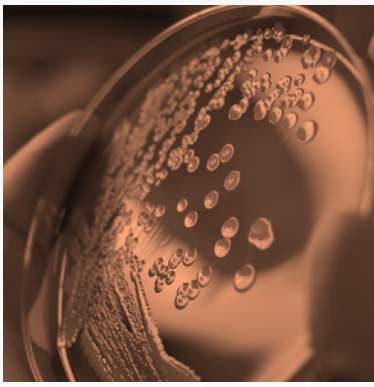
ANNUAL REPORT 2017



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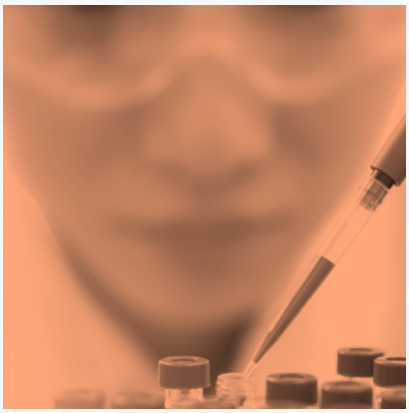
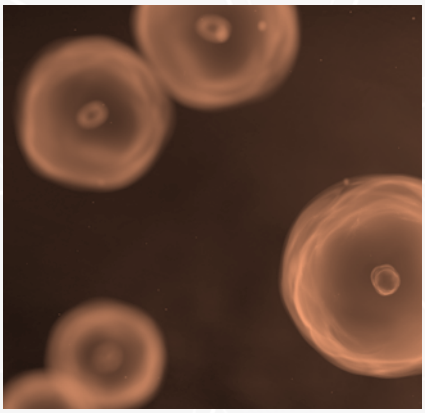


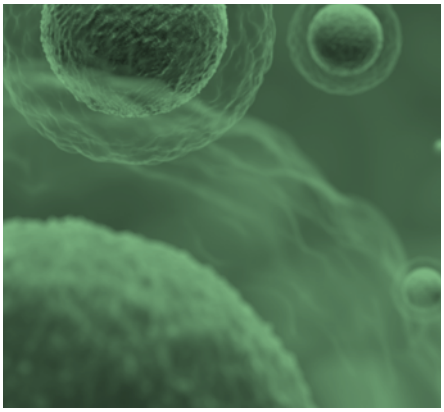


Mission Statement

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.




Erin Baker
Pharmacology

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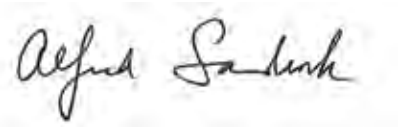
Message from the Chairman

These are exciting times in the evolution of our healthcare ecosystem and I am proud that the PhRMA Foundation is at the forefront of supporting positive change.

Our programs have the potential to radically transform healthcare, putting people and patients back at the center. Last year, we launched our Value Assessment Initiative which provided over $1.4 million to foster the development of value-based care models. We have also started a pilot program in regulatory science. Participating fellows will be fully immersed in rotations between industry and academia as they learn the complexities of drug development and the continuum of regulations that govern the process. Both of these efforts support the generation of real-world data, tools, and resources that empower all healthcare stakeholders with the knowledge to make well-informed, patient-focused decisions.

In the year ahead, we will build upon our 53-year record of success by investing in groundbreaking research and creating new programs that will advance value-driven care. We will continue to be forward thinking, nimble in an ever-changing landscape and bold in our support of new ideas.

Together, we will create a healthier tomorrow.



Alfred W. Sandrock, MD, PhD, Chairman

Message from the President

PhRMA Foundation programs are some of the most transformative in the country for young scientists. But they wouldn't be possible without the solid network of partners who help us make a powerful, lasting impact. Partnership is what moves the Foundation forward.

We want soaring success for these scientists. We want to clear their paths of the hurdles that might slow their progress. Real collaboration across all sectors lets us do this, keeping researchers focused on their research.

Foundation scientists are inspiring groundbreaking discoveries in all areas of biomedical research. But they know as well as we do that great ideas and novel concepts need solid backing to thrive.

Scientists whose projects fall outside of government research priorities are regularly turned away. With agency funding out of reach, novel concepts often dissolve, quickly and quietly.

Taking on the most challenging problems in health care today comes with a certain degree of unpredictability, but losing these bright ideas or the brilliant minds that create them is a much bigger risk. Because the Foundation's programs are not limited by federal focus areas, we can support a diverse range of research and catalyze innovative ideas that push the boundaries of science.

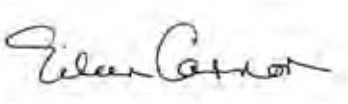
With our synergistic team of member companies and private and public funders, we implement programs that reach further and do more to support young scientists. It's an operation with many moving parts, but the Foundation brings all of these key players together in concert.

We have also partnered with prestigious universities and organizations to establish Centers of Excellence. These Centers represent the pinnacle of intensive training and research in clinical pharmacology, regulatory science, translational medicine, and comparative effectiveness.

Building on the success of our 10 Centers of Excellence, the Foundation is mobilizing a new program that will culminate in a more effective and efficient healthcare system. Our Value Assessment Initiative is designed to generate comprehensive knowledge about value in health and help patients and providers make informed care decisions. The goals are less waste, fewer errors, and better outcomes overall.

Two new multidisciplinary Centers of Excellence will build capacity in value assessment by creating collaborations, tools, and knowledge that support patient-centered, methodologically rigorous, and holistic value frameworks. With leadership from our partners Altarum and the University of Maryland School of Pharmacy, these Centers will enable the shift toward value-driven health care and ensure patient voices are an integral part of all medical decisions. A closer look at the missions and development of the Centers is featured on page 16.

Joining with partners who are as invested in the future of young scientists as we are makes us stronger. We share the rewards of watching the people we support bypass funding barriers, discover more, and accomplish truly great things in medicine.



Eileen Cannon, President

Awards in Excellence

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

The PhRMA Foundation's 2017 Awards in Excellence honor two leading academics and biopharmaceutical researchers for their research, their contribution to advancing our understanding of science and health, their dedication to students and mentoring and their commitment to the future. Each honoree embodies the very best in their chosen fields of Pharmacology/Toxicology and Clinical Pharmacology.

2017 AWARD IN EXCELLENCE IN PHARMACOLOGY/TOXICOLOGY

J. Craig Venter, PhD

1977 Research Starter Grant in Pharmacology/Toxicology

The PhRMA Foundation interviewed 2017 Award in Excellence in Pharmacology/Toxicology recipient J. Craig Venter about the power of precision medicine and how young scientists can make their mark.

John Craig Venter, PhD, is a renowned genomics researcher and one of the world's most influential scientists. He was the first to independently decode human DNA, pioneering the use of expressed sequence tags (ESTs) to find genes and explore their function. This discovery, and the many discoveries that followed, opened a new realm of possibilities for the early detection and treatment of disease.

Dr. Venter is founder, chairman, and CEO of the J. Craig Venter Institute (JCVI), a nonprofit research organization specializing in genomic medicine, infectious diseases, synthetic biology,

and informatics. He is also co-founder and co-chief scientific officer of Synthetic Genomics Inc., and co-founder, chairman, and CEO of Human Longevity Inc., a company that harnesses genomic and phenotypic data to measure an individual's risk for disease.

From 1967 to 1968, Dr. Venter served in Vietnam as a hospital corpsman for the U.S. Navy. "I was the doctor for a small village and orphanage," he said, "and I really loved what I was doing. My plan was to go to medical school. But when I switched from a community college to [the University of California], San Diego (UCSD), I was introduced to high-end science and high-end scientists."

At UCSD, Dr. Venter earned his bachelor's degree in biochemistry and his PhD in physiology and pharmacology. He accepted a position as assistant professor with the State University of New York at Buffalo, where he received a Research Starter Grant from the PhRMA Foundation.

"When you're starting out as an assistant professor, you are given some money to buy equipment and get going, but you have to find your own funds to really do research. Getting an initial grant from the PhRMA Foundation made a huge start in my research career."

In 1984, Dr. Venter came to the National Institutes of Health and developed a technique using ESTs, a revolutionary approach to gene discovery. Eight years later, he founded The Institute for Genomic Research (now part of JCVI), where he sequenced the first bacterial genome. He went on to map the full complement of human DNA in 2000 at his company Celera Genomics.

By identifying genetic variations that increase the risk of disease, Dr. Venter has driven precision medicine to new heights, unlocking the potential for highly customized treatments. His groundbreaking work has also broadened understanding of individual susceptibility for cancer and how different immune systems respond to the disease. "The goal is to find a companion diagnostic that defines who will really benefit from getting a drug," he said.

With that comes an emphasis on patient value that goes far beyond a treatment's cost. "[It's] not just the price of a drug, but actually how it affects them, what their priorities are, what they value. Do they [just] value feeling better, or do they want to be able to continue to work, and so on."

At JCVI, Dr. Venter and his team continue to blaze new trails in genetic research. They have sequenced and studied hundreds of genomes and published widely on environmental genomics, the first human diploid genome sequence, and the first self-replicating bacterial cell made with synthetic DNA.

Dr. Venter is among the most frequently cited scientists in biology and medicine. He has also received numerous public honors and scientific awards, including the 2009 U.S. National Medal of Science, the 2007 Nierenberg Prize, the 2002 Gairdner Foundation International Award, and the 2001 Paul Ehrlich and Ludwig Darmstaedter Prize.

When asked how young scientists can set themselves apart in the competitive quest for funding, Dr. Venter said it takes conviction. "The number one thing I learned from my mentor, the late Nate Kaplan, is to push limits. If you don't believe the experiment's going to work, you probably won't do it. And if you don't do it, you'll never push limits, and you'll never be successful as a scientist."

2017 AWARD IN EXCELLENCE IN CLINICAL PHARMACOLOGY

Craig W. Hendrix, MD

1997 Faculty Award in Clinical Pharmacology

Dr. Hendrix is a Professor of Medicine, Pharmacology and Molecular Sciences, and Epidemiology at Johns Hopkins University (JHU). He is also the Welcome Professor and Director of the Division of Clinical Pharmacology. Established in 1954, the Division of Clinical Pharmacology at Hopkins' School of Medicine is one of the oldest in the world and has a long history of laboratory and clinical research, teaching, and service activities. Dr. Hendrix has been a faculty member of JHU since 1994, and serves as Director of the university's Drug Development Unit, lead pharmacologist for the HIV Prevention Trials Network and Microbicide Trials Network, and Deputy Director of Hopkins Institute for Clinical and Translational Research, and Director of the Hopkins Center for AIDS Research Laboratory Core.

With more than 28 years of experience in the design and conduct of translational clinical pharmacology studies on antiretroviral drugs for HIV prevention and treatment, Dr. Hendrix's contributions range from first-in-human studies to international multi-center trials. His research has been supported by the Centers for Disease Control and Prevention; the National Institutes of Health (NIH); the United States Agency for International Development; the Bill and Melinda Gates Foundation; amfAR, The Foundation for AIDS Research; and other sponsors in the pharmaceutical industry.

Dr. Hendrix received his bachelor's degree in applied biology from the Massachusetts Institute of Technology in 1978, and his medical degree from Georgetown University, graduating magna cum laude in 1984. He completed an internship and residency in internal medicine on the Osler Medical Service at Johns Hopkins Hospital, and fellowships in infectious diseases and clinical pharmacology at JHU. Before joining the full-time faculty at JHU, Dr. Hendrix served 10 years on active duty for the U.S. Air Force (USAF), where he directed the HIV Research and Education Program at Wilford Hall USAF Medical Center in San Antonio, Texas. While assigned to the Division of Retrovirology at the Walter Reed Army Institute of Research, he developed HIV prevention education programs for the U.S. military, United Nations Department of Peacekeeping Operations, and other militaries worldwide.

For the past 15 years, Dr. Hendrix has been immersed in HIV chemoprevention research, focusing on the development of oral, topical, and injectable formulations. His group has developed novel methods for evaluating topical formulations for HIV pre-exposure prophylaxis (PrEP) combining imaging, multi-compartment pharmacokinetics, and behavioral assessments in first-in-human studies. In collaboration with biostatistical colleagues, he developed a three-dimensional tube-fitting algorithm to convert SPECT/CT data to concentration vs. distance data, which, using multiple scans over 24 hours, describes a concentration–distance–time surface. This method can be used to ensure that a microbicide product covers the radiolabeled HIV surrogate distribution surface in order to optimize topical formulation development. His group has applied

these methods to the early phase development of more than 20 different candidate vehicles or antiretroviral formulations for HIV prevention. In addition, as a protocol pharmacologist, he incorporated these methods to support nested pharmacokinetic–pharmacodynamic (PK–PD) designs in five of the initial randomized controlled clinical trials of antiretroviral PrEP. His group also provided essential contributions to the supplemental new drug application for Truvada's PrEP indication. PK data from these randomized trials, combined with several smaller studies, has enabled the quantitative assessment of adherence using drug concentrations as an objective adherence measure and provided substantial interpretive power to explain broad heterogeneity of protective response across trials due to large variation in adherence levels. Subsequently, Dr. Hendrix successfully advocated for real-time testing of adherence in two additional HIV prevention studies (MTN–017 and MTN–020), thus enabling improved adherence through targeted interventions while trials were ongoing, rather than as an explanatory variable at the study's end. His research has led or contributed to more than 205 original scientific publications, including 26 in 2017. Many of these papers were featured in leading peer-reviewed journals, including the New England Journal of Medicine, The Lancet, Science, and Cell.

For Dr. Hendrix, mentoring and teaching medical students, graduate students, and post-doctoral fellows has been a personal passion, integral to the success of his own research. In 2016, he assumed shared leadership of the NIH T32–funded Clinical Pharmacology Training Program at JHU. For the past 19 years, he has served on the Hopkins Institutional Review Board, which has provided him the opportunity to contribute more broadly to rational clinical study design. Dr. Hendrix is a recipient of the Hopkins Alumni Association Excellence in Teaching Award and the David M. Levine Faculty Mentoring Award.

Outside of his faculty work, Dr. Hendrix has served on the Food and Drug Administration's Antiviral Drugs and Oncologic Drugs Advisory Committees, an Institute of Medicine Ad Hoc Advisory Committee, and the National Center for Infectious Diseases' Board of Scientific Counselors. He is board certified by the American Board of Clinical Pharmacology and has been an active member of the American Society for Clinical Pharmacology and Therapeutics for 20 years, during which time he has served in multiple leadership positions, including roles on the Board of Directors.

An Interview with *Craig W. Hendrix, MD*

1997 Faculty Award in Clinical Pharmacology

Q **In 1997, you received the PhRMA Foundation Faculty Award in Clinical Pharmacology. How did it affect your career?**

A I received the award when I first transitioned from active duty in the Air Force to full-time faculty at Johns Hopkins University. It was absolutely essential to my transition. Hopkins is an academic institution where you have to raise 100 percent of your salary, and I had been raising none. The award provided a third of my salary for the first couple years. It reduced the burden on me to go from 0 to 100 percent support. I had a number of pharma-related clinical studies ready to start when I left active duty. There was also some ongoing work on HIV overseas that I wanted to continue. The funding was a critical bridge at a very high-risk, susceptible time in my career. It enabled me to begin my own research program. It helped me develop a broader skill set and preliminary data that could be used to garner federal grants. My career has been almost entirely dependent on federal grants since then. I'm not sure what I would have done without it, but I guess I would have had to get less sleep and find more pharma support! The things I accomplished during those years were the foundation for the research that I did thereafter. I'm forever thankful.

Q **How would you explain your research on infectious diseases and antiviral drugs?**

A Most of my research is focused on developing drugs to prevent HIV. There are a lot of drugs that treat, but there is only one licensed drug for prevention. Much of my work is developing other formulations of the licensed drug. Clinical pharmacology plays a big part in this. I have created methods for the lab and clinic to rationally develop and implement formulations in early phase studies and move forward into the clinical phases. Many approaches that we have been interested in focus on topical preventives. Little has been done to develop these drugs, especially for HIV.

Q **Why are PhRMA Foundation programs critical for younger scientists who haven't been able to get federal funding?**

A I liken the PhRMA Foundation Faculty Development Award to Career Development (K) Awards from the NIH. In my mind they both provide essential funding that really frees up a new faculty member to take risks and explore one's own ideas. This is a point when you are probably helping some senior investigators in their work, but the funding protects time in a way, so a faculty member starting out can invest in new ideas that mostly require just that—time. Time to think and read and do some early clinical investigation, and to write grants for longer durations and for more support. The grants provide a freedom and an ability to take some risks over a couple of years when you're not beholden to others. Risk taking in research and science is essential. You have to gin up creative juices and execute them at some point. Later in your career you sort of depend on having certain grant support, and once you have a team you carve out time to think about the next series of grants. It has to be done at any academic institution.

Q **Can you explain the importance of adherence in clinical trials? What have you done to improve adherence in HIV prevention studies?**

A It's hard to imagine anything more important than adherence. There is no way to demonstrate reliably that drugs work or are safe unless participants are highly adherent to a prescribed regimen. If they're not, even if you have an active drug that would work perfectly well once marketed, it directly erodes efficacy. This can kill a drug that would otherwise move forward. When a drug dies because of adherence, it's significant. You don't learn as much as you might about safety—about toxicity or needed frequency—if folks aren't taking the medicine. In my own HIV prevention work, adherence has had such a major impact on product development—especially topical products that could be very effective but will never go further because adherence was poor in randomized controlled trials.

There are successful interventions to improve adherence, however. For example, home visits and unannounced pill counts. The follow-up is basically beefed up counseling for people who fail to meet their pill counts. How you do this in a clinic is much more complicated. It's important to have counselors who understand the risks for poor adherence. People want to be good patients, so they might bias their reporting because they are struggling. Counselors can focus on ways to improve adherence by looking at routines, at organizational skills, and finding hooks in people's daily schedules that loop into pill taking. There's a greater challenge

in prevention, although in some ways it's even more important because there is no real natural enforcement with preventive treatments. This should be an active area of research in implementation science. If we can understand how to improve adherence in a number of different populations with one drug or in one prevention setting, it may be useful with another drug or treatment setting.

Q What would you say is your finest accomplishment in research? In teaching?

A I love teaching so much that if I wasn't a scientist, whatever else I did would be in an environment where I was teaching or mentoring in similar ways. The science is also a wonderful context for teaching. They are very closely related. Science enables me to teach, and the research enables me to work with young people. I have students at different levels whom I'm mentoring and doing research with, and I think in all these encounters, the high points of my week are meeting one on one with each of them to see their development and have a role in it. This is essential to the larger enterprise. If we are not training youngsters to come up through the academic ranks, there won't be practitioners in the community. It's a way we can continue beyond our own productive years in science.

Q Can you tell me about NIH–funded T32 fellowship in clinical pharmacology at Hopkins?

A The fellowship is linked to the Graduate Training Program in Clinical Investigation at Hopkins' School of Public Health. Fellows from another specialty or medicine—obstetrics, oncology, infectious diseases—will be doing their year of clinical work and looking for a research mentor. They might find what we are doing in anti-infective areas of particular interest, or they might have a basic interest in pharmacology and want a more rigorous understanding of clinical pharmacology. The first year is solely didactic; it's all in the classroom. When they enter the second year of the fellowship, they come into our program. In the third and fourth years, fellows have their research experiences, which are mentored directly or indirectly by clinical pharmacology faculty. The projects are very hands on. Fellows have a patient or patients whom they see in the clinic as part of the research. When someone is working with me, I become his or her primary clinical pharmacology mentor, and I involve the fellow in my own research. Or, the fellow's primary mentor could be an oncologist, if that is the specialty, and I would be the clinical pharmacology mentor. Either way, what we try to reinforce is that they will identify primarily as clinical pharmacologists. It's a very nice collaboration that brings together two different skill sets for the fellow. At the end, you have someone with a PhD in clinical investigation who is board eligible in their subspecialty and board eligible in clinical pharmacology. Most will have three to five publications by the time they finish the program. About 85 to 95 percent of fellows then become an assistant professor or take similar academic appointments, and others go into research-related programs like the ones at the FDA. In a way, the program expands others at Hopkins because of its synergy.

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

A The most important thing is to develop a broad skill set that will enable you to move nimbly to whatever area you get traction. Most faculty or fellows have been working on some projects as part of their training. Sometimes if they stay in one place, they will be able to keep on those projects. It's a good opportunity and it's efficient, but there might not be much additional work where they can pursue leadership roles. In this way, the kind of mentor you get attached to is important. If you are directly aligned with a more seasoned mentor, it can be difficult to establish yourself independently. On the other hand, if your mentor is more junior, you might not be able to lead projects. I am always conscious of this. The PhRMA Foundation Development Award is helpful for broadening in an area that might not be directly tied to a mentor. Because it's never clear where funding will come from, and even if a project starts with good funding, that can change. The science can change, the funding can change, or the problem itself might be solved. That's why you need broad skills. The other thing is to develop a diverse range of collaborators. Forming a group of colleagues over time whom you enjoy working with and who have subject matter expertise complementary to your own is very important. Then when you have to pull together a bigger interdisciplinary team, there are people you can call on. Thinking long term about relationships is essential. Finally, there's the role of serendipity—to be open to the likelihood that you are going to be doing something different 5 years from now that may be even better than what you're doing at the moment. You might need to retool early, middle, or late in your career, so you should be prepared to move agilely to another area. Keep your collaboration base multidisciplinary and hold on to those friendships so you can take advantage of new ideas. Also, experience at one institution can be very helpful at other institutions.

Value Assessment

Leading the Charge for Value-Driven Health Care

As health systems shift away from volume-based care, there is a movement to develop new approaches to defining and measuring value. Building tools and methods for measuring value across health care has the potential to improve treatments and services and lower costs. But first, value must go from conceptual to concrete.

The value of a treatment has long been associated with benefits and costs. Yet there are countless other factors that make a treatment meaningful to a patient. Does the treatment improve function? Does it have a manageable dosing regimen? What are its effects over the long term? Quantifying value in health care requires a long-term view that weighs both direct and indirect costs.

In 2017, the PhRMA Foundation launched its Value Assessment Initiative, a comprehensive effort to progress toward a value-driven healthcare system. The program supports the development of two Centers of Excellence that will identify high- and low-value health services and make recommendations for prioritizing the services that are most valuable to patients.

Value assessments cannot be built on scientific evidence alone. To improve healthcare decision-making by and large, they must incorporate patient preferences.

The Center of Excellence for Patient-Driven Value Assessment

Incorporating the voice of the patient when there are so many diverse health preferences is not about taking an average. What is most valuable about a treatment isn't the same from person to person, but the objective is not to explain away heterogeneity. Different populations have different needs.

Meeting these needs starts with understanding the tradeoffs that influence decisions a person makes about his or her care.

Dr. Susan dosReis, a professor of Pharmaceutical Health Services Research at the University of Maryland School of Pharmacy, leads the Center of Excellence for Patient-Driven Value Assessment. One of her team's core research objectives is to parse various aspects of healthcare decision-making based on patient feedback.

"If you think about purchasing anything in the market," said Dr. dosReis, "there are a number of different elements that matter to you. When you make a purchase, you are typically weighing the benefits of each of those elements. For instance, how much are you willing to compromise on one element because you really want something else?"

It's not so different in health care. If a patient is consistently sacrificing some part of his or her life to take one particularly effective drug, then the short-term benefits might not align with long-term outcomes.

"Healthcare reasoning is really a number of different tradeoffs," said Dr. dosReis. "What are people's values in making these tradeoffs? The answer becomes a quantifiable measure, with some values ranking higher than others."

Factors that mean the most to patients in healthcare decision-making become the "preference utilities" that inform value frameworks.

Dr. dosReis has a clear plan for involving patients at every level of the Center's work. They will have a central role in research protocols, not just as participants, but also as

members of the investigative team. Patients will also have a say in how the Center interprets its research.

Through advocacy groups, the Center will reach out to patients in underserved populations, providing guidance to help them make more informed decisions about their health.

The Health Care Value Research Consortium

Eliminating unnecessary medical tests, treatments, and procedures that have little or no benefit could save billions in healthcare costs each year.

On the flip side, many high-value services are being underused. The challenge is identifying both high- and low-value services, discouraging the use of unhelpful services, and incentivizing the use of services with a proven benefit.

Altarum, a nonprofit health systems research and consulting firm, and its partner, VBID Health, have developed highly effective strategies to identify services at both ends of the spectrum.

In its first year, Altarum's Health Care Value Research Consortium will conduct a quick-strike study that pinpoints the country's most and least valuable interventions. They have already identified the top five low-value tests and treatments.

"Our first task will be formulating and applying methods to measure the magnitude of these services," said George Miller, PhD, the Consortium's principal investigator and co-director. "They might not be the most expensive or necessarily the most harmful. But they are things we clearly shouldn't be doing."

Altarum has a number of multifaceted strategies to educate stakeholders on the need for identifying services by value. Its Value of Health tool, for example, assesses the long-term impacts of programs and initiatives designed to improve health. Another is the Healthcare Value Hub, which puts resources on reducing healthcare costs into the hands of advocates. A wealth of information is available in different formats, including webinars, reports, and case studies.

As new findings on low- and high-value health services are reflected in the recommendations of medical societies, task forces, and scholarly journals, the work of the Center will contribute to evolving practitioner care. Ultimately, the goal is for evidence-based solutions to influence everyday healthcare decision-making.

"We can't change physician practice, but it is our job to provide the materials that lead to these changes," said Paul Hughes–Cromwick, co-director of Sustainable Health Spending Strategies at Altarum.

The Health Care Value Consortium will also look at societal, economic, and environmental influences on healthcare services. Cultural barriers, for example, may keep some people from seeking services. "There are patients in underserved populations who tend to have some suspicion toward healthcare providers," said Dr. Miller. "We are looking at ways to overcome those barriers."

Of particular interest to Altarum is how vulnerable consumers find and use healthcare information. In a national study, they found that people with lower incomes tend to associate more care with better care. This can lead to unnecessary treatments.

The Consortium is studying patient perspectives at multiple points of the healthcare continuum. "All the various cancer and oncology treatments are a nexus for understanding patient preferences," said Mr. Hughes–Cromwick. "One of the classic problems is the asymmetry of knowledge. How do you cope as a patient when the physician knows all the things you don't and you know all the things about your body that he doesn't?"

The way to value-based care won't always be straight ahead. As value frameworks and attitudes about value in health evolve, so will the work of the Consortium.

"The systems aren't standing still anymore," said Mr. Hughes–Cromwick. "They are all trying to make care more efficient. You need a broad lens to understand the changes that are under way and how to respond to those changes."

Value Assessment Challenge Awards

The PhRMA Foundation solicited papers that answer a question key to moving the discussion about value-driven health care forward:

What are transformative strategies to measure or evaluate the value of health care interventions that could be implemented to advance a value-driven health care system in the United States?

Altarum

George Miller, PhD

"A Framework for Measuring Low Value Care"

IT HAS BEEN estimated that more than 30% of health care spending in the U.S. is wasteful, and that low-value care, which drives up costs unnecessarily while increasing patient risk, is a significant component of wasteful spending. There is a need for an ability to measure the magnitude of low-value care nationwide, identify the clinical services that are the greatest contributors to waste and track progress toward eliminating low-value use of these services. Such an ability could provide valuable input to the efforts of policy makers and health systems to improve efficiency. In this paper, Altarum summarizes and critiques existing methods that could contribute to measuring low-value care and describes an integrated framework that combines multiple methods to comprehensively estimate and track the magnitude and principal sources of clinical waste. The paper also outlines a process and needed research for moving incrementally toward full implementation of the framework while providing a near-term capability for measuring low-value care that can be enhanced over time.

National Eczema Association

Julie Block

"Shared Decision-Making Resource for Eczema Patients"

CHRONIC DISEASES NOW represent a cost majority in the U.S. health care system. With expensive novel and emerging therapies, under-treatment of disease, under-management of comorbidities and patient dissatisfaction with care results contributing to rising costs, a reliable model to measure value is critical to identifying replicable improvement methods. If value is understood within healthcare consumerism to be equal to a patient's health outcome improvement over cost (Value=Outcomes/Costs), and outcome improvement is measured using patient-generated health data, than this equation can be used to measure patient-centric value. Research and literature show that patient activation—the skills and confidence that equip patients to become actively engaged in their health care—impact health outcomes, costs, and patient experience. Reaching patient activation through engagement methods including shared decision-making (SDM) lead to improved value of care received, as the intervention becomes an exchange of knowledge between patient and provider with the joint goal to achieve measurable outcomes. The National Eczema Association (NEA) Shared Decision Making Resource Center can be a transformative strategy to measure or evaluate value of health care interventions for eczema patients to advance a value-driven health care system in the U.S. Through this Resource Center, NEA will measure patient value through validated PRO instruments and other patient generated health data. Assessment of this data will reveal findings that can assist researchers in evaluating the impact this care framework on value across other chronic diseases.

ALTARUM: Pictured from left are Corwin Rhyan, MPP, Paul Highes-Cromwick, Beth Beaudin-Seller, PhD, George Miller, PhD.

NEA Team: Picture from left are Tim Smith, MPP (VP, Advocacy & Access), Fran Quinn Van Bergen (Director, Development), Lisa Butler, MBA (VP, Strategic Partnerships), Julie Block (President & CEO), Lauren Hewett (Manager, Events & Marketing), Christine Anderson (Senior Manager, Operations), Karey Gauthier, MS (Director, Marketing & Communications), Jessica Bartolini (Manager, Community Engagement), Scott Sanford (VP, Operations) Not Pictured: Robin Blaney (Administrative Assistant), Wendy Smith-Begolka, MBS (Director, Research)

National Health Council

Eleanor M. Perfetto, PhD, MS

"Good Practices for Transforming Value Assessment: Patients' Voices, Patients' Values"

MEANINGFUL PATIENT ENGAGEMENT – in all aspects of value assessment – is a transformative strategy that can improve evaluations of the value of health care interventions to advance a value-driven health care ecosystem in the United States. At their inception, most U.S. value frameworks and subsequent assessments were developed with little to no patient engagement. To help increase and improve patient engagement, the National Health Council (NHC) implemented a Value Initiative in 2016 with multiple components including a Value Workgroup. Despite these specific efforts, a great deal still needs to be learned about the best ways to achieve meaningful and effective patient engagement in value assessment, and to understand the impact on value assessment findings. The objective of this study was to glean from patient-community experiences with value framework developers those emerging good practices in patient engagement to be disseminated, improved upon and replicated. While patient engagement was limited in the development of early value frameworks, patient advocacy group engagement with value framework developers and assessors has increased in the past two years. Groups report positive experiences in engagement that can serve as emerging good practices. They have also experienced challenges in their interactions and posed recommendations on good practices they believe can improve engagement experiences. The NHC will provide leadership in this area by encouraging use of these emerging good practices and continue to capture data on patient experiences, reporting on trends and the growing pool of patient engagement experiences that can be translated into good practices to advance a patient-centered, value driven health care ecosystem. Learnings from these early experiences can help recommend emerging good practices that can eventually get the field to best practices and standards over time.

University of Michigan

Joel Gagnier, ND, MSc, PhD

"Integration of Patient Reported Outcome Measures to Aid in the Assessment of Value in Health Care"

PATIENT REPORTED OUTCOME measures (PROMs) are tools to assess the patient's perspective on their health without interpretation by any other parties. PROMs have been suggested as key tools in clinical research and clinical follow-up of patients. Clinical decision-making can be influenced by the additional information that sound PROMs provide and can save significant resources and patient burden. The integration of electronically delivered PROMs in clinical practices (in patient, out patient, public and private) can dramatically change health outcomes by influencing decision-making. The authors propose that the implementation of generic and disease/condition specific PROMs across health care systems will advance a value driven health care system. These measures provide key information/feedback that can influence clinician decision making, save resources (e.g., insurance or out of pocket costs waiting times), and improve patient outcomes. The authors suggest that the integration of PROMs into clinical practice, in all settings, can dramatically increase value assessment of medicine and improve healthcare overall. Throughout the paper they note their past experience in these areas and propose the assessment of healthcare interventions can be improved using their expertise, methods and information technology platform.

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.

2017 PRE DOCTORAL FELLOWSHIPS IN HEALTH OUTCOMES

Maya L. Hanna, MPH
University of Maryland, Baltimore

"Geographic Variations of Screening and Diagnosis of Alzheimer's Disease and Related Dementias in the United States"

Cognitive impairment remains severely under-detected by primary care providers and leads to poor health outcomes. Early detection of cognitive impairment is a step toward timely and accurate diagnosis of ADRD. Recognizing the growing burden of Alzheimer's disease and related dementias (ADRD) on patients, families as well as the United States health care system, President Obama signed the National Alzheimer's Project Act (NAPA) into law in 2011. NAPA established a national plan to address ADRD with the goal of enhancing care quality and efficiency by ensuring timely and accurate diagnosis of ADRD. In the same year, the Affordable Care Act added the coverage of an Annual Wellness Visit (AWV) as a Medicare Part B benefit, of which detecting of cognitive impairment is a required component. The goal of this study is to evaluate whether geographic variations exist in screening for and diagnosing ADRD in the U.S. The central hypothesis is geographic variations in screening for and diagnosing ADRD exist as a result of varying health care practices and the availability of essential health care resources. These factors have a direct impact on burden of illness and may indicate socio-environmental contributions to ADRD detection, diagnosis, treatment, and outcomes. This study is the first of its kind to investigate whether routine cognitive impairment screening through the Medicare AWV lead to timely detection of ADRD, resulting in improved health outcomes in persons with newly diagnosed ADRD. The results of this study will inform policymakers on the impact of Medicare AWV implementations on detecting ADRD and primary care providers on potential benefits of routine cognitive impairment screening on health outcomes in the Medicare population.

Natalia Olchanski
Tufts Medical Center

"Value of Personalized Risk Information in Economic Analysis"

Better targeting of medical interventions is ever more important given the aging population in the U.S., high prices of new technologies and limited budgets of healthcare payers. Cost-effectiveness analysis (CEA) assesses the value of interventions, typically by comparing average population health gains to average costs. Because intervention value differs across individuals, this project aims to extend conventional CEA methods to address patient heterogeneity, when it can be predicted on the basis of pre-treatment characteristics. The research will conduct risk-based CEA of (1) diabetes prevention program for individuals with pre-diabetes, and (2) digitalis in patients with heart failure (HF), and assess whether cost-effectiveness varies by risk stratum and how the risk-based approach may potentially help target patients for intervention. Because the pre-diabetes population is particularly large, targeting of preventive measures may be necessary to make such programs economically feasible. Likewise, HF patients use substantial health care resources and have high hospitalization costs, and therefore it is important to understand how medications should be targeted to prevent hospitalizations. Additionally, this project will explore how clinical risk prediction model performance may influence the results of individualized economic analysis.

2017 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.

Joshua Brown, PharmD, PhD, MS

University of Florida

"Comparative Effectiveness of Direct-Acting Oral Anticoagulants (Doacs) in Non-Valvular Atrial Fibrillation (Nvaf): Contrasting Methodological Approaches Using Real-World Data"

Long-term anticoagulation is needed to prevent debilitating outcomes like stroke for patients with atrial fibrillation but also invoke a risk of bleeding. For decades, warfarin was the standard of care in the United States but newer agents have entered the market since 2010. Among these direct-acting oral anticoagulant options, clinicians are left to choose between these agents, judging their relative safety and effectiveness although there have been no clinical trials to assess this question. Real-world data and evidence are generated from daily clinical practice outside of the highly controlled environment of randomized clinical trials. While real-world evidence can have a role in conducting comparative effectiveness research and answer this clinical question, many assumptions about study design and analysis make these types of quasi-experimental research approaches difficult to interpret and rely on. This project is utilizing the example of direct-acting oral anticoagulants in patients with atrial fibrillation to survey the impact a myriad of design and analysis choices can have on real-world evidence. The approach is iterative in nature, changing one facet of the design and analysis at a time and evaluating the way that one effect can influence the interpretation of results. The goal is to create an educational guideline for clinicians to be able to more accurately evaluate medical literature and to make researchers more aware of how they conduct and report their research. Lastly, the project will continuously update the real-world evidence for direct-acting oral anticoagulants with the latest available data so that better decisions about anticoagulation can be made.

Wei-Hsuan Jenny Lo-Ciganic, PhD, MSCP, MS
University of Arizona

"Using Advanced Analytics to Predict Problematic Prescription Opioid Use in Medicare"

The opioid crisis has become a national emergency in the U.S. Prescription opioid overdose deaths more than quadrupled from 1999 to 2015. Efforts by health care systems and payers to combat the opioid epidemic are impeded by a lack of accurate and efficient methods to identify individuals and regions most at risk for problematic opioid use and overdose, leading to broad interventions that are burdensome to patients and expensive for payers. Successful interventions must accurately identify and target individuals and regions at highest risk of problematic prescription opioid use. However, potential risk factors for problematic opioid use/overdose have been identified using traditional statistical methods, but prior approaches have limited ability to discover hidden patterns in complex healthcare data, and focused on identifying individual risk factors rather than predicting actual risk. Alternatively, machine learning and space-time pattern mining are advanced data-driven techniques that uncover hidden patterns in complex data to yield precise prediction algorithms that are able to better guide decisions and interventions in real time. These innovative analytic approaches have not yet been applied to address the opioid epidemic. Accordingly, the proposed project will apply machine learning to 2011-2015 national Medicare claims data to develop prediction algorithms for identifying patients at risk of problematic opioid use and employ space-time pattern mining to identify "geographic hotspots" in problematic use to develop a forecasting mapping tool. The project's findings and new prediction tool will inform the Centers for Medicare & Medicaid Services and Medicare Part D Plan sponsors regarding opioid use policies and aid in developing effective prevention strategies and allow healthcare providers to better allocate resources for target interventions.

> “The Research Starter Grant in Health Outcomes has provided me with the resources needed to study the impact of polypharmacy on health outcomes. The findings from this research will establish a publication record and provide the data needed to obtain independent funding. I am very thankful to the PhRMA Foundation for supporting my career development.”
>
> Nicholas Schiltz, PhD | Case Western Reserve University

Nicholas K. Schiltz, PhD
Case Western Reserve University

“Modeling the Joint Impact of Polypharmacy and Multimorbidity on Health Outcomes”

More than one-third of all adults have multiple chronic health conditions (multimorbidity), and about 15% are taking five or more drugs concurrently (polypharmacy). These people have a high risk of mortality, adverse drug-interactions, poor quality of life, and excess health care utilization. Despite the fact that multimorbidity and polypharmacy are clearly related, research on these two concepts is often conducted separately, rather than in tandem. This research project has two specific aims. The first is to develop measures of polypharmacy using data mining methods (e.g. cluster analysis and association rule mining) and expert opinion. The second aim is to model jointly the impact of multimorbidity and polypharmacy on patient-reported quality of life and medical expenditures. This second aim will be accomplished using machine learning methods including classification and regression trees and random forest. Data on over 116,000 adults from the population-based Medical Expenditure Panel Survey will be used to conduct the proposed research. This research will provide new insights about the impact of specific combinations of therapy in the care management of patients with multiple chronic conditions, and can help identify subgroups of the population at high risk for poor health outcomes and high expenditures.

Adherence Improvement

Pre Doctoral Fellowship in Adherence Improvement

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

Medication adherence is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a treatment regimen. Extensive evidence demonstrates that medication adherence can yield better clinical and economic outcomes. However, many individuals do not take their medications as recommended. Closing the adherence gap is important to improving the quality of health care, encouraging better chronic care management, and promoting better outcomes.

2017 PRE DOCTORAL FELLOWSHIP IN ADHERENCE IMPROVEMENT

Adam Sage

University of North Carolina at Chapel Hill

"Optimizing Patient Comprehension of Information Visualizations for Medication Adherence and Blood Pressure"

Hypertension affects approximately 70 million (29%) adults in the U.S. and is associated with $46 billion in health care-related costs. In addition, research has shown that up to 45 percent of patients prescribed at least one anti-hypertensive medication discontinue their medication following an initial prescription fill. Such discontinuation contributes to approximately $290 billion of avoidable nonadherence-related costs per year in the U.S. Mobile health interventions have emerged in recent years that seek to improve patient medication adherence and clinical outcomes through the innovative use of technologies such as smart phones and wearable health tracking devices. Due to the use of health apps and wearable devices, people have unparalleled access to personal health data, but little work has investigated whether patients can effectively comprehend these data and use them to improve disease self-management. This study assesses optimal methods for presenting blood pressure and medication adherence data via graphical information visualizations (e.g., charts, tables, and graphs). By developing information visualizations that are easy for patients to interpret and understand, health monitoring technologies, such as mobile apps and wearable health tracking devices, can improve their ability to positively influence patient medication adherence and health-monitoring.

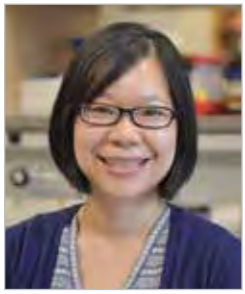
Translational Medicine and Therapeutics

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.

2017 POST DOCTORAL FELLOWSHIPS IN TRANSLATIONAL MEDICINE AND THERAPEUTICS



Isabel Lam, PhD
The Brigham and Women's Hospital

"Functional Investigation of Rare Genetic Variants Associated with Alpha-Synuclein Pathology and Parkinson's Disease"

Parkinson's disease is a chronic neurodegenerative disorder affecting nearly 6 million people worldwide, and its prevalence and socioeconomic impact is projected to increase proportionally with increasing population longevity. A substantial component of Parkinson's disease is heritable, but most of this heritability is currently unexplained. Advances in genome sequencing promise to uncover variants that account for this "missing heritability", but distinguishing pathogenic from neutral variants is a pressing issue in the field. Rare variants require exceedingly large sample sizes to achieve statistical power, and recent human divergence limits the use of replication across populations as a way to validate them. The goal of the proposed research is to implement a cross-species experimental platform to enable functional interpretation of rare variants found in patients with Parkinson's disease. The platform will (1) interrogate the ability of variants to modulate cellular toxicity in two complementary systems—the genetically tractable yeast, and human neurons derived from Parkinson's disease patients; and (2) test the effect of variants on molecular interactions at proteome scale. This multifaceted platform promises to uncover genetic risk factors for Parkinson's disease, and presents a biological approach for distinguishing normal from pathogenic variants. Insights gained into the genetic and molecular underpinnings of the disease may ultimately help uncover therapeutic targets and assist in precision medicine diagnostics.

Norelle Wildburger, PhD

Washington University

"In Vivo Stable Isotope Labeling and Quantitative Mass Spectrometry Imaging of Aβ Plaque Deposition in Human Ad"

Alzheimer's disease (AD) is a devastating neurological disease for which there is currently no effective therapeutics. Critical to the development of therapeutics that may treat and even cure AD is an understanding the dynamics (the change over time) of amyloid-beta (the likely cause of AD) in the human brain. This project is using the most advanced imaging technology to answer these questions in patients in order to accelerate drug development and improve patient outcomes. The goal is to measure, for the first time in human Alzheimer's disease (AD) brain, the rate of plaque pathology using the most advanced imaging technology. The project has developed an advanced imaging protocol called SILK-SIMS, which enables the ability to image and measure plaque growth at the nanometer level; this allows us to see structures much smaller than cells and measure the growth during life. Plaque growth is measured with a label given to patients (like a dye which tags newly made plaque), which are then imaged with SILK-SIMS, noting both the location and amount of the new growth of the plaque. The aim is to measure plaque growth, using SILK-SIMS imaging, in the brain of people with mild to severe cases of AD and compare these measurements to those taken from patients without dementia. These findings will enable the project to model how fast AD pathology occurs in the living human brain. This research is unique in that it will be providing the first direct measures of plaque growth rates in the human AD brain by utilizing cutting-edge methodologies never before leveraged in the AD field. The outcomes of this study will provide new insights in order to better understand AD amyloid pathology, which can accelerate drug development and inform clinical trials. In addition, the project will have established a blueprint for the investigation of other devastating neurodegenerative diseases, such as Parkinson's disease, frontal-temporal dementia, and amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease).

2017 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.

Mark T. W. Ebbert, PhD

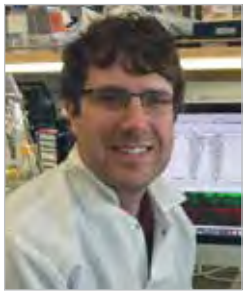
The Mayo Clinic

"Determining How Alzheimer's Disease Originates Through Multi-Omic Approaches in the Lateral Entorhinal Cortex and Cerebrospinal Fluid"

The underlying biology responsible for Alzheimer's disease remains unclear, and diagnostics and effective treatments have eluded researchers for over 100 years, despite extensive efforts. The impending healthcare crisis now requires advanced, assertive research where disease originates—the central focus of these studies. This will ultimately be the fastest, most cost-effective approach to reveal the underlying biology and facilitate effective diagnostics and therapeutics. Alzheimer's disease pathology generally begins in the entorhinal cortex, a brain region responsible for memory and navigation. What is especially unique about the studies outlined in this proposal is: (1) the proposal aims to sequence DNA and RNA obtained directly from the entorhinal cortex from deceased Alzheimer's disease patients and controls, and (2) the methods involve using a cutting-edge sequencing technology that makes it possible to resolve aberrations in the DNA and RNA driving disease that have not been previously identified. These approaches will provide exciting new insight into this devastating disease, and how to treat it.

“I am thankful to the PhRMA Foundation for supporting me with a Research Starter Grant during my transition to independence – a challenging period for all new principal investigators. With their support, I have exceeded all of the goals that I set for my first year running a laboratory. In particular, I am much closer to producing a publication than I had anticipated.”

A. Hunter Shain, PhD | University of California, San Francisco



A. Hunter Shain, PhD

University of California, San Francisco

“Genetic Discovery and Validation of Diagnostic and Prognostic Biomarkers in Melanocytic Nevi”

The common mole can serve as a precursor for melanoma. Accurately distinguishing moles from melanomas is critical to provide the proper course of clinical care. This assessment is currently made by removing the suspicious lesion and evaluating it under the microscope. Unfortunately, this process is subjective, as there are often disagreements among observers when evaluating the same lesion. Furthermore, it is currently not possible to distinguish moles that are at increased risk to become melanomas from moles that will remain harmless. Moving forward, it will be essential to develop objective algorithms for the diagnosis and prognostication of melanocytic lesions. New DNA sequencing technologies offer a powerful means to identify genetic alterations in tissues, and our preliminary work suggests that this is a rich source of biomarkers for melanocytic lesions. For this grant, melanocytic lesions closely bordering the benign and malignant junction will be sequenced to reveal genetic alterations that can distinguish moles from melanomas. Also, a nevi that progressed to melanoma and nevi that did not progress to melanoma will be sequenced to reveal genetic alterations that can flag nevi that are likely to become melanoma. Overall, completion of these studies will provide new sources of biomarkers to improve the diagnosis and prognostication of melanocytic lesions.

> “I am very honored and grateful to be a recipient of the precious PhRMA Foundation Research Starter Grant in Translational Medicine and Therapeutics. Translational Medicine focuses on transferring experimental discoveries in the research laboratory to clinical applications. This award has given me the opportunity to focus on my research developing better oral vaccines which can target the intestinal mucosal immune system. Receiving an award from the PhRMA Foundation has also provided my mentees of all backgrounds the opportunity to train, think, learn and explore science and ultimately make their own contributions to pharmaceutical research.”
>
> Qun Wang, PhD | Iowa State University

Qun Wang, PhD

Iowa State University

“Develop Oral Vaccines with Miniguts”

Vaccination via the intestinal mucosal is considered superior to vaccination by subcutaneous injection with regards to induction of a protective immune response. Contact of the lymphoid tissue of the mucosa to antigen generates a clonal expansion of B and T lymphocytes, and IgA dedicated B lymphoblasts move through the lymph nodes resulting in a superior immune response in mucosal sites throughout the body. While progress has been made increasing stability and immune activation of potential mucosal vaccines, very little is known about the specific and non-specific factors determining recognition and transport of vaccine candidates across the intestinal mucosal epithelia for oral administration. It is significant to explore and characterize the alternative routes and strategies of immunization that can specifically target and transport high levels of antigen across the gut mucosal barrier and into the mucosal associated lymphoid tissue to stimulate a strong and protective mucosal immune response. To address this challenge in the development of new oral vaccines, this research proposes to explore an ex vivo Minigut gastrointestinal mucosal system derived from intestinal stem cells (ISCs) to investigate and characterize new oral vaccine delivery systems. Understanding how nanoparticles-based oral vaccine delivery systems transport through digestive tract epithelium and how transport behavior can be manipulated through chemical modification to create guided transport pathways will provide critical knowledge on future design and development of effective vaccine delivery systems for oral administration. The overall objective of this proposal is to understand the mechanism of the transport of nano-vaccines through Miniguts that mimic the functionality of the normal gut, so that better oral vaccines can be developed which can target the mucosal immune system more effectively. This project, will specifically address the major gap in oral vaccine development.

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.

2017 PRE DOCTORAL FELLOWSHIPS IN INFORMATICS

Jacob Kimmel

University of California, San Francisco

"Inferring Cell State Dynamics From Cell Behavior by Novel Image Informatics"

Cells display remarkable heterogeneity at the single cell level, such that individual cells in a population may have distinct functional states. In many biological contexts, including stem cell biology and cancer, these heterogeneous cell states are dynamic. How frequently do cells change state? Do cell states transition in an ordered pattern, or are the changes random? Do cells have a memory of their past states? It is difficult to answer these questions using classical molecular biology, as these molecular assays destroy the very cells under investigation in order to measure them. Cell behavior by contrast is a rich phenotypic space that may be observed non-destructively using timelapse imaging. Although informative and easy to observe, cell behaviors are traditionally difficult to quantify. This project is developing novel informatics methods to enable inference of cell states from cell behaviors as a real-time cell state assay and to quantity cell state dynamics. Cell behaviors will be measured using a combination of deep learning based image analytics and heuristic feature engineering to consider cell geometry, motility, and division dynamics. The dynamical nature of cell states will be analyzed using Markov models and by adapting probability flux analysis tools from statistical physics to provide estimates of cell state transition rates and to infer cell state hierarchies. These informatics methods will be applied to the muscle stem cell system to understand how stem cells transition between distinct regenerative and non-regenerative states. Assays of cell state dynamics inferred from quantitative cell behaviors may serve as a novel phenotypic screening read-out in multiple biological contexts, and this approach will be validated by identifying inducers of muscle stem cell regenerative state transitions.

Bo Zhang
Pennsylvania State University

"Enhancing Hi-C Data Resolution with Deep Convolutional Neural Network"

Three-dimensional (3D) genome organization is critically important for the proper functions of cells. The 3D structure facilitate the distal DNA elements find their right targets along genome at the right time, which is essential for orchestrating spatial- and temporal-specific gene expression. Genetic mutations and structural variants disrupting those 3D interactions can lead to pathological conditions and even cancer. Hence, 3D genome structure can be used to discover potential biomarkers for diseases as well as therapeutic targets. Recently, several techniques have emerged and allows us to study chromatin interactions genome-wide. Among them, High-throughput Chromatin Confirmation Capture (Hi-C) technology is of particular interest due to its unbiased genome-wide coverage that can measure chromatin interaction intensities almost between any two given genomic loci. Although Hi-C technology is one of the most popular tools for studying 3D genome organization, due to sequencing cost, the resolution of most Hi-C datasets are coarse and cannot be used to link distal regulatory elements to their target genes. From the other hand, Deep Convolutional Neural Network (ConvNet), which is inspired by the organization of the animal visual cortex, has achieved great success recently in several disciplines, including genomics. Therefore, this project is aiming at boosting feature information from low resolution Hi-C data, which is the common quality of available data, by utilizing the power of deep ConvNet. In the next stage, this research is seeking to reveal regulatory networks that are important to biological context especially disease from enhanced high-resolution HiC data. In the last stage, this project will use experimental results to evaluate and improve the performance of the computational work.

2017 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. With this funding, many recipients have been able to secure their careers in informatics and establish independent labs.

Ben Mueller, PhD

Vanderbilt University

"Improving Computational Structural Predictions of Drug/Protein Interactions"

Three-dimensional computational modeling of how a molecule interacts with a protein in the body is a rapid and inexpensive way to screen compounds, and can hopefully lead to the development of safer and more effective drugs. One important class of interactions that are critical to how small drug-like molecules bind to proteins are partial covalent interactions (PCIs), which include hydrogen bonds, halogen bonds, chalcogen bonds, π-π and cation-π interactions. Quantum mechanical (QM) calculations are a precise way to measure this interaction, however they are too slow to evaluate large screens of molecules. Rosetta is a widely used macromolecular modeling program that allows for the evaluation of molecule to protein interactions. While rapid, Rosetta does not treat all PCIs uniformly, and does not explicitly measure many of these interactions. This research focuses on applying general trends determined using the slow QM calculations to better evaluate PCIs in Rosetta. Using a process known as Wannier fitting, orbitals are explicitly modeled on to a molecule; this allows for a more accurate measurement of the PCI energy between molecules. Currently, the project is working with collaborators to test this new method, determining how both known and novel small molecules bind to metabotropic glutamate receptors and G protein-coupled inwardly-rectifying potassium channels. In summary, three-dimensional computational prediction of drug to protein interactions helps guide researchers in the creation of new drugs, and helps to eliminate potential side effects. By adding greater detail into the chemical models the number of incorrect predictions is hypothesized to decrease, leading to improved drug design.

2017 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.

> "The PhRMA Foundation Research Starter Grant in Informatics has greatly encouraged me to pursue my research interests at the intersection of statistics and biology. Specifically, my research focuses on developing statistical and computational methods to address important questions in biomedical sciences and to extract abundant information from big genomic and health related data."
>
> Jingyi Jessica Li, PhD | University of California, Los Angeles

Jingyi Jessica Li, PhD

University of California, Los Angeles

"Statistical and Computational Methods for Comparing Large-Scale Epigenomic Data and Sequences"

While all human tissue and cell types largely preserve the DNA sequence of the human genome, there is considerable variation in their epigenomes, which are made up of chemical compounds and proteins that can attach to DNA and direct such actions as turning genes on or off. Epigenomes bridge genotypes and phenotypes, and studying genome-wide epigenomic signals using high-throughput sequencing can promote the discovery of biological mechanisms under various cellular contexts. Recently, the ENCODE and Roadmap consortia have generated large-scale human epigenomic datasets, providing an unprecedented opportunity for exploring human epigenomic landscapes using informatic approaches. This project aims to develop new statistical and computational methods for comparing large-scale epigenomic data and identifying characteristic epigenomic marks of different biological samples. The proposed methods will be implemented and distributed as open-source software packages, which will serve as useful tools for biomedical scientists who generate and analyze epigenomic data. Applying these methods to epigenomic data of disease samples will identify potential targets for understanding disease mechanisms.

Daniel Lobo, PhD

University of Maryland, Baltimore

"Automated Inference of Human Intra-Tumor Interaction Networks for Discovering Optimal Treatments"

Cancer is a tissue disease arising from the evolution of a variety of different types of tumor cells, called sub-clones. The dynamic interaction of the different sub-clones within themselves and the surrounding environment is essential for the formation and growth of the tumor, a process poorly understood. Treatments eliminating the tumor cells with the fastest proliferation rates fail due to the survival of slow sub-clone populations with the ability to induce tumor-promoting microenvironmental changes and signals sufficient for tumor growth. This project will develop a high-performance computational framework for the automated discovery of dynamic intra-tumor interaction networks directly from data of sub-clonal compositions and their factor levels, and the discovery and prediction of the precise interventions that would cause the tumor to collapse. The proposed work will advance our understanding of the dynamics of sub-clonal tumor heterogeneity, increase our modeling capabilities of tumor interaction networks, and develop a series of software algorithms and tools for the discovery of specific sub-clonal interaction networks and the precise targets to prevent and revert tumor growth. This research is grounded in mathematical formalisms, quantitative biology, and a systems approach to streamline the use of high performance computing and artificial intelligence to vastly improve the efficacy of cancer therapies with the use of tumor-specific interventions automatically developed by computational systems.

Jian Peng, PhD

University of Illinois at Urbana

"Large-Scale Network Integration with Applications to Drug Development"

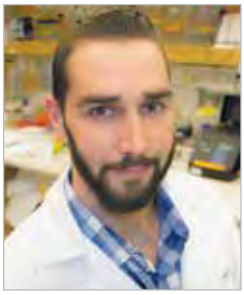
Computer-aided drug discovery methods have been widely used in the development of therapeutically important small compounds for decades. These traditional approaches mainly are based on the information of known ligands and/or target proteins, which are often not known for many diseases. The recent growth of genomic data and the advances in biotech and artificial intelligence have greatly enhanced the capability of understanding the underlying biological processes of diseases and identifying novel drug targets. With the support of the PhRMA Foundation Informatics Award, this project has developed algorithms that use existing molecular interactions to integrate functional genomic data into molecular networks that uncover novel disease-related pathways and possible drug targets. The research has also developed several other new artificial intelligence algorithms for drug target identification, drug sensitivity analysis, and molecular design.

Pharmacology/Toxicology

Pre Doctoral Fellowships in Pharmacology/Toxicology

Since the program's initiation in 1978, 399 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.

2017 PRE DOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY



Timothy Baffi

University of California, San Diego

"The Kinase Complex mTORC2 Regulates the Tumor Suppressor Protein Kinase C by a Chaperone Mechanism"

The aim of this research is to understand the molecular mechanisms of Protein Kinase C (PKC) activation by the mammalian Target of Rapamycin Complex 2 (mTORC2), and the impact on cancer cell fate when this process is impaired. The mTOR kinase exists in two functionally distinct complexes, mTORC1 and mTORC2. mTORC2 regulates two C-terminal phosphorylations on PKC that confer activity and stability to the enzyme; although, the mechanism of this regulatory step is unknown. Recently, mTOR has become a major therapeutic target in cancer due to the implication of mTORC1 in cell growth and proliferation; however, mTOR inhibitors are likely to have unanticipated effects on mTORC2-dependent enzymes such as PKC. Analysis of cancer-associated PKC mutations revealed that PKC is in fact a tumor suppressor. Accordingly, emerging therapeutic strategies that inhibit mTOR may actually have detrimental effects on patient outcome if they cause the loss of the tumor suppressor PKC, as low PKC levels in tumors are a prognostic marker for poor outcome in certain cancers. Therefore, it is critical to understand how mTORC2 controls PKC processing, so that the efficacy of therapeutics targeting mTOR can be properly evaluated and PKC function can be maintained in cancer patients receiving these treatments. To assess how mTORC2 regulation of PKC affects its tumor suppressive function, two approaches are employed: 1) to delineate the biochemical mechanism whereby mTORC2 facilitates the phosphorylation and activation of PKC, and 2) to compare two methods of targeting mTORC, Rapalogs and ATP-competitive mTOR kinase inhibitors, with respect to PKC function in pre-clinical cancer studies.

Erin Baker
Northwestern University

"Determining the Mechanisms of Action for GS967 Chronic Treatment of Epileptic Encephalopathy"

Over 100 de novo mutations in SCN8A have been associated with infantile-onset encephalopathy that includes seizures, delays in cognitive and motor development and increased risk of sudden unexpected death in epilepsy (SUDEP). Functional characterization of mutations demonstrated that elevated persistent current is a common defect. A mouse model carrying the N1768D gain-of-function mutation recapitulates many features of the patient phenotype, including spontaneous seizures and reduced lifespan. High-dose phenytoin has been reported as beneficial for seizure control in some individuals with SCN8A mutations, but the narrow therapeutic window of phenytoin is a concern. Additional drugs that preferentially block persistent current could benefit this patient population.

GS967 is a sodium channel blocker with greater potency and enhanced preference for suppressing persistent current compared to phenytoin. Electrophysiology studies demonstrated that elevated persistent current in neurons from untreated Scn8a-N1768D/+ mice was attenuated by acute application of GS967. Chronic treatment of Scn8a-N1768D/+ mice with GS967 rescued the premature lethality, with 100% surviving to 6 months of age compared to 20% of untreated. The beneficial effect was lost upon withdrawal of GS967 chow. Treatment with GS967 extended survival of homozygous Scn8a-N1768D/N1768D mice, with 50% of treated mice surviving for 4 weeks compared to none of the untreated mice.

Chronic GS967 administration prolonged survival of Scn8a-N1768D mice, which may be due to suppression of aberrant persistent sodium current in neurons. This study demonstrates a beneficial effect of GS967 in a mouse model of SCN8A encephalopathy and provides further support for GS967 as a novel anticonvulsant for refractory epilepsies.

"I am honored to receive the Pre-Doctoral Fellowship in Pharmacology/Toxicology. This funding has allowed me to dive deeper into my project exploring new antibacterial compounds to treat fluoroquinolone-resistant tuberculosis. My project has been able to expand to look at compounds to treat fluoroquinolone-resistant gonorrhea as well. I have been able to get more specialized training to look at these compounds in cells which has really expanded my dissertation research. Because I have my own funding, my PI has also allowed me to go to more conferences to present my research and network with other scientists in my field. I am very thankful for the PhRMA Foundation and the funding!"

Elizabeth Gibson, PharmD | Vanderbilt University

Elizabeth Gibson, PharmD
Vanderbilt University

"Novel Naphthyridone/Aminopipiridine-Derived Gyrase-Targeted Antibacterials"

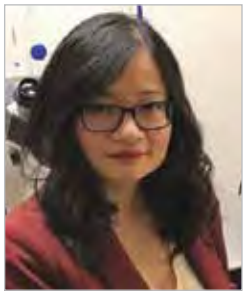
The bacterial type II topoisomerases, gyrase and topoisomerase IV, are the targets for fluoroquinolone antibacterials. This class, which includes levofloxacin, moxifloxacin, and ciprofloxacin, contains the most efficacious and broad-spectrum oral antibacterials in clinical use. Fluoroquinolones kill bacteria by increasing levels of double-stranded DNA breaks generated by gyrase and topoisomerase IV, effectively converting these enzymes to cellular toxins that fragment the genome. There is a growing crisis in antibacterial resistance. According to a recent review, deaths caused by antimicrobial resistant infections will surpass deaths caused by cancer by 2050, approximately 10 million deaths versus 8.2 million. Fluoroquinolone resistance specifically is becoming a worldwide threat. Initial fluoroquinolone resistance is often associated with specific mutations in gyrase and/or topoisomerase IV. Given the importance of the bacterial type II topoisomerases as drug targets, it is critical to develop new antibacterials that overcome this resistance. To address this issue, this project will focus on characterizing novel naphthyridone-based gyrase-targeted drugs, called "Mycobacterium Gyrase Inhibitors" (MGIs) and the parent class of compounds, called "Novel Bacterial Topoisomerase Inhibitors" (NBTIs). NBTIs, such as GSK126, display broad-spectrum antibacterial activity. In contrast, MGIs were developed to enhance activity against Mycobacterium tuberculosis, the causative agent of tuberculosis. The MGIs (GSK000 and GSK325) display high activity against wild-type and fluoroquinolone-resistant M. tuberculosis cells and infections in mice. GSK000 and GSK325 display activity against M. tuberculosis gyrase, with GSK000 being the most efficacious; however, the NBTI, GSK126 displays little activity towards M. tuberculosis gyrase. In marked contrast to fluoroquinolones (which induce double-stranded DNA breaks), MGIs induce gyrase-mediated single-stranded DNA breaks, even at high drug concentrations or long cleavage time courses. While increasing single-stranded cleavage, MGIs appear to suppress double-stranded DNA breaks. Like fluoroquinolones, MGIs act by inhibiting ligation of cleaved DNA. Although MGIs and fluoroquinolones induce DNA cleavage at similar sites, some of the sites are unique to the MGIs. This implies that MGIs have interactions with M. tuberculosis gyrase that are distinct from the fluoroquinolones. In competition studies, it takes ~10 times more moxifloxacin to compete off GSK000. GSK000 displays a strong preference for M. tuberculosis gyrase over Bacillus anthracis topoisomerase IV or gyrase, Escherichia coli topoisomerase IV, and Neisseria gonorrhoeae topoisomerase IV or gyrase, suggesting specificity for M. tuberculosis. Finally, MGIs retain activity against common fluoroquinolone-resistant mutant gyrase enzymes (GyrA A90V, D94H, and D94G) and displayed no significant activity against recombinant human topoisomerase IIa. These results suggest that MGIs are a novel class of gyrase poisons that have potential as antitubercular drugs. The implications of this work could help millions of people worldwide.

William Hedrich

University of Maryland, Baltimore

"The Role of the Constitutive Androstane Receptor in Cyclophosphamide-Based Treatment of Lymphomas"

The constitutive androstane receptor (CAR, NR1I3) is recognized as the key mediator of xenobiotic-induced expression of CYP2B6 in the human liver. CYP2B6 is the primary enzyme responsible for the biotransformation of CPA, an alkylating prodrug, to its pharmacologically active metabolite, 4-OH-CPA. Historically CPA has been utilized in combinational therapies for the treatment of cancers and autoimmune disorders. This project will investigate the impact of including a selective human CAR activator, CITCO, alongside the full CHOP (CPA, doxorubicin, vincristine, prednisone) chemotherapy regimen which is the frontline therapy for non-Hodgkin lymphoma. Although CPA is the most abundant drug in this regimen, major cardiotoxicity arises from doxorubicin. Preliminary data indicate that hCAR activation via CITCO leads to the preferential induction of CYP2B6 in human primary hepatocytes (HPH) while not having a significant impact on the expression of other drug metabolizing enzymes (DME) involved in the disposition of CHOP. The expectation is to see an increase in the formation of 4-OH-CPA corresponding with this increase in CYP2B6 expression in cultures of isolated human primary hepatocytes (HPH) which would allow for the administration of a lower overall CHOP load which should achieve comparable anticancer activity while attenuating the unwanted cardiotoxicity. These inductive gene expression profiles, CPA pharmacokinetics, and chemotherapeutic utility and off-target toxicity will further be evaluated in-vivo in a hCAR-transgenic mouse model.



Thuy Hoang

Johns Hopkins University School of Medicine

"Progesterone Supplementation for Prevention of Preterm Births"

Preterm birth (PTB) remains a significant global problem with an estimated 15 million babies born preterm per year. Thus far, the only clinically proven intervention for the prevention has been progesterone supplementation. In 2012, PREGNANT trial which investigated vaginal progesterone gel (Crinone®) for the prevention of PTB in women with sonographic short cervix showed a 44% reduction in PTB rate. Not all studies have shown a benefit for PTB prevention. The efficacy of prophylaxis has yet to be fully investigated. Furthermore, there remains a large gap in the understanding of mechanisms of action of progesterone in preventing PTB, especially on the "gatekeeper" cervix. Additionally, the dose, route and formulation have yet to be optimized. Lastly, although progesterone has been clinically used off-label for 80 years for PTB, little work has been done to assess its toxicology on the neonate. The initial goal of this project is to optimize a vaginal progesterone formulation to enhance its delivery and efficacy. Both the optimized formulation and clinical comparator (Crinone®) will be used to investigate the efficacy and mechanism of action of progesterone on birth outcomes and cervical remodeling

in two PTB animal models with distinct etiologies. Progesterone drug levels in various (tissue and plasma) compartments will be measured to provide an understanding of drug absorption, distribution and elimination after local vaginal dosing. Lastly, this project will assess the toxicology of progesterone on the fetal viability, neonatal and neurodevelopmental outcomes.

Anthony Jones

State University of New York, Buffalo

"Environmental Melatonin Receptor Modulators as Potential Risk Factors for Diabetes and Metabolic Disorders"

This study will identify environmental compounds that differentially modulate melatonin receptor signaling, which may disturb the intricate balance between the two melatonin receptor types (MT1 and MT2) leading to alterations in diabetes and obesity related processes. Structure-based screening for potential Environmental Melatonin Receptor Modulators (EMRMs) that differentially modulate MT1 and MT2 receptor activity requires validated theoretical models that predict receptor selectivity. The project's melatonin receptor models show two subsites within the MT1 and MT2 receptor binding pockets: Subsite A required for binding to the melatonin receptor target and hydrophobic Subsite B needed for receptor selectivity. The research hypothesis is that selectivity of EMRMs for either the MT1 or MT2 receptors will be determined by the flexibility or rigidity of the spacer connecting melatonin receptor subsite A and B targeting moieties. Ligands with rigid spacers will be selective for either MT1 (angular) or MT2 (linear) whereas the ones with flexible spacers will be non-selective. The project will use an integrated pharmacoinformatics approach to identify type selective EMRMs from a database of environmental compounds which will be evaluated for melatonin receptor selectivity and signaling processes in target tissues responsible for maintaining circadian rhythms and glucose homeostasis. These studies are expected to provide the rationale to further assess risk factors associated with EMRMs in animal models.

Jessica Murray
University of Pennsylvania

"Nrf2 Regulation of the Smoking Gene Battery: Implications for Human Lung Cancer"

Lung cancer is the leading cause of cancer death worldwide and is primarily caused by tobacco smoke exposures. However, air pollution and in particular diesel engine exhaust have been shown to increase lung cancer incidence in never smokers. Nrf2 inducers are being developed as lung cancer chemopreventive agents since the Nrf2-Keap1 signaling pathway is a primary cellular defense mechanism against oxidative and electrophilic stress. Nrf2 inducers upregulate expression of human aldo-keto reductases (AKRs), which are also part of the "smoking gene battery" - genes that are over-expressed in non-small cell lung carcinoma (NSCLC) and in the epithelial cells of smokers. AKRs play a key role in the metabolic activation of polycyclic aromatic hydrocarbons (PAHs), carcinogens in tobacco smoke and air pollution. AKR1A1 and 1C1-1C3 catalyze formation of electrophilic and redox-active PAH ortho-quinones that form mutagenic DNA lesions. It has been found that nitro-PAHs, probable carcinogens found in diesel exhaust are metabolically activated by the nitroreductase activity of AKR1C1-AKR1C3. This nitroreductase activity involves the sequential formation of nitroso-, hydroxylamino-, and amine derivatives as exemplified with 3-nitrobenzanthrone, where the hydroxylamino- intermediate is activated by sulfonation. This project hypothesizes that induction of AKRs by smoke and diesel exhaust or by Nrf2 inducers will exacerbate PAH and nitro-PAH activation and result in increased DNA adduct formation and mutagenesis. Use of Nrf2 inducers is already controversial because Nrf2 levels are often elevated in NSCLC patients due to epigenetic silencing of Keap1. This is associated with poor patient outcomes. This research aims to investigate whether chronic exposures to cigarette smoke condensate or diesel exhaust alters epigenetic regulation of Nrf2-Keap1 signaling to determine if these exposures can lead to acquired susceptibility to lung cancer. Positive results may question the proposed use of Nrf2 inducers as chemopreventive agents in the context of smoking and diesel exhaust exposures.

Elizabeth Mutter-Rottmayer
University of North Carolina at Chapel Hill

"Defining a Cancer Cell-Specific Mechanism of Resistance to Topoisomerase I Poisons"

Lung cancer has an 82% mortality rate, resulting largely from the failure of conventional chemotherapeutics. Cancer cells frequently rely on DNA damage tolerance and repair pathways to resist chemotherapy agents, yet the mechanisms by which these pathways are activated are not understood. This knowledge gap is a significant barrier that currently impedes the effective treatment of cancer. It has recently been discovered that the cancer cell-specific protein MAGEA4 binds and stabilizes RAD18, a key mediator of DNA damage tolerance. Preliminary studies have found that MAGEA4-RAD18 activates the Fanconi Anemia DNA repair pathway, conferring resistance to topoisomerase I (topo-I) inhibitors. This project aims to both identify the molecular mechanisms by which MAGEA4-RAD18 activates the Fanconi Anemia pathway, and to investigate how conditional MAGEA4 expression impacts therapeutic response to topo-I inhibitors in Kras-driven lung tumors in mice. This research addresses unanswered questions regarding cancer cell-specific genome maintenance mechanisms that may alter patient outcomes. This work has the potential to define a novel mechanism for acquired chemoresistance in cancer cells and could further validate MAGEA4 as a promising therapeutic target for enhancing the efficacy of current chemotherapeutics.

Adam Schaenzer

The University of Wisconsin-Madison

"A Pharmacologic Approach for the Elucidation of the PASTA Kinase Stk1's Role in Antibiotic Resistance in Staphylococcus Aureus"

Antibiotic resistance has become a problem of global proportions, threatening modern medicine with a "post-antibiotic era" where even simple medical procedures become increasingly hazardous. Therefore, it is imperative that novel antibiotic strategies are developed. One such novel strategy is to target bacterial signal cascades such as those governed by protein kinases. Of particular interest is a subfamily of eukaryotic-like serine-threonine kinases known as the Penicillin-binding-protein And Serine/Threonine kinase-Associated (PASTA) kinases. Although the exact signaling pathways remain poorly understood, the PASTA kinases have been found to play various roles in virulence, biofilm formation, cell wall metabolism, and β-lactam antibiotic resistance. Deletion of the PASTA kinase in bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) has been shown to increase susceptibility to β-lactam antibiotics. This project utilizes our recently identified PASTA kinase inhibitor GW779439X in combination with forward and reverse genetics to elucidate the bacterial signaling cascades that link the S. aureus PASTA kinase Stk1 to β-lactam antibiotic resistance. Completion of this project will yield a better understanding of GW779439X's effects on Stk1-driven maintenance of antibiotic resistance as well as identify potentially novel antibiotic targets.

2017 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.

> "Receiving the PhRMA Foundation postdoctoral fellowship has been instrumental in supporting my training towards an independent research career. Without this fellowship, it would have been extremely difficult to train at Vanderbilt University with Jeff Conn within the area of neuroscience drug discovery. The PhRMA Foundation fellowship has enabled us to assess the efficacy of two novel antidepressant mechanisms. Moreover, in the process of conducting this highly translational work, we have discovered and published novel observations in stress-induced changes in basic neurobiology. This publication record and postdoctoral training will tremendously help me towards my goal of leading an independent research program, and I will be continually thankful to the PhRMA Foundation for that opportunity."
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> Max Joffe, PhD | Vanderbilt University

Max Joffe, PhD

Vanderbilt University

"Negative Allosteric Modulators of Metabotropic Glutamate Receptor Subtype 3 for the Treatment of Major Depressive Disorder"

Major depressive disorder (MDD) is the most prevalent psychiatric illness, affecting over 6% of the U.S. population annually. MDD is characterized by blunted affect and loss of motivation, and most MDD patients are not adequately treated by available medications. Mounting evidence points towards dysregulation of the prefrontal cortex (PFC) as a hallmark feature of MDD. Specifically, multiple clinical and preclinical studies suggest that glutamate signaling in the PFC plays an important role in resilience to stress. A better understanding of the mechanisms regulating excitatory input to the PFC as well as the impact of stress on PFC function is essential for the development of novel treatments for MDD and other mental illnesses with motivational deficits. One exciting new antidepressant target that regulates excitatory transmission in the PFC is metabotropic glutamate receptor (mGlu) subtype 3 (mGlu3). Group II mGlu (mGlu2/mGlu3) antagonists exert rapid antidepressant-like effects in rodent models. However, the specific Group II mGlu receptor subtype responsible is unknown. Dr. Conn's lab has now developed the first selective negative allosteric modulators (NAMs) of mGlu3. The project has shown that mGlu3 induces robust long-term depression (LTD) on PFC pyramidal cells and mGlu3 NAMs acutely reduce helplessness behaviors. Thus, this project proposes the hypothesis that an mGlu3 NAM will ameliorate stress-induced impairments in motivation through actions on excitatory transmission in the PFC.

Michael Nedelcovych, PhD

Johns Hopkins University

"Targeting Glutamate Homeostasis for the Treatment of HIV Associated Neurocognitive Disorders (HAND)"

Despite widespread use of antiretroviral therapy (ART), mild to moderate HAND symptoms persist in about half of HIV patients representing a significant unmet medical need. HAND symptoms have been correlated with increased concentrations of the excitatory neurotransmitter glutamate suggesting that normalization of glutamate levels in the brain may offer a novel therapeutic approach. The cystine-glutamate antiporter xCT and the glutamate-producing enzyme GCPII are critical regulators of glutamate availability in the brain and have been found to exhibit increased activity in preclinical models of HIV infection. These observations prompted development of novel inhibitors of xCT and GCPII suitable for testing in the EcoHIV-infected mouse model of HAND which recapitulates the cognitive impairment and glutamate dysregulation of ART-treated patients. For this project, it will first be determined whether increased extracellular glutamate and impaired synaptic plasticity contribute to cognitive impairment in this mouse model. Pharmacologic or genetic inhibition of xCT or GCPII will then be evaluated for the ability to ameliorate cognitive impairment and normalize biomarkers of disease. This aim will be accompanied by simultaneous measurement of compound exposure and cerebrospinal fluid glutamate levels for translational assessment of pharmacokinetics/pharmacodynamics. These studies will provide valuable insight into the mechanisms that underlie HAND symptoms and possibly identify novel drug targets.

2017 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.

Jakub Kostal, PhD

George Washington University

"Re-Design of Tricresyl Phosphate (Tcp) for Safety and Increased Efficacy"

Over 85% of the 700+ commercial chemicals introduced to the domestic market each year have no health and safety data. Animal-based testing of existing and new chemicals is prohibitively expensive in both economic and ethical terms. Alternatively, in silico tools can be used to predict toxicity at greater speed and much lower costs; however, their accuracy is often unsatisfactory. There is critical need to not only improve the predictivity of in silico methods, so they can reliably substitute for animal testing, but also to develop state-of-the-art design tools that would generate novel compounds that are a priori safe yet functional for their desired purpose. Such tools would dramatically decrease the cost of developing new products; generate more sustainable manufacturing practices; and decrease negative impact of commercial chemicals on human health. This study proposes to address this need by transforming proven methodology from computational drug design, which will be used to discover safer analogs of existing commercial chemicals. The study will demonstrate this approach on tricresyl phosphate (TCP), a commercial flame retardant.

Jill R. Turner, PhD
University of South Carolina

"Disruption of Hippocampal NRG3-ErbB4 Signaling Ablates Nicotine Withdrawal-Induced Anxiety-like Behaviors"

Addiction to nicotine and the ability to quit smoking are influenced by genetic factors. Identifying altered gene networks and how those networks contribute to nicotine dependence and withdrawal will only accelerate therapeutic development of new smoking cessation aids. This research will demonstrate that SNPs across the Neuregulin 3 (NRG3) gene and its cognate receptor, ERBB4, are associated with smoking cessation outcomes. The project aim is to interrogate the functionality of this signaling pathway during nicotine and withdrawal, and examine how nicotine-induced changes in NRG3 and ErbB4 may contribute to anxiety-like withdrawal phenotypes in genetically modified mice. The current studies show that both mRNA and protein levels of NRG3 and ErbB4 are upregulated selectively in the ventral hippocampus during nicotine and withdrawal, suggesting that aberrant NRG3 signaling in this structure may underlie select nicotine withdrawal phenotypes. While the dorsal hippocampus has a well-documented role in learning and memory, the ventral hippocampus contributes to affective and anxiety responses. To evaluate the role of ventral hippocampal NRG3-ErbB4 signaling in mediating nicotine withdrawal anxiety-like phenotypes, the project disrupted this pathway via conditional hippocampal ErbB4 deletion in ErbB4-floxed mice and evaluated nicotine withdrawal anxiety-like behaviors. It was found that ErbB4 deletion results in the ablation of withdrawal-induced anxiety-like behavior as measured by both the novelty-induced hypophagia test and the open field exploration task, demonstrating a potential role of this signaling pathway in mediating anxiety-related withdrawal phenotypes. Ongoing studies are utilizing single molecule fluorescence in situ hybridization coupled with immunofluorescence to identify the underlying cell type and circuit-specific modulation of NRG3 signaling by nicotine within the hippocampus of these animals. Collectively, these data will provide insight into NRG3-ErbB4 dependent mechanisms underlying nicotine withdrawal-induced phenotypes.

2017 SABBATICAL FELLOWSHIP IN PHARMACOLOGY/TOXICOLOGY

Peter Tonge, PhD
Stony Brook University

"Interrogating the Relationship Between Drug-Target Kinetics and Drug Activity"

This research will explore the relationship between in vitro drug-target kinetics and in vivo drug activity through a collaboration with Genentech, Inc. The project hypothesizes that the reliance on thermodynamic parameters, such as IC_{50} values, to select and advance drug candidates, contributes to attrition in the R&D pipeline since these parameters are determined at constant drug concentration (e.g. at equilibrium), and thus are not able to fully quantify drug-target engagement in the non-equilibrium environment of the human body where drug concentration fluctuates. Instead the study postulates that both the thermodynamics *and kinetics* of drug-target interactions must be used to accurately predict drug efficacy. However, experimental proof for the importance of drug-target kinetics is sparse due to the limited number of published studies that employ structure-kinetic relationships to either predict or rationalize drug activity: the three published studies from this research group are an exception rather than the rule. The project goal is to work closely with Genentech Inc., an innovative pharmaceutical company that is open to exploring the role that drug-target kinetics play in drug activity. This collaboration will provide access to quantitative structure-kinetic data at different stages of the drug discovery pipeline that will be used to interrogate and inform the hypothesis.

Clinical Pharmacology

Paul Calabresi Medical Student Fellowship

The PhRMA Foundation began funding Medical Student Fellowships in 1974.

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

2017 PAUL CALABRESI MEDICAL STUDENT FELLOWSHIP

Nikhil Chavali
Vanderbilt University

"Precision Medicine with Human iPSCs for Congenital Long QT Syndrome"

Congenital long QT syndrome (LQTS) involves genetic mutations that cause prolonged electrical activity within the heart muscle resulting in rhythm abnormality, thereby increasing risk of sudden cardiac death. Current clinical guidelines recommend that patients with LQTS should avoid commonly used medications (termed QT-prolonging medications), restrict their activity level, and receive lifelong medical therapy often including medications with significant adverse effects. They may also undergo placement of an implantable cardioverter defibrillator (ICD). The goals of this research are twofold: first, to better understand the pathological significance of gene variants in LQTS, many of which are presently classified as being of "unknown significance". Correct classification of these variants as pathogenic can decrease the risk of sudden cardiac death, whereas incorrect classification causes major physical, psychological, and financial burden. Deciphering which variants are truly pathogenic versus which are benign "background genetic noise" could significantly enhance clinical decision-making and risk stratification in patients with LQTS. Second, the project aims to identify mutation specific drug therapy, in order to maximize efficacy and minimize drug exposure to patients that will not benefit. These research goals will be achieved by generating induced pluripotent stem cell (iPSC)-derived heart cells from patient blood samples and studying their electrical properties and responses to drugs in the lab. Using gene editing in iPSCs, we anticipate being able to quantify which variants are truly pathogenic. Moreover, by exposing these cells to therapeutic medications and QT-prolonging medication challenges, hypothetically this model system could have significant impact in clinical delivery of personalized medicine to patients with LQTS and other heritable electrophysiological abnormalities.

Richard Morgan
University of California, Los Angeles

"Optimized Lentiviral Vectors for the Stem Cell Gene Therapy of Hemoglobinopathies"

This research focuses on development of next generation lentiviral vectors (LVs) for the gene therapy of human hemoglobinopathies. Amongst the hemoglobinopathies, Sickle Cell Disease (SCD) and β-thalassemia (β-thal) have the greatest impact on morbidity and mortality worldwide. Although both conditions are inherited genetic disorders, SCD is defined by reduced red blood cell deformability and consequent vaso-occlusive crises, while β-thal is defined by reduced β-globin synthesis and subsequent severe-chronic anemia. For many patients, a diagnosis of either SCD or β-thal is indomitable as poor life quality and premature death represent normal characteristics of these afflictions. Gene therapy for both SCD and β-thal require the stable transfer of a β-globin-like gene into CD34+ hematopoietic stem cells (HSCs). By replacing a patient's native HSC population with genetically modified HSCs (gene therapy combined with autologous transplantation), SCD and β-thal can be permanently cured without risk of patients developing graft vs host disease that accompanies the more traditional approach of allogeneic bone marrow transplantation (when a rare match can even be found). Current clinical trials for the gene therapy of SCD and β-thal utilize β-globin expressing LVs based on decades-old design. Although these vectors are now in clinical trial, many suffer from low titer, sub-optimal gene transfer to HSCs, and expression likely insufficient to definitively cure β-thal. Vector development focused towards overcoming these limitations has been limited due to low-throughput: simple insertion and/or removal of large sections of DNA containing roughly predefined elements. To overcome current limitations in vector development, this project is designing a high-throughput method for engineering vectors that can be broadly applied to the design of any gene therapy requiring tissue-specific expression. Through developing novel vector engineering strategies, the performance of β-globin gene therapy vectors may be improved beyond their current limitations, bringing patients hope that their afflictions will not define the rest of their lives.

2017 FACULTY DEVELOPMENT AWARD IN CLINICAL PHARMACOLOGY

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

Michael Montana, MD, PhD

Washington University

"Opioid Sensitivity in Adults with Treated and Untreated Obstructive Sleep Apnea"

Using opioids to treat pain in patients with obstructive sleep apnea (OSA) is controversial. Patients with OSA are thought to have increased sensitivity to the deleterious effects of opioids, especially respiratory depression. In fact, practice guidelines warn against using opioids to treat pain in OSA patients. Nevertheless, objective evidence to support these guidelines is scant. If patients with OSA have unchanged opioid sensitivity, and physicians inappropriately withhold therapy, these patients will be deprived of appropriate pain relief. Alternatively, if OSA patients have increased opioids sensitivity, then there is risk for significant morbidity and mortality. Neither is acceptable, patients deserve better, and clinical practice should be evidence-based. A lack of knowledge to support pain treatment best practices may affect up to 5 million surgical patients with OSA annually in America alone. The immediate goal of this study is to test the hypothesis that a) untreated OSA increases the clinical response to opioids, b) the magnitude of any observed increase is proportional to the degree of nighttime hypoxemia that a given patient experiences, and c) that treatment of OSA with continuous positive airway pressure (CPAP) reverses these effects. These hypotheses will be tested by evaluating the clinical effects of a target-controlled, stepped-dose infusion of the mu-opioid agonist remifentanil in subjects without OSA, with untreated OSA, and with CPAP-treated OSA. Objective and subjective measures of opioid effects - including miosis, respiratory rate, end-expired CO2, sedation, and thermal analgesia - will be assessed at five remifentanil target effect-site concentrations. Remifentanil plasma concentrations will also be measured. Remifentanil will be used as the prototype mu-opioid agonist, because it has a rapid effect site equilibration, making it ideally amenable to multi-concentration PK/PD studies. Opioid pharmacodynamics (concentration-effect relationships) will be assessed in the three groups of subjects. Opioid pharmacokinetics will also be compared between the three groups, to eliminate altered disposition as a cause for any observed OSA-related differences in clinical effects. Ultimately, the long-term goal of this project is to seed an innovative new research program on pain, opioid clinical pharmacology, and OSA that will drive evidence based best practices for safely administering opioid analgesics to patients with OSA.

Pharmaceutics

Pre Doctoral Fellowships in Pharmaceutics

The PhRMA Foundation began funding awards in Pharmaceutics in 1972.

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

2017 PRE DOCTORAL FELLOWSHIPS IN PHARMACEUTICS

Joshua Gammon
University of Maryland

"Nanoparticle Mediated Controlled Delivery of Metabolic Modulators to Restore Tolerance in Autoimmunity"

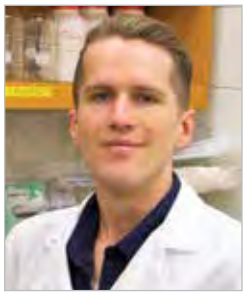
Multiple sclerosis (MS) is an autoimmune disease which occurs when the immune system aberrantly attacks myelin – an insulating coating which surrounds neurons in the central nervous system. An emerging strategy to treat MS is to redirect immune function to promote the development of regulatory T cells – a type of immune cell that can inhibit unrestrained autoinflammation. Recent studies have demonstrated small molecule drugs which modulate glutamate metabolism can promote regulatory T cells, and are highly protective in animal models of MS. However, these treatments have important drawbacks including toxicity, poor solubility, and the need for repeated daily administration to combat disease. Strategies to control the delivery of these candidate drugs are needed to improve their efficacy and enhance their clinical relevance. To this end, this research will utilize biodegradable nanoparticles to encapsulate and deliver drugs modulating glutamate metabolism. Nanoparticle properties will be tuned to optimize drug release rates in order to increase treatment efficacy and safety while reducing treatment frequency. This research will enable the development of novel pharmaceutical technologies to better combat MS, and these strategies can be broadly applied to a multitude of other autoimmune diseases.

Christine Lee

University of North Carolina

"Use of Human Intestinal Tissue and Physiologically-Based Pharmacokinetic Modeling to Predict the Pharmacokinetics of Orally Administered Amoxicillin in Adults and Infants"

Mechanistic physiologically-based pharmacokinetic (PBPK) modeling can predict pediatric PK parameters by incorporating metabolism/transport data, age-related changes in physiological parameters, and expression of drug metabolizing enzymes and transporters. While pediatric PBPK modeling is now an important tool in the development and regulatory review of pediatric drugs, significant knowledge gaps remain that limit the development of PBPK models for pediatric/infant oral drugs that require intestinal transporters for absorption. In vitro to in vivo extrapolation of transport kinetics is difficult due to the lack of information on the ontogeny of intestinal transporters, and the effect of age on intestinal permeability and its impact on drug absorption is not well understood. An in vitro to in vivo approach will be evaluated in this project, in which in vitro transport studies using age-relevant human intestinal tissue, kinetic modeling of the absorption process, and transport kinetics will be incorporated into a PBPK model that accounts for age-related changes in GI physiology and expression of intestinal transporters. In order to focus on the role of intestinal drug transporters and potential age-related differences in intestinal absorption, this approach will be tested by developing adult and infant PBPK models for the oral β-lactam antibiotic amoxicillin. Amoxicillin has low passive permeability but high oral bioavailability due to a significant contribution of an intestinal drug transporter, peptide transporter 1 (PEPT1). The goal of this research is to demonstrate the utility of this novel in vitro-in silico PBPK approach to improve predictions of oral bioavailability and PK in infant populations for drugs that are absorbed and cleared via transporter-mediated processes.



Max Purro
The University of Wisconsin-Madison

"Enhancing Outer Membrane Permeability to Increase the Activity of High Molecular Weight Antibiotics Against Multi-Drug Resistant *Pseudomonas aeruginosa*"

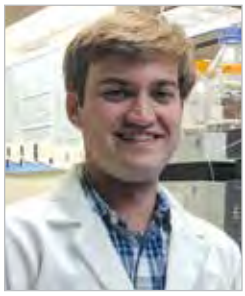
The increasing prevalence of multi-drug resistant (MDR) bacteria, combined with the diminished pace of antibiotic discovery, represents a major threat to public health. Treatment of Pseudomonas aeruginosa is particularly challenging due to its broad spectrum of intrinsic antibiotic resistance imparted by its impermeable outer membrane. This permeability barrier prevents the uptake of high molecular weight antibiotics, and limits the number of effective anti-pseudomonal treatment options to a select few antibiotics, to which P. aeruginosa is rapidly evolving resistance mechanisms. Previous studies have shown that outer membrane permeabilizers can increase the activity of high molecular weight antibiotics, but the nonspecific activity of these membrane permeabilizers leads to toxicity that makes them impractical for clinical applications. This project focuses on the rational design of novel permeabilizers that specifically target the outer membrane components of P. aeruginosa in order to increase the organism's sensitivity to antibiotics that are ineffective on their own. By targeting the unique iron acquisition systems present in P. aeruginosa, these polymeric outer membrane permeabilizers increase the activity of high molecular weight antibiotics without inducing host toxicity. Development of this innovative platform will expand the range of antibiotics capable of treating P. aeruginosa infections, thus increasing the number of effective treatments available in a clinical setting.

Jennifer Schiller

University of North Carolina at Chapel Hill

"Engineering Mutant Antibodies with Enhanced Pathogen Trapping Potency in Mucus Secretions"

Sexually transmitted infections (STIs) are global pandemics, and new methods for prevention and treatment are sorely needed. It was recently discovered that IgG antibodies can trap a variety of pathogens, including those responsible for STIs, in human cervicovaginal mucus (CVM) and enable effective protection in vivo. Based on computational analysis, this project has determined specific kinetic parameters between antibody and mucins that can markedly enhance trapping potency. The project will seek to engineer an optimal "muco-trapping" antibody that can be topically delivered into CVM for passive immunization against STIs. Through genetic modifications, IgGs will be created that 1) possess an extra Fc domain, 2) are hyperglycosylated, 3) possess an N-terminal J-chain, or 4) possess an N-terminal secretory component. Antibody constructs will be thoroughly characterized for stability, glycosylation, and ability to bind antigen. This study will apply multiple particle tracking to measure the virus-trapping potency of the different antibody constructs. Successful completion of this project will likely provide the platform for cost-effective passive immunization against various STIs, as well as other infections transmitted at mucosal surfaces.



Zachary Warnken, PharmD
University of Texas at Austin

"Nasal Deposition Characterization and Formulation Design for Improving Targeted Nasal Drug Delivery"

Medulloblastoma is currently the most common type of malignant brain tumor found in children. With current standard of care, the 10-year survival rate remains to be around 40-60%. Of the children which survive the disease, a majority suffer from long-term sequelae often caused by the radiotherapy and antineoplastic agents used to treat the disease. A barrier to treating brain diseases including medulloblastoma using systemic based administration methods is the blood-brain barrier. The nasal route of administration has been shown to assist in targeting drug delivery to the brain. Drugs deposited onto the nasal mucosa can be transported directly from the nasal cavity into the brain, bypassing the blood-brain barrier, allowing for increased drug concentrations in the brain of medications which poorly cross the blood-brain barrier while reducing the concentrations of the drug to systemic tissues. The targeting of nasal drug delivery to particular areas on the nasal cavity which promote nose-to-brain drug delivery can be complicated by the complexity and variability of the nasal cavity anatomy. This study explores device characteristics which control administration angles for patients and the use of patient specific administration parameters to enhance drug deposition to specific regions of the nasal cavity. Additionally, the use of amorphous solid dispersions as a formulation approach for overcoming the barriers of poorly water-soluble drugs for nose-to-brain drug delivery is investigated. Improving the absorption characteristics of poorly water-soluble drugs and improving deposition to its intended target in the nasal cavity will provide promising therapeutic options for the treatment of brain cancers such as medulloblastoma.

2017 POST DOCTORAL FELLOWSHIP IN PHARMACEUTICS

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

Naila Mugheirbi, PhD

Purdue University

"Inter-relations Between Spray Drying Process Parameters and Product Performance for Formulations of Poorly Water Soluble Drugs"

The vast majority of the drugs used to treat human immunodeficiency virus (HIV) and related infections are poorly soluble and therefore need to be formulated as amorphous solid dispersions (ASDs) to insure adequate bioavailability. Spray drying is a common manufacturing process to produce ASDs for commercial manufacturing. The aim of this project is to conduct a comprehensive investigation on how processing variables impact the robustness of amorphous solid dispersions produced by solvent evaporation processes such as spray drying. The impact of solvent system, solute concentration and evaporation rate on spin-coated drug-polymer films will be characterized using a state of the art techniques. The model drugs selected are ritonavir, an antiretroviral agent used in the treatment of HIV and posaconazole, an antifungal used as a prophylaxis or a treatment for fungal infections in severely immunocompromised patients such as HIV infected individuals. The presence of a possible correlations between miscibility prescreening using spin coating and the miscibility of drug-polymer system in spray dried particles will be assessed. In addition, an investigation, at the molecular level, into the effect of solvent choice on polymer conformation during spin coating and/or spray drying will be conducted and will, in turn, be linked to pharmaceutical performance, in particular dissolution and physical stability. This research is anticipated to lead to an enhanced understanding of the correlation between spray drying processing parameters and critical product properties and consequently enable effective and consistent delivery of the required amount of the medication to the patient.

2017 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 Pharmaceutics supports scientists who are beginning their academic research careers at the faculty level, and ensures the promising work of these researchers continues.

Eric Appel, PhD

Stanford University

"Prolonged Administration of Therapeutics for Long-Term Treatment of Chronic Diseases"

A constant clinical challenge in treatment of chronic disease in patient non-adherence. C. Everett Koop, the former Surgeon General of the United States, stated plainly that "drugs don't work if people don't take them." While many current treatments (e.g. pills or eyedrops) seem relatively simple to implement, frequent dosing regimens foster poor patient adherence, which is only exacerbated as the dosing frequency increases. This reality is particularly troubling as disease mismanagement often unnecessarily leads to disease progression, and in the case of eye diseases such as glaucoma, permanent blindness. Novel approaches are needed to develop minimally-invasive, long-term treatment strategies. This project will address this challenge through the development of fundamentally new syringe-injectable hydrogels exhibiting long-term (upwards of 6 months) release of either small molecule or protein drugs and excellent biocompatibility. The project aims to this exploit this system for prolonged delivery of glaucoma drugs in the eye to enable minimally-invasive physician-administered long-term treatment strategies dramatically reducing the number and frequency of required therapeutic interventions. The proposed studies constitute an innovative research strategy that will significantly advance the treatment of chronic eye diseases, leading to better technologies and more efficient therapies.

The Foundation was honored to present its 2017 awards at distinguished scientific annual meetings throughout the country.

2017 awards

American Society for Clinical Pharmacology and Therapeutics (ASCPT)
Washington, DC on March 15, 2017

Association for Clinical and Translational Science (ACTS)
Washington, DC on April 20, 2017

American Society for Pharmacology and Experimental Therapeutics (ASPET)
Chicago, Illinois on April 22, 2017

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
Boston, Massachusetts on May 24, 2017

American Association of Pharmaceutical Scientists (AAPS)
San Diego, California on November 13, 2017

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Treasurer's Report

I am pleased to report the PhRMA Foundation achieved its financial goals in 2017 and is poised to make an even greater impact in 2018 with expanded programming. Member company contributions were $3.1 million which is 5% lower than 2016. These contributions along with its investments are the Foundation's sole support.

The Foundation's total expenditures increased $392,428 over 2016. This is primarily due to an over 8.5% increase in grant spending. The new Value Assessment program was added and funding began in Q3 of 2017. A full-time Director of Development was added to the staff in Q1 and this also accounts for the 10.6% increase in expenditures.

Net Assets at December 31 were $23.4 million, an 9.7% increase from the prior year. The increase in net assets is attributable to the interest and investment earnings of $2.9 million. Financial details are shown in the accompanying Statement of Income and Expenditures.

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.

Andrew Plump, MD, PhD
Treasurer, PhRMA Foundation

Statement of Income & Expenditures

For the year ended December 31, 2017

INCOME	
Contributions	$3,048,140
Contributions – in kind from PhRMA[1]	$51,717
Interest and Dividends	$504,067
(Realized and Unrealized) Gains in Securities	$2,432,314
Other Income	$132,749
Total Income	**$6,168,987**

EXPENDITURES	
PROGRAMS	
Awards in Excellence	$15,415
Adherence Improvement	$60,187
Clinical Pharmacology Program	$147,000
Comparative Effectiveness Program	$97,160
Health Outcomes Program	$480,000
Informatics Program	$483,879
Pharmaceutics Program	$315,000
Pharmacology Programs	$700,000
Translational Medicine and Therapeutics	$581,656
Value Assessment	$282,000
AFPE Fellowship Award	$11,000
Other Grants	$20,000
Subtotal – Grants	**$3,193,297**
OTHER	
Committee Meetings, Travel and Honoraria	$149,216
Publications and Special Projects	$33,285
Subtotal – Other	$182,501
Program Total	**$3,375,798**
ADMINISTRATIVE	
Staff, Taxes, Depreciation & Insurance	$571,761
Rent & Accounting Services[1]	$51,717
Professional Services and Investment Expenses	$100,259
Office Expenses	$3,822
Subtotal – Administrative	**$727,559**
TOTAL EXPENDITURES	**$4,103,357**

[1] Rent and Accounting Services are donated by PhRMA

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PhRMA Foundation Programs for 2018

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, 2017 December 15, 2017 January–August
Post Doctoral Fellowships in Pharmacology/Toxicology (2002)	2 awarded/2 years	$160,000 total $40,000 per award per year	September 1, 2017 December 15, 2017 January–August
Research Starter Grants in Pharmacology/Toxicology (1972)	2 awarded/1 year	$200,000 total $100,000 per award per year	September 1, 2017 December 15, 2017 January 1, 2018
Clinical Pharmacology			
Paul Calabresi Medical Student Research Fellowships (1974)	1 awarded/ 6 months up to 2 years	$18,000 total $18,000 per award	February 1, 2018 April 15, 2018 July 1, 2018
Faculty Development Award in Clinical and Translational Pharmacology (1966)	1 awarded/2 years	$240,000 total $120,000 per award per year	February 1, 2018 April 15, 2018 July 1, 2018
Health Outcomes Advisory Committee			
Pre Doctoral Fellowships in Health Outcomes (2002)	5 awarded/2 years	$200,000 total $25,000 per award per year	February 1, 2018 April 15, 2018 July–December
Post Doctoral Fellowship in Health Outcomes (2002)	1 awarded/2 years	$110,000 total $55,000 per award per year	February 1, 2018 April 15, 2018 July–December
Research Starter Grants in Health Outcomes (2002)	1 awarded/1 year	$100,000 total $100,000 per award per year	February 1, 2018 April 15, 2018 July 1, 2018
Informatics			
Pre Doctoral Fellowships in Informatics (2009)	4 awarded/2 years	$150,000 total $20,000 per award per year	September 1, 2017 December 15, 2017 January–August
Post Doctoral Fellowship in Informatics (2002)	2 awarded/2 years	$160,000 total $40,000 per award per year	September 1, 2017 December 15, 2017 January–December
Research Starter Grants in Informatics (2002)	1 awarded/1 year	$100,000 total $100,000 per award per year	September 1, 2017 December 15, 2017 January 1, 2018

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)	7 awarded/2 years	$270,000 total $20,000 per award per year	September 1, 2017 December 15, 2017 January–August
Sabbatical Fellowship in Pharmaceutics	1 awarded/1 year	$40,000 total $40,000 per award per year	September 1, 2017 December 15, 2017 January–December
Research Starter Grants in Pharmaceutics (1972)	1 awarded/1 year	$100,000 total $100,000 per award per year	September 1, 2017 December 15, 2017 January 1, 2017
Translational Medicine & Therapeutics			
Post Doctoral Fellowships in Translational Medicine (2016)	2 awarded/2 years	$240,000 total $60,000 per award per year	February 1, 2018 April 15, 2018 July–December
Research Starter Grants in Translational Medicine (2016)	2 awarded/1 year	$200,000 total $100,000 per award per year	February 1, 2018 April 15, 2018 July–December
Value Assessment Initiative			
Challenge Awards (2018) for Value Assessment	4 awards	$5,000 - $50,000 per award	May 24, 2018 to be determined
Research Awards (2018) for Value Assessment	3 awarded/ 1 year	$300,000 total $100,000 per award per year	September 1, 2017 December 15, 2017 January 1, 2018
Center of Excellence Award (2018) for Value Assessment	2 awarded/3 years	$1,000,000 total $166,666 per award per year	November 1, 2017 December 15, 2017 January 1, 2018

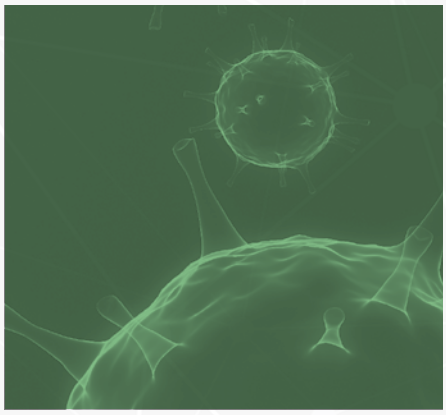
All of the above programs will accept applications for research on drugs for rare diseases

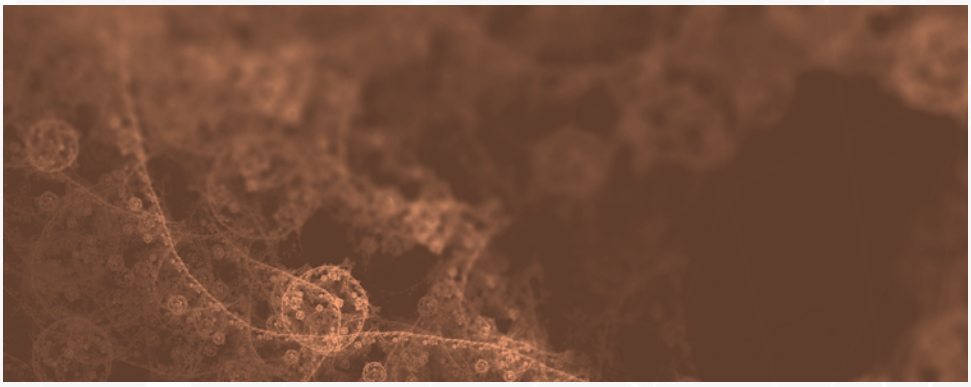
ETHICAL CONSIDERATIONS: The Scientific Advisory Committee as well as the program advisory committees of the PhRMA Foundation are dedicated to ensuring the appropriate use of animals and humans in research. In their deliberations, they consider all aspects of a proposal and may deny support for many reasons.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

PhRMA Foundation Staff

Eileen Cannon
President

Joanne Westphal
Director of Development





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