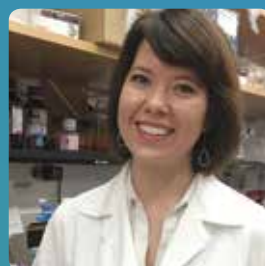


2016 ANNUAL REPORT



P/RMA
FOUNDATION

PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

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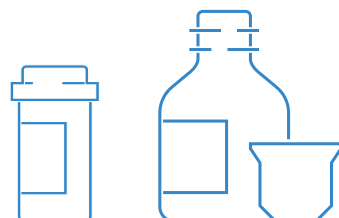
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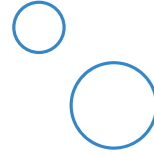
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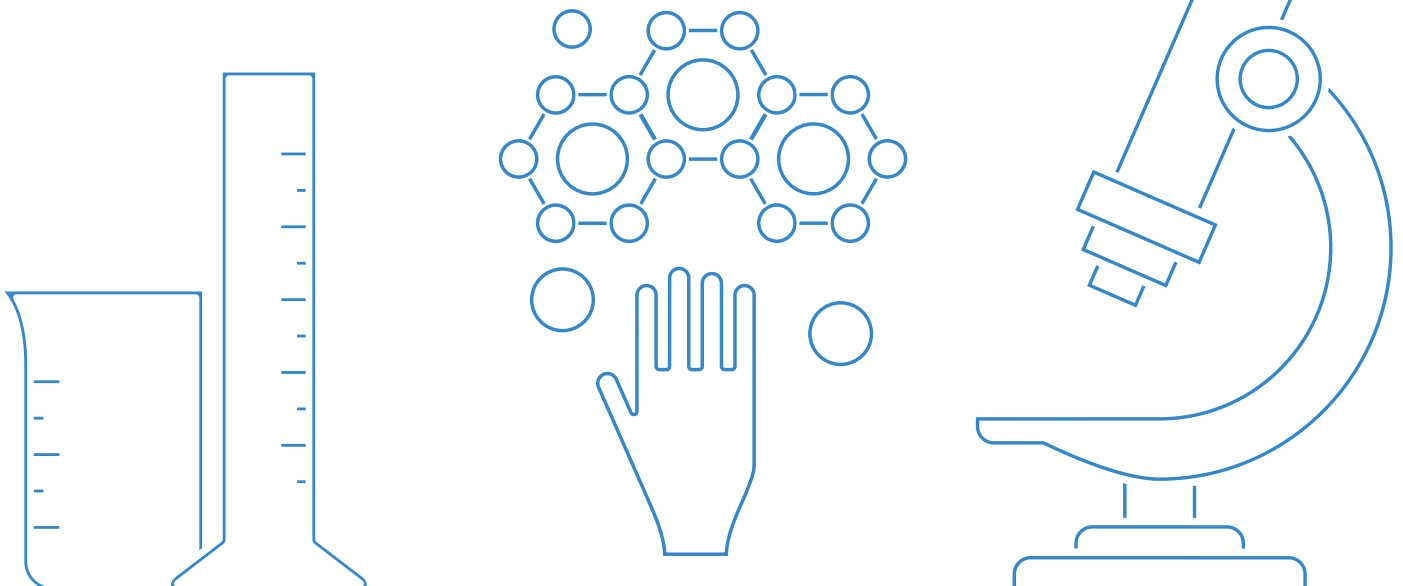


Mission Statement

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

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

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



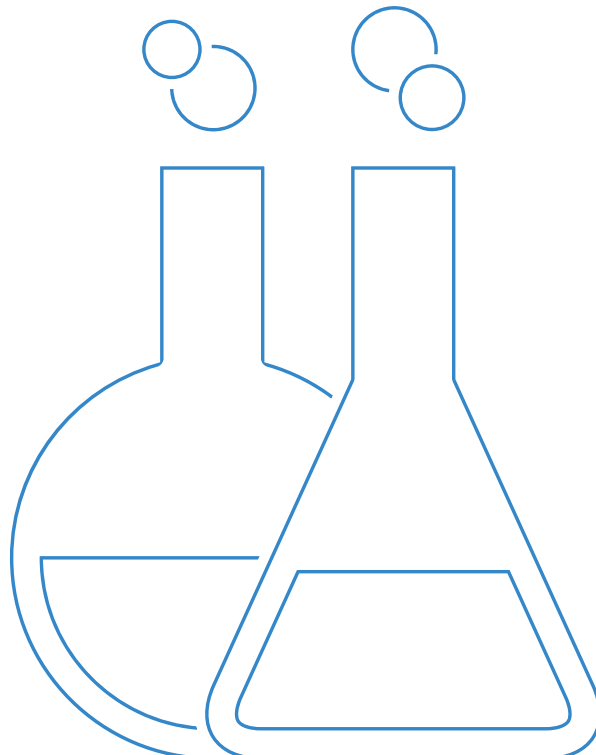
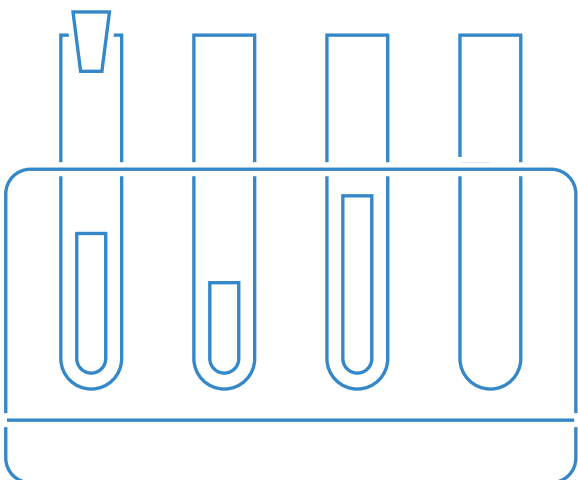


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Message from the Chairman



There is much discussion today about the need for greater value in health care. But what, exactly, does “value” mean?

From our perspective at the PhRMA Foundation, it is about one thing above all else – delivering meaningful benefit to the person at the center of the health care equation: the patient.

When we think about medicine from the patient’s perspective first, there are many things to consider beyond efficacy. We begin to understand the full impact of our work on patients’ lives. What are the side effects? The cost? How long will the person need to take the drug? How will it impact their relationships and their day-to-day activities? As we address these questions, we begin to understand the true “value” of a treatment to a patient – which may encompass much more than may at first be apparent.

Value and how to assess it across the drug development spectrum continues to grow as an important factor in health care, and this year we make it the focus of our Annual Report. With groundbreaking medicines and rising costs comes the demand to demonstrate value for patients, using robust, reliable, and sound evidence that supports individual needs and preferences. To help achieve this vision of a wholly quality-centric healthcare system, the PhRMA Foundation recently launched its Value Assessment Initiative, a three-pronged award program that will implement transformative, multistakeholder-guided strategies to better measure the value of medicines, improve patient outcomes, and reduce inefficiency. You can read more about this effort in the central piece on page 16.

PhRMA Foundation scientists are on the cusp of major medical breakthroughs for the millions of people who suffer from debilitating diseases, and on these pages you will read some of their inspiring stories. Two of our awardees are immersed in research on multiple sclerosis. Another is testing controlled-release drugs to reduce recurrent brain tumors. Others are pursuing novel targets for treating pain without addiction.

By operating within a patient-centered framework, Foundation researchers are accelerating the shift to a healthcare system that is based on value, not volume. I am so proud to be working on behalf of these scientists, who will undoubtedly change the field of medicine as we know it.

As their careers progress, they will see the faces and hear the voices of patients dealing with deadly diseases, and be compelled - just as I was, as a young neurology researcher 30 years ago – to work harder, and do more, to help them. This is another dimension of “value” – the fulfillment that comes when we reach exciting new medical breakthroughs that emerge as a result of always putting the needs of patients first.

In 2017, the Foundation is strong and fully committed to using its resources to help make these breakthroughs possible. Our new initiatives – including our work in the area of value assessment - demonstrate how we continue to evolve and adapt to meet the research needs of today and tomorrow.

This is my first year as chairman of the PhRMA Foundation, and I want it to be a meaningful one. If I could send just one message about the young scientists the Foundation supports, I would say this is where value-driven health care begins.

A handwritten signature in dark ink, reading "Alfred Sandrock". The signature is fluid and cursive, with the first name "Alfred" and last name "Sandrock" clearly distinguishable.

Alfred W. Sandrock, M.D., Ph.D., Chairman

Message from the President



In the first quarter of our 50th anniversary year at the PhRMA Foundation, we contracted with an outside firm to conduct a strategic review of our organization. Part of this review consisted of a survey of both stakeholders and former award recipients.

I am always delighted to hear the success stories of our awardees, so I was very eager to see where the careers of those scientists had taken them. The survey results demonstrated to me that the work we do through our Foundation clearly is making a difference.

When we asked about their whereabouts, past awardees told us they were still busy in the field, publishing novel concepts in journals, applying for patents, starting and running companies, conducting clinical trials, and training the next generation of pharmaceutical scientists.

Award recipients described their grants as the “jump start” they needed to move their research in the right direction. Many also connected their first publications to the preliminary findings that were made possible with the help of a Foundation grant. That data led to more funding, which led to more and more discoveries, more publications, and sometimes, significant scientific breakthroughs.

Nearly everyone who answered the survey called the awards transformative—many using the words “crucial,” “tremendous,” or “pivotal” to describe the timeliness and significance of that support. A number of awardees said it was the first grant money they had received, and that the process of applying for and securing funding for their research subsequently became much easier. Some said the money allowed them to hire interns and postdoctoral trainees, boosting the careers of other aspiring scientists and helping to build a pipeline for future research.

By accelerating the careers of thousands of young scientists, the PhRMA Foundation has had a measurable impact on pharmaceutical research and development. Perhaps this was most evident by the number of grantees who said the Foundation gave them the confidence to continue their research and make a long-term commitment to the field. One former awardee wrote, “My grant allowed me to stay in my chosen field and not give up. It gave me confidence, and it gave my work gravitas.”

With constant guidance from our Research and Development Board about current demands in drug discovery and development, we have been able to sustain programs that fulfill needs across academia, industry, and regulation, and modify our programs to further adapt to those needs. We pride ourselves on being a nimble organization that responds to both young scientists and an evolving field.

Just a few of the survey comments of our award grantees are featured on page 56 of this year’s report. I hope you will be as inspired by them as I was.

A handwritten signature in black ink, which appears to read "Eileen Cannon". The signature is fluid and cursive.

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 funding to young researchers to support and advance their careers.

The PhRMA Foundation's 2016 Awards in Excellence honor two 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 and Clinical Pharmacology.

2016 AWARD IN EXCELLENCE IN PHARMACOLOGY/TOXICOLOGY



James R. Halpert, Ph.D.

1984 Research Starter Grant in Pharmacology/Toxicology and the Faculty Development Award

Dr. James Halpert is Dean of the School of Pharmacy and Professor of Pharmacology and Toxicology at the University of Connecticut. He earned his B.A. in Scandinavian languages from the University of California, Los Angeles; his Ph.D. in biochemistry from Uppsala University, Sweden; and his M.S. in toxicology from the Karolinska Institute in Sweden. Following post-doctoral training with Dr. Robert A. Neal at Vanderbilt University's Center for Environmental Toxicology, Dr. Halpert returned to the Karolinska Institute as a research assistant professor. In 1983, he joined the Department of Pharmacology and Toxicology at the University of Arizona. He was promoted to Professor in 1991 and appointed Assistant Director of the Center for Toxicology, where he was the driving force behind the establishment of a center funded by the National Institute of Environmental Health Sciences (NIEHS). In 1998, Dr. Halpert accepted a position as

Professor and Chair of the Department of Pharmacology and Toxicology at the University of Texas Medical Branch at Galveston. While there, he recruited 10 tenure-track faculty members, developed a chemical biology program with support from the Robert A. Welch Foundation, and oversaw a fivefold increase in research funding. Dr. Halpert served as Director of the university's NIEHS Center in Galveston and Interim Director of the Sealy Center for Environmental Health and Medicine. He also held the Mary Gibbs Jones Distinguished Chair in Environmental Toxicology. From 1998 to 2004, he was a Foreign Adjunct Professor at the Karolinska Institute. In 2008, Dr. Halpert joined the University of California, San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences as Associate Dean for Scientific Affairs, taking a lead role in the recruitment of tenure-track faculty members and building the pharmacy school's ranking in the top 10 of National Institutes of Health (NIH) funding. At the University of Connecticut, he has been instrumental in obtaining a joint award with Yale for the \$10 million PITCH Program in Innovative Therapeutics for Connecticut's Health.

For the past 37 years, Dr. Halpert's research has focused on the structure and function of cytochromes P450 (CYPs) of the 2B and 3A subfamilies. Heterogeneity in the expression levels and activities of CYP450 is a major determinant of individual response to medications and susceptibility to environmental toxicants. P450s contribute significantly to species differences in xenobiotic metabolism and hence to the proper choice of animal models for evaluating the safety of drugs and other chemicals. CYP2B enzymes play a special role in the metabolism of environmental contaminants such as pesticides and polychlorinated biphenyls, whereas CYP3A4 metabolizes half of the clinically used drugs that require P450 action for elimination.

Dr. Halpert's Research Starter Grant and Faculty Development Award in 1984 led to the subsequent receipt of a Research Career Development Award and an NIEHS R01 grant on CYP2B enzymes that has been funded continuously since 1985. Highlights of his CYP2B research include the first identification of a specific amino acid adduct of a reactive intermediate and a mammalian protein, first elucidation of the isoform selectivity of a P450 inhibitor in any species, identification of P450 enzymes responsible for species differences in elimination of certain hexachlorobiphenyls, and the first X-ray crystal structures of human CYP2B6, rabbit CYP2B4 (including covalent complexes), and woodrat CYP2B35 and 2B37. His recent work has utilized X-ray crystallography, isothermal titration calorimetry, and hydrogen-deuterium exchange mass spectrometry to elucidate the role of enzyme plasticity in substrate recognition and binding, revealing how CYP2B6 can bind compounds that vary almost tenfold in molecular weight with comparable affinity.

In parallel with the structure–function studies of CYP2B enzymes, Dr. Halpert's group has used various solution biophysical approaches, including pressure-perturbation spectroscopy, fluorescence resonance energy transfer, and absorbance spectroscopy to establish the role of multiple ligand binding and protein–protein interactions in allostery of the major human drug metabolizing enzyme CYP3A4. This work, which has been supported by a MERIT Award from the National Institute of General Medical Sciences (NIGMS), helps explain the complexity of drug interactions involving CYP3A4.

Over the course of his career, Dr. Halpert has obtained more than \$30 million in extramural funding. His research and training have also been widely supported by numerous pharmaceutical companies, including Amgen, AstraZeneca, Boehringer Ingelheim, Bristol–Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Merck, and Pfizer. He is the author of 197 peer-reviewed publications and 19 invited reviews, with an H-index of 58 (as J. Halpert or J.R. Halpert) and 12,460 citations. In 2006, Dr. Halpert was named a Fellow of the American Association for the Advancement of Science. Four years later, he received the Bernard B. Brodie Award from the American Society for Pharmacology and Experimental Therapeutics (ASPET).

Dr. Halpert has devoted a great deal of time serving as a volunteer leader on various professional committees and boards. He was Chair of the NIH Pharmacology Study Section, a member of the NIGMS Biomedical Research and Research Training Review Committee, Editor of *Drug Metabolism and Disposition*, Secretary-Treasurer and President of ASPET, and a member of the International Advisory Committee for the 14th–20th Symposia on Microsomes and Drug Oxidations. He also serves as Treasurer-Elect of the International Society for the Study of Xenobiotics.

In addition to his extensive administrative responsibilities, Dr. Halpert maintains a laboratory funded by grants from NIEHS and the National Science Foundation. His lab's latest findings indicate an important role for halogen bonds in drug binding to cytochromes P450, which may contribute to the frequency of chlorinated compounds among medicines that survive the development process. He has trained 10 Ph.D. students, more than 30 post-doctoral fellows, and 10 research-track faculty. Six of his former trainees hold tenure-track or tenured faculty positions in pharmacology and toxicology, pharmaceutical sciences, or medicinal chemistry. Other former associates hold or have held scientist, senior scientist, or director positions at AbbVie, Allergan, AstraZeneca, Celgene, Merck, Pfizer, Pharmacia, Procter & Gamble, Sanofi, and Takeda. Dr. Halpert is currently working with three of Connecticut's major pharmaceutical companies to secure internship positions for Pharm.D. students and develop training programs directed to company staff at the B.S. and M.S. levels.

An Interview with *James R. Halpert, Ph.D.*

1984 Research Starter Grant in Pharmacology/Toxicology, Faculty Development Award;
2016 Award in Excellence in Pharmacology/Toxicology

Q When you were earning your degrees in biochemistry and toxicology, what kind of career did you envision?

A I was perhaps rather naive when I was working toward my Ph.D. in biochemistry. I simply fell in love with the topic of protein structure and function and was fascinated by the idea of pursuing it. About a year before graduation, I realized that jobs in biochemistry were scarce, so I obtained an M.S. degree in toxicology. I considered working at a regulatory agency for a while but soon knew I was too interested in experimental science to take a desk job. I certainly never envisioned being dean of a pharmacy school—or many of the interesting opportunities that have presented themselves during the course of my academic career.

Q How did your career progress in the years following your Faculty Development Award?

A The Faculty Development Award was absolutely pivotal in launching my independent career. I had been at the University of Arizona for about a year, having completed my graduate and much of my post-doctoral training in Sweden. I would characterize myself, like most assistant professors, as having a wealth of ideas but lacking the true confidence that anyone but me would find the ideas compelling or worth supporting. After receiving the PhRMA Foundation award, my outlook shifted completely from wondering about the quality of

my ideas to figuring out how to accomplish my goals. The award was followed by an R01 grant and a Research Career Development Award from the National Institute of Environmental Health Sciences.

Q What has 40 years of research taught you about the enzymes involved in drug metabolism and disposition?

A When I started in the field of drug metabolism, relatively little was known about so many important aspects of mammalian cytochrome P450 enzymes. We had yet to discover how similar P450s in humans were to those in other mammals, the function of individual human P450 enzymes, the role of P450 enzymes in drug–drug interactions, and how those interactions could be predicted or avoided. Knowing the actual three-dimensional structure of a human P450 was almost inconceivable. But today, anyone with access to Wikipedia can find the answers to all these questions! Probably the most important breakthrough in P450 research was recombinant DNA technology, allowing individual genes and cDNAs to be cloned and the pure protein products expressed. We know there are 57 human P450 genes, approximately one dozen of which encode proteins involved in metabolizing drugs and other foreign compounds. Selective substrates and inhibitors for these enzymes have been identified, so their function can be assessed in a

clinical setting. Structures can be used to predict metabolism and enhance drug design. These are impressive advances, but much still remains to be learned about so-called orphan P450s, which at the moment have no clear function.

Q How has new and emerging technology shaped your research?

A Throughout the course of my career, I have stuck to some of the same fundamental questions about the basis of mammalian P450 specificity and have taken great pains to incorporate the new technologies necessary to pursue the work at the most sophisticated level. This has taken my group into recombinant DNA technology, chemical synthesis, three-dimensional protein modeling, X-ray crystallography, calorimetry, and various advanced spectroscopic methods. Being an expert in none of the above, I have been very fortunate to work with a cadre of talented students, post-doctoral fellows, visiting scientists, and research faculty who could actually get the critical experiments done.

Q How do you think a young scientist benefits from having the freedom and wherewithal to pursue his or her research interests?

A I was fortunate to secure an independent fellowship from NIH as a post-doctoral fellow and later a fellowship from the Swedish Medical Research Council as a research-track assistant professor at the Karolinska Institute. Getting a

chance to hone my critical thinking and writing skills relatively early in my career was hugely important once I became independent. Looking back, I also realize what tremendous discipline, dedication, and resilience it has taken to pursue a scientific career for 40 years. The earlier one starts to acquire these qualities the better, and the best way to learn is by taking ownership of a scientific project and applying for a fellowship. I am very proud of the fact that most of my early post-doctoral trainees also obtained independent NIH fellowships and eventually parlayed them into faculty positions. A number of my trainees also joined me later at an advanced stage, when they were no longer eligible for post-doctoral awards. Many of them have become independent faculty members. The key was that they had the freedom while in my group to develop independent ideas.

Q What advice would you give yourself as a young pharmacologist at the beginning of an academic career?

A Probably the same implicit advice I ended up following myself. 1) Go into science because you really love it. 2) Make sure you are truly driven by intellectual curiosity. 3) Get the best advice you can from the top people in your field and show how appreciative you are for that advice. 4) Create a niche for yourself in an important field that is expanding. The niche will protect you from undue competition, and the growing field will ensure that others are interested in your work. 5) Always be on the lookout for new and better ways to solve

the problems you are working on.

6) Get out there and make sure people know your work. Oral presentations are crucial—create opportunities to give them, and make sure every talk is first rate.

7) Recruit people for your lab enthusiastically and judiciously. Getting a few great students in the beginning can make a world of difference. 8) Don't assume you know how to manage a lab group just because you can do research.

2016 AWARD IN EXCELLENCE IN CLINICAL PHARMACOLOGY



David J. Greenblatt, M.D.

1980 Unit Award in Clinical Pharmacology

Dr. David Greenblatt is Professor of Psychiatry, Medicine, and Anesthesia and holds the Louis Lasagna Endowed Professorship in the Department of Integrative Physiology and Pathobiology at Tufts University School of Medicine. He is also Director of the university's Clinical Pharmacology Group and a senior faculty member of the Pharmacology and Experimental Therapeutics program at Tufts' Sackler School of Graduate Biomedical Sciences. Dr. Greenblatt has served as Chair of the medical school's Department of Pharmacology and Experimental Therapeutics, as Program Director and Associate Program Director of the Clinical and Translational Research Center (formerly the General Clinical Research Center), and as Chair of the Institutional Review Board. He is Editor in Chief of the American College of Clinical Pharmacology's (ACCP's) Clinical Pharmacology in Drug Development, and Co-Editor in Chief, with Dr. Richard I. Shader, of the Journal of Clinical Psychopharmacology.

A native of Newton, Massachusetts, Dr. Greenblatt graduated magna cum laude from Amherst College in 1966. After college, he attended Harvard Medical School, graduating in 1970. He trained in internal medicine at the Montefiore Hospital in New York City from 1970 to 1971, and on the Harvard Medical Service at Boston City Hospital from 1971 to 1972. Following a clinical pharmacology fellowship at Massachusetts General Hospital under the mentorship of Dr. Jan Koch-Weser (1972–1974), he directed the hospital's Clinical Pharmacology Unit until 1979, at which time he joined the Tufts faculty.

Dr. Greenblatt has studied molecular and clinical pharmacology since the late 1960s. His PubMed listing comprises over 1,000 publications, more than 760 of which are original research reports. For more than 35 years, his work has been supported by the National Institutes of Health (NIH).

Dr. Greenblatt's early research focused on the pharmacokinetics, pharmacodynamics, and neuroreceptor properties of the benzodiazepine derivatives, including the influences of age, gender, and body habitus on drug disposition and response, and the molecular mechanisms and consequences of tolerance and withdrawal. This work (with colleagues Richard I. Shader, Jerold S. Harmatz, Darrell R. Abernethy, and Lawrence G. Miller) had an important impact on clinical comprehension of the properties of these drugs, their appropriate clinical use, and a realistic perspective on drawbacks and hazards. In the 1990s, Dr. Greenblatt's group initiated one of the first research programs on in vitro drug metabolism and transport, along with colleagues Lisa L. von Moltke and Michael H. Court. The group has made numerous contributions to understanding the enzymatic and genetic determinants of metabolic activity of cytochrome P450 (CYP) and glucuronosyl transferase (UGT) enzymes, including the application of in vitro models to identify and predict clinical drug–drug interactions. Specific targets of this research have included the azole antifungal agents, the class of antiretroviral agents, and

the serotonin-reuptake-inhibitor antidepressants. In retrospect, many of the group's previous studies on the clinical pharmacokinetics of benzodiazepine derivatives, such as triazolam and midazolam, fortuitously served as population-based studies of metabolic phenotypic activity of CYP3A. Over the past decade, Dr. Greenblatt and his colleagues have addressed the problem of drug interactions involving nutrients and natural products (such as grapefruit juice), again focusing on a critical evaluation of the value of in vitro models in the prediction of such interactions. Work is also ongoing on the pharmacokinetic properties of the benzodiazepine ligand zolpidem, used throughout the world as a sleep-inducing medication. The focus is on the public health problem of adverse reactions to zolpidem, and whether women in general are at increased risk.

Dr. Greenblatt is certified by the American Board of Clinical Pharmacology (ABCP) and is one of the charter members of ABCP. He has been a member of the American Society for Clinical Pharmacology and Therapeutics since the 1970s, receiving the Rawls–Palmer Progress in Medicine Award from the Society in 1980. He has also been a member of ACCP since the 1970s and served as the organization's President from 1996 to 1998. Dr. Greenblatt was recognized by ACCP in 1985 with the McKeen Cattell Award, in 2001 with the Distinguished Service Award, and in 2002 with the Distinguished Investigator Award. He received the 2005 Research Achievement Award in Clinical Sciences from the American Association of Pharmaceutical Sciences and the 2013 Outstanding Speaker Award from the American Association for Clinical Chemistry. In 2015, Tufts University School of Medicine presented Dr. Greenblatt with the Distinguished Faculty Award. The following year, he received the Man of Good Conscience Award from the Association of Women Psychiatrists. Throughout his career, Dr. Greenblatt has also served on many NIH study sections and advisory groups.

Dr. Greenblatt directs a number of required and elective courses for medical, graduate (Ph.D.), and master's students, and teaches subjects including pharmacokinetics, drug metabolism, pharmacogenomics, alternative medicines, and psychopharmacology. He has served as a postdoctoral training supervisor or dissertation supervisor for more than 45 trainees, most of whom have become university-based investigators or industry scientists.

An Interview with *David J. Greenblatt, M.D.*

1980 Unit Award in Clinical Pharmacology; 2016 Award in Excellence in Clinical Pharmacology

Q How would you explain your research on drug interactions to a person with little understanding of clinical pharmacology?

A We live in an era where it is commonly necessary for patients to take multiple medications at the same time. As such, drugs may interfere with each other's metabolism and elimination from the body, as well as with their clinical actions. Because of the large numbers of possible drug combinations, it is not possible to conduct all the studies needed on drug interactions in human volunteers or patients. Our group is investigating biochemical methods to examine drug interactions without actually giving drugs to humans.

Q How did the PhRMA Foundation Unit Award in Clinical Pharmacology advance your career?

A Our clinical pharmacology program at Tufts University began with modest institutional backing in 1979. The PhRMA Foundation award provided critical start-up resources that were used principally for acquiring state-of-the-art analytic instrumentation that allowed our program to rapidly enter the realm of contemporary excellence in basic and clinical research.

Q What are some of the unexpected skills you have acquired in your position?

A I have become way more involved in analytical chemistry, applied mathematics, and biomedical statistics than I ever anticipated.

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

A The most important point is to identify and work with mentors who can teach you the skills necessary to be competitively excellent in both basic and translational research. The basic science aspect is of major importance, since your proficiency and creativity in biomedical science are key factors that will be used to judge you. Be resilient—there will be lows as well as highs as you progress. You will need to rebound from non-successes and absorb with dignity criticism that is not always fair or polite.

Q How do you stay engaged and give back to the scientific community outside of your job?

A Over the years, I have served on the Board of Regents and as President of the American College of Clinical Pharmacology, on the Board of Directors of the American Society for Clinical Pharmacology and Therapeutics, and as a peer reviewer on many NIH study sections. I am Editor in Chief of Clinical Pharmacology in Drug Development and Co-Editor in Chief of the Journal of Clinical Psychopharmacology.

Q What is the best part of working in academia?

A The best part is that my colleagues and I get to do everything, so to speak ... initiate and

design studies, implement the study protocols, analyze the biological samples, aggregate and store the data, execute the data analysis and biostatistical procedures, and prepare the findings for presentations and publications. Many students, trainees, colleagues, and co-workers participate in the effort. Resources are scarce, and we are always worried about obtaining and sustaining extramural funding, but when something gets done, it comes from our own hands.



The Value Assessment Initiative: Seeking Transformative Solutions for a New Era of Healthcare Decision Making

The delivery of health care in the United States is rapidly shifting from a volume-based to a value-based model, a transition that will certainly impact all health care sectors – from patients to payers to providers. As this trend gathers momentum, there is a pressing need for accurate, transparent information about the value of health interventions. How do we determine empirically what is truly “valuable” as we consider where to place our interventional efforts? How do we align disparate factors such as patient preferences and engagement, real-world clinical practice, and methodology in assessing value?

To address this need, the PhRMA Foundation has launched the Value Assessment Initiative, which will provide funding for transformative, multi-stakeholder solutions that help assess the value of medicines and health care services to improve patient outcomes and reduce inefficiency. This exciting new funding opportunity, available for the first time in 2017, offers support in three categories:

Challenge Awards: Up to \$50,000

Support for papers that describe solutions to the following question: *What are transformative strategies to measure or evaluate value of health interventions that could be implemented to advance a value-driven health care system in the United States?*



Research Awards: Up to \$100,000

Support for proposals to identify and address challenges in approaches to assess the value of medicines and health care services.



Center of Excellence Awards: Up to \$500,000

Support for the development of multi-disciplinary, collaborative centers that will undertake activities to build evidence, tools and partnerships that can inform value assessment strategies and value-driven decision making.





Divining Value in the US Healthcare System

Bryan R. Luce, PhD, MBA

Bryan R. Luce, PhD, MBA, a health policy expert specializing in evidence based healthcare and clinical effectiveness research, offers his insights on the opportunities and challenges ahead for value-driven health care in the commentary below.

“An imprecise estimate of the right concept is superior to a precise estimate of a wrong concept.”¹

This year the PhRMA Foundation launched a new important ‘Value Initiative’ with a particular emphasis on value of health care as conceived, experienced and desired by patients. The Foundation is aiming to attract innovative and fresh thinking to tackle the surprisingly-elusive notion of value as it relates to healthcare interventions.

At present, debate on value in healthcare has never been stronger. The calls to shift our health system to one based on value rather than volume are growing louder in concert. In the fray of health reform, one issue is clear – cost growth is unsustainable and can best be managed by promoting delivery of high value care and avoiding waste in low value care.

Today, the field seems crowded with, arguably, the best talent in the country and, truth to tell, beyond our borders. Consider that major national organizations including notable medical societies have recently developed and are implementing so-called “value frameworks,”² Medicare has its own value initiative,³ a major new book on cost-effectiveness has just been published,⁴ the International Society of Pharmacoeconomics and Outcomes Research has established its Initiative on US Value Assessment Frameworks,⁵ and the journal *Value in Health* recently published a themed issue containing multiple articles by some of the most vaunted health economists and other health analytical intellects of our time.⁶ Further, from an historical perspective, the quest to specify value of health care interventions in the United States dates back at least three and half decades. For example, in the early 1980s, Congress funded \$1.6 million (in today’s dollars) for its Office of Technology Assessment to solve the value problem;⁷ a number of textbooks have been published on the subject,^{8, 9, 10} as well as hundreds of articles,¹¹ and a myriad of policy positions as well as regulatory and legislative efforts have been promoted in an attempt to define, propose or refine methodological approaches and demonstrate applications to healthcare value.

Despite great efforts, growing literature, experimental quests, and extraordinary brain power the path towards a value-driven healthcare system remains unclear. So, what can the Foundation’s Value Initiative expect to achieve? My answer is not to attempt to “out-expert” the experts or to marginally-improve existing methods or thinking. Rather it is to unleash novel (disruptive?) thinking to approach the essence of patient value as sought or experienced by the patient (or, sometimes, the patient’s care-giver) as well as other healthcare decision-makers. Whereas the notion of health care “value” is intuitive to the individual...we each recognize it when we experience it personally...value has proven to be remarkably elusive to define and empirically measure comprehensively, whether as it relates to individuals or more globally to populations.

To individual patients, healthcare value is very personal, often situational and even ephemeral. An intervention’s value to one person is often not viewed similarly by another; and that same “value” may be viewed differently by the same person at a different time, or under different circumstances, for instance if the intervention has to compete with a new intervention that has become available or the person has undergone significant life changes. As such, “value” is a continuous variable taking on multiple values situationally, as opposed to a static discrete concept. Value in healthcare to one person may also depend on the impact on and preferences of the loved ones surrounding him or her. To further complicate evaluation efforts, the value to an individual or group of individuals has multiple components, for example relative effectiveness, side effects, convenience; and each of the components are likely weighed differently by different individuals, and the weights themselves likely vary situationally even within the individual.

Most previous efforts to capture the notion of value to inform healthcare decision making have done so rather simplistically, and, in fact, quite bluntly, as

exemplified by the global cost per quality-adjusted life year (C/QALY) construct that is so pervasive across the western world. It is undeniable that the full concept of value cannot be adequately captured holistically and certainly cannot express the value of a healthcare intervention experienced by an individual patient at any one point in time. Consequently, as the patient-centered movement has gained steam in the US and around the western world, numerous efforts have been proposed to include, incorporate or disentangle the many underlying components of value that patients and other stakeholders hold dear.

One technique gaining some traction today is multi-criteria decision analysis (MCDA) which deconstructs value into components, each of which are weighted relative to one another or to some norm. MCDA offers a structure to decision problems and transparency in the components of value and evidence considered. Weights tied to each component can be solicited directly from patients and allowed to vary by individual preference or situation, or can be static and fail to capture the dynamic nature of actual patient-centric value as described above.

A significant barrier to implementing approaches like these to determine value is the challenge of operationalizing all components of value in accordance with how and when value is actually experienced. Analysts tend to count what they can measure reliably and ignore, assume away or simply make note of that which they cannot measure reliably, even when what they cannot measure may be significant if not critical to what is important to capture (e.g. labor force impacts, family spillover effects, aspects of quality of life). Too often, the result is to opt for reliability and precision of measurement over validity and precision of concept. Thus, there is much creative work still to be done to adequately characterize and capture value in its full expression as experienced by individual patients and others.

Stepping back, it shouldn't be a surprise that the United States is the main western country holdout from adopting some form of universal value construct for healthcare decision-making. American individualism and aversion to centralized decision-making has dominated cultural and political life since the country's founding. One size just doesn't fit all in the US. This uniquely American cultural phenomenon will likely need to be considered in any successful effort to define and measure patient-centric value in order for it to be generally accepted for routine healthcare decision-making in the United States of America.

All in all, it seems we need creative thinking, out-of-the-box intuition and transformative solutions to adequately capture value. In its announcement, the PhRMA Foundation appears to want to stimulate such.

And applicants would do well to consider Mishan's counsel, that "An imprecise estimate of the right concept is superior to a precise estimate of a wrong concept."¹

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A close-up photograph of a scientist in a laboratory. The scientist is wearing a white lab coat and blue nitrile gloves. They are holding a white and grey pipette with a yellow tip, dispensing a small amount of yellow liquid into a small vial held by their other gloved hand. The background is a blurred laboratory setting with various equipment and a green container visible.

Fellowships and Grants

Informatics

Pre Doctoral Fellowships in Informatics

The PhRMA Foundation has been awarding fellowships and grants in Informatics since 2002.

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.

2016 PRE DOCTORAL FELLOWSHIPS IN INFORMATICS



Neel Madhukara

Weill Cornell Medical College

“A Machine Learning Approach to Predict Drug Targets and Accelerate Compound Discovery”

One of the most challenging portions of drug development is target deconvolution, or identification of the proteins a small molecule binds to in a human body. A proper understanding of these can help explain drug efficacies and side effects, but this process is currently driven by slow and costly case-specific experimentation. To address this problem this project developed BANDIT, a computational method that integrates multiple different data types to predict drug target interactions. When tested on over 2,000 different drugs BANDIT outperformed other target prediction methods and achieved a target prediction accuracy of over 90%. The study examined how BANDIT could be integrated directly into the drug development pipeline and applied it to ONC201 – a promising first-in-class molecule that selectively kills cancer cells and is currently in various phase II clinical trials, yet, to date, there has been no validated binding target. Using BANDIT, the project both predicted, and experimentally validated, ONC201’s selective targeting of DRD2 – a dopamine receptor and G Protein Coupled Receptor (GPCR). This is the first time that GPCRs have been found to be viable cancer targets, and, while DRD2 has been hinted at as a relevant cancer gene, this is the first time targeting it has had such a dramatic effect. These results all indicate a potential new mechanism for targeting cancer that has yet to be exploited. Furthermore, when applied to a library of 50,000 small molecules with no known targets BANDIT identified a set of novel microtubule inhibitors that could be used as new chemotherapeutics. Remarkably, a subset of our compounds was identified to be active against tumor cells resistant to known microtubule depolymerizing drugs. Overall this result illustrates how BANDIT could be used to rapidly identify small molecules with potential clinical promise and identify novel treatments for resistant patients.

“ I’m honored to receive the 2016 Pre Doctoral Fellowship in Informatics. The award will allow me to focus on research without worrying about funding, and will provide me with access to additional resources that will help accelerate my work. Receiving this award reinforces my belief that my research is exciting and impactful; it also strengthens my ability to secure research grants for the rest of my career.”

Daniel G. Oreper, Ph.D. | University of North Carolina at Chapel Hill



Daniel G. Oreper, Ph.D.

University of North Carolina at Chapel Hill

“Methods to identify parent-of-origin effects on behavior via reciprocal mouse crosses”

Sometimes the effect of a genetic mutation depends on how it was inherited, with different consequences when it is transmitted from the mother versus the father. Such so-called “parent-of-origin effects” can arise through several mechanisms, but the most prominent of these is imprinting, whereby the activity of a gene is suppressed through a form of chemical DNA-tagging that can occur in utero. Among other medical conditions, genetic imprinting has been implicated in mental illness, a set of diseases estimated to affect nearly half of all Americans at some point in their life. This project will address gaps in how imprinted genes can be identified and characterized. It proposes development of a novel, computationally optimized experimental design along with an associated statistical procedure for analyzing the results. The experimental design involves selecting a set of genetically diverse mouse strains, mating these strains in a reciprocal fashion (i.e., swapping which strain acts as mother and father), and then testing their offspring for behavioral differences (anxiety/depression) as well as for biological differences (gene expression obtained by RNA-sequencing). The analysis of data from this experiment will focus on identifying imprinted genes that affect anxiety and depression. Successful completion of this project may lead to new biomarkers that could identify human individuals at risk for psychiatric diseases, as well as clues for developing new, individualized treatments.

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.

2016 RESEARCH STARTER GRANTS IN INFORMATICS



Zhengqing Ouyang, Ph.D.

The Jackson Laboratory for Genomic Medicine

“Decoding in vivo RNA structural regulatory elements in cancer transcriptomes”

Regulatory RNAs play crucial roles in diverse biological functions. Dysregulation of RNAs has been shown to contribute significantly to disease etiology, including cancer. Recent studies indicate that knowledge of RNA structure and its function is important for understanding the regulatory mechanisms of RNAs in human health and disease. However, while high-throughput sequencing technologies have enabled probing RNA structures at the genome scale, current analytical approaches do not allow for accurate inference of RNA structure and function in vivo, which is necessary to reflect actual cellular context. This project will develop novel computational and statistical approaches to characterize in vivo RNA structures at the transcriptome scale in cancer cells, and to identify structural regulatory elements by integrating large-scale RNA-protein interaction datasets. Results of this project will facilitate revealing the diversity of in vivo RNA structural regulatory elements in cancer and providing potential novel candidate targets for cancer therapies.



Kin Fai Au, Ph.D.

University of Iowa

“Identification of recurrent fusion genes in breast cancer by hybrid sequencing”

Fusion genes contribute to the development of many types of cancers by causing abnormal expression of endogenous genes, inactivation of genes, and expression of non-native fusion proteins. Since fusion genes and proteins are tumor-unique, they can serve as diagnostic markers and novel drug targets. However, analytic approaches for reliably identifying fusion events are still inadequate. The short sequencing length of Second Generation Sequencing (SGS) mean that existing methods for genome-wide fusion gene detection result in a high number of false positive hits, although SGS data is informative for quantitative analysis. The recent emergence of Third Generation Sequencing (TGS), such as Pacific Biosciences/PacBio, which can generate 10-100x longer reads, provides an unprecedented opportunity to comprehensively identify

fusion genes in a given cancer sample. In recently published studies, the project developed a bioinformatics software, IDP-fusion, that can detect fusion genes with high precision and high sensitivity by integrating TGS long reads and SGS short reads in a process termed “hybrid sequencing” (Hybrid-Seq). Using IDP-fusion, the research identified a novel fusion between the oncogene AIB1 fused with an intergenic region in chromosome 1, which is the first reported fusion event for AIB1 and a novel gene with complicated gene structure in breast cancer. The objective of this project is to identify and quantify recurrent fusion genes and fusion isoforms in a cohort of primary breast cancer samples by developing a specific statistical model for Hybrid-Seq data and implementing this model in IDP-fusion. This comprehensive identification of fusion genes from breast cancer samples will serve as a foundation for future studies to determine how particular fusion genes predict for disease severity and response to therapy and to guide development of novel drugs that target these unique fusion proteins.



Saad Mneimneh, Ph.D.

Hunter College, The City University of New York

“Multiple RNA Interaction: Beyond Two”

RNA interaction algorithms have been mostly considered in the context of pairs of RNAs. The project will develop techniques to handle multiple RNAs (more than two). In the first phase, Multiple RNA Interaction will be mathematically modeled as a problem in combinatorial optimization. As with pairs, however, the “optimal” solution is typically driven by an energy minimization-like algorithm; this may not entirely capture the actual biological structure. Moreover, a structure produced by interacting RNAs is not necessarily unique. Therefore, alternative sub-optimal solutions will be needed to cover the biological ground. In the second phase, the project will combine combinatorial optimization techniques with an approach based on Gibbs sampling and MCMC to efficiently generate a reasonable number of sub-optimal solutions. In addition, when viable structures are far from optimal, exploring the dependence among different parts of their interactions can lead to a refined scoring scheme that will boost their candidacy for the sampling algorithm. Clustering methods and distance metrics to compare the samples will be investigated to identify few representative clusters that are distinct enough to suggest possible alternative structures. The developed techniques will be applied to known interactions such as the CopA-CopT pair and ribozyme complexes of several RNAs, where the structures are not computationally optimal (for instance due to reversible kissing loops in CopA-CopT), and other examples; for instance, a four RNA complex in the spliceosome, where different structures have been reported.

Pharmacology/Toxicology

Pre Doctoral Fellowships in Pharmacology/Toxicology

Since the program's initiation in 1978, more than 390 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.

2016 PRE DOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY



Himanshu Sharma

Stony Brook University

“Dystroglycan: A Novel Regulator of Neural Stem Cell Development and Function”

Despite the recent finding that the brain houses stem cells that theoretically have the ability to replace neurons and glia lost to disease or injury, functional regeneration and recovery after brain injury remain extremely limited. One potential therapeutic strategy in these cases is to enhance the ability of endogenous neural stem cells to respond to insults by generating new progeny cells. These newborn cells could help recover the function of cells that have died off. The goal of this project is to characterize new pharmacologic targets for neural stem cell activation that may serve as potential leads for therapeutic intervention. Progress on this project thus far has already indicated that an extracellular matrix receptor known as dystroglycan, best known for its role in muscular dystrophy, plays a key role in brain development. Dystroglycan signaling in the developing postnatal brain is crucial for the production of appropriate number of oligodendrocytes. When this protein is either removed through genetic targeting or blocked pharmacologically, local neural stem cells generate large numbers of oligodendrogenic progeny cells that go on to myelinate the brain even as the stem cells themselves divide to replenish their numbers. The next steps of this project are to characterize the effects of pharmacologic loss of dystroglycan function in neural stem cells and their progeny on a cellular and molecular level and to track the newly generated cells as they migrate to their targets throughout the brain. Additionally, this research will examine the effects of blocking dystroglycan in a model of multiple sclerosis, a disease in which oligodendrocytes are preferentially killed off. These results will identify critical mechanisms underlying neural stem cell behavior, characterize how the extracellular environment can be modulated to affect neural repair and regeneration, and explore a novel therapeutic strategy for treating white matter disorders such as multiple sclerosis.



Makaia Papasergi-Scott

University of Rochester Medical Center

“Regulation of the G-protein alpha biosynthetic chaperone, Ric-8A by phosphorylation”

Heterotrimeric G-protein signaling aberrancies contribute broadly to disease, including cancers, neurodegenerative disorders and cardiovascular disease. Thus many current pharmaceuticals target G-protein coupled receptors (GPCRs) that signal immediately upstream of heterotrimeric G-proteins. The correct folding of G-protein alpha subunits is requisite to proper GPCR signal transduction. Ric-8A and Ric-8B have been identified as essential genes that encode folding chaperones for the G alpha i/q/13 and G alpha s/olf subunit classes, respectively. In Ric-8 deletion models, G alpha subunits do not obtain functional protein folds, fail to become membrane bound and are degraded rapidly. Control of Ric-8 folding activity may eventually be used clinically to alter G protein levels, permitting tuning of GPCR/G protein signaling outputs. Currently the mechanisms regulating Ric-8A are poorly understood. This study focuses on the modulation of Ric-8A activity via phosphorylation and dephosphorylation. Data obtained show Ric-8A from eukaryotic cells is phosphorylated at multiple sites and dephosphorylated Ric-8A has markedly attenuated ability to fold G alpha subunits. Additionally, the data suggests mitogenic oncogenes may deactivate Ric-8A by dephosphorylation to reduce total cellular G alpha i/q/13 levels. This project hypothesizes that Ric-8 activities are constitutive, but can be down regulated by phosphatase-mediated dephosphorylation. Future studies seek to explore the in vivo phospho-regulation of Ric-8A downstream of mitogenic signaling, and to develop an understanding of functional differences between activated and de-activated Ric-8A imparted by phospho-regulation. The insight this work provides will be valuable for development of Ric-8A targeting therapeutics to modulate G-protein activities. This novel class of pharmaceuticals would allow for a means to combat any GPCR or G-protein driven disease such as those listed above, by effectively evading the need for receptor-specific inhibitors.



Charles Warwick

University of Iowa

“The role of the complement cascade in pain”

Persistent pain affects 1 in 3 Americans and as the underlying causes of chronic pain are not well understood there are few useful drugs available to treat it. In most of these chronic pain conditions, the complement cascade (a part of the immune system) is strongly activated, but its role with regards to chronic pain is unknown. This research project examines the mechanism through which the complement cascade acts to produce pain and the potential for blocking the complement cascade to prevent the occurrence of chronic pain and reduce the intensity of existing pain. Preliminary studies have found that once triggered, the complement cascade strongly activates immune cells called macrophages. These cells then specifically sensitize the nerves responsible for painful sensation, which results in a long lasting pain. The results of this project will establish a novel target for pain treatment and will elucidate a mechanistic explanation for the complement cascade's effects on pain sensation.



Melissa Konopko

University of Maryland, Baltimore

“Role of placenta in valproic acid-induced defects in fetal brain development”

Autism is a common neurodevelopmental disorder whose cause remains unknown. One risk factor for autism is the use of valproic acid (VPA) by pregnant women; VPA is used to treat epilepsy and bipolar disorder. Fetal exposure to VPA by injection of pregnant mice has been used as an animal model for autism which mimics the male sex bias, behavioral deficits and physical brain changes seen in human autistic patients. The molecular action of this drug is to inhibit enzymes in the cell nucleus, termed HDACs, resulting in alterations in DNA structure and changes gene expression in the fetal brain. However, while the molecular mechanism is known, the genes and tissues in the fetus impacted by the drug remain a mystery. It has been assumed that VPA acts directly on the brain; however the focus of this study is the organ that acts as the fetus' interface with the environment; the placenta. Early in gestation, the placenta is the sole source of the essential neurotransmitter, serotonin, for the developing forebrain. Preliminary studies suggest that VPA reduces the placenta's ability to produce serotonin, resulting in a scarcity of this key molecule in the embryonic brain. The goal of this project is to explore the role of placental serotonin in this environmental model of autism.



Matthew Arvin

Purdue University

“Structural Plasticity of Dendritic Spines in Nicotine Dependence”

Nicotine abuse and dependence is directly responsible for several preventable causes of human death, including cardiovascular disease, lung cancer, and chronic pulmonary disease. Nicotine exposure is thought to cause physiological and psychological dependence primarily by altering dopaminergic and glutamatergic signaling within the mesolimbic pathway from the ventral tegmental area to the nucleus accumbens (NAc). Dendritic spines on medium spiny neurons (MSNs) in the NAc represent an important site where dopaminergic and glutamatergic signaling first converge in the mesolimbic pathway and are an important cellular structure for the integration of dopaminergic and glutamatergic transmission. It is known that the physical characteristics of dendritic spines have relevant and potent biophysical consequences on spine function. Despite the importance of dendritic spine morphology on glutamatergic and dopaminergic transmission within the NAc, few studies have addressed the effect of chronic nicotine on MSN dendritic spine structural plasticity. This project will use high-resolution confocal microscopy, biolistic labelling, immunofluorescence, and a novel mouse line to isolate the effect of nicotine on distinct subregions and subpopulations of MSNs in the NAc. This research will help determine the contributions of major, therapeutically essential, nicotinic acetylcholine receptor subtypes in structural plasticity during the expression and maintenance of nicotine dependence, as well as inform and direct drug discovery efforts towards mechanistically selective therapeutic strategies.

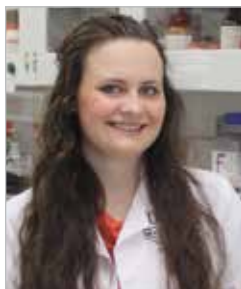


Kasi McPherson

University of Mississippi Medical Center

“The role of ET-1 in lipid accumulation during the development of glomerular injury associated with MetS”

Obesity-induced metabolic syndrome (ob-MetS) has become a serious public health problem in the United States. Ob-MetS is a condition defined by the presence of at least 3 of these criteria: abdominal obesity, high serum triglycerides, low high-density lipoprotein levels, elevated plasma glucose, and increased arterial pressure. The recognition that kidney disease is a risk factor for increased cardiovascular mortality has led to a heightened interest in obesity as a risk factor for chronic kidney disease (CKD) independent of diabetes and hypertension, which is the two most common cause of CKD. While a number studies have provided evidence that ob-MetS is associated with an elevated risk of kidney disease, the mechanisms involved are unknown, due in part to the lack of an appropriate animal model. Recently, this project created a genetically engineered rodent model that develops most of the characteristics of ob-MetS progressive renal injury independent of diabetes. Over the past decade, studies have revealed ob-MetS patients with CKD present with elevated levels of a vasoactive mediator, endothelin-1 (ET-1). While there is plenty of evidence that blockade of ET-1 in diabetes-induced renal disease is beneficial, its contribution to the development of renal disease associated with nondiabetic ob-MetS is unknown and needs to be investigated. This study observed the renal injury in nondiabetic ob-MetS model was associated with elevated ET-1 production and triglyceride deposits in the kidney. Therefore, the proposed project aims to investigate the effectiveness of ET-1 blockers on the development of renal injury in our model of nondiabetic ob-MetS. Overall, this work may contribute to the development of a novel therapeutic option for the treatment of CKD associated with ob-MetS.



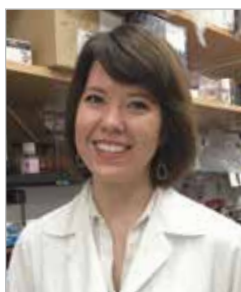
Amanda Stolarz

University of Arkansas for Medical Sciences

“Mechanism of doxorubicin inhibition of lymphatic function and potential therapeutics.”

More than 5 million women in the United States suffer from arm lymphedema (“swelling”) after surgery and/or radiation for breast cancer. The incidence and severity of arm lymphedema is worsened when doxorubicin (DOX) is used as part of the chemotherapy regimen. The mechanism by which DOX contributes to arm lymphedema is unknown, but is assumed to relate to its cytotoxicity. However, this project’s findings suggest that DOX may acutely and reversibly contribute to lymphedema by directly inhibiting the spontaneous contractions (“pumping”) of lymph vessels and compromising lymph flow. Real-time recordings of diameter in isolated lymph vessels revealed that clinically relevant concentrations of DOX inhibited these spontaneous rhythmic contractions (“pumping”), and this effect was partially reversed upon drug washout. DOX also exhibited a similar “lymphostasis” effect and reduced lymph flow in vivo

after IV injection. Normally, lymphatic contractions are tightly controlled by rhythmic changes in calcium ion concentrations. This research hypothesizes that DOX interferes with this tight control by activating intracellular calcium release channels known as ryanodine receptors (RyR) in lymphatic smooth muscle cells as an off-target effect, resulting in lymph vessel constriction and loss of lymph flow. Thus blocking these RyRs could prevent DOX-induced inhibition of lymphatic function and thereby alleviate lymphedema. Blockers of RyRs, such as dantrolene, are clinically available and currently used to treat malignant hyperthermia and muscle spasms. This project will explore if dantrolene or its analogues can be repurposed as anti-lymphedema agents to treat lymphedema associated with chemotherapy.



Katherine Lansu

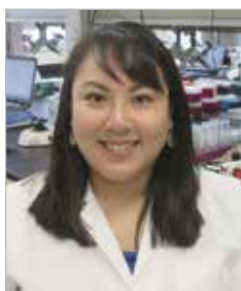
University of North Carolina at Chapel Hill

“Discovery of ligands for the novel opioid receptor MRGPRX2”

Chronic pain affects millions of people per year but standard analgesic drug therapies often have unpleasant and dangerous side effects, including addiction. Many widely used analgesic medications, such as hydrocodone and morphine, target the canonical opioid receptors, which are G protein-coupled receptors (GPCRs) that regulate the transmission of pain. To improve current treatment strategies for pain, it is necessary to examine other receptors involved in pain transmission and create drugs that target these receptors. Approximately 120 GPCRs are “orphan receptors” that have unknown activators and unknown function, but hold great potential to be important in physiology and disease. The MRGPRX2 orphan receptor is found in spinal cord neurons known to regulate pain transmission, but there are currently no known selective activators or deactivators of this receptor. Data from this project shows that the MRGPRX2 receptor is activated by FDA-approved opioid drugs and endogenous opioid peptides at clinically relevant concentrations. These data show that this receptor is a novel opioid receptor with distinct biochemical and functional properties. To discover small molecule activators and de-activators that selectively interact with the MRGPRX2 receptor, this research will use a combined experimental and computer modeling approach. Additionally, this work will test the effect of MRGPRX2 receptor activation in human neurons in vitro. In total, this project will identify novel molecular tools for selectively modulating an understudied receptor and will assess this receptor’s function in neurons. Ultimately, these data may lay the groundwork for identifying a novel target for the treatment of pain or for treating off-target side effects of frequently prescribed analgesic medications.

“ I am very honored and grateful to be a recipient of the Pre Doctoral Fellowship in Pharmacology and Toxicology from the PhRMA Foundation. Going through the grant writing process for this award has been invaluable for my future career as an independent scientist. This award has given me the opportunity to focus on my research investigating the co-morbidity of depression and addiction to help identify novel biochemical targets for therapeutic intervention and has motivated me to work even harder, knowing that the PhRMA Foundation wholeheartedly supports my work and my potential as a scientist.”

Sophia Kaska | Michigan State University



Sophia Kaska

Michigan State University

“Role of TORC2 activity in stress-induced changes in opiate reward and consumption”

Opiate addiction is a rapidly growing problem in the United States, and when coupled with co-morbid mood disorders such as depression, treatment outcomes for both addiction and depression worsen. Treatment of these co-morbid conditions is difficult, in part due to the lack of understanding of the neuroadaptations that occur. Multiple studies have identified similar neuroadaptations in the ventral tegmental area (VTA), a key region in reward, upon exposure to either chronic opiates or chronic social defeat stress (CSDS), a rodent model of depression. Previous work has established the role of mammalian target of rapamycin 2 (TORC2) in mediating opiate reward in the VTA and preliminary data demonstrate that opiate reward is increased in “depressed” mice. The goals of this project are to understand the molecular mechanisms underlying susceptibility to depression and depression-induced changes in opiate reward by investigating the role of TORC2, including the signaling mechanisms downstream of TORC2, to induce these neuroadaptations. Through the study of altered signaling mechanism in the VTA, this project may lead to the identification of novel targets for improved therapeutic intervention for opiate addiction and depression.

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.

2016 POST DOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY



Karen Ho, Ph.D.

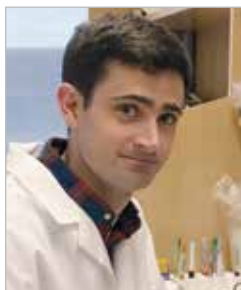
University of Rhode Island

“The Functional Interplay between TRPV1 Activation and Drug Metabolism”

Capsaicin, the active compound in chili peppers, is particularly useful in pain treatment and exhibits potential for multiple medicinal uses. Naturally found in many pungent foods, capsaicin activates the transient receptor potential vanilloid 1 channel (TRPV1), which is a non-selective cation channel. Activation of TRPV1 excites and desensitizes nociceptive neurons, leading to reduced pain sensation. Thus, the activation of and desensitization by TRPV1 are two strategies that have been explored for the development of analgesics. Several functional analogs of capsaicin have been characterized, notably capsazepine, resiniferatoxin and iodoresiniferatoxin. These compounds can undergo hydrolysis by carboxylesterases, a family of hydrolytic enzymes that play critical roles in drug metabolism. Preliminary data suggest that capsaicin and resiniferatoxin decrease hydrolysis of the carboxylesterase substrate p-nitrophenylacetate, suggesting competitive inhibition. In addition, these compounds significantly induced the expression of carboxylesterases and efficaciously activated the pregnane X receptor, a master regulator of genes involved in drug elimination and metabolism. The purpose of this project is to determine the mechanistic link between TRPV1 modulation and carboxylesterase-based hydrolysis and metabolism. Since many drugs undergo hydrolysis, completion of this project will determine a novel molecular pathway underlying carboxylesterase-based metabolism and elucidate potential drug-drug interactions with significant clinical implications.

“ My PhRMA Foundation Fellowship has provided me with invaluable financial support for my postdoctoral training. These funds have allowed me to complement my expertise in Neuroscience with in-depth training in Pharmacology both at the molecular and behavioral level. I cannot thank the PhRMA Foundation enough for their support to help further my career development.”

Daniel Edward O'Brien, Ph.D. | Vanderbilt University



Daniel Edward O'Brien, Ph.D.

Vanderbilt University

“Cellular and Molecular mechanism of M4 PAM therapeutic efficacy in a mouse model of OCD”

Repetitive behaviors are a hallmark of obsessive-compulsive disorders (OCD) and OC-spectrum disorders like Tourette's syndrome and trichotillomania. Since current treatment regimens using selective serotonin reuptake inhibitors (SSRIs) are ineffective in up to 40% of OCD patients, there is a need to identify and validate new approaches to treat OCD and related disorders. Both preclinical and clinical data suggest that dysregulation of the dopaminergic system, specifically increased striatal DA release, may contribute to OCD-like repetitive behaviors; however, studies have yet to directly test whether reducing striatal DA efflux can decrease repetitive behaviors. Recently, this project demonstrated that a selective, positive allosteric modulator (PAM) of the M4 subtype of the muscarinic acetylcholine receptor (mAChR) decreases evoked striatal DA release through M4-expressed on D1 receptor-expressing medium spiny neurons (MSNs). Therefore, the study hypothesized that, in a validated model of OCD, an M4 PAM would decrease excess striatal DA release and repetitive behaviors through activation of M4 on D1 MSNs. Using the validated Sapap3 KO mouse model of OCD, the project is testing these hypotheses in order to determine if preclinical studies support the use of an M4 PAM as a therapeutic for OCD with a novel mechanism of action.

Research Starter Grants in Pharmacology/Toxicology

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

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.

2016 RESEARCH STARTER GRANT IN PHARMACOLOGY/TOXICOLOGY



Emily M. Jutkiewicz, Ph.D.

University of Michigan Medical School

“In vivo consequences of bias signaling”

While many medications target G protein-coupled receptors (GPCRs), there is limited knowledge about their specific intracellular targets and the signaling pathways mediating therapeutic or behavioral endpoints. In the canonical pathway, GPCRs act as guanine nucleotide exchange factors (GEFs) for heterotrimeric G proteins, such that agonist binding catalyzes the exchange of GTP for GDP on the G protein alpha subunits and promotes the dissociation of alpha and beta-gamma subunits to activate signaling cascades. Recent work has demonstrated that GPCRs can adopt multiple active conformations and produce downstream signals independent of GEF activity (e.g., arrestin signaling). G protein-dependent and –independent pathways can be differentially activated by ligands that exhibit “bias” for one signaling cascade over another. Therefore, select signaling cascades may be exploited for the development of new types of drugs producing therapeutic effects with fewer side effects. In preclinical models, delta-opioid receptor (DOPR) agonists relieve pain and produce antidepressant and anxiolytic-like effects. However, some DOPR agonists, but not all, also produce convulsions. Structurally distinct DOPR agonists also produce different rates of receptor internalization independent of agonist efficacy. This has led to the theory that specific drug-receptor conformations and G protein-dependent and –independent pathways may also mediate different behavioral endpoints of DOPR agonists. The long-term goal of this research is to integrate knowledge about molecular and cellular mechanisms of drug action at DOPRs with their in vivo drug effects. The overall objective of this grant is to determine whether the behavioral effects of DOPR agonists are mediated by different signaling pathways in vivo. The current proposal will make a significant advancement in an understanding of the downstream signaling cascades induced by DOPR agonists in vivo and whether these signaling differences play a role in behavioral outcomes and can be exploited to improve potential therapeutic development.



Abdul Hye Khan, Ph.D.

Medical College of Wisconsin

“Novel Epoxyeicosatrienoic acid analog based therapy for focal segmental glomerulosclerosis”

Among the chronic kidney diseases, focal segmental glomerular sclerosis (FSGS) represents the most common primary glomerular disease that leads to end-stage renal failure. Therapeutic options to treat FSGS are very limited and associated with serious side effects including hypertension, kidney damage, seizures, growth retardation, and infectious complications. Moreover, there is a lack in the efficacy of the currently available therapeutic options to treat FSGS, and, indeed, warrant development of novel therapeutic approaches. This research focuses on the development of new therapy for FSGS by targeting a pathway that metabolizes omega-6 fatty acids to epoxyeicosatrienoic acid (EETs). Several studies as well as this project have demonstrated that EETs play an important role in chronic kidney diseases characterized by glomerular filtration barrier damage and sclerosis. These studies demonstrated that increased EET bioavailability resulted in reduced glomerular injury in animal models of chronic kidney diseases. Based on these earlier findings, the project recently developed a series of synthetic EET analogs and demonstrated their promising potential to treat chronic kidney diseases. Research support received from the PhRMA Foundation allowed further studies on the therapeutic potential of these analogs. The long-term goal is to develop novel therapy for chronic kidney disease like FSGS.



Health Outcomes

Pre Doctoral Fellowships in Health Outcomes

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

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.

2016 PRE DOCTORAL FELLOWSHIPS IN HEALTH OUTCOMES



Scott A. Davis

University of North Carolina at Chapel Hill

“Meducation: A Randomized Controlled Trial of an Online Educational Video Intervention to Improve Glaucoma Eye Drop Technique and Adherence”

A major reason that glaucoma patients do not achieve proper control of intraocular pressure, which can potentially lead to blindness, is problems with patients' eye drop instillation technique. There is an urgent need for effective educational interventions to improve patients' technique. The purpose of this study is to determine the effectiveness of a video intervention in improving self-efficacy, technique, and adherence to eye drops in glaucoma patients. Ninety-two patients with glaucoma, who self-administer their own eye drops and have less than perfect technique, will be enrolled in this pilot randomized controlled trial. They will be randomized to watch the Meducation® eye drop technique video in the intervention group, or a nutrition video in the control group. Eye drop instillation self-efficacy and technique will be measured before watching the video, immediately after watching it, and at 1-month follow-up. Adherence will be measured by Visual Analog Scale at baseline and 1-month. The central hypothesis of this project is that glaucoma patients who watch the Meducation video will have improved self-efficacy, technique, and adherence compared to patients who receive standard care. Completion of these aims is expected to fill a significant gap in the understanding of how providers can educate patients about correct eye drop technique at a very low cost with minimal time burden.

“ My pre-doctoral fellowship from the PhRMA Foundation has allowed me to fully immerse myself in my dissertation research by ensuring that I have protected time for my work. As a result, I have become much more engaged in the broader landscape of pharmacy quality to better understand how changes in healthcare policy and the movement towards value-based care may impact the future of medication management. I am very thankful for the opportunity to not only conduct my dissertation research but also to increase my understanding of the broader context of that research.”

Julie Patterson | Virginia Commonwealth University



Julie Patterson

Virginia Commonwealth University

“The Impact of Objective Quality Ratings on Patient Selection of Community Pharmacies: A Discrete Choice Analysis”

Pharmacy-related performance measures have gained significant attention in the transition to value-based healthcare. The Pharmacy Quality Alliance (PQA) develops medication use metrics that measure and report meaningful quality information with the goal of improving patient safety and outcomes. A number of these metrics are currently used in the Health Insurance Marketplace plan rating system and in the calculation of Medicare Part D Plan star ratings. Pharmacy-level quality measures are not yet publicly accessible. However, the publication of report cards for individual pharmacies has been discussed as a way to help direct patients towards high-quality pharmacies. This study will use a discrete choice experiment to quantify the importance of quality information to patients when choosing a community pharmacy relative to the importance placed on pharmacy characteristics reflecting structures and processes of care. A market segmentation analysis will then be used to identify and describe segments in the community pharmacy market based on patient preferences. The results of this study will inform pharmacies and pharmacist organizations of the potential impact of pharmacy report cards on patient decision-making and ascertain future needs for marketing efforts promoting the impact of pharmacists on the quality of medication management. Additionally, the identification of market segments may help pharmacies to provide more effective patient-centered care by targeting and personalizing services.



Kristen Aiemjoy

University of California, San Francisco

“Improving symptoms-based measures of pediatric diarrhea”

Diarrhea is the second leading cause of death and illness among children under five globally. Most studies of pediatric diarrhea rely on caregiver reported symptoms to quantify disease status. Caregiver reported diarrhea has never been validated against a gold standard measure in a community setting. Knowing the validity of caregiver reported diarrhea symptoms is crucial to accurately describe the global burden of diarrheal disease. It can also be used in quantitative bias analysis to adjust results to account for measurement error. Using pictures of stool consistency may improve the validity of caregiver reports. One such tool is the Bristol Stool Form Scale (BSFS), a pictorial scale of five stool consistency types. The BSFS has never been studied in developing country contexts with a gold standard comparison. The proposed study is nested within a two-year cluster randomized trial of a water quantity and quality improvement intervention at 14 sites in Ethiopia. Hand-dug wells were constructed in a central location in 7 randomly selected sites. During the final study visit of the trial, caregivers of all children up to 5 years old will be asked to report the consistency of their child's stool. Caregivers will be asked to obtain a stool sample for each child. Caregiver reported consistency will be compared to investigator rated consistency (gold standard). Half of caregivers (randomly selected) will then be asked to report the consistency of the collected stool sample using the BSFS, the other half will serve as controls and report without any graphic aid. The research program consists of three aims: 1) Determine whether the well intervention reduces childhood diarrhea as measured by caregiver report, 2) Establish the validity of caregiver reported diarrhea and quantify the impact of measurement error on the prevalence of childhood diarrhea between intervention and control and 3) Assess the impact of using the BSFS on the validity of caregiver reported stool consistency. Good outcome measurement is a cornerstone of rigorous quantitative research; the results of this research will provide valuable information on the validity of caregiver-reported stool consistency and a potential low-cost method to improve reporting accuracy.

2016 POST DOCTORAL FELLOWSHIP IN HEALTH OUTCOMES



Abram L. Wagner, Ph.D., MPH

University of Michigan

“Chinese Parents’ Valuation of Pediatric Combination and Co-Administered Vaccines”

China’s immunization schedule includes free, mandatory vaccines, such as diphtheria-tetanus-pertussis, measles, and polio vaccines, as well as optional vaccines, like influenza, pneumococcal, and Hib vaccines, which can be quite expensive and therefore have relatively low uptake. Chinese parents’ decision to immunize their child with these optional vaccines is based on various attributes, such as price, severity of disease it protects against, source of manufacturing (foreign vs domestic) and whether or not it is co-administered with other vaccine doses. By exploring parents’ perceptions of vaccines qualitatively and then quantitatively with a conjoint analysis approach, this study will measure parental and societal values for attributes of childhood vaccines. Attributes identified in this study can be used to promote vaccines and understand the general population’s perceptions of the immunization schedule. Additionally, this study will compare two important demographic groups found in large Chinese cities like Shanghai: locals and recent rural-to-urban migrants. It is likely these two groups may value preventive actions differently based on their experience with disease and financial background.

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.

2016 RESEARCH STARTER GRANTS IN HEALTH OUTCOMES



Salim Chahin, M.D.

University of Pennsylvania

“Impact of Gaps in Treatment on Patient Outcomes in Multiple Sclerosis: Maximizing the Utility of Medicare Claims Data”

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system and is a leading cause of non-traumatic disability in the United States. Relapses and disease progression are two major drivers of disability in patients with MS. Despite an increase in the number of medications approved for the treatment of relapsing MS, adherence to these

specialty medications is often suboptimal and treatment interruptions can negatively impact the disease course. This project will explore patterns of treatment interruptions among patients with MS using a large Medicare claims-based dataset. This study will also link the Medicare claims data to the medical records of Medicare patients with MS treated at the University of Pennsylvania Health System in order to develop and validate claims-based algorithms that can adequately capture disease subtypes and important disease outcomes in MS such as relapses, progression, and disability level. To accomplish this, the research will identify information on office visits, corticosteroid use, symptoms associated with MS and selected healthcare resource use in the claims data to build the algorithms which will then be validated by directly linking to available information in patients' medical records. This project represents a first step in a research program examining the incidence, predictors, and consequences of treatment interruptions among patients with MS. This work will also enable future claims-based analyses on long term health outcomes in MS.



Elizabeth Unni, Ph.D.

Roseman University

“Estimating Statin Adherence in Patient Beliefs after an Initial Cardiac Event”

Patients who have risk factors associated with cardiovascular events (CVEs), such as heart attacks, are often prescribed statin medications to help manage the risk. However, these medications cannot completely remove risk, and some patients may still experience a CVE. After this type of event, care providers will generally prescribe statins as part of the post-CVE treatment, but since the medication did not initially work as a preventive measure, the patient's view on the effectiveness of statin medication may change, and that can impact his or her adherence to the medication in the future. Since statins are an essential part of cardiovascular disease risk management, post-CVE medication adherence is critical. The goal of this research is to identify whether statin medication adherence changes after an event such as a heart attack, and if it declines, to study patients' changing beliefs about statins to better understand the reasons a patient might stop taking this medication. Identifying and understanding the possible changes in adherence and the reasons for the change can lead to better solutions for care providers who want to help patients reduce the risk of a future cardiovascular event.

Pharmaceutics

Pre Doctoral Fellowships in Pharmaceutics

The PhRMA Foundation began funding awards in Pharmaceutics in 1972.

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.

“ I am honored to be the recipient of the 2016 PhRMA Foundation Pharmaceutics Pre Doctoral Fellowship. Being recognized as a PhRMA Foundation Fellow has given me the opportunity to dedicate my time to completing my thesis project and has afforded me opportunities to network with prestigious PhRMA Foundation alumnae and individuals within the pharmaceutical field.”

Venecia Wilson | Purdue University

2016 PRE DOCTORAL FELLOWSHIPS IN PHARMACEUTICS

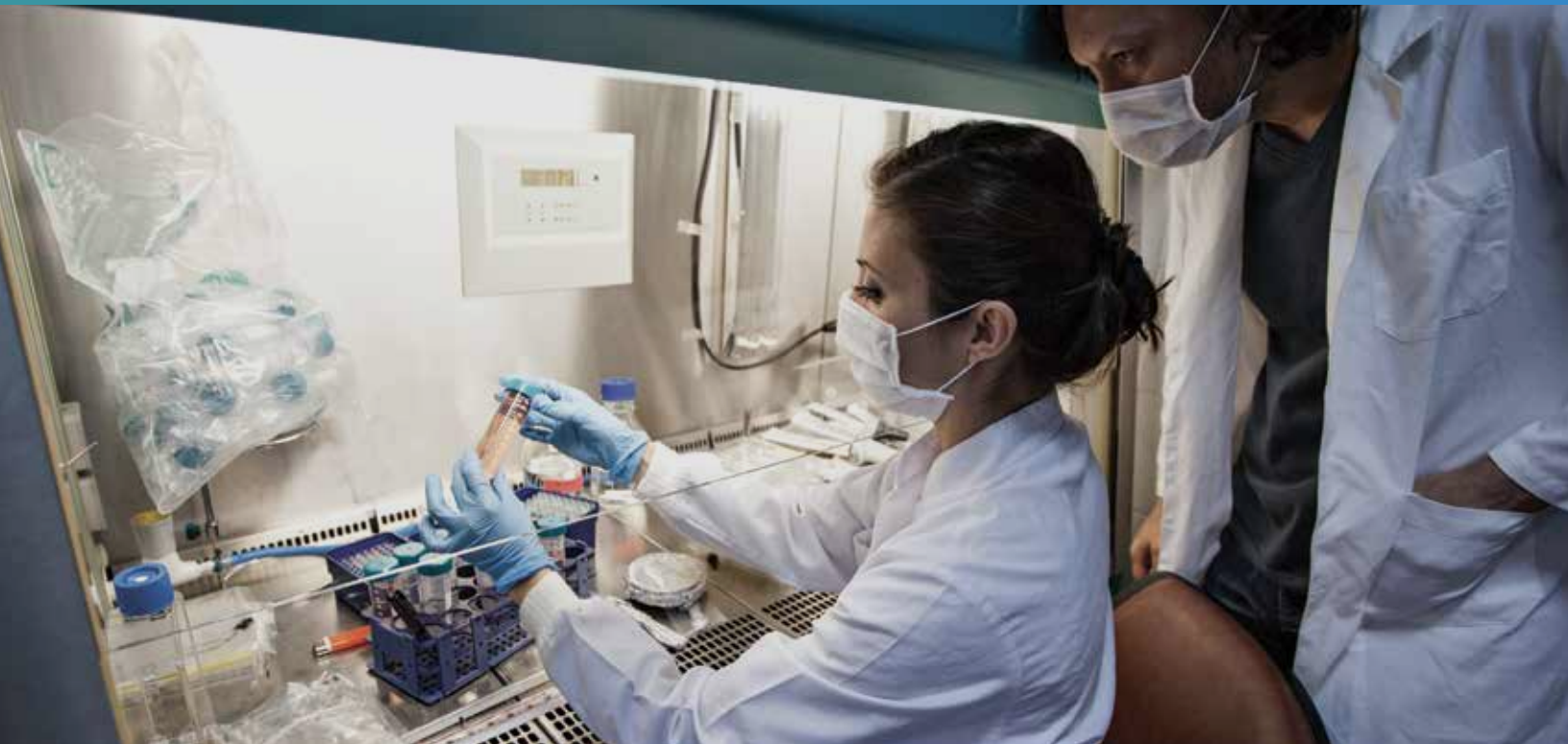


Venecia Wilson

Purdue University

“The Prediction of Amorphous Solid Dispersion Performance *in vivo* from *in vitro* Experiments”

The majority of drugs marketed, as well as, under development have poor aqueous solubility. This is problematic since the body is more than 50% water. Thus, formulation techniques must be employed to increase the aqueous solubility so the bioavailability is enhanced. An example of the formulation technique are amorphous solid dispersions (ASD), a homogeneous mixture of amorphous drug and polymer. Upon dissolution, a supersaturated solution is created and maintained but the mechanism of this phenomena is not well understood. In addition, there is a need for *in vitro* tests which can predict ASD *in vivo* performance. Upon successful completion of the proposed study, both the mechanism of stabilization of supersaturated drug during ASD dissolution will be identified, and *in vitro* tests will be developed which will predict the *in vivo* performance of ASD.



Dan Myers

Rutgers, The State University of New Jersey

“Orally Deliverable Peptide-Conjugated Nanoparticles to Improve Anti-HIV Drug Concentrations in the Intestinal Mucosa”

HIV-1 infection has remained a chronic condition despite current virus-suppressing treatments with antiretrovirals (ARVs) due to a combination of viral latency and the ineffectiveness of drugs in certain anatomical sites. These sites, such as the gastrointestinal (GI) tract, serve as a reservoir for the virus where it can persist in a dormant state in the absence of effective drug doses. This study will focus on developing a platform for delivering anti-HIV drugs, including ARVs, to the GI tract to not only achieve an effective dose, but also sustain that dose in order to eliminate the viral reservoir and, ultimately, destroy HIV infection. Encapsulation in polymeric nanoparticles (NPs) provides a drug delivery vehicle suitable to overcome poor stability in the small intestine and low aqueous solubility. In oral drug delivery research, however, little is known about exploitable mechanisms for NP translocation across the intestinal epithelium. Greater knowledge of potential mechanisms will be crucial for achieving effective concentrations of poorly absorbed therapeutics in the intestinal tissue. For this study, NPs will be formulated using flash nanoprecipitation (FNP) with the goal of encapsulating anti-HIV drugs. In order to target the small intestine and improve the permeability of NPs across the intestinal epithelium, an optimal peptide selected by a random peptide screening method, phage display, will be conjugated to the NP surface. By incorporating a peptide discovered in this manner, there is considerable potential for uncovering a novel mechanism for intestinal uptake. Finally, a dated pharmaceutical approach to improve drug solubility, called ordered mixing, will be used to improve NP dissolution in the gut by minimizing aggregation.



Elizabeth Zecca

University of Connecticut

“Characterizing Surface Hydrophobicity of Protein Molecules and the Role it plays in Protein-Protein Interactions”

Aggregation of protein molecules is a major concern, which often compromises the physical stability of a protein therapeutic. Understanding the underlying causes for a loss in protein stability can aid in developing safe and stable formulations. Protein aggregation is linked directly to protein-protein interactions, hydrophobicity having a main contribution. Hydrophobic interactions can occur by multiple pathways, between two native/folded proteins, or between proteins that have become partially unfolded exposing their hydrophobic core. The purpose of this research is to understand the extent to which hydrophobicity contributes to aggregation of folded and partially unfolded protein molecules. Nonpolar amino acids on the protein surface have to be first characterized structurally using multiple techniques such as Hydrophobic Interaction Chromatography, Nuclear Magnetic Resonance and Fluorescence Spectroscopy. This will help determine the impact of specific amino acids on protein stability based on their contribution to hydrophobic interactions. Additionally, it has been shown that aggregation can also be mediated through the air/liquid interface. Information is needed to determine if surface hydrophobicity leads to adsorption, or partial unfolding at the interface. Further studies need to assess if proteins are interacting at the interface, or the aggregation process occurs in the bulk. Understanding the interplay of surface hydrophobicity and aggregation can help in creating stable protein formulations.

“ The support from the PhRMA Foundation has become an invaluable resource for my continued research in the field of pharmaceuticals. The funding has given me the flexibility to explore and characterize a novel drug transporter which may establish a platform for downstream clinical utility. I will always be eternally thankful for supporters, such as the PhRMA Foundation, for trusting in my ability to advance my career as a scientific researcher.”

Robert Jones | University at Buffalo



Robert Jones

University at Buffalo

“Understanding the Functional Characteristics, Substrate Specificity, and Potential Drug Interactions with Monocarboxylate Transporter 6 (SLC16A5)”

Through the continuous search for alternative drug treatment strategies, the characterization of new drug targeting and delivery approaches has played a critical role in pharmaceutical research. By designing new drugs to have a high affinity for specific drug transporters, scientists

are able to enhance the systemic bioavailability of chemically-engineered xenobiotics. Members of the SLC16A family of drug transporters, or monocarboxylate transporters (MCTs), have been previously utilized in this fashion to successfully enhance the oral bioavailability of poorly absorbed compounds. Of the fourteen identified members of the MCT family, monocarboxylate transporter 6 (MCT6; SLC16A5) has been recently recognized for its role as an absorptive drug transporter. Primarily expressed in the human kidney and intestine, its localization resides at major sites of drug absorption and clearance. However, the significance of MCT6 interactions, its substrate specificity, and functional characterization remain largely unknown, classifying MCT6 as an orphan transporter. The project hypothesis is that MCT6-mediated transport possesses a fundamental biological role in endogenous monocarboxylate transport kinetics and represents an important mechanism of active drug absorption in the intestine and reabsorption in the kidney. Previously, this lab has developed an in silico comparative homology model of MCT6 in order to better understand the physiochemical motifs of its characteristic ligands. In silico pharmacophore comparisons of a small class of exogenous substrates for MCT6 suggest that its substrate specificity is unique to other MCT isoforms. In addition, further functional characterization of MCT6 in vitro could identify its distinct properties, which may be utilized in drug development in treating debilitating diseases. By utilizing a recently developed CRISPR/Cas9 MCT6 knock-out mouse model, metabolomic analysis may lead to the classification of MCT6-mediated transport within a fundamental biochemical pathway. Overall, this study will seek to determine MCT6 substrate specificity and functionality through cohesive in silico, in vitro, and in vivo approaches. This research will enhance existing knowledge regarding MCT6 as well as potentially “de-orphanizing” its role and importance in humans, which may lead to the development of a novel drug delivery or targeting strategy.



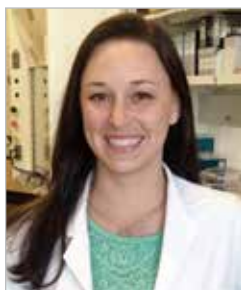
Post Doctoral Fellowships in Pharmaceuticals

Post Doctoral Fellowships in Pharmaceuticals support scientists seeking to further develop and refine their pharmaceuticals 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 Pharmaceuticals. The PhRMA Foundation recognizes the critical need for such well-trained scientific investigators.

“ I am excited to be a recipient of the 2016 Post Doctoral Fellowship in Pharmaceuticals. I am so grateful to PhRMA Foundation for this award! As a young researcher, this funding is so instrumental in my scientific growth. This award allows me to concentrate my efforts on research as well as developing the pharmaceutical skills and experience needed to become a successful scientist. I have no doubt that this will help advance my career in the long term. Thank you so much PhRMA Foundation!”

Elizabeth Gurysh, Ph.D. | University of North Carolina at Chapel Hill

2016 POST DOCTORAL FELLOWSHIPS IN PHARMACEUTICS



Elizabeth Gurysh, Ph.D.

University of North Carolina at Chapel Hill

“Novel Scaffold with Temporal Drug Release for Treatment of Glioblastoma”

Glioblastoma (GBM) is the most common primary brain tumor with 9,000 new patients diagnosed annually in the United States. GBMs are incredibly aggressive, invading the brain with tentacle like projections, making complete surgical removal difficult. Additionally, the blood-brain barrier prevents most chemotherapies from being effective. As such, even with current treatments, the median survival of patients remains only about 15 months and tumor recurrence and associated mortality is almost 100%. Since the successful completion of the Human Genome Project and the launch of the Precision Medicine Initiative, the scientific community has devoted an enormous amount of resources to understanding the genomic landscape of cancer to identify new therapeutic targets. The lethality of GBM has placed it at the forefront of these efforts, making it the first cancer type fully sequenced. From this, eight primary mutations have already been discovered. The goal of this project is to develop a library of scaffolds containing drugs that target these common mutations. These scaffolds will be engineered to allow tight control of the drug release over an extended period of time. A surgeon can then select the optimal scaffolds that will be effective against each specific patient's tumor and use them to line the resection cavity after the tumor is removed. Local application of the scaffold creates a sustained high concentration of a precise cocktail of drugs at the tumor site while simultaneously reducing systemic effects. This prolonged release will work to eliminate cancer cells left behind by surgery to reduce GBM recurrence and improve patient survival.

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.

2016 RESEARCH STARTER GRANTS IN PHARMACEUTICS



Debadyuti Ghosh, Ph.D.

The University of Texas at Austin

“A high-throughput approach to identify novel peptides with desired physicochemical properties for rapid transport through mucus-like barriers towards drug delivery”

In cystic fibrosis (CF), patients have abnormal mucus secretions and impaired clearance, which allows for the development of chronic infections and prevents the successful delivery of therapeutics through mucus to the diseased site. Current standard-of-care technologies are not curative and only modestly improve the function of patients. Treatment has been limited, in part to the lack of carriers that can effectively deliver therapeutics. Here, a high-throughput screening technology has been developed to identify biological-based carriers and their properties that achieve successful penetration through mucus barriers as seen in diseases like CF. This high-throughput approach allows for facile and rapid identification of the properties that drug carriers need for unhindered, rapid transport through mucus to deliver small molecule and nucleic acid drugs. While this project focuses on CF, the work can impact and significantly advance mucosal treatment of diseases as wide ranging from CF to HIV for improved patient outcomes.



Bret Ulery, Ph.D.

University of Missouri

“Vaccination Potential of Adjuvant-Entrapped Peptide Amphiphile Micelles”

The advancement of vaccines is one of humankind's greatest achievements having led to the eradication of small pox and near elimination of polio. While successful, in-tact vaccines (i.e. whole-killed or live-attenuated) have been associated with undesirable side-effects mostly due to their delivery of unnecessary pathogenic components. Peptide subunit vaccines are capable of presenting only the required immunogenic components, but are often very weak requiring high dosages and the inclusion of immune boosting substances (i.e. adjuvants) to be effective. Many different materials-based carriers have been studied for their capacity to improve host immune responses and though some have shown promise, they employ sacrificial constructs limiting their loading and delivery capacities. Additionally, most vaccines are delivered via subcutaneous or intramuscular routes, which while effective, requires the assistance of a medical professional to be administered creating a bottleneck for rapid dissemination to developing areas or after a pandemic outbreak. Vaccines that can be

effectively delivered through less invasive methods including by intranasal and ocular routes using nebulizers and eye drops, respectively, allow for easier distribution to the public and will likely improve compliance. To address these challenges, this proposal leverages a unique type of biomolecular material termed a peptide amphiphile micelle as a novel vaccine delivery system. When a hydrophilic peptide is tethered to a hydrophobic lipid the resulting product is amphiphilic and self-assembles in water into a micellar nanoparticle by clustering hundreds to tens of thousands of individual amphiphiles together. Peptide amphiphile micelles have high loading efficiencies (~ 100%) and capacities (60 - 90% by weight) as well as induce desirable peptide secondary structures and can entrap adjuvants within their nanostructures making them promising vaccine delivery vehicles. The overall goal of this project is to vary micellar physical properties, adjuvant entrapment, and delivery route to determine their effects on corresponding host immune responses against a model vaccine. This data will be leveraged to yield structure-function-activity relationships that will be used to determine micellar design rules governing future materials-based prophylactic and therapeutic vaccines against conventional pathogens like influenza and herpes and diseases like cancer and autoimmune disorders.

Clinical Pharmacology

Paul Calabresi Medical Student Fellowship

The PhRMA Foundation began funding Medical Student Fellowships in 1974.

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.

2016 PAUL CALABRESI MEDICAL STUDENT FELLOWSHIP



Krystian Kozek

Vanderbilt University

“Creating new tools to study the link between ion channels in the brain and drug addiction”

Opioid abuse and deaths due to opioid overdose are sharply on the rise in the USA. To understand why drug abuse and addiction are so problematic in our society, this project investigates specific cell membrane ion channels in the brain and their role in addiction. If the way in which these channels behave can be altered, this project hypothesizes that it may be able to stop addictions from developing. These ion channels, called G protein-gated inwardly-rectifying potassium (GIRK) channels, are found in neurons in the brain. GIRK channel behavior is difficult to alter with currently known molecules. This research aims to create new drug-like molecules that will target the structures in the brain associated with addiction and alter the behavior of GIRK channels in these areas. The discovery of such molecules will enable future researchers to further investigate GIRK channels in the development, prevention, and treatment of addiction.

“ The PhRMA Foundation faculty development award will help me obtain the perinatal pharmacology training necessary to launch an independent research career. With the necessary skill set, I look forward to advancing medication management for pregnant women.”

Crystal Clark, M.D., M.Sc. | Northwestern Feinberg School of Medicine

2016 FACULTY DEVELOPMENT AWARD IN CLINICAL PHARMACOLOGY



Crystal Clark, M.D., M.Sc.

Northwestern Feinberg School of Medicine

“Pharmacokinetics of Quetiapine Across Pregnancy.”

Poor birth outcomes (i.e., low birth weight, preterm birth), increased risk of pregnancy complications (placental abnormalities, preeclampsia), and increased mortality are associated with untreated bipolar disorder (BD) and schizophrenia (SCHZ) in pregnancy. The use of second generation antipsychotics (SGA) indicated for the treatment of SCHZ and BD has more than doubled in pregnant women in the past decade. Yet, evidenced-based algorithms to guide dosing of SGAs are lacking. This application proposes an interdisciplinary approach to understand the pharmacokinetics of medication in pregnancy, specifically the most commonly used SGA, quetiapine. This project is investigating the degree to which changes in quetiapine pharmacokinetics, especially quetiapine elimination clearance, across pregnancy impacts efficacy, toxicity, maternal-to-umbilical cord plasma concentration ratios, and maternal-to-cerebrospinal fluid plasma concentration ratios. To achieve this goal, the study investigation 1) utilizes a longitudinal pharmacokinetic protocol to characterize the elimination clearance of quetiapine and its major active metabolite across pregnancy and postpartum; 2) assesses mood symptoms, side effects, and function to determine association between plasma drug concentrations and efficacy and toxicity; and 3) obtains maternal and umbilical cord samples at delivery to examine fetal exposure to quetiapine in pregnancy through maternal-to-cord plasma concentrations ratios of quetiapine and its major active metabolite. This line of research also aims to determine the impact of genetic variants on the maternal-to-fetal transfer and maternal-to-cerebrospinal fluid plasma concentrations during pregnancy. Ultimately this study aims to be the building blocks toward the development of a personalized and precise dosing algorithm that maintains wellness for mothers with bipolar disorder and their unborn child.

Translational Medicine and Therapeutics

Post Doctoral Fellowships in Translational Medicine and Therapeutics

The first Translational Medicine and Therapeutics fellowships and grants were awarded in 2013.

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.

2016 POST DOCTORAL FELLOWSHIPS IN TRANSLATIONAL MEDICINE AND THERAPEUTICS



Jonathan Sockolosky, Ph.D.

Stanford University

“Potentiating adoptive T cell therapy through orthogonal cytokine-receptor engineering”

The human immune system has the remarkable capacity to protect our bodies against foreign pathogens and to destroy malfunctioning cells such as cancer cells. One type of immune cell, the T cell, acts as the body’s soldier in the battle against cancer. T cells infiltrate tumors and can directly kill cancer cells when armed with the appropriate weapons that allow them to specifically recognize tumor cells. This property has been exploited for treatment of human cancers by isolating a patient’s T cells, engineering tumor targeting properties, and re-infusing the engineered T cells back into the patient, a process termed adoptive T cell therapy (ACT). The transferred T cells require growth factors in the form of proteins called cytokines to survive and replicate in the body, and in the clinic this is achieved by administering the T cell growth factor interleukin-2 (IL-2). However, in addition to promoting the survival of cancer fighting T cells, IL-2 also supports the survival of cells that suppress the immune system and cause severe toxicity. Both of these properties limit the ability to treat cancer with ACT. This research aims to address this limitation by engineering a mutant version of IL-2 and a mutant version of the IL-2 receptor (IL-2R) that are specific for each other (orthogonal), but do not interact with their wild-type counterpart. In principle, the mutant version of IL-2 will only have activity on antitumor T cells engineered to express the mutant IL-2R. By directing the activity of IL-2 towards a T cell subset of interest, this approach should improve the ability of the transferred T cells to survive in the body and kill tumor cells while minimizing the off-target and toxic effects associated with the administration of the natural form of IL-2. In the clinic, this may translate to a more effective form of ACT for the treatment of human cancers that is also safer for patients.

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.

2016 RESEARCH STARTER GRANTS IN TRANSLATIONAL MEDICINE AND THERAPEUTICS



Emanuela Ricciotti, Ph.D.

University of Pennsylvania

“The translational impact of NSAID selectivity on the gut microbiome”

Nonsteroidal anti-inflammatory drugs (NSAID)s inhibit the activity of the more constitutive cyclooxygenase (COX)-1 and the more inducible COX-2. They are among the most commonly used drugs worldwide, but their cardiovascular and gastrointestinal side effects represent a major concern for patients, regulators and industry. This project aims to investigate individual specific factors that influence the outcome of NSAID therapy and that contribute to variability in drug-induced side effects and efficacy. The interaction between gut microbiota and host metabolism has emerged to play important roles in modulating host physiology, gut microbiome-related disorders, and metabolism of xenobiotics. Host-gut microbiome interactions may contribute to NSAID metabolism and may influence the outcome of NSAID therapy. Given that NSAID with different selectivity for COX-1 and COX-2 inhibition have different side-effect profiles, the proposed studies will investigate the effect of selective and nonselective NSAIDs on gut microbiome composition and function as well as the effect of the microbiome on NSAIDs metabolism both in mice and in humans. This study will provide a better understanding of host-microbial communication and interactions in the context of drug metabolism and pharmacology. Such knowledge will serve as a strong driving force for future developments in personalized medicine.



Nariman Balenga, Ph.D.

University of Maryland School of Medicine

“Mechanisms of RGS5-mediated tumorigenesis in parathyroid gland”

Tumor formation is the cause of some of the endocrine disorders, which disrupts the body's delicate hormonal balance. Neoplastic parathyroid cells secrete inappropriately high levels of parathyroid hormone (PTH) leading to primary hyperparathyroidism (PHPT), which causes bone loss and fracture, cardiovascular disease, and neurocognitive impairment. PHPT is the most common endocrine disease and the leading cause of hypercalcemia with a prevalence of 0.1-0.5% in US population. Although the only cure for PHPT is the surgical removal of the affected gland(s), the high rate of neoplastic gland recurrence after parathyroidectomy necessitates alternative noninvasive approaches. Abnormal expression of a cell cycle protein, PRAD1 causes parathyroid adenomas in only 20-40% of PHPT patients. However, uncoupling of calcium sensing by the parathyroid calcium-sensing receptor (CaSR), a G protein-coupled receptor (GPCR), to negatively regulate PTH secretion is the hallmark of the disease. The signaling pathways of CaSR are mitigated by regulator of G-protein signaling 5 (RGS5), a protein that is highly expressed in parathyroid adenomas. The goal of this study is to determine the molecular mechanisms by which RGS5 disturbs the calcium-PTH feedback via translational and pharmacological approaches. To this end a novel mouse model of PHPT that expresses RGS5 exclusively in parathyroid is generated for in vivo studies. Using bioinformatics approaches, the gene expression profile of parathyroid cells upon over expression of PRAD1 and RGS5 is compared and the corresponding pathway signatures will be used for categorization of PHPT patients. Overall, this study will broaden and deepen our understanding of the causes of PHPT and may provide a ground for developing precise patient-focused pharmaceuticals.



Paul M. Campbell, Ph.D.

Drexel University College of Medicine

“Targeting paracrine mediators in the primary and metastatic tumor microenvironments”

Pancreatic cancer is one of the most lethal forms of cancer; currently third and predicted to soon rise to the second leading cause of cancer related deaths per year in the US. Five-year survival rates for pancreatic cancer patients in the US are approximately 8%. In almost all pancreatic cancer patients, the disease spreads (metastasizes) to other organs, and this is the most deadly aspect of the cancer, as these new tumors are particularly resistant to current treatments. Research suggests that when pancreatic cancer cells spread to other parts of the body, some of them enter a resting stage. They then release chemicals called chemokines that make the cells surrounding them in their new environment also enter this resting stage. Because many of the anti-cancer drugs used today are designed work on cells that are not

quiet, but active, the resting cells avoid being killed by the chemotherapy. Once the rounds of chemotherapy treatment are finished, these cells can then switch back to active forms and grow into even more aggressive, resistant metastatic tumors. The research here focuses on understanding the chemical signals that the cells use to interact with each other, and how to block those chemicals to prevent the resting stage of these pancreatic cancer cells and the helper cells around them. By doing so, it will make these metastatic cells easier to kill with anti-cancer drugs.



Mehdi Javanmard, Ph.D.

Rutgers University

“The ProteOhmic CTC Surface Marker Analyzer: Rapid Prediction of Cancer Patient Response to Matriptase Targeted Therapy”

Due to its non-specific nature, the use of chemotherapeutic agents for therapy is known to result in severe side effects in cancer patients. To minimize these negative side effects, a novel therapy is being explored involving targeted delivery of anti-tumor drugs conjugated with antibodies that specifically target cancer cells exhibiting matriptase, a surface marker that is known to be expressed on the surface of varying types of tumor cells. This project sets out to develop a portable point-of-care tool which can rapidly assess the responsiveness of breast cancer patients to this targeted therapy. The proposed analyzer utilizes a novel ultra-sensitive bead-based impedance detection technique for rapidly quantifying marker levels on the surfaces of circulating tumor cells (CTCs) to achieve a fully functional miniaturized platform. Successful completion of this research will allow for effective patient selection and thus will aid to advance the development of this novel therapeutic approach (and a multitude of other drugs involving targeting of cell surface membranes) down the regulatory pipeline more rapidly.

Adherence Improvement

Pre Doctoral Fellowship in Adherence Improvement

The first Adherence Improvement fellowships and grants were funded in 2013.

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.

2016 PRE DOCTORAL FELLOWSHIP IN ADHERENCE IMPROVEMENT



Marisa Schauerhamer

University of Utah

“The Effect of a Value-Based Insurance Design on Adherence, Glycemic Outcomes and Costs in Patients with Diabetes in an Employer-Insured Population”

Diabetes is a prevalent, chronic and progressive disease that can be successfully treated with medications and lifestyle changes. Proper management of diabetes and adherence to prescribed therapies will prevent comorbidities, slow disease progression and reduce medical costs. Because of this, adherence to medications shown to be effective at treating diabetes is considered to have a highly valued impact on health. Factors affecting medication adherence are many and complex with costs of medications being one of these factors that can be targeted. Value-based insurance design (VBID) is a method used to lower costs of medications for patients with the goal to improve medication adherence. VBID is commonly used in chronic disease states like diabetes. However, the evidence that VBID improves diabetes medication adherence is conflicting. There is also a lack of data showing how VBID affects glycemic control and medical and pharmacy costs. The purpose of this study will be to assess what changes in adherence, glycemic control and medical and pharmacy costs occur after implementing a VBID that provides diabetes medications and insulins at a zero-dollar copayment. The hypothesis is that adherence and glycemic control will improve and that VBID implementation will have positive impacts on medical costs. The proposed study is innovative because it will merge data from multiple sources to measure impacts on adherence, glycemic control and medical and pharmacy costs in a single population.

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 Research Starter Grant helped me obtain recent Medicare beneficiary data that will help me understand for which patients adherence-improving interventions are most needed.”

Julia F. Slejko, Ph.D. | University of Maryland, Baltimore

2016 RESEARCH STARTER GRANTS IN ADHERENCE IMPROVEMENT



Julia F. Slejko, Ph.D.

University of Maryland, Baltimore

“Dynamic Predictors of Medication Adherence and the Value of Adherence Prediction”

Pharmacotherapy for cardiovascular disease prevention, statins in particular, often exhibit impressive risk reduction in clinical trials. These rates are seldom seen in the real world, in part due to patients' medication nonadherence. The real-world adherence of most patients is associated with more cardiovascular events than patients who exhibit adherence similar to that of clinical trial patients. Nonadherence to medications for chronic conditions is a research priority, as are interventions to improve adherence. However, very few studies examine the ability to predict patients' adherence, and the value of doing so. It is known that adherence is a dynamic process that often leads to discontinuation, but very few studies have examined dynamic factors to explain these patterns. As more tools are developed to help improve patients' adherence, it becomes critical to understand which patients are at higher risk for nonadherence, due to their characteristics and dynamic health factors, and furthermore, to use this information to guide patient-centered approaches for improving adherence. The overall objective of this research is to propose frameworks for medication adherence prediction and the value of adherence prediction. Specifically, models to predict patients' medication adherence will be developed using observed baseline characteristics such as comorbidities and past adherence, and by dynamic factors such as hospitalizations and disease progression. If these attributes are predictive of adherence, future research will assess the value of predicting adherence in terms of the investment in interventions needed to improve adherence and the subsequent improvement



Hayden Bosworth, Ph.D.

Duke University

**“Medication Adherence Conference”
Suboptimal Medication Use and Adherence – the Intersection of Research,
Implementation, and Policy Conference
December 2016 in Washington, DC**

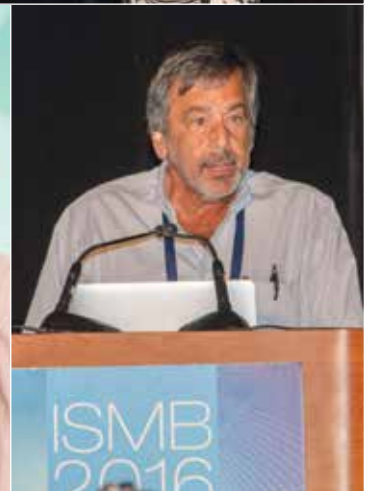
The burden of medication non-adherence is one of the largest public health challenges the United States and the world face. Half of the 3.2 billion annual prescriptions dispensed in the United States are not taken as prescribed. The clinical and economic consequences of suboptimal medication use are overwhelming, resulting in increases in hospitalizations and premature mortality. A significant barrier to identifying and disseminating practical strategies to improved medication adherence is the lack of collaboration between all stakeholders who are involved in patient care, including: providers, policy makers, purchasers, product makers, researchers, and payers.

Given the need to foster collaboration among the various stakeholders, faculty at Duke University (Hayden Bosworth, PhD), the Medication Adherence Alliance (Hayden Bosworth, PhD), Prescriptions for a Healthy America (Sloane Salzburg, MS), and PhRMA Foundation (Eileen Cannon, Samantha Dougherty, PhD, and Carolyn Ha, PharmD) assembled the ‘Suboptimal Medication Use and Adherence – the Intersection of Research, Implementation, and Policy’ Conference, held on December 5-6th 2016 in Washington, DC.

Approximately 75 participants with diverse backgrounds and perspectives in health care research and policy attended the conference to share and discuss strategies to help improve medication adherence, identify areas for future research and collaboration, and recommend policy options to help achieve these goals. The conference participants represented nearly every facet of the medication use process- patients, providers, researchers, payers, and pharmaceutical companies. Since suboptimal medication use and adherence are well documented, the focus of the conference was to identify strategies and solutions that will eventually lead to policy changes to attain significant improvements to medication use and optimize overall health outcomes. Collective discussions from conference participants focused on three high priority areas: incentives, information, and integration.

Next steps:

A list of approximately 15 topics was generated and participants were asked to prioritize which of the topics this group will work on over the next 12 months to improve appropriate medication use.





The Foundation was honored to present its 2016 awards at distinguished scientific annual meetings throughout the country.

Our thanks to the following organizations:

The American Society for Pharmacology and Experimental Therapeutics (ASPET)
San Diego, California on April 2, 2016

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
Washington, D.C. on May 25, 2016

The International Conference on Intelligent Systems for Molecular Biology (ISMB)
Orlando, Florida on July 11, 2016

American Society for Clinical Pharmacology and Therapeutics (ASCPT)
San Diego, California on March 9, 2016





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Washington, DC

Treasurer's Report



The PhRMA Foundation ended 2016 in solid financial shape. Member contributions were \$3.2 million which is more than 13% higher than the previous year. These contributions are the sole support for the Foundation's core grant programs.

The Foundation's total expenditures decreased \$781,000 from 2015. This is primarily due to reduction in grants awarded in 2016 in two of its eight disciplines. Fewer awards were granted in Adherence Improvement and a program shift occurred within Comparative Effectiveness Research. In addition, flexible start dates of the other awards contributed to the lower grant expenditure. Non-grant program and administrative expenses were slightly higher due to special 50th Anniversary activities. Net assets at December 31 were \$21.6 million, an 8.1% increase from the prior year. The increase in net assets is attributable to 1) interest and investment earnings of \$1.7 million, 2) increased contributions of \$400 thousand and 3) \$.5 million spend from long-term commitment funds for Translational Medicine and Therapeutics. 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. 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 and we are proud of the numerous accomplishments of our scientists. Through our multiple collaborations, we are building strong relationships and partnerships throughout the biopharmaceutical research sector, bringing together scientists who have dedicated their careers to improving the health of patients around the world.

The Foundation's financial position as of December 31, 2016, has been audited by the accounting firm of Tate and Tryon of Washington, D.C. A full report can be obtained by contacting the Foundation.

A handwritten signature in dark ink, appearing to read 'A. Plump', with a long horizontal flourish extending to the right.

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

Statement of Income & Expenditures

For the year ended December 31, 2016

INCOME	
Contributions ¹	\$3,205,200
Contributions – in kind from PhRMA	\$46,197
Interest and Dividends	\$485,057
(Realized and Unrealized) Gains in Securities	\$1,178,845
Other Income	\$170,630
Total Income	\$5,085,929
EXPENDITURES	
PROGRAMS	
Awards in Excellence	\$16,097
Adherence Improvement	\$220,415
Clinical Pharmacology Program	\$103,500
Comparative Effectiveness Program	\$166,666
Health Outcomes Program	\$346,250
Informatics Program	\$364,000
Pharmaceutics Program	\$390,000
Pharmacology Programs	\$693,333
Translational Medicine and Therapeutics	\$620,000
AFPE Fellowship Award	\$10,000
Other Grants	\$12,837
Subtotal – Grants	\$2,943,098
OTHER	
Committee Meetings, Travel and Honoraria	\$147,952
Publications and Special Projects	\$32,759
Subtotal – Other	\$180,711
Program Total	\$3,123,809
ADMINISTRATIVE	
Staff, Taxes, Depreciation & Insurance	\$440,871
Rent & Accounting Services	\$46,197
Professional Services and Investment Expenses	\$97,212
Office Expenses	\$2,840
Subtotal – Administrative	\$587,120
TOTAL EXPENDITURES	\$3,710,929

¹ Rent and Accounting Services are donated by PhRMA

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PhRMA Foundation Programs for 2017

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, 2016 December 15, 2016 January 1, 2017
Pharmacology/Toxicology			
Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)	9 awarded/up to 2 years	\$330,000 total \$20,000 per award per year	September 1, 2016 December 15, 2016 January–August
Post Doctoral Fellowship in Pharmacology/Toxicology (2002)	2 awarded/2 years	\$160,000 total \$40,000 per award per year	September 1, 2016 December 15, 2016 January–December
Sabbatical Fellowship in Pharmacology/Toxicology (1972)	1 awarded/1 year	\$40,000 total \$40,000 per award per year	September 1, 2016 December 15, 2016 January–August
Research Starter Grants in Pharmacology/Toxicology (1972)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	September 1, 2016 December 15, 2016 January 1, 2017
Clinical Pharmacology			
Paul Calabresi Medical Student Research Fellowships (1974)	2 awarded/ 6 months up to 2 years	\$36,000 total \$18,000 per award	February 1, 2017 April 15, 2017 July 1, 2017
Faculty Development Award in Clinical Pharmacology (1966)	1 awarded/2 years	\$240,000 total \$120,000 per award per year	February 1, 2017 April 15, 2017 July 1, 2017
Health Outcomes Advisory Committee			
Pre Doctoral Fellowships in Health Outcomes (2002)	2 awarded/2 years	\$100,000 total \$25,000 per award per year	February 1, 2017 April 15, 2017 July–December
Research Starter Grants in Health Outcomes (2002)	3 awarded/1 years	\$300,000 total \$100,000 per award per year	February 1, 2017 April 15, 2017 July 1, 2017
Informatics			
Pre Doctoral Fellowships in Informatics (2009)	2 awarded/2 years	\$80,000 total \$20,000 per award per year	September 1, 2016 December 15, 2016 January–August
Post Doctoral Fellowship in Informatics (2002)	1 awarded/2 years	\$80,000 total \$40,000 per award per year	September 1, 2016 December 15, 2016 January–December
Research Starter Grants in Informatics (2002)	3 awarded/1 year	\$300,000 total \$100,000 per award per year	September 1, 2016 December 15, 2016 January 1, 2017

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Pharmaceutics			
Pre Doctoral Fellowships in Pharmaceutics (1987)	5 awarded/2 years	\$200,000 total \$20,000 per award per year	September 1, 2016 December 15, 2016 January-August
Post Doctoral Fellowships in Pharmaceutics	1 awarded/2 years	\$80,000 total \$40,000 per award per year	September 1, 2016 December 15, 2016 January-December
Research Starter Grants in Pharmaceutics (1972)	1 awarded/1 year	\$100,000 total \$100,000 per award per year	September 1, 2016 December 15, 2016 January 1, 2017
Translational Medicine & Therapeutics			
Post Doctoral Fellowships in Translational Medicine (2016)	2 awarded/2 years	\$240,000 total \$60,000 per award per year	February 1, 2017 April 15, 2017 July - December
Research Starter Grants in Translational Medicine (2016)	3 awarded/1 year	\$300,000 total \$100,000 per award per year	February 1, 2017 April 15, 2017 July - December
Value Assessment Initiative			
Challenge Awards (2017) for Value Assessment	to be determined	\$5,000 total \$50,000 per award per year	March 27, 2017 June 9, 2017 to be determined
Research Awards (2017) for Value Assessment	to be determined/ 1 year	\$100,000 total \$100,000 per award per year	September 1, 2017 December 15, 2017 January 1, 2018
Planning Awards (2017) for Value Assessment	4 awarded/4 years	\$25,000 each	May 1, 2017 June 15, 2017 July 1, 2017
Center of Excellence Award (2017) for Value Assessment	1 awarded/3 year	\$500,000 total \$166,666 per award per year	November 1, 2017 December 15, 2017 January 1, 2018

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



Eileen Cannon
President



Charlotte Lillard
Associate



Joanne Westphal
Director of Development

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