



50th

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

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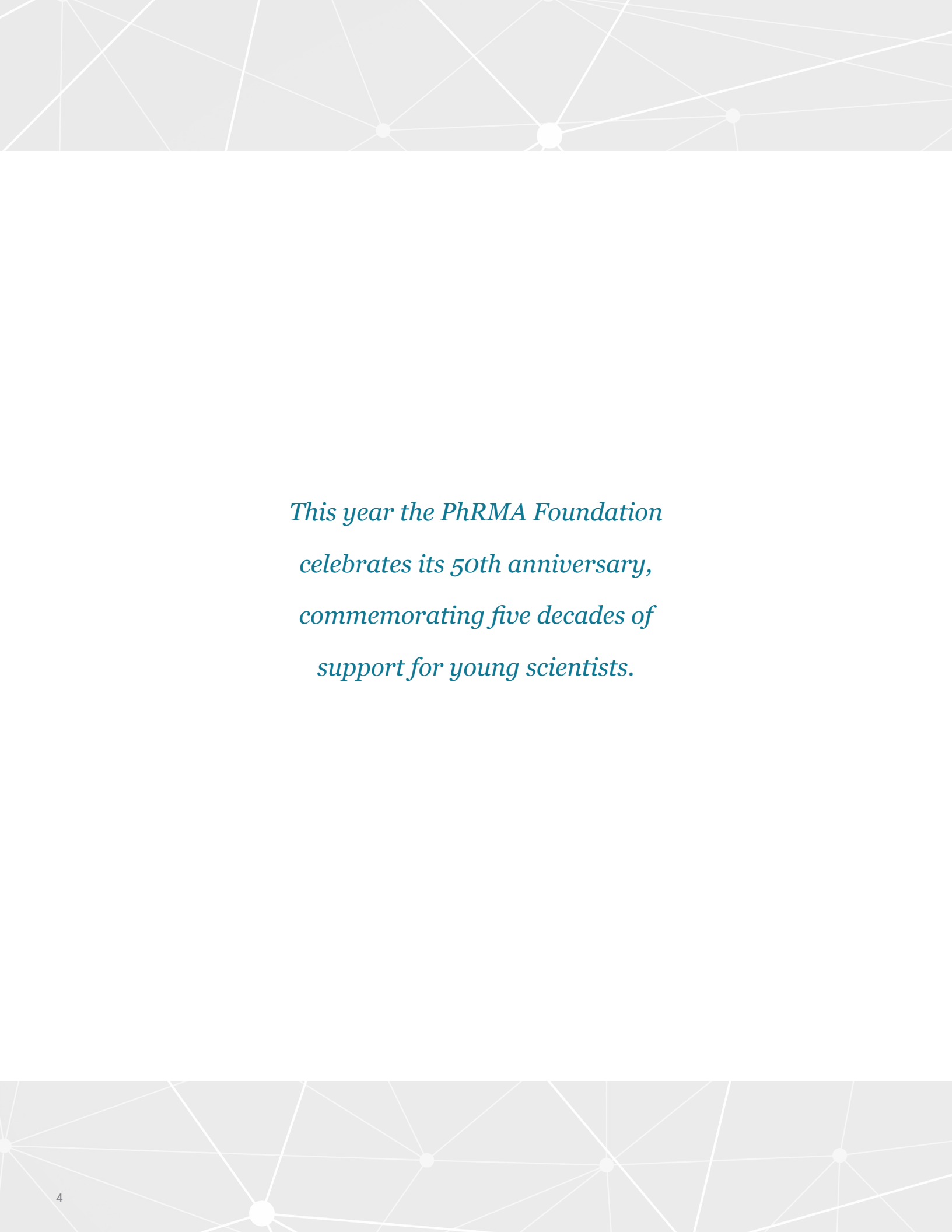
MISSION STATEMENT

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.





*This year the PhRMA Foundation
celebrates its 50th anniversary,
commemorating five decades of
support for young scientists.*



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Message from the Chairman



In the pharmaceutical industry we talk about the right drug for the right patient at the right time. Timing is critical in this formula, and it is equally important for a young scientist struggling with the questions most of us ask ourselves early in our careers. Is my research really worth pursuing? Do I have the means to pursue it? Where do I see myself in 10 or 20 years?

I asked myself these very questions as my work in medicine was just unfolding. I knew what I loved—people and science—and what I really wanted to do was bridge the two with medicine. R&D was the place where I felt I could do the most good. The first time I wrote a prescription for a drug I helped develop, I knew I had made the right choice.

The twists and turns a career path takes over its course can be exhilarating, and for those just beginning the journey, the PhRMA Foundation is a pillar. Our programs were designed to support the research of budding investigators and inspire them to explore the exciting opportunities that come with working in the biomedical field.

Timing, again, comes into play as the need grows for more medical research, particularly studies that focus on preventing and treating cancer. The research we fund serves a central purpose: to improve public health. However, Foundation grants and fellowships have another vital function in providing a period of intensive training and professional growth. This time to learn and progress has paved the path for some phenomenal successes.

Take, for example, Susan Band Horwitz of the Albert Einstein College of Medicine. Dr. Horwitz received a Research Starter Grant from the PhRMA Foundation in 1972. Over the next three decades, her studies

advanced widespread clinical use of Taxol—one of the most effective drugs for breast cancer. There are many, many others who have launched and led some of the best-known pharmaceutical companies in the world after receiving Foundation funding, not to mention countless medical directors, college deans, and distinguished professors.

The support we provide at the outset of a scientist's career has a lasting effect. When we asked nearly 600 former award recipients where they are today, 85 percent reported being active in research full or part time. Fifty-three percent had published a key finding that contributed to drug discovery or development, and 70 percent had been funded by the National Institutes of Health. More than 80 percent of these Foundation scientists said the grant or fellowship they received was important or "critically important" to their careers.

These achievements, as well as our meaningful influence within the scientific and medical communities, are the result of collaboration, generous investment, and the dedication of our board, committees, and member companies.

To ensure that Foundation programs are aligned with the research and development priorities of an evolving healthcare system, our board is run by some of the most formative leaders in the pharmaceutical industry. Many are also members of PhRMA's BioMedical Advisory Council and as such, serve as a valuable source of guidance. Our multidisciplinary advisory committees bring together professionals from academia, industry, and government to lend strategic input, insight, and a broad range of expertise.

With the support of every PhRMA member company, a better, brighter future is within reach. Together we can give young pharmaceutical scientists the resources they need to explore a new scientific landscape rife with opportunities for improving the health of people worldwide.

A handwritten signature in black ink that reads "Michael Rosenblatt".

Michael Rosenblatt, M.D., Chairman

Message from the President



As a true believer in the enriching experiences the PhRMA Foundation has to offer, I am honored to serve as its president. It's a role that is both inspiring and humbling, especially as we celebrate our 50th year in service.

This is an exciting time for drug development, with new opportunities on the horizon to fight disease and help patients live healthier, longer lives. When it comes to promoting the education and training that prepare young pharmaceutical scientists to excel in the field, the Foundation has always valued collaboration over competition. Now more than ever, we are seeing the benefits of our lasting relationships with diverse professional groups and associations that contribute to drug discovery. By partnering with award recipients, university faculty, and regulatory and industry leaders, we are moving the needle in new and emerging disciplines.

The multidisciplinary nature of many Foundation programs exposes award recipients to important work in a broad range of specialty areas and settings. One example is our newest initiative, which is designed to enhance regulatory science education by establishing rotations within industry and academia. These opportunities will offer real-world training on the increasingly complex technologies, tools, and skills needed to excel as a regulatory scientist.

We are also organizing and sponsoring conferences to support educational efforts in two critical areas: comparative effectiveness research (CER) and medication adherence. The first, "Educating the Users of CER," will

address gaps in CER and patient-centered outcomes research training and ensure CER users can easily access and apply available evidence in their daily practice. We will focus on developing a framework for recommendations to users of CER-PCOR evidence and tools for training. The second conference, "Suboptimal Medication Use: A Population Health Perspective," will convene stakeholders from diverse backgrounds to identify and disseminate effective strategies for improving medication use. Presenters will discuss how proper use of medication can improve health outcomes and examine policy surrounding adherence.

I have no doubt that our Foundation, an organization with a robust network of partners, alliances, and highly engaged member companies, has contributed significantly to biomedical training over the past five decades.

Anchored by our successful history and inspired by our potential to contribute even more to the careers of young scientists, the PhRMA Foundation will continue to lead educational efforts in the field. I assure you I am committed to achieving the Foundation's mission to support biomedical research and training and meet the challenges of a changing healthcare system. Like my predecessors, I strive to create great opportunities for us all.

A handwritten signature in black ink, reading "Eileen Cannon". The signature is fluid and cursive, with a large, stylized "E" and "C".

Eileen Cannon, President



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 2015 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, Pharmaceuticals, and Clinical Pharmacology.

2015 AWARD IN EXCELLENCE IN PHARMACOLOGY/TOXICOLOGY



David L. Eaton, Ph.D.

Dr. David Eaton is dean and vice provost of the University of Washington (UW) Graduate School and professor of toxicology in the Department of Environmental and Occupational Health Sciences at UW's School of Public Health and Community Medicine. For more than 20 years, he directed the National Institute of Environmental Health Sciences (NIEHS) P30 Core Center, which supports multidisciplinary work on gene-environment interactions.

In 1978, Dr. Eaton received his Ph.D. in pharmacology from the University of Kansas Medical Center. Two years later, he was awarded a PhRMA Foundation New Investigator grant, which allowed him to compete for his first National Institutes of Health Research Project Grant. He joined the UW faculty as assistant professor after a 6-month post-doctoral fellowship and has since served the university in a range of leadership and research roles.

Dr. Eaton was the first director of UW's toxicology program in the Department of Environmental Health. In 1991, he was named associate chair of the department. He served as associate dean for research at the School of Public Health from 1999 to 2005 and as associate vice provost for research from 2006 to 2013.

During his 36-year tenure at UW, Dr. Eaton has fostered innovative, interdisciplinary approaches to graduate research and education. He is an adjunct professor of medicinal chemistry in the School of Pharmacy, co-teaches a graduate course on the fundamentals of pharmacogenetics and toxicogenomics, serves on dissertation and reading committees for doctoral students, and has trained 36 graduate and post-doctoral students—many of whom now hold positions in industry and academia.

For most of his career, Dr. Eaton's research has focused on understanding species and interindividual differences in the way drugs and non-drug chemicals are metabolized in the liver. Many of his studies have looked at substances that act as human liver carcinogens. He was the first to demonstrate that resistance of laboratory mice to the potent human hepatocarcinogen aflatoxin B1 (AFB) was due exclusively to the constitutive expression of a form of glutathione S-transferase in the mouse liver. Dr. Eaton's lab cloned and sequenced the gene (mGSTA3) in 1992 and showed it had more than 10,000-fold higher specific activity toward the carcinogenic epoxide of AFB than human alpha class GSTA1. His lab further demonstrated that both human CYP1A2 and CYP3A4 effectively form AFB-8,9-epoxide. With these kinetic differences in biotransformation, Dr. Eaton and his team demonstrated that at relatively low concentrations of AFB encountered in the human diet, human hepatic CYP1A2 is likely responsible for the vast majority of epoxide formation in vivo. His laboratory also showed that human GSTM1 plays an important role in detoxifying AFB-epoxide, even though it has a small fraction of the catalytic function of mouse GSTA3.

Dr. Eaton has published 180 peer-reviewed papers, book chapters, and full-length proceedings and edited two books. He was a lead author of the "Principles of Toxicology" chapter of Casarett and Doull's Toxicology in the past four editions.

Dr. Eaton was secretary and later president of the Society of Toxicology (SOT) and treasurer of the American Board of Toxicology. In 1993, he received the SOT Achievement Award, and in 2014, he was recognized with the SOT Public Communications Award and Pacific Northwest Society of Toxicology Achievement Award. Dr. Eaton has received numerous awards from NIEHS, the National Cancer Institute, and the National Institute of General Medical Sciences. He is an elected fellow of the American Association for the Advancement of Science and Academy of Toxicological Sciences.

Dr. Eaton has also served on more than a dozen National Academy of Sciences (NAS) and Institute of Medicine (IOM) committees and as chair for several important NAS reports, including the National Research Council review of the Environmental Protection Agency's controversial assessment of dioxin exposure. In 2004, Dr. Eaton's service to the Academy was recognized with a lifetime appointment as national associate. He was elected to the IOM in 2011.

An Interview with *David L. Eaton, Ph.D.*

1980 Faculty Award in Pharmacology/Toxicology; 2015 Award in Excellence in Pharmacology/Toxicology

Q How did receiving the PhRMA Foundation Faculty Award in Pharmacology/Toxicology affect your research and career development?

A This award came at a very important time in my career—just as I was starting a new career as an assistant professor, with only a short post-doctoral experience to build on. The award provided me with the resources necessary to collect some preliminary data that subsequently led to my first NIH R01 grant. Without the NIH grant success, I likely would have had a difficult time getting the publications needed for promotion and tenure. So I view the award as very important to my early career, which then set the stage for the rest of it.

Q Could you explain some of your cancer and environmental toxins research?

A Although most people traditionally think of environmental and food contaminants—especially potential cancer-causing chemicals—as a by-product of industrial activities, Mother Nature has crafted some remarkably toxic substances. One of these is produced by a common mold that grows on corn, peanuts, and other common foods. The mold is called *aspergillus flavus*, and the toxin it produces is called aflatoxin (*Aspergillus FLA*vus *TOXIN*). The most potent form of this natural chemical is called Aflatoxin B1, or AFB for short. AFB was first discovered when it was identified as the chemical

responsible for poisonings and liver cancer in farm-raised turkeys and trout. It was subsequently shown to be a common contaminant of the human diet in regions of the world where subsistence farming of corn and/or peanuts is common and where high heat and humidity are common. Many of these same areas (certain regions in China, Southeast Asia, and Central Africa) have among the world's highest rates of mortality from liver cancer, and numerous epidemiological studies have demonstrated that AFB contamination of the diet is a very important contributor to this.

Early in my career, I was fascinated by the finding that rats were exquisitely sensitive to the cancer-causing effects of AFB, whereas mice were almost completely resistant. This suggested a genetic susceptibility potential, so my lab set out to discover the molecular basis for the species difference and determine where humans fit ... are we more like rats, or more like mice, and if we are more like rats (highly sensitive, as suggested by epidemiological data), is there something we could do to make us more like mice (resistant to the cancerous effects of AFB)? We discovered adult mice are highly resistant to the cancer-causing effects of AFB because they express a special form of a common gene called glutathione-S-transferase (mGSTa3), which is remarkably effective at detoxifying the carcinogenic form of AFB (called AFB₁, readily made in the

livers of rats, mice, and humans). Rats had a GST gene (rGSTA5) very similar to the form of the mouse GST that made mice resistant, but rats did not normally express that gene in their liver and thus were not good at detoxifying AFB₁. However, we and others showed the gene for rat GSTA5 could be turned on [to start producing] the GST enzyme that could detoxify AFB₁, making rats resistant.

Q How has the field of toxicology changed over the years?

A The biggest change has been the remarkable insights and understanding of the molecular mechanisms of biological action of chemicals that have come from the rapid development of molecular approaches (so-called "omics" tools) applied to toxicology. With this knowledge has come a fundamental shift in the way scientists view toxicological effects of chemical substances, especially the dose–response relationship. It is now evident that many chemicals can induce subtle changes in cell signaling at doses well below those that cause an immediate or evident toxic response. Often, these changes represent an adaptive response to an external stressor, but we are beginning to recognize that such changes, especially if they occur continuously over a long period, may have important consequences in health by promoting—or in some instances inhibiting—disease processes associated with normal aging. This is perhaps best evident in the

relatively new field of endocrine disruption, where seemingly non-toxic doses of certain chemicals that interfere with normal hormonal signaling processes may eventually alter the incidence of hormonally related chronic diseases such as breast cancer. Such changes are often too small to be of apparent significance to an individual, but they may have public health implications for large populations that are exposed for many years. In these circumstances, the chemical exposure is not *causing* the disease, but it may modify the disease process such that the ultimate incidence of disease in a large population is altered. This, of course, also provides opportunities for developing new drugs that favorably alter the disease outcome in a population.

Q As someone who is very involved with medical societies and environmental health committees and boards, could you talk about the importance of staying engaged and giving back to the scientific community?

A Research and the scientific discoveries that come from research are important, but their value is greatly diminished if the science that is produced is not effectively disseminated to the boundaries of the academy. Thus, it is imperative that researchers become engaged in ways that facilitate the dissemination of discoveries to the rest of the world. Participating in professional societies, public interest groups, industry trade associations, governmental agency committees, and nonprofit organizations can be very rewarding personally and professionally. Many federally funded research

programs, especially center grants from the NIH, [require] some community outreach and engagement activities. One of the most rewarding and impactful opportunities for scientists to put their knowledge and experience to use is serving on National Academies of Sciences/National Research Council committees that address important policy implications where science can be an integral component of important decisions made by the federal government.

Q What is your advice for a young investigator planning to pursue an academic career?

A Stay focused and build on your strengths. Learn to say no to too many outside commitments/committees that will distract you from your research. Of course, you have to be judicious in your choices, and it is not advisable to say no to everything, as being a “team player” is also very important to your success in academia. Be persistent in your efforts to obtain NIH funding, and look for sources of funding beyond NIH for your research. Support from “non-NIH” sources can be extremely important to your success and may allow you to succeed even without getting an NIH R01 grant in your first few years of independent research. Finally, find some good collaborators who can help you take your research to the next level. There is strong interest in interdisciplinary research, and seasoned investigators in peripheral but related areas may help you find an innovative twist to your work that will help land that grant!

Q What is the most rewarding part of your job?

A In my current position as Dean and Vice Provost of Graduate Education at a large public research university, the most rewarding part of my job is seeing the incredible potential of the next generation of scientists who, with the remarkable gain in technologies and “big data,” will literally change the world. Having the opportunity to foster the development of innovative, interdisciplinary approaches to graduate research and education in a variety of fields is very rewarding. In my current job, I get to see this happen across fields that extend well beyond biomedical sciences and into engineering, social sciences, and even arts and humanities. From a scientific perspective, I’ve been blessed with the opportunity to collaborate with many really smart people across various fields, and this has made my own research career much more rewarding than if I had stayed within my own silo of biochemical toxicology. And of course, having the opportunity to work with and mentor outstanding young scientists seeking their master’s and doctoral degrees remains a highlight of my professional life.

2015 AWARD IN EXCELLENCE IN CLINICAL PHARMACOLOGY



Mark Ratain, M.D.

Dr. Mark Ratain is the Leon O. Jacobson Professor of Medicine at the University of Chicago (U of C), director of the Center for Personalized Therapeutics at U of C, and chief hospital pharmacologist at UC Medicine (UCM). He is also associate director of clinical sciences at the university's Comprehensive Cancer Center, leads U of C's phase I oncology trials program, and co-directs the Pharmacogenomics of Anticancer Agents Research Group, which connects experts throughout the country to develop tools and methodologies for pharmacogenomics research.

Dr. Ratain graduated from Harvard College in 1976 and Yale University School of Medicine in 1980. He completed postgraduate training in internal medicine, hematology, and oncology at Johns Hopkins Hospital and U of C. In 1993, he received the PhRMA Foundation Unit Award in Clinical Pharmacology.

An international leader in pharmacogenetics, phase I clinical trials, and clinical trial methodology, Dr. Ratain focuses on developing new oncology drugs and diagnostic tests to produce individualized anticancer therapies. His studies have become a model for understanding variability in responses to newer targeted therapies. Dr. Ratain and his colleagues uncovered the molecular mechanisms of toxicity in the topoisomerase 1 inhibitor irinotecan, allowing scientists to predict which cancer patients would experience severe toxicity with irinotecan treatment. The finding led to a Food and Drug Administration–approved label revision of irinotecan, including a warning and recommendation for certain patients to first take a reduced dose. In 2005, Dr. Ratain created and patented a genetic test to personalize treatment decisions—the first of its kind to be approved by the FDA. Dr. Ratain and his team showed a variant in the UGT1A gene could be used to individualize irinotecan dosing and illustrated the clinical value of genotype-guided dosing of a chemotherapy drug linked with severe toxicity.

To address adverse drug reactions—one of the leading causes of death in the United States—Dr. Ratain and Dr. Peter H. O'Donnell created the “1200 Patients Project.” This study aims to assess how preemptive pharmacogenomic test results can help determine which drugs and doses are the most effective for a patient, and which patients could experience negative side effects. The ultimate goal is to improve patient outcomes through more informed and personalized treatment decisions.

Dr. Ratain's work has been recognized with numerous honors and awards, including the Emil J. Freireich Award for Clinical Research from the MD Anderson Cancer Center, the Director's Service Award from the National Cancer Institute (NCI), the Research Achievement Award in Clinical Pharmacology and Translational Research from the American Association of Pharmaceutical Scientists, and the Rawls–Palmer Progress in Medicine Award from the American Society for Clinical Pharmacology and Therapeutics (ASCPT). In 2012, Dr. Ratain was invited to be a visiting professor at FDA's Center for Drug Evaluation and Research. He is an honorary fellow of the American College of Clinical Pharmacology.

Dr. Ratain was the first chair of the National Institutes of Health Pharmacogenetics Research Network Steering Committee and served as one of the first co-chairs of NCI's Investigational Drug Steering Committee. He has also served on committees for the U.S. Pharmacopeia, American Board of Clinical Pharmacology, American Association for Cancer Research, and Alliance for Clinical Trials in Oncology. He was an ad hoc reviewer and member of various NIH steering committees, working groups, and study sections. Overall, Dr. Ratain has served on 23 U of C and 12 UCM institutional committees. He has participated on external scientific advisory committees for Georgetown University and Thomas Jefferson University and has been a member of the St. Jude Children's Research Hospital External Advisory Board since 2005.

Dr. Ratain has held various leadership positions at ASCPT, including chair and vice chair of the Scientific Program Committee. He has been a member of the Board of Directors, Executive Committee, Membership Committee, and Committee on the Coordination of Scientific Sections. For the American Society of Clinical Oncology, Dr. Ratain has served on the Board of Directors, Executive Committee, and Strategic Planning Committee.

Having published more than 470 original papers, reviews, and book chapters, Dr. Ratain is a recognized voice in pharmacogenetics. He is co-editor in chief of *Pharmacogenetics and Genomics*, former editor in chief of *Current Pharmacogenomics and Personalized Medicine*, and past associate editor of the *Journal of Clinical Oncology*. He also participates on the editorial boards of *Investigational New Drugs* and *Clinical Cancer Research*. Dr. Ratain was a keynote speaker at Hospital Pharmacy Europe Live and the 5-year celebration of Emory University's Phase I Clinical Trials Unit in 2014.

An Interview with *Mark J. Ratain, M.D.*

1993 Unit Award in Clinical Pharmacology; 2015 Award in Excellence in Clinical Pharmacology

Q What is your advice for a young investigator planning to pursue an academic career?

A Find your niche. Ideally, this will be the result of joint mentorship by faculty working in distinct but related areas. My own niche was at the vertex of oncology, clinical pharmacology, and genetics.

Q How important are grants and fellowships like the ones awarded by the PhRMA Foundation to younger scientists who haven't been able to tap into the federal-grants pipeline?

A Grants and fellowships such as the ones the PhRMA Foundation provides are critically important for the development of young scientists. This type of funding provides initial support for investigators who are often just starting out and who may be able to develop projects that may ultimately be fundable through the federal-grants pipeline.

Q What are the potential long-term outcomes of an intensive research training period early in a pharmaceutical scientist's career?

A An intensive research training period is critical to developing successful pharmaceutical scientists. The initial training of individuals is one of the most important aspects of their development and is critical for them to become well-rounded scientists. This intensive training period provides them with the tools they will need to have a long and prosperous career.

Q Could you put some of your cancer and pharmacogenetics research into layman's terms?

A My research focuses on the development of new oncology drugs and developing diagnostic tests to create individualized anticancer therapies based on each person's genetic makeup.

Q What are the economic benefits of personalized therapy?

A Personalized therapy lets the clinician give the best therapy to [his or her] patient the first time. This allows the patient the earliest possible chance to respond to therapy and avoid side effects. Without personalized therapy, there is often a trial-and-error period in which treatments are administered that ultimately do not work or, in the worst-case scenario, make a condition worse and harder to treat in the long run. This longer process is worse for the patient and also tends to cost a lot more. Personalized therapy provides better care at less cost.

Q Where do you see pharmacogenomics and pharmacogenomics testing 10 years from now?

A In the previous 10 years, there has been great progress in the pharmacogenomics discovery arena. In addition, there has been tremendous improvement in technology used to develop pharmacogenomic tests. Many investigators have identified important pharmacogenomic drivers of disease conditions and continue

to explore the role of these genes in the disease process. In 10 years from now, we would expect these drivers of disease conditions to be validated and implemented into standard medical practice.

Q What do you think can be accomplished with personalized medicine by the 1200 Patients Project?

A Adverse reactions to medications are one of the leading causes of death in the United States, and many patients take medications that are not effective for them. The Genomic Prescribing System (GPS) is an online portal that allows physicians enrolled in the 1200 Patients Project to access information about how their patients respond to certain medications based on their genetics. Patient-specific results are provided not as raw genetic data but as a patient-tailored synopsis of the information translated into clinical meaning and include prescribing recommendations and suggested alternative medications. Ultimately, the GPS enables physicians to make patient-specific treatment decisions, improving patient outcomes.

“Grants and fellowships such as the ones the PhRMA Foundation provides are critically important for the development of young scientists.”

—Mark J. Ratain, M.D.



2015 AWARD IN EXCELLENCE IN PHARMACEUTICS



Christopher M. Sinko, Ph.D.

In 1987, Dr. Christopher Sinko was awarded the PhRMA Foundation Pre Doctoral Fellowship in Pharmaceuticals, which he said “helped validate the importance of his research.” Today he is senior vice president of pharmaceutical development at Bristol–Myers Squibb (BMS).

Dr. Sinko earned his B.S. in chemical engineering with a concentration in materials engineering from Rutgers University. He received his M.S. and Ph.D. in pharmaceuticals at the University of Michigan College of Pharmacy.

In 1989, Dr. Sinko joined the Upjohn Company to develop formulations for monoclonal antibodies targeting HIV. He was later recruited to Pfizer Central Research to establish a materials science laboratory for producing solid dosage forms. From 1991 to 2008, he held several leadership roles at Pfizer, including executive director of global materials science, senior director of analytical R&D, and director of pharmaceutical R&D. In 2008, Dr. Sinko accepted a position to lead Drug Product Science and Technology at BMS. His current role spans chemical, analytical, and formulation development for small molecules and biologics, as well as clinical supplies manufacturing and distribution.

Dr. Sinko's research is rooted in materials science, solubilization, and the application of fundamental scientific principles in risk-based approaches to commercial technology development. He led the development of spray-dried dispersion technology, which aimed to significantly improve the aqueous solubility of drugs. He also created and implemented a risk-based management process for all new products transferred from R&D to commercial manufacturing. This system, which establishes the optimal investment for minimizing risk in new manufacturing processes, is now the basis for experimental planning across all BMS products transferred globally into commercial manufacturing. It has also been extended as the technical definition of design space per ICH Q8 guidelines and accepted by the Food and Drug Administration in a pilot program for risk-based reviews of chemistry, manufacturing, and controls sections.

Dr. Sinko had a major role in BMS's transformation from a broad-based, diversified pharmaceutical company to a focused “BioPharma” company. As part of the Executive Leadership Team, he helped develop an R&D strategy focused on novel immune therapy approaches for cancer and HIV/HBV treatment and introduced new platforms, such as antibody drug conjugates and millamolecular technology.

In 2006, Dr. Sinko was invited to lead the Product Quality Lifecycle Initiative's integration team, which provided an industry response to Quality by Design (QbD) implementation. The team produced three best practice guides on QbD application in product development that were published by the International Society for Pharmaceutical Engineering (ISPE). Dr. Sinko served on the Product Quality Lifecycle Implementation (PQLI) Criticality Sub-Team in 2008

and PQLI Technical Committee and QbD Roadmap Integration Task Team from 2009 to 2011. He also worked with PhRMA and the FDA on a Pharmaceutical Science Advisory Committee addressing barriers to implementation of ICH Q8–Q10 in contemporary submissions.

Dr. Sinko has presented and lectured on solid dosage forms and formulation for the American Association of Pharmaceutical Scientists (AAPS), Drug Information Association, and ISPE. His work has also been featured in publications such as the *International Journal of Pharmaceutics* and *Pharmaceutical Research*. In 1990, Dr. Sinko received the Upjohn Laboratories Special Recognition Award, and in 1995, he received the Central Research Achievement Award. He is a member of ISPE and AAPS.

An Interview with *Christopher M. Sinko, Ph.D.*

1987 Pre Doctoral Fellowship in Pharmaceutics; 2015 Award in Excellence in Pharmaceutics

Q Why did you decide to follow a career in industry?

A I wanted to integrate my engineering background with my pharmaceutics training and apply this to manufacturing systems. I believed, and still believe, that industry was the best place to achieve this.

Q How did receiving the PhRMA Foundation Pre Doctoral Fellowship in Pharmaceutics affect your career development?

A It helped validate the importance of my research in the field of pharmaceutics. Not having undergraduate training in pharmacy, this was important to me.

Q From your perspective, what are the benefits of continued funding for medical research?

A There are many unmet medical needs. Cures and treatments do not get realized by accident. It takes the entire governmental/academic/industry framework to make it all happen. An important component

is funding for medical research. This leads to fundamental insights into biology, and translational R&D will allow society to make a transformational leap.

Q How can implementing Quality by Design improve drug development and manufacturing?

A QbD does two things, among others. First, it clearly ties the objective, identified in the target product profile, to the experimental components of the product development plan, and it raises the value of quality in the plan. The latter is important because there are myriad competing voices regarding the design of the product. Second, it embeds risk-based decision making in the development and manufacturing of a product. From a development perspective, it helps the scientist focus on where the greatest technical risks are [and remove those risks]. From a manufacturing perspective, it helps the manufacturer focus its control strategy on the areas of greatest

manufacturing risk (as opposed to everything).

Q What are the regulatory benefits of Quality by Design?

A It sharpens and focuses the dialogue between the innovator and health authorities during the review process. The advantage is that we address risks and agree to ways to mitigate those risks. It seems like more work, but I do believe we get products to patients much quicker by focusing only on risks.

Q Can you offer some advice to a young scientist planning to pursue a career in industry?

A Focus on the scientific fundamentals. You always go back to them to solve the myriad problems you will face in industry.

Q What is the most rewarding part of your job?

A Creating opportunities for all colleagues who want to do (and do it) better.



50th

ANNIVERSARY

Why Fund Pharmaceutical Research?

America's investment in medical research has had a profound impact on prolonging life. Deaths from heart disease continue to drop. Cancer mortality rates have gone down nearly 23 percent since the 1990s, thanks to breakthroughs in prevention, detection, and treatment. While these statistics are nothing short of extraordinary, there is far more to discover. A new world of knowledge awaits, and biomedical research holds the key.

For young investigators, grants and fellowships build confidence and pave the way to research independence. Unrestricted awards can be used for professional development, whether it is to start and staff a lab or generate enough preliminary data to qualify for federal funding.

Many promising researchers leave the field because they cannot afford to stay. With financial assistance, early career scientists have the autonomy to pursue the projects that most inspire them. The freedom to cultivate personal research interests is crucial, as one's passion can powerfully influence academic and professional choices.

One of the PhRMA Foundation's fundamental objectives is to support research proposals the government may have turned down in the face of more pressing demands. These studies, often at risk for falling through the cracks, are now forging ahead, filling gaps in areas of great importance to medicine and industry.

Intensive research and training early in a scientist's career can lead to more proficiency, more productivity, and more success down the line. The Foundation has provided more than \$80 million in funding to over 2,300 young investigators—scientists who have subsequently led successful clinical trials, made significant drug discoveries, built companies from the ground up, and helped countless patients live healthier, longer lives. Fifty-three percent of these scientists have published a key finding that contributed to drug discovery or development, and 70 percent have been backed by the National Institutes of Health (NIH). Their good work continues. A remarkable 8,000 students have been taught, trained, or otherwise influenced by Foundation grantees.

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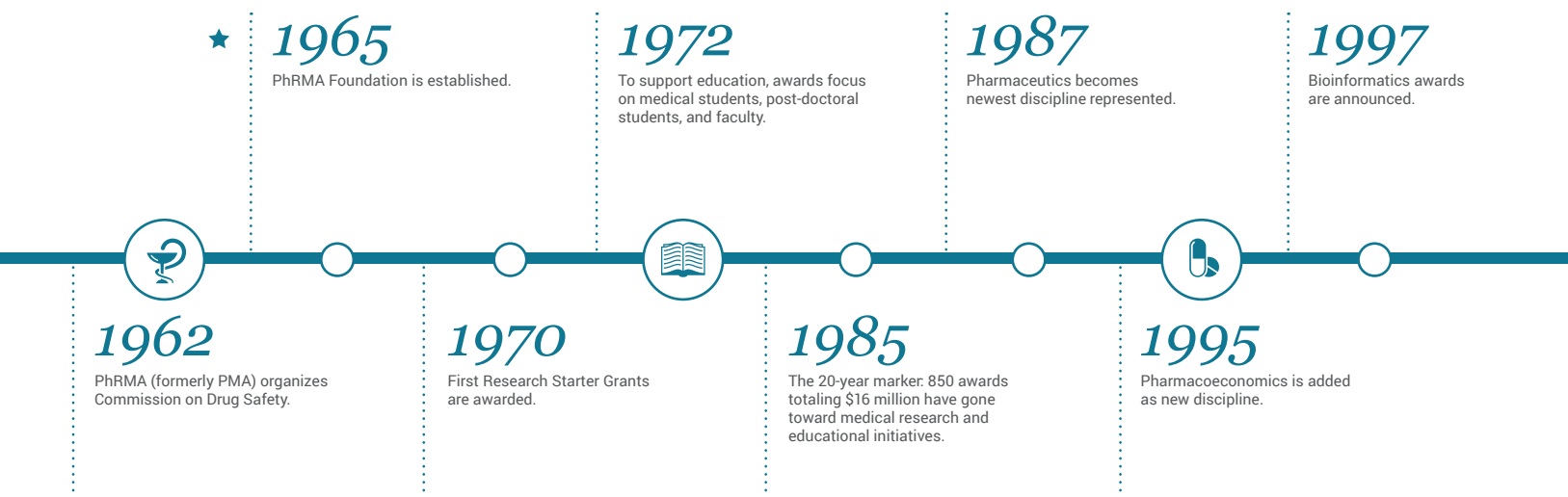
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A Look Back

The PhRMA Foundation was established in 1965 as an interface between scientific research and public health. As its first order of business, the Foundation set out to make drug studies a central part of medical curricula.

Mobilizing an organization to support the study and progress of therapeutics was a direct response to the thalidomide tragedy of the 1960s. Consequently, the Foundation's initial programs focused on toxicology, pathology, and pharmacology. In 1967 the Advisory Committee received its first applications for the Faculty Development Awards in Clinical Pharmacology, and a stringent review process commenced. Submissions were read and re-read, as the committee whittled down the pool of candidates. In the end, three scientists were selected, and so continued the promising careers of Drs. Donald Robinson, William Au, and Arthur Hayes. Fourteen years later, Dr. Hayes was appointed to the prestigious post of FDA commissioner. He later served as provost and dean of New York Medical College.

In the 1970s, ensuring a bright future for pharmacology students became the Foundation's utmost priority, with three of every five dollars going to education. Research Starter Grants were born, and by 1972 the awards were financing the work of medical students, post-doctoral students, and beginning faculty.

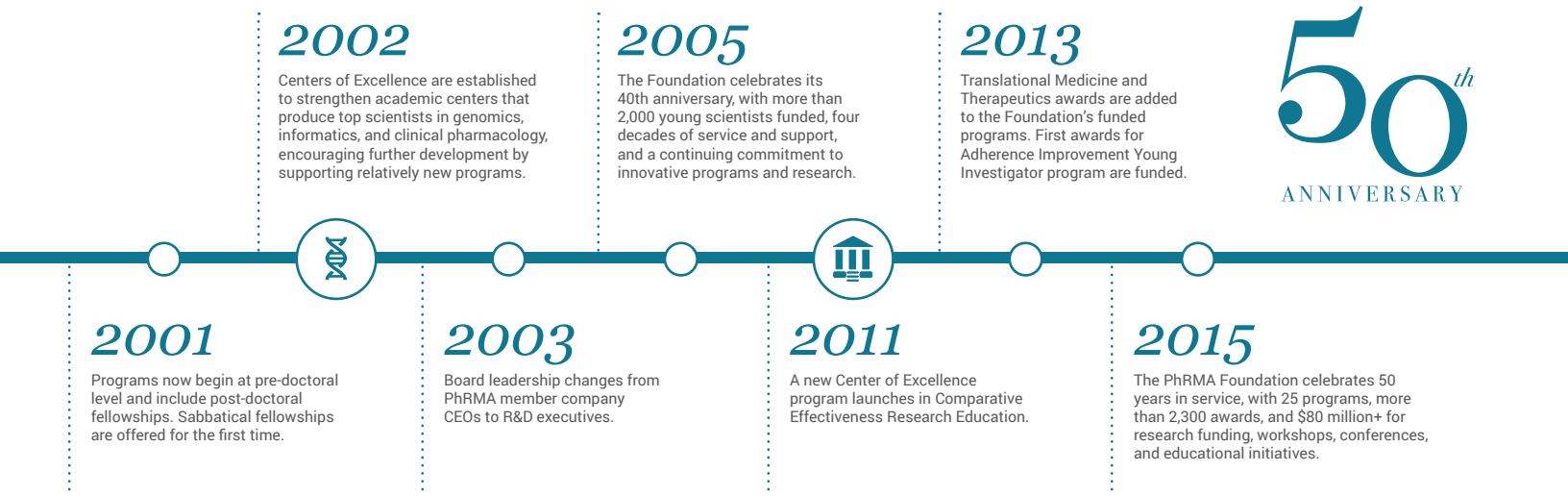
With a strong infrastructure in place, the programs began to branch out to new and emerging disciplines. In 1987 the first awards in pharmaceutics were announced. Fellowships in pharmacoeconomics followed, and in 2002

the program took a new name: Health Outcomes. The Informatics program also took off that year—its roots in the bioinformatics awards that began in 1997.

In 2001, Foundation programs were restructured to provide funding for all disciplines at the pre-doctoral and post-doctoral levels. Through Sabbatical Fellowships, young faculty were given stipend support to work outside their institutions, acquire new skills, and make valuable research connections.

The launch of the Centers of Excellence program in 2002 was a major milestone that reflected one of the earliest priorities of PhRMA's Commission on Drug Safety. By the mid-2000s, the Foundation had selected four colleges and universities to create centers for intensive training in clinical pharmacology, genomics, and informatics.

Today, PhRMA Foundation programs span the spectrum of drug discovery, development, and outcomes research—from toxicology to translational medicine to treatment adherence. Although the awards have evolved to align with contemporary health needs and a changing healthcare system, the Foundation's focus on education has never wavered.



Forming Strategic Partnerships

By 2003 the Foundation's Board of Directors consisted solely of R&D executives from PhRMA member companies. Under their direction, the organization has built strategic partnerships with key players in biopharmaceutical research and convened a wide range of stakeholders to listen, cooperate, and act.

Growing a skilled workforce that can effectively translate research into real and sustainable healthcare improvements is best accomplished through multidisciplinary collaboration. Over the years the Foundation has formed lasting, productive relationships with federal agencies such as the NIH and Agency for Healthcare Research and Quality, independent organizations such as the Patient-Centered Outcomes Research Institute and Reagan-Udall Foundation, and professional associations such as the American Society for Clinical Pharmacology and Therapeutics, American Society for Pharmacology and Experimental Therapeutics, American Association of Pharmaceutical Scientists, and International Society for Pharmacoeconomics and Outcomes Research.

In recent years the PhRMA Foundation and its partners have focused on starting and expanding programs that support biomedical research and training in five crucial areas—regulatory science, comparative effectiveness, translational medicine, safe and effective prescribing, and medication adherence. To this aim, the Foundation has designed course modules for competent prescribing and formulated an educational infrastructure for comparative effectiveness research (CER), creating curricular guidelines, establishing six CER Centers of Excellence, and hosting the first national meeting on CER education and training. The regulatory science education initiative began in September 2014 when a panel of experts from government, PhRMA member companies, academia, and several partner organizations was assembled to discuss curricular guidelines for academic programs in regulatory science. A new rotation program will strive to enhance regulatory science by understanding the requirements and demands of federal agencies, industry, and academic institutions.

A Lifesaving Investment

Eliminating disease, alleviating pain, and restoring function are some of the tangible ways in which scientific study champions human health. To a certain extent, these are the benefits of medical research that can be measured. But for anyone whose quality of life has improved as a result of breakthroughs in science, the benefits are incalculable. With a 50-year investment from PhRMA

member companies in the most promising research and researchers, the Foundation remains on the front line of the fight against disease, supporting the development of drugs and treatments that have helped millions of people live better lives.



FELLOWSHIPS AND GRANTS

Translational Medicine and Therapeutics

Post Doctoral Fellowships 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 fellowships and grants were awarded in 2013.

“The PhRMA Foundation Post Doctoral Fellowship in Translational Medicine and Therapeutics has provided me with a wonderful opportunity to continue my current research and training on tumor immunogenomics. The award also encouraged me greatly by strengthening my confidence in the importance of my research. I am grateful to the PhRMA Foundation for all of this.”

Jing Sun, Ph.D. | Dana Farber Cancer Institute

2015 POST DOCTORAL FELLOWSHIPS



Jin Sun, Ph.D.

Dana-Farber Cancer Institute

“Discovering Personal Tumor Neoantigens Arising From Alternatively Spliced Isoforms”

A growing body of compelling mouse and human data strongly support the idea that therapeutic targeting of tumor neoantigens – which bypass central tolerance and are exquisitely tumor-specific – can lead to potent cytolytic anti-tumor immune responses. Neoantigens could be generated from tumor-specific somatic mutations, such as missense and frameshift mutations. Recent sequencing studies have highlighted the common presence of mutations in genes involved in RNA splicing. Alternative splice isoforms generated by either alternatively spliced exons or aberrantly retained introns can potentially generate tumor-specific novel open reading frames (neoORFs), which would be highly attractive neoantigen targets. The goals of this project are to 1) discover the extent to which tumor-specific altered

splice variants are present in cancer cells, 2) predict the neoepitopes generated from these transcripts, and 3) test if cytotoxic T lymphocyte responses are generated against neoepitopes and autologous cancer cells. Finally, the computational and experimental infrastructure developed will be applied to clinical studies. This project is anticipated to enhance the effective targeting of tumor neoantigens and for building active personalized cancer vaccines.



Adam Swick, Ph.D.

University of Wisconsin School of Medicine

“Autophagy Suppression to Enhance EGFR Targeted Therapy in Head and Neck Cancer”

With approximately 40,000 new cases of head and neck cancer (HNC) annually in the United States and a five-year survival rate of only 50%, there remains great need for improvement in treatment of this disease. Despite some success for chemotherapies targeting specific cellular proteins, such as the epidermal growth factor receptor (EGFR), the initial promise of this therapeutic strategy has been blunted by a high frequency of tumors that are resistant to this class of drugs. For EGFR targeting drugs, the poor response is due to mutations in EGFR and related proteins in a significant fraction of patients. More recent research, however, has revealed that the cellular process of autophagy may drive an additional method of resistance. Autophagy or “self-eating” is a normal cellular mechanism recycles protein and nucleic acid components to maintain proper cell health, but it can be turned up during periods of cellular stress, such as those undergone during chemotherapy, to promote tumor cell survival. Intriguingly, it has recently been shown that the inactive form of EGFR that is generated by the use of drugs targeting this molecule can directly stimulate this process. This work will investigate if the cellular mechanism of inactive EGFR driving autophagy actually impacts therapeutic resistance, using a model system where human tumors from patients are directly grafted onto mice to study the effect of different drugs. In addition the effect of drugs suppressing autophagy combined with EGFR targeting therapies will be investigated as a potential clinical combination treatment for HNC.

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.

2015 RESEARCH STARTER GRANTS IN TRANSLATIONAL MEDICINE AND THERAPEUTICS



Leonid Kagan, Ph.D.

Rutgers University

“Optimization of Dosing of Monoclonal Antibodies in Obese Population”

Obesity has reached epidemic proportions worldwide. Overweight and obesity pose significant health risks, and the data supporting dosing of medication in obese patients are inadequate. Monoclonal antibodies (mAbs) are a rapidly growing class of biotherapeutics agents used for treatment of a variety of disorders, including various forms of cancer. Effects of obesity on pharmacokinetics (absorption, disposition, and elimination) of mAbs have not been sufficiently studied. There is an urgent need to more accurately estimate the most efficient and safe dosing strategies for mAbs in obese population. The overall goal of this project is to investigate the relationships between various measures of body size and the pharmacokinetics of mAbs and to develop strategies for optimization of dosing of mAbs in obese patients. Specifically, the time course of concentration of test antibodies will be measured after different modes of administration in diet-induced animal model of obesity. Furthermore, biodisposition of mAbs will be evaluated in normal weight and obese cancer patients. Advanced mathematical models will be used for data analysis. Proposed studies will improve the efficacy and safety of treatment with mAbs and will support the design of prospective clinical studies in obese patients treated with mAbs.

“ I continue to be an active scientist, owing mainly to the PhRMA Foundation’s Research Starter Grant in Translational Medicine and Therapeutics. The PhRMA grant came to me at a difficult time in my academic career when funding and support for young scientists was negligible. My PhRMA grant has helped me regain confidence and validate myself as a good scientist. It has supported the development of my high risk-high potential research idea into a larger fundable project and helped me acquire an independent standing in the field. I cannot thank the PhRMA Foundation enough for saving my career.”

Ritika Jaini, Ph.D. | The Cleveland Clinic



Ritika Jaini, Ph.D.

Cleveland Clinic

“Enhancement of Target Expression On Breast Tumors via Hormone Receptor Antagonism: A Novel Strategy for Enhancing Immunotherapeutic Efficacy”

Cancer vaccines and other immune strategies harness the power of the immune system to attack specific proteins or antigens on the tumor and have been shown to provide effective and long lasting treatment against cancers. These immune-therapeutic strategies are mostly

effective in cancers like melanoma where the tumor expresses abundant target antigens and is therefore highly antigenic. However, immunotherapy has not been very successful in poorly antigenic tumors such as breast cancers. Numerous strategies aimed at enhancing the strength of immune responses against such cancers have been tested, but few address making the tumor more “targetable”. It is known through studies in autoimmunity models, that increased antigen load within a tissue enhances immune reactivity against it. Therefore, the goal of this project is to enhance expression of target antigens on breast tumors in order to increase efficacy of immunotherapy targeted against them. A known effective immunotherapeutic target on breast tumors is alpha-Lactalbumin, a lactation protein significantly overexpressed in triple negative breast cancer patients (15-20% of all breast cancers), but only moderately expressed in the larger subset of hormone receptor positive breast tumors (over 75% of breast cancers). This project proposes to increase expression of the alpha-Lactalbumin target protein on breast tumors by utilizing its physiological negative regulation mechanism by the progesterone (PR) and estrogen hormone receptors (ER). The experimental plan will test upregulation of alpha-Lactalbumin expression on human breast tumors after treatment with clinically approved hormone receptor antagonists. Further, the effect of this increased tumor antigen availability on efficacy of anti-tumor immunotherapy will be analyzed in murine tumor models. This study will provide a novel clinical strategy for enhancing efficacy as well as expanding population coverage of immunotherapy via increasing target antigen expression. Findings from this study are expected to be applicable not only for breast tumors but possibly also for other hormonally driven cancers such as that of the prostate, testis and ovary.

“ The PhRMA Foundation Research Starter Grant allowed me to pursue the translational studies that were the logical continuation of my research in animal models. The award gave me the opportunity to fund clinical studies that provided another dimension in my research.”

Georgios Paschos, Ph.D. | University of Pennsylvania



Georgios K. Paschos, Ph.D.

University of Pennsylvania

“The Circadian Clock of Humans With Night Eating Syndrome”

The goal of this research is to understand how deviating from the daily rhythms imposed to our physiology by the rotation of earth contributes to the development of obesity. Of particular interest is understanding how our endogenous clock anticipates the most advantageous time of the day for metabolic processes and contributes to metabolic homeostasis. The project is using animal models of clock disruption to generate mechanistic hypotheses of how deviations between the endogenous rhythms and behavioral rhythms increase the risk of obesity. In

two of these models this research has shown that the clock regulates the timing of feeding and dictates how calories taken at different times metabolize. The project is investigating the unknown etiology of the Night Eating Syndrome in humans, based on study findings in animal models. This project is specifically testing the integrity of the clock in humans diagnosed with Night Eating Syndrome and exploring circadian clock related mechanisms that cause night eating. It is expected these studies will be relevant to the broader population and the obesity epidemic given the increased introduction of artificial light and the subsequent changes in modern lifestyle.

“ One of the frustrations of starting out in research is that typical career development awards, while providing a secured salary, do not sufficiently support getting the project done. The Research Starter Grant has been a tremendously valuable tool for me to actually do my research and plan for next steps.”

Michelle Ormseth, MD, MSCI | Vanderbilt University Medical Center



Michelle J. Ormseth, M.D., MSCI

Vanderbilt University Medical Center

“Functional Impact of HDL Transport of MicroRNA in Rheumatoid Arthritis”

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disorder affecting nearly 1% of the US population. Patients with RA have double the risk of heart attack compared to people who don't have RA. This is largely why patients with RA die eight to ten years prematurely. HDL, or the “good cholesterol” may not be good in patients with RA, and may be partly to explain for the increased cardiovascular risk in RA. HDL transports small strings of nucleic acids called “microRNAs” to cells, leading to altered gene expression. HDL-microRNA cargo can be altered by different disease states and may be responsible for some disease sequelae, such as increased cardiovascular disease, but underlying mechanisms are unclear. Currently, nothing is known about HDL-miRNA cargo in patients with RA. The goal of this study is to determine if in patients with RA altered HDL-miRNA cargo delivery modulates responses of cells that promote vascular inflammation and endothelial dysfunction, which are common in RA and are known to occur early in the development of cardiovascular disease. This novel mechanism of intercellular communication by HDL-miRNA delivery will offer new avenues of therapeutics for RA and potentially the general population to decrease cardiovascular risk.

Adherence Improvement

Pre Doctoral Fellowship in Adherence Improvement

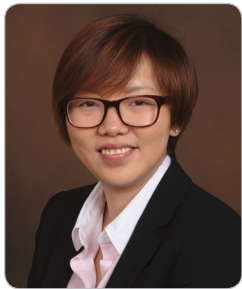
Medication adherence is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a treatment regimen. Extensive evidence demonstrates that medication adherence can yield better clinical and economic outcomes. However, many individuals do not take their medications 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 first Adherence Improvement fellowships and grants were funded in 2013.

“ The PhRMA Foundation Pre Doctoral Fellowship Award will provide support for my doctoral dissertation work and help me grow as an independent health services researcher. I will be able to pursue my interests in evaluating independent effects of drug plan policies, individual characteristics and geographic factors on adherence.”

Xian Shen | University of Maryland, Baltimore

2015 PRE DOCTORAL FELLOWSHIP IN ADHERENCE IMPROVEMENT



Xian Shen

University of Maryland, Baltimore

“Effects of Medicare Part D Plan Policies, Beneficiary Characteristics and Geographic Factors on Medication Adherence among Randomized Beneficiaries with Low-Income Subsidies”

This research project seeks to understand independent effects of Medicare Part D plan policies, beneficiary characteristics, and regional factors on medication adherence for oral hypoglycemic agents (OHA), statins and renin angiotensin system (RAS) antagonists. This work is inspired by an ongoing debate regarding appropriateness of risk adjustment for adherence-based quality measures used in the Medicare Star Ratings Program. In 2015, Star Ratings are assigned to Part D contracts based on an assessment of 13 quality measures, of which three emphasize on medication adherence for OHAs, statins and RAS antagonists. Currently, ratings for these three adherence-based quality measures are unadjusted for differences in beneficiary characteristics between contracts. The controversy lies in an unsolved question whether these adherence measures actually capture quality of a Part D contract in managing beneficiaries' medication adherence or whether they are reflections of beneficiary mix in that contract. It is challenging to address this question in an observational study in which selection bias is a critical threat to drawing causal inference. This study addresses this challenge in the context of a natural experiment created by an auto-assignment

process under Medicare that randomly assigns beneficiaries receiving low-income subsidies to benchmark Part D plans within their regions. Randomization balances both observable and unobservable beneficiary characteristics among plans, and creates a unique research opportunity for separately estimating plan, enrollee, and regional effects on medication adherence. Findings of this study will provide insights into how drug plan policies, such as utilization management tools and medication therapy management rules, contribute to individuals' medication adherence. Additionally, findings on independent effects of beneficiary characteristics will inform design of adherence-based quality measures, while results on regional influences will help to explain geographic variations in medication use beyond differences in population health.

“The PhRMA Foundation Pre Doctoral Fellowship in Adherence Improvement has provided the necessary financial support and protected time to work on my dissertation and has enabled me to advance my knowledge in the field of adherence research. I am very thankful to the foundation for boosting my confidence in my research, empowering me to realize my potential as a researcher, and for providing a platform to share and disseminate my research findings to a larger audience.”

Satya Surbhi | University of Tennessee Health Science Center



Satya Surbhi, MS

University of Tennessee Health Science Center

“Does Medication Adherence Mediate the Positive Impact of a Care Transitions Program on Health Care Utilization and Costs Among Vulnerable Populations?”

Medication non-adherence is a major health care concern, with studies showing that it is associated with poor health outcomes and higher health care utilization and health care costs. During care transitions processes from hospital to the community setting, patients often experience difficulty in medication management, medication discrepancies and drug therapy problems being key factors in making these care transitions complex. Studies have evaluated the impact of interventions on medication adherence and health care utilization and costs, with some showing a positive impact on both adherence and health outcomes. However, there is little evidence showing an impact of care transitions programs on medication adherence and outcomes among vulnerable populations with high health care needs. This project intends to explore the causal pathway linking interventions to the final outcomes, through the mediating effect of medication adherence. Therefore, it is imperative to demonstrate whether care transitions interventions that are designed to affect patients' adherence are successful in improving adherence and whether the change in the adherence is impacting the health outcomes among vulnerable populations who can benefit the most from such interventions. The SafeMed Program is a unique care transitions program targeting vulnerable populations in Memphis with complex health care needs. Using Medicare and Tennessee Medicaid claims

data, this study will examine the impact of the SafeMed Program on medication adherence and explore the causal pathway linking the program interventions to health care utilization and health care cost, through the potential mediating effect of medication adherence. The study findings have the potential to demonstrate the central importance of adherence in improving transitions of care—that care transitions programs focusing on medication management can improve adherence and that improvements in adherence are essential to broader impacts on healthcare utilization and costs.

Research Starter Grants 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 Grant has helped us collaborate with Managed Care Organizations and develop projects that directly benefit diabetic patients.”

Sujit S. Sansgiry, Ph.D. | University of Houston

2015 RESEARCH STARTER GRANTS IN ADHERENCE IMPROVEMENT



Sujit S. Sansgiry, Ph.D.

University of Houston, Texas Medical Center

“Development and Validation of a Prognostic Tool to Identify Diabetes Patients at High Risk for Non-adherence to Medications”

The total estimated cost of diabetes patient care is around \$300 billion. Approximately 59% of all health care expenditures attributed to diabetes are for health resources that are used by the elderly population, much of which is borne by the Medicare program. Oral antidiabetic drugs (OADs) can delay or prevent the development of complications and comorbidities in diabetes patients; however the poor adherence rates to OADs (77% in 2013) among the Medicare beneficiaries prevents optimal clinical outcomes and increases healthcare costs. The purpose of the project by Dr. Sujit S Sansgiry at the University of Houston is to develop Prescription Medication Adherence Prediction Tool for diabetes medications (RxAPT-D), a prognostic tool to identify patients at high-risk for non-adherence to OADs in the next year, using claims data generated from the previous year. The prognostic algorithm would be tested for internal validity and temporal validity. RxAPT-D will help identify patients in need for adherence assistance, thus avoiding the need to spend on resources for patients who are likely to be adherent, and focusing on only those in need. Since the claim-based prognostic algorithm can be used as a web-based tool to calculate individual probabilities on a routine basis, no

additional resources are needed once an automated process is initiated. The study may also lead to identification of novel predictors of future non-adherence that can be calculated using data available in claims files. The tool will be designed to ensure feasibility and real-world applicability. RxAPT-D is an important first step for a cost-effective patient targeted approach to identify patients in need for adherence intervention.

“ Receiving the 2015 Research Starter Grant in Adherence Improvement was a critical step in building my career as an adherence researcher. Implementing the project provided the preliminary data needed to apply for larger federal grants to further enhance the medication-taking behavior among patients with chronic illnesses and their subsequent health outcomes. It also opened the door to receive funding from other sources. I am grateful for the opportunity.”

Susan Abughosh, Ph.D. | University of Houston



Susan Abughosh, Ph.D.

University of Houston, Texas Medical Center

“A Motivational Interviewing Pharmacy Student Intervention to Improve Medication Adherence”

Diabetes and hypertension are independent risk factors for cardiovascular disease and are major public health issues. The two conditions frequently coexist, and when combined, the risk of developing diabetes complications significantly increases. Angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) are highly recommended, with well-documented benefits, for patients with both diabetes and hypertension. Poor adherence however, remains a significant barrier to achieving full effectiveness and optimal long-term outcomes. The purpose of this project is to evaluate the effect of a motivational interviewing based pharmacy student telephone intervention on ACEI/ARB medication adherence as well as on blood pressure and glycemic control. Motivational interviewing fosters behavior change and promotes self-efficacy in a supportive, collaborative, and empathetic way. Pharmacist interventions have been shown to improve medication adherence. Pharmacy students have the knowledge base and training to provide comparable services at a lower cost. A randomized trial will be carried out among non-adherent patients with combined hypertension and diabetes that are enrolled in a Medicare Advantage plan. The pharmacy students, trained in motivational interviewing, will contact patients to identify and address adherence barriers. Students will also assess patient medications for appropriateness, safety and adherence and will review with the patient, focusing on the achievement of desired clinical and patient goals. Findings are expected to demonstrate the benefit of a low cost intervention in enhancing medication adherence and subsequent health outcomes in a real world setting.

Comparative Effectiveness Research Center of Excellence

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 has provided 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.

The first Comparative Effectiveness Research Centers of Excellence were established in 2012.

“Funding from the PhRMA Foundation to establish a Center for Excellence in Comparative Effectiveness Research Education at our university will have long lasting benefits for countless number of students and working professionals who will be exposed to the education and training programs developed by the Center.”

Glen Schumock, PharmD, MBA, Ph.D. | University of Illinois



Glen T. Schumock, PharmD, MBA, Ph.D.

A. Simon Pickard, Ph.D.

The University of Illinois at Chicago

Comparative effectiveness research (CER) is a rapidly expanding and important area of investigation in health care. Advances in methods used to conduct CER, together with its increasing use, has contributed to an escalating demand for training and expertise in the field. While both the NIH and AHRQ have invested in mentored training awards for CER researchers, these have focused on individual trainees and are few in number. Further, while there are a variety of academic institutions that grant degrees in related fields (including epidemiology, health economics, health services research, biostatistics and others), these do not cover the entire spectrum of methods and applications unique to CER, nor do they provide a cogent understanding of how these disciplines contribute to the field CER. As a result, there is critical need for specialized new degree programs to educate and train researchers in CER. The Pharmaceutical Research and Manufacturers of American Foundation has attempted to address this need by funding the University of Illinois at Chicago (UIC) as the sixth center under its Centers of Excellence in Comparative Effectiveness Research Education Program. UIC has extensive infrastructure and faculty expertise in CER. Under the PhRMA Foundation program UIC will develop a Master's of Science degree in CER that is designed for working professionals, particularly those in pharmaceutical industry and health care organizations,

where a significant need exist for education and training in CER yet where contemporary methods of teaching are important – such as online coursework. Other goals of the UIC effort are to 1) act in a supportive role together with private and public partners to achieve the goal of producing high caliber comparative effectiveness researchers and practitioners who are able to interpret and use research results; 2) furnish the necessary resources that can be used to develop corroborating evidence on the usefulness and value of sound CER; 3) convene public forums and seminars for interested members of the public from the wider university/college community to discuss topical CER issues; 4) promote, with other groups, the development of a CER curriculum that offers the appropriate discipline-specific educational skills, research methodology training, and case experience needed to produce highly desirable comparative effectiveness researchers and practitioners; 5) sponsor lectures and presentations on different programs and venues, e.g., AHRQ, NIH, Industry, Universities, and other institutions that promote conscientious discussions on important CER topics; 6) work with representatives from government, industry and education to determine the number and types of CER trained experts needed to fill the personnel demands of these societal sectors; and 7) make available to interested members of the public, by electronic publication or other easily accessible means, CER educational training tools developed with funding provided by the Foundation.



Informatics

Pre Doctoral Fellowships 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 has been awarding fellowships and grants in Informatics since 2002.

2015 PRE DOCTORAL FELLOWSHIPS IN INFORMATICS



Namita Gupta

Yale University

“Probing Adaptive Immunity by Computational Analysis of B Cell Repertoire Sequencing Data”

Antibodies are created by B cells with such diversity that they can adapt to neutralize any pathogen as part of an immune response. When a B cell encounters a pathogen it recognizes, it undergoes multiple rounds of mutation and expansion to create a pool of clonally related B cells that target the pathogen. These B cell clones then undergo selection for affinity of their antibodies to bind antigen, resulting in optimized antibodies that can neutralize the infection. Next-generation sequencing of antibody mRNA molecules allows a high-throughput characterization of an antibody-mediated immune response. However, there is currently no way to know the binding target of an antibody given its nucleotide sequence. Furthermore, there is no proven method of identifying antibody sequences that are members of the same B cell clone, as it can be difficult to quantify similarity between sequences. This project will develop a robust computational method to identify clonally related sequences and machine learning models to classify antibody sequences based on binding target, with a focus on influenza and HIV. Project completion will lead to understanding the specific mutations within a B cell clone that contribute to high affinity neutralization, which can help in the development of vaccines or therapeutic neutralizing antibodies.



Kaitlyn Gayvert

Weill Cornell Graduate School of Medical Sciences

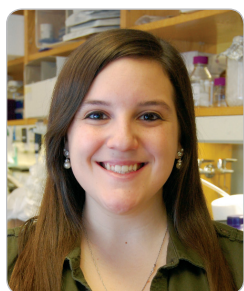
“Computational Drug Repositioning Approach for Targeting Transcription Factors”

Inhibition of oncogenes and reactivation of tumor-suppressor genes have become well-established goals in anticancer drug development. Yet despite the prevalence of transcription

factor genes that fall into these categories, they have been uncommon targets in anticancer drug development as they have been generally considered undruggable. If a strategy could be developed for safely and effectively modulating the activity of specific transcription factors, it would have a wide impact on the treatment of cancer subgroups driven by oncogenic transcription factors. This project proposes to develop a broadly applicable systems-level drug repositioning approach that identifies small molecules that can indirectly but specifically perturb transcription factor activity. The proposed work exploits the tendency of most transcription factors to bind and regulate many genes. It will focus on a subset of data to computationally identify drugs modulating transcription factors important in prostate cancer biology. Extensive experimental validation of key nominated compounds in multiple prostate cancer model systems will then be performed. In addition, this work will aim to increase our understanding of the targets of key transcription factors in cancer and how transcription factor perturbations occur mechanistically.

“Receiving the PhRMA Foundation Pre Doctoral Fellowship in Informatics has allowed me to dedicate more time to research, writing papers, and presenting my work at both national and international conferences rather than writing grants and focusing on funding. I have gained more experience and advanced my thesis work over this past year more than I could have imagined, and I look forward to continuing the work I am most passionate about.”

Caitlyn Mills | Northeastern University



Caitlyn Mills

Northeastern University

“Functional Characterization of Structural Genomic Proteins in the Crotonase Superfamily”

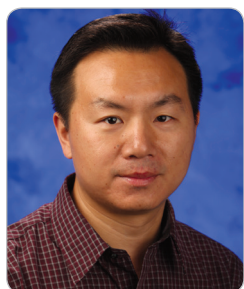
While genomics holds tremendous promise for future benefits to society, including many potential novel therapeutics, a key step toward the realization of this potential is the ability to determine the function of the thousands of protein structures whose biochemical functions are currently unknown or uncertain. Over 13,000 new protein structures have been reported by Structural Genomics (SG) initiatives, but the determination of the biochemical function of these structures has proved to be much more difficult than originally envisioned. Reliable methods for the prediction of the function of proteins from their 3D structures constitute a critical current need and will open the door to untold innovations in medicine. The goal of this research is to develop, implement, and experimentally validate a method to predict the biochemical functions of these SG proteins. Specifically, the Crotonase Superfamily will be used to test our new methodology. This superfamily consists of five diverse functional subgroups that are well characterized structurally and functionally, representing different types of reactivity. In addition to the proteins of known function, this superfamily also contains at least 70 SG proteins with

putative functional assignments. These SG proteins are first analyzed to predict their function based on local structure matching at the computationally predicted active site by Partial Order Optimum Likelihood (POOL) and Structurally Aligned Local Sites of Activity (SALSA). Then, the predicted functions of these SG proteins are tested through biochemical assays. The main goal of this research is to successfully classify the members of the representative superfamily. With this information, these methods can be applied to other superfamilies. Automation of the method will enable high-throughput functional prediction for thousands of SG proteins.

Research Starter Grants 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.

2015 RESEARCH STARTER GRANTS IN INFORMATICS



Feng Yue, Ph.D.

Pennsylvania State University

“A Random Forest-based Computational Framework for Predicting Disease-causal Variants”

Genome-wide association studies (GWASs) have successfully identified thousands of genetic mutations involved in many complex human diseases such as cancer, heart disease and obesity. However, the majority of them are not located in gene-coding regions, and it remains challenging to illustrate how exactly these mutations contribute to the diseases. Here, we propose to develop a computational framework to predict/prioritize the causal variants by investigating their interplay with histone modifications, epigenetic signatures, specific TF binding sites, and evolutionary conservation. To demonstrate its power and as a proof of concept, these studies will validate those predictions with high throughput functional experiments using childhood acute lymphoblastic leukemia (ALL) as a disease model. The computational model would be easily adopted for the study of other complex disease. In summary, this project can advance our understanding of the genetic basis for thousands of complex diseases, which would have critical applications in improving their diagnosis and treatment.



Alan A. Chen, Ph.D.

University at Albany, SUNY

“Physics-Based RNA 3-D Structure Prediction”

Recent breakthroughs in RNA biology have spurred great interest in developing RNA-targeting therapeutics. Unfortunately, folded RNAs are exceedingly difficult to characterize at atomic resolution, as evidenced by the fact that less than 3% of PDB structures contain RNA. While protein structures can be routinely solved via NMR, X-ray crystallography, and homology modelling; the lack of equivalently effective methods for establishing RNA structure-function relationships has led to RNA being declared “undruggable”. The proposed research will directly address this need by creating an atomic, physics-based model that can predict the 3D conformation of RNAs to Angstrom-level resolution, including tertiary and non-canonical interactions characteristic of structured RNAs. The “ground-up” modelling approach relies on calibrating the intermolecular forces directly from biophysical measurements of nucleotides in aqueous environments - a departure from heuristic approaches to structure prediction that rely on data-mining of structures found in the PDB. This physics-based, experimentally calibrated model has demonstrated initial early successes in folding hyperstable RNA tetraloops from a random unfolded states, recapitulating to sub-Angstrom the unique non-canonical loop-loop interactions characteristic of these common RNA motifs. Since the model is not built “on top of” a nearest-neighbor secondary structure model, it does not inherit their intrinsic limitations in treating RNA bulges, junctions, pseudoknots, etc. as two dimensional objects. These intrinsically 3D motifs require a 3D physical model to adjudicate how their conformational preferences respond to changes in their local environment during the folding process. Furthermore the calibration method is easily extendable to include interactions with non-natural, chemically modified nucleotides and drug-like molecules, even if they are not found in any PDB structure. In this manner, this model directly encodes the underlying driving forces known to impact RNA folding such as base-pairing, stacking, salt-dependence, steric exclusion, solvation, and conformational entropy. Predicted structures for small viral RNA loops and aptamer sequences known to recognize small molecules will be tested by our experimental collaborators who will synthesize, crystallize, and functionally assay each RNA along with strategically selected mutants.



Yana Bromberg, Ph.D.

Rutgers University

“Computational Analysis of Genome Variation For Elucidation of Pathogenesis Pathways”

Every individual genome predisposes its carrier to some set of diseases. Despite all research efforts, however, heritable causes of complex disease remain elusive. This is largely due to the inherent complexity of pathogenesis pathways and the interaction of individual genomic determinants with the environment. Elucidating causative genetics of pathogenesis will spur the development of better treatments and prevention tactics. Using the PhRMA Foundation funding, work was started on building a computational method for evaluating the role of DNA

variants in complex diseases. This pipeline can then be used to predict individual disease predisposition and spur further research.

The PhRMA Foundation Informatics Starter Grant is being used for one of the most important steps of building this pipeline – data collection and annotation. The project will further use this data to build a unique predictor of the impact of genetic variation on gene function. Each patient or healthy individual can then be represented as a profile of his or her affected genes. Based on commonalities and differences between the sets of healthy and disease-affected profiles, computational techniques can identify new disease-genes. Further, this study will develop an algorithm to recognize the functional differences in sets of these selected genes and make evaluations of individual disease predisposition. Due to their generalizability, these methods will be useful for drawing conclusions on existing sequencing data and on newly sequenced genomes. Moreover, this pipeline will generate hypotheses of pathogenesis by pinpointing the causative genes and molecular functions. Finally it is expected that this method will be prognostic, allowing determination of disease predisposition prior to clinical diagnosis.



Juliee Thakar, Ph.D.

University of Rochester

“Inference of Regulatory Logic Between Immune Cells, Cytokines and Transcription Factors Induced During Influenza Infections”

Despite vaccines and antiviral substances, influenza still causes significant morbidity and mortality worldwide. To develop efficient means of prevention and treatment of influenza; better understanding of the molecular mechanisms of pathogenesis and host immune responses is required. The immune response to influenza emerges from dynamic interactions of multiple elements, including the interaction of molecular host defense mechanisms in specialized immune cells and viral determinants over time. Transcriptomic data from different cell-types offer an unbiased approach to investigate host immune responses, and have identified several markers associated with severe influenza infections. However, inference of mechanistic insight from high-throughput data is still a challenge. In order to identify mechanisms of immune regulation and antagonism from transcriptomic data, the proposed study will develop novel computational tools to infer regulatory logic between immune cells, cytokines and transcription factors involved in influenza infections. Thus, the study will facilitate analysis of probable trajectories of the immune response to influenza infections; predicting outcomes of future infections.

Health Outcomes

Pre Doctoral Fellowships 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.

The first Health Outcomes fellowships and grants were awarded in 2002.

2015 PRE DOCTORAL FELLOWSHIPS IN HEALTH OUTCOMES



Michael Harvey

University of Michigan

“Determining the Cost-effectiveness and Optimal Vaccination Timing of the Herpes Zoster Vaccine”

Herpes zoster virus, commonly known as shingles, is a disease that nearly every person can develop, and yet is not well understood by the general population. This disease has the highest incidence of any neurological disease and approximately 95% of Americans are at risk. Common symptoms include a blistering rash and debilitating pain. Herpes zoster (HZ) cannot be cured, but a vaccine is available that can be used to prevent the disease and its complications, making it an extremely important tool for public health practice. People are more at risk of infection and disease complications as they age. However, initial vaccine efficacy is higher when administered at younger ages, but wanes over time. Further, the vaccine provides a different duration of protection based on when it is administered. Therefore, understanding how vaccine administration affects health outcomes and costs can help societal and health system decision makers make good decisions about when to vaccinate. The question of an optimal age for vaccination remains largely unanswered. Given that the age at vaccination can dramatically affect vaccine efficacy and duration, even a marginal change in the age of administration could affect the long term outcomes and produce sub-optimal results. The objective of my research is to estimate the optimal age for vaccination against HZ using cost-effectiveness analysis and a markov decision process model.

“ The PhRMA Foundation Pre Doctoral Fellowship has given me the support to focus exclusively on my dissertation. The impact of this support on the productivity of my work has been immense. The PhRMA Foundation has been an incredible partner in this effort.”

William J. Canestaro, MSc, | University of Washington



William J. Canestaro
University of Washington

“Publication Bias: Impact and Adjustment”

Large numbers of studies have described the phenomenon of publication bias and identified characteristics of studies associated with dissemination level. Furthermore, methods have been developed to identify and account for publication bias including funnel plots, ‘trim and fill’ and advanced applications of meta-regression. Despite this, a comprehensive up-to-date systematic evaluation of the various methods and their performance under different scenarios of publication bias is lacking. In parallel, value of information methods have been developed and refined to inform decisions about adopting medical interventions based on current evidence or conducting additional research. These methods have been extended to estimate a net economic return of previously conducted research. However, neither of these approaches have been applied to evaluating investment in efforts to identify studies that went unpublished and estimation of the potential clinical and economic consequences thereof. This research project attempts to address these shortcomings in the field.

“ My PhRMA Foundation Fellowship has provided me with the freedom to think more creatively about my dissertation topic. Specifically, it has allowed me to invest the time to perform a systematic review with the help of a research librarian and to utilize a more comprehensive data source that would have otherwise been beyond reach.”

Elisabeth M. Oehrlein | University of Maryland, Baltimore



Elisabeth M. Oehrlein
University of Maryland

“Using Patient Centered Outcomes Research and Epidemiology to Assess Atrial Fibrillation Treatment and Outcomes Among an Under-65 Privately Insured Population”

In determining who among the estimated 5.2 million Americans diagnosed with atrial fibrillation (AF) should receive anticoagulation therapy, clinical treatment guidelines recommend use of the CHADS₂ and CHA₂DS₂-VASc risk-stratification schemes. While the CHADS₂ considers congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, the CHA₂DS₂-VASc

also considers gender, vascular disease, and patient's age (65-74 years). Clinical guidelines recommend treating "high-risk" patients with anticoagulants and lower-risk patients with aspirin. Critical evaluation of these tools is necessary, as some studies have shown that segments of the population, including females, are less likely to receive anticoagulants. Furthermore, validation studies for these risk stratification schemes were undertaken in elderly populations, making it unclear how applicable they are to younger AF populations. Using a large, private insurance claims database, this study will examine the CHADS₂ and CHA₂DS₂-VASc among an under-65 population. This study will analyze how risk factors and outcomes differ between this population versus an elderly AF population, evaluate the ability of these tools to predict stroke and bleeding risk in this younger population, identify disparities between men and women, and examine how closely physician prescribing of anticoagulants aligns with recommendations according to guidelines. The quantitative analysis will be complemented by a qualitative study that gathers information directly from physicians and patients experiences with risk stratification in AF.

Research Starter Grants 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.

“ The PhRMA Foundation Research Starter Grant allowed me to build collaborations and carve out an area of research with lots of potential for future work. I am grateful to the PhRMA Foundation for giving me this opportunity.”

Aasthaa Bansal, Ph.D. | The University of Washington

2015 RESEARCH STARTER GRANTS IN HEALTH OUTCOMES



Aasthaa Bansal, Ph.D.

University of Washington

“Comparative Effectiveness of Molecular Response Guided Sequential Treatment Strategies In Chronic Myeloid Leukemia”

Although targeted therapies in chronic myeloid leukemia (CML) offer survival benefits to many patients, questions have emerged about how to effectively sequence therapies to maximize the likelihood of favorable long-term outcomes, while addressing treatment effect heterogeneity among patients. Specifically, there are open clinical questions regarding the choice of first-line therapy, optimal monitoring of patients, choice of second-line therapy for patients who develop disease progression, and whether discontinuation of therapy is possible. These questions are all part of the bigger challenge of developing individualized sequential treatment strategies,

where each decision in the sequence impacts long-term outcomes. This research project will combine existing clinical trials data on CML patients and apply advanced statistical methods to determine how to best use molecular response history as a marker for patient outcomes and compare marker-guided individualized sequential treatment strategies. The results of these analyses will provide evidence that may help inform CML treatment guidelines. Furthermore, the project's novel application of complex statistical methods to existing data can pave the way for similar analyses in other clinical areas with a similar need for individualized treatment sequences but devoid of direct clinical trial evidence.

“ I am honored and excited to receive the 2015 PhRMA Foundation Research Starter Grant in Health Outcomes. This award will be fundamental to my success as a young scientist. It will allow me to independently pursue research projects I am passionate about and recruit talented collaborators to my lab, improve my scientific reputation, and increase my probability for future funding to sustain my research program. The award will also allow me to develop other skills and gain the experience needed to be a successful independent researcher. In the long-term, I anticipate that this award will accelerate accomplishment of my career objectives. Thank you, PhRMA Foundation!”

Kelly R. Reveles, Ph.D. | The University of Texas at Austin



Kelly R. Reveles, Pharm.D., Ph.D.

The University of Texas at Austin

“Preventative Therapies For Recurrent Clostridium Difficile Infection”

Clostridium difficile infection (CDI) is a gastrointestinal disease often linked to antibiotic use. CDI affects nearly half a million patients in the United States every year and rates are increasing. Unfortunately, once a patient has experienced one episode of CDI, they often experience additional episodes. Nearly 25% of patients will experience CDI recurrence despite successful treatment of the initial episode. Recurrent CDI places a heavy burden on patients, as it is associated with prolonged symptoms, repeated courses of antibiotics, and re-hospitalization. Certain medications, when prescribed during the initial CDI episode, might help reduce the risk for recurrent CDI. Prior studies have found that newer antibiotics and other medications that affect the normal gut bacteria or immune system might reduce the risk for recurrent CDI, but larger studies are needed to confirm these findings. This project will study approximately 75,000 patients with CDI from the national Veterans Health Administration to identify effective antibiotic and non-antibiotic medications that reduce the risk for recurrent CDI. The results of this study are expected to have a positive impact on human health by more effectively guiding clinician decision-making to prevent recurrent CDI.



Joel Gagnier, Ph.D.

The University of Michigan

“Establishing a Minimal Important Difference for the PROMIS Physical Function Upper Extremity CAT Instrument In Patients With Rotator Cuff Disease”

Rotator cuff (RC) diseases are among the most common pathologies in our aging population. Clinical studies of RC disease include an array of outcome measures, many with drawbacks in their psychometric properties. The minimally important difference (MID) is the smallest change in an outcome measure that is perceived by patients as important. The Patient Reported Outcomes Measure Information System (PROMIS) is multi-year cooperative agreement between the NIH and several research and academic medical institutions. There are many PROMIS item banks and scales. The PROMIS physical function (PF) upper extremity computer adaptive test (CAT) does not have an MID established. Establishing MIDs for patients with known RC disease will help determine if differences in outcomes are clinically relevant. This project will administer the PROMIS PF upper extremity CAT to patients with RC disease and assess their change over time. It will then establish distribution-based and anchor-based MIDs for this health outcome measure and test the influence of several variables (intervention, patient, outcome measure timing) on MID variation. This information will directly improve the ability to: (1) Determine when patients with RC disease are changing in a meaningful manner; (2) Identify characteristics of the intervention, patients and follow-up period that predict variations in the MID values; (3) Appropriately power planned clinical studies using this PROMIS instrument as the primary outcome.

Pharmaceutics

Pre Doctoral Fellowships 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.

The PhRMA Foundation began funding awards in Pharmaceutics in 1972.

2015 PRE DOCTORAL FELLOWSHIPS IN PHARMACEUTICS

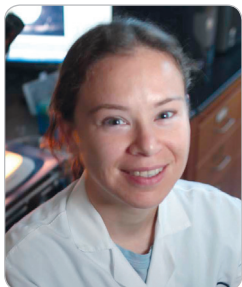


Michelle Fung

University of Minnesota, Twin Cities

“Effect of Plasticizer On the Physical Stability of Amorphous Solid Dispersions”

The oral bioavailability of poorly water soluble active pharmaceutical ingredients (APIs) can be a serious drug delivery challenge. Amorphization has been widely used as a strategy for improving the oral bioavailability of poorly water soluble APIs. However, physical instability of amorphous API, leading to crystallization, can negate the solubility advantage and lead to product failure. Amorphous solid dispersion (ASD), wherein an API is molecularly mixed with a hydrophilic polymer, helps impede drug crystallization. Studying reaction kinetics at elevated temperatures and extrapolating to temperatures of interest, an approach used for predicting chemical stability, cannot be used for physical stability (crystallization) prediction. Drug crystallization propensity dramatically decreases near and below the glass transition temperature (T_g) of the system. This project has previously measured an important kinetic factor, molecular mobility, with dynamic dielectric spectroscopy and established a correlation between molecular mobility and the physical stability of amorphous pharmaceuticals. The project goal is to develop a predictive model for evaluating the physical stability of ASDs. However, it may take a very long time to observe crystallization. Since the addition of a small molecule plasticizer to ASDs increases the molecular mobility and accelerates drug crystallization, experiments conducted in short timescales can help determine the coupling between molecular mobility and crystallization. By understanding the impact of small molecule plasticizers on the physical stability of ASDs, prediction of drug crystallization at relevant storage temperatures is possible. In turn, ASDs with improved stability profiles can be formulated using these predictive tools.



Mary Kleppe

University of Connecticut

“Investigating the Effects of Hydrated Glass Transition Temperature and Degree of Supersaturation on Crystallization of Amorphous Drugs during Dissolution”

An alarming fraction of early discovery drug candidates suffer from limited oral absorption/bioavailability in their crystalline form due to poor solubility. One approach to improve solubility and bioavailability is generating a non-crystalline form of drug, e.g. the amorphous form. Amorphous solids dissolve rapidly to achieve higher drug concentrations, relative to their crystalline counter form. This higher drug concentration (often referred to as supersaturated) in gastrointestinal tract, can result in greater bioavailability. However, this supersaturated state is unstable and the drug often precipitates/crystallizes to leave a lower dissolved concentration, a phenomenon called solution-mediated phase transformation (SMPT). SMPT from supersaturated concentration can lower the potential bioavailability enhancement of the amorphous solid of many drugs in the development pipeline. In an effort to improve prediction of SMPT of drug in the amorphous form during dissolution, this study aims at delineating the contribution(s) of the molecular mobility of the amorphous drug in water and the extent of supersaturation relative to temperature.

With increasing demands to reduce drug development time and costs, early predictors of drug developability are critical to meet goals. Poorly soluble drug candidates require novel formulation strategies that include a degree of risk (e.g., crystallization during dissolution of amorphous drug), which would reduce oral bioavailability. Early prediction of the potential for success of the amorphous route for poorly soluble drugs would reduce development resources and create more potential effective drug candidates.



“ Being a recipient of the PhRMA Foundation Fellowship has externally validated my confidence as a young scientific researcher. The fellowship has provided a source of funding for me to be able to focus on conducting my own creative research without feeling restricted by what I am able to explore. I am grateful for the fellowship and the positive impact it has on my success as a researcher.”

Heather J. Boyce | University of Maryland, Baltimore



Heather J. Boyce

University of Maryland

“Investigating the Physical Properties and Interactions of Pharmaceutical Excipients in Abuse Deterrent Formulations”

Abuse deterrent formulations (ADFs) are designed to deter misuse and abuse of prescription narcotics and other drugs prone to abuse. One technology for developing an ADF is to incorporate a physical barrier, to increase the tablet strength, thereby reducing ease of tablet chewing, grinding, cutting and crushing. Increasing the tablet strength could be accomplished by several approaches including, but not limited to, incorporation and sintering of polyethylene oxide (PEO) in the formulation. Polymers such as PEO will also form a gel when exposed to moisture and retard the release of the drug. Understanding the properties of different grades of PEO and other similar polymers and how they can be manufactured to affect tablet strength is of importance for ADF formulation development. Additionally, interactions with other pharmaceutical excipients in an ADF, such as anti-oxidizing agents, and plasticizers and how they can affect the final ADF performance is important to investigate as well.

This work seeks to investigate the mechanisms involved in tablet sintering to understand how thermal treatment of the tablets can produce tablets of great strength. Furthermore, this project will evaluate the different formulations with varying key excipients by assessing their tablet strength and resulting ability to form viscous solutions under user manipulated and non-manipulated conditions. Finally, methods to assess nasal abuse will be developed. Vertical diffusion cells will be used to assess the ability of the formulation to increase the time for a model drug to diffuse through a membrane compared to a pure drug substance.

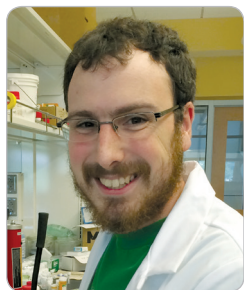
Post Doctoral Fellowships in Pharmaceutics

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 PhRMA Foundation Postdoctoral Fellowship in Pharmaceutics has given me a great opportunity to continue my education as a postdoctoral fellow. The fellowship will allow me to stay in my current position for a full three years, gaining invaluable experience in the combined fields of pharmaceutics and solid-state nuclear magnetic resonance that I would not have been able to get otherwise.”

Sean Delaney, Ph.D. | University of Kentucky

2015 POST DOCTORAL FELLOWSHIPS IN PHARMACEUTICS



Sean Delaney, Ph.D.

University of Kentucky

“Theoretical and Experimental Investigation of Amorphous Dispersion Stability”

Bioavailability is of great interest to the pharmaceutical industry. Biopharmaceutics Classification System (BCS) Class II drugs have high permeability and make up ~70% of the available drugs, but have low solubility. Finding a way to transition these low soluble Class II drugs into the more desirable high solubility Class I drugs is important, especially given the large percentage of new pharmaceuticals that fall into Class II. Recently, pharmaceutical companies have been using the amorphous form of the active pharmaceutical ingredient (API) to enhance the bioavailability of the poorly-water soluble compounds. Specifically, the use of the amorphous form of the drug increases solubility while also having faster dissolution rates than the crystalline forms of the drug. Although amorphous drugs have great potential, they render the active ingredient in a metastable state relative to the crystalline form, which can result in poor bioavailability if the compound were to crystallize. One solution to overcome the observed stability issues of the amorphous drug forms is to add a polymer to increase the stability. These mixtures of drug and polymer (amorphous solid dispersions) have been illustrated to increase the overall stability of the drug, while maintaining the high solubility of the general amorphous material. The long-term physical stability of amorphous solid dispersions is a significant risk in the development and commercialization of an amorphous solid dispersion. The discovery and development of new techniques that enable rapid decision making regarding polymer selection to de-risk the potential for physical instability during clinical development and commercial manufacture of an amorphous solid dispersion are needed in the pharmaceutical industry and community. Investigating the overall stability of model amorphous dispersions in terms of miscibility, mobility, and hydrogen bonding will allow for a more thorough understanding of the components relative to physical stability. The goal is to fundamentally investigate why crystallization occurs particularly as a function of manufacturing and storage conditions (e.g., residual solvent and sorbed water).

Research Starter Grants 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.

2015 RESEARCH STARTER GRANTS IN PHARMACEUTICS



Keith Chadwick, Ph.D.

Purdue University

“Controlling Crystallization on Polymeric Excipients for the Advanced Manufacture of Drug Formulations”

One of the most significant challenges in human healthcare in the 21st century is medication affordability. The increasing costs associated with bringing new drug products to market and declining productivity from research and development (R&D) investment for pharmaceutical companies often mean that, in order to recoup investment, many medications are unaffordable to a significant percentage of the global population. The costs associated with manufacturing drug products represent a significant proportion of a pharmaceutical companies cost structure. A recent study estimated annual global manufacturing costs for pharmaceuticals in excess of \$200 billion. Therefore the need to develop new manufacturing practices and technologies to improve efficiency and reduce costs is essential towards improving medication affordability. This project addresses this need through the design and implementation of novel process intensification technologies that utilize crystallization of the drug compound inside porous polymeric excipients to manufacture products with desired efficacy. The research goals are to investigate (1) the interplay between particle design, manufacturing and the final material properties, (2) crystal nucleation mechanisms on heterogeneous surfaces for the application of crystal size, crystal shape and polymorph control, and (3) effect of polymer/crystal properties on the mechano-chemical properties of composite particles. This work will enable the development of new technology platforms for the continuous polymerization of micro-porous materials and continuous heterogeneous crystallization of drug compounds. The implementation of continuous process intensification technologies will reduce the number of required unit operations by eliminating the need for steps such as milling, blending and granulation. This will improve efficiency and reduce the footprint of manufacturing leading to a substantial reduction in costs.

“ The PhRMA Foundation Research Starter Grant gave me the confidence to pursue my proposed research studies and the freedom to train additional personnel and venture into risky but potentially rewarding areas of research. I am confident that the latter will lead to significant contributions to the pharmaceutical field as a result of this generous grant from the PhRMA Foundation.”

Christopher Alabi, Ph.D. | Cornell University



Christopher Alabi, Ph.D.

Cornell University

“Dual Ligand Bioconjugates for Targeted siRNA Delivery”

Synthetic short interfering RNAs (siRNAs) are an example of a new and promising class of therapeutic modalities that can silence the expression of disease-associated genes. Transforming *in vitro* validated siRNA drug targets into active therapeutics necessitates the safe and efficient delivery of the siRNA drug into the cytoplasm. The central objective of this research project is to enhance the cytoplasmic delivery of siRNA therapeutics by way of a dual ligand bioconjugate (DLB) approach. The DLB is composed of modular protein-siRNA and protein-polymer bioconjugates that work in concert with the cell's natural machinery to facilitate delivery. This approach decouples the requirements of cellular entry from endosomal escape, thus facilitating a detailed investigation into endosomolytic agents that can facilitate efficient cytoplasmic delivery of siRNAs. It is anticipated that this study will provide a comprehensive understanding of the intracellular pathways and key structural features of endosomolytic biomaterials that are required for the efficient cytosolic delivery. The modularity and simplicity of DLB approach lends itself to rapid optimization and should thus accelerate the development of potent siRNA therapeutics for the treatment of many intractable diseases.

Pharmacology/Toxicology

Pre Doctoral Fellowships 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.

“ The PhRMA Foundation Pre Doctoral Fellowship has provided an outstanding boost to my research career. In addition to financial support, this fellowship has helped me initiate a track record of self-sufficiency and success in research. Most importantly, receipt of this award afforded me the opportunity to forge invaluable relationships with an entire network of successful researchers.”

Dante Merlino | Thomas Jefferson University

2015 PRE DOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY



Dante Merlino

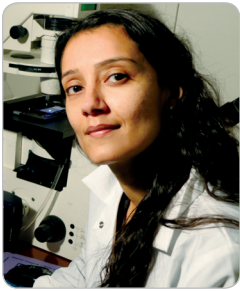
Thomas Jefferson University

“Investigation of the Neuroprotective Effects of Guanylyl Cyclase C”

Obesity is a pandemic, and its sequelae represent a leading cause of morbidity, mortality, and healthcare expenditures worldwide. Diets that induce obesity disrupt appetite and metabolic regulation through hypothalamic injury, mediated by oxidative stress, inflammation, and reactive gliosis. Recent work has demonstrated that guanylyl cyclase C (GUCY2C) is expressed in the hypothalamus, representing the distal end of a gut-brain axis controlling appetite, metabolism, and obesity. Ingestion of food results in the secretion of the intestinal GUCY2C ligand uroguanylin (GUCA2B) into the bloodstream, resulting in the activation of hypothalamic GUCY2C and the production of its second messenger, cyclic GMP (cGMP). In intestine and liver, GUCY2C activation opposes many of the pathophysiological processes that mediate diet-induced hypothalamic injury, including oxidative stress, inflammation, and fibrosis. Additionally, cGMP has established neuroprotective effects throughout the central nervous system, including the hypothalamus. In the present study, the pathophysiologic aim will determine whether diet-induced suppression of uroguanylin expression in intestine reduces GUCY2C activity in the hypothalamus which, in turn, amplifies neuronal injury disrupting satiety circuits. Conversely, the therapeutic aim of this study will explore the efficacy of uroguanylin replacement to reconstitute GUCY2C signaling, prevent and mitigate diet-induced hypothalamic injury, and repair dysregulated appetite and satiety mechanisms contributing to over-eating and obesity.

“ The PhRMA Foundation Fellowship in Pharmacology/Toxicology has allowed me to explore neural systems within the brain that contribute to our understanding of neuropsychiatric disorders, to work toward clearer answers to the questions that continue to arise in the field, and to expand that body of knowledge for the improvement of medicine and human health.”

Nayna Sanathara | University of California, Irvine



Nayna Sanathara

University of California, Irvine

“Oxytocin Modulation of Melanin Concentrating Hormone Neurons: Implications for Autism Spectrum Disorders”

Autism spectrum disorders (ASD) affect the development of the brain. Persons diagnosed with ASD have difficulty communicating and socializing with others, and perform repetitive stereotypic behaviors. ASD affect 1 in 68 individuals and males are 4 times more likely to be affected. How individuals acquire ASD is unclear. It appears that both genetic and environmental factors are involved. Genome wide studies show that a number of genes are disrupted, including oxytocin and its receptor. The oxytocin signaling pathway has been linked to the etiology of ASD and oxytocin pharmacotherapy has shown to improve ASD behavioral impairments. However, the neural circuitry through which it acts is not yet fully understood. The melanin-concentrating hormone (MCH) system is a potential mediator of oxytocin actions in ASD behavioral impairments. Oxytocin increases MCH neurotransmission and the MCH system has been shown to regulate several behavioral responses important in sensory integration and neuropsychiatric disorders. The proposed study will use immunohistochemistry, double label in situ hybridization and rabies mediated circuit mapping to define the neuroanatomical link between oxytocin and MCH. Behavioral experiments will use pharmacological antagonism of the MCH system to show that oxytocin acts through the MCH system to reduce behavioral impairments in ASD. The combination of neuroanatomical, pharmacological, and genetic approaches will help us understand oxytocin regulation of previously undefined neurocircuits that may regulate ASD and define novel roles for the MCH system.



Julie Lade

Johns Hopkins University School of Medicine

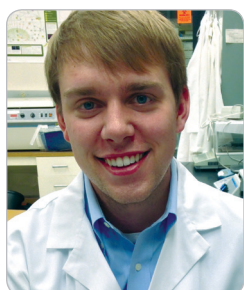
“Mechanisms of Dyslipidemia in Response to the Anti-HIV Drug Efavirenz”

Efavirenz is the most prescribed antiretroviral worldwide for the treatment of human immunodeficiency virus (HIV) infection. Moreover, efavirenz is within a class of antiretrovirals that target the HIV-1 reverse transcriptase enzyme and these drugs are commonly known as non-nucleoside reverse transcriptase inhibitors. Rilpivirine is a more recently FDA approved second generation non-nucleoside reverse transcriptase inhibitor that has a

flexible diarylpyrimidine structure enabling a greater genetic barrier to viral resistance relative to efavirenz and demonstrates an improved safety profile. Interestingly, efavirenz-based regimens have been observed to increase high-density lipoprotein, low-density lipoprotein and total cholesterol levels, whereas rilpivirine-based regimens exhibit less of an impact on lipid profiles. Dyslipidemia is characterized by the elevation of lipoprotein and total cholesterol levels and is a primary risk factor for developing atherosclerosis and cardiovascular disease. Studies probing the molecular mechanism(s) by which efavirenz stimulates the onset of dyslipidemia have yet to be reported. This project will investigate the impact of efavirenz and rilpivirine on signaling pathways that regulate cholesterol and lipid homeostasis in the liver. Further, as antiretrovirals are life-long therapies, the findings from this research can provide a foundation for the development of future drugs that retain their antiviral activity but exhibit reduced off-target effects.

“ I feel incredibly fortunate to have received the PhRMA Foundation Pre Doctoral Fellowship in Pharmacology and Toxicology. Beyond providing critical funding for my research, obtaining this award has been a great source of pride and motivation as I progress through my training. I am very thankful that the PhRMA Foundation supports basic research and is committed to the development of early career scientists such as myself.”

Joe Varberg | Indiana University School of Medicine



Joseph Varberg

Indiana University School of Medicine

“Regulators of Parasite Autophagy As Novel Drug Targets for Infectious Disease”

Apicomplexan parasites including *Plasmodium spp.*, the causative agent of malaria, and *Toxoplasma gondii*, the causative agent of toxoplasmosis, are responsible for the deaths of millions of people worldwide each year. Current treatment options are poorly tolerated and are further complicated by the emergence of drug resistant parasites. Recently, a novel class of anti-malarial drugs was found to work by inhibiting the *Plasmodium falciparum* autophagy pathway, a multi-functional catabolic process that allows for recycling of cellular components. Studies in both *P. falciparum* and *T. gondii* suggest that a functional autophagy pathway is essential for parasite survival, is required for organelle biogenesis and maintenance, and is induced in response to various anti-parasitic drugs. Like other critical cellular pathways, autophagy is tightly regulated by post-translational modifications (PTMs). This project recently identified an acetylated lysine residue located near the critical binding pocket of the *T. gondii* homologue of the autophagy protein Atg8, which may regulate Atg8's interactions with other autophagy proteins. It is hypothesized that manipulation of autophagy protein PTMs and thus alteration of the autophagy protein interactions is a novel target for pharmacological intervention to treat parasitic infections. Studies are currently underway using *T. gondii* as a model system to characterize the interacting partners and PTMs present on a group of core autophagy proteins, and to identify drugs that enhance the anti-parasitic effects of known autophagy modulators by altering the PTM landscape of these autophagy proteins.



Rachel Navarra

Drexel University College of Medicine

“Methylphenidate Enhancement of Early Stage Sensory Processing”

Methylphenidate (MPH) is a psychostimulant drug prescribed to treat attention deficit hyperactivity disorder (ADHD) and used off-label for performance enhancement. Although the biochemical actions of MPH have been known for some time, the neural circuit mechanisms that underlie the drug's performance enhancing effects are largely unknown. Improving the efficiency of signal processing is hypothesized to be a significant component of psychostimulant-induced performance enhancement. The proposed studies will use a combination of electrophysiological and behavioral approaches to characterize the impact of MPH on early-stage visual processing during performance in a signal detection task. This research is expected to provide key insight towards understanding psychostimulant-induced performance enhancement and the underlying mechanisms responsible.

“ I am very grateful to have received a Pre Doctoral Fellowship in Pharmacology/ Toxicology from the PhRMA Foundation. Not only is the fellowship facilitating my current Ph.D. studies, but it will also enhance my future career opportunities and has built confidence in my ability to succeed in a career in pharmaceutical sciences. Thank you and congratulations to the PhRMA Foundation on 50 years of service to the drug discovery and development community!”

Rachel Crouch, Pharm.D. | Vanderbilt University Medical Center



Rachel Crouch

Vanderbilt University Medical Center

“Novel Role of Drug Metabolism in Allosteric Modulation of M₄ Muscarinic Receptors: Impact on Discovery of New Treatments for Schizophrenia”

Current treatment options for schizophrenia are often ineffective and frequently induce a variety of undesirable side effects. The muscarinic acetylcholine receptor subtype 4 (M₄) has been implicated as a potential target in the treatment of schizophrenia. Selective targeting of M₄ decreases the risk of side effects associated with modulating muscarinic receptors; however, developing a drug to target only M₄ is challenging due to the high degree of similarity between the structures of M₄ and the other four muscarinic receptor subtypes. Allosteric modulators have been developed for different receptors to overcome this challenge. Allosteric modulators either enhance or inhibit receptor activity by interacting with a site on the receptor that is separate from the natural ligand's binding site. M₄ positive allosteric modulators (M₄ PAMs) are highly M₄-selective, novel pharmacological tools that augment the activity of the body's natural ligand acetylcholine at the M₄ receptor, and provide an unprecedented

opportunity to investigate the role of M_4 in basic neurobiology and disease pathology and have the potential to become a superior treatment option for schizophrenia and related CNS diseases. It has been found, however, that allosteric modulators are often very sensitive to modifications in the drug's structure, where minor alterations may result in changes in its pharmacological activity, such as gaining activity at another receptor subtype, switching modes of receptor modulation from activation to inhibition, or altering the bias towards a particular receptor signaling pathway. Drugs are eliminated from the body through enzymes that metabolize the drug, resulting in minor (or sometimes major) alterations to its structure. This project focuses on investigating the potential for drug-metabolizing enzymes to alter the structure of M_4 PAMs such that they modify their pharmacological activity. These studies will be important in forming accurate conclusions about the consequences of modulating M_4 receptor activity, developing M_4 PAMs that will be successful clinical therapeutics, and will provide insight into the role that drug metabolism can play in the pharmacological activity of allosteric modulators.

“ The PhRMA Foundation Pre Doctoral Fellowship has provided me with the financial resources to explore scientific hypotheses in the field of pharmacology/toxicology. In addition, this award was invaluable for other aspects of my graduate training, including grant writing and networking. I am extremely grateful for this opportunity.”

Robert N. Helsley | University of Kentucky



Robert N. Helsley
University of Kentucky

“A Novel Mechanism for ARV-drug Associated Dyslipidemia”

Despite reduction in the morbidity and mortality associated with HIV infection, the highly active antiretroviral therapy (HAART) has been associated with dyslipidemia and increased risk of CVD. Current optimal HAART options consist of a combination of several drug classes including HIV protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, and integrase inhibitors. We and others have identified several widely used PIs, including ritonavir and amprenavir, as potent agonists for the pregnane X receptor (PXR), a nuclear receptor activated by numerous endogenous hormones, dietary steroids, pharmaceutical agents, and xenobiotic chemicals. PXR functions as a xenobiotic sensor that induces the expression of genes required for xenobiotic metabolism in the liver and intestine. PXR is remarkably divergent across mammalian species with the LBDs sharing only ~60-80% identity compared with the ~90% typically exhibited by orthologous nuclear receptors. PXR exhibits significant differences in its pharmacology across species (e.g., mouse vs. human) and its specific role in mediating the pathophysiological effects of xenobiotics in humans and animals remains obscure. The identification of PXR as a

xenobiotic sensor provides an important tool for the study of new mechanisms through which xenobiotics, including pharmaceutical agents, impact diseases. For instance, many clinically used PXR ligands have been reported to elevate cholesterol levels, including amprenavir, rifampicin, ritonavir, carbamazepine, phenobarbital, and cafestol. However, the mechanisms underlying PXR ligand-elicited hyperlipidemia remain largely unknown. The proposed studies will investigate the impact of ARV drugs on lipid homeostasis using novel animal models that enables us to determine the effects of ARV drugs on human and murine PXR activity, and to address the molecular mechanisms by which these drugs promote hyperlipidemia.

“Receiving the PhRMA Foundation Pre Doctoral Fellowship has allowed me to spend more time to focus on my research and hone my skills as a scientist since I no longer have to TA to receive my funding. It has also given me confidence in myself as a scientist and the importance of the work I am doing.”

Lisa Tremmel | University of Texas at Austin



Lisa Tremmel

University of Texas at Austin

“The Role of Pdc4 in the Inhibitory Action of Metformin on Skin Tumor Promotion”

Metformin, a medication commonly used for the treatment of type-2 diabetes, has been shown to decrease cancer incidence in retrospective studies. However, the mechanisms responsible for this are not clearly understood. Pdc4 is a known tumor suppressor that is downregulated in many tumors and by treatment with TPA, a known tumor promoter. Preliminary studies show that metformin given in the drinking water inhibits skin tumor promotion by TPA in a two-stage skin carcinogenesis mouse model. Furthermore, metformin also partially reversed the effects of TPA treatment on the levels of Pdc4. This decrease in Pdc4 causes an increase in key processes involved in tumor promotion and progression such as cell proliferation, migration and invasion. This project will analyze signaling downstream of Pdc4 in the presence of metformin during skin tumor promotion by TPA. Additionally, transgenic mouse models in which Pdc4 is either deleted or overexpressed will be used to characterize the importance of Pdc4 signaling for the mechanisms by which metformin acts. Ultimately, this research will elucidate the role that Pdc4 plays in the cancer prevention action by metformin.

“ I am truly honored to be a recipient of the PhRMA Foundation Pre Doctoral Fellowship in Pharmacology/Toxicology. Receiving this award has not only helped by providing funding resources, but has bestowed confidence that I can write competitive grants in the current funding environment. Thank you to the PhRMA Foundation for providing many critical career development opportunities to young scientists.”

Natividad Robert Fuentes | Texas A&M



Natividad Roberto Fuentes

Texas A&M University

“A Novel Role for Dietary Bioactives in Modulating Oncogenic KRas”

Approximately 30% to 50% of colorectal cancers contain KRas mutations, which confer resistance to standard therapy and have therefore been termed “undruggable.” Since no curative treatments for KRas driven colon cancer are available, there is a critical need to develop toxicologically innocuous KRas therapeutic approaches that are free of safety problems intrinsic to drugs administered over long periods of time. High fidelity signaling of KRas is dependent on its spatial organization into defined membrane nanodomains, termed nanoclusters. Recently, it was demonstrated that select amphiphilic agents, through direct modulation of the biophysical properties of the plasma membrane, alter oncogenic KRas nanoclustering and modulate signal transduction. This suggests that Ras nanoclusters could be a novel new therapeutic target. This is consistent with preliminary findings that a specific class of polyunsaturated fatty acids (n-3 PUFA) found in over the counter supplements and prescription therapeutics, suppress Ras signaling. Therefore, the overall goal is to define the role of n-3 PUFA in the suppression of oncogenic KRas-driven colon cancer. Biophysical properties of the plasma membrane influence nanocluster formation, which is critical for oncogenic KRas signaling. Therefore, by altering biophysical properties of the membrane, n-3 PUFA will reduce oncogenic KRas signaling leading to reduced tumorigenesis. This novel research project will address the utility of a unique class of novel innocuous dietary bioactives for membrane targeted colon cancer therapy.

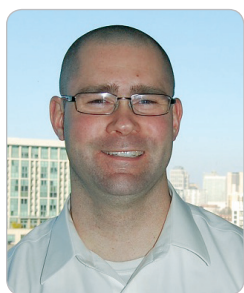
Post Doctoral Fellowships in Pharmacology/Toxicology

The PhRMA Foundation has been awarding Post Doctoral Fellowships in Pharmacology/Toxicology since 2002. This fellowship 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.

“ A Pharmacology/Toxicology Post Doctoral Fellowship from the PhRMA Foundation has provided me with a stable source of funding while conducting research on a novel class of pharmacotherapies with the potential to treat those suffering from neurodevelopmental disorders such as Autism Spectrum Disorder. It has given me the individual resources necessary to conduct this valuable work while at the same time affording me the opportunity to continue down the path of building a career as an independent research investigator.”

Matthew J. Robson, Ph.D. | Vanderbilt University Medical Center

2015 POST DOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY



Matthew J. Robson, Ph.D.

Vanderbilt University Medical Center

“p38α MAPK Signaling: Novel Therapeutic Target for the Treatment of Autism Spectrum Disorder”

Autism Spectrum Disorder (ASD) is a neurodevelopment disorder characterized by deficits in language and social development and excessive repetitive behaviors. The prevalence of ASD is believed to be increasing and the disorder is currently estimated to affect 1 in every 68 children within the United States. Compounding this problem is the current lack of effective pharmacotherapies aimed at treating ASD. Currently, there are only two FDA-approved medications for the treatment of ASD, neither of which treat the core deficits of the disorder. The advent of new genetic animal models of ASD provide a critical opportunity to investigate molecular signaling in these animals to probe for novel therapeutic targets. Across these various models, perturbation of molecular signaling and function related to the immune system appears to be a common theme. One crucial component of immune system signaling that is also known to modulate serotonin transporter (SERT) activity within the CNS is p38α MAPK. Recently, five genetic variants in SERT have been linked to ASD, all of which result in an increase in the activity of SERT. A construct and face valid murine model expressing one of these variants, the SERT Ala56 knock-in mouse, exhibits ASD-like phenotypes and altered SERT regulation, an effect that is linked to p38α MAPK signaling. The primary aim of this project is to determine whether the antagonism of p38α MAPK signaling using a novel, selective and CNS penetrant inhibitor reverses ASD-like phenotypes in the SERT Ala56 knock in mouse. Additionally, genetic approaches will be utilized to further characterize the involvement of p38α MAPK signaling in the ASD-like phenotypes present in SERT Ala56 mice. These studies have the potential to elucidate a novel molecular target that represents a convergence point between both the environmental and genetic factors believed to contribute to ASD. The elucidation of such a target may ultimately lead to the development of pharmaceutical treatments aimed at ameliorating the core deficits associated with ASD.



Lyndsey Anderson, Ph.D.

Northwestern University, Feinberg School of Medicine

“Genetic Susceptibility to Drug Interactions”

Adverse drug reactions account for nearly 30% of emergency room visits, 5% of all hospital admissions, 5% of in-hospital deaths and an estimated \$3.5 billion in additional medical costs annually. Two major contributors to adverse drug reaction susceptibility are genetic variation in drug metabolizing enzymes and drug interactions. Hundreds of variants within genes encoding drug metabolizing enzymes have been identified, but the functional characterization and clinical relevance of each variant has lagged behind due to the time- and labor-intensive nature of such analyses. The goal of this study is to assess the impact of genetic variants on CYP450 metabolic capacity using a novel, label-free mass spectrometry technique (SAMDI) capable of performing high-throughput analysis of enzymatic reactions. Additionally, this research will investigate the impact of genetic variants in the context of drug-drug interactions as we hypothesize that the risk for drug-drug interactions and associated adverse drug reactions are great in the setting of genetically compromised metabolizing enzyme function. As a proof-of-principle experiment, the project will determine the enzymatic activity of all known CYP2C9 variants. The knowledge gained from these investigations will be useful for predicting drug interactions in genetically susceptible persons and enabling more individualized drug treatment plans.



Sean Emery, Ph.D.

University of Kansas

“Modulating Schwann Cell ER Stress in Diabetic Neuropathy”

Insensate diabetic peripheral neuropathy (DPN) causes a loss of sensation in the limbs of about 50-60% of the over 20 million individuals affected with Type 1 or Type 2 diabetes, and is a contributing factor to diabetic amputations. It is well regarded that mitochondrial dysfunction is integral to the pathophysiology of DPN, but endoplasmic reticulum (ER) stress, a cellular stress response associated with improper protein structure and organization, may also contribute to DPN progression. Schwann cells, a group of cells highly sensitive to ER stress in the peripheral nervous system, support neuron signaling through production of an insulating substance called myelin. This research project aims to further understand the role that ER stress has in schwann cells and its affects on mitochondrial bioenergetics (mtBE) in DPN. Previous work has developed a novel class of inhibitors called novologues that improve mtBE and reverse insensate DPN in mouse models of Type 1 and Type 2 diabetes. These novologues act on the naturally occurring stress response protein, heat shock protein 90 (Hsp90), and lead to increased expression of the related protein Hsp70 to mediate their effects. Based on supporting data from this previous work, this project will test the hypothesis that novologues efficacy in improving mtBE in DPN may be mediated by modulating ER stress in schwann cells, which will help clarify the novologue mechanism of action. Combined, these studies will help further the fundamental understanding of DPN pathobiology, and promote novologue translational advancement in treating DPN.

Research Starter Grants in Pharmacology/Toxicology

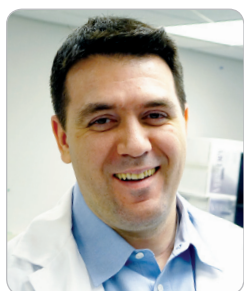
For faculty members without sufficient sources of funding, the PhRMA Foundation offers the Research Starter Grant: a one-year award to help launch independent research careers. This grant aims to assist academic scientists in pursuing studies that shed light on individualized drug therapy and optimal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

The first research starter grants in Pharmacology/Toxicology were funded in 1972.

“The PhRMA Foundation Research Starter Grant has been crucial for advancement of my research capabilities as an independent investigator by allowing me to conduct research and generate data that will hopefully lead me to future success of attracting new funding. I am very grateful to be given this outstanding opportunity and honor.”

Vanja Duric, Ph.D. | Des Moines University

2015 RESEARCH STARTER GRANT IN PHARMACOLOGY/TOXICOLOGY



Vanja Duric, Ph.D.

Des Moines University

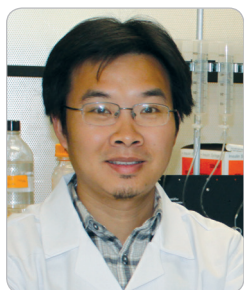
“Role of MKP-1 in the Pathophysiology and Treatment of Depression”

Recent studies suggest that MKP-1 plays an important role in major depressive disorder (MDD). However, there is a gap in understanding how brain region-specific MKP-1-mediated inhibition of MAPK signaling promotes development of MDD. The objective for this project is to determine molecular brain mechanisms whereby MKP-1 overexpression promotes development of MDD. The central hypothesis is that MKP-1 promotes the development of MDD by inhibiting JNK signaling within the hippocampus and/or other connected brain areas (i.e., PFC). This hypothesis will be tested by pursuing two specific aims where 1) a mutated MKP-1 that selectively inhibits JNK signaling will be overexpressed to determine to what extent JNK is the primary MKP-1 substrate responsible for depressive effects, and 2) MKP-1 shRNA will be used to inhibit local MKP-1 activity to determine if MKP-1 blockade is sufficient to reverse depressive behaviors in rodent chronic stress models. This project is innovative, as it represents a new and substantive departure from the status quo by shifting focus to phosphatases and negative regulation of MAPK signaling pathways. The research is significant because it is expected to constitute the first step toward acquiring an understanding of the role that phosphatases play in stress processing that may ultimately help guide development of more effective treatment, diagnostic, and prevention strategies for MDD and other psychiatric disorders.



“ The PhRMA Foundation Research Starter Grant made it possible for my group to generate essential preliminary data for my first NIH grant application. This grant also helped transition an urgently needed anti-influenza drug a step closer to human clinical trials.”

Jun Wang, Ph.D. | University of Arizona



Jun Wang, Ph.D.
University of Arizona

“Structure-based Design of M2-S31N Channel Blockers As the Next Generation of Antivirals”

The global health burden of annual influenza epidemics, coupled with increasing drug resistance, highlights the urgent need for new, effective treatments. The majority of current circulating seasonal influenza viruses, as well as highly pathogenic avian influenza viruses, carry the S31N mutant in their M2 genes, which confers resistance to adamantanes (amantadine and rimantadine). Influenza viruses that are resistant to oseltamivir, the only orally available drug, are continuously on the rise. Thus there is a persistent need of novel anti-influenza drugs. This proposal concerns the development of antivirals against the M2-S31N channel which confer drug resistance to adamantanes. We implement a multi-faceted approach that includes structure-based drug design, electrophysiology, and virology to design M2-S31N channel blockers. In the proposed studies, we will optimize the potency and the drug-like properties of our recently discovered M2-S31N inhibitors. To address the skepticism that targeting M2 might not be an ideal strategy to conquer drug resistance since resistance arises rapidly after amantadine treatment, we will perform drug resistance selection experiments of S31N inhibitors as well as combination therapy experiments with oseltamivir. The goal is to develop M2-S31N inhibitors that are active against clinically relevant drug-resistant influenza viruses with a low tendency to elicit drug resistance.

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.

2015 PAUL CALABRESI MEDICAL STUDENT FELLOWSHIP

The PhRMA Foundation began funding Medical Student Fellowships in 1974.



Joyce Chen

University of California, San Diego

“Physical and Functional Interactions of OGT and TET Proteins”

The physical interaction between the enzyme O-GlcNAc transferase (OGT) and the Ten-Eleven-Translocation (TET) proteins has garnered a large amount of interest because it suggests a new link between epigenetic modifications, gene expression and metabolism. Both OGT and TET have important physiologic functions in the body. OGT participates in a wide variety of signaling processes and metabolic pathways, and is required for cell viability. TET proteins contribute to the successive oxidation of methylated cytosine bases, an epigenetic modification that influences gene expression. Because TET proteins and OGT separately have been linked to cancers and cancer cell metabolism, it is possible that the interaction of OGT and TET plays a unique role in cancer pathogenesis in addition to its physiologic function. The goals of this research are twofold: first, to understand the OGT-TET interaction by examining the differences in each individual protein's functional interactions when its interacting partner is absent, which will be achieved through the use of TET and OGT knockout mouse models and measurements of OGT substrate levels and genome-wide mapping of the initial TET oxidation product. Second, the project aims to identify OGT's involvement with genes that have a role in cell viability in either physiological or pathological states, or in both, through the design and execution of a genomic screen. The significance of understanding the epigenetic influence on an enzyme involved in cell viability such as OGT has important implications for cell growth and cell death that may be applicable to our knowledge of cancer. Together, this will ultimately begin to identify genetic factors involved in and new targets for the next generation of cancer therapies.



The Foundation was honored to present its 2015 awards at distinguished scientific annual meetings throughout the country.

Our thanks to the following organizations:

The American Society for Pharmacology and Experimental Therapeutics (ASPET)
Boston, Massachusetts on March 28, 2015

The American Association of Pharmaceutical Scientists (AAPS)
Orlando, Florida presented on October 25, 2015

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
Philadelphia, Pennsylvania on May 20, 2015

American Society for Clinical Pharmacology and Therapeutics (ASCPT)
New Orleans, Louisiana on March 4, 2015



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Washington, DC

Treasurer's Report



The PhRMA Foundation ended 2015 in solid financial shape. We awarded a record high number of grants and fellowships in eight different disciplines throughout the year. Member contributions were \$2.4 million which was consistent with 2014. These contributions are the sole support for the Foundation's core program of grants. The Foundation has also continued the programs implemented as part of PhRMA's priorities and funded by contributions from PhRMA. In 2015 PhRMA contributed \$375,000 for these programs, which included a new Medication Adherence Alliance Project. The total contributions to the Foundation were \$2.86 million in 2015, which includes the PhRMA funds.

We awarded an unprecedented amount of \$3.75 million in grants, an increase of 13.4% over the previous year. Non-grant program and administrative expenses were held to below the 2014 level. Total expenditures were \$4.5 million. Net assets at December 31 were \$19.9 million, an 8% decrease from the prior year. The decrease in our investments is attributable to unrealized losses of \$1.5 million, offset by realized gains and investment income of \$1.3 million and investment transfer of \$.5 million from long-term commitment funds for the Translational Medicine and Therapeutics program. Financial details are shown in the accompanying Statement of Income and Expenditures.

On behalf of the Board and staff, I give special thanks and recognition for the continuing support of our generous benefactors that are listed on page 2 of this report. We continue to work toward our goal of having all PhRMA members become full contributors, so that we can continue our support of young scientists and the important strategic initiatives of the Foundation. With your help, 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 the very best facets of our industry and its commitment to innovation in research and the development of talented young investigators.

The Foundation's financial position as of December 31, 2015, 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, appearing to read 'A. Plump', with a long, sweeping horizontal line extending to the right.

Andrew Plump, M.D., Ph.D.
Treasurer, PhRMA Foundation

Statement of Income & Expenditures

For the year ended December 31, 2015

INCOME	
Contributions ¹	\$2,831,750
Contributions – in kind from PhRMA	\$29,612
Interest and Dividends	\$474,333
(Realized and Unrealized) Gains in Securities	-\$686,169
Other Income	\$94,686
Total Income	\$2,744,212
EXPENDITURES	
PROGRAMS	
Awards in Excellence	\$23,563
Adherence Improvement	\$500,332
Clinical Pharmacology Program	\$193,500
Comparative Effectiveness Program	\$333,328
Health Outcomes Program	\$401,250
Informatics Program	\$620,000
Pharmaceutics Program	\$441,403
Pharmacology Programs	\$610,000
Translational Medicine and Therapeutics	\$540,000
AFPE Fellowship Award	\$7,500
Other Grants	\$79,875
Subtotal – Grants	\$3,750,751
OTHER	
Committee Meetings, Travel and Honoraria	\$91,156
Publications and Special Projects	\$121,602
Subtotal – Other	\$212,758
Program Total	\$3,963,509
ADMINISTRATIVE	
Staff, Taxes, Depreciation & Insurance	\$419,392
Rent & Accounting Services ²	\$29,612
Professional Services and Investment Expenses	\$74,938
Office Expenses	\$4,007
Subtotal – Administrative	\$527,949
TOTAL EXPENDITURES	\$4,491,458

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 2016

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	1 awarded/1 year	\$25,000 total \$25,000 per award per year	September 1, 2015 December 15, 2015 January 1, 2016
Research Starter Grants in Adherence Improvement (2013)	1 awarded/1 year	\$50,000 total \$50,000 per award per year	September 1, 2015 December 15, 2015 January 1, 2016
Basic Pharmacology Advisory Committee			
Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)	10 awarded/up to 2 years	\$370,000 total \$20,000 per award per year	September 1, 2015 December 15, 2015 January–August
Post Doctoral Fellowship in Pharmacology/Toxicology (2002)	2 awarded/2 years	\$160,000 total \$40,000 per award per year	September 1, 2015 December 15, 2015 January–December
Research Starter Grants in Pharmacology/Toxicology (1972)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	September 1, 2015 December 15, 2015 January 1, 2016
Clinical Pharmacology Advisory Committee			
Paul Calabresi Medical Student Research Fellowships (1974)	1 awarded/ 6 months up to 2 years	\$18,000 total \$18,000 per award	February 1, 2016 April 15, 2016 July 1, 2016
Faculty Development Award in Clinical Pharmacology (1966)	1 awarded/2 years	\$240,000 total \$120,000 per award per year	September 1, 2015 December 15, 2015 July 1, 2016
Health Outcomes Advisory Committee			
Pre Doctoral Fellowships in Health Outcomes (2002)	3 awarded/1–2 years	\$125,000 total \$25,000 per award per year	February 1, 2016 April 15, 2016 July–December
Post Doctoral Fellowship in Health Outcomes (2002)	1 awarded/2 years	\$110,000 total \$55,000 per award per year	February 1, 2016 April 15, 2016 July–December
Research Starter Grants in Health Outcomes (2002)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	February 1, 2016 April 15, 2016 July 1, 2016

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Informatics Advisory Committee			
Pre Doctoral Fellowships in Informatics (2009)	2 awarded/2 years	\$80,000 total \$20,000 per award per year	September 1, 2015 December 15, 2015 January-August
Post Doctoral Fellowships in Informatics (2002)	0 awarded/2 years	\$0 total \$40,000 per award per year	September 1, 2015 December 15, 2015 January-December
Research Starter Grants in Informatics (2002)	4 awarded/1 year	\$400,000 total \$100,000 per award per year	September 1, 2015 December 15, 2015 January 1, 2016
Pharmaceutics Advisory Committee			
Pre Doctoral Fellowships in Pharmaceutics (1987)	4 awarded/2 years	\$120,000 total \$20,000 per award per year	September 1, 2015 December 15, 2015 January-August
Post Doctoral Fellowships in Pharmaceutics	1 awarded/2 years	\$80,000 total \$40,000 per award per year	September 1, 2015 December 15, 2015 January-December
Research Starter Grants in Pharmaceutics (1972)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	September 1, 2015 December 15, 2015 January 1, 2016
Translational Medicine Advisory Committee			
Post Doctoral Fellowships in Translational Medicine (2015)	2 awarded/2 years	\$240,000 total \$60,000 per award per year	February 1, 2016 April 15, 2016 July - December
Research Starter Grants in Translational Medicine (2015)	3 awarded/1 year	\$300,000 total \$100,000 per award per year	February 1, 2016 April 15, 2016 July - December

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

ETHICAL CONSIDERATIONS: The Scientific Advisory Committee as well as the program advisory committees of the PhRMA Foundation are dedicated to ensuring the appropriate use of animals and humans in research. In their deliberations, they consider all aspects of a proposal and may deny support for many reasons. Careful consideration is given to ensure the humane use and care of animal subjects. For human and animal research, the project review committee requires, in writing, a statement of adherence to prevailing standards of ethical research practices. Institutional Review Board approval is required before any research project may be initiated. In addition, informed consent is required before any person can participate in a research project.

PhRMA Foundation Staff



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