presynaptic D₂ DA autoreceptors exist on rat striatal neurons. While developing a real-time method to analyze DAT-mediated DA uptake, Dr. Zahniser discovered DAT-associated currents. She also helped characterize a new tagged-DAT knock-in mouse – a significant advance that allows DAT trafficking and regulation studies to be conducted in brain tissue, rather than model cell expression systems. Her findings support the concept that DAT activity is critical for sculpting DA neurotransmission.

Dr. Zahniser's work has been supported by the National Institutes of Health (NIH) since 1981, with MERIT, Research Scientist Development, and Senior Scientist Awards. In 2009, she received the Distinguished Alumna Award from the University of Pittsburgh School of Pharmacy. She has been a distinguished lecturer at CU, the University of Pittsburgh, Loyola University, and the University of Texas Health Science Center at San Antonio. In 2013, the Zahniser Addiction Symposium was held in her honor at University of Florida's Center for Addiction Research and Education.

Throughout her career, Dr. Zahniser has overseen the research projects of 9 thesis students and 22 postdoctoral fellows. She directs the Pharmacology Predoctoral Training Program at CU and co-directs the CU Summer Undergraduate Research Fellowship Program for underrepresented students. She has also participated in the Education and Career Development component of the Colorado Clinical Translational Science Institute (CCTSI) and CCTSI Leadership Program.

Dr. Zahniser has served as a regular member of two NIH study sections. She is part of the NIH National Advisory Council on Drug Abuse and National Institute on Drug Abuse Intramural Research Program Board of Scientific Counselors. She participates on the external scientific advisory boards of the Waggoner Center for Alcohol and Addiction Research, Methamphetamine Abuse Research Center, and Center for Drug Abuse Research Translation. Dr. Zahniser was the American Society for Pharmacology and Experimental Therapeutics secretary-treasurer in 2001, and was elected as fellow of the Executive Leadership in Academic Medicine Program for Women in 2005. She has co-authored more than 150 original papers, reviews, and book chapters, and serves on the editorial boards for three scholarly journals.

2014 Award in Excellence in Pharmaceutics:



Teruna J. Siahaan, Ph.D.

Dr. Teruna Siahaan is a professor and associate chair in the Department of Pharmaceutical Chemistry at the University of Kansas (KU), where he has worked for more than 24 years. Dr. Siahaan leads the Biotechnology Training Program at KU, a National Institutes of Health (NIH) – supported initiative through which students help develop therapeutic agents and vaccines.

Born in Medan, Indonesia, Dr. Siahaan traveled to the University of Arizona in 1982 to complete his Ph.D. in organic chemistry. He conducted his postdoctoral research in the Department of Chemistry at the University of California, Santa Barbara, and worked at the La Jolla Cancer Research Foundation (the Burnham Institute), designing cyclic RGD peptides to inhibit cell adhesion during tumor metastasis and thrombosis. In 1993, Dr. Siahaan was awarded the PhRMA Foundation Research Starter Grant, and in 2000, his student received the Foundation's Undergraduate Research Fellowship. He accepted

a position at the Sterling Winthrop Pharmaceutical Company, where he continued developing treatments for metastatic tumors and rheumatoid arthritis.

Dr. Siahaan's studies aim to enhance drug permeation through biological barriers and improve targeted drug delivery for the treatment of autoimmune diseases. In his research at the Berkland Lab, Dr. Siahaan uses cadherin peptides to modulate cell–cell adhesion proteins to increase permeation of small and large molecules through blood–brain barriers and intestinal mucosa. Cadherin peptides have been shown to enhance brain delivery of marker molecules and anticancer drugs.

Dr. Siahaan's research has been continually funded, with support from the NIH, PhRMA Foundation, and American Heart Association. He is a fellow of the American Association of Pharmaceutical Scientists and has received the Madison and Lila Self Faculty Scholar Award and Pfizer Research Scholar Award. Dr. Siahaan serves on the executive committee of KU's School of Pharmacy and the executive board of directors of the Globalization Pharmaceutical Education Network. He has also participated in various study sections as a grant reviewer for the NIH, Department of Defense, and Alzheimer's Association.

An active contributor to scholarly literature, Dr. Siahaan is an editorial board member for the *Journal of Pharmaceutical Sciences*, *Medicinal Research Reviews*, *Journal of Antibody Technology*, *Open Medicinal Chemistry Journal*, and *Makara Journal*, an Indonesian publication. He has published 170 papers and obtained 11 patents.

Dr. Siahaan has recruited underrepresented students to KU, and invited Indonesian scientists to conduct research at his lab. He has trained several visiting scientists from Indonesia who now work at Indonesian universities.

With a genuine commitment to teaching, training, and mentoring, Dr. Siahaan has prepared undergraduate and graduate students for careers in the pharmaceutical industry, academia, and government research.

2014 Award in Excellence in Clinical Pharmacology:



Terrence F. Blaschke, M.D.

In 1980, Dr. Terrence Blaschke received the PhRMA Foundation Faculty Award in Clinical Pharmacology. He has given back ever since, serving on the Foundation's Clinical Pharmacology Advisory Committee for 22 years.

Dr. Blaschke is a senior program officer in Global Health Discovery and Translational Sciences at the Bill and Melinda Gates Foundation and emeritus professor of medicine and molecular pharmacology at Stanford University. A longtime member of the Stanford faculty, Dr. Blaschke has held various posts at the university, including associate dean for medical student

advising and associate director of the General Clinical Research Center. He is also an adjunct professor of bioengineering and therapeutic sciences at the University of California, San Francisco (UCSF) and adjunct professor of medicine at Indiana University. From 2000 to 2002, he was vice president of methodology and science at Pharsight Corporation.

After earning his medical degree from Columbia University, Dr. Blaschke began his residency in internal medicine at the University of California, Los Angeles. He spent two years at the National Institutes of Health and completed a clinical pharmacology fellowship at UCSF before joining the Stanford faculty in 1974.

Dr. Blaschke is an expert in the optimization of drug therapy—particularly medicines used to treat HIV-infected patients—and the application of modeling and simulation to improve clinical trial design. His research has explored relationships between antiviral drug exposure and virological and toxicological responses as well as how variability in therapy adherence impacts drug efficacy. Throughout his career, Dr. Blaschke has sought out better drug access for people in low- and middle-income countries.

For 44 years, Dr. Blaschke has served as a consultant for various regulatory agencies, pharmaceutical firms, and clinical trial organizations. He is the former chair of the Food and Drug Administration's Generic Drugs Advisory Committee and U.S. Pharmacopeia Drug Utilization Review Panel. He was an original member of the AIDS Clinical Trials Group (ACTG), chair of ACTG's Pharmacology Committee, and member of the Executive Committee. Dr. Blaschke was on the boards of the Therapeutic Discovery Corporation and Crescendo Pharmaceuticals and currently serves on the board of DURECT Corporation—a specialty pharmaceutical company. He also served on the scientific advisory boards at Merck, Sharpe, and Dohme Research Laboratories, and is an advisor to the Guthy–Jackson Charitable Foundation, which focuses on diagnosis and treatment of Neuromyelitis Optica, a rare orphan disease.

Dr. Blaschke has received the American Society for Clinical Pharmacology and Therapeutics (ASCPT) Rawls–Palmer Progress in Medicine Award, Henry W. Elliott Distinguished Service Award, and Oscar B. Hunter Memorial Award. He also served as president of ASCPT and is an honorary fellow of the American College of Clinical Pharmacology. He was an executive editor of the British Journal of Clinical Pharmacology and is associate editor of the Annual Review of Pharmacology and Toxicology. Dr. Blaschke has been extensively published, with more than 180 original works.

Throughout his career, Dr. Blaschke has been a mentor to students, fellows, and residents, working with some of the most promising pharmacologists. Many of these scientists have also benefited from PhRMA Foundation programs, launching their own successful careers in drug discovery and development.

Regulatory Science: A Public Health Responsibility



Joan Adamo, Ph.D.
University of Rochester



Erin Wilhelm, MPH,
Georgetown University



Scott Steele, Ph.D.,
University of Rochester

As scientists uncover more about biological systems and disease, they expand the potential for developing safer and more effective drugs. But while research and technology have unlocked opportunities for preventing, treating, and curing illness, the process of translating biopharmaceutical discoveries into the next generation of therapies presents new challenges.

Regulatory science is devoted to creating knowledge, tools, approaches, and standards to assess the safety and effectiveness of drug products. As a catalyst for advances in medicine, the field of regulatory science can be a powerful weapon in the global fight against disease. It is building new means for scientists to make better decisions and ensure drugs perform as expected, which can lead to faster development of these products for the patients who need them most. With an armamentarium of resources to evaluate novel therapies, those immersed in drug discovery, development, and approval will be able to sooner predict and prevent adverse events and identify which patients would most benefit from a drug's capabilities.

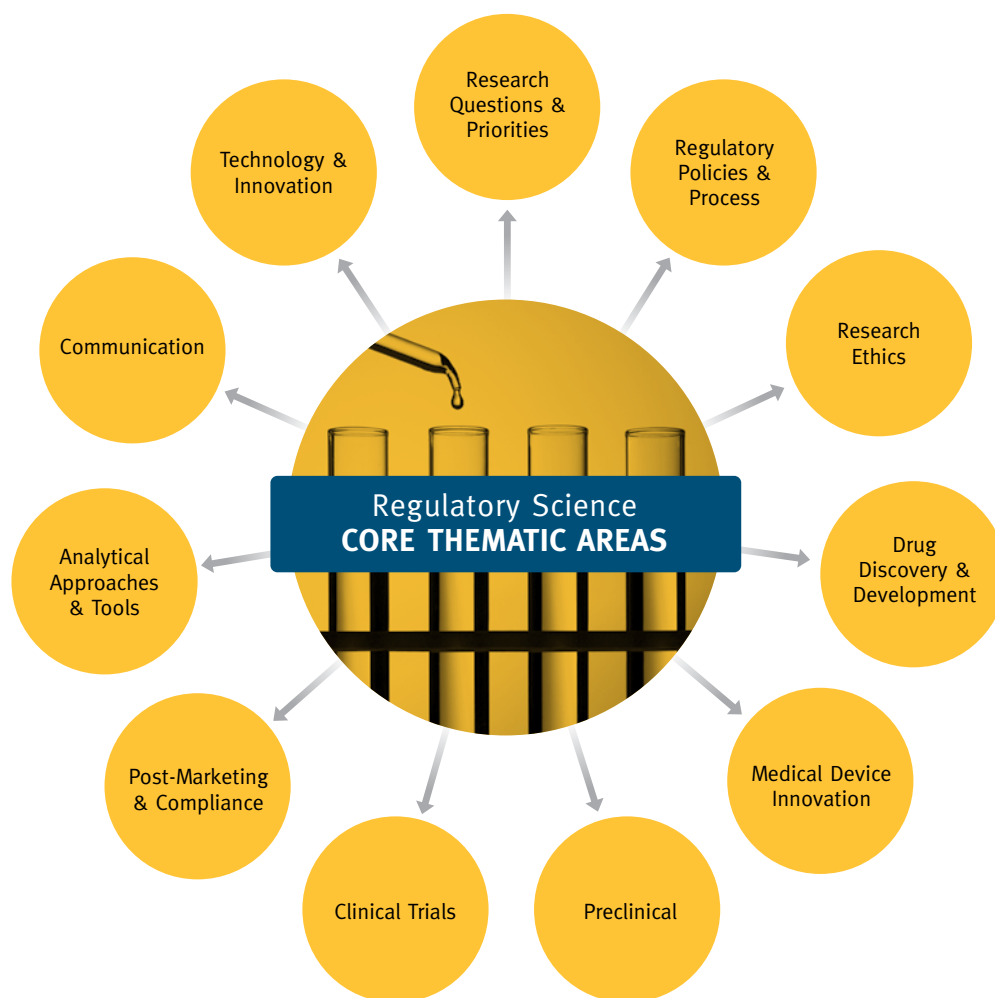
What It Takes to Build a Regulatory Science Workforce



Regulatory science is part of the Food and Drug Administration's (FDA's) strategic plan for standardizing and strengthening its decision-making process. The FDA must base its choices on the best available data, using advanced tools and methods to protect the integrity of all drug products and foster innovation, improvement, and efficiency. To promote regulatory science research and career development, the FDA has funded Centers of Excellence in Regulatory Science and Innovation at universities throughout the country. FDA has also partnered with the National Institutes of Health in a leadership program to oversee several regulatory science initiatives.

Establishing a workforce that addresses the needs for specialists in regulatory science requires tailored education and training. There has been a call for more colleges and universities to offer masters, doctoral, and certificate programs in this pivotal area.

On September 23, 2014, the PhRMA Foundation hosted a regulatory science workshop with Georgetown University and the University of Rochester. More than 35 attended the meeting—the first of its kind—to develop core competencies and curricular guidelines. With representation from government, industry, academia, and other organizations devoted to advancing regulatory science, the demands for teaching, training, and career development in this vital field were fully addressed.



The workshop expanded on draft competencies designed in part by the Clinical and Translational Science Awards (CTSA) – initiated Regulatory Science Workgroup. To refine the competencies, the Foundation convened an expert panel of diverse stakeholders. The panel was tasked with making recommendations for a model curriculum (a blueprint by which universities could create or enhance regulatory science education), and identified teaching methods and case studies for central thematic areas and pathways for professional growth.

Regulatory science is not confined to a laboratory or a particular branch of drug development. It is a multidisciplinary field that thrives on expertise from many specialties, including bioinformatics, pharmacology, public health, and regulatory affairs.

Drug discovery and development brings hope and help to millions of patients worldwide. While the Foundation’s effort to enhance regulatory science education is in its early stages, the ultimate goal is to create a well-trained, highly skilled pool of regulatory scientists who will bring safe and effective drugs to the patients who need them, when they need them.

Regulatory Science Workshop

Panel Members



“Assuring a robust pipeline of cutting edge regulatory scientists within the biopharmaceutical industry, academia, and at the FDA is critical to the health of drug development. One major initiative of The PhRMA Foundation is to develop a broad-based curriculum in regulatory science to train a workforce capable of ensuring the development and earliest availability of safe and effective medical products to improve the public health.”

Michael Rosenblatt, M.D.
Executive Vice President and Chief Medical Officer
Merck & Co., Inc.



“Regulatory science is an integral part of the FDA decision-making process to ensure public health. Through our Advancing Regulatory Science Initiative, FDA expands efforts, internally and in collaboration with stakeholders, to build and sustain regulatory science education and training programs that strengthen professional competencies in this field.”

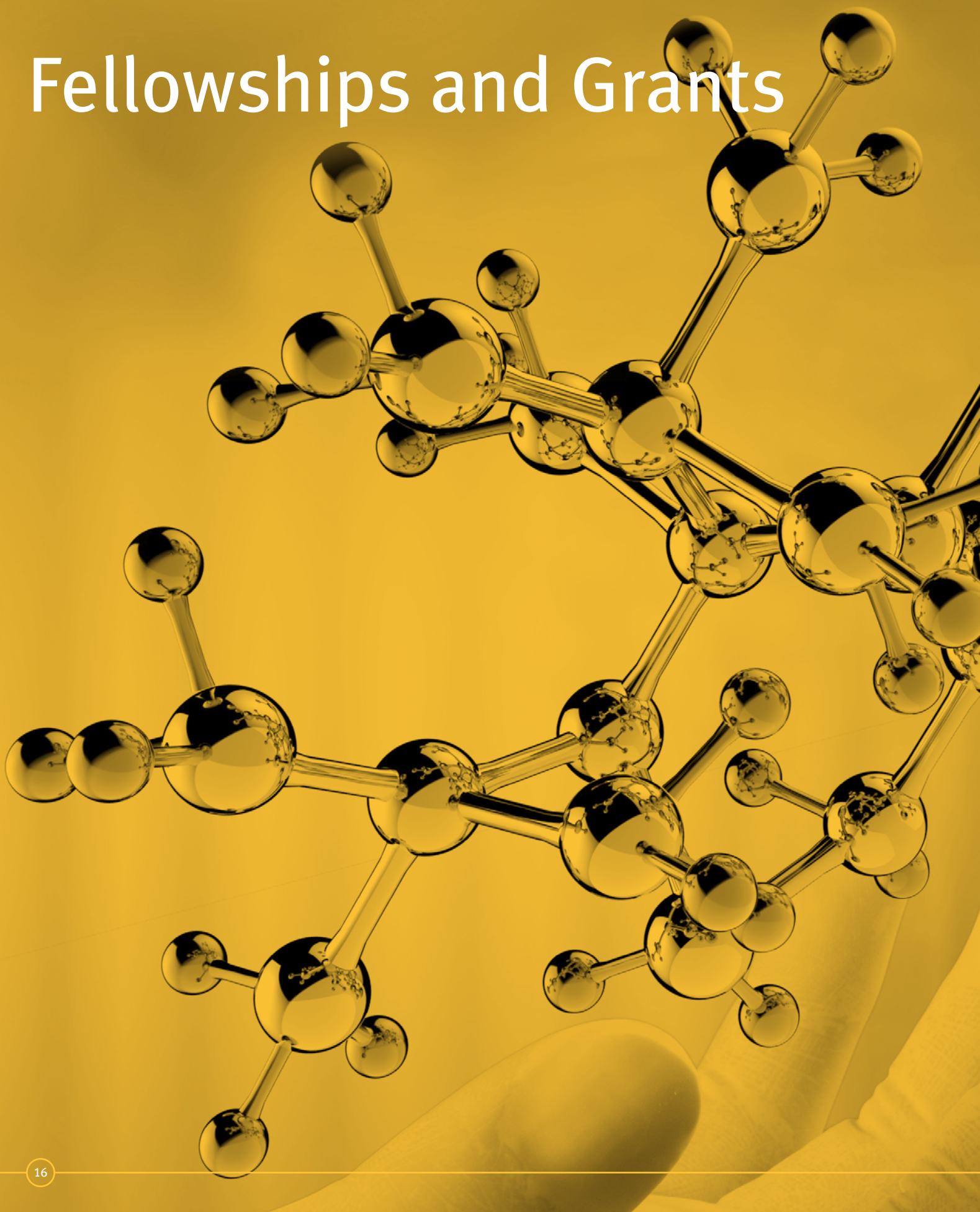
Khaled Bouri, PhD., MPH.
Office of Regulatory Science and Innovation
Office of the Chief Scientist
Office of the Commissioner
Food and Drug Administration



“The workshop was the first of its kind to bring together an interested community of those on the front lines in their respective institutions moving the regulatory science initiative forward. The sharing of ideas and the act of reaching consensus on competencies will be hugely beneficial to all planning to design regulatory science education programs.”

Emma Meagher, M.D.
Director, Translational Research Training Programs
Associate Dean, Clinical Research
University of Pennsylvania
Director at Large, ACTS

Fellowships and Grants



Informatics

Pre Doctoral Fellowship in Informatics

At universities throughout the country, students are researching new avenues to find, process, and translate information about human health and disease. Their work stands to advance the state of the art in informatics, improving pharmaceutical research and patient care. To support these bright young scientists as they integrate information technology with biological, chemical, and pharmacological sciences, the Foundation provides an annual stipend for up to two years.

“

The PhRMA Foundation Pre Doctoral Fellowship came at an important time in my scientific career when it is key to focus on research. The fellowship allowed me to work on research matters without having to worry about funding or teaching. Additionally, it's always a confidence booster to have your proposal independently evaluated and validated.”

Darwin Yu Fu | Vanderbilt University, 2014 Pre Doctoral Fellowship in Informatics

2014 Pre Doctoral Fellowship in Informatics



Darwin Yu Fu

Vanderbilt University

“Integrating Computational Tools With Experimental Data for Drug Discovery”

The discovery of small molecule ligands for protein binding (e.g. drugs, probes) is often split into two questions: “what will bind?” and “how will it bind?”. The “what” problem identifies small molecules that have substantial binding affinities against a given protein structure. The “how” question examines the critical interactions at the protein-ligand interface. Computationally, the two questions often require distinct methodology. This project focuses on developing new computational tools that merge the two aspects and improve predictions by integrating experimental data. One example of highly useful data is structure-activity relationships, which are generated by testing a series of related compounds for binding activity against a common target. By computing similarities and differences between binding and non-binding compounds, the new methods can give insight on how to improve existing chemical scaffolds and what new scaffolds to test. Targets of particular interest include the muscarinic and metabotropic glutamate families of G-protein coupled receptors, which have been implicated in the treatment of neurological disorders such as schizophrenia, Parkinson's, and depression.

Post Doctoral Fellowship in Informatics

The PhRMA Foundation supports postdoctoral research activities that will enhance the expertise of informatics specialists and bridge experimental and computational approaches in genomic and biochemical studies. With this funding, many recipients have been able to secure their careers in informatics and establish independent labs.

“

It's not hyperbole to say that the PhRMA Foundation award allowed me to keep my position; after sequestration caused a huge cut in our lab's funding, receiving the award was the only way I was able to stay on. Instead, I could focus on doing compelling research and making discoveries that could, I hope, one day help people lead cancer-free lives.”

Yevgenia Khodor, Ph.D. | Massachusetts Institute of Technology, 2014 Post Doctoral Fellowship in Informatics

“

Receiving a PhRMA Foundation Informatics Postdoctoral Fellowship has given me a great opportunity to focus on research I'm passionate about without being distracted by how it will be funded. It gave me the confidence to move forward as a postdoctoral fellow and, further, to commit my career to researching genetics of age-related eye diseases. In addition, writing the fellowship was a great learning experience for the future.”

Jessica Cooke Bailey, Ph.D. | Case Western Reserve University, 2014 Post Doctoral Fellowship in Informatics

2014 Post Doctoral Fellowship in Informatics



Orr Ashenberg, Ph.D.

Fred Hutchinson Cancer Research Center

“Mutational Scanning of the Sensitivity of Influenza Nucleoprotein to Innate-Immune Restriction Factors”

Influenza virus has been a persistent, public health threat for at least 100 years, and the worst pandemic killed over 50 million people worldwide. Influenza continually evolves to evade recognition by both the innate and adaptive branches of the human immune system, which makes this virus a significant, public health threat. The innate immune system deploys specialized antiviral proteins, known as restriction factors, to help control influenza. This places selective pressure on the influenza proteins to evade recognition by these restriction factors and the subsequent inhibition of viral growth. However how influenza proteins can adapt to evade recognition is largely

unknown. This study will propose novel experimental and computational tools to better understand this adaptive process. The project's approach, will characterize the effect each possible mutation in influenza nucleoprotein has on influenza being recognized by restriction factors. Because there are thousands of possible mutations in nucleoprotein, it is impossibly time-consuming to characterize each of them individually. Instead, the study will take advantage of the new technology of next-generation sequencing, which makes it possible to characterize all the nucleoprotein mutations in parallel. Identifying how these mutations affect influenza recognition by the innate immune system will significantly expand our understanding of influenza evolution. It will also aid efforts to monitor circulating influenza strains for the gain of any dangerous mutations that could help influenza better evade human immunity.



Jessica Cooke Bailey, Ph.D.

Case Western Reserve University

“Teasing Apart the Genetics of Age-Related Macular Degeneration”

Age-related macular degeneration (AMD) is a progressive neurodegenerative disease that is the primary cause of irreversible blindness in older individuals living in developed countries. It is well known that a significant portion of the disease is due to genetic variation; however, the identified genetic loci account for less than two thirds of the heritability. Thus, there is a great deal more genetic information relevant to AMD that has not yet been located or explained. The Amish, in whom AMD prevalence is comparable to the general European American population, comprise a relatively isolated subpopulation that may be enriched for rare genetic variation. Identifying and explaining this type of variation could aid in the discovery of new AMD loci that can be evaluated in populations including and beyond the Amish. This project will seek to further define the roles of known and novel of genetic mediators of AMD, especially rare coding variants, by assessing the impact of rare variation on AMD and evaluating genetic differences between individuals with different grades or levels of AMD. This project will primarily evaluate coding variation from 184 Amish (including 84 with AMD) typed on an Exome array that targets >200,000 common and rare single nucleotide polymorphisms (SNPs). Variants will be further evaluated in additional Amish and European American samples, including in the International Age related Macular Degeneration Genomics Consortium (IAMDGC) exome chip dataset of approximately 50,000 additional samples. Completing these analyses will be highly valuable to helping determine unidentified genetic mediators of AMD susceptibility and pathology. The long-term goal of this and subsequent related projects is to translate the knowledge gained into clinically implementable methods to improve disease treatment and prevention strategies



Yevgenia Khodor, Ph.D.

Massachusetts Institute of Technology

“Investigating the Dynamic Changes in Splicing and Translational Across the Epithelial-Mesenchymal Transition On a Genomic Level”

The vast majority of human malignant tumors result from carcinomas, or solid, epithelial primary tumors. One way these malignancies have been shown to arise is through a process known as epithelial-mesenchymal transition (EMT). During EMT cells lose organization and contacts they have with neighboring cells and gain traits including enhanced migration, invasiveness, and increased resistance to apoptosis. A lot of work has focused on how genes are turned off or on during EMT, but there has been very little work exploring how the products of those genes are modified via splicing and controlled during translation into protein. This project uses the molecular techniques known as RNA-seq and Ribosomal Footprint Profiling to observe changes in splicing and translational control across EMT with temporal resolution. These changes will be quantified and explored through numerous bioinformatics approaches, such as clustering and comparative analyses. Successful completion of this project will lead to discovery of novel diagnostic targets for early detection and aid in the development of drugs against metastasis.

Research Starter Grant in Informatics

At the PhRMA Foundation, we aim to help early-career researchers navigate their current paths, especially in teaching and training. The Research Starter Grant offers support to beginning faculty members launching independent research careers. This funding provides assistance to informatics scientists who have no other financial backing. We see it as a way to encourage and sustain the good work of young investigators who are stepping out at their colleges and institutions.

“

The PhRMA Foundation award gave me the freedom to take risks and conduct experiments that were otherwise not fundable by federal institutions. The award money helped, in part, to develop a novel systems pharmacology method to identify adverse drug reactions, develop a method for identifying patient cohorts from medical records, and design and implement a high-throughput experimental system for exploring drug combinations.”

Nicholas Tatonetti, Ph.D. | Columbia University, 2014 Research Starter Grant in Informatics

2014 Research Starter Grants in Informatics



Patrick J. Flaherty, Ph.D

Worcester Polytechnic Institute

“Ultrasensitive Detection of Rare Mutations in Heterogeneous Cell Populations Using Next-Generation Sequencing”

Next-generation sequencing technology has been successfully used to identify mutations in homogeneous cell populations in recent years. Now, with significant reductions in the cost of sequencing, it is beginning to be possible to identify mutations heterogeneous samples and thus detect rare sub-populations and measure intra-sample genomic heterogeneity. However, the algorithms that were originally developed to identify mutations in homogeneous samples do not perform well on heterogeneous samples. The goal of this project is to improve data analysis methods to enable specific and accurate identification of causal single nucleotide mutations in heterogeneous clinical samples. This technology would facilitate many clinical diagnostics including: detection of antiviral resistance in influenza, non-invasive diagnostics from cell-free DNA, monitoring of tumor progression during treatment for many types of cancer.



Nicholas P. Tatonetti, Ph.D.

Columbia University

“The Data Science of Drug Design: Modeling Drug Safety and Therapeutic Combinations”

Metabolism is a core cellular process and dysregulation is central in many human diseases, including diabetes, obesity, heart disease, and several types of cancer. However, approval rates for drugs that treat these diseases has largely stagnated. In an effort to bridge this productivity gap, the drug design community is exploring alternative development strategies focusing on drug combinations, polypharmacy, and genomic medicine. However, these new drug paradigms rely on a systems level view of pharmacology. This project developed two independent methodologies to construct data-driven computational models of systems pharmacology. First, the study presents the Modular Assembly of Drug Safety Subnetworks (MADSS), which combines graph theoretic models and whole proteome network biology to predict four severe adverse drug reactions: myocardial infarction, gastrointestinal bleeding, kidney failure, and liver failure (Lorberbaum et al., 2015 *Clinical Pharmacology & Therapeutics*). The project demonstrates the utility of the method in the setting of pharmacovigilance where this network-based approach is the more sensitive and more specific than existing methods. Further, it is shown that the performance of MADSS is robust even for drugs that have only very few validated protein targets — potentiating its use in pre-clinical studies. Second, the study has developed the first high-throughput

functional assay designed for high-order combinatorial drug discovery (Chang et al. *In Preparation*). Drug combinations of even the second order are largely a mystery. The project is using a well-studied and pharmacologically relevant pathway (coagulation) to study the functional effects of drugs (synergistic, antagonistic, additive, and others) in combination. This project's model is singular in that it couples this experimental exploration with a mathematical model of the pathway (using ordinary differential equations) and a computational model of the pathway (using graph theory).

Pharmacology/Toxicology

Pre Doctoral Fellowship in Pharmacology/Toxicology

Since the program's initiation in 1978, more than 380 Pre Doctoral Pharmacology and Toxicology Fellowships have helped expand the nation's pool of highly-trained pharmaceutical researchers. The PhRMA Foundation provides awardees with a two-year stipend as they move toward completion of their research for pharmacology and toxicology doctoral dissertations.

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I thank the PhRMA Foundation for helping me progress in my career as a young scientist. The Pre Doctoral Fellowship in Pharmacology/Toxicology has given me confidence in my research and the competitive application process gave me an invaluable experience in grant writing. It gives me great security to have this award at a time when funding is so difficult to attain.”

Melanie Pleiss | University of Kentucky, 2014 Pre Doctoral Fellowship in Pharmacology/Toxicology

“

I am very honored to be a recipient of the PhRMA Foundation Pre Doctoral Fellowship in Pharmacology and Toxicology. This award has provided me with the resources necessary to conduct critical research investigating novel therapies for the treatment of heart failure, while simultaneously promoting my professional development. Thank you to the PhRMA Foundation for their unwavering support of early career investigators and the next generation of pharmaceutical researchers.”

Josh Travers | University of Cincinnati, 2014 Pre Doctoral Fellowship in Pharmacology/Toxicology

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I am very grateful to be a recipient of the 2014 Pre Doctoral Fellowship in Pharmacology/Toxicology. Scientific research can be challenging and at times discouraging, particularly in our current funding environment. But for my PI and my department to have nominated me for this award, and for this prestigious foundation to have been impressed enough by my proposal to fund it, has really helped to motivate and encourage me to continue pursuing a career in research. I know that any future success I may have in my career will be in large part thanks to the PhRMA Foundation.”

Sarah Head | Johns Hopkins University, 2014 Pre Doctoral Fellowship in Pharmacology/Toxicology

2014 Pre Doctoral Fellowship in Pharmacology/Toxicology



Hannah Stoveken

University of Rochester Medical Center

“The Mechanism of Adhesion GPCR GPR56 Activation of G Proteins in Physiology and Cancer Progression”

GPR56 is an orphan adhesion G protein-coupled receptor (GPCR) with important roles in adult cancer progression and in the developing brain. GPR56 regulates migration of neuronal precursor cells and *GPR56* reduction of function mutations result in over migration, disrupting brain morphology in the recessive disease Bilateral Frontoparietal Polymicrogyria. In multiple cancers, including breast cancer and certain brain cancers, *GPR56* expression is altered. Forced *GPR56* expression increased markers associated with cancer progression, including enhanced vascular endothelial growth factor (VEGF) secretion. During synthesis and trafficking, GPR56 cleaves itself between its extracellular domain (ECD) and 7-transmembrane domain (7-TM), generating two protein fragments. The ECD remains bound to the 7-TM domain in a manner thought to suppress intracellular signaling through heterotrimeric G proteins. Binding of natural receptor ligands present in the extracellular matrix may relieve the ECD inhibition and activate signaling. This project aims to elucidate the unique mechanism of GPR56 activation and how signaling through this receptor is dysregulated in cancer. A biochemical assay was developed specifically to measure direct coupling of GPR56 to purified heterotrimeric G proteins and this approach was utilized to define the heterotrimeric G protein subtypes that GPR56 activates. This assay will be used to functionally measure the effects of putative ligands on GPR56 signaling and to identify unknown GPR56 ligands and modulators. Ligands will be pharmacologically characterized and tested for inhibitory activities in established cell-based cancer assays. A clear understanding of how GPR56 signals physiologically and pathologically is requisite to the design of therapies against GPR56-directed cancers. This research will also provide useful mechanistic information of the functioning of the other members of the adhesion GPCR class, also with known roles in disease.”



Joshua Gregory Travers

University of Cincinnati

“Exploring the Therapeutic Potential of Small Molecule G $\beta\gamma$ -GRK2 Inhibition in Cardiac Fibroblasts, Fibrosis and Remodeling”

Heart failure (HF) is a devastating disease characterized by chamber remodeling, interstitial fibrosis and reduced ventricular compliance. Despite significant advances in therapeutic interventions, cardiovascular disease remains the leading cause of death worldwide, underscoring a desperate need for innovative treatment strategies. The β -adrenergic receptor (β -AR), a G-protein coupled receptor (GPCR), plays a crucial role in the regulation of cardiac function. HF progression involves elevated stimulation of the heart to compensate for reduced cardiac output; this chronic overstimulation initially improves cardiac output, however, excess signaling through G-protein G $\beta\gamma$ subunits ultimately results in β -AR desensitization and downregulation. This is mediated predominantly by GPCR kinase 2 (GRK2), which is recruited to the ligand-bound receptor by activated G $\beta\gamma$ subunits. This project has recently demonstrated the therapeutic potential of the small molecule G $\beta\gamma$ -GRK2 inhibitor Gallein in limiting the progression of HF in animal models, including a dramatic reduction of myocardial fibrosis. Chronic activation of the cardiac fibroblast (CF), a key cellular component of the myocardium, induces the transition to a pathological or ‘myofibroblast’ phenotype, and a concomitant increase in collagen deposition. The myofibroblast plays a critical role in pathologic cardiac remodeling, including cardiac hypertrophy, fibrosis and inflammation. The recent project data suggest that chronic activation of the β -AR is a key component of pathologic CF signaling and HF progression, however, the role of the CF as a HF mediator remains poorly understood. Utilizing innovative tools, including a small molecule G $\beta\gamma$ -GRK2 inhibitor and novel fibroblast-restricted GRK2-knockout mice, this project proposes to evaluate the role and therapeutic potential of G $\beta\gamma$ -GRK2 inhibition in CFs in a clinically relevant surgical model of HF and in primary cells from adult mice and failing human myocardial tissue. It is believed this CF-targeted approach will lead to the refinement of existing targets and compounds, and the development of a novel, targeted therapy for HF.



Sarah Head

Johns Hopkins University School of Medicine

“Identification and Validation of Novel Targets for Angiogenesis Inhibition”

During early tumor development, cancer cells obtain the nutrients required to grow by simple diffusion. However, once the tumor reaches a certain size, it requires the in-growth of new blood vessels to supply it with nutrients needed for continued proliferation. This process is called angiogenesis, and without it the tumor will essentially starve itself to death. Inhibition of angiogenesis is therefore a promising strategy for treating cancer, yet only a few such drugs have been approved, and these are designed to act on a very limited number of cellular targets. The goal of this project is to identify new targets for angiogenesis inhibition, with the long-term aim of developing a mechanistically distinct

class of antiangiogenic drugs. To achieve this, the group screened a library of clinically used drugs, most of which have known cellular targets, for inhibition of endothelial cell proliferation. One hit that emerged was itraconazole, an antifungal drug that works by inhibiting lanosterol 14- α demethylase (14DM) in yeast. Although it has since been validated as an antiangiogenic and anticancer agent *in vivo* and is currently in clinical trials, subsequent mechanistic work revealed that 14DM inhibition cannot fully explain the activity of itraconazole in human endothelial cells. Therefore attention was given to identifying additional itraconazole-binding proteins that may mediate its antiangiogenic effects. Thus, an affinity probe of itraconazole was developed that retains the activity of the parent compound and can bind to its target proteins in live cells. These studies have led to the identification of multiple novel itraconazole-binding proteins, none of which has previously been implicated in angiogenesis. This project will evaluate the physiological relevance of these proteins in angiogenesis using biochemical and genetic methods, as well as a zebrafish model of angiogenesis in which each target protein will be knocked down in the developing animal. Identification of the target(s) mediating itraconazole's antiangiogenic activity will pave the way for the development of a mechanistically distinct class of angiogenesis inhibitors, and further our understanding of the molecular processes underlying blood vessel growth.



Maya Woodbury

Boston University

“miR-155/STAT3 Signaling: a Novel Pharmacological Target for Down Syndrome”

Down syndrome (DS), the most common cause of congenital intellectual disability in humans, is a developmental disorder caused by trisomy 21. DS is characterized by neurogenic dysfunction in the hippocampal subgranular zone (SGZ), accompanied by an early neuroinflammatory response and aberrant immune function. Neuroinflammation alone reduces SGZ neurogenesis in rodents and humans, but it is unknown whether it is directly involved in DS developmental abnormalities. This project hypothesizes that inflammatory glial cells play a direct role in DS neurodevelopmental deficits. A possible mediator connecting inflammation to neurogenesis is interleukin-6 (IL-6), a pro-inflammatory cytokine implicated in reduction of neurogenesis which signals through Signal Transducer and Activator of Transcription 3 (STAT3). The preliminary study shows that microglial activation suppresses neuronal differentiation in an IL-6-dependent manner *in vitro*, and a specific microRNA, miR-155, critically regulates IL-6 gene induction in activated microglia. miR-155 is located on trisomic chromosome 21 and its expression is enhanced in human DS brain and in brain of DS mouse model Ts65Dn. Several miR-155 targets are highly expressed in hippocampus and are implicated in cognitive function and DS immune response. Moreover, treatment with STAT3 inhibitor WP1066 enhances neurogenesis *in vitro*. Thus, the miR-155/IL-6/STAT3 axis is a highly promising therapeutic target for neurodevelopmental treatment of DS. This pre-clinical study, will pharmacologically target the miR-155/IL-6/STAT3 axis with anti-miR155 or STAT3 inhibitors and hypothesize that this will reduce neuroinflammation and correct SGZ neurogenesis in Ts65Dn mice.



Melanie Pleiss

University of Kentucky

“Astrocytic Calcineurin and Connexin43 Gap Junctions in Alzheimer’s Disease”

As the sixth leading cause of death that affects over 5.2 million people, Alzheimer’s disease (AD) is a health crisis with no cure. Because previous clinical trials have been disappointing, it is imperative that new and alternative molecular targets be explored. This project aims to study key molecular targets inherent to astrocytes: the most abundant type of neural cell with key neuroprotective functions. With injury, AD, or other neurodegenerative conditions astrocytes can lose their protective properties and instead promote harmful inflammatory signaling. Previous work from our lab suggests that a key messenger protein, calcineurin (CN), drives many of the detrimental changes in astrocytes. Although CN is highly expressed in the brain, it only appears in high levels in astrocytes under injurious conditions. Furthermore, preliminary work from our lab suggests that CN may interact with and disrupt connexin43 (Cx43), a gap junction (GJ) protein that mediates direct intercellular communication between astrocytes. Thus, the proposed project will test the overarching hypothesis that CN and Cx43 interactions inhibit GJ coupling in astrocytes during the progression of AD leading to detrimental changes in neurologic function. This project will use a multi-disciplinary approach to investigate this hypothesis using human hippocampal specimens, APP/PS1 transgenic mice, and rat primary astrocyte cultures. This work will increase the understanding of astrocyte signaling/interactions in neurodegenerative diseases, and may provide valuable information into a new potential therapeutic target for AD.



Adrian Stecula

University of California, San Francisco

“Mapping the Structural and Functional Landscape of the Concentrative Nucleoside Transporters (SLC28 Family)”

Many anticancer drugs are purine or pyrimidine analogs, which are used to treat both hematological and solid tumors. Human nucleoside transporters (NTs) mediate salvage of nucleosides and transport of therapeutic nucleoside analogs, and therefore are pharmacological determinants of drug disposition and response to therapy. Of the two major classes of NTs in human tissues, the SLC28 gene family encodes the concentrative NTs (CNTs), which are characterized by a selective, high-affinity transport of nucleosides in a Na⁺-coupled manner. Three members of the family have been identified, each with unique transport characteristics. CNT1 (SLC28A1) is predominantly pyrimidine-selective, CNT2 (SLC28A2) is purine-selective, and CNT3 (SLC28A3) exhibits broad specificity. Although the body of knowledge on the CNTs is growing, the current research lacks understanding of the structural characteristics and motifs that lead to ligand (either substrate or inhibitor) selectivity of each of the SLC28 family members and fails to predict the functional implications of their SNPs. Knowledge of the

mechanism of these transporters is necessary to understand nucleoside metabolism and signaling, as well as to facilitate drug design and nucleoside drug delivery. In light of the recent crystal structure of a SLC28 homolog, it is now possible to model the human SLC28 family members, and use the structural information to form new hypotheses and guide functional studies. The X-ray crystal structure shows that the prokaryotic homolog (vcCNT) forms a homotrimer. This surprising finding could lead to a significant advancement within the field of nucleoside transport as multimerization of membrane proteins frequently provides a mechanism for the regulation and stability of membrane structures. Based upon the high sequence identity of the trimerization regions between the human and prokaryotic members, the project hypothesizes that the human SLC28 family members also form trimers. For the human SLC28 family members, the study will investigate the trimerization behavior, determine the quaternary structure, and find ligands that modulate their structure and function. The innovation here lies in the nature of the question asked as well as the combination of the novel experimental and computational methods used to address it.



Kristin Bircsak

Rutgers University

“Genetic and Dietary Risk Factors for Glyburide-Induced Hypoglycemia in Neonates”

Gestational Diabetes Mellitus (GDM) is one of the most common complications of pregnancy, affecting more than 200,000 pregnant women per year in the United States. Previous pharmacological management of GDM was limited to insulin injections as it was suspected that oral hypoglycemic medications could cross the placenta and induce hypoglycemia in the fetus. However, recent research has shown that the breast cancer resistance protein (BCRP/*ABCG2*) efflux transporter in the placenta restricts fetal accumulation of the hypoglycemic drug glyburide by actively extruding the drug back into the maternal circulation. As a result, there has been a significant increase in the prescribing of glyburide to treat GDM. Investigation of risk factors that may decrease the ability of BCRP to efflux glyburide and prevent fetal exposure is therefore important for optimizing obstetrical care. For example, a genetic polymorphism at nucleotide position 421 (C/A) can decrease the ability of BCRP to transport drugs. Similarly, the dietary soy isoflavone, genistein can inhibit the activity and reduce the expression of BCRP in human placental choriocarcinoma cells. This project will determine whether dietary concentrations of genistein impair the ability of BCRP to efflux glyburide from the placenta by directly inhibiting transporter function and reducing its expression in placental trophoblasts. The proposed research will provide much needed data regarding genetic (C421A BCRP) and dietary (genistein) risk factors for fetal glyburide exposure and potentially neonatal hypoglycemia. Significant knowledge gaps will also be filled in the fields of placental transport and developmental toxicology, which may lead to future clinical studies that improve the individualized prescribing of glyburide for women with GDM.



Forrest Connell Jessop

University of Montana

“Regulating Chronic NLRP3 Inflammasome Activity in the Lung Through Autophagy”

Chronic inflammation is critical to the development and progression of pulmonary fibrosis, a condition that is associated with poor prognosis. There are no cures for progressive pulmonary fibrosis, and lung transplantation is currently the most viable option to extend an individual's life. The inability to effectively treat pulmonary fibrosis is primarily due to poor understanding of mechanisms that perpetuate and regulate chronic inflammation. The NLRP3 Inflammasome, which mediates the active secretion of the pro-inflammatory cytokine IL-1 and alarmin HMGB1 from macrophages, is a point of convergence in chronic inflammatory signaling. Though many pathogens, environmental particulates (e.g. crystalline silica), and pharmacological agents (e.g. bleomycin) can induce NLRP3 Inflammasome activation, there is limited information regarding how subsequent activity is regulated. Autophagy is an inherent degradative pathway for NLRP3 Inflammasome components. Incompetence of autophagy to suppress inflammation and promote tissue repair is indicated in chronic disease, though mechanistically this relationship is not understood. The overall long term goal of this research is to define mechanisms that regulate chronic inflammation in the lung. The overall objective of this project is to delineate the mechanism by which the NLRP3 Inflammasome remains activated in macrophages in chronic lung diseases. This research aims to 1) elucidate the relationship between autophagy and NLRP3 Inflammasome activity in models of chronic inflammatory lung disease, including a murine model of silicosis and alveolar macrophages isolated from individuals with sarcoidosis, and 2) determine the effectiveness of therapeutically targeting autophagy to prevent chronic inflammation and reverse fibrosis. Due to the central importance of NLRP3 Inflammasome activity and autophagy in chronic inflammatory disease, findings from this investigation will impact diseases beyond silicosis and sarcoidosis. Furthermore, the work from this proposal will provide the biological feasibility of targeting autophagy as an anti-inflammatory therapy for future clinical studies.



Kelly Marie McGregor

Wayne State University

“Chronic Antidepressant-Induced Homeostatic Plasticity of Serotonergic Neurons”

The idea that serotonin contributes to the pathology of depression and its pharmacotherapy is one of the central concepts in modern biological psychiatry. This is most dramatically supported by the prominent position of Selective Serotonin Reuptake Inhibitors (SSRIs) in the treatment of depressive disorders. While these drugs are clearly effective, one limitation is that despite having immediate effects on reuptake, their clinical benefits are not observed for weeks upon continuous dosing. Previous studies have suggested that one factor contributing to this delay is the fact that serotonin cell firing is suppressed by SSRIs, thus countering the facilitatory effect of reuptake inhibition on serotonergic synaptic transmission. Consistent with this idea, preclinical studies have

shown that serotonergic neuronal activity returns to baseline during prolonged SSRI administration with a time course consistent with the therapeutic response. A current limitation in our understanding of SSRIs is that the precise mechanisms underlying this phenomenon remain poorly understood. This project will test the hypothesis that chronic SSRI exposure leads to homeostatic changes in the main mechanisms thought to regulate serotonergic cell firing. Understanding how persistent SSRI administration regulates serotonin neuronal activity should contribute to the development of more effective pharmacotherapies for neuropsychiatric disorders.

Post Doctoral Fellowship in Pharmacology/Toxicology

The Post Doctoral Fellowship in Pharmacology/Toxicology provides a two-year stipend to scientists who seek to gain new skills in pharmacologically relevant areas. Eligible candidates are actively pursuing a multidisciplinary research training program to enhance their expertise and education, or embarking on a research project that aims to integrate information on a drug's molecular or cellular mechanisms of action with the agent's effects on the intact organism.

2014 Post Doctoral Fellowship in Pharmacology/Toxicology



Courtney Donica, Ph.D.

The University of Texas

“Zero Tolerance for Chronic Pain”

It is estimated that over 100 million Americans suffer from chronic pain at an annual cost to society of over 500 billion dollars. For centuries, opioid narcotics such as morphine have been the first-line treatment for severe pain. However, over time tolerance to the pain-relieving (analgesic) properties of opioid narcotics develops. Because there are few alternatives to opioids for the treatment of chronic severe pain, marked increases in opioid dose may be needed to compensate for inadequate pain relief as tolerance develops. However, tolerance to the unpleasant or potentially life-threatening side effects of opioids, such as respiratory depression, constipation, urinary retention, and delirium, does not occur as rapidly as analgesic tolerance. Therefore, patients face increased risk as well as suffering when opioids lose effectiveness. Recently, it was reported that tolerance to the pain-relieving effects of opioids is selectively caused by platelet-derived growth factor (PDGF) signaling. Preliminary results discovered that blocking epidermal growth factor (EGF) signaling in animals also completely reversed morphine tolerance. These were extremely surprising results, as growth factor inhibitors are currently used clinically to treat cancer. The goals of this project generously funded by the PhRMA Foundation is to determine if 1) EGF signaling also selectively causes morphine tolerance, and 2) Whether PDGF and EGF work together to cause tolerance. This research will dramatically improve understanding of the molecular mechanisms causing opioid tolerance. They could also define a completely new approach to the treatment of chronic pain. Project findings have the potential to dramatically reduce human suffering and improve the quality of life for the untold millions of patients suffering from intractable pain.



Robert Warren Gould, Ph.D.

Vanderbilt University Medical Center

“M1 Muscarinic Acetylcholine Receptor Activation as a Treatment for Sepsis-Associated Brain Dysfunction”

Approximately 19 million individuals are admitted annually into the ICU for the treatment of sepsis, a systemic inflammatory response syndrome caused by severe infection that can lead to multi-organ failure. Recent clinical studies report that sepsis-associated delirium, an acute brain dysfunction represents a primary predictor of sepsis-associated long-term cognitive impairments (SA-LTCIs) comparable to those observed in patients with mild traumatic brain injury and/or dementia. To date, there are no available treatments for delirium or SA-LTCIs. Reduced function of cholinergic neurotransmission may represent a critical risk factor for increased susceptibility to sepsis-associated delirium and SA-LTCIs. The proposed studies will systematically characterize the role of reduced central cholinergic tone, using a choline transporter heterozygous (CHT +/-) mouse model that demonstrates demand-dependent decreased cholinergic tone, on systemic inflammation, brain function utilizing electroencephalography and SA-LTCIs induced by administration of the pro-inflammatory agent lipopolysaccharide (LPS). This project will evaluate whether selective activation of the M1 muscarinic acetylcholine receptor using either the M1 allosteric agonist VU0357017 or M1 positive allosteric modulator BQCA can attenuate LPS effects in the CHT +/- mouse model. Taken together, these studies may provide a novel therapeutic strategy for preventing sepsis-associated acute brain dysfunction and SA-LTCIs observed with sepsis-associated delirium in patients.



Sara Sebag, Ph.D.

Vanderbilt University Medical Center

“Novel Strategies to Disrupt the Pathogenesis of Left Ventricular Hypertrophy”

Thickening of the walls of the heart (myocardial hypertrophy) is a common response of the human heart to pathological stressors. When the heart develops myocardial hypertrophy in the left heart chamber (aka ventricle) it is referred to as left ventricular hypertrophy (LVH). Humans with LVH are at increased risk of developing congestive heart failure and lethal heart arrhythmias. LVH occurs secondary to a variety of stimuli, such as long standing hypertension or mutations in genes involved in the proper function of cardiomyocytes. When LVH develops secondary to genetic mutations, it is referred to as hypertrophic cardiomyopathy (HCM), a disease that affects 1:500 individuals and contributes to a significant percentage of heart failure and sudden cardiac death in young individuals. However, despite an increased understanding of the fundamental biology regulating cardiomyocyte hypertrophy and heart failure, finding novel chemical or genetic modifiers of the disease has been limited. Studies previously utilized a transgenic zebrafish model to identify chemical compounds that interrupt hypertrophic signaling pathways. This project involves further analyzing these

compounds using pharmacological and toxicological experiments in animal models and cell based assays. Further studies will then investigate if chemical inhibition can prevent the development of cardiac disease in a mouse model of hypertrophic cardiomyopathy. The long term goal of this work is to identify novel methods to prevent myocardial hypertrophy and heart failure from developing in humans.

Research Starter Grant in Pharmacology/Toxicology

For faculty members without sufficient sources of funding, the PhRMA Foundation offers the Research Starter Grant: a one-year award to help launch independent research careers. This grant aims to assist academic scientists in pursuing studies that shed light on individualized drug therapy and optimal therapeutic options.

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The PhRMA Foundation Research Starter Grant supported the establishment of my fledgling lab and important research that discovered new mechanisms contributing to intestinal inflammation. This starter funding supported gathering essential preliminary data that I used to successfully apply for substantial federal funding.”

Brian Gulbransen, Ph.D. | Michigan State University, 2014 Research Starter Grant in Pharmacology/Toxicology

2014 Research Starter Grants in Pharmacology/Toxicology



Michelle Mazei-Robison, Ph.D.

Michigan State University

“Role of Serum- and Glucocorticoid-inducible Kinase 1 in a Novel Model of Co-morbid Opiate Use and Mood Disorders”

Co-morbidity of opiate dependence and mood disorders such as depression and post-traumatic stress disorder (PTSD) is a significant health and financial burden, one that will likely grow given the increase in both abuse and prescription of pain-relieving opiate drugs in the US. Despite the widespread and often long-term use of opiate drugs and their known addictive liability, there is still little known about the neuroadaptations that occur with chronic use and how these changes may influence susceptibility to mood disorders. Correspondingly, treatments for opiate dependence, mood disorders, and their co-morbid manifestations are limited and often unsuccessful. This void is partially due to inadequate preclinical models to interrogate the neurobiological mechanisms of co-morbidity that could yield novel therapeutic targets. Thus, one objective of this work is to employ a mouse model of depression and post-traumatic stress disorder, chronic social defeat stress (CSDS), to determine how opiate

reward and consumption are altered by mood disorders. Preliminary data suggest that susceptibility to CSDS, or a depressive-like phenotype, increases morphine reward and consumption. Given that both the depressive-like symptoms of CSDS and opiate reward are dependent on changes in the activity of dopamine neurons in the ventral tegmental area (VTA), another goal of this work is to identify the signaling changes in the VTA that mediate these behavioral effects. One promising target that will be investigated is serum- and glucocorticoid-inducible kinase 1 (SGK1), as our preliminary studies indicate that SGK1 expression and activity is robustly increased in the VTA in response to chronic opiate administration. The results of this work are expected to provide a model of co-morbid mood disorders and opiate use that can be utilized to explore novel mediators of co-morbidity, such as SGK1, a necessary step in the development of novel pharmacological interventions for these diseases.



Brian David Gulbransen, Ph.D.

Michigan State University

“Mechanistic Basis of Antioxidant–Mediated Neuroprotection in Inflammatory Bowel Disease: Role of Enteric Glia”

Reflex behaviors of the intestine such as peristalsis are essential for digestion and thus, human life. These local reflexes are orchestrated by the enteric nervous system (ENS); a complex neural network embedded in the gut wall. Breakdown of ENS control causes the failure of gut functions in the inflammatory bowel diseases (IBDs; Crohn’s and ulcerative colitis). Over 75% of individuals with IBD will require surgery to remove diseased bowel and most will experience a postoperative recurrence because current therapeutics are ineffective. Preliminary studies point to oxidative stress as a key factor driving enteric neuron death. The goal of this project is to determine the mechanistic basis of antioxidant-mediated neuroprotection. Emerging evidence suggests that enteric glial cells that surround enteric neurons regulate neuron survival and oxidative stress within the ENS. This proposal will test the hypothesis that antioxidants protect enteric neurons by limiting the release of toxic compounds from enteric glia. Collectively, the experimental aims of this study investigate enteric glial cells as important drug targets to treat a common, and debilitating human disease. It is anticipated that the project findings will identify glial cells as novel drug targets to help patients who are not responsive to currently available treatments.

Health Outcomes

Pre Doctoral Fellowship in Health Outcomes

With a focus on healthcare and its effects on the well-being of patients and populations, outcomes research provides crucial information to doctors, patients, policymakers, and clinicians. The Foundation's Pre Doctoral Fellowships in Health Outcomes seek to increase the number of trained investigators studying all aspects of drug therapies by providing a stipend to students two years away from completing doctoral dissertations.

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As a recipient of the PhRMA Foundation's Pre Doctoral Fellowship in Health Outcomes, I have been able to focus on my dissertation methods and research while not having to also work as a graduate assistant. The experience of planning, writing, applying for, and being awarded this fellowship has solidified my belief in the importance of my research, and helped me collaborate with researchers outside of my field.”

Emily Reese | University of Maryland, Pre Doctoral Fellowship in Health Outcomes Recipient

2014 Pre Doctoral Fellowship in Health Outcomes



Julieta Scalo, PharmD

University of Texas at Austin

“Assessment of Hypnotic Use and Associated Outcomes in Persons With Cancer”

More than half of patients receiving cancer treatment report disturbed sleep, and a quarter of patients rate the problem as moderate to severe. Disturbed sleep can have many detrimental effects for patients with cancer, including worsened pain and fatigue, increased risk of depression and anxiety, disrupted immune function, and decreased quality of life. Recent evidence suggests that disturbed sleep may hinder a patient's recovery and even promote cancer progression. Clinicians and researchers agree, therefore, that therapies to improve sleep are essential for patients with cancer. Reliance on sleep medications (*hypnotics*) has been common in past decades, but there is little recent research on hypnotic use in the setting of cancer. Over the last two decades, several new hypnotics have been introduced. Because patients with cancer have additional risk factors for sleep disturbance and markedly higher risks of adverse medication events, they may have unexpected responses to these hypnotics. Thus, there is a critical need for current studies of hypnotic use in this population. This study is a secondary analysis of data collected during a large (> 3,000 subjects), comprehensive (19 symptoms, 6 quality of life measures) survey of cancer symptom



burden in patients being treated for breast, lung, colorectal, or prostate cancer. The purpose for this study is to characterize patterns of sleep disturbance and hypnotic use in people with cancer, and to evaluate the symptom burden and quality of life of patients with sleep disturbance and those using hypnotics. This study will also evaluate relationships between sleep disturbance and other cancer symptoms. Findings from this study will serve as a preliminary step towards identifying optimal medications and clinical practices for managing disturbed sleep in patients with cancer. Increased understanding of the complex relationships between a patient's sleep, medications, and cancer symptoms will enable clinicians and researchers to develop more effective guidelines for sleep management as well as to make more strategic choices for individual patients.

Post Doctoral Fellowship in Health Outcomes

Post Doctoral Fellowships in Health Outcomes support scientists launching research projects that represent the promising field of health outcomes at schools of pharmacy, medicine, and public health. Scientists beginning careers in this area are eligible to receive an annual stipend for up to two years.

“

Receiving the Health Outcomes Fellowship from the PhRMA Foundation has allowed me to pursue my own research ideas, bridging the gap from student to independent researcher. Through the fellowship I am able to work closely with great mentors and have protected time to work on my project. I am excited about the potential of this project to inform health policy.”

Jean McDougall, Ph.D. | University of Washington, 2014 Post Doctoral Fellowship in Health Outcomes

2014 Post Doctoral Fellowship in Health Outcomes



Jean McDougall, Ph.D.

University of Washington

“Estimating the Elasticity of Demand for Tyrosine Kinase Inhibitors Across Disease Settings”

This research aims to estimate and compare across disease settings the elasticity of demand for TKIs as a function of changes in out-of-pocket expenses measured at three levels; out-of-pocket TKI expenditures, total out-of-pocket expenditures for all medical goods and services, and total out-of-pocket expenditures for all medical goods and services for family members insured under the same plan. The project proposes a retrospective cohort study of commercially insured chronic-phase CML, metastatic RCC, or metastatic NSCLC patients age 21 and older who initiated TKI use between 2007 and 2013. Eligible study participants will be identified from Truven MarketScan database Commercial Claims and Encounters files. International Classification of Disease 9 (ICD-9) codes will be used to create a cohort of chronic-phase CML (205.1) patients. In addition, individuals with metastatic RCC (189) or NSCLC (162) will be identified by the presence of one inpatient or two outpatient codes for metastasis (196-199). To classify metastasis, two outpatient codes occurring at least 30 days apart are required in order to avoid misclassifying patients treated in the outpatient setting where rule-out codes may remain in the record, while a single inpatient code will suffice. In order to create a cohort of incident TKI users, the study will be restricted to individuals with continuous prescription drug coverage for six months prior to the first TKI claim appearing in the pharmaceutical claims records. The six-month look-back period will be used to establish that no prior use of TKIs occurred for a given patient.

Research Starter Grant in Health Outcomes

Scientists beginning independent research careers at the faculty level are eligible to receive funding for one year to study patient-centered outcomes, data, systems, and technologies for improving the effectiveness of pharmaceutical interventions.

“

Receiving a PhRMA Foundation Research Starter Grant has allowed me to acquire data resources which are making my current study possible but will also help me conduct many additional studies in the coming years. I will see the impact of this award far into the future and I could not be more grateful.”

Hayley Gershengorn, M.D. | Albert Einstein College of Medicine, 2014 Research Starter Grant in Health Outcomes

2014 Research Starter Grants in Health Outcomes



Susan Hutfless, Ph.D.

Johns Hopkins University

“Treatment Strategies for Newly Diagnosed Crohn’s Disease and Ulcerative Colitis”

The armamentarium for Crohn’s disease and ulcerative colitis has increased dramatically since the introduction of biologic treatments in 1998. If certain initial therapies truly alter disease course, the study of incident cases and their initial treatment is essential to evaluate treatment algorithms and their effectiveness. Using information from the electronic medical systems of the U.S. Department of Defense, which contains incident cases of Crohn’s disease and ulcerative colitis as well as complete pharmacy and inpatient and outpatient records since enlistment in the military, two aims will be pursued. Aim 1 will examine factors associated with initial treatments for Crohn’s disease and ulcerative colitis using a high-dimensional data mining technique developed by Dr. Hutfless. The mined data sources will include field and text string searches from demographic, inpatient, outpatient, laboratory, endoscopy, pathology and pharmacy records as well as information about the health care providers. Aim 2 will examine the association between initial treatments and need for hospitalizations and surgeries related to Crohn’s disease and ulcerative colitis by performing time to event analyses by first treatment for disease as well as the treatments used within 6 months of diagnosis and associate these treatments with incident hospitalization and surgery accounting for disease activity at diagnosis.



Hayley Beth Gershengorn, M.D.

Albert Einstein College of Medicine

“Identification of the Optimal Antibiotic Regimen for Legionella Pneumonia”

Legionella pneumonia (Legionnaires Disease, LD) is a relatively recently recognized entity and its incidence is increasing. Outcomes for patients hospitalized with LD have improved in the past decades, yet up to one quarter of patients require invasive mechanical ventilation and, for those with acute respiratory failure, mortality remains high—greater than one third die in the hospital. Current guidelines recommend the use of one of two antimicrobial medications (azithromycin or a quinolone) for treatment in hospitalized patients, yet it is unknown whether one regimen or perhaps combination therapy is superior. Using a national database of hospitalized patients encompassing approximately one fifth of all United States discharges, a retrospective analysis to identify antibiotic regimens associated with better outcomes in LD will be conducted. Using, primarily, a propensity-score matching strategy, the mortality associated with different treatment approaches in patients with LD will be compared. Experts hypothesize that azithromycin has similar efficacy to quinolones. If this is the case, it may be cost-effective to use azithromycin as the sole first-line agent; conversely, if quinolones are associated with better outcomes, they should be used preferentially.

Pharmaceutics

Pre Doctoral Fellowship in Pharmaceutics

As one of the Foundation's longest-standing programs, the Pre Doctoral Fellowship in Pharmaceutics assists students engaged in dissertation research on relationships among drug delivery systems, gene therapy, and clinical applications. A stipend is provided when coursework has been completed and Ph.D. candidates begin their final research project.

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The PhRMA Foundation Pre Doctoral Fellowship reaffirms the value and potential implications of my research and ideas to the pharmaceutical community and allows me to devote more time on research. The writing experience helped me improve my ability to communicate science to scientists and the general public. It has also allowed me to engage with other fellows who share a passion for discovering and developing safe and effective medicines.”

Chelsea Hosey | University of California, San Francisco, 2014 Pre Doctoral Fellowship in Pharmaceutics

2014 Pre Doctoral Fellowship in Pharmaceutics



Daniel John Wolak

University of Wisconsin-Madison

“Exploring the Diffusion Properties of Antibodies and Viral Vectors Within the Brain”

While many attempts at drug delivery to the brain focus on bypassing the blood-brain barrier, all drugs must ultimately diffuse through brain extracellular space to reach their target sites. As drugs have become more complex (e.g. larger in size, highly bound by tissue components, or uniquely shaped with complicated geometries), diffusion limitations on distribution will become more important. Two intriguing classes of therapeutics to treat diseases of the central nervous system (CNS) are antibodies, which are currently under investigation to treat Alzheimer's disease and other CNS disorders, and viral vectors that could potentially treat neurodegenerative diseases or lysosomal storage disorders. This project will use integrative optical imaging to measure brain diffusion coefficients of fluorescently labeled antibodies and viral vectors, providing the first ever measurements in the living brain, and interpret the results using existing models. These diffusion measurements allow for the development of new distribution models of therapeutics after delivery to the brain that can aid in proper dosing and drug development. Another goal of this proposed work is to explore novel attempts to improve distribution within the brain by altering the diffusion characteristics of these therapeutics. By investigating the challenges associated with

biotherapeutic delivery to the brain, this research aims to provide new insights into recently failed clinical trials and suggest future directions for treatment.



Nicole Zane

University of North Carolina at Chapel Hill

“Impact of Age-Dependent Changes in Oxidative Metabolism in the Neonatal and Pediatric Populations”

First-pass metabolism, an important intestinal and hepatic clearance mechanism during absorption of an orally administered drug, can affect bioavailability, clearance, and the ability of a drug to achieve therapeutic levels. It is well established that expression of drug metabolizing enzymes undergo major qualitative and quantitative expression changes with age. Therefore, pediatric dose-normalization derived from adult data of many metabolically cleared drugs may lead to toxicity or therapeutic failure. This project aims to demonstrate that for drugs cleared predominantly by oxidative metabolism, *in vitro* metabolism with liver/intestinal tissues from children, coupled with physiologically based pharmacokinetic (PBPK) modeling, can predict clearance, oral bioavailability, and systemic exposure in the pediatric population. Sildenafil and voriconazole, used for life-threatening conditions and with unpredictable pharmacokinetics (PK) in neonatal and pediatric populations, respectively, will be used as probe substrates to describe enzymatic and physiologic changes. In addition, genetic variability and age-dependent differential expression of hepatic and intestinal enzymes will be characterized. These *in vitro* data will be integrated into a PBPK model to establish differences in PK behavior between adults and children. Extrapolating this approach to other pediatric medications can improve drug safety and efficacy with better formulation designs and dosing regimens in children.



John Maxwell Mazzara

University of Michigan-Ann Arbor

“Self-Healing in PLGA and Application to Controlled Release Microneedles”

Microneedles are a promising new drug delivery tool for utilizing the advantages of intradermal administration. They are projections less than 1 mm tall that penetrate the dermis without causing significant pain or bleeding, thus they are an attractive alternative to standard hypodermic needles. Because of the skin's potent immune system, microneedles are particularly well suited for use as vaccine administration devices. However, research into long-acting controlled release microneedles, which would reduce booster dependence, is limited. PLGA is a commonly used controlled release polymer, and recent studies have discovered a more efficient way to load PLGA devices with vaccine antigens by utilizing the self-healing of PLGA surface pores to trap antigen. By studying the physics underlying the self-healing phenomenon it may be possible to translate this loading approach to PLGA microneedles. This could lead

to the development of a self-stable microneedle patch that can quickly be loaded with a variety of vaccine antigens without the need to pre-formulate different patches for different vaccines. These patches could potentially be self-applied by the patient, and controlled release would reduce dependence on boosters. This would likely increase patient acceptance and lead to more widespread immunization, while also cutting the costs associated with storing, handling, and disposing of hypodermic needles.



Chelsea Mariah Hosey

University of California, San Francisco

“Physicochemical Properties and In Vitro Behavior Dictating Drug Disposition”

When designing and developing a drug, it is essential to consider how the molecular structure affects the physiological disposition of the drug. Predicting the disposition allows for successful delivery to target organs, consideration of when disease will change the safety or efficacy of a drug, how often the drug will need to be dosed, what types of toxicity may be expected, and when other drugs will affect the safety or efficacy of an administered drug. Drug transporters and metabolizing enzymes change the concentration of drug in the body, as well as where the drug goes in the body. The Biopharmaceutics Drug Disposition Classification System (BDDCS) can predict many aspects of drug disposition. BDDCS classifies drugs using the extent of metabolism, which is highly correlated with permeability rate in humans, and solubility of drugs. This project has shown that extent of metabolism can be predicted by *in vitro* permeability rate or computational predictions of permeability rate. Computer models of solubility will be incorporated to predict BDDCS class. Additionally, this project has used computer-predicted molecular properties and *in vitro* permeability rate experiments to successfully predict how a drug will be primarily eliminated from the body (i.e. metabolism, biliary excretion of parent drug, or renal excretion of parent drug). This project aims to determine the impact of hepatic basolateral drug transporters on biliary and renal elimination. The goal of this project to elucidate how molecular properties of orally administered drugs can be harnessed to predict the transport potential of drugs in development as a mechanism of delivery to target organs by considering drug access to and disposition in major drug-eliminating organs, cellular access through active transport, and predicting transporter effects based on molecular structure.

Post Doctoral Fellowship in Pharmaceutics

Post Doctoral Fellowships in Pharmaceutics support scientists seeking to further develop and refine their pharmaceutics research skills through formal postdoctoral training. The program was initiated to encourage more qualified graduates to obtain the post doctoral research training so vitally needed in the area of Pharmaceutics. The PhRMA Foundation recognizes the critical need for such well-trained scientific investigators.

“

Receiving a fellowship from the PhRMA Foundation has been an important part of my postdoctoral experience and training,” said Jessica Rouge, Ph.D. of Northwestern University and recent recipient of a Post-Doctoral Fellowship from the Foundation. “The grant has given me the freedom to delve deeper into the promising area of nanoscale drug delivery and development, which I hope to incorporate into my future career path.”

Jessica Rouge, Ph.D. | Northwestern University, 2014 Post Doctoral Fellowship in Pharmaceutics

2014 Post Doctoral Fellowship in Pharmaceutics



Jessica Rouge, Ph.D.

Northwestern University

“Enzyme-Mediated Construction of miRNA Hairpin Spherical Nucleic Acids for In Vivo Applications”

When cellular RNA levels change drastically, the effects can turn a healthy cell cancerous. The central goal of this research is to design a nanoscale, genetically tunable therapy capable of correcting dysregulated RNA expression levels inside a cell. Using nanotechnology, the deployment of RNA molecules with various therapeutic effects (i.e. siRNA, microRNA) within cells has been realized in recent years. Although promising, research to date has mainly focused on the delivery of short RNA (<25 bases). It is well known that structure is a key component of RNA function. Therefore the delivery of larger, more highly structured molecules such as aptamers and pre-microRNA (80-120 bases) will help expand the breadth of RNA therapies that can be developed for treating a wider variety of cancers. The miRNA hairpin (HP) mir211 (96 bases) has been chosen for this project as it has been shown to be implemented in many forms of cancer, including melanoma. To date, delivery of mir211 into metastatic skin cells has only been possible with the use of toxic transfection agents, therefore limiting its study to that of in vitro analysis. Using spherical nucleic acid (SNA) architectures as a delivery platform, a mir211-conjugated SNA will be designed and optimized for delivering mir-211 RNA hairpin structures into skin cells. SNAs have been shown to enhance cellular uptake and decrease degradation of nucleic acids by endogenous nucleases within the cell. In addition, the assembly of the mir-211 SNAs will be mediated by an enzymatic ligation - a novel approach in RNA attachment strategies on colloidal nanoscale surfaces. This strategy has the potential to improve the coverage and assembly of miRNAs at a NP surface, and, upon successful delivery, improve the likelihood of therapeutic genetic effects within cells.

Sabbatical Fellowship in Pharmaceutics

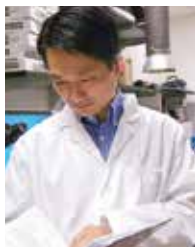
This program provides stipend funding to enable faculty members at all levels with active research programs an opportunity to work at other institutions for periods of six months to one year to learn new skills or develop new collaborations that will enhance their research and training activities in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

“

The PhRMA Foundation Sabbatical Fellowship enabled me to take the full year off, instead of just six months, to learn a new skill. The new skill will be applied in my future research to answer questions that are otherwise difficult for me to tackle. The sabbatical experience has already led to several exciting new research ideas. The positive impact of the sabbatical experience to my research is evident and long lasting.”

Calvin Sun, Ph.D. | University of Minnesota, 2014 Sabbatical Fellowship in Pharmaceutics

2014 Sabbatical Fellowship in Pharmaceutics



Calvin Sun, Ph.D.

University of Minnesota

“Novel Methods for Expanding Solid State Landscape of Drugs”

The selection of a superior solid form of an active pharmaceutical ingredient (API) is one of the most important decision points affecting the ease with which a drug product can be developed and the speed from drug discovery to market. For all API molecules, the generation of as many solid forms as possible is essential for enhancing the probability of identifying an optimum solid form with balanced pharmaceutical properties, which is critical to the expedited development of high quality products and robust manufacturing processes. In fact, screening, characterization, and selection of a suitable solid form early in the drug development process is essential for establishing clinical efficacy and safety of any experimental compounds. In this regard, any new methodology or strategy for discovering new solid forms of a drug gives enormous advantages in terms of expedited preclinical investigation, more efficient formulation development, and broadened patent protection. This work focuses on systematically developing a method to enable the synthesis of a class of crystals formed between a pair of conjugate acid-base of a drug from ionic liquids.

Research Starter Grant in Pharmaceuticals

A grant can do more than facilitate research. It can also motivate scientists who have no other viable funding sources and lay the groundwork for successful academic careers. The Research Starter Grant in Pharmaceuticals supports scientists who are beginning their academic research careers at the faculty level, and ensures the promising work of these researchers continues.

“

The PhRMA Foundation Research Starter Grant is a wonderful opportunity for early stage investigators to jump start their research career. This award has been a critical source of funding for me to establish a strong research program in my relatively early faculty career.”

Anthony Kim, Ph.D. | University of Maryland, Baltimore, 2014 Research Starter Grant in Pharmaceuticals

2014 Research Starter Grants in Pharmaceuticals



Anthony Kim, Ph.D.

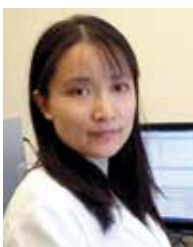
University of Maryland, Baltimore

“Fn14-targeted Therapeutics for Invasive Brain Cancer”

A long-standing problem in the treatment of glioblastoma (GBM), the most common and deadly primary brain cancer, is delivery of therapeutics to invading tumor cells that are inaccessible with surgery and the source of disease progression. Systemically administered therapies reach these cells in very low concentrations due in part to the intact blood brain barrier, and in part due to the far distance of the cells from the resectable tumor mass in functioning brain tissue. Unfortunately, local chemotherapy, provided by either biodegradable polymer implants or convection-enhanced delivery, has had limited clinical success; in part due to inefficient delivery of therapeutics to distant invading tumor cells. Therefore, effective delivery to the invading cancer cells, in particular modulation of genes and cellular pathways responsible for the disease pathogenesis, represents a promising therapeutic approach. To address these challenges, this innovative proposal couples a brain-penetrating nanoparticle technology with a promising tumor cell-targeting strategy. Fibroblast growth factor-inducible 14 (Fn14), a member of the tumor necrosis factor receptor superfamily, is an emerging target for GBM therapy. High Fn14 expression correlates with higher brain tumor grade and poor patient outcome, and is found in both migrating glioma cells in vitro and invading glioma cells in vivo. The overall hypothesis of this project is that Fn14-targeted brain-penetrating nanoparticles will suppress brain cancer invasion by: (1) specifically targeting to and efficiently trafficking within glioblastoma cells, (2) improving the delivery of therapeutic constructs into the regions of the brain that contain infiltrating tumor cells, and (3) effectively inhibiting Fn14 signaling pathways in invading tumor cells.



These studies will provide an important next step in the application of brain-penetrating delivery technologies; specifically, directly targeting treatments to the key infiltrating tumor cells not accessible with surgery. This work has the potential to overcome many of these critical delivery barriers and significantly improve treatments for patients with malignant brain tumors.



Guohua An, M.D., Ph.D.

University of Iowa

“Mechanistic Physiologically-Based Pharmacokinetic Model of Anthracyclines and Taxanes from Mice to Humans: Application in Safety Assessment and Anticancer Therapy Optimization”

This project is aimed to build highly novel and mechanistic Physiologically-Based Pharmacokinetic (PBPK) models for anticancer drugs anthracyclines and taxanes and utilize these models in anticancer treatment optimization and safety assessment. Although anthracyclines and taxanes have wide spectrum of antitumor activities, their clinical use is hampered by the occurrence of severe and unpredictable toxicities, such as anthracycline-induced cardiotoxicity. Both anthracyclines and taxanes have extensive tissue distribution, and their tissue concentrations tie closely to both anticancer effects and toxicities. Considering the difficulty of collecting human tissue samples, establishing an approach to estimate and accurately predict the concentration of anthracyclines and taxanes in human tissues is highly valuable in preventing their toxicity and optimizing their dose regimen. Anthracyclines and taxanes are known to exert their anticancer effects through targeting DNA and tubulin, respectively. The hypothesis of this project is that DNA and tubulin are not only the key factors of their anticancer effect, but also major determinants of their tissue distribution. The overall goal of this proposed work is to establish an approach to assess their efficacy and safety through developing comprehensive, mechanism-based PBPK models to predict their tissue concentrations, taking into account not only physicochemical drug properties, anatomical and physiological system-specific properties, but also pharmacological targets of anthracyclines and taxanes (DNA and tubulin, respectively). The results of this project are expected to play an important role in preventing the toxicity of anthracyclines and taxanes and optimizing their dose regimen.

Clinical Pharmacology

Paul Calabresi Medical Student Fellowship

Named in honor of Dr. Paul Calabresi, who served the PhRMA Foundation as committee chairman and member for 25 years, the Paul Calabresi Medical Student Fellowship gives students an opportunity to spend up to two full years conducting an investigative project in pharmacology. By engaging scientists involved in important research projects at a point when their professional interests may lead them in different directions, the program aims to pave the path for research and teaching careers in clinical pharmacology.

2014 Paul Calabresi Medical Student Fellowship



Ranjodh Singh

Weill Cornell Medical School

“Molecularly-Defined Combinatorial Targeted Therapy in a Diffuse Intrinsic Pontine Glioma Mouse Model Using Convection-Enhanced Delivery”

Diffuse intrinsic pontine glioma (DIPG) is a lethal pediatric brain tumor lacking definitive therapy. Convection-enhanced delivery (CED) is a local drug delivery method that bypasses the blood brain barrier and optimizes therapeutic indices, with promising potential in treating DIPG. Up to 50% of DIPGs harbor amplifications in the receptor tyrosine kinase (RTK)/ phosphatidylinositol 3 -kinase (PI3K)/ Protein Kinase B (AKT)/ mammalian target of rapamycin (mTOR) signaling network responsible for tumorigenesis, with platelet derived growth factor receptor (PDGFR), a RTK, being the most commonly amplified and over-expressed component. The ultimate goal of this project is to test whether CED of dasatinib (PDGFR inhibitor), perifosine (AKT inhibitor) and everolimus (mTOR inhibitor) in varying combinations optimizes therapeutic concentrations for extended periods and improves therapeutic efficacy in a PDGFR-driven DIPG mouse model. The project hypothesizes that CED with dasatinib plus perifosine plus everolimus will have a therapeutic advantage in comparison to single agent or dual agent combinations. Therapeutic concentrations will be assessed using magnetic resonance imaging and therapeutic efficacy will be assessed by animal survival, tumor size, cell death and cell proliferation, and by the activation status of the mitochondrial apoptotic pathway, the PI3K/AKT/mTOR and parallel signaling pathways. This study converges several contemporary principles of DIPG research, and has the potential to translate into an innovative clinical trial and significantly improve DIPG treatment.

Faculty Development Award in Clinical Pharmacology

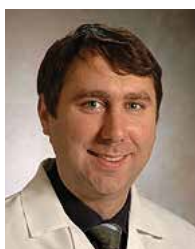
Established by the PhRMA Foundation in 1966, the Faculty Development Award in Clinical Pharmacology recognizes the many challenges of drug investigation, particularly those related to ensuring a highly trained and competent workforce. This program stimulates clinical pharmacology teaching, training, and research by providing annual awards to medical schools in support of full-time junior faculty members. The ultimate goal is to maximize the research potential of clinical pharmacologists during the years immediately following formal training programs.

“

As a junior faculty, the PhRMA Foundation award has been instrumental in my career development. This award has allowed me the protected time to build a research program and create a pathway toward independence. Further, this award has allowed me the opportunity to acquire the necessary skills to compete for federal funding and facilitate a long-lasting career applying clinical pharmacology principles to important research questions.”

Michael Eadon, M.D. | Indiana University School of Medicine, 2014 Faculty Development Award in Clinical Pharmacology

2014 Faculty Development Award in Clinical Pharmacology



Michael Eadon, M.D.

Indiana University School of Medicine

“Genetic Susceptibility to Nephrotoxicity”

This proposal seeks to uncover genetic predictors of drug-induced acute kidney injury. Acute kidney injury is a common unintended consequence of prescribed medications that leads to increased mortality, hospital stay, medical expenditures, and may result in discontinuation of or delay in treatment of malignancy and other life threatening conditions. The central hypothesis of this proposal is that specific genes and genetic variants associated with drug-induced cytotoxicity in a cell-based model also modulate *in vitro* renal cell toxicity and *in vivo* development of acute kidney injury in mouse nephrotoxicity models. The relationship between variants and gene expression will be validated in renal cells as well as *in vivo* using 2’O-methylated siRNA knockdown in mice. The genetic associations validated in this project should produce a predictive model for colistin, clofarabine, and cisplatin nephrotoxicity that serves as an impetus for dose reduction or alternative therapy selection in patients. This approach would be *paradigm shifting* - moving from the current clinical approach of monitoring for and managing acute kidney injury consequences, to a strategy of nephrotoxicity prevention through personalized medicine.

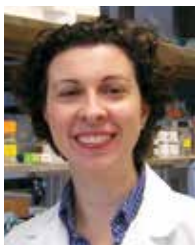
Translational Medicine and Therapeutics

Post Doctoral Fellowship in Translational Medicine and Therapeutics

The PhRMA Foundation Post Doctoral Program in Translational Medicine and Therapeutics provides stipend support for individuals engaged in multidisciplinary/collaborative research training programs that will create or extend their credentials in this evolving area. The intent of this program is to support postdoctoral career development activities of individuals preparing to engage in research that will bridge the gap between discoveries using experimental and computational technologies and in the research laboratory and their application in clinical research and the clinic. A key component of postdoctoral training in this area involves collaborative programs that span the non-clinical and clinical domains, potentially involving multiple laboratories, advisers and/or institutions.

The first Translational Medicine and Therapeutics awards were awarded in 2013.

2014 Post Doctoral Fellowship in Translational Medicine and Therapeutics



Katherine Theken, Ph.D., PharmD

University of Pennsylvania Perelman School of Medicine

“Cyclooxygenase Expression and Cardiovascular Effects of Non-Steroidal Anti-inflammatory Drugs”

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to relieve pain and inflammation, but cause serious cardiovascular adverse events in some patients. Understanding the factors that influence an individual patient's risk of adverse cardiovascular outcomes will allow physicians to prescribe NSAID therapy rationally to maximize benefit and minimize cardiovascular risk. The expression of cyclooxygenase (COX)-1 and COX-2, the molecular targets of NSAIDs, is highly variable among individuals, and we hypothesize that COX expression level influences a patient's susceptibility to adverse cardiovascular events following NSAID treatment. The proposed studies will investigate the relationship between COX expression level and the biochemical and cardiovascular effects of NSAIDs in mice and humans, as well as identify genetic variants that influence expression of the COX pathway in humans. These studies will provide insight into the factors that influence response to NSAIDs and regulate COX pathway expression in humans, as well as lay a foundation for future studies to identify biomarkers to personalize NSAID therapy.



Jun T. Wang, Ph.D.

University of California, Davis

“Increased Mitochondrial DNA Damage and Neurodegeneration in Fragile X-Associated Tremor/Ataxia Syndrome”

The fragile X mental retardation 1 (*FMR1*) gene has a dynamic CGG repeat region in its promoter region downstream of the sites of transcription initiation. While normal *FMR1* alleles contain up to 45 CGG repeats, somewhat larger (premutation) alleles, with 55-200 CGG repeats, are now known to be vulnerable to a spectrum of clinical conditions including neurodevelopmental problems, psychiatric disorders, premature ovarian failure, and a late onset progressive neurodegenerative disorder, fragile X-associated tremor/ataxia syndrome (FXTAS). Among these conditions, FXTAS is particularly devastating, presenting not only core impaired motor function, but also cognitive deficits progressing to dementia, and problems in autonomic control, sensory, and the immune system in some of the patients. FXTAS is characterized by partial penetrance, which affects approximately 40% male and 13% female premutation carriers after 50 years of age. The main neuroimaging findings include generalized brain atrophy and microstructural damage. The basis for FXTAS pathogenesis has been hypothesized to be substantially elevated *FMR1* mRNA. One of the downstream consequences of the molecular dysregulation in FXTAS is mitochondrial dysfunction, which could lead to increased oxidative stress and age-related accumulation of mitochondrial DNA mutations. However, a direct link between mitochondrial dysfunction and neurodegeneration has not been demonstrated. The goal of the proposed study is to determine whether age-related accumulation of mtDNA mutations underlies neurodegeneration in FXTAS and explains the partial penetrance. Understanding the role of mitochondrial DNA mutations in FXTAS may help us design effective therapeutic treatments and identify vulnerable patients who may develop FXTAS. Since carriers of *FMR1* premutation are common in the general population (1 in 100-200 females and 1 in 250-500 males), improvement of disease outcomes for the premutation-associated disorders, including FXTAS, would have a significant benefit to society. Moreover, the knowledge gained and methods developed during the study are broadly applicable to aging and common neurodegenerative diseases such as Alzheimer's and Parkinson's where mitochondrial DNA mutations have been found to play an important role.

Research Starter Grants in Translational Medicine and Therapeutics

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 Research Starter Grant Program in Translational Medicine and Therapeutics aims to support individuals beginning independent research careers in academia or research institutions and where long term training of students and/or scientists is an expected outcome in conjunction with their research. This program focuses on supporting the career development of scientists engaged in bridging research and discoveries using experimental and computational technologies to their application in clinical research and the clinic. The program is not focused on supporting the application of standard technologies to experimental biology or medicine but specifically to explore innovative and collaborative projects that bridge the non-clinical:clinical interface.

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My PhRMA Foundation Translational Medicine and Therapeutics Award has been instrumental in establishing my independent research career. It was my first funding as an independent investigator, supporting my research and propelling me to compete for additional funding. More importantly, the award is allowing me to translate my basic research findings from animal models to humans, potentially identifying new therapeutics in colorectal cancer.”

Adam Snook, Ph.D. | Thomas Jefferson University, 2014 Research Starter Grant in Translational Medicine and Therapeutics

2014 Research Starter Grants in Translational Medicine and Therapeutics



Adam Snook, Ph.D.

Thomas Jefferson University

“GUCY2C-Specific Tolerance in Colon Cancer Patients”

There is an evolving focus to exploit the specificity and efficacy of the immune system to treat cancer through vaccination. However, cancer vaccines have limited efficacy in patients, reflecting self-tolerance mechanisms limiting responses to self-antigens. Guanylyl cyclase C (GUCY2C or GCC) is a protein selectively expressed in apical membranes of intestinal epithelial cells and is universally over-expressed by metastatic colorectal cancer, making it an attractive target in cancer immunotherapy. However, tolerance severely limits the efficacy of adenoviral GUCY2C (Ad5-GUCY2C) vaccination in mice. In contrast to the current paradigm suggesting that all lineages of immune cells are equally impacted by tolerance, recent studies demonstrate that CD4+ T-helper cells, but not CD8+ T cells or B cells, are tolerant to GUCY2C in mice. Importantly, the absence of T cell help provided by CD4+ T cells severely limits GUCY2C-specific CD8+ T and B cell responses and antitumor immunity. The proposed research will examine CD4+ T cell tolerance in colon cancer patients receiving the Ad5-hGCC-PADRE vaccine in a phase I clinical trial. Moreover, these

studies will examine the ability of exogenous T-helper responses directed to the PADRE epitope to rescue GUCY2C-specific CD8+ T and B cell responses in patients. Successful completion of these studies will direct future studies examining GUCY2C tolerance mechanisms, leading to next-generation immunotherapeutics.



Sony Tuteja-Stevens, PharmD, MS

University of Pennsylvania, Perelman School of Medicine

“Metabolomics Guided Pharmacogenomics of Niacin”

Atherosclerosis is the leading cause of death in the United States, with 450,000 deaths occurring annually due to coronary heart disease (CHD). Statins medications lower low-density lipoprotein cholesterol (LDL-C) and reduce the risk for CHD. However even after statin therapy there remains a high level of coronary event risk in some individuals. Therefore there is an unmet need for new medications to reduce this risk. High-density lipoprotein cholesterol (HDL-C) has been identified in population studies as an independent, inverse predictor of cardiovascular events. However, recent studies with drugs that raise HDL-C, such as niacin have been disappointing, creating controversy on the contribution of HDL-C to CHD risk. The mechanism by which niacin modulates HDL-C and other lipids remains poorly understood. This project will apply cutting-edge metabolomic methods, which measure small biomolecules with high resolution, in several human cohorts of niacin treatment. The goals of this study are to discover genetic predictors of niacin response that point to the mechanism by which niacin raises HDL-C and uncover potential drug targets to modulate HDL-C and CHD risk.



Sihem Ait Oudhia, Ph.D., PharmD

University at Buffalo

“Systems Pharmacological Approach to Support Novel Drug Sequencing to Overcome Lapatinib Resistance in HER2 Positive Breast Cancer”

HER2 positive (HER2+) breast cancer is an aggressive cancer of younger women, but responds well to Lapatinib. However, resistance emerges to Lapatinib, presenting the significant clinical challenge of identifying efficacious alternative therapies. Kadcyla® (T-DM1) was recently FDA-approved for HER2+ breast cancer patients unresponsive to Lapatinib. The long term goal of the proposed research project is to improve survival of Lapatinib-resistant breast cancer by developing novel pharmacological approach involving a sequential combination therapy. The hypothesis is that a specific treatment of sequence of paclitaxel, T-DM1, and bevacizumab (BmAb) is synergistic and can overcome Lapatinib-resistance. The specific aims are: 1) investigate whether priming Lapatinib-resistant breast cancer tumors with paclitaxel improves deposition and efficacy of T-DM1, 2) investigate whether subsequent modulation of tumor blood supply with BmAb reduces T-DM1 tumor efflux and improves efficacy. The suggested experimental approach is to: 1) measure over time the drug responses of key proteins

in paclitaxel, T-DM1, and VEGF signaling pathways and cellular responses such as apoptosis, cell survival, cell-cycle arrest, and antibody-dependent cell cytotoxicity; 2) build a systems pharmacological model that captures the dynamic interaction of these responses; 3) test the fidelity of the in vitro systems model to predict in vivo antitumor responses. The final mathematical model will predict optimal dosing regimens for Lapatinib-refractory breast cancer by simulation, which will be tested experimentally. This project is relevant to cancer treatment and cure because it introduces a novel therapeutic approach based upon a sequential combination of three drugs of different but complementary mechanisms of action, with the intent to cure drug-resistant breast cancer in a patient population having the potential for long and productive lives.

Comparative Effectiveness Research

As Comparative Effectiveness Research (CER) continues to evolve, specialized educational programs have the potential to bridge gaps in current training and ensure students are proficient in the field. In an effort to diversify and integrate training for those interested in this area, the Foundation provides funding for schools and universities to develop or expand degree-granting CER programs that could serve as national models. It is our belief that established CER programs will ensure optimal comparisons of tools and treatments for disease prevention, diagnosis, management, and treatment.

2014 Comparative Effectiveness Research Center



Eleanor Perfetto, Ph.D., M.S.

University of Maryland

“PROEM: A Center of Excellence in CER-PCOR Training”

The Patient-Centered Research for Outcomes, Effectiveness, and Measurement (PROEM) Center of Excellence in Comparative Effectiveness and Patient-Centered Outcomes Research Training at the University of Maryland, Baltimore (UMB) aims to expand and improve training in comparative effectiveness research and patient-centered outcomes research (CER-PCOR). Supported by an interdisciplinary team from six professional schools and five research centers across UMB—as well as a range of committed external partners from government, nonprofit, professional, trade, and private organizations—the PROEM Center of Excellence builds upon the University’s strengths in CER-PCOR, graduate and continuing education, community outreach, and collaborative partnerships to support its innovative programs. PROEM employs two approaches to enhance CER-PCOR education and training opportunities for researchers and health care professionals: 1. Expanding the School of Pharmacy’s existing PhD and MS programs in Pharmaceutical Health Services Research to include a new concentration in CER-PCOR, and 2. Developing and offering continuing education (CE)



programs in CER-PCOR for established researchers and health care professionals. With this expansion of the graduate program, new CER-PCOR courses have been added to the curriculum. These cutting edge courses are taught by faculty members from the Schools of Pharmacy, Medicine, Nursing, and Law; the program has attracted a range of external experts to serve as adjunct and guest faculty. The Center offers a variety of options for health care professionals and researchers to advance their skills in this specialized and increasingly vital area of research through interdisciplinary continuing education programs. In 2015, PROEM will host its first annual CER-PCOR Summer Institute, a five-day course for researchers, clinicians, faculty, government and policy makers, students, and postdoctoral fellows. In 2015, an introductory CER-PCOR online module CE series to introduce researchers, clinicians, and other health care professionals to the fundamentals of CER-PCOR will be launched. PROEM is committed to the dissemination of CER-PCOR training materials and information on CER-PCOR in general: The newly launched PROEM webpage serves as the platform for our dissemination efforts and is linked to other CER-PCOR resources on campus, such as the UMB CER-PCOR website, which highlights CER-PCOR funding opportunities for researchers, and the UMB PATIENTS program, which is developing infrastructure to support patient engagement.

Young Investigator Award in Adherence Improvement Program

Research Starter Grant in Adherence Improvement

The purpose of the PhRMA Foundation Research Starter Grant is to offer financial support to individuals beginning independent research careers in academia who do not have other substantial sources of funding. Relevant research goals include the development or evaluation of policies, interventions, or tools that are potentially successful in improving medication adherence.

“

The PhRMA Foundation Research Starter Grant in Adherence Improvement has already significantly bolstered my career. With this grant, I have been able to set up a proper research lab with equipment, research assistants, and medical collaborators—and I have gained the experiences required to continue this kind of research with medical patient populations. Beyond the invaluable experience and infrastructure this grant has provided to me and my lab, the data I have collected with this particular project will serve as the necessary preliminary evidence I need for a larger external grant I am applying for from the National Institutes for Health. Lastly, above and beyond the monetary support I have received from the PhRMA Foundation, I have gotten immense personal and professional support from the PhRMA Foundation staff; the Foundation clearly cares about their award recipients as individuals and developing professionals.”

Leigh Allison Phillips | George Washington University, 2014 Research Starter Grant in Adherence Improvement

2014 Research Starter Grant in Adherence Improvement



Anna Hall, PharmD, BCACP

University of Florida

“The Effect of Tailored Interventions Driven by Predictive Analytic Modeling on Improving Medication Adherence for Medicare Advantage Prescription Drug Plan Members”

As a result of non-adherence, many individuals do not reach their intended therapeutic goals. Non-adherence adds \$100-\$289 billion in costs for the US healthcare system on an annual basis. Medication adherence is a complex issue, affected by both behavioral and system barriers. There is no one-size fits all intervention that aids in improving

adherence. Battling non-adherence requires comprehensive efforts to understand patients' behavior, knowledge, and perception of their health in an effort to provide specific, tailored interventions to improve medication use. In line with the Institute for Healthcare Improvement's Triple Aim for healthcare improvement, the Centers for Medicare and Medicaid Services (CMS) has adopted quality measures that focus on adherence to medications for chronic conditions. Medicare Advantage Prescription Drug (MAPD) plans are currently rated on three measures of adherence: diabetes medications, RAS antagonists for hypertension, and statins for cholesterol. WellCare Health Plan, Inc. has contracted with both RxAnte and the University of Florida (UF) College of Pharmacy's Medication Therapy Management Communication and Care Center (UF MTMCCC) to provide their plan members tailored interventions intended to improve medication adherence. Interventions are provided based on predictive analytic modeling and a telephonic assessment of patient-reported barriers to medication adherence. Based off of this assessment the MTMCCC offers interventions tailored for individual patients and provides ongoing follow-up support to encourage both medication adherence and persistence. The objectives of this research are to determine the ability of the UF MTMCCC adherence program to improve medication adherence for WellCare MAPD plan members selected for outreach by RxAnte's predictive analytics as well as the effectiveness of the program on an MAPD plan's performance for each of the CMS adherence quality measures. Findings from this research can contribute to national efforts to determine which intervention, or combination interventions may be effective in improving adherence to critical medications.



Rory O'Callaghan, PharmD

University of Southern California

“The Impact of Clinical Pharmacy Teams on Medication Adherence for Diabetic Patients in a Patient-Centered Medical Home”

Evidence shows that improving glycemic control in patients with Type 2 diabetes has the potential to slow and possibly prevent the development of diabetic complications. Doing so can lead to decreased healthcare costs and improved quality of life. In order to achieve and maintain glycemic control, patients must receive appropriate medication therapy and learn self-management skills. Diabetes management is more difficult in low-income patient populations, who may be more likely to have poor health literacy and face the challenges of managing a complex set of chronic conditions on a limited budget. To address these concerns, the University of Southern California and AltaMed Health Services developed a study integrating clinical pharmacy services into patient-centered medical homes. The proposed study aims to expand upon this ongoing intervention to assess its impact on medication adherence and patient self-management in high-risk patients with type 2 diabetes. This study will assess medication adherence rates in the treatment group compared to a matched control population. Furthermore, there are multiple channels through which the intervention



of clinical pharmacy teams may impact patients' self-management and medication adherence, however it remains unclear which aspects of the program are the most effective. Therefore patients in the treatment and control groups will be surveyed regarding their knowledge of diabetes, self-management, and adherence. This data will provide a better understanding of the mechanisms through which clinical pharmacy services impact medication adherence and glycemic control.



Leigh Alison Phillips, Ph.D.

The George Washington University

“Developing a Tool to Improve Providers’ Detection and ‘Diagnosis’ of Patients’ Non-Adherence to Type II Diabetes Medications Via a Web-Portal ‘Triage System’”

This project seeks to develop a “Patient Non-Adherence Triage Protocol” that can be implemented via online communication portals or in the provider-patient medical encounter. The non-adherence protocol aims to first identify if a patient with Type 2 Diabetes is adherent or non-adherent to the prescribed treatment for the condition using standardized and evidence-based questions that assess the strength of the patient’s routine, or habit, for taking the medication(s). If the patient is categorized as non-adherent in this first step of the protocol, the provider then uses the protocol to evaluate the reasons for non-adherence, so that he/she can provide evidence-based intervention(s) appropriate to the particular barriers a patient is facing. There are three categories of adherence-barriers that a patient may be placed into using the triage protocol, based on basic health and social psychological theory: the patient may be lacking a routine (stable context cues to automate the behavior); the patient may be lacking experience that the treatment works as expected; the patient may be lacking treatment-favorable beliefs. The purpose of the proposed project is to further substantiate the theoretical framework in this Type 2 Diabetes population, having been tested only in primary care and hypertension populations, and to determine

the parameters of the non-adherence categorizations. Patients on daily pill-form medication for Type 2 Diabetes will answer the triage-protocol questions (standardized and open-ended interview questions) in an in-person baseline session and use an electronic monitoring pill bottle for one month after the baseline session, as an objective measure of adherence. Patients' physical activity will also be assessed in the questionnaire and for one month using a 'Fitbit' accelerometer. Data will be used to evaluate the theoretical framework and to determine the parameters of the triage protocol, which will then be validated in a separate sample of patients.

Quantifying the Benefits of Innovation in Cancer Treatment

Research Starter Grants in the Benefits of Innovation in Cancer Treatment

The purpose of this grant is to encourage research aimed at quantifying the benefits to society that have accrued from innovations in cancer treatment.

Researchers and clinicians have made remarkable progress in the fight against cancer, and death rates are falling. However, the disease still causes enormous suffering and represents a substantial economic burden in the United States. While cancer medicines have extended millions of lives and offer trillions in societal benefits, this value often is not well understood or fully characterized. Social and economic benefits accrue across a range of direct and indirect effects (e.g., overall survival, quality of life, and productivity) and evolve over time as the body of evidence and standards of practice change. As our understanding of the basic science of cancer grows, and this understanding is translated into novel diagnostics and treatments, patients and society benefit from continual innovation in cancer care.

“

The support of the PhRMA Foundation has been critical in my efforts to measure the true value of cancer care. As federal funding for cancer outcomes research becomes more and more restricted, funding and interest from nonprofit foundations is even more important. The support from the PhRMA Foundation has allowed me to purchase data, support data infrastructure, and obtain sophisticated programming and statistical analysis so that the research can be performed in a rigorous and comprehensive manner.”

James Yu, M.D. | Yale University, 2014 Research Starter Grant in the Benefits of Innovation in Cancer Treatment

2014 Research Starter Grant in Assessing the Benefits of Treating Cancer



James Yu, M.D.

Yale University

“Quantifying the Benefit of Modern Cancer Therapy for Elderly Patients: A Population Level Measurement”

In recent years, though there has been measurable improvement in the how long cancer patients live, the cost of cancer care has steadily increased. As a result, the Institute of Medicine, argued that costs are unsustainable, pointing to an oncoming “crisis” in cancer care, in particular for the elderly. Therefore, quantifying the improvement in national cancer outcomes for these cancers over the past decade is a critical area of investigation. Using the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) – Medicare Health Outcomes Survey (MHOS) linked database, this project attempts to calculate difference in quality of life of patients who were treated a decade apart: in 1998-1999, and 2008-2009 for elderly patients with breast, prostate, and lung cancer. In this way, this project attempts to quantify the progress that has been made over the past decade in cancer care in a manner that can directly translate into discussions of the cost-effectiveness of modern cancer care.



Jennifer Lund, Ph.D.

University of North Carolina at Chapel Hill

“Evaluating Heterogeneity of Cancer Treatment Benefits Among Older Adults”

The majority of patients diagnosed with colon cancer are over 65 years old, and this number is expected to grow over the coming years. At colon cancer diagnosis, older adults have more chronic conditions and functional disabilities than younger patients, which can complicate their cancer treatment decision-making. Unfortunately, older colon cancer patients tend to be underrepresented in clinical trials, therefore little is known about which cancer treatments are most effective and safe for this complex patient population. This study will use a large dataset from the National Cancer Institute that collects information about older Medicare beneficiaries diagnosed with cancer across the United States. This research study of over 5,000 colon cancer patients diagnosed over the age of 65 years old will describe trends in the use of two approved chemotherapy treatments and compare whether a newer treatment is better at extending survival and preventing adverse treatment events than an older treatment, both overall and within smaller groups of patients who are similar with respect to their chronic condition and functional disability profile. Results from this research study will provide older colon cancer patients and their physicians with information about the benefits and harms of the two available chemotherapy treatments that can be used to make personalized decisions about colon cancer treatment.

Adherence Intervention Evaluation

Adherence Intervention Evaluation Award

Medication adherence is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a treatment regimen. Extensive evidence demonstrates that medication adherence can yield better clinical and economic outcomes. However, many individuals do not take their medications as recommended. Closing the adherence gap is important to improving the quality of health care, encouraging better chronic care management, and promoting better outcomes. The purpose of this award is to fund research that will advance knowledge of innovative and effective approaches to improve medication adherence in community and clinical settings.

2014 Adherence Intervention Evaluation Award



Hayden Bosworth, Ph.D.

Duke University

“Evaluating CVD Medication Adherence Program in Low SES”

Medication adherence is one of the largest public health dilemmas; up to 50% of individuals are non-adherent with their medications. Up to 22% improvements in pill refill and 4-fold improvements of medication self-reported adherence have been demonstrated. For this project, we will examine the implementation of a 6-month efficacious medication adherence program in a safety-net primary care clinic that provides care to patients with low socioeconomic status and high risk for cardiovascular disease (CVD). The program consists of patients receiving/responding to e-reminders to take medications via (SMS; text messaging and email), also supported by a tailored (e.g. low socioeconomic status, low literacy), self-management program administered by a pharmacist via telephone. In addition to medication reminders, our multi-delivery platform will also deliver messages regarding side-effects, risks/benefits to medication treatment, and potential barriers to medication adherence. All patients who meet study eligibility will receive the program. The goal of this project is to enroll at least 100 patients who have uncontrolled BP ($>140/90$), a diagnosis of hypercholesterolemia or diabetes mellitus type 2, and who are under-insured. The implementation fidelity of this adherence program will be measured to examine cardiovascular outcomes, such as, reduced SBP (by 5mmHG), Hgb A1c (by 0.5%), LDL-C (by 20 mg.dl), as well as pill refill adherence (an improvement by 10%). This project will result in a leap forward in CVD risk management among those patients who need it most. Data from this project is being used as preliminary data for a NIH resubmission for a multi-site trial that scored well last cycle.



The Foundation was honored to present its 2014 awards at distinguished scientific annual meetings throughout the country.

Our thanks to the following organizations:

The American Association of Pharmaceutical Scientists (AAPS)

San Diego, California presented on November 2, 2014
AAPS President, Alice E. Till, Ph.D. is pictured at the presentation.

The American Society for Clinical Pharmacology and Therapeutics (ASCPT)

Atlanta, Georgia presented on March 19, 2014
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 26, 2014
by Terry L. Bowlin, Ph.D., Chairman of the Basic Pharmacology Advisory Committee

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

Montreal, Canada presented on June 4, 2014
By Jean Paul Gagnon, Ph.D. Chairman of the Health Outcomes Advisory Committee

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Treasurer's Report

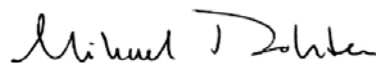


The PhRMA Foundation ended 2014 in solid financial shape despite a financially challenging year. Member contributions were \$2.4 million consistent with 2013. These contributions are the sole support for the Foundation's core program of grants and newer strategic partnerships on CER, Translational Science and Safe and Effective Prescribing. Beyond these programs, the Foundation has also implemented programs designed as part of PhRMA's priorities and funded from PhRMA's budget. In 2014 PhRMA contributed \$500,000 for these programs, which included the programs for Adherence Improvement and Quantifying the Benefits of Innovation in Cancer Treatment. Together with the PhRMA-funded programs, total contributions to the Foundation were \$2.9 million in 2014.

We awarded over \$3.3 million in grants, an increase of 23.5% over the previous year. We held down non-grant program and administrative expenses and stayed within budget. Total expenditures were \$4.1 million. Net assets at December 31 were \$21.7 million, a \$346,000 increase from the prior year. 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 benefactors, who are listed in this report. We urge all PhRMA members to become full contributors, so that we may continue the important strategic initiatives of the Foundation. With your support, the Foundation will continue building strong partnerships and increasing collaboration throughout the biopharmaceutical research sector, bringing together scientists who have dedicated their careers to improving the health of patients around the world. Our programs continue to represent our industry's commitment to innovation in research and the development of the young investigators of tomorrow.

The Foundation's financial position as of December 31, 2014, 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 black ink, reading "Mikael Dolsten". The signature is fluid and cursive, with the first name clearly legible.

Mikael Dolsten, M.D., Ph.D.
Treasurer, PhRMA Foundation

Statement of Income & Expenditures

For the year ended December 31, 2014

INCOME	
Contributions ¹	\$2,906,410
Contributions – in kind from PhRMA	\$54,584
Interest and Dividends	\$484,499
(Realized and Unrealized) Gains in Securities	\$744,543
Other Income	\$232,223
TOTAL INCOME	\$4,422,259
EXPENDITURES	
PROGRAMS	
Awards in Excellence	\$23,116
Adherence Improvement	\$212,326
Clinical Pharmacology Program	\$267,000
Comparative Effectiveness Program	\$416,660
Health Outcomes Program	\$332,500
Informatics Program	\$290,000
Pharmaceutics Program	\$452,490
Pharmacology Programs	\$733,333
Translational Medicine and Therapeutics	\$485,000
AFPE Fellowship Award	\$7,500
Other Grants	\$86,950
Subtotal – Grants	\$3,306,875
OTHER	
Committee Meetings, Travel and Honoraria	\$189,022
Publications and Special Projects	\$35,663
Subtotal – Other	\$224,685
PROGRAM TOTAL	\$3,531,560
ADMINISTRATIVE	
Staff, Taxes, Depreciation & Insurance	\$373,274
Rent & Accounting Services ²	\$54,584
Professional Services and Investment Expenses	\$111,674
Office Expenses	\$4,398
Subtotal – Administrative	\$543,930
TOTAL EXPENDITURES	\$4,075,490

¹ Includes contributions from PhRMA for Adherence Program

² Rent and Accounting Services are donated by PhRMA

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PhRMA Foundation Programs for 2015

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Adherence Improvement			
Pre Doctoral Fellowships in Adherence Improvement	2 awarded/1 year	\$50,000 total \$25,000 per award per year	September 1, 2014 January 1, 2015 January 1, 2015
Research Starter Grants in Adherence Improvement (2013)	3 awarded/1 year	\$150,000 total \$50,000 per award per year	September 1, 2014 December 15, 2014 January 1, 2015
Adherence Intervention Evaluation Award (2014)	1 awarded/18 months	\$150,000 total \$150,000 per award	July 1, 2014
Assessing the Benefits of Treating Cancer (2014)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	September 1, 2014 December 15, 2014 January 1, 2015
Basic Pharmacology Advisory Committee			
Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)	9 awarded/up to 2 years	\$360,000 total \$20,000 per award per year	September 1, 2014 December 15, 2014 January–August
Post Doctoral Fellowship in Pharmacology/Toxicology (2002)	2 awarded/2 years	\$160,000 total \$40,000 per award per year	September 1, 2014 December 15, 2014 January–December
Research Starter Grants in Pharmacology/Toxicology (1972)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	September 1, 2014 December 15, 2014 January 1, 2015
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, 2015 April 15, 2015 July 1, 2015
Faculty Development Award in Clinical Pharmacology (1966)	1 awarded/2 years	\$240,000 total \$120,000 per award per year	September 1, 2015 January 1, 2016 July 1, 2015
Comparative Effectiveness Advisory Committee			
Center of Excellence Award	1 awarded/3 years	\$250,000 total \$83,333 per award per year	September 15, 2014 December 15, 2014 January 1, 2015

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.

Programs for 2015, continued

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Health Outcomes Advisory Committee			
Pre Doctoral Fellowships in Health Outcomes (2002)	2 awarded/1–2 years	\$100,000 total \$25,000 per award per year	February 1, 2015 April 15, 2015 July–December
Post Doctoral Fellowship in Health Outcomes (2002)	1 awarded/2 years	\$110,000 total \$55,000 per award per year	February 1, 2015 April 15, 2015 July–December
Research Starter Grants in Health Outcomes (2002)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	February 1, 2015 April 15, 2015 July 1, 2015
Informatics Advisory Committee			
Pre Doctoral Fellowships in Informatics (2009)	3 awarded/2 years	\$120,000 total \$20,000 per award per year	September 1, 2014 December 15, 2014 January–August
Post Doctoral Fellowships in Informatics (2002)	0 awarded/2 years	\$0 total \$40,000 per award per year	September 1, 2014 December 15, 2014 January–December
Research Starter Grants in Informatics (2002)	4 awarded/1 year	\$400,000 total \$100,000 per award per year	September 1, 2014 December 15, 2014 January 1, 2015
Pharmaceutics Advisory Committee			
Pre Doctoral Fellowships in Pharmaceutics (1987)	3 awarded/2 years	\$120,000 total \$20,000 per award per year	September 1, 2014 December 15, 2014 January–August
Post Doctoral Fellowships in Pharmaceutics	1 awarded/2 years	\$80,000 total \$40,000 per award per year	September 1, 2014 December 15, 2014 January–December
Research Starter Grants in Pharmaceutics (1972)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	September 1, 2014 December 15, 2014 January 1, 2015
Translational Medicine Advisory Committee			
Post Doctoral Fellowships in Translational Medicine (2014)	2 awarded/2 years	\$240,000 total \$60,000 per award per year	February 1, 2015 April 15, 2015 July–December
Research Starter Grants in Translational Medicine (2014)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	February 1, 2015 April 15, 2015 July–December

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

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