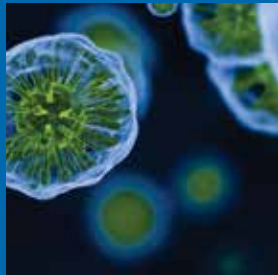


2019 ANNUAL REPORT





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MISSION STATEMENT

The PhRMA Foundation works to improve public health by proactively investing in innovative research, education and value-driven health care.

We achieve our mission by:

- Remaining scientifically independent and nimble in an ever-evolving health care ecosystem.
- Investing in the patient perspective, including patient-centered value assessment, to empower patients and improve outcomes and efficiencies.
- Supporting and encouraging young scientists to pursue novel projects to advance innovative and transformative research efforts.
- Using data, sound methodologies and advanced technology to inform decisions.
- Supporting collaborative efforts that promote innovative research, support emerging data science and drug discovery, and build frameworks that accurately characterize the value of outcomes for a wide variety of stakeholders.







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MESSAGE FROM THE CHAIRMAN



We are at the beginning of a new decade and a new era for the PhRMA Foundation. Some exciting changes are on the horizon and many others are well under way.

We welcomed a new mission statement to guide our actions:

Mission: The PhRMA Foundation works to improve public health by proactively investing in innovative research, education and value-driven health care.

We achieve our mission by:

- *Remaining scientifically independent and nimble in an ever-evolving health care ecosystem*
- *Investing in the patient perspective, including patient-centered value assessment, to empower patients and improve outcomes and efficiencies*
- *Supporting and encouraging young scientists to pursue novel projects to advance innovative and transformative research efforts*
- *Using data, sound methodologies and advanced technology to inform decisions*
- *Supporting collaborative efforts that promote innovative research, support emerging data science and drug discovery, and build frameworks that accurately characterize the value of outcomes for a wide variety of stakeholders*

We developed a plan for achieving that mission that plays on our strengths. Our restructured core programs reach across disciplines and embrace collaboration and crosscutting knowledge. The programs align with what is happening right now in health care, but they also empower us to evolve and adapt, as the ebb and flow of drug discovery and development constantly tests our agility.

The same is true of the Foundation's Value Assessment Initiative.

Value assessment is changing tremendously. The criteria by which we evaluate a treatment are evolving, with aims to better include factors that matter most to patients and society. Methods are becoming more flexible to account for differences across patients — but there's much more work to be done.

The PhRMA Foundation has invested more than \$3.5 million to improve patient-centered value assessment in the United States. Yet, this is a beginning step. At four different sites throughout the country, the Foundation's Centers of Excellence have discovered that there are many ways to measure value in health care. Some are looking outside of traditional value assessment methodology, while others are engaging directly with patients and other stakeholders to develop techniques that explicitly account for what matters to them. We have to take into account not only all of what we know about a particular treatment—its potential interactions and side effects, the cost, the required dose, etc.—but also, all of what we know about the people who will use that treatment. When value becomes embedded in medical decision-making, then all stakeholders, like policymakers, practitioners or payers, can choose wisely and well, based on the best interests of patients.

With this sweeping shift in health care, we have some very promising opportunities to learn even more about our patients and to parlay that understanding into information. The Foundation's new Data and Technology program will support novel pathways for leveraging technologies, services and systems at the intersection of medicine and technology.

It's a new decade and a new day for the PhRMA Foundation, yet our commitment to our proud history of providing career-starting grants and fellowships to young scientists will remain a strong structural component of our new mission and program structure. These are exciting times in the evolution of our health care ecosystem, and I am proud that the PhRMA Foundation is at the forefront of supporting positive change.

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

Alfred W. Sandrock, MD, PhD
Chairman, PhRMA Foundation

MESSAGE FROM THE PRESIDENT



At a time when health care is changing so rapidly, we must always be looking forward. Over the last two years, the PhRMA Foundation's Value Assessment Initiative has sought to offer transformative solutions to improve value in health care.

We restructured our focus with a new mission to encompass a broader multidisciplinary scope across the drug development spectrum and promote new, innovative uses of data and technology, all of which embrace the voice and needs of patients.

From early clinical trials to commercialization of pipeline therapies and health technology assessments, more must be done to incorporate the perspectives and outcomes that matter most to patients. With assistance from the PhRMA Foundation, researchers around the country have been redefining traditional approaches in ways that align with the needs of patients and ensure progression towards a value-driven health care system.

These partnerships have begun to yield dividends. The four PhRMA Foundation Centers of Excellence, each of which have their own unique focus, are working towards establishing a greater understanding of value within the health system.

Last fall, representatives from each Center joined leading health economics researchers, patient advocates and health care policy professionals to discuss how best to connect the latest value assessment research with practical applications for health care decision making. This gathering, which was hosted in partnership with the National Health Council, marked the Foundation's inaugural value assessment conference and drew a wide audience from across the health policy and health economics communities.

Looking to the future, the Foundation aims to continue its value assessment work with an emphasis on being more patient centered. Through our research investments, we want to broaden our understanding by focusing on outcomes that matter most to patients. Patients will benefit if these research findings and recommendations are used in decision making when it comes to their care. We plan to start by supporting new efforts to identify, validate and potentially measure patient-centered outcomes where the most significant gaps exist. We see this as a pathway to contributing to a repository that truly captures the patient perspective and can be utilized by multiple stakeholders.

We look forward to continuing to support research that aligns with our mission of having value assessment better serve the interests of patients. The PhRMA Foundation is pleased to play a role in the collective effort to enhance the quality of health care for all of us.

A handwritten signature in black ink, reading "Eileen Cannon". The signature is fluid and cursive.

Eileen Cannon
President, PhRMA Foundation



AWARDS IN EXCELLENCE



2019 Award in Excellence in Pharmacology/Toxicology

Jay Goodman, PhD

1972 Research Starter Grant in Pharmacology & Toxicology

Jay Goodman, PhD, is an internationally known toxicology expert. Throughout his career, Dr. Goodman's research has focused on enhancing understanding about chemicals and how they might affect human health, with a specific emphasis on the role certain substances play in cancer formation. His work has shed light on why some chemicals cause harm, and helped lay the foundation for a more rational approach to risk assessment.

Dr. Goodman received his bachelor of science from the Long Island University College of Pharmacy, New York, and his PhD in pharmacology from University of Michigan. He completed a postdoctoral fellowship at the University of Wisconsin's McArdle Laboratory for Cancer Research. As one of the first to study the role of epigenetics as a significant nongenotoxic mechanism underlying carcinogenesis, Dr. Goodman's research helped establish a role for nonmutational events involved in the process. When the Environmental Protection Agency issued its revised Guidelines for Carcinogen Risk Assessment in 2005, a new section titled "Nonmutagenic and Other Effects" referenced findings from his lab.

During his tenure as professor in the Department of Pharmacology and Toxicology at Michigan State University, Dr. Goodman has greatly enriched the toxicology graduate program. For 18 years, he chaired the department's Graduate Committee, which has a key role in student recruitment, course development, and academic progress. His students have gone on to highly successful careers in academia, industry, and government.

Dr. Goodman was the first American member of the Education Subcommittee of the Federation of European Toxicologists and European Societies of Toxicology (EUROTOX), which promotes the study and science of toxicology throughout Europe. He is a past president of the Society of Toxicology and former chair of the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute. He has also served on the ILSI Board of Trustees and Executive Committee, the National Toxicology Program Board of Scientific Counselors, the National Institutes of Health Board of Scientific Counselors, the Centers for Disease Control and Prevention Advisory Committee to the Director, and the Food and Drug Administration Nonclinical Studies Subcommittee of the Advisory Committee for Pharmaceutical Science.

With more than 130 published studies, Dr. Goodman is a frequently cited source on toxicology. He served on the Toxicological Sciences and Toxicology editorial boards and as an associate editor for *Toxicological Sciences*, *Regulatory Pharmacology and Toxicology*, and *Toxicology*.

Dr. Goodman's contributions to toxicology training and research have been widely recognized. In 2014, he received the International Achievement Award from the International Society of Regulatory Toxicology and Pharmacology and the Merit Award from the Society of Toxicology. He is also a recipient of the John Barnes Prize from the British Toxicology Society, the George H. Scott Memorial Award from the Toxicology Forum, and the Distinguished Alumnus Award from the University of Michigan and was recently named a Fellow of the American Association for the Advancement of Science. He has delivered lectures and presentations at toxicology and pharmacology conferences throughout the world.



AN INTERVIEW WITH JAY I. GOODMAN, PhD

1972 Research Starter Grant in Pharmacology & Toxicology

Q. Boiling down to a basic understanding of toxicology, there are good, useful chemicals and dangerous or harmful chemicals. In the safety assessment of a new substance, what factors must be considered to differentiate the two?

A. People often think of toxicologists as the ones who “find the poisons.” I look at toxicology as part of the solution. Toxicology helps define conditions under which chemicals can benefit people and the environment. The most important thing to understand is that the dose makes the poison. A key aspect is the level of exposure and level of the internal dose that it results in. Certainly, the route of exposure is also important—for example, inhalation or oral administration, such as through water or food. Chemicals differ in their potential to cause adverse effects, depending on the route of exposure. That’s why it is important to mimic the human situation as closely as possible when testing a chemical’s potential adverse effect. Some individuals will be more susceptible [to a chemical] than others based on their genetic background. Nutritional status also plays a role. Overall health can play a role. But certainly, dose is most important.

Q. Can you explain epigenetics and its role in cancer formation?

A. When we think about genetics, it’s typically genes composed of DNA. We can view the genetic material like the blueprint for a building. You might have a very good, very detailed blueprint, but you cannot construct the building unless you read the blueprint properly. Epigenetics refers to the control, superimposed on DNA, of how this blueprint—the way genetic information—is read. Cancer involves the abnormal growth of cells in the body, not only as a result of damaged DNA leading to mutations, but also because of the abnormal reading of genetic material—that is, aberrant epigenetic parameters.

Q. How has your work improved risk evaluation in toxicology?

A. My research involves understanding how normal cells transform into cancer cells, and using this knowledge to make better safety assessment decisions. Our main advances have been in the understanding that susceptibility to carcinogenesis might be inversely related to the capacity for maintaining normal epigenetic parameters.

Q. What were some of your early research interests? Were you able to better pursue them after receiving the Research Starter Grant in Pharmacology and Toxicology?

A. My PhD is in pharmacology, and my thesis research focused on methyl alcohol, which is uniquely toxic to people. Studying the biochemical basis for resistant rodents, as compared with people, gave me a real appreciation for species’ differences in terms of the adverse effects of chemicals. When I finished my thesis research, I became interested in studying cancer. So I began postdoctoral research at the University of Wisconsin. I studied chemicals that had the ability to damage DNA and how, if not repaired, the damaged DNA could lead to cancer. I became aware of the increasing dichotomy between chemicals that cause cancer but don’t appear able to damage DNA directly. That was the beginning of my interest in the epigenetics of carcinogenesis. The starter grant played a key role in launching my early career. In addition to the funding, it was a pat on the back—a shot in the arm, to know that this important Foundation thought my ideas were worthy of support. I was a rather new assistant professor at Michigan State, so the grant gave me more confidence and allowed me to pursue more high-risk research. It also provided freedom to do some very important redirecting and reorienting of my research interests. Over the years, I’ve watched others who have received Research Starter Grants from the Foundation and seen their careers flourish. I think the Foundation’s program is phenomenal, and I’m really very grateful and honored to be part of the group of awardees.



Q. What components should toxicology teaching programs offer to prepare students for careers in academia, industry, and government?

A. I think the most important aspect is giving students a strong foundation in molecular biology and biochemistry, while providing solid training in physiology and basic statistics, so students don't lose sight of the whole person aspect. It's not [as simple as] knowing that a chemical affects a particular receptor or target organ. You must account for absorption, distribution, elimination.

Q. How do you envision the future of toxicology research?

A. I think things will have changed for the better. Right now, we are engaging in the third revolution of biology. The first revolution was molecular biology—the identification of genes and gaining an understanding of biology at the molecular level. The second was genomics—how genes are organized and regulated. The third revolution is a convergence of the life sciences with the physical sciences and engineering. Toxicology is embracing this. What excites me is the combination of the theoretical and the practical. While performing research to discern the mechanisms of action for a chemical of interest, we learn more about basic biology. Eventually, we will be able make better qualitative and quantitative predictions, with the understanding that mathematical models must always be based in biology.

Q. Please tell me a little about your role on the EUROTOX committee.

A. I served two 3-year terms on the Education Subcommittee. One activity was developing courses for toxicology curricula that could be used and adapted to enhance training across Europe. The other was making the annual EUROTOX meeting more inclusive of graduate and postdoctoral students. I wanted students and fellows to be a bigger part of the program, to have plenty of opportunities to meet and network [with their colleagues], and to get a general sense of

the importance of doing this at an early age. Because of my service on the subcommittee and long-term involvement, I was named an honorary member of EUROTOX in 2019.

Q. Which research project has been your most memorable, and why?

A. The first was a collaboration between my lab and Hoffmann–La Roche to test the hypothesis that epigenetic parameters would be less stable in mice sensitive to liver tumors and more stable in resistant strains. This led to important findings on the potential mechanisms of sensitivity versus resistance, and [we published] two papers that further defined the role of epigenetic parameters in carcinogenesis. These bolstered an earlier publication from my laboratory that was picked up by the Environmental Protection Agency and cited in their 2005 cancer risk assessment guidelines. The second was a joint project between my lab and the National Institute of Environmental Health Sciences (NIEHS). NIEHS was looking at the gene that encodes the constitutive androstane receptor (CAR), and had shown that knocking it out blocked liver tumorigenesis in mice. They shared some of their liver tissue with us, which provided the opportunity for a joint publication that opened the door to discerning CAR-mediated alterations in DNA methylation—an epigenetic parameter involved in regulating gene expression—during chemical-induced rodent liver tumorigenesis.

AWARDS IN EXCELLENCE



2019 Award in Excellence in Clinical Pharmacology

Janice B. Schwartz, MD

1982 Faculty Development Award in Clinical Pharmacology

Janice Schwartz, MD, is a board-certified cardiologist and professor of medicine in the Division of Geriatrics at the University of California, San Francisco (UCSF). She earned her medical degree from the Tulane University School of Medicine and completed an internship in internal medicine at Los Angeles County+USC Medical Center. Dr. Schwartz trained in cardiology and internal medicine at Cedars-Sinai Medical Center in Los Angeles. She continued her training at Stanford University in a clinical and research fellowship, focusing on the evaluation of new cardiovascular drugs.

Dr. Schwartz began her career on the medical school faculty at Baylor College, where she received the Faculty Development Award from the PhRMA Foundation. With this support, Dr. Schwartz pursued her goal to better understand drug responses among older patients. She joined the UCSF faculty as an assistant professor in 1984, accepting joint appointments in the Schools of Medicine and Pharmacy, and became a central member of the clinical pharmacology fellowship training program as an associate professor. From 1991 to 1995, Dr. Schwartz led the UCSF Gerontology and Geriatric Medicine Training Program. She

was named chief of geriatrics and clinical pharmacology at Northwestern University Medical School in 1995, and taught multiple subjects at Northwestern as a professor of medicine, molecular pharmacology, and biological chemistry. During this time, she was also associate director of the university's Buehler Center on Aging, director of the Geriatric Medicine Fellowship Program, and chair of Northwestern Memorial Hospital's Pharmacy and Therapeutics Committee.

In 2000, Dr. Schwartz returned to UCSF as core faculty for the clinical pharmacology training program and graduate training programs in pharmacy and medicine. She was appointed director of research at the San Francisco Campus for Jewish Living's Center for Research on Aging, where she is presently a visiting research scientist.



For more than 40 years, Dr. Schwartz has been immersed in understanding the body's response to drugs, particularly the impact of various medications on the autonomic nervous system and heart in older adults. Her work has greatly expanded knowledge on drug effects and interactions in the aging population, and elucidated gender differences in drug metabolism. Dr. Schwartz has been named one of medicine's Best Doctors in the United States.

As a teacher, trainer, and mentor, Dr. Schwartz is preparing the next generation of clinical pharmacologists to continue improving therapies for older patients. She is an active member of numerous medical societies and has served as president of the Society for Geriatric Cardiology and vice president of the American Society for Clinical Pharmacology and Therapeutics (ASCPT). In 2012, she received the ASCPT William B. Abrams Award in Geriatric Clinical Pharmacology.

Dr. Schwartz has also served as a consultant and subject matter expert for the U.S. Pharmacopeia Convention Advisory Panel on Geriatrics, the Institute of Medicine Committee on Pharmacokinetics and Drug Interactions in the Elderly, and the Centers for Medicare and Medicaid Services Technical Expert Panel on Chronic Disease and Preventive Services, as well as for several National Institutes of Health peer review committees. She is a member of the advisory board for At Home with Growing Older, a Bay Area nonprofit that aims to improve the lives of older adults in the community.

Dr. Schwartz's research has been widely disseminated and published in more than 140 peer-reviewed papers, supported by 35 years of continuous funding from the National Institutes of Health. She is the author of 18 book chapters, including one on treating older people with cardiovascular disease featured in three editions of Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. She has also served on the editorial boards for a number of scientific journals, including ASCPT's *Clinical Pharmacology and Therapeutics*, and is currently an associate editor of *Trends in Cardiovascular Medicine*.



AN INTERVIEW WITH JANICE SCHWARTZ, MD

1982 Faculty Development Award in Clinical Pharmacology

Q. The number of adults 60 and older is expected to double globally by 2050. What are the highest priorities for optimizing pharmacotherapy so it best fits the needs of this fast-expanding population?

A. We are at an interesting point, trying to balance the potential benefits of pharmacotherapy with the potential adverse effects of prescribing multiple medications. Our highest priority should be getting the data to determine what works in the older adult encountered in clinical practice, not just in the highly selected older adults recruited for clinical research studies. There is a longstanding problem with under-enrolling older adults in therapeutic trials—even if they make up the majority of patients who are likely to receive the medication after it is approved. The challenge is getting enough information on the typical older adult population before drugs get approved. Otherwise, you're trying to treat the patient in the real world in what we call a "data-free zone," where there's no definitive data—at least not enough to be conclusive about the benefits or risks. We're typically dealing with multiple chronic conditions and multiple medicines for older adults, yet there is no universal agreement on multidrug regimens or interactions. A patient may be taking drugs 1, 2, 3, 4, and 5, which have all been studied separately. Of those, maybe drugs 1, 2, or 3 have been studied together. But they've never all been studied together. So it's a major challenge to choose the right medicine and the right dose, with no side effects, at the right cost, all while considering multiple potential interactions and complications. It would be great to have additional point-of-care guidance on drug combinations, and I think that is something we will see in the future. It will also be important to recognize there is a spectrum across older age, so redefining the parameters around aging or older age groups may be necessary. Traditional guidelines target age 65 as "older," but big changes

happen between 65 and 75, and again over 80, when functional decline becomes more prominent. Looking only at birthdays, some people do better at their age than others. We need biomarkers for aging and function that can be incorporated into our drug evaluation process, and we need to incorporate patient goals into our therapeutic recommendations.

Q. What are the common concerns and expectations of older adults when it comes to pharmaceutical treatments?

A. Older adults want to feel and function better now and for the next few years. Most are focused on quality of life and not extension of life without good functional abilities. They do not want to be a burden. Many access the Internet and other information sources to research medications and may [value] peer concerns over the recommendations of health care professionals. Older patients are usually willing to try therapies that will relieve symptoms, but may not be as eager to start a new medication [to prevent] developing a disease. Patients usually have a good understanding of their health status and will often approach therapy in the framework of whether there will be immediate benefit or harm and whether a drug will make them feel better. Will it lengthen their life, and by how much? If the benefit is 1 or 2 more years of life, what are the tradeoffs? Maybe that's the reason for medication non-adherence in this population, especially for preventive therapies. Why take a medicine that doesn't make you feel better or help you do what you want, when you may not get the disease or live long enough to benefit from the therapy?



Q. What are the greatest challenges for health care professionals treating older adults with cardiovascular disorders?

- A.** Heart failure of a type specific to older adults is one of the biggest challenges. There's a unique kind of heart failure in older people, where the heart can pump enough blood out at rest or low workloads, but it cannot meet the demand with the stress of exercise or rapid [beating]. We call this condition heart failure with preserved ejection fraction, or HFpEF, and it is one of the most common reasons for hospital admissions among older patients. There are no proven effective therapies for HFpEF, in contrast to the multiple medications and interventions that can improve life for people with heart failure that results from coronary artery disease and heart attacks. We need drugs that target this specific problem. Another concern is managing hypertension in older adults. What are the right blood pressure numbers? How low should we go for older patients? What are the best combinations of medicines to get us there? And how can we balance the need for blood pressure medication with the need for other medicines, without increasing the risk for falls?

Q. Describe the research you were doing at Baylor when you received the PhRMA Foundation Faculty Development Award. How did it help you pursue your studies at the time?

- A.** My story will resonate with physicians who have read *The House of God*. I had been training in cardiology at Stanford, thinking about studying medicines for cardiovascular disease. My husband and I were recruited to faculty positions in cardiology at Baylor College of Medicine, but 2 weeks later, the person who recruited us left. So I picked up *NEJM* and saw this ad for Faculty Development Awards in Clinical Pharmacology from the PhRMA Foundation. It

looked like what I wanted to do—continue [studying] cardiovascular medicines in aging patients. I sought the support of my chairman and the division chief of clinical pharmacology, and we applied for the award. When I received the award, I began exploring metabolism and the changes of aging with Darrell Abernethy. We ended up working on the calcium channel blockers that have become some of our main treatments today. I learned how to do assays in the lab and experimented with a range of models. At the same time, I was mentored in grant writing and received my first NIH grant, which put my entire career on track. I guess you could say that without the PhRMA Foundation funding, I wouldn't have gotten my start.

Q. What advice would you give or have you given an early career scientist studying geriatric medicine?

- A.** There is so much potential for growth with a career in academic medicine. It is a wonderful pathway with endless possibilities. You can investigate what's important to you or important to the world. This kind of flexibility, where you can be both intellectually stimulated and changing things for the better is not something you'll find everywhere. I would say the idea is finding something you really love—something you think about in your free time because it fascinates you—and then seeking out the best place to work and the best people to work with. It's also important to know that what you want to do is going to change over the course of your career. You have to realize ahead of time that your choices are not permanent or fixed. We need flexible tracks, especially for women and young people, because our lives change, and our responsibilities change too. I'm working at a time when I think my predecessors would have already retired. Many of my colleagues are also working way past [typical] retirement ages because they love what they do.

CULTIVATING THE NEXT GENERATION OF VALUE ASSESSMENT



As value assessment continues to galvanize the health care industry in an unprecedented way, traditional methods for attempting to measure the value of treatments and interventions are expanding to embrace new benchmarks. Once characterized by volume, speed and single-size solutions, health systems are starting to re-evaluate longstanding notions of what constitutes good care. Wellness and quality are no longer buzzwords but standards to which treatments can be held.

The PhRMA Foundation has made great strides in advancing innovation in methods in value assessment. Over the past three years, the Foundation has championed the integration of patient voices in value assessment research and has funded efforts to broaden conversations around value and ensure that health care decisions are transparent and address the needs of all health care stakeholders, including patients, payers and providers.

With support from the PhRMA Foundation's Value Assessment Initiative, four Centers of Excellence are exploring novel ways to capture and measure value in health. The centers promote research, innovation, and the development of tools and partnerships that advance value-driven decision-making and patient-centered care models

The Center for Patient-Driven Value in Healthcare Assessment (PAVE) - University of Maryland School of Pharmacy, Baltimore, Maryland.

PAVE is a unique collaboration between the University of Maryland School of Pharmacy, the National Health Council, patient community leaders, and payer and industry leaders that is dedicated to developing and advancing new methods to incorporate the patient perspective into value assessment and value-based decision-making. For the past several years, PAVE has been working to build a diverse and extensive network of partners to build technical expertise in patient-centered health outcomes research, education, and dissemination.

PAVE's current research aims include identifying the factors most important to people living with chronic diseases, including chronic obstructive pulmonary disease (COPD) and Hepatitis C, and working to develop novel value elements that can be incorporated into economic evaluations of health care treatments. PAVE is also working to expand minority and underserved patient populations' capacity to engage in value assessment through direct outreach to Hispanic communities in the Baltimore-Washington Metropolitan region.





Research Consortium for Health Care Value Assessment (Value Consortium)
- Ann Arbor, Michigan

The Value Consortium is a partnership between Altarum and VBID Health that aims to promote the pursuit of value in health care delivery within the U.S. by identifying high-and low-value clinical services, tracking the use of such services, and helping to ensure that consumer and patient preferences are incorporated into the health care decision-making process.

This year, the Value Consortium completed two major research projects. The first tracked the under-utilization of five high-value services and inappropriate use of five low-value services by a commercially insured population in order to determine the extent to which, if at all, spending is shifting from low-value to high-value care. A second project extended this tracking framework of low-value care to a set of 20 services and developed both national and state-level estimates of low-value use of these services. The Consortium also developed a Low-value Care Visualizer tool meant to help large organizations better understand their health care spending and identify where low-value care is most prevalent.

Identifying and measuring low value care is just one component of the Value Consortium's mission to align health care spending with value. Researchers at the Value Consortium are also working to communicate key findings through an ongoing series of concept papers that rationalize a wider use of evidence-based frameworks, reduce the use of low-value care, and address the barriers that complicate those efforts.

Center for Pharmaceutical Value (pValue)
- University of Colorado Anschutz Medical Campus, Aurora, Colorado

Researchers at pValue are advancing innovative value assessment methods that better account for elements of value that matter most to patients. Specifically, pValue aims to quantify criteria involved in health decision-making using multi-criteria decision analysis (MCDA). MCDA comprises various methodologies in which elements of value not traditionally captured in value assessment can be selected, structured, weighted and mapped to a framework — offering decision makers a flexible tool with both qualitative and quantitative applications.

pValue is also working to educate stakeholders who can benefit from utilizing MCDA in value assessment. Given the flexibility and adaptability of its potential applications in health care, MCDA could contribute to more balanced, value-based decisions on pharmaceutical coverage and reimbursement.





*The Center for Enhanced Value Assessment (CEVA)
- Tufts Medical Center, Boston, Massachusetts*

CEVA aims to explore the incorporation of non-traditional elements of value into cost-effective analyses and provide a more holistic view of value to decision makers across the health care spectrum. Recognizing that traditional measures of value do not fully capture patient and societal well-being associated with health, such as disease severity, equity of access, or unmet need, CEVA is working to engage stakeholders – including patients, health insurers, and therapeutic area leaders – to identify important novel and non-standard elements to inform coverage, reimbursement, and access decisions.

Bringing Stakeholders Together

In addition to providing financial support to researchers working to broaden the conversation around value, the Foundation is also working to convene stakeholders from across the value-assessment community. On November 12, 2019, the PhRMA Foundation hosted more than 100 health economics researchers, scientists, association leaders and patient advocates in Washington, D.C. at a conference dedicated to discussing how best to connect the latest value assessment research with practical applications for health care decision-making.

This conference, which was led by the Foundation's four Centers of Excellence in Value Assessment, provided an opportunity for stakeholders to hear directly from the

Foundation's grant recipients and learn more about the work they are doing to overcome the limitations to current value assessment methodologies and highlight new approaches that embrace the patient perspective.

The voices of leading patient advocate organizations were also represented, many of whom stressed the need to involve patients in the value assessment process from the very beginning to help reduce health inequalities.

"For the disability community, a lot of [this] is patient education," said Karl Cooper, Director of Public Health Programs at the American Association on Health and Disability. "We need to educate the patient about the process and let them understand how the calculations are done."

Others noted that patient-centered value frameworks must also reflect the needs and interests of those they stand to benefit most.





“It isn’t just heterogeneity with regard to choice and patient preference,” said Leah Howard, Chief Operating Officer of the National Psoriasis Foundation, “but also with regard to how therapies work, and the response of individual patients.”

“We know that approximately 30 percent of people with psoriasis may go on to develop psoriatic arthritis at some point, as well as other comorbidities requiring multiple treatments. We need to think about the whole health of the individual patient and not just this one particular characteristic of their health,” said Ms. Howard.

With all that has been learned thus far about the potential of evidence-based, transparent frameworks, it is more important than ever to ensure all stakeholders can share their knowledge. To that end, the PhRMA Foundation is exploring the creation of a digital repository of validated outcomes and measures for scientists immersed in the work of value assessment. Access to a database of validated patient-centered methodologies and strategies will bring the field one step closer to widespread implementation of value assessment and a holistic health care system that puts patients first.



Knowledge, Transparency, and Implementation

More stakeholders are joining the effort to make value assessment a comprehensive, inclusive process, but there are still areas where a clear voice is missing. With more than 60 percent of U.S. adults covered by workplace health insurance, employers have a predominant role in health decision-making and the health of their employees. Therefore, value frameworks that reflect the needs of employers and its employees have the potential to reduce spending, improve productivity and generate better outcomes.

To become part of daily practice in all health settings and systems, value frameworks must be logical and adaptable, built on solid evidence and with sound methods. Certain objectives should also be inherent in the framework-building process: improving outcomes, reducing costs, ensuring equity and honoring patient preferences.



2019 CENTERS OF EXCELLENCE

In 2019 two new national Value Assessment Centers of Excellence were established. These multi-disciplinary centers will promote research, innovation, and the development of tools and partnerships that advance value-driven decision making and patient-centered care models. Each Center received a \$500,000 grant over a funding period of three years. The PhRMA Foundation is now funding four Centers of Excellence.

“The PhRMA Foundation Center of Excellence award in novel value assessment, alongside matching financial support from Data Science to Patient Value initiative at University of Colorado, provides our team the opportunity to pursue creative and groundbreaking scholarship and training at the cutting edge of our field. This award is a testament to the cohesion within our investigator team. We are grateful to build off of this award with the continued goals of generating evidence to improve population-level decision making and health.”

Jonathan D. Campbell, PhD

University of Colorado Anschutz Medical Campus Center Director | pValue Center of Excellence



From left to right:

Melanie D. Whittington, PhD; R. Brett McQueen, PhD; and Jonathan D. Campbell, PhD.

“Center of Excellence for Pharmaceutical Value (pValue)”

Pharmaceutical Value (pValue) – headquartered within the University of Colorado’s Anschutz Medical Campus – aims to apply and test novel methods for value assessment that encourage stakeholder engagement and promote value-based decision making. pValue is a recipient of the PhRMA Foundation’s Value Assessment Initiative Centers of Excellence Award.

Traditional measures of value used in cost-effectiveness analyses are not, by definition, fully comprehensive or sufficiently flexible to allow for the inclusion of all the criteria that patients, payers, clinicians, or other health care stakeholders care about. Multi-criteria decision analysis (MCDA) offers a scientifically rigorous decision-making tool capable of including multiple criteria that are important to stakeholders. MCDA has been applied in a variety of sectors, such as investment banking and environmental management, but applications in U.S. healthcare decision making have been limited.

MCDA can improve decision making in health care by engaging key stakeholders and by capturing and weighing criteria not found in traditional measures of value, for example severity of disease, quality of evidence, and family burden. By encouraging a comprehensive understanding of value, MCDA offers an opportunity to systematically weigh non-traditional aspects of value that fall outside traditional measures of value.

The University of Colorado’s Pharmaceutical Value (pValue) initiative is exploring how MCDA can add evidence on value to improve decision making in health care.

“While cost-per-QALY analyses provide a useful starting point for discussion about the value of interventions, we know that some aspects of health that matter to patients and other stakeholders may not be well captured. CEVA is working to understand how to incorporate such aspects and how much difference they make in value assessments.”

Peter J. Neumann, ScD

Tufts Medical Center | Center Director | CEVA Center of Excellence



From left to right:

David Kim, PhD; Anna Legassie; Natalia Olchanski, PhD; Joshua Cohen, PhD; Daniel Ollendorf, PhD; Peter Neumann, ScD, and Madison Silver.

“The Center for Enhanced Value Assessment (CEVA)”

The Center for Enhanced Value Assessment (CEVA) sits within the Center for the Evaluation of Value and Risk in Health (CEVR) at Tufts Medical Center and serves as a platform to focus on a relatively recent phenomenon: namely, the proliferation of health technology value assessment frameworks in the United States. CEVA's mission is to explore the quantitative implications of incorporating non-traditional value elements into cost-effectiveness analyses. CEVA will also characterize stakeholder preferences related to novel value elements through the engagement of patients, health insurance companies, and therapeutic area leaders. By seeking to account for all elements of value that matter to decision makers, CEVA will help decision makers as they consider coverage and reimbursement of new technologies. CEVA has four broad aims: 1) quantify the extent to which published CEAs include broader elements of value; 2) develop case studies to incorporate broader elements of value into existing CEA models; 3) conduct a patient and stakeholder survey; and 4) create a user-friendly “dashboard” display. In the first year of the project, we analyzed more than 8,000 studies catalogued in the Tufts Medical Center's CEA Registry (a database of cost-per-quality-adjusted-life-year [QALY] studies) and in the Global Health CEA Registry (a database of cost-per-disability-adjusted-life-year [DALY] studies) to determine how often published CEAs have included novel elements like patient time, transportation costs, productivity, and other non-healthcare sector impacts. We compared the cost-per-DALY and cost-per-QALY literature with regard to their inclusion of these elements, the perspective used, and intervention types. Results show that the health care sector perspective was most prevalent in the CEA literature, but many studies have not clearly stated the perspective used. This work was featured in presentations at several conferences in 2019, including the International Health Economics Association (Basel), the Society for Medical Decision Making (Chicago), and the PhRMA Foundation-National Health Council Conference on New Approaches to Value Assessment (Washington, DC). We are in the process of conducting several case studies to quantify the impact of including novel value elements, such as the value of hope, insurance value, option value, and caregiver impact.

2019 RESEARCH AWARDS

Value assessment in health care comprises a broad set of methods to synthesize and evaluate the relative benefits and costs of health care interventions. The goal of value assessment is to assist stakeholders, including patients, providers and payers, in making informed decisions to improve health and care efficiency. The PhRMA Foundation sought proposals to identify and address challenges in research conducted to assess the value of medicines and health care services. The following researchers were selected in 2019.

“My colleagues and I hope that these three policy analyses will help us to move beyond the QALY to a broader concept of the value of innovative medicines that enables our global research and development enterprise to better reward innovation that efficiently improves global population health.”

Louis Garrison, PhD | University of Washington, US



Louis Garrison, PhD

University of Washington, US



Adrian Towse, MA, MPhil

Office of Health Economics, UK



Bernarda Zamora, PhD

Office of Health Economics, UK

“Implementing Augmented Cost-Effectiveness Analysis: Challenges and Next Steps”

In its 2018 report, the ISPOR Special Task Force (STF) on U.S. Value Assessment Frameworks recommended using the quality-adjusted life year (QALY) as a starting point for health technology assessment of new medicines, and also recommended further work on the best way to incorporate it by exploring the use of “augmented cost-effectiveness analysis” (ACEA) and “multi-criteria decision analysis” (MCDA). In our proposal, we laid out a research agenda of nine potential topics to support further development of ACEA. Based on input from the reviewers and colleagues, we selected three topics for analysis. Our first policy analysis paper is titled: “Aligning Value Assessment Frameworks for Medicines across Decision Contexts: The Case for Using the Quality-Adjusted Life Year (QALY) as the Core Element.” The STF emphasized the importance of “decision context” in thinking about how the health system assesses value. We discuss four decision contexts that can be viewed as a cascade: regulatory approval, inclusion in the health plan benefit package, management of health benefits and utilization, and finally, clinical shared decision making. We argue that for the efficient use of new medicines at a system level, these decisions should be aligned in a manner that promotes their efficient interaction, and that the metric of the QALY can provide the backbone that connects and aligns these contexts. Our second paper is titled: “Reconciling ACEA and MCDA: Is There a Way Forward for Measuring

Cost-Effectiveness in the U.S. Healthcare Setting?” We explore the idea of a “QALY-anchored” MCDA and compared with a form of ACEA where elements of value are either classified as health or consumption attributes—and ultimately monetized. We argue that trade-offs derived from an ACEA and a QALY-anchored MCDA model are similarly affected by budget changes; and they are aligned and would result in similar decisions. Our third paper is titled: “Applying ACEA to Innovative Medicines for Rare and Ultra-Rare Health-Catastrophic Conditions.” Here we argue that due to greater uncertainty and the potential for financial and health catastrophe, there would be greater insurance value in this situation. This would imply the need to add additional value beyond the QALY—in effect, applying a higher societal willingness-to-pay threshold.

“I am truly grateful and honored to be part of the PhRMA Foundation’s Value Assessment Initiative. The Value Assessment Research Award has allowed me to focus my research on values, preferences, and outcomes that are directly relevant to patients as well as to financially support the Postdoctoral Fellowship program in Pharmacoeconomics and Health Outcomes Research at our institution.”

Quang A. Le, PharmD, PhD | Western University of Health Sciences



Quang A. Le, PharmD, PhD

Western University of Health Sciences

“Value Assessment of Health Interventions using Doubly Randomized Preference Trial (DRPT) Design”

Randomized clinical trial (RCT) is the gold standard in research. While continuing to remain the most robust method to obtain quality data for efficacy and safety, RCT assumes clinical equipoise and removes the most important factor in how medical care is actually delivered; i.e., by choosing one among alternative options. A significant limitation of the traditional RCT is that strong preferences for (or against) one treatment may influence outcome and/or willingness to receive treatment. If preference is a moderator, then the treatment may be maximally effective and/or adherent for those who prefer it and minimally effective and/or adherent for those who do not. In fact, health outcomes may depend on which treatment is received (treatment effect), whether choice of treatment is given (choice effect), whether a received treatment is the preferred therapy (preference effect), and whether a specific treatment is preferred (selection effect). The current recommendations for the U.S. Value Assessment Frameworks by the International Society for Pharmacoeconomics and Outcomes Research Special Task Force emphasized that the patient perspective and preferences needed to be reflected in all discussions in assessing the value of health care. With a doubly randomized preference trial (DRPT) design, the effects of choice, preference, and selection may be separated from the effect of treatment on health outcomes; thus, it can provide important information to further improve health outcomes. This project will formalize methods to estimate treatment, choice, preference, and selection effects in DRPT design and evaluate these effects on health-related quality-of-life outcomes using data from a clinical trial using DRPT design for treatment of posttraumatic stress disorder. The findings will be important, especially in the current U.S. value-assessment frameworks, and help to enable more application of the DRPT design for assessing value of health interventions.

“It’s important to note that researchers who work on RWD studies are not expected to be the ones collecting the patient-provided information. That information, collected by others, can be leveraged by RWD researchers who are skilled at working with large data sets, but might not be experienced with patient engagement.”

Eleanor M. Perfetto, PhD, MS | National Health Council



Eleanor M. Perfetto, PhD, MS

National Health Council

“Methods Principles for Using Patient-Provided Information to Improve Real-World Evidence for Patient-Centered Value Assessment”

Despite growing availability of real-world data (RWD) sources, concerns over bias, confounding, and lack of universally accepted methodological standards inhibits uptake of real-world evidence (RWE) by value assessment bodies (VAs). To improve the quality and patient-centricity of RWE, the Joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-International Society for Pharmacoepidemiology (ISPE) Special Task Force on RWE in Health Care Decision Making included patient/stakeholder engagement as one recommended good-procedural practice when designing, conducting, and disseminating RWE. The objective of this project was to develop research-methods, good-practice recommendations on how and at which RWD study-design stage, patient-provided information (PPI) (e.g., experiences, preferences, perspectives, desired outcomes, etc.) should be used by researchers. Specifically, the project sought to identify how to use PPI to inform methods decisions (e.g., covariate identification, meaningful outcomes, etc.) to improve the rigor of RWE for use in patient-centered VA. A multi-disciplinary Advisory Board was established to guide the development and dissemination of recommendations. RWE-researchers (n=15) were presented with case studies (hypothetical research question and PPI) and asked to identify how they could apply PPI to study-design decisions using an RWE research-design framework. Interview responses were analyzed and translated into draft recommendations. A multistakeholder e-Delphi panel was assembled and draft recommendations were adapted into an e-Delphi survey to gain consensus on good-practice recommendations. Seventeen preliminary recommendations were identified and are currently being refined through an e-Delphi survey. Recommendations fall into key themes, including “Developing a Refined Research Question,” “Developing a Research Protocol,” and “Translation Phase.” Final recommendations will be described in an upcoming report. Applying PPI when designing studies will improve the rigor of RWE because study decisions will be based on patients’ lived experiences instead of researcher or clinician assumptions. PPI-informed RWE will contribute to a patient-centered evidence base to inform patient-centered VA.

2019 CHALLENGE AWARDS

The Challenge Awards program pursues papers that describe solutions to a pressing question related to value assessment in health care. In 2019, the Foundation sought papers that offered alternatives to the quality-adjusted life year (QALY) measure by asking: **What are innovative, patient-centered approaches to contribute to health care value assessment that move beyond the inherent limitations of analyses based on the quality-adjusted life year metric?**



Lori Frank, PhD
RAND Corporation



Thomas W. Concannon, PhD
RAND Corporation

“Optimizing Representativeness and Enhancing Equity through Patient-Engaged Healthcare Valuation”

In their Challenge Award submission, Lori Frank and Thomas W. Concannon of the RAND Corporation addressed an important topic: ensuring equitable and representative inclusion of patient views in valuation of healthcare interventions. To address this challenge, they propose incorporating new methods into existing value frameworks and health technology assessment. Specifically, they propose a three-part Strategy for Patient-Engaged Health Valuation: 1) establish large, standing patient stakeholder panels, with members trained in decision-analytic methods; 2) use crowd-sourcing to enhance patient engagement in valuation work; and 3) actively adopt patient-engaged multi-criteria decision analysis (MCDA) in health technology assessment. Their proposal brings active patient engagement into the healthcare valuation process, and addresses the ethically critical question of who is “representing” whom in deliberations. A unique element of the strategy is creating a connection between patient input and the deliberative process using a form of Goal Attainment Scaling, allowing for a range of patient-important outcomes to be captured early in the process.



Charles E. Phelps, PhD

University Professor and Provost Emeritus, University of Rochester

“Expanding Use of Multi-Criteria Decision Analysis for Health Technology Assessment”

In his paper, “Expanding Use of Multi-Criteria Decision Analysis for Health Technology Assessment,” Professor Phelps discussed potential benefits of using multi-criteria decision analysis (MCDA) to assess value in health care. MCDA can include many dimensions of value that standard cost-effectiveness analysis cannot capture. At organizational or societal levels, these include features such as focus on disadvantaged populations, scientific spillover possibilities, “fit” with local health care systems, and others. At individual or societal levels, MCDA can include such values as “insurance” (reducing financial or health outcome uncertainty), “hope” (increased chances of highly beneficial outcomes) or “option value” (staying alive until a true cure is found).

Professor Phelps also emphasized the need to improve MCDA models’ usability, both for individual decision-makers (e.g., patients choosing among available therapies) and in groups that advise or make organization decisions (e.g., coverage determinations, investments in new services). Key among potential improvements are reduced user-burden, and (in groups) voting methods that both work well and provide user with a rich vocabulary of ways to express their preferences.



Surachat Ngorsuraches, PhD

Associate Professor, Department of Health Outcomes Research and Policy, Harrison School of Pharmacy, Auburn University

“Using Patient Experience Data and Discrete Choice Experiment to Assess Values of Drugs”

Dr. Ngorsuraches proposed a patient experience value framework that utilizes patient experience data, generated by using FDA guidance, to develop discrete choice experiments (DCEs) to assess the value of drugs and account for heterogeneity of patient preferences. This framework is an approach to value assessment that is more centered on patients and moves beyond the use of the quality-adjusted life-year (QALY) metric. He described the application of this framework to assess the value of disease-modifying therapies for multiple sclerosis.



Darius N. Lakdawalla, PhD

Quintiles Chair in Pharmaceutical Development and Regulatory Innovation
at the School of Pharmacy and the Sol Price School of Public Policy,
University of Southern California



Charles E. Phelps, PhD

University Professor and Provost
Emeritus, University of Rochester

“A New Method to Incorporate Uncertainty into Healthcare Technology Evaluations”

In “A New Method to Incorporate Uncertainty into Healthcare Technology Evaluations,” Professors Lakdawalla and Phelps explain and illustrate with extensive graphs and figures their new approach to incorporating measures of uncertainty about treatment effects into formal measures of their value. People dislike uncertainty, and are willing to pay to reduce uncertainty, as extensive markets for insurance prove. Lakdawalla and Phelps show how to formally incorporate uncertainty in health outcomes of medical treatments, directly assessing the value gained from reduced uncertainty in addition to average improvements in health that are commonly used in health technology assessments. They also show that unusually large chances for beneficial outcomes can also boost a treatment’s value, in addition to average benefits, and even after adjusting for changes in the uncertainty of health outcomes (variance). These measures of uncertainty in health outcomes from medical interventions will likely become increasingly important in the future as incremental gains in average outcomes decline through the steady advance of medical progress.

A close-up photograph of a person with dark hair, wearing a white lab coat and blue nitrile gloves, looking through the eyepieces of a white and black compound microscope. The person's face is partially visible, showing concentration. The background is a blurred laboratory setting.

FELLOWSHIPS AND GRANTS

HEALTH OUTCOMES

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

2019 PREDOCTORAL FELLOWSHIPS IN HEALTH OUTCOMES

With a focus on health care 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 Predoctoral Fellowships in Health Outcomes seek to increase the number of trained investigators studying all aspects of drug therapies by providing a stipend to students two years away from completing doctoral dissertations.

“The PhRMA Foundation's Predoctoral Fellowship in Health Outcomes really allowed me to focus on my dissertation while also juggling the responsibilities of motherhood. In addition, it helped me to fund data access and analyst time at a local health maintenance organization. I have been able to attend conferences to network with other researchers in the value-based insurance design field and consider different facets to my research questions.”

Elizabeth D. Brouwer, MPH | University of Washington



Elizabeth D. Brouwer, MPH

University of Washington

“Characterizing Copay Coupon Use Among Specialty Drug Claims”

As increasing portions of specialty drug costs are passed on to patients through specialty drug tiers, there is concern that high cost-sharing is adversely affecting patient access and adherence to essential medication. The current literature on pharmaceutical cost-sharing largely overlooks the use of copayment assistance programs, also referred to as “copay coupons,” in which drug manufacturers supplement patient out-of-pocket (OOP) costs. Because information on copay assistance is not captured in standard pharmacy claims data, its prevalence and impact are not well understood, and its omission from price-elasticity discussions likely distorts general understanding of patient behavior and incentives. This study examines copayment assistance among multiple sclerosis (MS) drug users and the effect of this assistance on drug demand in a managed care plan. Specifically, this work will characterize the prevalence of copayment assistance for users of seven MS specialty drugs and then measure price elasticity of demand using a two-part model at the patient-drug-month level. Demand will be measured by first predicting the probability of any claim and then the number of days supplied, given a claim was made. The results should inform the role of cost-sharing for specialty drugs considering industry-funded copayment assistance, and whether cost-containing strategies such as value-based insurance design could be feasibly applied to high-price specialty medications.

“I am very grateful for the support of the Predoctoral Fellowship in Health Outcomes from the PhRMA Foundation. This award has provided me the opportunity to devote my time to my dissertation and accelerate my progress in research.”

Huey-Fen Chen, MHA | University of Michigan



Huey-Fen Chen, MHA

University of Michigan

“Cost-Effectiveness Analysis and Budget Impact Analysis of Newborn Screening and Treatment of Spinal Muscular Atrophy in the United States”

Newborn screening combined with treatment can be extremely effective in diagnosing and treating children with rare pediatric disorders before symptoms are present, saving lives and improving long-term health outcomes. Spinal muscular atrophy (SMA), a rare pediatric disorder, was recommended for national screening in the United States in July 2018. However, the high cost of the only available drug treatment (nusinersen) and a potential future gene therapy (onasemnogene abeparvovec-xioi) raises the question of whether newborn screening for SMA will be economically attractive while maximizing patient benefits. The objective of this study is to evaluate the cost-effectiveness and budget impact of newborn screening and treatment for SMA in the United States. This study will use decision analysis and simulation modeling: A state-transition model will be developed to simulate the progression of newborns with SMA, and different intervention strategies of newborn screening and treatment of SMA will be evaluated. Utilizing a modeling approach as a form of evidence synthesis is an important approach for leveraging the scarce data available for rare pediatric disorders. The results of this study will provide crucial information for public and private health plan decision makers. In particular, results from the budget impact analysis will provide information for states that are planning or in the process of implementing newborn screening for SMA. In addition, the model developed will also serve as a reference for other countries considering newborn screening and treatment of SMA and for related policy or drug reimbursement decisions, and it could be modified for other countries to conduct an analysis using their local data.

“I am honored to be a recipient of the PhRMA Foundation Predoctoral Fellowship in Health Outcomes. This award has been instrumental for advancing both my research and professional development. It has allowed me to focus my efforts on completing my dissertation work, pursue additional trainings as needed, and disseminate my work’s findings through publications and academic conferences.”

Kimberly M. Deininger, MPH | University of Colorado



Kimberly M. Deininger, MPH

University of Colorado

“Clinical Utility of Pharmacogenomics in Solid Organ Transplantation”

A major obstacle impeding the translation of pharmacogenomic testing, also known as drug-gene testing, to the transplant setting is the lack of data demonstrating its clinical utility, or its relevance and usefulness in post-transplant care. To address this gap in knowledge, this study will use a multifaceted approach to evaluate the clinical utility of pharmacogenomic testing following solid organ transplantation. First, this study will evaluate provider perspectives regarding the clinical utility of pharmacogenomic testing in kidney, liver, lung, and heart transplantation using a national web-based survey. Second, this study will estimate the association between time in therapeutic drug range for tacrolimus, a commonly used immunosuppressant post-transplant, and acute kidney injury or acute organ rejection, in kidney, liver, lung, and heart transplant recipients in the first six months post-transplant. Finally, this study will conduct a cost-effectiveness analysis comparing tacrolimus-induced adverse effects and short-term costs associated with pharmacogenomic-guided therapy vs. standard-of-care guided therapy in kidney, liver, lung, and heart transplant recipients. Together, this study will address a major unmet need in the transplant community – evaluation of the clinical utility of pharmacogenomic testing – and will help advance personalized treatment strategies in solid organ transplant recipients.

“The PhRMA Foundation Predoctoral Fellowship in Health Outcomes helped me to devote my full concentration to my dissertation project and research activities. I am really grateful to the PhRMA Foundation for this fellowship, which will surely help me as an independent researcher in my future endeavors.”

Ahmed Ullah Mishuk, BPharm, MS | Auburn University



Ahmed Ullah Mishuk, BPharm, MS

Auburn University

“Systematic and Comprehensive Study of the Utilization and Safety of Proton Pump Inhibitors (PPIs) Among United States Population”

In the United States, PPIs are among the highest-selling classes of drugs, but their utilization patterns and safety profile evaluation among patient subgroups is limited. The overall objective of this research is to systematically and comprehensively assess the safety of post-marketing use of PPIs among the real-world population living in the United States. In this study, multiple population

level datasets and medical literature will be used: In aim 1, a retrospective, serial cross-sectional analysis using the 2002-2015 Medical Expenditure Panel Survey will be conducted to assess the trends, expenditure, and factors affecting the use of PPIs in the United States population. In aim 2, FDA Adverse Events Reporting System data (2004-2018) will be used to detect safety signals of PPIs through disproportionality analysis and Medicare claims data (2013-2016) will be used to identify risk factors and high-risk populations associated with PPI-related AEs among new users of PPIs. Finally, a comprehensive systematic review and meta-analysis, consisting of different level of evidence, will characterize how the magnitude of specific risks associated with PPI-use compare across hierarchical evidence. Findings in distributions of PPI-use, factors and cost associated with PPI-use, and factors related to PPI-related AEs will provide a thorough assessment of PPI use among the United States population overtime, which in turn, will guide policymakers to improve the cost-effectiveness assessment and appropriate use of PPIs.

“I am extremely grateful to the PhRMA Foundation for making its Predoctoral Fellowship in Health Outcomes available to international students, like myself, to obtain funding for their dissertation research. The support I have received as a Predoctoral Fellow has allowed me to hone my skills as an independent researcher by giving me the opportunity to focus my time on my dissertation research. The goal of which is to translate evidence obtained from randomized controlled trials to real world data in order to improve the health outcomes of youth diagnosed with depression.”

O'Mareen Spence, MPH | University of Maryland Baltimore



O'Mareen Spence, MPH

University of Maryland Baltimore

“Early Symptom Improvement as a Predictor of Antidepressant Response in Youth Diagnosed with Depression: Translating Evidence from Randomized Controlled Trials to Community Practice”

Over half of children and adolescents diagnosed with depression do not respond to an antidepressant. A critical barrier to improving treatment response is that the translation of clinical trial evidence into population outcomes is lacking. Rich data from pediatric antidepressant randomized clinical trials (RCT) are underutilized to predict response in pediatric outpatient settings. This research applies a Bayesian approach to pediatric antidepressant RCT data to investigate symptom changes early in treatment that predict initial and sustained response among children and adolescents diagnosed with depression. Combined-sample multiple imputation is implemented to impute symptom change measures in outpatient data. The prediction model from the RCT data is then applied to community outpatient data for a pediatric cohort with depression. In the outpatient data, this project will test whether a youth with a high probability of response is less likely to augment the antidepressant with another psychotropic. Here, treatment augmentation is a proxy for treatment non- response. The ultimate goal is to translate response prediction from RCTs to community practice for more effective depression management in pediatric populations. This project will answer the question, “Who would benefit, and when, from antidepressant treatment?” The scientific impact will be advancing translational research of clinical efficacy data to population outcomes.

2019 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.

“I am very thankful for the PhRMA Foundation Health Outcomes Research Starter Grant. This award has provided me with the support I need to eventually obtain a career development award from the National Institutes of Health, which is essential for me to successfully pursue a career as a physician-scientist.”

Horacio A. Duarte, MD, MS | Seattle Children's Research Institute



Horacio A. Duarte, MD, MS

Seattle Children's Research Institute

“Health Policy Modeling to Address Maternal HIV Pretreatment Drug Resistance in Kenya”

Treatment for HIV, known as antiretroviral therapy (ART), first became available in sub-Saharan Africa in the early 2000s. Since then, ART programs have delivered treatment to more and more people living with HIV over time, resulting in great strides in improving the health of this population, reducing the transmission of HIV, and reducing HIV death rates. However, one major challenge ART programs face is that as the availability of ART in resource-limited settings has increased, the prevalence of HIV drug resistance has also increased. This could decrease the effectiveness of ART programs because drug resistance decreases the probability that ART will effectively fight the HIV virus in the patient's body. While this poses challenges for all patients living with HIV, it is especially important to address HIV drug resistance in women of reproductive potential, in order to decrease mother to child transmission of HIV. The goal of this research project is to expand an existing Kenya-based HIV simulation model to project the population-level costs and health benefits of potential strategies to address HIV drug resistance in women of reproductive potential. This work can provide policy makers with valuable data to inform the allocation of limited resources aimed at improving the treatment and prevention of HIV in Kenya.



Satya Surbhi, PhD

University of Tennessee Health Science Center

“Improving Adherence Through Full Subsidy and Direct Delivery of Essential Medications for Medicaid Super-Utilizers”

Medication nonadherence is a major barrier to achieving optimal treatment goals. A preliminary analysis showed that only 20.5% of Medicaid super-utilizers (beneficiaries with frequent hospitalizations incurring high health care costs) were adherent to their chronic disease medications following a hospital discharge. Vulnerable patients experience major gaps in care during and after transitions from hospital to community setting. They are often unable to fill all prescriptions immediately after hospital discharge and have poor medication adherence over time. Major barriers to medication adherence after hospital discharge among super-utilizers are financial, transportation, and system-level barriers (not being given all necessary medications prior to discharge). Strategies such as eliminating medication copays and providing medications at hospital bedside and through home delivery improve medication adherence. However, these strategies have not been rigorously assessed in Medicaid super-utilizers. This study is a pilot randomized controlled trial among 60 hospital inpatients in Memphis, Tennessee. Study participants will be randomized to: 1) usual care, 2) full medication subsidy, 3) bedside delivery at discharge and home delivery of medications, or 4) full medication subsidy and bedside delivery and home delivery of medications. The study will examine the impact of these interventions relative to usual care over 3 months on 1) medication adherence, 2) hospitalizations, 30-day readmissions, and ED visits, 3) health care costs, and 4) patient-reported quality of life. By directly addressing the major financial, transportation, and system-level barriers to medication adherence, this pilot study will demonstrate the feasibility of these approaches to improve medication adherence and quality of life while reducing preventable inpatient and ED use and costs among Medicaid super-utilizers.



TRANSLATIONAL MEDICINE AND THERAPEUTICS

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

2019 POSTDOCTORAL FELLOWSHIPS IN TRANSLATIONAL MEDICINE AND THERAPEUTICS

The PhRMA Foundation Postdoctoral 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.

“Being awarded the PhRMA Foundation Postdoctoral Fellowship in Translational Medicine and Therapeutics was a great achievement in my early career development. The Foundation has given me the courage and support to start building a career in academia as an independent scientist in the field of quantitative pharmacology, which has always been my dream professional goal.”

Maria Garcia-Cremades Mira, PhD | University of California, San Francisco



Maria Garcia-Cremades Mira, PhD

University of California, San Francisco

“Individual Level Data Meta-Analysis from HIV Pre-Exposure Prophylaxis (PrEP) Clinical Trials”

There are approximately 1.8 million new HIV infections occurring each year. To reduce the risk of infection, the World Health Organization recommends people at high-risk use pre-exposure prophylaxis (PrEP) therapy. Tenofovir has proven efficacy in lowering the probability of HIV infection in high-risk populations. However, the prophylactic concentration of tenofovir has not been reliably characterized using HIV outcome as the main endpoint and with large databases including different populations at high-risk of infection. Identifying characteristics of high-risk individuals and predictors of infection within these target populations is essential to improve PrEP access, use, and efficacy and to curb HIV transmission. This research aims first to develop an algorithm to quantitatively estimate an individual's risk of HIV infection and second to describe the concentration-response relationships of tenofovir in plasma and effect sites (cells and tissue), adherence, and other influential variables in PrEP therapy, through the development of comprehensive pharmacokinetic-pharmacodynamic (PKPD) models. Data from 13,727 individuals obtained from large PrEP randomized controlled trials (iPrEX, VOICE, Partners, Bangkok and TDF2) with multiple HIV risk groups (men and transgender women who have sex with men, young women at high sexual risk, HIV negative partner of serodiscordant heterosexual couples, people who inject drugs, and high-risk heterosexual individuals) involving treated (oral and topical vaginal dosing) and placebo arms will be used. The resultant PKPD framework will

provide a quantitative understanding of HIV risk in target populations and estimate the target in vivo drug concentration to prevent HIV infection. These models could be used to optimize prevention strategies, to guide future PrEP clinical trials, and to inform the development of new PrEP formulations.

“I am thankful to receive the PhRMA Foundation Fellowship at this juncture in my training. The support from the PhRMA Foundation will grant me more resources to generate a detailed and accurate model of human breast cancer. I am excited for the opportunity to advance my career as an early independent researcher while performing higher-impact experiments.”

Arun J. Singh, PhD | Oregon Health and Sciences University



Arun J. Singh, PhD

Oregon Health and Sciences University

“Manipulating the Tumor Microenvironment in Hormone-Receptor Positive Breast Cancer to Increase Immune Surveillance”

Breast Cancer is a leading cause of cancer-related mortality in women, with an estimated 250,000 new invasive cases, and 40,000 deaths in 2017 in the United States alone. The hormone receptor-positive subtype (HRBC), which expressed the estrogen receptor (ER+), accounts for 70% of all BC cases. The standard treatment of endocrine therapy only reduces the risk of relapse by 40% due to resistance that inevitably evolves, which leads to approximately 11,000 deaths per year from relapses. As such, there is a need to develop new therapies that are able to overcome evolved resistances in such cases. These therapies should also demonstrate improved efficacy and tolerability, to both enable a higher patient response rate and alleviate adverse events associated with current treatment options. One such therapy that has shown promise in other cancer types is immunotherapy, which works by strengthening the abilities of the immune system. So far, they have not translated well to HRBC subtype. The reason for this is largely unknown, but likely is due in part to the unique tumor microenvironment that is relatively rich in stroma and low in immune cells. A large portion of the stroma is composed of fibroblasts, which secrete proteins that have been demonstrated to exclude invading immune cells, and confer drug resistance to tumor cells. As such, an opportunity exists to increase the efficacy of endocrine and immunotherapies by developing a deeper understanding of how interactions between immune cells, fibroblasts, and cancer cells cooperate to regulate immune function in HRBC. In particular, this research will focus on strategies to disrupt the stromal barriers that appear to exclude invading immune cells from physical contact with cancer cells. The overall goals of this project are to identify the stromal cell types that form barriers, develop therapeutic strategies that target those cells, and test the efficacy of these therapeutic strategies in disrupting the stromal barriers and increasing cancer cell death in conjunction with immunotherapies.

2019 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.

“I am so grateful for the PhRMA Foundation because its support has allowed me to develop our Colombian clinical research site and establish the animal models necessary to move towards an evidenced-based treatment for arthritis caused by chikungunya. Personally, the PhRMA Foundation has provided funding during a critical period of my development as a clinical translational researcher that has facilitated further training in laboratory based analytics and clinical trial management on the pathway to scientific independence.”

Aileen Chang MD, MSPH | George Washington University



Aileen Chang, MD, MSPH

George Washington University

“The Role of Interleukin-2 Therapy for Relapsing-Remitting Chikungunya Arthritis”

This project seeks to identify an effective treatment for the arthritis caused by chikungunya virus. Chikungunya virus is spread by mosquitoes and causes a debilitating arthritis that can last for years. The research team works in Colombia to better understand what causes this arthritis and how it can be treated. There is currently no evidence-based treatment for chikungunya arthritis. The study discovered that interleukin-2 (IL-2), a cytokine important for the development of regulatory T-cells, was low in patients who developed chronic arthritis after chikungunya infection. Therefore, in Aim 1, the project will determine if low IL-2 levels correlate with low regulatory T-cell populations in chikungunya patients with arthritis flares and if novel IL-2 therapy could be effective in chikungunya arthritis. In Aim 2, the project will test the efficacy of low-dose IL-2 therapy in a chikungunya arthritis mouse model. The goal of this research is to identify a targeted treatment for chikungunya arthritis.

“I am very grateful to the PhRMA Foundation Research Starter Grant for playing a crucial step toward achieving my career goals, as it provided protected time, resources, mentorship, hands-on laboratory-based research experience and invaluable career development that will secure my successful future in obtaining and sustaining research funding. Receiving this grant will prove invaluable in permitting me to independently develop my own line of research and to subsequently acquire multidisciplinary team science-based grants as I embark on a long and productive academic career that will make the PhRMA Foundation proud.”

Ivan Jozic, PhD | University of Miami Miller School of Medicine



Ivan Jozic, PhD

University of Miami Miller School of Medicine

“Targeting Caveolin-1 for Treatment of Non-Healing Chronic Wounds”

Chronic wounds represent a major healthcare burden, affecting more than 6 million people annually and hindering the health care system with ~\$60 billion in costs. Every chronic wound is considered colonized by opportunistic pathogens, which deregulate the healing process. However, specific mechanisms that inhibit healing and facilitate wound infection are not well understood and are the main focus of this project. Inability of wounds to close properly brought about by deregulated cell migration, together with increased pathogen colonization, are two hallmarks of non-healing chronic wounds. Successful completion of this project will advance an understanding of the molecular pathophysiology of chronic wounds. The strength of this study is the identification of a candidate molecule, which can serve as a potential biomarker and theragnostic target for treatment of non-healing chronic wounds by targeting two hallmarks of non-healing chronic wounds: 1) the inability of cells to move properly to re-epithelialize the wounds, and 2) the establishment and persistence of pathogenic bacterial infection. Such findings will facilitate development of more specialized targeted therapies and help explain why most recombinant growth factor therapies failed in clinical trials.

CLINICAL AND TRANSLATIONAL PHARMACOLOGY

2019 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.

“I’m deeply grateful for this opportunity to grow as a physician-scientist. My time as a Paul Calabresi Medical Student Fellow has allowed me to combine my scientific interests and work at the nexus of immunology, pharmacology, and metabolism. The PhRMA Foundation provided me with the ideal training opportunity for developing a career as a physician-scientist.”

James P. O’Brien | University of Pittsburgh School of Medicine



James P. O'Brien

University of Pittsburgh School of Medicine

“Nitro-Oleic Acid, an Electrophilic Fatty Acid Nitroalkene Derivative, Regulates Innate Immune Cell Metabolism and Attenuates Effector Function in a Murine Model of LPS-Induced Acute Lung Injury”

Acute lung injury (ALI) is characterized by a rapid inflammatory response that results in respiratory failure. Multiple conditions, including pneumonia, sepsis, and shock, can cause ALI, ultimately leading to death in 30-50% of cases. Despite pharmacological advances in targeting the immune system, there is still no effective treatment for ALI. Herein, a novel approach to treat ALI is proposed that leverages the pleiotropic anti-inflammatory properties of a bioactive fatty acid, nitro-oleic acid (NO₂-OA). NO₂-OA attenuates inflammatory responses by targeting two molecules within the cell, nuclear factor (NF)- κ B and nuclear factor (erythroid-derived 2)-like 2 (NRF2)-regulated gene. Furthermore, activation of the immune system is accompanied by changes in the metabolism of immune cells. Critical for this metabolic change are two proteins—inducible nitric oxide synthase (iNOS) and NRF2, known targets of NO₂-OA. Initial work in this research project demonstrates that NO₂-OA suppresses immune cell activation and alters the metabolism of these cells. This research is designed to define the mechanisms accounting for NO₂-OA regulation of immune cell metabolism in a manner that limits inflammation in ALI. It is hypothesized that NO₂-OA alters metabolism in active immune cells and thereby reduces inflammation.

“The PhRMA Foundation Paul Calabresi Medical Student Fellowship has allowed me to devote a year to research immunotherapy in pancreatic cancer. Because of the PhRMA Foundation’s generous support, I have gained invaluable skills in experimental design, critical thinking and lab-based research which I am excited to use in my future as a physician-scientist.”

Lyndsey Sandow | Dell Medical School



Lyndsey Sandow

Dell Medical School

“Determining the Role of Focal Adhesion Kinase on Tumor Immunogenicity and T cell Function in Tumor and Cancer Stem Cells”

Immunotherapy has proven to be an effective treatment in many drug resistant tumors; however, pancreatic ductal adenocarcinoma (PDAC) has shown little response to these therapies, making it one of the most lethal cancers. It is hypothesized that PDAC’s tumor microenvironment (TME) plays a significant role in the failure of immunotherapy. Recent studies have shown that the inhibition of focal adhesion kinase (FAK) can sensitize PDAC to checkpoint inhibitors and FAK is thought to play a role in immunosuppression and fibrosis. The exact mechanism of FAK in maintaining the TME is unknown, as is its effect on tumor immunogenicity and T cell function. Building upon these studies, this project hopes to demonstrate the mechanism of FAK and elucidate its effect on tumor immunogenicity and cytotoxic T cells to enhance PDACs response to immunotherapy. FAK has also been implicated in the regulation of cancer stem cells (CSCs); however, the role of immunotherapy in limiting growth and metastasis of CSC has yet to be studied. Accordingly, the project hopes to determine the role of FAK in the expression of immunomodulatory factors in PDAC CSCs. The objective is to understand the mechanism behind FAK inhibition in both tumor and CSC in order to improve PDACs response to immunotherapy and improve disease progression and metastasis.



2019 FACULTY DEVELOPMENT AWARD

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

“This PhRMA Foundation award has elevated my career trajectory from being a clinician to becoming a clinician researcher well versed in applying pharmacologic principles to better study and optimize therapies for preterm birth prevention. The research time funded through this award allows me to have dedicated time for training in laboratory techniques and computational methods, conducting novel clinical trials, and generating results that will bolster future research proposals and ultimately improve obstetric care and perinatal outcomes.”

Rupsa C. Boelig, MD, MS | Sidney Kimmel Medical College, Thomas Jefferson University



Rupsa C. Boelig, MD, MS

Sidney Kimmel Medical College, Thomas Jefferson University

“Utilization of clinical and translational pharmacology to optimize interventions for preterm birth prevention”

Preterm birth is one of the major causes of neonatal morbidity and mortality. While there are a number of pharmacologic interventions to prevent preterm birth, their use has been based on empiric dosing, generally from studies outside of pregnancy and efficacy determined from observational study or phase III trials without phase I/II study to determine optimal dose/route or fetal effects. Preterm birth is multifactorial, and one size does not fit all. This research portfolio aims to apply pharmacokinetics, pharmacodynamics, and pharmacogenomics to individualize and optimize therapies for preterm birth prevention, with a focus on aspirin, azithromycin, and progesterone. Aspirin is used for prevention of preeclampsia, a major source of preterm birth, and maternal and neonatal morbidity and mortality. The optimal dose of aspirin, balancing safety and efficacy, has not been established, and there is noted to be significant individual variability in response to aspirin therapy. Using a mix of computational methods and clinical and translational studies, pharmacokinetics, pharmacodynamics, and pharmacogenomics of aspirin in preeclampsia prevention will be elucidated so that dosing may be individualized and optimized. Azithromycin is used to delay delivery in the setting of preterm premature rupture of membranes, a high-risk condition that inevitably results in preterm birth. However, azithromycin dosing varies by institution and is not based on pharmacologic studies in pregnancy. By comparing the pharmacokinetics and pharmacodynamics of two common doses of azithromycin in maternal serum and pregnancy specific tissues (placenta, membranes, amniotic fluid, cord blood), the optimal dose/timing may be determined to improve both maternal and neonatal outcomes. Progesterone is one of the oldest and most used medications for preterm birth prevention; however, there are different routes, doses, and formulations used without regard to pregnancy specific pharmacology. Patient level characteristics, including both ultrasound and biologic markers, will be evaluated for association with progesterone therapy and perinatal outcomes.

PHARMACOLOGY/TOXICOLOGY

The first Pharmacology/Toxicology fellowships and grants were awarded in 1978 with predoctoral fellowships.

2019 PREDOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY

Predoctoral Fellowships in Pharmacology/Toxicology 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.

“I was honored and excited to receive my letter from the PhRMA Foundation, offering me the fellowship. This fellowship has allowed me to include additional experiments into my dissertation research and relieved a financial burden. The recognition of receiving this award has also made me more competitive when applying for postdoctoral positions in government and industry research, and for that, I am very grateful.”

Laura Ewing, MS | University of Arkansas for Medical Sciences



Laura Ewing, MS

University of Arkansas for Medical Sciences

“Role of Methionine-Gut Microbiome Interaction in Radiation-Induced Gastrointestinal Toxicity”

Radiation-induced gastrointestinal syndrome (RIGS) is the primary factor limiting the dose-range and duration of radiotherapy treatment, leading to the cessation of treatment and poorer long-term outcomes. RIGS is exacerbated by various comorbidities, including poor diet, infections, inflammation, and genetic polymorphisms in DNA repair mechanisms. Radiation also affects the microbiome, favoring microbial populations that could produce infections or endotoxins. Even single dietary changes, such as supplementing methionine, exacerbate normal tissue toxicity and changes in gut ecology after radiation. Thus, this project proposes to study the mechanisms of toxicity underlying methionine supplementation, the microbiome, and the development of RIGS utilizing stereotactic body radiotherapy. To understand how methionine and disturbances in gut ecology alter the development of RIGS symptoms, a variety of novel techniques will be used, including next-generation and third-generation metagenomic, metatranscriptomic, and metabolomic approaches, to characterize microbial populations and methionine metabolism in internal organs before and after irradiation and under different doses of methionine. These data will be used to parameterize a computational model relating tissue concentration to external Met and radiation doses in mice to translate the findings to humans in order to develop mitigation strategies.

“I am honored to be a recipient of the Predoctoral Fellowship in Pharmacology/Toxicology from the PhRMA Foundation. This funding has given me the opportunity to test novel therapies for colorectal cancer and has undoubtedly helped advance my career as a researcher. Thank you PhRMA Foundation!”

John Flickinger | Thomas Jefferson University



John Flickinger

Thomas Jefferson University

“Development of A *Listeria* Vaccine Targeting Guanylate Cyclase C for Metastatic Colorectal Cancer”

Colorectal cancer is the second leading cause of cancer death and the fourth most common cancer in the United States. Previous work has focused on developing a vaccine for metastatic colorectal cancer utilizing the intestinal receptor and tumor antigen guanylate cyclase C (GCC) as a target. A recent phase I clinical trial demonstrated that a previous version of this vaccine safely induces GCC immune responses in patients. However, this trial also revealed a limitation of current GCC vaccines. Specifically, this project found that 50% of patients possessed pre-existing neutralizing antibodies against the adenovirus vaccine vector, which resulted in a lack of GCC immune responses in these patients. To directly address limitations of antibody neutralization observed in the clinical trial, the project is leveraging the unique biology of the bacterium *Listeria monocytogenes*. While other vaccine vectors induce neutralizing antibodies that limit responses upon re-exposure, *Listeria monocytogenes* does not generate neutralizing antibody responses, thereby making it possible to repeatedly administer vaccine and induce antitumor immunity. Moreover, this project is studying fundamental mechanisms of how *Listeria monocytogenes* induces therapeutic immune responses with a focus on enhancing antitumor properties of these vaccines. Ultimately, it is anticipated these studies will lay a framework for metastatic colorectal cancer vaccination that can hopefully one day be translated to the clinic.



Robert Fuchs

Louisiana State University Health Sciences Center, New Orleans

“The Search Continues: Determination of a Lipid Raft Targeting Motif in Cytochromes P450”

The cytochromes P450 are a set of enzymes in the liver critical for metabolism of drugs, toxins, and hormones. These proteins interact extensively with the endoplasmic reticulum (ER), a membranous organelle composed of heterogeneously organized lipids. Most of the ER surface area is composed of anionic phospholipids; such regions are termed disordered microdomains (ld). Conversely, select parts of the membrane contain cholesterol, sphingomyelin, and other specialized lipids; these areas are called ordered microdomains (lo, “lipid rafts”). Many membrane-related proteins show strong preference for ordered or disordered regions. It is currently unclear what factors drive enzymes into their preferred microdomains and whether microdomain localization plays a role in maintaining enzyme activity. This project will study whether specific cytochrome P450 enzymes preferentially sort into specific ER membrane regions. It is hypothesized that a specific amino acid motif targets P450 proteins into ordered or

disordered regions, and that disruption of normal microdomain localization influences enzyme activity. To test this hypothesis, chimeric fusion proteins will be generated for two specific P450s, CYP1A1 and CYP1A2, which respectively localize to disordered and ordered regions. Microdomain localization for each chimera will be determined using detergent solubilization. It is expected that chimeric CYP1A1 containing a critical amino acid motif from CYP1A2 will show microdomain localization pattern characteristic of CYP1A2, and vice versa. For chimeric proteins that mobilize outside their native microdomain, enzyme activity on CYP1A1- and CYP1A2-specific substrates will be measured, and it is predicted that constructs that do not localize to their native microdomains will exhibit altered enzyme activity. Results from this project will reveal a basic mechanism for regulation of P450 activity in live cells, and will guide future research on variability in P450 enzyme activity.

“Earning a Predoctoral Fellowship in Pharmacology/Toxicology from the PhRMA Foundation is an honor that is incredibly gratifying on a personal level, and it is a crucial step in my development and pursuit of a career in industry. More than that, however, fellowships such as this drive innovative research that can have a real impact on patient care.”

Timothy E. G. Krueger | Johns Hopkins University



Timothy E. G. Krueger

Johns Hopkins University

“Targeting LSD1 for Direct Effects and Induction of Anti-Tumor Immunity Against Lethal Prostate Cancer”

Lysine-Specific Demethylase 1 (LSD1) was the first protein discovered to be able to remove methyl marks from histone proteins, thus repressing transcription of associated genes. LSD1 has been found to be overexpressed in numerous cancers, causing pro-tumorigenic disruptions in numerous processes including cell cycle control, glycolytic metabolism, metastasis, and differentiation. Inhibition of LSD1 has been shown to be able to reverse these abnormal gene expression patterns and have direct efficacy against cancer cells. These efforts have resulted in numerous ongoing clinical trials to test LSD1 inhibitors against a variety of blood malignancies. Additionally, inhibition of LSD1 directly induces the expression of inflammatory chemokines and endogenous retroviruses (ERVs) in cancer cells. This triggers a viral response that leads to production of inflammatory stimuli and recruits CD8⁺ T cells to tumors that are normally immunologically unresponsive. While small cell lung cancer is the only solid malignancy to have been tested with LSD1 inhibitors in clinical trials to date, prostate cancer (PCa) is an enticing candidate due to the additional pivotal role of LSD1 in mediating the androgen receptor signaling that is the key driver of PCa progression. This study will test both the direct anti-proliferative effects and indirect immunological effects of LSD1 inhibition against lethal castration resistant PCa. CRISPR-Cas9 has been employed to obtain LSD1 knock-out PCa cell lines, and IMG-7289 will be used as a novel, specific, and readily translatable small molecule LSD1 inhibitor. RNA-Seq, ChIP-Seq, and NanoString analysis will inform of broad transcriptional changes following pharmacologic or genetic inhibition of LSD1 and will help identify critical pathways controlled by LSD1 in PCa. Additionally, flow cytometry analysis of syngeneic Myc-CaP tumors in FVB mice treated with IMG-7289 will identify any changes in immune populations and surface markers that either trigger immune reactivity on their own or that could be targeted/enhanced with potential combinatorial immunotherapies.

“The PhRMA Foundation Predoctoral Fellowship in Pharmacology/Toxicology has provided me with the funding that was necessary to expand my dissertation work further. It has enabled me to travel to and present at more conferences than anticipated, therefore benefiting me professionally and scientifically. I am grateful to be a recipient as this Fellowship was truly a catalyst to aid in my dissertation research.”

Stacia I. Lewandowski | Drexel University College of Medicine



Stacia I. Lewandowski

Drexel University College of Medicine

“In Vivo Studies of the Role of ERK1/2 Phosphatase MKP3 in Dopaminergic Neurons on Cocaine-Associated Dopamine Signaling, Gene Expression and Behavior”

Abundant evidence indicates that repeated exposure to cocaine results in cellular and molecular adaptations in the mesolimbic dopamine (DA) reward system, which is comprised of dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Adaptations resulting from cocaine exposure reorients behavior towards drug seeking and drug use, making cocaine addiction a vicious cycle. Despite this knowledge, there are no FDA-approved pharmacotherapies for cocaine use disorder, suggesting that a more detailed understanding of the neurobiology that underlies cocaine addiction is needed. Cocaine exerts its addictive effects by blocking the dopamine transporter (DAT), leading to excess DA in the synaptic cleft, resulting in the euphoric “high” that is often sought-after during addiction. This leads to the activation of intracellular signaling pathways, such as the ERK1/2 Map Kinase signaling pathway. ERK1/2 signaling is abundantly distributed in the mesolimbic DA reward system, suggesting the importance of ERK1/2 signaling in the regulation of DA neurotransmission. This study describes the cell-specific modulation of the ERK1/2 pathway in vivo by expressing the ERK1/2 phosphatase MKP3 in dopaminergic neurons only. This is accomplished by generating adeno-associated viral (AAV) vectors with Cre recombinase (Cre)-dependent expression of MKP3. This construct is injected into the VTA of Long Evans rats expressing Cre in tyrosine hydroxylase positive cells (TH-Cre rats), thus achieving a decrease of the ERK1/2 signaling in DA neurons of the VTA. This study has found that cell-specific ERK1/2 inhibition results in the attenuation of cocaine-associated behaviors, which may be driven by observed changes in DA neurotransmission in the NAc. Using ex vivo brain slice biotinylation, this project has revealed that there are significant differences in cell surface levels of DAT in the striatum, suggesting ERK1/2 signaling may regulate DA tone by managing DAT surface availability as well as expression of key DA proteins. This demonstrates the importance of ERK1/2 signaling in the cellular and molecular adaptations associated with cocaine use. The goal of the proposed research is to identify specific downstream targets of this pathway to reveal novel therapeutic targets for treating cocaine use disorders.

“The PhRMA Foundation Predoctoral Fellowship in Pharmacology/Toxicology provided me with crucial resources to explore new options for targeted cancer therapies. This fellowship gave me the confidence and freedom to combine my interests in translational research with my mentor’s expertise in cancer biology. I am so grateful to have had this opportunity early in my scientific career and to the PhRMA Foundation for helping to support graduate students.”

Emily Mason-Osann | Boston University School of Medicine



Emily Mason-Osann

Boston University School of Medicine

“Defining Mechanisms and Therapeutic Targets Within the Alternative Lengthening of Telomeres Pathway”

Telomeres are repetitive DNA sequences that cap the ends of all human chromosomes and function to maintain the integrity of the genome. Telomeric DNA undergoes progressive shortening with each cell division, eventually halting the cell from continuing to divide. However, the ability to divide indefinitely, called replicative immortality, is a hallmark feature of cancer cells. Approximately 10-15% of cancers maintain telomere length using the Alternative Lengthening of Telomeres (ALT) pathway. ALT promotes telomere elongation using a mechanism that resembles homologous recombination, a specific type of DNA repair. ALT is found across a variety of different cancer types, though it tends to be more prevalent in sarcomas, such as osteosarcoma. The high prevalence of ALT in osteosarcoma is of interest because osteosarcoma is a pediatric bone cancer that currently has no targeted therapies available. If the ALT pathway could be targeted, it could make a significant impact for patients with this disease. The exact proteins and mechanisms regulating the elongation of ALT telomeres are currently unclear, making it challenging to identify therapeutic targets within the ALT pathway. RAD54 is a protein with many known functions in recombination, including stimulating the formation and resolution of branched DNA structures formed as intermediates during recombination. Preliminary data generated through this project demonstrate that loss of RAD54 leads to a decrease in ALT activity, and a significant decrease in elongation events at ALT telomeres, suggesting that RAD54 is a crucial regulator of the ALT pathway. While RAD54 has previously been shown to be involved in repairing DNA breaks, the role of RAD54 at ALT telomeres has not yet been characterized. Therefore, this project aims to determine whether ALT cells rely on RAD54 to promote telomere maintenance, thus making RAD54 a possible therapeutic target for ALT positive cancers.



Carmen Mitchell

Indiana University School of Medicine

“A New Mechanism of Serotonin Transporter Regulation by Simvastatin and the Isoprenylation Pathway”

Statins are cholesterol lowering drugs and are the most widely prescribed class of drugs in the United States. In addition to their well-known vascular effects, statins produce a variety of unwanted neurological effects, including mood and cognitive irregularities. However, the mechanism behind the adverse neurological effects of statins are unknown despite their brain-permeability. To address this knowledge gap, this proposal examines the neuropharmacological effects of statins and more specifically, the effects of simvastatin on the serotonergic system in the brain. Serotonin neurotransmission is largely regulated by the serotonin transporter (SERT) and the regulation of SERT is the focus of the project. Results reveal a significant enhancement in the activity of SERT in neurons after statin treatment both in vitro in neuronal cell models and in vivo in rat brain tissue. Statin treatment increased SERT activity that was independent of cholesterol per se, but dependent on cholesterol biosynthetic precursor intermediates, farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). Both FPP and GGPP are lipid signaling intermediates. These intermediates constitute the isoprenylation pathway, a biosynthetic pathway that diverges from cholesterol synthesis and is important for insertion of proteins into the plasma membrane where they act. The current role for the isoprenylation pathway in the regulation of SERT is unknown. The overall goal is to investigate isoprenylation intermediates involved in the modulation of SERT that could underlie the neurological consequences associated with statin drugs.

“I am very grateful to have received a PhRMA Foundation Predoctoral Fellowship. Receiving this award has provided me the opportunity to pursue my thesis research in immune co-receptor signaling, a new biological area for our lab. The funding from this award has been instrumental in allowing me to complete key experiments to drive my project forward. Furthermore, this award has provided a network and resources to help me begin a career in the pharmaceutical industry after graduate school. The support from the PhRMA Foundation has had a positive and lasting impact on my research, and has been an invaluable part of my graduate school experience.”

Courtney M. Smith | Yale University



Courtney M. Smith

Yale University

“Understanding TIM3 Signaling”

Reactivating the immune response against cancer cells by immune checkpoint blockade (ICB) has revolutionized cancer treatment. This therapeutic strategy blocks the interaction between immune cell inhibitory receptors and their ligands, releasing the inhibitory “brake” on the immune system to allow it to target and kill tumor cells. For example, therapies targeting the PD-1/PD-L1 axis have been shown to reactivate immune responses to cancer. However, the majority of patients fail to respond to ICB, and those that do respond can develop resistance and progress.

Therefore, new strategies are needed to overcome these current limitations to ICB therapy. A potential strategy is to target some of the many additional checkpoint receptors. One such target is TIM3, a receptor that – like PD-1 – is expressed on dysfunctional T cells in the tumor microenvironment. In mouse models, combined PD-1 - TIM3 blockade is synergistic, supporting the potential of TIM3 blockade. However, a major challenge for TIM3 – and for many other immune checkpoint receptors – is the lack of understanding of how these receptors signal and are regulated by ligand. The goal of this project is therefore to understand how TIM3 modulates T cell signaling, how TIM3 is regulated by its putative ligand(s), and further, to improve the translation of candidate TIM3 therapies to the clinic. To address these questions, putative TIM3-ligand interactions were validated using biophysical approaches, and cellular signaling assays evaluated their biological relevance. Additionally, therapeutic antibodies will be assessed to interrogate relevant ligand-binding sites. Ultimately, this project will provide new insight into the mechanism of a novel target for ICB, aid the design of more mechanistically focused therapies, and help with stratification of the clinical utility of TIM3 therapies currently in early stage clinical trials. Moreover, this project will more generally inform the field of signaling by T cell co-receptors.

“I am deeply honored to have received the PhRMA Foundation Predoctoral Fellowship in Pharmacology/Toxicology. The financial support from this award has allowed me to focus solely on my dissertation work, furthering our understanding of genetic-related pediatric epilepsies. Additionally, I have been able to grow as an independent scientist and make connections that will propel my future career.”

Brittany Spitznagel, PharmD | Vanderbilt University



Brittany Spitznagel, PharmD

Vanderbilt University

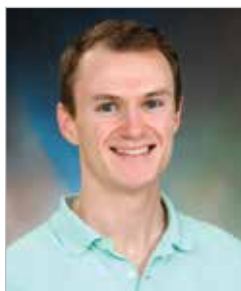
“Pharmacological and Genetic Approaches Probing the Role of the Slack Potassium Channel in Childhood Epilepsies”

Malignant migrating partial seizures of infancy (MMPSI) is a rare, severe form of early-onset epileptic encephalopathy, characterized by focal seizures that arise from various regions of either brain hemisphere and can migrate between brain regions. The majority of these patients experience recurrent seizures before six months of age, ranging from 5 to 50 seizures per day. Due to the severity and number of seizures, affected individuals suffer profound developmental delays and intellectual impairment. Most notably, MMPSI patients have arrest or regression of motor skills obtained prior to the onset of seizure activity. The majority of MMPSI cases are considered pharmacoresistant, causing patients to progress in their disease and not survive past early childhood. Growing evidence suggests a genetic etiology for the development of MMPSI. To date, thirty-one de novo mutations affecting three functional domains of the potassium (K⁺) channel Slack have been reported in greater than 50% of patients with MMPSI, making it the most frequent known genetic signature associated with MMPSI. This project focuses on these Slack mutations, their link to epilepsy and attempting to correct this epileptiform behavior with pharmacologic tools. Slack is a member of the Slo family of K⁺ channels, encoded by the gene KCNT1. This channel family is a critical regulator of electrical activity in the nervous system. Slack channels are widely distributed throughout the central nervous system, where they contribute to the slow hyper-polarization of neurons following action potential firing. A large number of mutations have been reported in Slack. All mutations described have been shown to induce

a dominant gain-of-function by several mechanisms, including 3-12 fold increases in current amplitudes, a left shift in the current-voltage relationship or increasing the channel's sensitivity to Na⁺ ions. This research has focused on the A934T mutation as it is associated with the most severe human MMPSI phenotype and was used to generate a transgenic mouse. The lack of potent and selective pharmacological tools has inhibited researchers from understanding the role Slack plays in childhood epilepsies and investigating it as target for therapeutic intervention. The development of such tools is well underway, with the first selective Slack modulator identified through a high-throughput screening efforts. Additionally, this project has generated an MMPSI-associated mutant Slack mouse model to explore changes in EEG activity, anxiety-related behaviors, motor and sensorimotor function. Together these pharmacologic and genetic approaches have allowed for significant advances in the fields of Slack and MMPSI research.

“Since embarking on my graduate studies, I have been intrigued by the idea of defining new drug targets for the treatment of CNS disorders. The PhRMA Foundation Fellowship in Pharmacology/Toxicology, through its commitment to providing comprehensive training in drug development, has enabled me to devote all my efforts toward impactful research in neuropsychopharmacology and fostered my development as a physician scientist.”

Paul Wadsworth | University of Texas Medical Branch



Paul Wadsworth

University of Texas Medical Branch

“Targeting Protein: Protein Interactions at the Voltage Gated Sodium Channel Complex for Pharmacologic Development”

As fundamental determinants of neuronal function, voltage-gated Na⁺ (Nav) channels are important targets for therapeutic development against a wide range of health conditions. Dysfunction of Nav channels in the CNS is associated with disorders ranging from neurological (i.e., epilepsy) to psychiatric (i.e., major depression disorder). Unfortunately, commercially available drugs targeting Nav channels are largely non-specific, giving rise to severe side effects such as movement disorders. Thus, there is an unmet need for discovering new therapeutically relevant probes and pathways. Recent evidence suggests that protein:protein interactions (PPI) between Nav channels and their accessory proteins play a key role in regulating neuronal firing, and that minimal disturbances to these tightly controlled PPI can lead to persistent maladaptive plasticity. These PPI interfaces are highly specific and provide ideal targets for drug development, especially in the CNS, where selectivity and specificity are vital for limiting side effects. Therefore, the goal of the present study was to develop a screening platform capable of identifying new regulators of the Nav channel complex. Specifically, the project focused on the PPI between Nav1.6 and its regulatory protein, FGF14. Beginning with a newly developed series of cell-based assays, this research discovered a mechanism by which the JAK2 tyrosine kinase might directly influence neuronal firing through phosphorylation of FGF14. Furthermore, a high-throughput screening of ~45,000 small molecules was conducted, identifying two potent modulators of the FGF14:Nav1.6 complex that are functionally active and predicted to be permeable to the blood-brain barrier. While providing a robust in-cell screening platform that can be adapted to search for any channelopathy-associated regulatory protein, these results lay the potential groundwork for a new class of drugs targeting Nav channels with a broad range of applicability for CNS disorders.

2019 POSTDOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY

The PhRMA Foundation has been awarding Postdoctoral Fellowships in Pharmacology/Toxicology since 2002. This fellowship provides a two-year stipend to scientists who seek to gain new skills in areas relevant to pharmacology. 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.

“As academic research scientists we live or die by our publications, grants, and other forms of professional achievement/recognition. This fellowship was an important first step for me as I seek to thrive in this challenging field. Importantly, it freed up funds in our lab to accelerate the pace of research, and through the PhRMA Foundation I have made contacts that will foster collaborations for years to come.”

Scott D. Barnett, PhD | The Medical College of Wisconsin



Scott D. Barnett, PhD

The Medical College of Wisconsin

“Dual Inhibition of sEH and COX-2 for the Treatment of Focal Segmental Glomerular Sclerosis”

Focal segmental glomerulosclerosis (FSGS) is the single most common form of kidney disease. Unchecked, this devastating disorder leads to end stage renal disease (ESRD), a terminal diagnosis in the absence of a kidney transplant. The progression of FSGS is defined by damage to the glomerulus, the primary filter of blood in the kidney. This research seeks to better understand the protective effects of a family of small molecules found in the glomerulus called epoxyeicosatrienoic acids (EETs), as well as the potential adverse effects caused by their metabolism. PTUPB is a novel drug that has a two-fold action on EETs. First, it acts to prevent EET breakdown by inhibiting an enzyme called soluble epoxide hydrolase (sEH). Second, it limits the formation of EET metabolites through inhibition of cyclooxygenase-2 (COX-2). The objective of this research is to determine if PTUPB exerts a protective/therapeutic effect on glomerular function by limiting EET metabolism, while concurrently decreasing the amount of deleterious EET metabolites. The long-term goal of this study is to mitigate the glomerular damage caused by FSGS by better understanding the role of EETs and their metabolites in the kidney. The proposed research is innovative because it investigates a new class of renal therapeutics using pharmacology, physiology, and medicinal chemistry, and it will expand knowledge of the role of EET metabolites in FSGS. There is a dearth of effective treatment options for FSGS, and if successful, PTUPB will represent a new and much needed therapy for this common and life-threatening disease.



Jeffery L. Dunning, PhD

Vanderbilt University

“Arrestin-Derived Peptides as Novel Tools to Bias Cell Signaling and Combat L-DOPA Induced Dyskinesia”

Arrestins ensure the termination of signaling by G protein-coupled receptors (GPCRs). Arrestins also simultaneously act as scaffolds for other proteins, initiating G protein-independent signaling within the cell. Dopaminergic signaling is mediated by GPCRs and plays a critical role in controlling multiple forms of behavior. Abnormalities of signaling by dopamine receptors have been strongly implicated in Parkinson’s disease (PD) and severe motor complications caused by dopamine replacement therapy, such as L-DOPA-induced dyskinesia (LID). Arrestins likely contribute to LID via their actions in targeting and colocalizing effector molecules. Mice lacking the genes for arrestin-3 demonstrate suppressed LID behaviors and the restoration of arrestin-3 in the basal ganglia restore these behaviors. Studies using arrestin-3 derived peptides in cell culture have identified that arrestin-3 may exert its effects through activation of the JNK pathway. It remains unknown, however, if arrestin-3-dependent JNK activation is the mechanism underlying LID. This project investigates the monofunctional elements of arrestin-3, their molecular targets, and tests the therapeutic potential “mini-scaffolds” in dampening cell signaling. The goal of this research is to explore how modulation of arrestin-3-dependent activity of the JNK pathway affects LID and will explore the feasibility of using the arrestin-3 derived peptides capable of preventing the arrestin-3-dependent JNK activation as anti-LID therapy. The results of these experiments will shed light on the pharmacology of arrestin-3 action in regulating dopaminergic signaling in the brain, providing promising new molecular targets to meet unmet clinical needs.



Daniel Felsing, PhD

University of Texas Medical Branch

“Kinetics of Ligand Binding as a Basic Mechanism Driving Biased Signaling of Novel Dopamine D1 Receptor Agonists”

Dopamine (DA) is a neurotransmitter acting through five G protein-coupled receptors (GPCRs) to modulate multiple physiological functions. Abnormal dopaminergic neurotransmission underlies the pathophysiology of several neuropsychiatric diseases. Recently, transformative research indicates that GPCRs signal not only via G protein-dependent mechanisms but also via G protein-independent interactions with Beta-arrestins. Ligands that activate GPCRs to signal specifically to one of these pathways are termed “biased ligands,” which provide the opportunity to fine tune GPCR activity with potentially superior therapeutic efficacy. This proposal is focused on understanding the mechanism-of-action of novel agonist ligands targeting the dopamine D1 receptor (D1R). D1R agonists have long been pursued as a therapeutic target for treating neurological and psychiatric disorders (esp., Parkinson’s disease), but drug-like agonist ligands have remained elusive. Pfizer recently discovered the first drug-like D1R agonists that show signaling bias for activating G-s/cAMP signaling in the absence of Beta-arrestin signaling and receptor desensitization. The mechanism by which these new ligands cause biased signaling is unknown. This project Hypothesizes that the kinetics of ligand binding of D1R agonists is a driving factor that determines signaling bias towards G proteins or Beta-arrestins. This research project will expand currently limited knowledge of ligand properties and mechanisms governing biased signaling at GPCRs.

2019 RESEARCH STARTER GRANTS IN PHARMACOLOGY/TOXICOLOGY

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

“I am extremely honored to have received the PhRMA Foundation Research Starter Grant in Pharmacology/Toxicology. The award has served as a springboard for my independent career and enhanced my laboratory’s research efforts.”

Adam Lauver, PhD | Michigan State University



Adam Lauver, PhD

Michigan State University

“Evaluating Differences in the Biological Actions of Clopidogrel Metabolites”

Cardiovascular diseases remain the leading cause of death in the United States. Dual anti-platelet therapy using aspirin and a P2Y₁₂ antagonist, such as clopidogrel, is the standard therapeutic intervention in patients with coronary artery disease. The efficacy of this treatment strategy has been demonstrated in numerous clinical trials; however, like many antithrombotic therapies it is frequently associated with adverse bleeding events. Furthermore, clopidogrel-treated patients demonstrate significant variability in their responses and frequent drug-drug interactions occur. These factors limit clopidogrel’s use and are due to a complex bioactivation process which results in the formation of at least a dozen different metabolites that are thought to possess actions beyond the inhibition of platelets. However, due to a lack of stable synthetic metabolite standards for pharmacological evaluation, a specific comparison of the biological actions clopidogrel metabolites has not been performed. Based on the available literature and this study’s preliminary data, it is proposed that the observed adverse bleeding effects are mediated, in part, by the action of clopidogrel metabolites at sites other than the platelet P2Y₁₂ receptor. To investigate, this project has developed DT678, a disulfide prodrug of the sole clopidogrel metabolite responsible for the inhibition of P2Y₁₂. The data demonstrates that at equally effective antiplatelet doses, DT678 has a reduced bleeding risk compared to clopidogrel and it is likely that the P2Y₁₂-independent effects of the other metabolites account for the differences observed. The overall objectives of this project are to compare the actions of clopidogrel and DT678 on platelet activation and vascular function. The results of this project will contribute significantly to the knowledge of the bleeding side-effects associated with antiplatelet drug therapy and therefore improve clinical outcomes in patients at high risk for thrombotic events.

“I am extremely thankful for the PhRMA Foundation supporting my research endeavors. As a new investigator, funds are limited and the support provided by the receipt of a PhRMA Foundation Research Starter Grant has allowed my research group to generate data that has been invaluable for grant applications for future, sustained support of my laboratory. PhRMA Foundation support is the driver of studies within my independent lab that may provide the scientific foundation for the generation of the first clinical pharmacotherapy for TBI.”

Matthew J. Robson, PhD | University of Cincinnati



Matthew J. Robson, PhD

University of Cincinnati

“Role of Sigma-1 Receptors in Traumatic Brain Injury”

Nearly 3 million Americans suffer a traumatic brain injury (TBI) annually, creating an enormous medical and economic burden that can persist long beyond the acute stages of injury. TBI predisposes individuals to increased rates of debilitating neurodegenerative disorders and the generation of enduring neuropsychiatric disorders such as depression, anxiety, social withdrawal and post-traumatic stress disorder (PTSD). Although a large amount of work has been conducted in the attempt to identify molecular targets for pharmacotherapies aimed at treating TBI, there is currently a lack of any FDA-approved medications for TBI. Sigma-1 receptors are ubiquitously expressed protein modulators that are highly amenable to pharmacologic manipulation and are posited as molecular targets for the development of therapies to treat various neurodegenerative and neuropsychiatric disorders. Sigma-1 receptors are known regulators of critical cellular functions, including mitochondrial function, cellular stress, calcium signaling and the activity of several ion channels/transporters. Additionally, these proteins are known modulators of Tau phosphorylation, a pathology correlated with the development of several neurodegenerative disorders. The purpose of the proposed preclinical studies is to ascertain whether the activation of sigma-1 receptors may be a viable strategy for the acute treatment of TBI. Studies herein utilize a preclinical model for TBI in combination with genetic and pharmacologic manipulation of sigma-1 receptor expression and function, respectively, to determine whether sigma-1 receptors modulate secondary injury cascades within the brain associated with the chronic, debilitating deficits of TBI. Ultimately, this project will elucidate the actions of sigma-1 receptors in the context of neurotrauma and may be the foundational studies in the development of sigma-1 receptor agonists as clinically utilized pharmacotherapies for the treatment of TBI.

INFORMATICS

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

2019 PREDOCTORAL FELLOWSHIPS IN INFORMATICS

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

“The PhRMA Foundation provided me with the resources to jump-start my career as a scientist, while allowing me to become part of a larger community of world-class minds working towards improving human health. The PhRMA Foundation Informatics Fellowship gave me the unique opportunity to utilize my strengths in algorithm development to help us get one step closer towards achieving this goal.”

Shannon Smith | Vanderbilt University



Shannon Smith

Vanderbilt University

“Pipeline for Ultra-Large Virtual Screening Using RosettaGPCR and DOCK: A Test Case for PAR4 Inhibitor Development”

Structure-based drug discovery has become a valuable tool during early stages in pharmacological development campaigns. This project develops a computational pipeline for structure-based virtual screening in G-protein coupled receptors (GPCRs), a protein family targeted for countless disease indications. Inhibition of the protease-activated receptor 4 (PAR4) GPCR has demonstrated promise as a target in anti-platelet drug development. The goal of this screening effort is to obtain new chemistries for drug development that probes PAR4 deeper in the transmembrane region of the binding pocket, a feature critical for PAR4 inhibition. This pipeline uses an array of computational tools, including multiple-template comparative modeling in Rosetta, DOCK ultra-large screening libraries, Rosetta ligand docking and machine learning-based cheminformatics to prune new small-molecule chemistry. For broader impact, this protocol is general enough to be used across the GPCR super-family and potentially towards other protein targets for small molecule development.

“I am very thankful to be a recipient of the PhRMA Foundation Informatics Fellowship. This fellowship has allowed me to delve into fascinating questions of public health importance using a novel data source and innovative methodology. I believe receiving this fellowship has helped me to grow as a scientist, and has shaped my research and skills so that I can continue to pursue a career of exciting translational research at the intersection of public health and informatics.”

Casey Zipfel | Georgetown University



Casey Zipfel

Georgetown University

“The Interplay Between Infectious Disease Dynamics and Human Behavior”

The relationship between human behavior and infectious diseases is subject to dynamic feedback. Infectious disease transmission is governed by social behavior, which can change during the course of an epidemic in response to disease spread. Dynamic social behavior is often ignored in infectious disease models or studied in a theoretical manner, due to lack of relevant, appropriate data. This work integrates large-scale, digital data from medical claims on health and behavior with mathematical models of infectious disease to address this gap in data, and to characterize epidemiological and behavioral mechanisms relevant to understanding and controlling infectious disease. Specifically, this work investigates the effects of health disparities on social behavior and dynamics of seasonal influenza, the effects of vaccine-preventable disease outbreaks (like measles and pertussis) on vaccine refusal behavior, and the effects of proposed drivers on childhood vaccination behavior and the resulting landscape of immunity for vaccine-preventable diseases in the United States. Findings from this work will inform public health policy regarding sick leave, vaccination, resource allocation, and pandemic planning. It will also guide future infectious disease surveillance processes, and public health education and practice regarding the integral role of the individual. This will also inform appropriate use of digital data in epidemiological modeling, illustrate the power of public health informatics, and guide model complexity for problems of infectious disease and behavior.



2019 POSTDOCTORAL FELLOWSHIPS IN INFORMATICS

The PhRMA Foundation supports postdoctoral research activities that will enhance the expertise of informatics specialists and bridge experimental and computational approaches in genomic and biochemical studies. This award has served to provide a strong base for development of professional careers in research, both in academia and in industry.

“Being awarded the PhRMA Foundation Postdoctoral Fellowship in Informatics has enabled me to pursue research in areas that I’m the most passionate about as well as increased my confidence in designing research plans that have the potential to significantly impact future research and technologies. I am thankful for the PhRMA Foundation for supporting me as I transition into an independent researcher.”

Asa Thibodeau, PhD | The Jackson Laboratory for Genomic Medicine



Asa Thibodeau, PhD

The Jackson Laboratory for Genomic Medicine

“Machine Learning Models to Classify Regulatory Elements and Predict Their Gene Interactions from Clinical ATAC-seq Samples”

Genome-wide association studies (GWAS) revealed that over 90% of disease-associated genetic variants are found in non-coding sequences that lead to dysregulated gene expression programs through disrupting regulatory elements (REs). REs are DNA sequences that mediate binding of proteins to DNA for regulating gene expression in a cell-specific manner and play a critical role in individual- and condition-specific gene regulation. An effective method for interrogating REs from clinical samples is Assay for Transposase Accessible Chromatin using sequencing (ATAC-seq), which captures genome-wide open chromatin regions (OCRs) with as little as 500-50,000 cells. By targeting OCRs, ATAC-seq effectively narrows the scope of where REs are found in a cell type of interest. However, determining a RE’s function (e.g., enhancer, insulator, etc.) and its target genes from ATAC-seq data alone remains a challenge. For this purpose, Classification of Regulatory Elements with ATAC-seq (CoRE-ATAC), was developed. CoRE-ATAC implements novel ATAC-seq data encoders that are used by a deep learning model to infer promoter, enhancer, and insulator classes of REs from OCRs. Training CoRE-ATAC on data from 4 cell types (Monocytes, GM12878, HSMM, and K562) achieved an average accuracy of 84% when applied on held-out test data from the same cell types. Moreover, high precision (~0.8) was observed after applying CoRE-ATAC on 40 samples across 7 cell types not used in model training, suggesting that CoRE-ATAC is an effective and robust model for determining RE function from ATAC-seq. Predictions from CoRE-ATAC will enable the development of future machine learning models for inferring enhancer-promoter interactions. Focusing on CTCF insulators, which have been shown to regulate chromatin structure by looping DNA, genomic regions that are most likely to be in close proximity and will be identified to infer target promoters/genes of predicted enhancers. These models will enable the study of epigenetic landscapes at the individual level, bringing us closer towards the development of individual specific therapies.

2019 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.

“I am grateful to the PhRMA Foundation for supporting my research. The PhRMA Foundation Research Starter Grant in Informatics will help to generate a unique dataset to connect my biostatistics research with a deep interest in the clinically-oriented analysis of medical genomics data. This dataset will serve as a unique resource for the development of novel biostatistics methods and bioinformatics software, and for better understanding of treatment options of metastatic breast cancer.”

Mikhail G. Dozmorov, PhD | Virginia Commonwealth University



Mikhail G. Dozmorov, PhD

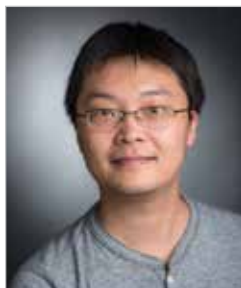
Virginia Commonwealth University

“Druggable 3D Genomics of Metastasis”

The human genome is non-random—DNA from each chromosome is folded into the highly organized three-dimensional (3D) structure. The three-dimensional (3D) structure has emerged as a higher-order regulatory layer orchestrating cell type-specific gene expression and other cellular processes. Abnormal changes in the 3D structure of the genome are now a well-established hallmark of cancer. However, their role in cancer metastasis, the primary cause of death, is unknown. This lack of understanding is particularly exacerbated for triple-negative breast cancer (TNBC) patients that currently lack treatment options at the metastatic stage of their disease. Comparing the 3D structure between primary and metastatic cancers will enable the detection of changes in the 3D structure that are associated with metastasis. Linking those changes with genes and cellular pathways will help to define druggable biomarkers that can be targeted to prevent metastasis. However, recently developed sequencing technologies for capturing the 3D structure of the genome remain imperfect, requiring proper normalization and statistical analysis of the data. This project will create biostatistical methods and bioinformatics software to maximize the detection of biologically relevant changes in the 3D structure of the genome. The methods will have broad application for defining statistically significant 3D changes in any experimental conditions. This project will compare primary and metastatic 3D structures obtained from patient-derived xenograft (PDX) models and identify metastasis-associated changes in the 3D genome. Using pharmacogenomics database and literature mining, genes associated with the 3D changes will be linked with the Food and Drug Administration (FDA)-approved drugs and prioritized for further drug screening in efforts to prevent metastasis.

“I am extremely honored to receive the PhRMA Foundation Research Starter Grant in Informatics. It was critical for me to start my informatics laboratory as an assistant professor. Furthermore, it has enabled me to explore the opportunity to use data intensive approaches to understand the Achilles heel of cancer cells and to inform novel drug targets.”

Wei Li, PhD | Children's National Hospital and George Washington University



Wei Li, PhD

Children's National Hospital and George Washington University

“Genome Engineering and Data Science Approaches for Cancer Drug Discovery”

CRISPR/Cas9 is an evolutionary tool that allows the manipulation of human DNA. One exciting application of CRISPR/Cas9 is CRISPR screening that quickly identifies interesting genes from tens of thousands of candidates. Unfortunately, data generated from CRISPR screening is inherently biased towards different factors (e.g., copy number variation, different cell conditions, etc.). Furthermore, people still don't know how to inform precision medicine from CRISPR screening. This research project seeks to facilitate an understanding of cancer essential genes and a search of drug targets, by developing computational frameworks for CRISPR/Cas9 screening. The project builds algorithms to correct biases that are widely present in current CRISPR screening data, process combinatorial screening data that directly knocks out two genes, and use genomics profiles to predict cancer essential genes and “synthetic lethal” genes (genes whose knockout kills cancer cells but keeps normal cells intact). This project will provide necessary tools for scientists around the world to better analyze and interpret CRISPR screening results, and to identify and predict synthetic lethal targets to accelerate the search of potential drug targets. Furthermore, novel cancer driver genes and synthetic lethal targets will be identified, leading to novel therapeutic targets in cancer.





Elsje Pienaar, PhD

Purdue University

“Integrating In Vitro and Computational Approaches to Accelerate Drug Development for TB/HIV Co-Infection”

Tuberculosis (TB) and HIV are deadly infections and TB/HIV co-infection is common. TB/HIV co-infection further complicates the individual infections and presents treatment challenges, including drug-drug interactions, excessive inflammation and reduced treatment efficacy. TB/HIV co-infection is more than the sum of its parts, and it is becoming clear that treatment should be more than standard anti-TB and anti-retroviral treatment given together. Treatment design in the context of host-pathogen-drug interactions can be challenging using experiments alone. This project aims to build a drug development tool integrating experimental models with computational simulations of co-infection. This integrated system considers complex interactions as well as physical structures at the site of infection, all of which affect treatment efficacy. In this project, the team is developing a co-infection disease simulation, building on existing simulations of TB and experimental co-infection results. The disease simulation will set the stage for future applications to quickly and cost-effectively explore large treatment design spaces, predicting optimal treatment strategies to be tested in the experimental model. This integration of experimental and computational approaches advances a drug development strategy in which sophisticated and mechanistic computational tools become part of routine data analysis, complementing usual statistical and image analyses.



PHARMACEUTICS

The PhRMA Foundation began funding awards in Pharmaceuticals in 1972.

2019 PREDOCTORAL FELLOWSHIPS IN PHARMACEUTICS

As one of the Foundation's longest-standing programs, the Predoctoral Fellowship in Pharmaceuticals 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 PhD candidates begin their final research project.

“The PhRMA Foundation's Predoctoral Fellowship in Pharmaceuticals has enabled me to devote an entire year to the advancement of my proposed research strategy. I have been able to focus on publishing and sharing my research with other scientists at various professional conferences, due to the financial independence this fellowship has afforded me.”

Irnela Bajrovic | University of Texas at Austin



Irnela Bajrovic

The University of Texas at Austin

“Evaluation of Thermostable Thin Films as a Novel Vaccine Dosage Form”

Five of the top ten leading causes of death in low-income countries are caused by infectious agents because existing vaccine technologies require expensive production techniques, such as freeze-drying, as well as cold chain maintenance. Therefore, this study aims to be the first to successfully stabilize live vaccine in a thin film that is administered to the buccal cavity. Preliminary results have shown that films stabilize virus in an amorphous matrix of polymers and excipients. Furthermore, sublingually vaccinated mice and guinea pigs had stronger immune responses, and comparable protective efficacy, to intramuscularly immunized animals when challenged with Ebola virus. Therefore, the project hypothesizes that the presence of a novel surfactant stabilizes virus at elevated temperatures and results in increased permeability of virus across the buccal membrane, which induces a strong immune response and protective efficacy against Ebola challenge. To test this hypothesis, studies evaluating the ability of films to withstand a wide range of temperatures will be prepared alongside analytical tests to identify the mechanism behind viral stabilization; permeability studies will optimize formulations using buccal explants for in vivo delivery; and the optimal dose to elicit an immune response in mice and guinea pigs will be determined and animals will be lethally challenged with Ebola virus, under biosafety level 4 conditions at The University of Texas Medical Branch in Galveston.

“The Predoctoral Fellowship in Pharmaceuticals has given me the freedom to pursue my own research goals. With support from the PhRMA Foundation I am able to be fully immersed in my research, allowing me to become a better scientist and build skill sets that will make me a competitive candidate for a career in the pharmaceutical industry.”

Lia M. Bersin | Purdue University



Lia M. Bersin

Purdue University

“Understanding the Solid State Mechanisms of Two Chemical Degradation Reactions in Proteins and Peptides: Pyroglutamate Formation and Asparagine Deamidation”

A significant challenge for pharmaceutical scientists during protein therapeutic development is maintaining the molecule's native structure, which ensures safety and efficacy of the drug product. For this reason, understanding and controlling protein degradation is critical. Large molecules, such as therapeutic proteins, monoclonal antibodies (mAbs), and antibody drug conjugates (ADCs), are particularly challenging because of their immense size and complexity. To overcome these instabilities, protein therapeutics are often freeze-dried and stored in the solid form. The removal of water and decreased molecular mobility is thought to minimize degradation potential. However, reactivity is still often sufficient to cause instability. Formulating in the solid state is particularly challenging because there are significant gaps in the understanding of chemical degradation reactions in this phase. The effect of pH is often an important factor in the solution state, however there is no true definition of pH in the absence of water. It is often assumed that solid-state reactions simply parallel those of the solution state, but that is not always the case. Therefore, the objective of this work is to gain a better understanding of two chemical degradation reactions in the solid state: pyroglutamate formation and asparagine deamidation. Specific attention will be given to the influence of solution pH prior to freeze-drying. Using these two reactions as models, this work will also investigate the use of solid-state hydrogen deuterium exchange mass spectrometry (ssHDX-MS) as a means to measure hydrogen ion activity in solids, and thus serve as a surrogate for solid pH measurement.



Matthew DeFrese

University of Kentucky

“Investigations of Nanoscale Structural Organization Within the Disordered World of Amorphous Spray Dried Dispersions”

Enabling formulations for the enhancement of solubility have become increasingly necessary in modern drug development, as an estimated 90% of new chemical entities are found to be poorly water-soluble. Amorphous solid dispersions (ASDs) have become a proven and powerful strategy to address the insufficient bioavailability of such compounds by greatly enhancing the dissolution rate through disruption of the crystal lattice and delivering the drug in a high energy disordered state, which is generally stabilized by a polymer additive. The success of this approach is evidenced by the striking growth of FDA approvals of such products since the turn of the century. Yet, despite their growing prevalence, many open questions remain with respect to the effects of formulation and processing factors on critical attributes – such as the stability and dissolution

of ASDs. For example, spray drying is one of the leading methods of manufacture for these formulations – yet the role of solvent-polymer-drug interactions and their effects on product performance and quality are poorly understood. This project seeks to understand how the role of solvent interactions in spray dried dispersions (SDDs) may dictate product performance by controlling the nanoscale structural organization of these materials in the solution state, which can then be frozen into the solid dispersion due to the rapid drying and solvent removal of the spray drying process. Through the use of advanced characterization techniques, it is expected that a fundamental understanding of drug-polymer interactions on product performance can be developed to aid in the design of robust and reliable medicines of the future.

“The Predoctoral Fellowship in Pharmaceuticals has given me the freedom to explore the promise of my project with greater focus. I can let the science lead towards exciting new avenues for application and commit to understanding process fundamentals that will help bring this new technique to the clinic. I am excited for the possibilities of my project and am grateful for the role the PhRMA Foundation has played in advancing it.”

Chester E. Markwalter | Princeton University



Chester E. Markwalter

Princeton University

“Enabling Biologics Encapsulation in Polymeric Nanocarriers: Technology Design from Process to Application”

The encapsulation of water-soluble therapeutics and biologics into nanocarriers to achieve novel therapeutic behavior has been envisioned for decades, but clinical translation has been hampered by complex production strategies. The methods that have been developed are not economically viable because each approach loads the therapeutic into the carrier inefficiently. To address this unmet need, this project has developed a scalable and efficient method to form polymeric nanocarriers encapsulating water-soluble therapeutics. Called “inverse Flash NanoPrecipitation,” the technique achieves biologic loadings (wt% of total formulation) that are 10 times higher than currently possible. This work has demonstrated the broad applicability of the process by formulating over a dozen different oligosaccharides, antibiotics, peptides, proteins, and RNA into nanocarriers on the order of 100 nm with high reproducibility. Model enzymes such as lysozyme and horseradish peroxidase have been shown to release from the nanocarriers with 99% retained activity in a sustained manner. In vivo tests of the nanocarrier, examining biodistribution of the constructs and demonstrating potency of the encapsulated therapeutic, are being carried out. These results demonstrate the potential for commercial implementation of this technology, enabling the translation of novel treatments in immunology, oncology, or enzyme therapies.

2019 POSTDOCTORAL FELLOWSHIPS IN PHARMACEUTICS

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



Ameya Kirtane, PhD

Massachusetts Institute of Technology

“High Throughput Adjuvant Discovery for Treating Metastatic Melanoma”

Melanoma patients who do not respond to immunotherapies will benefit significantly if these therapies are combined with cancer vaccines. An ideal cancer vaccine should contain adjuvants that deliver the antigen to dendritic cells and stimulate them to produce a CD8+T cell response. Unfortunately, most adjuvants perform only one of these functions, often suboptimally. Hence, there is a critical need for adjuvants that deliver tumor antigens intracellularly and activate dendritic cells. Delivering antigens adsorbed on nanoparticles enables intracellular delivery. Moreover, the materials used in some nanoparticles can activate dendritic cells, though what material properties are required for such activation remains unclear. To generate an effective cancer vaccine, this project will synthesize a library of nanoparticles from >300 novel polymers. The project will measure their ability to deliver antigen and activate dendritic cells using high throughput flow cytometry. Finally, it will test the anticancer efficacy of lead vaccines in combination with FDA approved immunotherapies in a mouse melanoma model. Completion of this work will help identify a vaccine for melanoma. Additionally, multi-parametric data obtained from the screens will help establish a structure-function relationship between polymers and dendritic cell activation, providing critical information for future vaccine development.

2019 RESEARCH STARTER GRANTS IN PHARMACEUTICS

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.

“I am honored to be a recipient of the PhRMA Foundation Research Starter Grant in Pharmaceuticals. With this award, the PhRMA Foundation jump-started my independent research program and allowed me to focus my efforts on my passion to improve clinical translation of nanomedicines. This grant has already resulted in training aspiring pharmaceutical scientists, several conference presentations, a research manuscript, and federal funding that focuses our work on health disparities in African American breast cancer patients. Thank you PhRMA Foundation for your support and your efforts to advance pharmaceutical innovation.”

Michail Kastellorizios, MSc, PhD | University of North Texas Health Science Center



Michail Kastellorizios, MSc, PhD

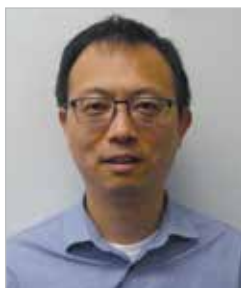
University of North Texas Health Science Center

“A Biopsy-based Method to Improve Clinical Translation of Anticancer Nanomedicines”

In the fight against cancer, nanomedicine has offered several breakthrough innovations that have led to improved therapies and diagnostic tools. However, translation of successful animal testing to clinical efficacy has been challenging for nanomedicines, even more so than conventional anticancer drugs. In addition, due to their complexity, nanomedicines, even clinically successful ones, are difficult to manufacture in a reproducible way; in fact, availability has been interrupted in the past due to manufacturing limitations, as was the case for Doxil® (pegylated liposomal doxorubicin). In this project, interfacial tension measurements are investigated as a potential physicochemical characterization tool to demonstrate reproducibility. Furthermore, interfacial tension was used to quantify interactions between clinically available nanomedicines and tumor biopsies as well as tissues from animal models that are typically used in the drug development process. A major part of this work focuses on developing a patient biopsy processing method that will allow researchers to test their experimental nanomedicines against specific patient groups. The method that is being developed is designed to use the minimum amount of biopsy material with minimum processing in order to preserve each patient's individual tumor characteristics. Future work will build on the foundational knowledge to be gained here and will be geared towards clinical studies to correlate tumor/nanomedicine affinity with treatment outcomes per patient group. Ultimately, this work aspires to improve the clinical translation of novel nanomedicines and ensure the delivery of the right cancer treatment to the right patient.

“I am grateful for the PhRMA Foundation’s Research Starter Grant. It gave me the financial support to carry out my research plan to gain fundamental knowledge of this novel pharmaceutical processing and to establish my research team as the leader in the field of continuous granulation.”

Feng Zhang, PhD | The University of Texas at Austin



Feng Zhang, PhD

The University of Texas at Austin

“Mechanistic Investigation of Continuous Twin-Screw Melt Granulation”

Continuous manufacturing holds great promise for improving the American drug market. Continuous manufacturing can improve drug quality, address the shortage of medicines, lower drug costs, and bring pharmaceutical manufacturing back to the United States. Continuous manufacturing integrates traditional multi-step batch processes into a single system that is based on modern process monitoring and controls. A steady output of drug products is achieved using a steady input of raw materials. Twin-screw melt granulation (TSMG) is an emerging manufacturing technology that has been proven with a limited number of drug products on the market, and it holds the promise of becoming a leading granulation process. It offers the benefits of both melt granulation processing and continuous processing. This study presents a systematic approach for investigating the applicability and mechanisms of TSMG. This project is the first reported attempt to assess the thermal and mechanical stresses that occur during TSMG. Novel concepts, including pre-plasticization and transient plasticization, as well as split feeding as methods to reduce thermal and mechanical stresses, are investigated. The results from this study can be used to guide a rational formulation and process design to melt granulation in order to improve the flow and compaction properties.





The Foundation was honored to present its 2019 awards at distinguished scientific annual meetings throughout the country and its own conference in Washington, DC.

2019 AWARDS

Association for Clinical and Translational Science (ACTS)

Washington, DC on March 7, 2019

American Society for Clinical Pharmacology and Therapeutics (ASCPT)

Washington, DC on March 14, 2019

American Society for Pharmacology and Experimental Therapeutics (ASPET)

Orlando, Florida on April 6, 2019

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

New Orleans, Louisiana on May 22, 2019

American Association of Pharmaceutical Scientists (AAPS)

San Antonio, Texas on November 4, 2019

The Next Generation of Value Assessment: Including the Patient Voice

Washington, DC on November 12, 2019





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TREASURER'S REPORT



Thanks to the ongoing support of our generous benefactors, the Foundation has continued to move forward with important new initiatives developed with our board of directors in alignment with PhRMA member company priorities. The Foundation is dedicated to improving public health by proactively investing in innovative research, education and value-driven health care and I am excited to share the details of our progress with you.

I am pleased to report the PhRMA Foundation achieved its financial goals in 2019 and is planning to make an even greater impact in 2020 with restructured core programs and expanded programming. Member company contributions were \$3.2 million, which is 9% higher than 2018. These contributions, along with its investments, are the Foundation's sole support.

The Foundation's total expenditures were \$5.2 million in 2019 versus \$4.2 million in 2018. The increase is due to the Value Assessment Initiative as this program completes its second year of funding awards. This program is now fully implemented and is funding four Centers of Excellence as well as grants and awards. The program spending in this category alone increased 44% over the previous year. We invested in bolstering the Value Assessment communications activities in 2019 to promote the activities of our researchers, who are focused on patient-centered value assessment.

Net Assets at December 31 were \$23.4 million, a 7.6% increase from the prior year. The increase in net assets is attributable to the return on the Foundation's investments. Financial details are shown in the accompanying Statement of Activities.

Sincerely,

A handwritten signature in dark ink, appearing to be 'A. Plump', with a long, sweeping horizontal line extending to the right.

Andrew Plump, MD, PhD
Treasurer, PhRMA Foundation

STATEMENT OF ACTIVITIES

For the year ended December 31, 2019

INCOME	
Contributions	\$3,201,620
Contributions – in kind from PhRMA ¹	\$67,478
Interest and Dividends	\$578,459
(Realized and Unrealized) Gains in Securities	\$3,264,964
Other Income	\$144,775
Total Revenue and Support	\$7,257,296

EXPENSES	
PROGRAMS	
Awards in Excellence	\$15,413
Clinical Pharmacology Program	\$207,000
Health Outcomes Program	\$338,333
Informatics Program	\$525,000
Pharmaceutics Program	\$421,667
Pharmacology Program	\$678,553
Regulatory Science Program	\$105,000
Translational Medicine and Therapeutics Program	\$435,975
Value Assessment Initiative	\$1,186,778
AFPE Fellowship Award	\$11,000
Subtotal – Grants and Awards	\$3,924,719

OTHER	
Program Expenses and Services	\$981,259
Events and Meetings	\$48,499
Total Program Services	\$4,954,477

SUPPORTING SERVICES:	
Management and General	\$197,537
Rent & Accounting Services ¹	\$67,478
Fundraising	\$1,290
Total Supporting Services	\$266,305

TOTAL EXPENSES	\$5,220,782
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¹ Rent and Accounting Services are donated by PhRMA

Change in net assets	\$1,775,513
Net assets beginning of year	\$21,622,391
Net assets at end of year	\$23,397,904

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PhRMA FOUNDATION PROGRAMS FOR 2020

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Pharmacology/Toxicology			
Predocutorial Fellowships in Pharmacology/Toxicology (1978)	8 awarded/up to 2 years	\$400,000 total \$25,000 per award per year	September 1, 2019 December 15, 2019 January 2020
Postdoctoral Fellowships in Pharmacology/Toxicology (2002)	2 awarded/2 years	\$200,000 total \$50,000 per award per year	September 1, 2019 December 15, 2019 January 2020
Research Starter Grants in Pharmacology/Toxicology (1972)	1 awarded/1 year	\$100,000 total \$100,000 per award per year	September 1, 2019 December 15, 2019 January 2020
Health Outcomes			
Predocutorial Fellowships in Health Outcomes (2002)	3 awarded/2 years	\$150,000 total \$25,000 per award per year	February 1, 2020 April 15, 2020 July 2020
Postdoctoral Fellowship in Health Outcomes (2002)	1 awarded/2 years	\$110,000 total \$55,000 per award per year	February 1, 2020 April 15, 2020 July 2020
Research Starter Grants in Health Outcomes (2002)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	February 1, 2020 April 15, 2020 July 2020
Informatics			
Predocutorial Fellowships in Informatics (2009)	5 awarded/2 years	\$250,000 total \$25,000 per award per year	September 1, 2019 December 15, 2019 January 2020
Postdoctoral Fellowship in Informatics (2002)	2 awarded/2 years	\$200,000 total \$50,000 per award per year	September 1, 2019 December 15, 2019 January 2020

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Pharmaceutics			
Predoctoral Fellowships in Pharmaceutics (1987)	2 awarded/2 years	\$100,000 total \$25,000 per award per year	September 1, 2019 December 15, 2019 January 2020
Postdoctoral Fellowship in Pharmaceutics (1992)	1 awarded/2 years	\$100,000 total \$50,000 per award per year	September 1, 2019 December 15, 2019 January 2020
Research Starter Grants in Pharmaceutics (1972)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	September 1, 2019 December 15, 2019 January 2020
Translational Medicine & Therapeutics			
Postdoctoral Fellowships in Translational Medicine (2016)	2 awarded/2 years	\$240,000 total \$60,000 per award per year	February 1, 2020 April 15, 2020 July 2020
Research Starter Grants in Translational Medicine (2016)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	February 1, 2020 April 15, 2020 July 2020
Value Assessment Initiative			
Challenge Awards (2018) for Value Assessment	4 awards	\$5,000 - \$50,000 per award	Fall 2020
Research Awards (2018) for Value Assessment	3 awarded/ 1 year	\$300,000 total \$100,000 per award per year	September 1, 2019 December 15, 2019 January 2020

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.



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