



2018

ANNUAL REPORT



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MISSION STATEMENT



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

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

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



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MESSAGE FROM THE CHAIRMAN



As chairman of the PhRMA Foundation, I am a devoted champion of our extraordinary scientists. Foundation grantees are designing and piloting so many exciting and innovative studies on treatments for diseases like tuberculosis, Parkinson's, diabetes, lupus, addiction, and HIV, just to name a few. I can't think of a better place to share some of this groundbreaking research than right here in this letter.

Hunter Shain, an assistant professor of dermatology at the University of California, San Francisco, is exploring the time course of disease progression for melanoma, a cancer estimated to affect more than 190,000 people this year alone. To determine when genetic alterations occur, Dr. Shain examines malignant tissue as it first surfaces from an existing mole, as well as surrounding healthy skin. His process has paved the way for diagnostic biomarkers that can distinguish benign from malignant nevi and anticipate which moles are more likely to become melanomas.

This is just one example of the trailblazing studies supported by the PhRMA Foundation. Other funded scientists—many featured in this Annual Report—are engineering novel strategies and methods to make medicine more affordable, more personalized, and more manageable.

All of this phenomenal science begins with Foundation grants and fellowships and we are constantly asking ourselves how we can better serve our young scientists. Over the past year, we have laid the groundwork to help grantees fulfill critical needs across the pharmaceutical industry by reshaping our core programs.

In 2020, we will roll out four new programs: Drug Discovery, Drug Delivery, Translational Medicine, and Outcomes Research.

Driving this restructuring is our shift from a skill and discipline based focus to a broader, multidisciplinary scope that covers more territory across the drug development spectrum. With the support of our member companies, we will forge new pathways in value assessment and other promising fields, like digital medicine.

Health IT is poised to spur innovation throughout the biopharmaceutical industry. By leveraging real-world data and sophisticated technologies, we can learn more about patients, expand access to quality services, reduce excessive spending, and achieve greater outcomes. The Foundation's new Data and Technology program will bring much-needed funding opportunities to this emerging area.

As we evolve the infrastructure of the Foundation's core programs, our commitment to people and patients has never been stronger. Foundation scientists are bringing real change to medicine and solving some of the greatest healthcare dilemmas of our time. And it all starts right here.

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

MESSAGE FROM THE PRESIDENT



To keep pace in a complex and ever-changing healthcare environment, we are always looking forward. Even our most successful programs can't rest on their laurels. We strive to be nimble, responsive, and relevant, moving with the tide and playing a pivotal role as our industry redefines itself.

Take the dynamic field of health outcomes, for example. The Foundation established its pharmacoeconomics grant in the 1990s, a precursor to the comprehensive program we offer today. The transformative years of our early funding in outcomes research taught us so much of what we now know about strengthening health systems and infusing value across health settings and services. As the field evolves, so does our program, adopting new insights on healthcare delivery, comparative effectiveness, and patient preferences.

Defining value and assessing the value of health care is becoming a more inclusive practice, and we are supporting efforts to bring more patients to the table. With meaningful input from health stakeholders, we are advancing new tools and methods to bring better, more affordable treatments to as many people as possible. To date, we have contributed more than \$2.8 million toward the design and development of value frameworks that capture the patient perspective and deliver sound evidence on new and existing therapies.

Our four Centers of Excellence in Value Assessment are leading the charge. Each has a different focus in its approach to measuring value, but there is a common thread. All four centers are empowering patients to voice their concerns and priorities when making decisions about a particular treatment. From parsing patient-reported data to partnering with patient advocacy groups, the centers involve patients at every level. A much greater understanding of value from the patient perspective has emerged, with personal but universal values like “hope” and “uncertainty” often holding as much weight as cost or side effects.

Some of the most innovative research in value assessment is under way at the Centers of Excellence, where multidisciplinary teams are working together to address inefficiencies in health care. These groups have developed and tested strategies to make value a formal standard of care, informing treatment decisions, reducing wasteful spending, and eliminating medicines and services that have little or no clinical benefit.

Over the coming years, we will continue to support initiatives that connect better health outcomes to value. Committed to our mission to make life-saving, cost-effective medicines available for all, we are preparing the next generation of scientists and practitioners to overcome even the most complex challenges in health care and help shape a system where patients always come first.

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

Eileen Cannon, PhRMA Foundation President



AWARDS IN EXCELLENCE

The PhRMA Foundation annual Awards in Excellence recognize former grant recipients whose academic and scientific achievements distinguish them as leaders in their fields. In 2018, the Foundation was honored to name two accomplished scientists, Dr. Darrell Abernethy and Dr. Gavril Pasternak, as recipients of the Award in Excellence. Sadly, both of these brilliant scientists have passed away, but their legacies live on in clinical and translational pharmacology and neuropharmacology.

Dr. Abernethy and Dr. Pasternak received PhRMA Foundation grants at the outset of their careers, while they were still deciding on specialty areas. The funding helped propel their careers and led to discoveries that have significantly improved modern medicine.

The Foundation proudly pays homage to Dr. Abernethy and Dr. Pasternak, whose lifetime dedication to research, education, science, and public health will continue to inspire the future generation of pharmacologists.

2018 AWARD IN EXCELLENCE IN PHARMACOLOGY/TOXICOLOGY



Gavril W. Pasternak, MD, PhD

1979 Research Starter Grant in Pharmacology/Toxicology

Gavril Pasternak was the Anne Burnett Tandy Chair in Neurology at Memorial Sloan–Kettering Cancer Center in New York. A specialist in neuropharmacology and pain management, Dr. Pasternak held joint appointments as an attending neurologist and attending physician at the Sloan–Kettering Institute. He was also a professor of neurology, neuroscience, and pharmacology at Cornell University’s Weill Medical School. He passed on February 22, 2019.

Dr. Pasternak earned his MD in 1973 from Johns Hopkins University (JHU) School of Medicine in Baltimore, Maryland. He continued his education at the university, receiving his PhD in pharmacology and experimental therapeutics two years later. From 1975 to 1978, he completed postdoctoral training at Hopkins.

One of the first to identify and characterize the opiate receptor in the 1970s, Dr. Pasternak later discovered the “Sodium Effect” and proposed that sodium ions play a role in the interconversion of agonist and antagonist receptor conformations. Today this finding applies to almost all G–protein coupled receptors. Following the discovery of the mu opioid receptor gene *Oprm1*, his group identified a vast array of mu receptor splice variants. Dr. Pasternak synthesized a series of compounds targeting a previously identified truncated isoform, which yielded opiate drugs up to 100-fold more powerful than morphine, but without respiratory depression or physical dependence. From these, a lead compound has been selected for clinical development.

Dr. Pasternak’s work has greatly improved our understanding of opioid action and patient variability. For his innovative research in pain therapy, he received many awards and honors, including the Frederick W. L. Kerr Basic Science Research Award from the American Pain Society, the Millennium Prize from the Norwegian University of Science and Technology, the S. Weir Mitchell Award from the American Academy of Neurology, and a Senior Scientist and MERIT Award from the National Institute on Drug Abuse (NIDA). In 1993, Dr. Pasternak was elected to the JHU Society of Scholars. He was a fellow of the American Neurological Association and American Academy of Neurology and ranked among ISI’s most “Highly Cited Researchers.” He was listed in the *Best Doctors in America* for more than 15 years.

From 1989 to 1997, Dr. Pasternak directed and co-directed the Graduate Program for Neuroscience at Cornell University. He also co-directed the university’s Summer Minority Science Program, an opportunity for college students to explore potential careers in science and medicine. He has mentored more than a dozen thesis students and fellows.

Dr. Pasternak was a member of the NIDA Board of Scientific Counselors. He served on the *Cellular and Molecular Neurobiology* editorial board since 1987, the *Synapse and Analgesia Reviews* editorial boards since 1994, the *Molecular Pharmacology* editorial board since 1998, and the *Neuropeptides* editorial board since 2009. From 1998 to 2010, Dr. Pasternak was the executive editor for *Neuropharmacology*. He published more than 430 research articles, 14 patents, and five books.

An Interview with *Gavril W. Pasternak, MD, PhD*

1979 Research Starter Grant in Pharmacology/Toxicology

Q How is your research on opioid receptors and alternative splicing changing pain treatment?

A Clinicians have always known that patients respond to opioids with subtle differences. But trying to explain this kind of diverse activity is not so simple. With a single receptor, the reaction should [theoretically] be the same, because that receptor always works the same way. However, the pharmacology of these drugs isn't consistent with a single receptor that can explain all their actions. Genes are made up of introns and exons—stretches of DNA. An intron is a stretch of DNA that never makes it into a protein; an exon is a stretch of DNA that does. Not every exon makes it into every protein, but you can pick and choose the exons that do. Depending on the exons in your protein, you get moderate variations. We have shown these slight distinctions have a major impact on opioid actions. With alternative splicing, where there are multiple receptors, you can create drugs that are rather unique ... they lack the traditional side effects associated with opioid use. For example, we've been working with drugs that are potent analgesics but will not cause respiratory depression or physical dependence. Other groups have taken different approaches, but what's coming through across the field is a consensus that we will be able to make these drugs safer. That's the goal.

Q Given what's happening with widespread opioid addiction and overdose deaths in the United States, why is your work more crucial now than ever?

A The opioid epidemic has a major inherent problem. On one hand, these drugs play a significant role in clinical care. On the other, there's the potential for abuse and addiction. So you can't just say let's get rid of them all. In many cases, opioids are the best and most effective option for pain relief. We want to be able to use these drugs but modify their danger. That also entails getting the maximum efficacy at the lowest dose.

Q Why is it so important to individualize therapy for every patient in pain?

A Mainly because not every patient will respond to every drug in the same way. When you think about it, that makes sense. People don't look the same. We don't all have the same hair color; we don't wear the same shoe size. Genetic differences lead to variability. We see this all the time in other diseases, like cancer. Individualization has to be based on markers, on genes.

Q You received the PhRMA Foundation Research Starter Grant in Pharmacology/Toxicology in 1979. How do you think it has affected your career?

A In those days, a \$5,000 grant went far. For me it meant having flexibility in my research to try and do new things. It gave me a sense of self-confidence, which is crucial. And it made the people who hired me more confident too. When you take a new job, you have no track record and no one really knows how you're going to fare. But when you are evaluated by your peers and your work is found to be good, it's very validating. There was this impression that maybe I was worth the time and investment. All of this made an enormous difference in terms of pushing my career forward.

Q As a mentor, how do you think other young scientists benefit from having the same freedom and wherewithal to pursue their research interests?

A Anyone can have great ideas, but until your ideas can be translated into real science and real results, there's this nebulous quality about them. Giving a young scientist the opportunity to jump in and prove his or her ability to accomplish things is so important. Many people don't get that chance.

Q You've worked with kids as young as teenagers in your lab. Have any of them gone on to pursue scientific careers?

A Back in the 80s and 90s, I'd easily have five or six high school kids in my lab at any given time. Quite a few went into medicine or medical fields. My goal is not so much to train scientists but to train young people to think critically. To me, a PhD is not an accomplishment of papers—it's a method of assessing a question, designing an approach, designing an answer, and then solving that question. Whether these kids go into science or not, critical thinking is a skill that can be extrapolated to any job, anywhere.

Q How do you stay engaged with the scientific community outside your work at the cancer center?

A Nothing can take the place of one-to-one interaction. Meetings are the best way for me to learn and establish collaborations. The American Society for Pharmacology and Experimental Therapeutics Annual Meeting is one I try not to miss. I also have a very strong connection with the National Institute on Drug Abuse, and I serve on a number of their committees. I really consider this work my civic duty, but it's also rewarding to talk to people with a different perspective—for example, people from the treatment profession. It's fascinating to hear their views because they are so different from the clinical view.



2018 AWARD IN EXCELLENCE IN CLINICAL PHARMACOLOGY



Dr. Darrell Abernethy *1974 Medical Student Award*

On November 18, 2017, the PhRMA Foundation lost Dr. Darrell Abernethy, a brilliant scientist, trusted advisor, and colleague. Dr. Abernethy was a beloved member of the clinical and translational pharmacology community who dedicated his career to serving the public good. Throughout his 30 years in medicine, he sought to better understand the effects of drugs in older adults and improve treatments for this population. He was a longtime volunteer leader for the PhRMA Foundation, serving on the Clinical and Translational Pharmacology Advisory Committee for 23 years and for 12 years as chair. He was also an active member of the Scientific Advisory Committee and Translational Medicine Advisory Committee.

Dr. Abernethy fell in love with science at a young age. His passion for chemistry and medicine led him to the University of Kansas, where he earned his MD and PhD degrees. He received the PhRMA Foundation Medical Student Award in 1974 and studied internal medicine at the University of Miami, Harvard Medical School, and Tufts University, completing his residency and fellowship at Jackson Memorial Hospital, Massachusetts General Hospital, and Tufts–New England Medical Center.

For 8 years, Dr. Abernethy was associate director for drug safety at the Center for Drug Evaluation and Research, where he explored new ways to optimize medicine use among geriatric patients. From 1999 to 2007, he was chief of the Laboratory of Clinical Investigation at the National Institute on Aging. In 2005, Dr. Abernethy was elected president of the U.S. Pharmacopeia (USP) Convention, later serving as chief science officer of USP. He held various positions, including professor, internist, and programs director at Johns Hopkins, Tufts, and Brown Universities and was the Frances Cabell Brown Professor of Medicine and Pharmacology at Georgetown University. All the while, Dr. Abernethy was a trusted mentor and advisor to hundreds of students and early career scientists. He taught as a visiting professor at 17 universities and medical centers across the country and developed a digital training module on the pharmacodynamics of aging.

In 2000, Dr. Abernethy received the Rawls–Palmer Progress in Medicine Award from the American Society for Clinical Pharmacology and Therapeutics (ASCPT). He received the Nathaniel Kwit Award in Clinical and Translational Pharmacology from the American College of Clinical and Translational Pharmacology (ACCP) in 2008 and ACSPT's William B. Abrams Award in Geriatric Medicine in 2011. He was a fellow of ACCP and the American Association for the Advancement of Science.

Though his work demanded much of his time, Dr. Abernethy continually gave back to the field. He served as editor in chief of *Pharmacological Reviews*, as deputy editor of *Pharmacology Research and Perspectives*, as associate editor for the *Journal of Pharmacology and Experimental Therapeutics*, and as an honorary editorial board member for the journal *Drugs* for more than 25 years. He also chaired the Clinical Division of the International Union of Basic

and Clinical and Translational Pharmacology and the Pharmacology Test Committee for the National Board of Medical Examiners.

For the National Institutes of Health, Food and Drug Administration, and USP, Dr. Abernethy served on numerous advisory and steering committees. He also participated on many hospital and university review committees, including the Investigation Review Board for Human Studies at Johns Hopkins Bayview Medical Center, the Research Committee for the Division of Geriatrics at Johns Hopkins University, and the Doctoral Program Advisory Committee for Georgetown University.

Dr. Abernethy's contributions to clinical and translational pharmacology leave a legacy in the field. His wisdom, compassion, and wholehearted dedication to people and patients will always be remembered.





THE EVOLVING ROLE OF VALUE ASSESSMENT IN A COMPLEX HEALTH LANDSCAPE

In 2018, some of the most influential voices in health care challenged conventional notions about value. Standard measures used to select one treatment versus another came into question as a wide range of patient communities and health stakeholders embraced a broader view of value and how to calculate it.

Although methodologies that simplify health care decision-making vary widely, contemporary models and tools are reconceptualizing value, incorporating comprehensive criteria and factors that represent diverse perspectives across the health care spectrum. The value of a treatment changes over time, not just with price fluctuations, but also as new evidence provides a more complete picture of a drug's utility. Assessment frameworks must be flexible and reflect the dynamic and subjective nature of value.

Since launching its Value Assessment Initiative in 2017, the PhRMA Foundation has supported the development of tools and frameworks that assess the value of medicines and health care services from a wide lens. The Value Assessment Initiative is a comprehensive effort to move toward a value-driven health care system that prioritizes both scientific evidence and patient preferences to improve outcomes, minimize inefficiency, and ultimately reduce health care spending.

The Foundation's Challenge Awards, Research Awards, and Center of Excellence Awards promote research, innovation, and the development of patient-focused strategies and methods that facilitate value-driven decision-making. At its four Centers of Excellence in Value Assessment, researchers and health care practitioners are collecting real-world evidence and tracking individual preferences. Armed with this knowledge, they are building frameworks that reflect the value of treatments and outcomes for a wide range of stakeholders.

- At the **University of Colorado Center for Pharmaceutical Value (PValue)**, researchers are testing a quantitative tool to inform decisions around drug coverage and payment. Multicriteria decision analysis (MCDA) draws on stakeholder perspectives, assigning relative importance to the myriad factors that influence health care choices. While traditional cost-effectiveness analysis has been criticized for overlooking such factors—for example, how patients differ and whether a treatment's clinical benefits are worth its cost, MCDA is a structured decision-making tool that incorporates multiple criteria, including patient preferences.

- The **Center for Enhanced Value Assessment (CEVA) at Tufts Medical Center** is capturing novel and non-standard value components by engaging patients and other health stakeholders. Over the next three years, CEVA will develop procedures to quantify a range of value factors and enhance cost-effectiveness analyses.
- Researchers from the **Patient-Driven Values in Healthcare Evaluation (PAVE) Center of Excellence at the University of Maryland School of Pharmacy** have produced patient-derived comparisons of treatment alternatives that incorporate diverse value factors and reflect heterogeneity across populations. PAVE is working with members of the Latinx community, an underserved and minority population, to establish and test these value components. In addition to updating and adapting introductory value assessment training modules for Latinx patient advocacy groups, the PAVE team is designing an intermediate training module to further advance the skills and knowledge of patient organizations.
- In 2018, **ALTARUM and VBID Health established the Research Consortium for Health Care Value Assessment (RC–HCVA)** to pinpoint major sources of wasteful spending. RC–HCVA conducted the first in a series of quick-strike studies in its inaugural year, identifying five low-value and five high-value health services. The methods formulated for this analysis were tested on an all-payer claims dataset for Rhode Island and later implemented with a national dataset of commercial claims.

Better Methods, Better Models: Championing New Research

When CVS Health announced it would exclude certain medicines from health insurance plans, patient groups vehemently opposed. Many faulted the company for endorsing assessments from the Institute for Clinical and Economic Review (ICER), which relies heavily on the quality-adjusted life-year (QALY) metric. These organizations claimed that ICER evaluations disregarded patient needs and preferences in favor of a one-size-fits-all approach.

Collecting data from sources beyond clinical trials and conducting precise, rigorous, and transparent assessments that reflect patient values and differences will lead to greater understanding of the way medicines fully affect an individual's health. To consider the effect of a treatment on overall functioning and quality of life, for example, one must look at a host of factors including and in addition to cost.

As real-world evidence and patient perspectives come together in value assessment, opportunities abound to personalize health care decisions and meet patient needs.

The American Heart Association, the Memorial Sloan Kettering Cancer Center, and the National Comprehensive Cancer Network are a few of the many nonprofit, policy, and research organizations building flexible and responsive assessment frameworks to help define value and address concerns about increasing health care costs. In these models, preferences are not set in stone, but shift and change to represent both practical and personal values associated with a given treatment.

In 2017, the **Innovation and Value Initiative announced its Open-Source Value Project**, a fully transparent, patient-centric platform capable of measuring the value of treatments for diseases like rheumatoid arthritis and lung cancer. The project takes a multidisciplinary approach to understanding and assessing value, incorporating patient input at all stages of research.

The application of real-world evidence, generated largely by patients, has strengthened efforts to bring value assessment to early oncology drug development and across the regulatory paradigm. The **Food and Drug Administration's Framework for Real-World Evidence** seeks to move beyond existing metrics like cost per QALY, culling evidence from patients and the medical community to inform decisions about new and approved medicines. Supported by real-world data, there is potential for more accurate and more rapidly available post-market revisions to labeling, indications, dosing, and administration for various treatments.

Excess costs account for nearly one-third of annual health care spending in the United States—a statistic that spurred the **Pacific Business Group on Health (PBGH)** to create a “waste-free formulary.” PBGH says self-insured employers and prescribers can refer to this list, which includes only medicines with proven clinical value and low-cost alternatives.

Building on recent efforts to make patient voices a key component of medical decision-making, researchers at the **Patient-Driven Values in Healthcare Evaluation** Center of Excellence will continue testing elements of value within its target therapeutic area, chronic obstructive pulmonary disease (COPD). Conducting discrete choice experiments to identify benefit–risk tradeoffs, value factors will be parlayed into quantifiable measures to better inform economic models and evaluations.

The **Research Consortium for Health Care Value Assessment** is extending its initial quick-strike project to track low-value health services and is pursuing new projects within its wheelhouse. The first will assess the methodology of an existing framework that tracks low or no value health care services among a specific population, while the second is a PhRMA–funded effort to streamline spending estimates for low-value care.

The PhRMA Foundation’s Centers of Excellence are leading a revolutionary shift from volume to value across the U.S. health care system. Over the next year, the Foundation will continue to support innovative concepts that challenge traditional measures of quality in favor of patient-centric, holistic, and sustainable strategies. These efforts coupled with our Research Awards and Challenge Awards, highlighted further in this report, create a three-pronged approach to transforming healthcare delivery and remaining at the forefront of positive change.



2018 CENTERS OF EXCELLENCE

In 2018 two 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’s support has been instrumental in ensuring PAVE can continue researching novel ways to incorporate the patient perspective in value assessment, promote value-based decision-making among diverse stakeholders, and engage underrepresented patient communities in discussions of treatment value.”

Susan dosReis, PhD | University of Maryland, Baltimore



Susan dosReis, PhD

University of Maryland, Baltimore

“Center of Excellence for Patient-Driven Value Assessment”

Value assessment must reflect heterogeneity across patients and their preferences. Even though patient centricity and heterogeneity are essential components of value frameworks, there has been insufficient focus on patient-driven value assessment. This leads to erroneous, one-size-fits-all conclusions. The Patient-Driven Values in Healthcare Evaluation (PAVE) Center’s primary mission is to promote the inclusion of diversity in patient voices regarding the elements of value most important to patient communities. The Center’s vision is for patient communities and other stakeholders, such as value framework developers and users, to co-produce reliable and meaningful value assessments to support patient-centered health care decision-making. The PAVE Center’s mission is to enhance the inclusion of the patient community voice in value assessment. Through a partnership between the University of Maryland, Baltimore and the National Health Council, the PAVE Center’s goals are to: a) partner with a broad range of patients and other stakeholders who will be involved in the every aspect of the Center’s planning and key decision-making; b) increase capacity for engagement among patient and research communities, including minority and underserved groups; c) advance methods in capturing the voice of the patient in value assessment; and d) disseminate findings through the wide-reaching communication streams so that messages will reach groups within the patient and research communities. Knowledge gained from meaningful patient community engagement in the education and research on value assessment can lead to better decision-making regarding the value in healthcare interventions.

“ We are extremely grateful to the PhRMA Foundation for funding our Research Consortium for Health Care Value Assessment as part of the Foundation’s Value Assessment Initiative. This grant has enabled my colleagues and me to continue our work on tracking the use of high and low-value clinical services via a series of projects that advance the science of value assessment, use the results of these projects to encourage improvements in the efficiency of health care delivery, and create a learning community of ‘colleagues in value’ to facilitate collaboration and dissemination of the work of other groups conducting research on value in health.”

George Miller, PhD | Altarum



George Miller, PhD

Altarum

“Research Consortium for Health Care Value Assessment”

Traditional approaches to reducing health care spending often involve eroding coverage for care indiscriminately and fail to take a holistic perspective on all sources of costs and value. In contrast, affordability in health care delivery is best achieved by efficiently allocating costs across the entire budget and spectrum of care. The proper framework is to move from how much we spend to how well it is spent. Inefficient spending not only drives up costs, but can negatively impact patient outcomes and consumes resources that could be redirected towards both underutilized routine care (e.g., colonoscopies, lifestyle counseling by primary care providers, and vaccinations), and underutilized innovative care that offers higher value (e.g., Hepatitis C drugs). A more efficient allocation creates the “headroom” for additional spending on high-value services. The Research Consortium for Health Care Value Assessment (RC-HCVA) was created in recognition of this need for greater efficiency. The consortium is working toward optimizing the allocation of resources and promoting value in health care delivery by identifying the greatest contributors to waste and supporting efforts to redirect resources towards high-quality, high-value care. Co-directed by George Miller at Altarum and Mark Fendrick at VBID Health, the RC-HCVA brings together researchers working in the health care value space to collaborate, share findings and develop research ideas to aid decision-makers seeking to address health care inefficiencies. Partnerships between the RC-HCVA and organizations that serve as data repositories will help link researchers with needed data. The RC-HCVA conducts “quick-strike” projects that can be used as the foundation for building more sophisticated research endeavors and models of identifying and addressing low-value care, interventions to promote the use of high-value care, and best practices in allocation to optimize resources and spur affordability.

2018 RESEARCH AWARDS

The purpose of these awards is to improve value assessments by ensuring they are patient-centered, evidence-based, appropriately account for the nature of medical progress, take a system-wide perspective, and are developed through an open and transparent process allowing for input from a range of stakeholders.

The funding supports projects that identify and address challenges in research conducted to assess the value of medicines and health care services. Three scientists received this award in this inaugural program.

“The value assessment award from the PhRMA Foundation has allowed me to expand my research scope into a new and interesting area and has provided an opportunity to support and train graduate students as they pursue their degrees.”

Josh J. Carlson, PhD | University of Washington



Josh J. Carlson, PhD

University of Washington

“Exploring Alternatives to the Conventional QALY”

The quality-adjusted life-year (QALYs) is a convenient measure that combines quantity and quality of life into one metric, allowing analysts to compare changes in health status across conditions. The commonly used form, A.K.A. the “conventional QALY,” was developed to inform resource allocation decisions across various healthcare interventions. However, use of the QALY in decision making has been a contentious issue since its inception due to the required assumptions, the source of sample used to value health states, and issues related to equity and distributional considerations. For value frameworks to inform decision making that incorporates all perspectives, alternative approaches to estimating the QALY may need to be developed and/or implemented. This research project will bring together theoretical work on improving the QALY with established health economic models for multiple myeloma, multiple sclerosis, atopic dermatitis, plaque psoriasis, osteoporosis, inherited retinal disease, non-small cell lung cancer, asthma, and rheumatoid arthritis. The objective is to inform current policy discussions about value assessment in the United States by identifying proposed methods of utility adjustment, characterizing them in terms of feasibility, and evaluating their use in a set of policy relevant decision models and a newly developed generic simulation model. Overall, the work will advance previous work on this topic with a systematic and comprehensive approach leveraging unique access to a set of recent policy relevant cost-effectiveness models. Should one or more alternative methods be found to be robust, feasible and likely to impact model findings they could become part of a more comprehensive tool kit for cost-effectiveness analysis in the U.S. and allow for stakeholder-specific evaluations.

“ I am appreciative of the PhRMA Foundation having the vision to fund projects related to patient-centered value. There are relatively few funding opportunities to conduct this type of research.”

Shelby Reed, PhD, RPh | Duke Clinical Research Institute



Shelby Reed, PhD, RPh

Duke Clinical Research Institute

“Quantifying the Value of Hope in Cancer Care”

Cancer patients participating in focus groups at the Duke Cancer Institute, conducted to elucidate factors associated with value in cancer care, consistently expressed ‘hope’ as an important feature, often described as living longer and doing things they enjoy. The value of hope concept is represented conceptually in both ASCO’s value framework in its ‘tail of the curve’ domain and as a novel element in ISPOR’s US value framework. To move from conceptualization to application, it is necessary to quantify the relative importance of hope in comparison to other aspects of value. Traditional utility theory defines value as how much people would give up of one desirable object to obtain another desirable object. Thus, to quantify the value of hope, it is necessary to determine what patients are willing to give up to obtain it. Traditional cost-effectiveness analysis multiplies probabilities and health-outcomes to measure the expected effectiveness of treatments. The expected-utility assumption posits that preferences are linear in probabilities and outcomes; thus, small probabilities of large health improvements will be valued the same as large probabilities of small improvements, given the same expected outcome. While this approach facilitates comparisons of alternative treatments, it precludes the possibility of finding differential value between the alternatives based on the certainty of their outcomes. Previous valuation studies have estimated willingness to pay or willingness to reduce expected survival for uncertain but significantly longer survival, and defined this value as the value of hope. One recent U.S. study elicited willingness-to-pay values using a single open-ended question and likely invoked cognitive biases due to poor risk communication. To obtain quantitative measures of the value of hope in cancer care, our project team, including experts in health economics, stated-preference research, decision psychology, oncology, and health policy will design a best-practice discrete-choice experiment (DCE) using novel graphical displays to more clearly depict survival periods and probabilities. We will design survey modules representing different stages of cancer, with expected survival of 18 and 48 months. Survey participants first will choose among treatment options or indicate their indifference to therapies that represent equal amounts of expected survival, but differ with regard to probabilities of shorter and longer survival to test the expected-utility assumption. Then, we will administer a DCE in which survival outcomes will be shown along with two opportunity ‘costs’, out-of-pocket expense and health status. The addition of these two costs will allow us to quantify the value of hope relative to changes in respondents’ income, while moderating survival gains with the health-related quality of life they would experience. The survey will be administered to 150 adults with a history of cancer and 150 adults without a history of cancer.

“ The Value Assessment Research Award has allowed our team to explore how various perspectives impact value assessment and decision making. The findings from this work will provide insight into the utility of incorporating additional perspectives beyond those of society and the healthcare sector into economic analyses, particularly those being done to support value-based care approaches. I am very thankful to the PhRMA Foundation for supporting the value assessment portfolio of projects and believe the research will strengthen the methods supporting evidence-based assessment of healthcare interventions.”

Gillian Sanders Schmidler, PhD | Duke University



Gillian Sanders Schmidler, PhD

Duke University

“Exploring Value-Based Care from Various Perspectives”

Value-based care approaches require some initial judgement about the relative value of different options for addressing a particular health problem so that incentives and disincentives are designed to encourage use of the most effective, and, ideally, cost-effective, strategies. These judgments are often based on formal evidence-synthesis methods, including meta-analysis and cost-effectiveness analysis (CEA). Many key aspects of CEA, including which costs and outcomes to include and the analytic horizon over which those costs and outcomes are measured, are determined by the perspective of the analysis. Differences in perspective may lead to differences in judgments about relative value, which in turn may contribute to difficulty with design and implementation of value-based care. This project seeks to compare the effect of changing analytic perspectives in decision analytic models on conclusions about the relative value of different strategies across several therapeutic areas. We will re-analyze three previously published cost-effectiveness analyses from four different perspectives: (a) society, (b) overall healthcare sector, (c) individual payer, and (d) patient. Differences between these perspectives include the inclusion or exclusion of out-of-pocket and nonmedical costs, the analytic horizon, and the choice of aggregate outcomes such as quality-adjusted life years (QALYs) or discrete benefits (such as cancer deaths prevented) and harms (such as specific treatment complications or side effects). By illustrating the impact of changing perspective on value estimation in terms of both traditional economic measures such as cost/QALY, and in clinical metrics such as the ratio of discrete harms to benefits, this project will provide insight into the utility of incorporating additional perspectives beyond those of society and the healthcare sector into economic analyses, particularly those being done to support value-based care approaches. This insight should prove helpful in design, communication, and dissemination of those approaches by identifying potential conflicts in value conclusions earlier in the process, and by enhancing transparency during dissemination.

2018 CHALLENGE AWARDS

The Challenge Awards program encourages the development and implementation of innovative approaches, methods, models, and tools that measure the full scope of value in health care. In 2018, the Foundation supported three institutions advancing value within the realm of personalized medicine.

This award was designed to encourage innovative approaches in defining and measuring value in health care. In 2018 the PhRMA Foundation and the Personalized Medicine Coalition (PMC) partnered to support this award and the recipients were recognized for submitting research proposals that focus specifically on novel methods for assessing the value of personalized medicine.

The awards were provided to the researchers, who answered the question: ***What are potentially transformative strategies and methods to define and measure value at all levels of decision making that are aligned with personalized/precision medicine?***

2018 Award recipients include:



Lou Garrison, OHE Senior Visiting Fellow and Emeritus Professor at the University of Washington School of Pharmacy and Dr. Adrian Towse of the Office of Health Economics in London, are joint recipients of the first prize of the 2018 Value Assessment Challenge Awards designed to encourage innovative approaches in defining and measuring value in health care.

In their winning paper,

“A strategy to support the efficient development and use of innovations in personalized and precision medicine”



Drs. Garrison and Towse call for a broadening of the concepts of value in personalized/precision medicine, laying out six basic policy principles as pathways to help determine value. These range from the need for flexible, value-based pricing to real-world evidence generation in personalized/precision medicine and the challenging implications for assessing and rewarding value.



Their proposed strategy weaves together various threads of our joint research over the past ten years—much of it in collaboration with others in their field. They recognize the new challenges for health technology assessment in precision medicine and call for a greater focus on ensuring genuine value creation is rewarded appropriately to support optimal rates of long-term innovation.

There is much work to be done to implement this strategy, and they look forward to working together and with other colleagues to move this approach forward.



SickKids

The Hospital for Sick Children, Toronto: Second Place: \$25,000 Award

Robin Z. Hayeems, ScM, PhD, Stephanie Luca, Eleanor Pullenayegum, PhD, and Wendy J. Ungar, PhD, the Hospital for Sick Children, Toronto.

M. Stephen Meyn, MD, University of Wisconsin

“Genome diagnostics: Novel strategies for measuring value”

In their research proposal, Dr. Hayeems and colleagues discuss the substantial medical and economic benefits of genome wide sequencing (GWS) as a means to enhance personalized medicine across a broad range of therapeutic areas, noting that assessing the full value of these technologies requires a set of metrics that extend beyond laboratory-based performance parameters. The authors summarize their progress in developing a methodology for measuring the clinical and personal value of genome diagnostics, building on preliminary findings from the Hospital for Sick Children’s Genome Clinic, a translational genomics research platform that routinely generates genomic data on children with a range of clinical phenotypes.

Building on these preliminary findings, researchers from the University of Wisconsin and the Hospital for Sick Children are developing a methodology to assess the medical and economic benefits of genome-wide sequencing. Stakeholder input and cohort studies will establish construct validity, and a comparative-effectiveness assessment will gauge the value of different genetic tests.



Western University of Health Sciences: \$10,000 Award

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

“Discrete-event simulation: An alternative patient-level modeling approach for value assessment—A cost-effectiveness study of current treatment guidelines for women with postmenopausal osteoporosis”

In his research proposal, Dr. Le discussed discrete-event simulation (DES), an event-driven, continuous time, patient-level modeling method for health economic evaluations that addresses some limitations of other common modeling techniques. Flexibility, the ability to reflect patient heterogeneity, increased precision, and better characterization of modeling uncertainty are advantages in the DES model. Dr. Le’s proposal aims to describe and demonstrate an application of the DES model to evaluate the cost-effectiveness of the current treatment guidelines for women with postmenopausal osteoporosis.

FELLOWSHIPS AND GRANTS



HEALTH OUTCOMES

Pre Doctoral Fellowships in Health Outcomes

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

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

2018 PRE DOCTORAL FELLOWSHIPS IN HEALTH OUTCOMES

“My research goal is to advance the profession of pharmacy through the adoption of innovations in real world organizations. The PhRMA Foundation Pre Doctoral Fellowship in Health Outcomes has strengthened my ability to conduct rigorous research by providing me with the opportunity to focus my time on my doctoral dissertation, improving implementation of immunization registries in community pharmacies. The support provided by the PhRMA Foundation through this award has been instrumental in my growth toward becoming an independent researcher.”

Tessa J. Hastings, MS | Auburn University



Tessa J. Hastings, MS

Auburn University

“Assessing Barriers and Increasing Use of Immunization Registries in Pharmacies: A Randomized Controlled Trial”

In the past decade, the role of pharmacists and others as non-traditional vaccine providers is becoming more common. However, as the number of providers administering vaccines increases, there is a concern of fragmented immunization records in state and regional registries. This is a serious issue at the State level as well as at the provider level. Complete immunization records are necessary for the State to monitor vaccination rates and facilitate outbreak response efforts and recalls. For providers, complete records can be used to determine gaps in vaccinations and ensure that individuals are not over-vaccinated. In order for immunization registries to have complete records, it is critical that each provider administering vaccines, including those non-traditional providers such as pharmacists, participate and update the registry each time a vaccine is administered to a patient. In Alabama participation in the registry is not mandatory; as a result, less than 25% of adults over the age of 19 have immunization data recorded in the state registry. Lack of pharmacy participation may have contributed to these incomplete registry records (only 27% of Alabama pharmacies enrolled). Participation of independent pharmacies is of particular concern as approximately 40% of Alabama pharmacies are independent, but only 4% of independent pharmacies are enrolled in the registry. The purposes of this study are to identify barriers to utilization of immunization

registries within a pharmacy context and *tailor the information learned about barriers into a novel immunization registry training program with strategies specific to individual subsets of pharmacies, independent pharmacies in rural areas*. Doing so will help achieve the long-term goal which is to increase the use of immunization registries in community pharmacies in Alabama. The research design is a mixed methods approach to qualitatively identify contextual barriers and facilitators to registry utilization and quantitatively assess effectiveness of the training program and implementation guide through a randomized controlled trial. The specific aims are to 1) identify barriers and best practices of immunization registry implementation, 2) use a participatory design approach to develop an immunization registry training program, and 3) disseminate and assess the impact of the immunization registry training program among community pharmacies' registry participation rates. The impact of the training program on registry participation rates will be assessed using a randomized controlled trial design comparing Alabama community pharmacies' registry data as well as intention to participate. The expected outcome is to create an effective training program that is scalable and ready for dissemination. If successful, this resource can be replicated and used to significantly impact the completeness and accuracy of immunization registries across the U.S., providing the potential for registries to be used consistently in assessing immunization status and recommending additional vaccines in the pharmacy setting, thereby improving vaccination coverage and making the provision of immunizations safe and efficient.



Nathaniel Hendrix, PharmD

University of Washington

“Using Health Economics Tools to Enhance the Clinical Utility of Machine Learning-Based Diagnostic Algorithms: A Case Study in Breast Cancer Screening”

This research seeks to use the tools of health economics to improve the clinical applicability of diagnostic machine learning. The project will consist of two parts, the first of which will survey clinicians to understand the attributes that would be required of a useful and clinically acceptable artificial intelligence agent that makes decisions about patients without being overseen by a human clinician. For example, the clinicians may be asked how important it is that the algorithm can provide an explanation for its decisions and whether it would affect their attitudes toward the algorithm if it considered patient characteristics not known to be related to the disease. The second section of the project will use health outcomes modeling to assess and compare the performance of machine learning algorithms for diagnosis. As most machine learning algorithms are extremely abstract, it can be difficult to assess how generalizable their performance is. Therefore the aim of this study is to show how modeling patient outcomes that would result from algorithmic decisions can allow their overall performance to be assessed.

“ Through being awarded the PhRMA Foundation Pre Doctoral Fellowship in Health Outcomes, I have been afforded the luxury of being able to focus on my dissertation research, and I can aim to achieve and publish more during my PhD than what was possible without it.”

Ruixuan Jiang, PharmD | University of Illinois at Chicago



Ruixuan Jiang, PharmD

University of Illinois at Chicago

“Assessment of Mode of Survey Administration and Study Design Effects on Preference Elicitation in Health”

With increasing access to the internet and technology in the general population, movement toward online data collection continues to grow. This trend includes studies that assess preferences for services and goods, including health care and the product of health care, i.e. health outcomes. Online data collection is convenient, fast, and cost-efficient, but there may be trade-offs about the validity and generalizability of this data compared to traditional approaches, such as face-to-face or mail-out surveys using pen and paper. In face-to-face data collection, comprehension, attentiveness, and cognitive burden can be managed by a well-trained interviewer; in the interviewer’s absence, such as in online, unsupervised data collection, data quality could suffer as respondents may not understand the task, be careless, and/or feel overwhelmed by the information presented. These concerns are particularly applicable to preference elicitation tasks such as the time trade-off (TTO). TTO tasks are complicated to understand, and face-to-face administration of the TTO is considered the gold-standard. There are fewer concerns about online administration of the discrete choice experiment (DCE), another type of preference elicitation task, and numerous health preference studies have been done using DCE data collected online, increasing in recent years. Modifications to the format of presentation or the study design can reduce the cognitive burden or increase respondent attentiveness to enhance validity of the results for both TTO and DCE tasks. Health preferences are used in important areas of healthcare decision making, both at the population and individual level. Thus, it is important to understand how measurement may vary by mode of data collection and study design. The results of this study will contribute important information regarding how different study specifications compare as well as inform future preference elicitation studies.

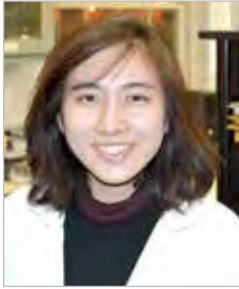


Uriel Kim

Case Western Reserve University School of Medicine

“A Multilevel, Data-driven Approach to Facilitate Precision Lung Cancer Prevention Interventions”

Many of the most common cancers, including lung cancer, display significant racial and ethnic disparities. Even when adjusting for smoking, African Americans have a higher rate of lung cancer incidence than their White counterparts. Once diagnosed, lung cancer mortality disparities are concentrated in African American men, who have a 21.6% higher mortality rate than their White counterparts. These disparities are tremendously magnified in scale because lung cancer is currently the second most common cancer diagnosed across both genders, and it is the most common cause of cancer mortality. To most effectively address these disparities, we must understand which subpopulations (geographically and demographically) have the worst outcomes; and we must do so at a level specific enough to guide interventions. This study will utilize a multilevel data infrastructure to identify census tracts that are “hotspots” of lung cancer disparities and to identify combinations of individual and contextual-level factors that are most closely associated with lung cancer disparities. Our data-driven approach will utilize both Geographic Information System (GIS) approaches and Machine Learning techniques. Utilizing our unique data infrastructure will allow us to examine lung cancer disparities using a rich and complex data source, an opportunity made rare by the often siloed nature of individual data repositories. Collectively, this project will allow us to examine the interactive, interdependent, and intersectional role geographical, contextual, and individual factors play in lung cancer. By providing this specific and actionable information to health systems, public health officials, and advocacy organizations, we hope to significantly enhance our abilities to address lung cancer disparities.



Kathy Trang, MA

Emory University

“Reducing Health Disparities in the HIV Prevention and Care Continuum Through Patient-Centered Mental Health Research”

Extension of pre-exposure prophylaxis (PrEP) and antiretroviral therapy globally has contributed to a reduction in HIV infection, mortality, and morbidity. However, Post-Traumatic Stress Disorder (PTSD), a highly comorbid but treatable psychiatric condition associated with trauma exposure, continues to interfere with treatment uptake, adherence, and outcome, increasing the odds of sexual transmission risk behavior and virologic failure. Emerging evidence further suggests that HIV may not only exacerbate psychosocial stress contributing to general health vulnerability, but also biologically potentiate the development of PTSD through shared neurobiological pathways. To optimize HIV prevention and care, the proposed cross-sectional study (N=200) with nested prospective cohort study will leverage existing infrastructure at Hanoi Medical University (HMU) to test the neurobiological interactions between HIV and PTSD among young men who have sex with men (YMSM), one of the highest risk groups for HIV infection, in Hanoi, Vietnam. While male-to-male transmission is one of the primary routes of HIV transmission worldwide, the pronounced risk ratio (19:1) of YMSM relative to their heterosexual peers in the Asia-Pacific region coupled with the rising HIV prevalence within Vietnam allow for empirically useful comparisons to be made. Thus, focused on a detrimental but understudied comorbidity, this study will first determine the extent to which trauma exposure predicts the frequency and severity of PTSD symptoms among HIV-positive YMSM and HIV-negative high-risk YMSM. Second, it will employ state-of-the-art psychophysiological assessments to assess the biological mechanisms mediating between trauma and long-term HIV-related treatment outcomes (PrEP initiation and viral load). Lastly, using mobile and wearable technologies, this study will translate these measures outside of clinical settings to assess the impact of trauma on everyday risk-taking behaviors vis-à-vis YMSM's stress environments and social relationships. This research will not only advance our scientific understanding of HIV and PTSD neurobiology, but will also strengthen global mental health and HIV treatment and prevention by leveraging our most robust and cutting-edge technologies to identify and intervene in a highly comorbid and understudied yet highly treatable psychiatric comorbidity. In doing so, it aims to set the grounds for the design and delivery of an innovative precision medicine solution that efficiently and effectively provisions resources when, where, and to whom it is most needed.

2018 POST DOCTORAL FELLOWSHIPS IN HEALTH OUTCOMES



Andrew D. Wiese, MPH, PhD

Vanderbilt University Medical Center

“Benzodiazepine Restrictions and Prevention of Adverse Outcomes”

The use of benzodiazepines, one of the most commonly prescribed medications in the United States, is linked to serious health outcomes, including falls, fractures, motor vehicle accidents, and opioid-related overdoses. Although interventions to reduce benzodiazepine use have been implemented in the past, it remains unclear whether those led to the intended reduction in these adverse outcomes or led to other unintended consequences. Therefore, this study will evaluate the impact of benzodiazepine restriction policies on the incidence of falls, fractures, motor vehicle accidents and opioid-related overdoses in the Tennessee Medicaid population. Additionally, the study will determine whether benzodiazepine restriction policies led to an increase in the use of other psychotropic medications. Careful evaluation of the impact of benzodiazepine restriction policies, including their intended and unintended effects, will inform policies that aim to reduce drug-related adverse outcomes, including drug overdoses.



2018 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.



Brittany Lapin, PhD MPH

Cleveland Clinic

“Validity of Proxy Responses: Improving the Interpretation and Utilization of Patient-Reported Outcome Measurements in Clinical Research”

Self-reported health status measures are increasingly utilized to assess outcomes following stroke. As many as 25% of people who have a stroke may be unable to report their status due to language and cognitive impairments. Assessment of outcomes from a caregiver, or proxy, is often substituted for the patient's self-report. While outcome information from a proxy is preferable to no information, research has demonstrated that proxies tend to rate patient outcomes worse than patients rate their own outcomes, and this disparity increases with severity of disease. This is particularly pronounced for the more subjective domains like emotional well-being and fatigue. The proposed research aims to quantify the extent and variability of proxy-introduced bias in a cross-sectional study of 200 patient-proxy dyads answering patient-reported outcome measures (PROMs) across 8 health domains. Patient-proxy agreement for response to treatment will be evaluated within a subset of acute stroke patients who undergo rehabilitation. Additionally, optimal methods will be developed for limiting the bias introduced by proxy responses through comparing a variety of methods including adjustment, weighting, and imputation. These proposed aims, coupled with robust statistical methodology, will greatly enhance understanding of the impact of proxy responses on PROMs following stroke and ability to more effectively utilize PROMs to assess treatment responses in clinical research and care. Findings from this research should be generalizable across many conditions, providing valuable insight into the clinical applicability of proxy responses in PROMs.

TRANSLATIONAL MEDICINE AND THERAPEUTICS

Post Doctoral Fellowships in Translational Medicine and Therapeutics

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

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

2018 POST DOCTORAL FELLOWSHIPS IN TRANSLATIONAL MEDICINE AND THERAPEUTICS

“ I am grateful for the PhRMA Foundation’s fellowship during this exciting time of my training. The PhRMA Foundation’s support has given me the financial freedom to plan and conduct additional experiments. These results will allow me to gain additional publications, as well as preliminary data as I start an independent research career.”

Maureen Carey, PhD | University of Virginia



Maureen Carey, PhD

University of Virginia

“Identification of Pan-*Cryptosporidium* Drug Targets Using a Combined Computational & Experimental Approach”

Cryptosporidium parasites inflict a major health burden as a leading cause of enteric disease, the second leading cause of death in children under five years old. In addition to causing diarrheal disease, *Cryptosporidium* infection in infants negatively impacts growth and cognitive development. Unfortunately, both prevention and treatment of cryptosporidiosis remain challenging. No vaccine exists for this disease, and there are no effective therapeutic drugs available for vulnerable populations, like children, pregnant women, and immunocompromised patients. Drug development is hindered by the lack of biological knowledge of the parasite and the challenges associated with in vitro growth, preventing efficient genetic or drug screens. Additionally, the burden of disease associated with each species of *Cryptosporidium* is only beginning to be appreciated; at least three species of *Cryptosporidium* infect humans and only one of which can be grown in vitro.

This project uses leveraging computational tools and clinical data to identify pan-*Cryptosporidium* drug targets. Specifically, genome-scale metabolic models built from both reference genomes and clinical isolates will be used to conduct an *in silico* drug screen in multiple *Cryptosporidium* species. High-confidence predictions generated from this computational work will be validated in multiple models of disease, *in vitro* and *in vivo*. Ultimately, the goal of this project is to improve our understanding of these important human pathogens and identify novel pan-*Cryptosporidium* drug targets using a combined computational and experimental pipeline.



Kasi McPherson, PhD

University of Alabama at Birmingham

“Early Life Stress Induced Regulation of ET-1 and Vascular Disease”

Exposure to adverse childhood experiences, also known as early life stress (ELS), is an independent risk factor for the development of cardiovascular disease (CVD) in adulthood. Endothelial dysfunction is a major contributor to the development of CVD and has been linked to childhood adversity induced CVD risk. We previously reported circulating endothelin-1 (ET-1) levels are significantly elevated in young adults exposed to childhood adversity in humans. Similar cardiovascular and immunological consequences associated with ELS in humans have also been observed in maternal separation and early weaning (MSEW) in mice, a mouse model of ELS. The preliminary studies have revealed MSEW in mice induced elevated pro-inflammatory mediators and aortic macrophage infiltration as well as increased levels of circulating and vascular derived ET-1. ET-1 via the ETA receptor promotes endothelial dysfunction and vascular inflammation. Hence, the project's previous human studies along with the preliminary data in MSEW mice suggests elevated ET-1 production and, consequently, enhanced ETA activation is associated with the development of vascular dysfunction and inflammation that may contribute to the ELS-induced CVD risk. However, the regulation of ET-1 by ELS and the mechanistic link between elevated ET-1 levels and ELS-induced increased CVD risk remains unknown. Therefore, the overall goal of this postdoctoral fellowship is 1) To test the hypothesis that enhanced ET-1/ETA signaling initiates vascular dysfunction and inflammation in young MSEW mice and 2) To test the hypothesis that increased exposure to childhood adversity is associated with elevated ET-1 levels and biomarkers of future cardiovascular disease in young humans. This translational proposal uses a synergistic, integrated approach with a mouse model of ELS and human correlates to identify novel mechanisms sensitive to ELS that promote the development of CVD.

2018 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.



Sam Emaminejad, PhD

The University of California, Los Angeles

“A Non-invasive and Wearable Pharmacokinetic Monitoring Platform for Personalized Pharmacotherapy”

This work aims to overcome the barriers to personalized dosing and pharmacotherapy by creating an unprecedented non-invasive wearable pharmacokinetic monitoring platform. Currently, medication dosage is prescribed based on statistical averages. Therefore, with no insight into the individual patient's dynamic body chemistry and drug pharmacokinetic profile, it is common for the recommended dosage to fall outside the optimal therapeutic concentration window, triggering adverse events in patients and/or rendering the prescribed pharmacotherapy ineffective. To access the drug's pharmacokinetic profile, the excreted drug in non-invasively retrievable biofluids can be alternatively measured as a proxy measure. Accordingly, a wearable platform is being developed that tracks the target pharmaceutical drug concentration in sweat and correlates the readings to that in blood. The outcome will be an unprecedented wearable pharmaceutical monitoring platform, with real-time information sensing and transmission capabilities, that can facilitate large-scale investigations and remote patient monitoring for a broad range of drug development and clinical applications.



Yong (Tiger) Zhang, PhD

University of Southern California

“Novel Immunotherapeutics for Colorectal Cancer”

Colorectal cancer is the third most common cancer globally. Current first-line treatments for colon cancer include surgery and chemotherapy. However, more effective and safer drugs are still urgently needed due to continuously developed resistance of tumor cells to current chemotherapy. In contrast to conventional treatments, therapeutic agents that can effectively activate the immune system for robustly attacking tumor cells have emerged as increasingly important anti-cancer therapies, attributing to their remarkable therapeutic efficacy and specificity. This work proposes to design and develop novel nanomedicines that selectively redirect and activate immune effector cells against colorectal cancer cells for immunotherapy. The proposed immunotherapeutics in this study are unique and distinguished from conventional regimens, which prove to be unsafe and lack of effectiveness. By combining knowledge and technologies from nanotechnology, cell biology, and protein engineering, innovative agents will be rationally designed and synthesized to activate immune system for the specific killing of colon tumor cells with enhanced efficacy and safety, which are expected to show excellent safety and effectiveness in animal models bearing colon cancer patients' tumor cells. Successful completion of this project will result in an innovative class of therapeutics for more effective treatment of colon cancer. The results from this study as a proof of concept will provide the basis for following early clinical trials. Translation of these innovations into practical applications can be particularly beneficial to patients with refractory and relapsed colon cancer and likely patients with other epithelial cancers.



CLINICAL AND TRANSLATIONAL PHARMACOLOGY

Paul Calabresi Medical Student Fellowship

The PhRMA Foundation began funding Medical Student Fellowships in 1974.

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

2018 PAUL CALABRESI MEDICAL STUDENT FELLOWSHIP



Mihailo Miljanic

Dell Medical School

“Assessing the Effect of Combinatorial Immunotherapy Directed at Micro-Satellite Stable Colorectal Cancer”

Although drug therapy involving immune activation against cancer cells (immunotherapy) has proven to be an effective approach in multiple different types of cancer, it has not shown promising results thus far in micro-satellite stable colorectal cancer. Considering colorectal cancer is the second leading cause of death due to cancer in the U.S., this represents both a major health burden, as well as current gap in treatment for this devastating disease. The lack of response of micro-satellite stable colorectal cancer to immunotherapy has been attributed to the finding that these cells do not express sufficient markers on the cell surface for the immune system to recognize and attack. However, data suggest that these cells can be sensitized to immunotherapy if treated first with other medications such as MEK inhibitors, which increase receptors on tumor cells and enhance recognition of the tumor by the immune system. In addition, Histone Deacetylase (HDAC) inhibitors are FDA-approved anti-cancer drugs that have been shown to increase tumor recognition by the immune system. Building upon this data and aiming to enhance clinical response, this research will center around the use of triple-drug therapy in combining the anti-proliferative and immune-stimulatory effects of MEK inhibitors with that of HDAC inhibition in the presence of a third immune-stimulatory molecule to augment anti-tumor activity. The project objective is to increase the efficacy of immunotherapy directed at micro-satellite stable colorectal cancer in order to address current gaps in treatment for this major health burden.

2018 FACULTY DEVELOPMENT AWARD IN CLINICAL AND TRANSLATIONAL PHARMACOLOGY

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.

“The PhRMA Foundation award has allowed me to concentrate on what I am passionate about — antimalarial drug pharmacology in sub-Saharan Africa — while retaining a position in an academic institution where I can continue to benefit from superb mentorship, rewarding collaborations, and an intellectually stimulating environment.”

Matthew M. Ippolito, MD | Johns Hopkins University School of Medicine



Matthew M. Ippolito, MD

Johns Hopkins University School of Medicine

“Pharmacokinetics and Pharmacodynamics of Artemisinin-based Combination Therapies for Malaria Control and Elimination”

Malaria remains the leading parasitic cause of morbidity and mortality worldwide despite concerted control efforts that have spanned decades and continents. While the scientific pursuit of a highly effective malaria vaccine has been so far unfruitful, antimalarial chemotherapeutics continue to occupy a critical role in malaria control and elimination programs. Specifically, artemisinin-based combination therapies (ACTs) have come to the fore, combining rapidly acting, high-potency artemisinin derivatives with long-acting partner drugs. The World Health Organization has approved several ACTs, among which artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) are two of the most commonly used. Whereas preclinical and clinical investigations of these agents have established them as equally efficacious against clinical malaria, little is known about their differential effects on malaria gametocytes, the transmissible form of the parasite, as well as a post-treatment chemoprophylactic effect conferred by the long-acting companion drugs. The aim of this research is to characterize the pharmacokinetic/ pharmacodynamic profiles of AL and DP as they relate to the drugs' differential effects on malaria gametocytes, and residual protection against malaria recurrences. New knowledge about the pharmacologic drivers of antigametocyte and transmission-blocking effects of antimalarials is needed to update and optimize malaria drug policy, especially in regions of sub-Saharan Africa where gains against the deadly disease have stalled and, in some cases, reversed. This project represents a small but relevant contribution to the global community's efforts to roll back malaria in our lifetime.

PHARMACOLOGY/TOXICOLOGY

Pre Doctoral Fellowships in Pharmacology/Toxicology

Since the program's initiation in 1978, 409 Pre Doctoral Pharmacology and Toxicology Fellowships have helped expand the nation's pool of highly-trained pharmaceutical researchers. The PhRMA Foundation provides awardees with a two-year stipend as they move toward completion of their research for pharmacology and toxicology doctoral dissertations.

2018 PRE DOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY

“The support from the PhRMA Foundation Pre Doctoral award has been a catalyst for my dissertation work. By securing this funding, I was able to perform critical experiments that are central to my hypothesis. This award has also opened up resources that allowed me to travel and present at conferences. These experiences have enriched me both scientifically and professionally. Thank you to the PhRMA Foundation for the funding that shaped my graduate career.”

Katelyn Arnold | University of North Carolina at Chapel Hill



Katelyn Arnold

University of North Carolina at Chapel Hill

“Targeting Sterile Inflammation with Sulfated Oligosaccharides”

While implicated in several diseases, the mechanisms that cause sterile inflammatory pathogenesis remain poorly understood. Damage-associated molecular patterns, including high mobility group box 1 (HMGB1), released by dying cells trigger an innate immune response in acetaminophen (APAP)-induced acute liver failure. Interestingly, the anticoagulant drug heparin decreases early phase liver injury after APAP overdose. However, the use of heparin is complicated with the risk of bleeding. Reports have demonstrated that preparations of non-anticoagulant heparin are protective in this disease model. However, mechanistic studies are severely limited since non-anticoagulant heparin is still a heterogeneous mixture of oligosaccharides that vary in chain length and sulfation pattern. This research utilizes a chemoenzymatic approach to synthesize pure heparin and heparan sulfate oligosaccharides. Using these pure oligosaccharides, the project have demonstrated that a non-anticoagulant oligosaccharide significantly increases the survival rate after APAP overdose in vivo. This research seeks to understand the molecular mechanism and validate the target of the pure oligosaccharide in this model. The approach includes in vivo and in vitro studies as well as chemical biology synthesis techniques and binding studies. This project reveals a potential novel therapeutic strategy for APAP toxicity that targets the sterile inflammatory mediator HMGB1. In doing so, not only will this work lead to a deeper understanding of injury propagating mechanisms in sterile inflammation but will also demonstrate a new way of probing complex biological systems using chemoenzymatically synthesized oligosaccharides.

“ Being from a university not traditionally known for research makes funding harder to come by. This is even more so when the research being done by our lab is a relatively unknown disease like endometriosis. For these reasons financial support from the PhRMA Foundation is much appreciated. With this funding, I am hoping that more light can be shed on this growing disease and the mechanisms behind it. Once the mechanisms are understood, more treatments can be utilized that are tailored to treat the disease itself and not just the symptoms. This fellowship gives me the funding needed to continue and push forward the research and discoveries already being made by our lab.”

Sarah Elizabeth Bruntz | Marshall University



Sarah Elizabeth Bruntz

Marshall University

“Testing New Drug Treatments in Endometriosis Through Targeting Epigenetic Changes”

Endometriosis is an enigmatic disorder that is defined by the growth and presence of endometrial tissue, or lesions, outside of the uterus. Approximately 10-15% of women of childbearing age suffer from endometriosis, but that number may be higher as many women suffering from this disease have not yet been diagnosed. The mechanisms behind endometriosis are not well known or understood at this time. Due to this, treatment options are not specific for the disease. Current treatments are either with medications, such as pain relievers or birth control pills, or surgery, which could include a full hysterectomy if severe enough. It is thought, however, that epigenetics, the stable inheritance of phenotypes of cells and organisms without changes in DNA sequence or content, plays a role in the initiation and disease progression of endometriosis. There has been an observed increase in expression of certain epigenetic marks in endometriosis and it is thought that the environment within women with this disease is causing these epigenetic changes. These epigenetic marks have also been seen in certain types of cancers and have also been targets for treatment as these drugs have been shown to inhibit growth. The goal of this project is to test if the epigenetic modulating drugs will act in the same manner in endometriosis as it does in certain cancers. The project will use animal models of endometriosis to demonstrate if epigenetic modulating drugs are able to inhibit endometriotic lesion formation in vivo. Overall, it is the hope that this project will contribute to a new treatment option for women suffering from this disease.



Amanda Davis

University of Michigan

“Activation of Heat Shock Protein 70 as a Potential Therapeutic Strategy for the Treatment of Neurodegenerative Disease”

Heat shock protein (Hsp70) plays an essential role in protein quality control by selectively promoting the ubiquitination and subsequent degradation of damaged and misfolded client proteins. Thus, activation of Hsp70 is of great interest in the treatment of protein folding diseases. We have shown that activation of Hsp70 enhances the degradation of misfolded neuronal nitric oxide synthase (nNOS) and a polyglutamine mutant of the androgen receptor (polyQ-AR) in cells and alleviates neurotoxicity in a *Drosophila* model of Kennedy's disease, a rare genetic muscular and neurodegenerative disease caused by misfolding and aggregation of polyQ-AR. In the long-term goal of developing disease modifying therapeutics for the treatment of Kennedy's disease, this project is currently carrying out a thermal shift-based high-throughput screen to identify novel compounds that bind Hsp70. The goal of the proposed research is to develop a novel workflow to efficiently identify compounds that enhance Hsp70-mediated ubiquitination and subsequent degradation of misfolded chaperone client proteins. This work flow will include quantitative assays to measure the ubiquitination and degradation of misfolded nNOS and polyQ-AR in vitro, in intact cells, and in mouse brain slices. Moreover, in collaboration with the Protein Folding Diseases Initiative at the University of Michigan state-of-the-art 2D-NMR, X-ray crystallography, and computational modeling will be utilized to characterize the site of binding to Hsp70. This workflow has the potential to advance the development of therapeutics that enhance the degradation of misfolded client proteins for the treatment of Kennedy's disease and other neurodegenerative diseases such as Alzheimer's, Huntington's, and Parkinson's disease which are caused by misfolding and aggregation of the Hsp90/70 client proteins tau, huntingtin, and α -synuclein.

“ I’m extremely honored and lucky to receive the PhRMA Foundation Pre Doctoral Fellowship in Pharmacology/Toxicology. This fellowship not only provides the financial support to allow me to focus on my dissertation research in the home stretch to my PhD, but it has also provided me with the network and resources to support and strengthen my career in the pharmaceutical industry.”

Riann Egusquiza | University of California, Irvine



Riann Egusquiza

University of California, Irvine

“Exposure to PCB-153 Induces Oxidative Stress During SXR Loss-of-Function Resulting in Anemia and Tumor Development”

It is known that many environmental and industrial toxicants can cause or predispose us to adverse health consequences. However, the mechanisms underlying how these chemicals might induce these harmful effects are not always well understood, preventing the development of accurate methods to prevent or treat these conditions following exposure. A class of synthetic chemicals, called polychlorinated biphenyls (PCBs), are persistent environmental toxins that have been classified as probable human carcinogens due to the incidence of cancer in exposed individuals and in rodent studies. Although the risks associated with PCB exposure are well-documented, the molecular mechanisms through which they might elicit these effects remain poorly understood. In a preliminary study, mice lacking a nuclear hormone receptor called the Steroid and Xenobiotic Receptor, SXR, (a key regulator of inducible xenobiotic metabolism) developed anemia and intestinal tumors when chronically exposed to PCB-153. Molecular analyses indicate that tumor bearing mice were under oxidative stress, revealing this as a potential causal factor for the observed tumor and anemia phenotypes. This project aims to investigate the role of oxidative stress in the development of tumors and anemia in mice exposed to PCB-153 and to investigate the importance of SXR in protecting against these harmful effects. The results from this project will provide insight into how environmental toxicants, such as PCB-153, result in an increased incidence of cancer in exposed individuals, as well as establish SXR as an important therapeutic target to prevent the development of or treat these harmful effects of PCB exposure and other conditions related to oxidative stress.



Tamara Escajadillo

University of California, San Diego

“Targeting Cholesterol-Dependent Cytolysin Streptolysin O: Novel Virulence Factor-Based Therapeutics Against Invasive Group A Streptococcal Infection”

Bacterial infections continue to be a significant cause of morbidity and mortality worldwide due to the escalating prevalence of antimicrobial resistance. Therefore there is an acute need to develop innovative strategies to combat the global threat of antibiotic resistance. Among the most promising approaches is boosting host immune cell function and neutralizing key pathogen virulence factors. One important class of virulence factors present in many leading bacterial pathogens, including several antibiotic-resistant strains, is the pore-forming toxins (PFTs). PFTs comprise about 25% of all known bacterial toxins and are produced by both Gram-positive and Gram-negative bacterial pathogens. Due to the deceptive simplicity of their mechanism of action, the downstream effects of these toxins on cell signaling and immune responses have been vastly understudied. Because of the multifaceted role of PFTs in disease pathogenesis, infectious disease therapeutics that neutralize the ability of PFTs to damage host cells can slow the development of bacterial resistance, since it is the virulence mechanism and not the viability of the pathogen that is targeted. This research explores two different approaches for counteracting SLO toxicity, the first is with a pharmacological agent that mimics the target cell membrane and can act as a decoy for the toxin, thereby reducing contact of the PFTs with the host membrane. Second is using CRISPR based-haploid cell genetic screen to identify host factors whose downregulation promote host cell resistance to SLO cytotoxicity. Validated targets will then be screened for pharmacological agents that can mimic the genetic screen results and promote host cell resistance to SLO. Given the wide distribution of PFTs among important human pathogens, these studies have the potential for future expansion to a wide range of bacterial infections in the clinical setting, promoting better patient outcomes and reducing the selective pressures for antibiotic resistance.

“ I am honored to receive a Pre Doctoral Fellowship in Pharmacology/Toxicology from the PhRMA Foundation. The funding has helped make possible our research on intestinal hormone signaling and the early genetic events leading to colorectal tumorigenesis. These insights will directly inform novel hormone replacement strategies for colorectal cancer. On a personal level, this award has provided an invaluable foundation for a career as an independent investigator, for which I am deeply grateful.”

Jeffrey Rappaport | Thomas Jefferson University



Jeffrey Rappaport

Thomas Jefferson University

“Hormone Suppression Silencing GUCY2C is Required for Colorectal Cancer”

Colorectal cancer is the fourth most common cancer and the second leading cause of cancer death in the United States. In over 90% of sporadic colorectal tumors, transformation begins with mutations in APC or its degradation target β -catenin, producing a gain-of-function in TCF-dependent nuclear transcription that drives tumorigenesis. However, mechanisms coupling these mutations to tumorigenesis continue to be refined. GUCY2C is the membrane-bound guanylate cyclase expressed by intestinal epithelial cells, and serves as the receptor for the hormone, guanylin, secreted by the colorectal epithelium. The guanylin-GUCY2C signaling axis contributes to intestinal homeostasis by regulating the continuous regenerative cycles that maintain intestinal epithelial architecture. Interestingly, guanylin, but not GUCY2C, is among the most commonly lost gene products in colorectal cancer in humans and mice. Furthermore, GUCY2C agonists reduce epithelial transformation in genetic, carcinogen, and inflammatory mouse models of intestinal tumorigenesis. Together, these observations suggest a pathophysiological model in which transformation reduces guanylin expression, silencing GUCY2C signaling and driving tumorigenesis. The present studies test the hypothesis that APC- β -catenin-TCF signaling suppresses guanylin expression. In turn, this novel step in tumor formation represents a therapeutic opportunity where reconstitution of GUCY2C signaling with oral agonists could replace lost guanylin to prevent tumorigenesis. Linaclotide (Linzess™) and plecanatide (Trulance™) are FDA-approved oral GUCY2C agonists that could be leveraged for hormone replacement therapy, transforming colorectal cancer from an irreversible disease of genetic mutation, to a reversible syndrome of hormone insufficiency.

“ I am deeply honored to be awarded the PhRMA Foundation Pharmacology/Toxicology Predoctoral Fellowship. It truly has represented a lifeline for me in pursuing my doctoral degree. Over the past year, the funding has given me the opportunity to grow as a researcher in my field. The award has lifted my financial burden and allowed me to focus solely on my dissertation project, which holds important translational medicine implications with regards to the use of epigenetic therapies.”

Taha Yasin Taha | University of Illinois at Chicago



Taha Yasin Taha

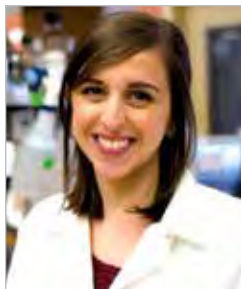
University of Illinois at Chicago

“Histone Deacetylase Target Engagement as a Tool to Individualize Epigenetics-Based Therapeutics and Decipher Their Clinical Efficacy and Toxicity”

Histone deacetylases (HDACs) are enzymes that regulate many cellular processes through the removal of acetyl groups on histone and non-histone substrates. HDAC inhibitors (HDACi) are promising therapeutic agents in multiple diseases including cancer. The use of HDACi remains limited because of suboptimal efficacy and toxicity potentially due to lack of isoform selectivity and off-target effects. Increasing evidence shows that each HDAC isoform may carry out both duplicate and unique biological functions; therefore, by inhibiting a single isoform, one could achieve the desired therapeutic effects while minimizing toxicity. However, current HDAC isoform-selective inhibitors have not held promise and this could be due to the lack of knowledge of HDAC isoforms available for inhibition and HDAC isoforms actually inhibited by HDACi in cells and tissues. This project addresses this critical barrier in the field by using unique pharmacological tools – druglike cell-permeable photoreactive probes (PRPs) – to profile HDAC target engagement (binding of inhibitor to target) in cells/tissues. Preliminary studies have found that HDAC target engagement by HDACi is highly context dependent and can be substantially different from that determined using biochemical assays with recombinant HDACs. Hence, a mere difference in the ability of HDACi to engage a specific subset of HDAC isoforms in a cell- or tissue-specific fashion may be an underlying cause of therapeutic efficacy or toxicity. The goals of this project are to develop a PRP-based assay to profile HDACs available for inhibition and HDACs engaged by FDA-approved and commonly researched HDACi in a panel of cancer cells and tissues. The outcomes of this project will lay the ground work for not only understanding HDAC biology, but also providing a clinical tool to individualize HDACi therapeutics and creating opportunities for discovering novel cell-, tissue-, and disease-specific HDACi.

“ I am so honored to be a recipient of a PhRMA Foundation Pre Doctoral Fellowship in Pharmacology/Toxicology. This funding has played a crucial role in allowing me to expand my dissertation research investigating pharmacological manipulation of immune cells in models of multiple sclerosis. I am incredibly grateful for the opportunities I have been afforded under this fellowship and of course, the fellowship itself!”

Kaitlyn Koenig Thompson | Stony Brook University



Kaitlyn Koenig Thompson

Stony Brook University

“Repurposing Guanabenz as a Modulator of the Microglia/Macrophage Response in Multiple Sclerosis”

Multiple sclerosis (MS) is a currently incurable central nervous system (CNS) disorder that afflicts over 2.5 million people worldwide. It is a leading cause of disability in young adults, especially women, who are twice as likely to develop the disease. In MS, the immune system mounts an attack on myelin, a component of the CNS which nurtures and protects neurons. This attack results in demyelination, as myelin is detached from neurons, and manifests in symptoms such as weakness, pain, cognitive dysfunction, and eventually, paralysis. Unfortunately, current therapies for MS only suppress these symptoms and are unable to prevent the inevitable progressive disability, leaving most patients fated for a wheelchair. Moreover, the available drugs have severe side effects which can drastically reduce a patient's quality of life. The goal of this project is to characterize guanabenz, an FDA-approved drug with only minor side effects, as a novel MS drug capable of improving disease symptoms through modulating the immune system. Progress in this project indicates that guanabenz alters the responses of two innate immune cells, macrophages and microglia (CNS-resident macrophages), in a model of MS. Both microglia and macrophages play a significant role in MS progression by contributing to demyelination and neuronal damage. However, the function of these cells can be pharmacologically manipulated to prevent damage and promote neuronal repair. Current studies are investigating if microglia and macrophages treated directly with guanabenz exhibit effects on their functions and by what mechanism this occurs. Future work will also combine guanabenz with the FDA-approved drug benztropine, seen to promote production of myelin. This dual therapy could potentially result in disease regression by targeting repair mechanisms while concurrently dampening the autoimmune response. Since guanabenz (and benztropine) is FDA-approved, it is likely that this therapy will reach patients significantly faster than a non-FDA-approved drug.

“ It felt like an unbelievable and at the same time very encouraging experience to receive the PhRMA Foundation PreDoctoral Fellowship. My plan is to pursue a career in industry and receiving this award in recognition of my ongoing work will be an important step in making me a competitive applicant for future job prospects and realizing my goals.”

Julia Tobacyk | University of Arkansas for Medical Sciences



Julia Tobacyk

University of Arkansas for Medical Sciences

“The Regulation of Mitochondrial Fusion in Cold Storage Kidney Preservation”

A major hurdle in the field of renal transplantation is the shortage of suitable donor kidneys. A large gap remains between graft survival of renal allografts from deceased donors versus living donors. Kidneys from deceased donors must undergo cold preservation before transplantation to allow time to find a suitable recipient. However, cold storage also leads to mitochondrial and renal injury impairing overall graft outcome. This study will focus on determining the role of mitochondrial fusion in cold storage kidney transplantation and delineate its mechanism of toxicity due to cold storage. Overall, the clinical implications of these findings are to identify pathways of injury and then evaluate new targeted therapies in a relevant renal transplant model.

“ The Pre Doctoral Fellowship in Pharmacology/Toxicology has given me the opportunity to explore a variety of research directions for my thesis project. I have been able to train with multiple models and advanced techniques to answer important biological questions with in-depth and comprehensive analyses. Most importantly, the PhRMA Foundation has given me the confidence and encouragement to pursue a career in translational research. Thank you PhRMA Foundation!”

Shira Yomtoubian | Weill Cornell Medicine



Shira Yomtoubian

Weill Cornell Medicine

“The Role of Ezh2 Histone Methyltransferase in Triple Negative Breast Cancer Metastasis”

The 5-year survival rate for triple negative breast cancer (TNBC) is as low as 40% due to enhanced propensity of recurrence and distant metastasis. Despite this clinical significance, there is a conspicuous lack of FDA approved therapies for TNBC metastasis. In order to develop a potential anti-metastatic therapeutic for TNBC, this project focused on an enhancer of zeste homolog 2 (EZH2), a histone methyltransferase, because breast cancer patients expressing elevated EZH2 levels exhibit higher metastatic recurrence, worse disease free survival and lower overall survival. Strikingly, using cell line-based TNBC models, a highly selective small

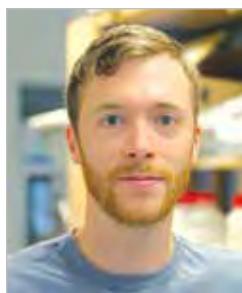
molecule inhibitor of EZH2 methyltransferase and a precise genetically inactivated EZH2 mutant did not impact primary tumor growth, but impaired dissemination and metastatic outgrowth in the lungs. Using a unique SOX2 reporter, the research identified a population of EZH2high tumor cells with tumor-initiating properties, enhanced metastatic potential, and marked sensitivity to EZH2 inhibition. Together, these findings have led to the hypothesis that EZH2 promotes metastasis, and that specific inhibition of EZH2 histone methyltransferase activity may constitute a viable anti-metastatic approach. This project will test this hypothesis by elucidating specific cellular and molecular mechanisms by which EZH2 promotes metastasis and assess its potential in the prevention and treatment of TNBC metastasis.

2018 POST DOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY

The PhRMA Foundation has been awarding Post Doctoral Fellowships in Pharmacology/Toxicology since 2002. This fellowship provides a two-year stipend to scientists who seek to gain new skills in pharmacologically relevant areas. Eligible candidates are actively pursuing a multidisciplinary research training program to enhance their expertise and education, or embarking on a research project that aims to integrate information on a drug's molecular or cellular mechanisms of action with the agent's effects on the intact organism.

“ The PhRMA Foundation has enabled me to pursue research questions relevant to modern clinical needs and provided me with opportunities to launch my career as an independent scientist. It has freed up critical time at the bench to test new hypotheses, generate data for publication, and share my results with others. I am grateful for the PhRMA Foundation's support and mission for young scientists.”

Daniel Blackwell, PhD | Vanderbilt University Medical Center



Daniel Blackwell, PhD

Vanderbilt University Medical Center

“Mechanisms and Treatment of Calcium-Induced Arrhythmias”

The mechanisms of cardiac arrhythmias – electrical defects in the heart – are not completely understood and current drugs largely target the symptoms, rather than the underlying mechanisms. Irregular, spontaneous calcium release within the heart has been associated with atrial fibrillation, catecholaminergic polymorphic ventricular tachycardia (CPVT), and sudden death in heart failure, presenting a valuable target for treatment of arrhythmias. This research is focused on elucidating the function of calcium-handling proteins in the heart under normal and pathological conditions. This will help determine better ways to treat patients, improve outcome, and possibly prevent the progression of these diseases. A second focus is the discovery and development of new drugs to target calcium-handling proteins in the heart. A recent finding has been a synthetic compound – not found in nature – that prevents spontaneous calcium release and reduces arrhythmias. This has exciting potential to be developed as a therapeutic option for patients at risk for arrhythmias.



Joseph Tillotson, PhD

Johns Hopkins University School of Medicine

“The Impact of AK2 Genetic Variants on the Phosphorylation of the Anti-HIV Drug, Tenofovir”

Tenofovir (TFV) is a nucleotide reverse transcriptase inhibitor used for the treatment of hepatitis B and HIV. It is also a component of the only FDA approved regimen for HIV pre-exposure prophylaxis (PrEP). However, it has been demonstrated in PrEP clinical studies that even when participant adherence to the TFV-containing regimen is high, certain individuals are not protected against HIV infection and seroconvert following exposure to HIV. In addition, nephrotoxicity have been reported in individuals taking TFV. The molecular mechanisms underlying these outcomes remain underexplored. This research discovered that AK2 catalyzes the phosphorylation of TFV to TFV-monophosphate (TFV-MP), which is the first step in the TFV activation pathway. TFV requires two sequential phosphorylation steps to form the pharmacologically active compound TFV-diphosphate (TFV-DP). Interestingly, it was found that AK2 also catalyzes the formation of TFV-DP, indicating that AK2 may be critical to TFV pharmacology. This project will test whether naturally occurring genetic variants of AK2 impact the phosphorylation of TFV, thereby modulating the activation of TFV and also potentially the cytotoxicity of TFV. It is anticipated that these studies will provide a foundation for understanding the mechanisms that underlie interindividual differences in TFV activation/efficacy as well as TFV-induced toxicity.



2018 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.



John A. Allen, PhD

University of Texas Medical Branch

“Small Molecule Discovery and Target Validation for Striatal Human Orphan Receptors”

Mental health, neurological and substance use disorders are an enormous medical, societal and economic burden and new drug targets and therapeutics are needed. Proteins that impact the function of an area of the brain known as the striatum are strongly implicated in several brain diseases, including addiction, Parkinson’s disease and schizophrenia. Advances in understanding the pathophysiology of these disorders provide compelling evidence to implicate G protein-coupled receptor (GPCR) neurotransmitter receptors as key targets for current and future therapeutics. As a large drug target family, GPCRs play an essential role in human medicine with approximately 35% of all medications regulating these receptors. This study recently identified five new GPCRs located in the striatum of the human brain, and the project will screen chemical libraries against these new receptors with the goal of discovering small molecule modulators suitable to medicinal chemistry development. In addition, the research aims to identify brain biochemical and physiological functions of the striatal receptor GPR88, providing a validation of the therapeutic potential of the receptor. The project will address fundamental gaps in knowledge about brain GPCRs and exploits new approaches to drug discovery for GPCRs which are selectively expressed in the striatum.



Ryan S. Funk, PharmD, PhD

University of Kansas

“A Biochemical Strategy to Mitigate Methotrexate Toxicity in Patients with Down Syndrome”

Down syndrome (DS) is a chromosomal disorder represented by trisomy of chromosome 21, resulting in an extra copy of genetic material on the 21st chromosome. In addition to being the most common cause of intellectual disability in the U.S., children with DS are at a greater risk of developing numerous co-morbid conditions, including a three- to six-fold increased risk of developing chronic inflammatory arthritis, as well as a ten- to twenty-fold increased risk of developing leukemia, compared to non-affected children. Unfortunately, the drug methotrexate (MTX), which represents the cornerstone of both anti-neoplastic and anti-arthritis drug therapy, is poorly tolerated by this population and MTX toxicity continues to represent a significant barrier to the safe and effective treatment of these conditions in patients with DS. Interestingly, a number of the genes involved in the pharmacologic response to MTX are located on the 21st chromosome and are over-expressed in patients with DS and have been associated with the enhanced toxicity of MTX in these patients. MTX dose modification and dietary supplementation with folates represent two possible approaches to reduce MTX toxicity, and thus allow for the safe and effective use of MTX in patients with DS. In this research the biochemical and genetic basis for MTX toxicity in DS will be investigated at the molecular level and will be used to design novel treatment approaches to enhance both the safety and efficacy of MTX in children with DS.

INFORMATICS

Pre Doctoral Fellowships in Informatics

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

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

2018 PRE DOCTORAL FELLOWSHIPS IN INFORMATICS

“ I thank the PhRMA Foundation for enabling me to complete my research and my PhD in Pharmaceutical Sciences. Without the PhRMA Foundation’s support, I could not have done it. The PhRMA Foundation Fellowship enabled me to complete an informatics project about which I was very passionate, and which I hope will revolutionize drug safety analysis and streamline animal research studies and first-in-human trials in the future.”

Cynthia Dickerson, PhD | University of Kentucky



Cynthia Dickerson, PhD

University of Kentucky

“Applying a Novel Statistical Method to Determine the Safety of a New Treatment for Ebola”

This project applied a new statistical method to the problem of experimental drug safety. QBEST is a novel statistical method. QBEST provides the ability to visualize complicated datasets as points on one graph, allowing the comparison of whole datasets to each other based on the distance between the points. This novel statistical method was applied to the problem of estimating a safe starting dose of a new drug compound for human clinical trials. The standard statistical method currently used for this process is the Benchmark Dose method (BMD), but the BMD has some drawbacks. QBEST is similar to the BMD, but more intuitive for researchers trying to understand how increasing the dose of a new drug causes increasingly severe side effects in patients. QBEST was used to calculate a safe starting dose of ellagic acid, a component of a new drug made to treat Chikungunya infections. This calculation was based on published studies of ellagic acid doses that caused effects or caused no effects in animals. Also, simulated data was used to compare the accuracy and efficiency of the QBEST method in general to other mathematical models. The result of this project is that a new statistical method was introduced that can be used when experimental pharmaceuticals are first tried in human patients after being tested on animals.

“ The PhRMA Foundation Informatics Fellowship has given me the freedom to pursue my research with all of the enthusiasm and intensity it deserves.”

Jonathon Gast | Purdue University



Jonathon Gast

Purdue University

“Method for Identifying Synthetic Lethal Combinations of Pre-Existing Therapeutics in Chemoresistant Cancer Contexts”

Since 2002, cancer has surpassed heart disease as the leading cause of death in individuals younger than 85 years. While cancer treatment has made great strides, there are still persistent problems in the development of chemoresistance by recurring tumors. Radiation treatment, DNA damaging agents, and mitogenic therapies, while effective against tumors early on, often come with a host of side effects. There are also large subgroups of cancer patients that have few to no options including castration-resistant prostate cancer and triple-negative breast cancer. While currently limited in their use, personalized therapies and synergistic drug combinations have seen increasingly positive results that represent the future of cancer therapy. However, widespread personalization of therapy for high efficacy drug combinations based on single disease markers is an unlikely solution due to the frequent plasticity and diversity of tumors. Utilizing the genomic data of patients with protein-protein interaction networks novel drug combinations are hypothesized in silico. This can often provide too many options, not all of which have current therapeutics able to take advantage of these discoveries. These hypotheses would take decades to both validate and to produce novel therapeutics. This project would look to limit the search to only include well studied antagonists, FDA approved or those that have passed Phase II clinical trials, in highly disease specific networks. This would provide novel combinations with a much higher likelihood of clinical relevance in the immediate future providing therapeutic opportunities in high-risk tumor contexts.

“ I am extremely thankful for the PhRMA Foundation Pre Doctoral Fellowship in Informatics. The fellowship has enabled me to focus on my research full time and has greatly accelerated my progress toward a PhD. With the support from the PhRMA Foundation, I’ve been able to dive deeper into my research on computationally predicting the effects of mutations on protein function. My experiences with this project have cultivated my interest in further pursuing this type of research.”

Sam Gelman | University of Wisconsin, Madison



Sam Gelman

University of Wisconsin, Madison

“Predicting the Effects of Mutations on Protein Function Using Deep Neural Networks”

Deep mutational scanning is a new experimental approach for measuring the functional properties of up to a million mutant versions of a protein. These experiments provide direct insights into how mutations in a protein’s amino acid sequence affect its function. However, despite the relatively large scale of deep mutational scanning experiments, it is still not feasible to test all possible mutations. The purpose of this research is to create computational models of protein function by combining machine learning with the sequence-function data from deep mutational scanning. Computational models could be used to fill the gaps in experimental data and predict the effects of mutations on protein function. This project is specifically focused on deep neural networks, which have enjoyed widespread success over the past decade and are well-suited to this task. Through the use of novel neural network architectures and data encodings, these models can incorporate biological context such as protein structure, evolutionary conservation, and amino acid properties. This work could ultimately be used to engineer new proteins with desired functional properties or enhance our understanding of how mutations affect important proteins such as those that play a role in disease.



Anna Ulrika Lowegard

Duke University

“Computational Design of Peptide Inhibitors for KRas Protein-Protein Interactions”

KRas is a small protein and GTPase commonly implicated in several difficult-to-treat cancers such as pancreatic ductal adenocarcinoma (PDAC), the deadliest of solid tumors. KRas forms protein-protein interactions with other proteins in order to regulate various important signal transduction pathways. When mutated, KRas is constitutively activated, which leads to signal transduction pathway dysregulation that subsequently increases and sustains tumorigenicity and invasiveness. KRas has long been considered an “undruggable” target due to its picomolar affinity for its substrate, GTP. However, blocking the protein-protein interactions between KRas and its effectors eliminates these harmful downstream effects. This project seeks to implement computational structure-based protein design in conjunction with biochemical characterization to design a peptide inhibitor that binds to KRas and consequently blocks effector binding. To

design and optimize the peptide inhibitor's inherent stability and affinity for KRas, OSPREY, Open Source Protein REdesign for You, a state-of-the-art software package for computational structure-based protein design (CSPD), is used in cooperation with iterative biochemical characterization. This work will validate the use of CSPD to target protein-protein interfaces of undruggable proteins while targeting KRas, a keystone of crucial signal transduction pathways that initiate and sustain difficult-to-treat cancers such as PDAC.

2018 POST DOCTORAL 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.

“ I am extremely grateful for the support provided by a Post-Doctoral Fellowship in Informatics from the PhRMA Foundation. This fellowship has enabled me to work at the interface of evolutionary biology and immunology, and encouraged me to focus on issues underlying human disease.”

Kenneth B. Hoehn, DPhil | Yale University



Kenneth B. Hoehn, DPhil

Yale University

“Evolutionary Models of B Cell Migration and Differentiation”

Antibodies are a critical defense against the threat of diverse, rapidly evolving pathogens faced by humans. Development of these proteins underlies processes such as immunological memory and vaccination, but also forms of autoimmunity. Antibodies are produced in B cells, where they are originally expressed as membrane-bound B cell receptors (BCRs). In contrast to most human cell types, the population of B cells in individual humans is genetically diverse and constantly evolving. Namely, B cells, when activated, undergo rounds of mutation and selection of their BCRs for increased ability bind to molecular structures identified as foreign and harmful (e.g. pathogen surface proteins). Next-generation sequencing of BCRs from populations of B cells has recently given unprecedented potential to understand the complexities of how B cells develop and shape the adaptive immune response. The spatiotemporal regulation of B cell selection, differentiation, and migration between tissues - both in healthy and disease states - is critically important to this process; however, many aspects of it remain mysterious. An important reason behind this is that there are no rigorous, model-based approaches yet developed to estimate B cell migration and differentiation patterns. Because B cell development closely parallels evolution in natural populations, this project focuses on drawing inspiration from techniques in molecular evolution to develop evolutionary models of B cell selection, differentiation, and migration. Once developed, this framework will have broad potential to shed light on immunological issues ranging from B cell responses to influenza vaccination to migration of B cells to the brain in multiple sclerosis.

“ I am very honored to be a recipient of the prestigious PhRMA Foundation award in Informatics. The impact of receiving the competitive PhRMA Foundation award has been profound. It has been extremely valuable to my career development as it allowed me to continue to conduct my research in the ideal setting, surrounded by state of the art resources. Receiving this award has provided me the freedom to develop my research in an independent way. Moreover, it has given me an important reinforcement to the importance of my proposed study and will serve as a pivotal credential on future applications for other grants. Thanks to the award I was able to conduct a study that revealed thousands of novel small proteins encoded by human associated microbes and provide initial hints about their function. This work has generated a rich resource for future exploration in diverse areas including drug mining and design, cellular biology, defense against phage and antibiotic resistance.”

Hila Sberro Livnat, PhD | Stanford University



Hila Sberro Livnat, PhD

Stanford University

“Large-Scale Analyses of Human Microbiomes Reveal Thousands of Small, Novel Genes and Their Predicted Functions”

Small proteins likely abound in prokaryotes, and may mediate much of the communication that occurs between organisms within a microbiome and their host. Unfortunately, small proteins are traditionally overlooked in biology, in part due to the computational and experimental difficulties in detecting them. To systematically identify novel small proteins, this project conducted a large comparative genomics study on 1,773 HMP human-associated metagenomes from four different body sites (mouth, gut, skin and vagina). The research describes more than four thousand conserved protein families, the majority of which are novel; ~30% of these protein families are predicted to be secreted or transmembrane. Over 90% of the small protein families have no known domain, and almost half are not represented in reference genomes, emphasizing the incompleteness of knowledge in this space. This analysis exposes putative novel ‘housekeeping’ small protein families, including a potential novel ribosomally associated protein, as well as ‘mammalian-specific’ or ‘human-specific’ protein families. By analyzing the genomic neighborhood of small genes, it is possible to pinpoint a subset of families that are potentially associated with defense against bacteriophage. Finally, the project will identify families that may be subject to horizontal transfer and are thus potentially involved in adaptation of bacteria to the changing human environment. This study suggests that small proteins are highly abundant and that those of the human microbiome, in particular, may perform diverse functions that have not been previously reported.

2018 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.



Rendong Yang, PhD

The University of Minnesota

“Accurate Detection of Structural Variation From DNA Sequencing of Circulating Tumor Cells”

Circulating tumor cells (CTCs) are malignant cells in peripheral blood that are the metastatic precursors, which may have potential roles not only in predicting the risk of metastatic relapse, but also in acting as a therapeutic target for preventing metastasis of cancers. Comparing with tissue biopsies, liquid biopsies through CTCs enable characterizing tumor genome and monitoring treatment efficacy by minimally invasive means. Advances in next generation sequencing have enabled comprehensive analyses of cancer genomes which promise to inform prognoses and precise cancer treatments. However, genomic characterization of genomes in CTCs remains challenging. A major barrier is to detect structural variations (SV) from CTCs. Due to low-input material, sequencing CTCs requires whole-genome amplification which will introduce chimera artifacts that prevent the identification of true SVs. This research aims to develop novel algorithms to robustly and accurately detect SVs from CTCs sequencing data and the approaches will be validated using large-scale CTCs and matched primary and metastatic tissue sequencing data in prostate cancer. The proposed methods will address the growing need for accurate detection of SVs and facilitate prognosis and the selection of cancer therapies from CTC based liquid biopsy in clinical practice.

PHARMACEUTICS

Pre Doctoral Fellowships in Pharmaceuticals

The PhRMA Foundation began funding awards in Pharmaceuticals in 1972.

As one of the Foundation's longest-standing programs, the Pre Doctoral 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.

2018 PRE DOCTORAL FELLOWSHIPS IN PHARMACEUTICS



Christine Bowman

University of California, San Francisco

“Equilibrium vs. Steady State Plasma Protein Binding in the Presence of Transporters and Its Implications in Drug Delivery”

In vivo, drug molecules reversibly bind to proteins such as albumin in plasma or tissues, and given the effects that this protein binding can have on the delivery, pharmacodynamics, and pharmacokinetics of a molecule, the process is crucial to consider in drug discovery. The widely accepted free drug theory explains that plasma protein binding is a rapid equilibrium process, allowing a constant concentration of free drug, and only this free drug can reach the site of action or be metabolized. One of the main principles of the free drug theory is that free drug concentration is the same on both sides of a membrane, and it is common to measure protein binding in vitro at equilibrium. However, as the transporter field has evolved, exceptions to the free drug theory have emerged, and it has become clearer why measuring free drug at equilibrium in vitro is inaccurate. This project explores the fact that transporters are able to control a drug's access to cells, and uptake transporters specifically can elevate the intracellular free concentration significantly above that in plasma, violating the first principle of the free drug theory. This means that measuring the unbound concentration at equilibrium in static assays may not yield accurate results, and instead, protein binding measurements should be done at steady state to more accurately mimic the dynamic processes that are occurring in vivo. Drug uptake studies in several cell types are being conducted in both protein-free buffer and plasma incubations to test the idea of a transporter-induced protein binding shift. High affinity binding to transporters may be able to change the equilibrium of the nonspecific binding between drugs and plasma proteins, meaning that protein binding is not restricting the access of these compounds to cells. Recognizing the principles behind equilibrium vs. steady-state protein binding may yield a more accurate understanding of the delivery, distribution, and clearance of drugs.



Julie Calahan

University of Kentucky

“Correlating Magnesium Stearate Physicochemical Properties with Functional Properties”

Tablets contain both an active ingredient, commonly called the drug, and inactive ingredients, which are called excipients. The inactive ingredients play several important roles in the performance of the tablets, such as ensuring the tablet does not break apart during shipping and that it dissolves properly when taken by the patient. One of the inactive ingredients, magnesium stearate, is used to ensure that the tablet is ejected from the tablet press by serving as a lubricant. Many scientists have observed batch-to-batch and lot-to-lot variability between magnesium stearate samples during manufacturing, causing inconsistent lubrication and dissolution results. Poor lubrication causes the powder to stick to the tablet manufacturing equipment, producing chipped tablets. Over-lubrication can result in decreased dissolution, bioavailability and absorption problems. It is therefore important to use magnesium stearate material which delivers consistent performance. To solve this problem, the significant variation inherent in magnesium stearate properties, corresponding to variability in performance, must be understood. Several variables have been identified which affect magnesium stearate performance, including chemical composition of the magnesium stearate, the molecular ordering of the molecules, and the size and shape of the magnesium stearate particles. This research aims to characterize magnesium stearate using advanced characterization methods to develop correlations between the material properties of magnesium stearate and its dissolution and lubrication performance.

“ The Pre Doctoral Fellowship in Pharmaceuticals allows me to focus on my research goals. I have the latitude to define my own direction and more time to concentrate on the results of my experiments. Consequently I have been able to accelerate the pace of my investigation and explore new ideas. I am very thankful to the PhRMA Foundation for supporting my research.”

Lauren K. Fontana | University of Connecticut



Lauren K. Fontana

University of Connecticut

“Development of a Raman Spectroscopic Method to Detect Protein Conformation in Amorphous Solids: Application to Protein Formulation and Stability”

Protein drugs are a growing type of medication with better targeting and fewer side effects. However, they are not as stable as traditional drugs, meaning that they are more likely to get damaged during manufacturing or degrade over time on the shelf. Due to inadequate stability in the solution or liquid state, approximately 30% of protein drugs are freeze dried and stored in solid form. Freeze-drying can lead to additional challenges, as the process can cause conformational changes in protein structure. The degree of these structural changes

may impact both in-process and storage stability, with partially unfolded protein molecules expected to be less stable against both aggregation and chemical degradation. Current analytical methods are limited in their ability to identify and measure protein structural changes, especially in the tertiary structure. For example, FTIR can only be used reliably on solid-state proteins and only detects changes in the secondary structure. This lack of structural information on proteins in the solid-state affects the ability to make critical decisions during the development and manufacturing of these drugs. Consequently, new methods must be developed to ensure these drugs retain their potency before being administered to patients. The objective of this study is to develop a new Raman spectroscopic method that detects changes in protein tertiary structure in the solid and liquid states that are associated with decreased protein stability and subsequently reduced shelf life. Using this method as a screening tool will enable companies to make improved drug products in a shorter amount of time, benefiting both the patients and the manufacturers.

“ Being awarded this fellowship is a great honor and has validated the importance of the work I have done so far. This opportunity has supported my interest in understanding and developing extracellular vesicles as an emerging class of therapy.”

Anjana Jeyaram | University of Maryland



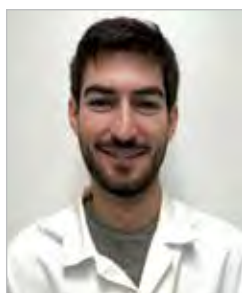
Anjana Jeyaram
University of Maryland

“Engineering Extracellular Vesicles to Enhance Therapeutic Efficacy and Clinical Translatability”

Recently, extracellular vesicles (EVs) have garnered increasing interest as cell-derived biotherapeutics and drug delivery vehicles, due to their role in cell-to-cell communication. Unlike synthetic carriers and liposomes, these cell-derived vesicles are able to cross biological barriers that inhibit drug delivery. Despite the advantages of using EVs as therapeutic carriers, there remain several obstacles to clinical translation. Current cargo loading methods are inefficient and may damage EV and cargo integrity, which can ultimately impair bioactivity. Even if the therapeutic cargo can be loaded effectively, the stability of these formulations must be evaluated to preserve potency after storage for use in clinical settings. Lastly, despite the benefits of EVs over synthetic carriers, their delivery remains limited by conventional routes of administration, which cause non-specific biodistribution. The proposed project aims to enhance the therapeutic efficacy of EVs by using a novel technique to controllably increase levels of specific therapeutic miRNAs and by delivery within a biomaterial platform to promote sustained retention in the target site. Further, studying the long-term stability and assessing methods to preserve biological function over time will enhance the clinical translatability of EVs. Success in these aims will lead to a versatile platform for EV-based therapeutics delivery.

“ I am extremely grateful to receive the PhRMA Foundation’s Pre Doctoral Fellowship in Pharmaceuticals. This fellowship has allowed me to develop my project from the point of chemical synthesis through to preliminary animal studies. I have been able to produce a more compelling story with my project in the area of immunotherapy, a field I am very excited to be a part of. The knowledge and techniques I’ve been able to develop under this fellowship will undoubtedly allow me to continue to pursue work within an area of research very near and dear to me for years to come.”

Peter Kleindl | University of Kansas



Peter Kleindl

University of Kansas

“Localized Delivery of Potent Immunosuppressants for Treatment of Ulcerative Colitis”

Ulcerative colitis (UC) is a chronic inflammatory bowel disease in which remitting and relapsing periods of inflammation and ulceration occur within the large intestine due to aberrant immunological activity. Current pharmacotherapies are often effective in suppressing periods of active inflammation, reestablishing remittance. However, patients frequently become refractory to current treatments over time, as the underlying immunological dysfunction is not adequately addressed. Recently, more potent immunosuppressants have been used off-label to effectively treat UC in otherwise refractory patients. These drugs are frequently shown to elevate regulatory T-cell populations, which can suppress active inflammation and have the potential to establish lasting, self-regulating homeostasis. Unfortunately, several limitations such as toxicity, interpatient variability and systemic immunosuppression limit these drugs’ practicality for long term use and widespread application. By utilizing a prodrug approach these limitations can be mitigated, targeting delivery of active drug solely to the large intestine, thus reducing systemic exposure and subsequent side effects. This research focuses on synthesizing prodrug forms of several potent immunosuppressants, and testing their ability to effectively treat UC without producing the undesirable side effects characteristic of their respective parent drugs. Conjugation of specific substrates for enzymes primarily expressed in the colonic microflora can provide a means for targeted release of parent drug, while simultaneously limiting their absorption into the bloodstream. Select prodrugs will be screened for stability in various gastrointestinal environments (stomach, small intestine, colon), their absorption into the systemic circulation, and their ability to effectively treat UC in a relevant model of disease. This research will hopefully provide additional treatment options that can provide lasting, self-regulating relief to UC patients for whom currently approved pharmacotherapies eventually fail.



William M. Payne

University of Nebraska Medical Center

“Methods and Tools for Computer-Aided Formulation Design of Polymeric Nanocarriers”

As the cost and development time required for new drugs to reach clinical use continues to increase, the field of nanomedicine has emerged as a promising area of research in an attempt to substantially improve therapeutic outcome, particularly in cancer chemotherapy. However, while the number of nanomedicine publications has continued to rise, very few of these inventions make it to market. This problem is exacerbated by the lack of meaningful methods to determine the efficacy and efficiency of a given formulation; comparing one nanomedicine to another or even objectively describing how well the nanomedicine treats a given disease is nearly impossible. Furthermore, choosing an ideal drug carrier vehicle is difficult and there are very few established design strategies for the development of new nanoformulations, which has resulted in calls from government, industry, and academic institutions for increased development in design processes. To overcome the challenges preventing successful clinical adoption, and to further integrate nanoformulation into the industrial research and development process, quantitative, standardized methods of evaluating and designing nanomedicine must be developed. This research project seeks to develop new metrics to describe important attributes of new polymeric nanoformulations through computational methods, and then to incorporate these metrics into a set of tools for computer aided formulation design (CAFD), with the aim of ultimately decreasing the development time and cost for new nanomedicines.



Davin Rautiola, MS, MEng

University of Minnesota

“Reactive Formulations for Intranasal Delivery of Insoluble or Unstable Drugs”

Systemic drug delivery by intranasal administration has been gaining popularity in recent years because the route offers a host of advantages that cannot be achieved by other routes. Dense capillary beds and thin epithelium in the nasal cavity allow drugs to quickly enter the blood stream, leading to a rapid onset of therapeutic effect. There is even potential for drugs targeting the central nervous system to bypass the blood brain barrier through direct nose-to-brain pathways. The intranasal route can be leveraged to avoid first-pass metabolism or degradation of drugs in the gut. Furthermore, operation of a nasal spray device is generally intuitive. Nasal sprays are non-invasive, convenient, and discrete, making the intranasal route of drug administration preferable to many patients.

However, not all drugs are amenable to formulation as a rapid acting nasal spray. Drugs with poor aqueous solubility or poor solution stability are often not even considered for formulation as a nasal spray. This will soon change with the introduction of reactive nasal spray formulations. A new paradigm in intranasal delivery is emerging based on the idea that metastable formulations can be created at the time of administration. Reactive components of

a formulation are kept in separate compartments in a specially engineered nasal spray device. The components are metered, mixed, and atomized during actuation of the device.

One example of this reactive nasal spray formulation strategy utilizes a highly soluble prodrug of an insoluble active drug and an exogenous enzyme to efficiently convert the prodrug into the active drug. The prodrug and fragile enzyme are stabilized for storage in the device as a homogeneously mixed solid lyophilizate. When a patient actuates the device, the solid lyophilizate is automatically reconstituted with buffer and simultaneously atomized into a spray. In the nasal cavity, the deposited droplets containing prodrug and enzyme react to produce a metastable supersaturated solution of the active drug. The active drug is then rapidly absorbed into the body. Other reactive nasal spray formulations utilize acid/base chemistry, click chemistry, and even simple non-reactive physical phase changes. This research is at the cutting edge of pharmaceuticals and destined to enable many life-saving therapies that might not otherwise be possible.

2018 RESEARCH STARTER GRANT 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 committed to the cross-disciplinary approach in cancer research. As a scientist, I have seen the impact of non-traditional, cross-disciplinary training on my own career and research interests, shaped dramatically by my education and experience in physics, chemistry, materials engineering, and cancer biology. This insight fuels my goal to inspire and train young scientists able to approach problems in ways that are not limited by the constraints of current scholastic disciplines. Thank you to the PhRMA Foundation for funding for my research.”

Shunji Egusa, PhD | University of North Carolina, Charlotte



Shunji Egusa, PhD

University of North Carolina, Charlotte

“Evaluation of Nanochemistry Conferring Targeting Modality Onto Standard Leukemia Drugs”

Traditional cancer treatments that destroy normal cells along with the cancer cells can result in substantial toxicities to the patients, an enduring and fundamental problem of therapeutic index in cancer medicine. Destruction of normal cells is especially problematic when treating myeloid cancers (e.g., acute myeloid leukemia, AML), where normal hematopoietic stem cells are needed to reverse low blood counts that can lead to morbidity and death. An obvious solution to this problem is to deliver drugs selectively to cancer cells and thereby spare normal ones.

However, existing technologies, such as monoclonal antibody-drug conjugates (ADCs) and drug encapsulating liposome/polymer vehicles, have limitations. We examine a novel nanochemistry, Au nano-linker, exploiting ligand-exchange chemistry to release a drug payload selectively at redox-stressed cancer cells. Au nano-linker uses precisely-engineered nanometer-scale gold (Au) core as intermediaries to which drug and targeting moieties are simultaneously attached by simple, yet different chemistries. In essence, the Au nano-core acts as the linker (~2 nm in size; comparable to the length of typical chemical linkers), and readily turns a standard drug into an advanced cell lineage-targeted therapeutic. Outcomes include in vitro proof of versatility, stability and effectiveness of this technology, and will be used to justify concrete advancement into in vivo studies, toward investigational new drug (IND)-enabling studies and clinical applications.

2018 SABBATICAL FELLOWSHIP IN PHARMACEUTICS

“ The PhRMA Foundation Sabbatical Grant has immensely helped me to pursue collaborative research and learn a lot from the world class experts located at different universities across the globe.”

Bodhisattwa Chaudhuri, PhD | University of Connecticut



Bodhisattwa Chaudhuri, PhD

University of Connecticut

“Experimentally Validated Computational Modeling of Pharmaceutical Manufacturing Processes of Solid Dosage Forms”

The multibillion-dollar sales of drugs make the pharmaceutical industry one of the most important pillars in the world economy. However, many of the pharmaceutical manufacturing processes have been designed empirically and known to be more of an art than science. The proposed research will entail systematic experiments and development of multi-scale computer models of three different pharmaceutical manufacturing processes in collaboration with world class experts of these particular processes in three universities across the globe. These robust computational models will enhance scientific understanding of the manufacturing processes, aid in optimization, reduce the regulatory burden, and lower the manufacturing cost of medicines.

REGULATORY SCIENCE

2018 REGULATORY SCIENCE

“ I am honored to be a recipient of the PhRMA Foundation’s Regulatory Science Fellowship. This is a truly unique and immersive experience. One of the hallmark features of this new program is the ability to learn and interact within a fast-paced pharmaceutical company. In Janssen’s Global Regulatory Affairs, I have the unique opportunity to learn about the important work of regulatory affairs professionals and their impactful contribution to drug development. With this fellowship, I can engage in key regulatory policy activities with experts in a dynamic learning environment. This opportunity is essential for my growth as a regulatory affairs professional.”

Miranda D. Johnson, PhD | Former Post Doctoral Fellow at Johns Hopkins University



Miranda D. Johnson, PhD

Former Post Doctoral Fellow at Johns Hopkins University

“Regulatory Considerations in the Development of Antimicrobial Therapies: The Role of Informed Consent”

While streamlined regulatory approval pathways and incentive programs are available and intended to encourage antimicrobial drug development, there remains a shortage of novel therapies entering the market. Although reasons for this shortage are multi-faceted, clinical trial design is an important aspect. To combat time-sensitive treatment windows, innovative strategies such as clinical trial networks for antibiotics and the pre-identification of susceptible patient populations are among the potential solutions to assist in this clinically-pervasive therapeutic area. There may be additional trial design elements which could support antimicrobial development. The overall focus of this regulatory policy project will be to propose alternatives and advances in the informed consent process. Furthermore, this project will assess the implementation feasibility of these new policies from a clinical and regulatory perspective. These potential solutions may expedite the development of novel antimicrobial products. Identifying ethical, scientific, and regulatory policy considerations will facilitate a transparent dialogue and lead to enhanced opportunities for antimicrobial development.

“ The PhRMA Foundation Regulatory Science Fellowship has completely transformed my career trajectory. It has allowed me to leverage my pharmacology and data-science backgrounds to pursue my interest in regulatory science and policy, an opportunity I would not have had otherwise. I am energized to explore the possibilities in this fast-evolving field.”

Cameron M. Kieffer, PhD | Creighton University School of Medicine



Cameron M. Kieffer, PhD

Creighton University School of Medicine

“Using Data-Driven Policy to Advance Regulatory Science”

Data science techniques are underutilized by private pharmaceutical sponsors to support their regulatory science and policy goals. Data science uses computational methods, statistical analysis, and large data sets to uncover insights and support hypotheses. In this project, data science techniques will be applied to the pharmaceutical regulatory landscape to develop regulatory science tools in support of data-driven policy approaches. A primary goal is to establish an evolving compendium of accessible databases (e.g. open FDA, clinicaltrials.gov) that contains information pertinent to regulatory policy decisions in the pharmaceutical industry. The project will focus on U.S. based information from the FDA as well as CMS, HHS, NIH and other organizations. While the project will be U.S. focused, a survey of databases from Europe, Japan, China, and other global regulatory agencies will be performed. Together, these datasets will be leveraged to provide data-driven analysis of relevant regulatory policy issues to augment and support the expertise of internal stakeholders. Simultaneously, Sanofi subject matter experts will be leveraged to develop questions appropriate for a data-driven approach. Suitable topics would include trend analysis of pharmaceutical sector investment following policy implementation and model development for prospective research or regulatory trends. Using data-driven policy to answer important regulatory science questions has the potential to streamline the evaluation of novel policies and regulations, and better understanding their impact on drug development.





The Foundation was honored to present its 2018 awards at distinguished scientific annual meetings throughout the country.

2018 AWARDS

American Society for Clinical Pharmacology and Therapeutics (ASCPT)
Orlando, Florida on March 22, 2018

Association for Clinical and Translational Science (ACTS)
Washington, DC on April 20, 2018

American Society for Pharmacology and Experimental Therapeutics (ASPET)
San Diego, California on April 21, 2018

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
Baltimore, Maryland on May 23, 2018

Intelligent Systems for Molecular Biology (ISMB)
Chicago, Illinois on July 9, 2018

American Association of Pharmaceutical Scientists (AAPS)
Washington, DC on November 5, 2018

Personalized Medicine Coalition (PMC)
Boston, Massachusetts on November 15, 2018



A woman with dark hair tied back, wearing a white lab coat, is shown in profile, focused on her work. She is holding a black pipette and is in the process of dispensing liquid into a multi-well plate. The background is a blurred laboratory setting with various equipment and shelves. The entire image has a blue color overlay.

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TREASURER'S REPORT



On behalf of the Board, staff and all those whose lives will be impacted by the research we fund, we give our heartfelt thanks to our benefactors whose ongoing support is improving the health of patients around the world. Through their generosity we are able to invest in groundbreaking research, support talented young scientists at critical junctures in their careers, advance patient-centered healthcare and collaborate with the many stakeholders who make up our ever-changing healthcare ecosystem. We look forward to furthering these relationships and expanding programming in the coming year in alignment with our member companies' priorities.

The PhRMA Foundation's sole means of support are contributions and investment earnings. Not taking the market downturn at the end of the year into account, the Foundation ended 2018 meeting its financial objectives. Member company contributions were \$2.9 million, which is 5% lower than 2017.

The new Value Assessment program completed its first full year of awards totaling almost \$700,000. This program was introduced in 2017 with awards totaling \$282,000. Total overall grant expenditures were down 5% from the previous year due to the conclusion of two programs.

Net Assets at December 31 were \$21.6 million, representing a drop of \$1.7 million, which reflects net losses on the Foundation's investments. Financial details are shown in the accompanying Statement of Income and Expenditures. With expanded programming in 2019, the Foundation is poised to make an even greater impact.

Sincerely,

A handwritten signature in black ink, appearing to read 'AP', written over a light blue horizontal line.

Andrew Plump, MD, PhD
Treasurer, PhRMA Foundation

STATEMENT OF INCOME & EXPENDITURES

For the year ended December 31, 2018

INCOME	
Contributions	\$2,940,500
Contributions – in kind from PhRMA ¹	\$85,869
Interest and Dividends	\$540,585
(Realized and Unrealized) Gains in Securities	-\$1,658,240
Other Income	\$75,258
Total Income	\$1,983,972
EXPENDITURES	
PROGRAMS	
Awards in Excellence	\$7,500
Adherence Improvement	\$12,500
Clinical and Translational Pharmacology	\$204,750
Health Outcomes	\$347,500
Informatics	\$255,250
Pharmaceutics	\$373,084
Pharmacology	\$671,667
Regulatory Science	\$35,412
Translational Medicine and Therapeutics	\$444,044
Value Assessment	\$668,336
AFPE Fellowship Award	\$11,000
Other Grants	\$5,000
Subtotal – Grants	\$3,036,043
OTHER	
Committee Meetings, Travel and Honoraria	\$159,380
Publications and Special Projects	\$148,159
Subtotal – Other	\$307,539
Program Total	\$3,343,582
ADMINISTRATIVE	
Staff, Taxes, Depreciation & Insurance	\$630,562
Rent & Accounting Services ¹	\$85,869
Professional Services and Investment Expenses	\$134,496
Office Expenses	\$5,463
Subtotal – Administrative	\$856,390
TOTAL EXPENDITURES	\$4,199,972

¹ Rent and Accounting Services are donated by PhRMA

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PHRMA FOUNDATION PROGRAMS FOR 2019

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Pharmacology/Toxicology			
Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)	10 awarded/up to 2 years	\$360,000 total \$20,000 per award per year	September 1, 2018 December 15, 2018 January–August
Post Doctoral Fellowships in Pharmacology/Toxicology (2002)	2 awarded/2 years	\$160,000 total \$40,000 per award per year	September 1, 2018 December 15, 2018 January–August
Research Starter Grants in Pharmacology/Toxicology (1972)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	September 1, 2018 December 15, 2018 January 1, 2019
Clinical and Translational Pharmacology			
Paul Calabresi Medical Student Research Fellowships (1974)	2 awarded/ 6 months up to 2 years	\$36,000 total \$18,000 per award	February 1, 2019 April 15, 2019 July 1, 2019
Faculty Development Award in Clinical and Translational Pharmacology (1966)	1 awarded/2 years	\$240,000 total \$120,000 per award per year	February 1, 2019 April 15, 2019 July 1, 2019
Health Outcomes Advisory Committee			
Pre Doctoral Fellowships in Health Outcomes (2002)	5 awarded/2 years	\$212,500 total \$25,000 per award per year	February 1, 2019 April 15, 2019 July–December
Post Doctoral Fellowship in Health Outcomes (2002)	0 awarded/2 years	\$0 total \$55,000 per award per year	February 1, 2019 April 15, 2019 July–December
Research Starter Grants in Health Outcomes (2002)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	February 1, 2019 April 15, 2019 July 1, 2019
Informatics			
Pre Doctoral Fellowships in Informatics (2009)	2 awarded/2 years	\$80,000 total \$20,000 per award per year	September 1, 2018 December 15, 2018 January–August
Post Doctoral Fellowship in Informatics (2002)	1 awarded/2 years	\$80,000 total \$40,000 per award per year	September 1, 2018 December 15, 2018 January–December
Research Starter Grants in Informatics (2002)	3 awarded/1 year	\$300,000 total \$100,000 per award per year	September 1, 2018 December 15, 2018 January 1, 2019

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Pharmaceutics			
Pre Doctoral Fellowships in Pharmaceutics (1987)	4 awarded/2 years	\$150,000 total \$20,000 per award per year	September 1, 2018 December 15, 2018 January–August
Post Doctoral Fellowship in Pharmaceutics (1992)	1 awarded/2 years	\$80,000 total \$40,000 per award per year	September 1, 2018 December 15, 2018 January–December
Research Starter Grants in Pharmaceutics (1972)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	September 1, 2018 December 15, 2018 January 1, 2019
Translational Medicine & Therapeutics			
Post Doctoral Fellowships in Translational Medicine (2016)	2 awarded/2 years	\$240,000 total \$60,000 per award per year	February 1, 2019 April 15, 2019 July–December
Research Starter Grants in Translational Medicine (2016)	2 awarded/1 year	\$200,000 total \$100,000 per award per year	February 1, 2019 April 15, 2019 July–December
Value Assessment Initiative			
Challenge Awards (2017) for Value Assessment	4 awards	\$5,000 - \$50,000 per award	May 1, 2019 to be determined
Research Awards (2017) for Value Assessment	3 awarded/ 1 year	\$300,000 total \$100,000 per award per year	September 1, 2018 December 15, 2018 January 1, 2019
Center of Excellence Award (2017) for Value Assessment	2 awarded/3 years	\$1,000,000 total \$166,666 per award per year	September 1, 2018 December 15, 2018 January 1, 2019

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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