

Pharmaceutical Research and Manufacturers of America Foundation



ANNUAL REPORT



Supporting Innovative Science for 46 Years



BENEFACTORS

The PhRMA Foundation owes its success to the pharmaceutical companies that have provided their generous support over the past 46 years. We thank all of you for continuing to invest in the future of pharmaceutical research and the scientists of tomorrow.

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MISSION STATEMENT

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

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

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



CONTENTS

i	Mission Statement
iv	Message from the Chairman
V	Message from the President
vi	Awards in Excellence
3	Building the CER Workforce with
	a Cadre of Trained Professionals
7	Fellowships and Grants
7	Informatics
10	Pharmacology/Toxicology
19	Health Outcomes
22	Pharmaceutics
27	Clinical Pharmacology
30	Board of Directors
31	Treasurer's Report
32	Statement of Income and Expenditures
33	Advisory Committees
36	PhRMA Foundation Programs for 2012

iii Contents

MESSAGE FROM THE CHAIRMAN

The PhRMA Foundation has long supported components of drug development that foster innovation—extensive training, creativity, and the resources needed to optimize discovery. Now we are poised to be a key player in an emerging field: translational medicine and therapeutics. In our efforts to cultivate nextgeneration leaders in biomedical research, we are creating a program that will support scientists who specialize in this multidisciplinary area. Translational medicine has the

potential to bridge research and clinical practice, with vast implications for patient care. In April 2011, the Foundation's Board of Directors unanimously approved development of the Center of Excellence in Research Training for Translational Medicine and Therapeutics, a three-year fellowship program that will award up to \$350,000 annually to researchers beginning January 2013.

Instead of building the center from the ground up, the Foundation will collaborate with existing research institutes to leverage available resources, expertise, and formal training programs. Our goal is to forge partnerships between academic and industry professionals, and shape the center as a countrywide model for education and training. An I8-member panel of experts in academia, industry, and government, including former Foundation award recipients—will spearhead the program's development.

Another Foundation initiative supports graduate-level training programs in comparative effectiveness research (CER) at medical



schools throughout the U.S. In September 2011, Johns Hopkins University and the University of Washington were awarded grants to create the first CER Centers of Excellence. In collaboration the universities will develop comprehensive curriculums, promote awareness of CER education with other stakeholders, and establish standards for principal CER training. A three-year graduate certificate program will provide specialized training in areas not addressed by current

curricula and assess personnel needs for CER researchers, practitioners, and decision makers in the pharmaceutical sciences. The centerpiece article in this Annual Report presents a blueprint for the program's progress over the next year.

As the PhRMA Foundation continues to customize its programs to accommodate the changing needs of the field, the support we provide will also evolve. We remain committed to helping young scientists establish themselves while we pursue new organizational and institutional partnerships to broaden our presence. As the next phase of this evolution, the Centers of Excellence will expand the Foundation's reach and set the stage for our next contributions to translational medicine and CER.

Our grants and fellowships have been stepping stones for great achievements in medicine—but the Foundation's work would not be possible without the support of our member companies. We are truly fortunate to have such support, and owe the success of our programs to the ongoing generosity of our benefactors.

GARRY A. NEIL, M.D.

iv Message from the chairman

MESSAGE FROM THE PRESIDENT

Every year, the PhRMA Foundation helps facilitate the careers of young pharmaceutical scientists. The support we provide has been a determining factor in the direction these individuals take—whether in toxicology, informatics, pharmaceutics, health outcomes, or pharmacology.

Although other organizations provide support to scientists in similar disciplines, what distinguishes the Foundation is the lasting

impact of our funding and the ongoing involvement and connections we maintain with award recipients. Our programs are unique in their design to acknowledge the drive, creative interests, and potential of scientists at two significant points in their careers. For more than I4 years, the Foundation's Awards in Excellence have recognized extraordinary educators and industry leaders who received a grant or fellowship from us in the early development of their careers and used that award to make a remarkable contribution to the field. Their successes exemplify the importance of early career support. Our 2011 Award in Excellence recipients, highlighted beginning on page vi, are perfect examples of the outstanding individuals who have received this prestigious award over the years.

Building and sustaining relationships with former award recipients has also helped the Foundation flourish. Those who have benefitted from our awards continually reach out to assist us with new programs and initiatives. For example, our recent



efforts to establish graduate training programs for comparative effectiveness research and for translational medicine have involved several former award recipients.

In short, PhRMA Foundation funding has been a catalyst for scientists to become leaders in their organizations and fields. Today, we provide even broader support to esteemed medical schools at Harvard University, University of California, Univer-

sity of Pennsylvania, and University of Chicago.

We played a fundamental role in the success of the Reagan-Udall Foundation, a partnership between the FDA and pharmaceutical industry that is delivering high-caliber regulatory science and technology to improve agency-managed products. Currently, they are working with the FDA to improve tuberculosis therapy and postmarket product surveillance. Our support of organizations like the Reagan-Udall Foundation provides springboard funding that often leads to additional sources of aid. In this case, it helped finance a multipronged fellowship program to offer even more expertise to the FDA.

The involvement and diverse expertise of our award recipients and contributors gives us great potential and opens doors for future fellows—the next generation of educators, government officials, and corporate leaders in drug discovery and development.

DEL PERSINGER

MESSAGE FROM THE PRESIDENT

AWARDS IN EXCELLENCE

The annual PhRMA Foundation Awards in Excellence honor past awardees who have gone on to distinguish themselves through their scientific and/or academic achievements. At the outset of their careers, when they were deciding on their area of specialization, these scientists received PhRMA Foundation grants in a discipline important to the research-based Pharmaceutical industry. These awardees are dramatic proof that our foundation program fills a critical need in the career development of young researchers and makes a substantial difference in their ability to succeed. The two awardees for 2011 exemplify the very best in their chosen fields of clinical pharmacology and pharmacology/toxicology. The PhRMA Foundation is proud of their achievements and is gratified to have been of assistance to them at the beginning of their outstanding careers. Their successes typify the outstanding achievements of all of our awardees and underscores the importance of continuing support to those who follow in their footsteps.

2011 Award in Excellence in Pharmacology/Toxicology

Bryan L. Roth, M.D., Ph.D. Michael Hooker Distinguished Professor University of North Carolina at Chapel Hill



Bryan L. Roth

Bryan Roth is currently the Michael Hooker Distinguished Professor of Protein Therapeutics and Translational Proteomics in the Department of Pharmacology at the University of North Carolina at Chapel Hill School of Medicine. Dr. Roth is also the Director of the National Institute of Mental Health Psychoactive

Drug Screening Program (NIMH-PDSP). Dr. Roth received his MD/PhD in Biochemistry from St. Louis University Medical School and completed post-doctoral training in the Laboratory of Preclinical Pharmacology at the NIH under the supervision of Dr. Erminio Costa. Dr. Roth also performed clinical training in Psychiatry at Stanford University where he was a Dana Foundation Fellow in the Nancy Pritzker Laboratory of Molecular and Developmental Neurobiology. Dr. Roth's research is devoted to discovering how CNS drugs exert their actions at levels ranging from the most fundamental (e.g. atomic) to the most applied (e.g. human). Among his major discoveries are:

- Many basic discoveries related to serotonin receptor pharmacology and molecular biology (Berger et al, Ann Rev Medicine 2009; Ann Rev of Pharmacology *in progress for 2011*).
- Identification of molecular target responsible for the side-effects of fenfluramine (aka 'Fen/Phen'; see Roth, NEJM 2007 for review).
- Identification of the molecular target responsible for the actions of the hallucinogen salvinorin A (Roth et al, PNAS 2002).
- Creation of engineered GPCRs to selectively modulate cellular signaling *in vivo* and *in vitro* (see Armbruster et al, PNAS 2007; Alexander et al, Neuron 2009; Guettier et al, PNAS 2009; Rogan et al, Nature Protocols, *in press*).
- Identification of 'off-target' targets responsible for drug side-effects and new therapeutic uses (Roth et al, Nature Rev Drug Discov 2004; Keiser et al, Nature 2009).
- Discovery that topoisomerase inhibitors may be effective in treating Angelman Syndrome (Huang et al, Nature 2012).

Dr. Roth has published more than 250 articles with a large number of papers published in journals of highest impact (*Science, Nature, Neuron, New England Journal of Medicine, PNAS*). in the past year alone, for example, Dr. Roth published papers in *PNAS* (2), *Neuron, Annual Reviews of Medicine* and a full article in *Nature*.

Dr. Roth has received many honors including the Award for Outstanding Basic Science Research from the Heffter Research Institute, a Distinguished Investigator Award from NARSAD, an Independent Investigator Award from NARSAD where he was also awarded the title *Sandoz Investigator*, the Chauncy Leake Memorial Lecture (University of Texas Medical Branch) and the SG Ferguson Memorial Lecture (Robarts Research Institute). Dr. Roth is a member of the American College of Neuropsychopharmacology and also serves on NARSAD's Board of Scientific Advisors.

Dr. Roth has served on the editorial boards of 8 major

scientific journals including the Journal of Biological Chemistry, the Journal of Pharmacology and Experimental Therapeutics, Psychopharmacology, Neuropsychopharmacology, Medicinal Chemistry Research and the Journal of Receptors and Signal Transduction Research. Additionally, Dr. Roth is currently an Associate Editor for the Journal of Pharmacology and Experimental Therapeutics.

Dr. Roth is a frequent consultant to major pharmaceutical and biotechnology companies and has served as a regular member for three separate NIH Study sections and served as Chair of the Molecular Libraries Screening Centers Review Group.

Dr. Roth's work has led to the successful filing and awarding of several US Patents for novel candidate medications for the treatment of psychiatric and neurological medications; recently some of these have been licensed to Galenea Pharmaceuticals for further development.

2011 Award in Excellence in Clinical Pharmacology

Scott A. Waldman, M.D., Ph.D., FCP Department Chair and Professor Thomas Jefferson University



Scott A. Waldman

Dr. Scott A. Waldman is the Chair of Pharmacology and Experimental Therapeutics, the Director of Clinical Pharmacology in the Department of Medicine, the Director of the GI Cancer Program of the Kimmel Cancer Center, and the Samuel MV Hamilton Professor at Thomas Jefferson University. He completed a BS

(Biology) from the University at Albany (New York; 1975) and a PhD in Anatomy and Cell Biology from Thomas Jefferson University (1980). He continued his training in Clinical Pharmacology at the University of Virginia (1979–1981) and Stanford University (1981–1983) as a postdoctoral fellow with Dr. Ferid Murad (1998 Nobel Prize in Physiology or Medicine). He completed his MD (1987) and residency in Medicine (1990) at Stanford, after which he returned to Philadelphia and Thomas Jefferson University as an assistant professor in the Division of Clinical Pharmacology in the Departments of Medicine and Biochemistry and Molecular Pharmacology. He became the Director of the Jefferson Clinical Research Unit in 1992 and the Director of the Division of Clinical Pharmacology in 1997. In 2005, he became the inaugural Chair of the Department of Pharmacology and Experimental Therapeutics, which includes the Divisions of Clinical Pharmacology, Experimental Pharmacology, and Biostatistics and Quantitative Biology.

Dr. Waldman's research has focused on illuminating disease pathogenesis, its translation to new diagnostics and therapeutics, and its integration into platforms that enhance patient health, to provide innovative preventive and curative algorithms across the disease spectrum. His recognition that colorectal cancer is a disease of hormone insufficiency silencing a novel tumor suppressor pathway provides a mechanistic adjunct to the oncogenomic view of tumorigenesis, and a therapeutic opportunity for prevention through hormone replacement that is under consideration by the NCI Chemoprevention Network. His identification of molecular markers identifying occult metastases, the first to be validated in prospective multicenter clinical trials, is positioned to advance prognostic and predictive staging paradigms in colorectal cancer. Moreover, his discovery of cancer mucosa antigens offers a solution to the constraints reflected by the paucity of immunotherapeutic targets in tumors, advancing the field of cancer vaccines. His sustained leadership across the domains of basic and clinical pharmacology and bed-to-bedside translation, which has produced more than 200 scholarly articles and book chapters, uniquely position him in the emerging discipline of individualized medicine.

Beyond the laboratory and patient care, Dr. Waldman has maintained an enthusiastic and enduring commitment to clinical pharmacology education. He continues as the inaugural director of the NIGMS-sponsored Jefferson Clinical Pharmacology Postdoctoral Training Program (1996). Moreover, he is the inaugural director of the NIH-sponsored Training Program in Human Investigation (2001), one of the only K30 programs in the country based in a Department of Therapeutics. He has spearheaded the training of medical students and house officers in therapeutics at Jefferson, supervising the medical school sophomore pharmacology and senior therapeutics courses, and the Masters program in clinical pharmacology. Individually, he has trained I6 graduate students and 34 postdoctoral fellows in clinical pharmacology, and most have developed independent durable careers in the discipline in academia, regulatory agencies, and the private sector. At the international level, he

has co-edited the first major new textbook in the field in many years, *Waldman and Terzic's Pharmacology and Therapeutics: Principles to Practice* (Elsevier 2009).

Dr. Waldman has been privileged to enjoy leadership roles within the field at the international level. He has served on numerous peer review panels, and chaired several, most recently NCI Subcommittee J (2006–2008, reappointed as a member 2009–2014), and the NIGMS panel reviewing the Pharmacogenomics Research Network (2004, 2009). He served as the second Chair of the Molecular Therapeutics Section of the American Society for Clinical Pharmacology and Therapeutics (ASCPT; 1995–1999), contributing to its growth as one of the largest sections in the Society. He was a member of the American Board of Clinical Pharmacology (1998–2003), and a Regent of the American College of Clinical Pharmacology (1999–2004). Moreover, he was a member of the Board of Directors, and served as Vice President and President of ASCPT (1995-2003). His role in the field has evolved, and his vision for clinical pharmacology is now extended through access to international communities of practice in science and medicine through editorial leadership of principal journals in clinical pharmacology and human therapeutics, including Clinical Pharmacology and Therapeutics (Nature Publishing Group, Editor in Chief 2006–2011, renewed through 2016), Clinical and Translational Science (Wiley, Founder and Inaugural Deputy Editor in Chief, 2008-2012), and Biomarkers in Medicine (Future Science Group, Founder and Senior Editor, 2008–2012). •

Building the CER Workforce with a Cadre of Trained Professionals

he right medicine at the right time—in the most effective dose—is the ultimate and sometimes elusive goal for medical practitioners. In this pursuit, comparative effectiveness research (CER) is quickly becoming an important tool for optimizing therapeutics and dramatically improving health care.

How CER is implemented and practiced over the next decade will have broad implications in medical advances and spending in the U.S. Through assessment of the efficacy, benefits, and possible side effects of different drugs, diagnostics, and devices, CER provides an opportunity to better understand current therapies. This insight can contribute to informed and effective medical decisions at all points on the health care spectrum.

Although some universities already train students in CER methodologies, courses across various departments and schools may not be sufficiently integrated, diverse, or multidisciplinary. Certificate programs can leverage existing knowledge in health services and pharmaceutical outcomes research to provide effective training for the conduct and use of CER. A curriculum devoted solely to CER could encourage students to pursue a career in this emerging field. Such programs can also help determine workforce needs for trained CER professionals. A strong emphasis on communication, collaboration, and oversight at the outset of the program's design is essential.

The emergence of CER in crucial areas of health care calls for a well-designed system to fund training programs. In 2009, the PhRMA Foundation began this process, culminating in the 2011 launch of our first three-year awards to establish Centers of Excellence for CER training. The initial goal was to define core competencies for CER education and training and lay the groundwork for graduatelevel programs that would build and hone relevant skills.

To provide researchers and practitioners with the educational tools they need, the CER Centers of Excellence grant supports existing programs, similar to those underway at the Patient Centered Outcomes Research Institute (PCORI). As part of the 2010 Patient Protection and Affordable Care Act, PCORI's focus on CER will "assist patients, clinicians, purchasers, and policy-makers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed through research and evidence synthesis ..."

PCORI Executive Director Joe Selby, MD, MPH, emphasized the necessity and timeliness of CER training programs:

PCORI believes that by studying outcomes that are meaningful to patients, comparative effectiveness research can shed light on how to better serve patients and their caregivers and provide them, as well as their clinicians, with the tools needed to better address their concerns. Investing in such research, and working with a wide range of stakeholders to identify how to do this work in a way that will improve health care decision-making broadly, will go a long way toward improving the quality of care that our health system provides.

Unfortunately, research has not always reflected patients' values, preferences, and goals—the very considerations that they take into account when making decisions about their health and health care. When patients don't have the information needed to make the decisions that will be best for them, they suffer, and the health care system as a whole doesn't work as well as it should. When patients are true partners in research, study results will better match their needs and be better suited for use in helping them and their clinicians make real-world decisions about care. Amid growing concerns about high health-care costs and the related demand for skilled CER professionals, the CER Centers of Excellence program is a timely initiative that could establish a national model for degree-granting programs.

CER CENTERS OF EXCELLENCE

In December 2009, the PhRMA Foundation convened a symposium with experts from government, industry, and academia to discuss the fundamentals of a comprehensive CER curriculum model. The curriculum would consist of required and elective classes that address core components of public health and clinical investigation and span epidemiology, health economics, biostatistics, and population health. Primary learning objectives would include interpretation of systematic reviews and meta-analyses, clinical heterogeneity, cost effectiveness, health technology assessment, and risk adjustment methods.

When implemented, CER curricula will bridge existing gaps in current training. Courses will be designed for those seeking careers in the development, conduct, and use of CER reviews and research methodologies, and will serve as program models for colleges and universities that offer similar competencies. Upon completion of the program, students will be proficient in the direct comparisons of tools and treatments for disease prevention, diagnosis, management, and health-care delivery.

Johns Hopkins University (JHU) and the University of Washington (UW) have each received a \$250,000 grant from the PhRMA Foundation to establish three-year graduate certificate programs in CER. "Graduates of these new educational programs will use their CER skills to compare and contrast meaningfully useful products, diagnostics, and devices in pharmaceutical companies, health institutions, and government organizations for the purpose of identifying products that improve patient health outcomes," said Jean Paul Gagnon, PhD, Chair of the Foundation's Comparative Effectiveness Research Committee.

JHU will offer a one-year onsite certificate program for students, as well as a potential CER track within their current MPH or MHS program. Introduction to Comparative Effectiveness Research is a three credit class geared toward scientists, government officials, and those who could contribute to late-stage translational medicine. As the first discrete CER course of its kind, the introduction will precede more inten-



Jodi B. Segal, MD, MPH The Johns Hopkins University Bloomberg School of Public Health

sive components of the JHU certificate program and allow students to preview coursework required for competency. Eventually, introductory courses will be available online and accessible to a broader range of students and distance learners. Non-degree courses will also be available, including an online class for recent college graduates, physicians seeking research training, patient

advocates, members of the media who disseminate CER findings, and others interested in general training.

"We aim to make CER relevant to the training of clinical researchers as well as health services researchers," said Jodi Segal, MD, MPH, principal investigator (PI) of the CER initiative and Associate Professor of Medicine at JHU.

JHU is also considering a capstone course to help students process and synthesize what they learn throughout the year, and a discussion-based weekly seminar on related topics and current events. "We plan to try to better integrate with the existing graduate and training program in clinical investigation, which offers master's and PhD degrees in clinical investigation to fellows and faculty who already possess medical degrees," said Dr. Segal. "We also think we can work through [Clinical and Translational Science Awards (CTSA)] and through [the National Center for Advancing Translational Sciences] to promote degree programs in CER if we do not divorce CER from translational medicine. A large component of CER is late-stage translational research with a focus on research that informs decision making and is patient-focused."

Louis Garrison, PhD, Professor and Associate Director of UW's Pharmaceutical Outcomes Research and Policy Program, said the university will leverage its existing interdisciplinary approach to comprehensive training. "We have a wonderful collaboration between medicine, pharmacy, and nursing in CER focusing more on [postdoctoral] training. The [CER program] adds a predoctoral element."

Serving as the PI, Dr. Garrison and his co-investigators, Anirban Basu, Associate Professor of Health Services in the School of Public Health, and Beth Devine, Associate Professor of Pharmaceutical Outcomes Research and Policy, have designed a graduate CER program based on their strengths in health services and pharmaceutical outcomes research. They have also begun promoting the program and established a timeline for student recruitment. "The PhRMA Foundation has provided generous support for core program activities and for fellowships and dissertation awards that will allow us to jump-start this new program," said Dr. Garrison.

Colleges and universities that offer health-care-related programs with CER components will become national models for CER education and training, and those that wish to modify or expand existing courses can look to UW and JHU for guidance. Both universities offer seminars and courses that address a range of CER topics.

Dr. Segal has proposed building the certificate program to parallel JHU's Health Economics Certificate and Quality, Patient Safety and Outcomes Research Certificate. "We have a large DrPH program and would like to ensure these students have exposure to CER," she said.

Dr. Garrison and his colleagues are building on existing CER research and interdisciplinary doctoral training programs to create the UW graduate certificate in CER. "Our graduate certificate in CER will support the objectives of our UW Centers for Comparative and Health System Effectiveness (CHASE) Alliance—an interdisciplinary, multiunit research and training center for CER within the UW Health Sciences campus," he said. "The CHASE Alliance brings together existing successful UW research groups and community partners with a common mission to undertake multidisciplinary, high-impact comparative and systems effectiveness research and implementation ... and involves participation with stakeholders in real-world settings."

The way CER has been characterized over the past few years may require changes in methodology and training. "This new predoctoral certificate program, with PhRMA Foundation support, will enable us to diversify and integrate the training for our most promising predoctoral students with interests in CER," said Dr. Garrison.

WORKING TOGETHER

The development of CER training programs calls for collaboration—not only between university faculty and administrators, but among stakeholders in the pharmaceutical sciences—researchers, practitioners, and policy makers. As



Louis P. Garrison, Jr., Ph.D. The University of Washington Pharmaceutical Outcomes Research & Policy Program

the two universities work with these stakeholders to determine personnel needs for CER, they will become highly cognizant of the current and developing CER workforce.

"One of the key ways they will collaborate to develop—and more importantly—hone their curricula to ensure students receive high quality training is by periodically meeting with each other and users of

CER outcomes to discuss progress results," said Dr. Gagnon. The Foundation and universities also agreed to meet on a quarterly basis to exchange experiences, strategies, and course materials, and share their findings with major stakeholders.

"We see an extensive web of stakeholders surrounding the activities that generate CER," said Dr. Gagnon. "Early phase researchers are stakeholders who need the skills of scientists who perform CER in usual care settings, and thus translate their discoveries into practice. The patients, study coordinators, physicians, and nurses who refer patients and collect data in CER studies are stakeholders in the process and have educational needs. Members of the media translate the results of CER so it can be widely consumed. Decision makers who act on the results of CER and implement change also require education about CER and the processes of generating this evidence."

Because stakeholder involvement will be relevant to the implementation of CER, researchers must successfully collaborate with health-care educators, providers, government agencies, insurers, and patients to design and conduct definitive observational and experimental research, and translate this information into functional applications. Furthermore, multidisciplinary training, practical experience, and strong mentorship will ensure CER experts effectively facilitate CER methodology and knowledge. A willingness to share their expertise and make CER training tools readily accessible to those interested in this emerging discipline is crucial.

The significant role of stakeholders cannot be overstated, said Dr. Garrison. "Our current conception of CER involves three key elements: stakeholder involvement in research prioritization, design, interpretation, and implementation; ensuring the comparative dimension includes policy-relevant choices; and assessing alternatives in terms of real-world outcomes (i.e., 'effectiveness,' not 'efficacy')."

INCREASING AWARENESS

JHU and UW will also work together to share information and promote awareness about CER training at other academic institutions. Faculty involved in the program will meet to develop and hone CER curricula.

"How the two universities will spread awareness about the program is key," said Dr. Segal. "We can disseminate [information about the courses] through the CTSA Key Function Committee on Comparative Effectiveness Research. We are also developing a website for the Center for Health Services and Outcomes Research, where we can advertise our programs."

The universities will also present at patient, government, and industry meetings; publish articles on the development of CER teaching programs; and distribute press releases about the curricula.

At the same time, the PhRMA Foundation will share information and promote awareness about CER training by circulating news releases and holding conferences on JHU and UW's progress.

STUDENT INVOLVEMENT

Students in the CER program's first cohorts will eventually fill positions in health services research and public health. Those who become instructors of future iterations of the program could greatly contribute to course expectations and outcomes. "Student experiences and suggested changes will be periodically sought by CER faculty of the two universities to improve the curriculum and make it relevant to the intended program objectives of each university," said Dr. Gagnon. "In addition, it is highly probable that some will serve as mentors and offer residencies and internships after they graduate for students in these programs."

"We expect students may return as teaching assistants in subsequent years," added Dr. Segal, who said JHU would welcome students back for postdoctoral fellowships in CER. "We presently have six fellows funded by a NRSA T32 doing CER training."

JHU plans to obtain student feedback and incorporate suggestions from course evaluations into revised curricula. "Students will be expected to evaluate all courses and the certificate program as a whole," said Dr. Segal. "Because we are making the introductory course and one additional key course available online, we expect the material will be much more widely available to the distance MPH students, of which there are many."

THE POTENTIAL OF CER

The development, exchange, and application of evidence on medical treatments are increasingly recognized as necessary steps for improving health care. Such measures can coordinate and track the quality of care to avoid adverse reactions, ineffective therapies, and excessive costs.

As the evolution of CER continues, the time to shape its teaching, training, and practice is now. The development of specialized CER educational programs will ensure this critical area of health care is properly understood and practiced in both private and public sectors. •

6 BUILDING THE CER WORKFORCE

Fellowships and Grants

INFORMATICS

Pre Doctoral Fellowships in Informatics

The PhRMA Foundation Pre Doctoral programs aim at supporting promising students during their thesis research by providing assistance in the form of stipend and funds to cover costs incidental to the training. This fellowship program provides a stipend of \$20,000 annually for up to two years. Up to \$500 a year of the funding may be used for incidentals directly associated with the preparation of the dissertation. The goal of this fellowship is to increase the number of well-trained investigators in pharmaceutical research that incorporates Informatics.

2011 Pre Doctoral Fellowships in Informatics

Karen G. Dowell University of Maine "Exploring Stem Cell and Cancer Biology Through Bayesian Network Machine Learning"

The molecular mechanisms involved in stem cell self-renewal and differentiation are elaborate, involving a complex interplay of genetic regulation, signaling pathway crosstalk, intracellular interactions, and external signaling cues. Despite this inherent complexity, most models of self-renewal oversimplify the intricate dynamics associated with these processes. A systems-level view of stem cell fate mechanisms will not only enrich our understanding of stem cell biology, but also catalyze ongoing oncology research on cancer stem-like cells. The goal of this project is to develop Bayesian network machine learning techniques that can be applied to perform an extensive comparative systems analysis of mouse and human stem cells, initially focusing on different classes of pluripotent stem cells, such as embryonic stem cells and induced pluripotent stem cells, and a subset of tissue-specific adult stem cells and related cancer stem-like cells. Through this study, a new strategy for evaluating and optimizing the



performance of Bayesian classifiers trained on mammalian highthroughput data will be developed and implemented. A statistically principled machine learning approach will be used to integrate cell-type specific genomic and proteomic data, and produce predictive networks that capture accurate and informative biological

Karen G. Dowell

details about stem cell self-renewal and related early developmental processes. Predicted gene and protein functional relationships will be evaluated computationally and top novel candidate genes will be selected for experimental validation. Preliminary results using mouse embryonic stem cell data confirm that Bayesian network integration of high-throughput data restricted to a single cell type can significantly enhance predictive clarity of mammalian functional relationship networks. Project deliverables will include an online resource of stem cell networks and dynamic data visualization tools that provide the research community with a framework for evaluating hypotheses and discovering novel genes involved in different classes of stem cell self-renewal and cell fate.

Post Doctoral Fellowships in Informatics

The PhRMA Foundation Post Doctoral program in Informatics provides stipend support for individuals engaged in a multidisciplinary research training program that will create or extend their credentials in informatics. The intent of this program is to support post doctoral career development activities of individuals preparing to engage in research that will bridge the gap between experimental and computational approaches in genomic and biochemical studies. It is anticipated that this research training will be accomplished in academic and/or industrial laboratory settings where multidisciplinary teams are organized to address problems which span the range of biological complexity rather than focus on the application of single technologies.

The post doctoral award consists of a \$40,000 annual stipend for up to two years. The second year of this award is contingent upon a progress report approved by the Foundation and submission of a financial report. The award is intended solely as a stipend and may not be used otherwise.

2011 Post Doctoral Fellowships in Informatics

Samantha Riesenfeld, Ph.D.

University of California, San Francisco

"A Novel Approach to Decoding Vertebrate Gene Regulation"

Deciphering the gene regulatory code is one of the major challenges of the post-genomic era. In vertebrates, most studies of regulatory variation have taken a top-down approach, such as experimentally characterizing binding sites of individual transcription factors. Although many known regulatory regions are large and complex, preliminary in vivo



functional studies indicate that DNA sequences as short as six base pairs (bp) drive precise expression of a reporter gene to specific tissues, and that a twonucleotide substitution leads to a change in the domain of the expression. This project will pioneer a novel bottom-up approach to deciphering the vertebrate

Samantha Riesenfeld, Ph.D.

regulatory code. The first aim is to computationally design a collection of reporter constructs that covers all 6-bp sequences compactly and enables their efficient functional characterization using zebrafish transgenesis. The second aim is to compute and analyze the genomic distributions of experimentally validated enhancers, and use the results to interpret expression data. By building and functionally translating a regulatory language from scratch, the project's approach complements top-down efforts to understand the regulatory code. This project will have an enormous impact on numerous biological fields, from genome annotation to developmental and synthetic biology. Various clinical applications will benefit from the findings, such as reprogramming strategies for stem-cell-based regenerative therapies. The constructs designed will pave the way for gene therapy by genetically engineered regulatory elements that drive compounds to specific tissues.

John A. Capra, Ph.D.

University of California, San Francisco "Quantifying the Impact of Biased Gene Conversion on Human Disease and Gene Function"

Humans differ from their closest living relative, the chimpanzee, in their susceptibility to a number of diseases, including AIDS, Alzheimer's disease, and atherosclerosis. Many of these diseases with human-specific etiologies are



attractive targets for pharmaceutical intervention due to their devastating symptoms and prolonged durations. However, these diseases have complex causes that have not been fully characterized. The sequencing of the genomes of several primate species has created the potential to determine the genetic basis for

John A. Capra, Ph.D.

these and other human-specific traits by exploring the evolution of the human genome over the past several million years. This project investigates the impact of biased gene conversion (BGC) on the human genome. BGC is an evolutionary process that has been active in many regions of the human genome that are significantly different from the chimp genome. Preliminary results indicate that this process can introduce harmful genetic changes; genes with known disease associations show more evidence of BGC than non-disease genes. Developing computational models of this process and integrating data from disease experts will pinpoint regions of our genome that differ between human and chimp, are involved in human disease, and have been affected by BGC. This will provide a set of candidate regions of relevance to human-specific disease, and comparing them to the corresponding chimp sequences will provide clues about how they affect function. Understanding the evolutionary processes and resulting genetic changes responsible for human-specific diseases will ultimately lead to a deeper understanding of their mechanisms and more refined therapeutic approaches.

Ying-Ja Chen, Ph.D. University of California, San Francisco "Functional Analysis and Design of Sequences that Control Transcriptional Termination"

DNA sequence encodes for the function of each gene, whose expression determines the behavior of an organism.



To understand and control gene expression, it is important to understand the correspondence between DNA sequence and function quantitatively. In this project, the DNA sequence that controls transcriptional termination will be studied using biophysical modeling and high-throughput DNA sequencing methods to

Ying-Ja Chen, Ph.D.

predict its functionality from sequence. A model based on thermodynamic principles will be used to link sequence properties to transcriptional termination efficiency. The termination efficiency of tens of thousands of terminator sequences will be measured using an in vitro transcription assay followed by high-throughput sequencing of the transcripts to determine the termination position to singlebase resolution and the termination efficiency. Combining the model with the measured data, this project will develop a program that can predict termination efficiency from DNA sequence and design sequences for efficient termination. This program will be a useful tool for designing synthetic genetic circuits that can be used for producing pharmaceuticals, biosensors, or energy.



On April 9, 2011, at the American Society for Pharmacology and Experimental Therapeutics (ASPET) Annual Meeting in Washington, DC, Basic Pharmacology Advisory Committee Chairman, Dr. Terry Bowlin presented the PhRMA Foundation Pharmacology / Toxicology Post Doctoral awards. Pictured from left are Foundation Executive Director, Eileen Cannon; Ditte Lovatt, Ph.D., University of Pennsylvania; Megan Montgomery, Ph.D., University of California, San Francisco; and Dr. Bowlin.

PHARMACOLOGY/TOXICOLOGY

Pre Doctoral Fellowships in Pharmacology/Toxicology

The goal of this program is to increase the number of well-trained investigators in pharmaceutical research. This program is designed to encourage and support promising students during their thesis research and is aimed at those candidates who are within two years of completing their research for doctoral dissertations in pharmacology and toxicology. The fellowship program provides a stipend of \$20,000 annually for up to two years. Up to \$500 a year of the funding may be used for incidentals directly associated with the preparation of the dissertation.

Three hundred and sixty fellowships have been awarded under this program since it began in 1978 including the ten fellows awarded in 2011.

2011 Pre Doctoral Fellowships in Pharmacology/Toxicology

Jennifer Furman University of Kentucky "Astrocytic Calcineurin/NFAT Activity: A promising target for Alzheimer's therapy"

Alzheimer's Disease (AD) is a devastating neurodegenerative disease, characterized by severe cognitive deficits, striking personality changes, loss of everyday life skills, and ultimately, death. A reported 5.3 million Americans suffer from AD,

carrying an annual price tag of

172 billion dollars. To date, there

billions of dollars and millions of

is still no cure for AD, although

lives hinge upon the discovery

of successful anti-AD therapies.

is challenging, as the molecular

processes that cause or drive the

Unfortunately, finding a treatment



Jennifer Furman

disease remain largely unknown. This project targets an inflammatory signaling pathway in a specific cell type, astrocytes. Astrocytes are the most abundant cells in the brain and are generally considered "protective" cells by helping to keep neurons strong and communicating effectively with one another in normal, healthy tissue. With injury, aging, AD, and/or other neurodegenerative diseases, astrocytes can lose their protective properties, and instead help promote harmful inflammatory signaling. Previous work from our lab suggests that these

detrimental astrocytic changes are driven in large part by a specialized protein called calcineurin (CN). Although CN is one of the most abundant proteins in the brain, it only appears at high levels in astrocytes under injurious conditions. Similar to its role in immune cells outside of the nervous system, CN turns on the gene expression of several inflammatory mediators by activating another specialized signaling molecule named NFAT. The lab's previous work using postmortem human brain tissue shows that CN/NFAT signaling is hyperactivated in the early clinical stages of AD, a condition that progressively worsens as pathological symptoms become more severe. Accordingly, this research project proposes that the inhibition of CN/NFAT signaling in astrocytes prior to the onset of cognitive deficits and pathology may alleviate the development or progression of these biomarkers. Using a transgenic mouse model that displays several AD-like characteristics, makes it possible to selectively infect astrocytes with a novel viral reagent that inhibits CN/NFAT signaling in the hippocampus—an area that deteriorates with AD. At an old age when untreated mice would generally display severe AD-like traits, several outcome measures will be scored, including amyloid plaque deposition, neuroinflammation, synaptic function, and learning and memory to determine if astrocytic CN/NFAT blockade does, indeed, improve or prevent development and/or severity of these biomarkers. This work will greatly increase our understanding of astrocyte signaling in neurodegenerative diseases and will provide the first insight of its kind detailing contributions of the CN/NFAT pathway to common biobehavioral markers seen in AD mouse models.

Jason Kehrl

University of Michigan

"Pharmacogenomic Factors Influencing Thermal Side-Effects"

Drugs vary in their efficacy and side-effect profiles within the population. To delineate molecular mechanisms underlying the variability in patient response this project is focusing on thermal side-effects as one model system. Neuroleptic Malignant Syndrome (NMS) is a life-threatening side-effect of anti-psychotic treatment characterized by hyperthermia that occurs in 2-3% of treated patients. To date few predictors have been established as to which patients will suffer from NMS, and no genetically susceptible animal model exists. In addition to anti-psychotics many other psychotropic drugs such as antidepressants, baclofen and Ecstasy can cause dangerous thermal side-effects. Unfortunately as recently as 2004 the standard of care for drug-induced hyperthermia

was to use ice baths. One common

downstream target of the afore-

family of heterotrimeric G pro-

signaling may be responsible for

observed inter-individual differ-

teins. Thus pharmacogenomic factors that influence Gi/o

mentioned drugs is the Gi/o



Jason Kehrl

ences in drug-induced side-effects. To test this hypothesis the research will determine how genetically enhancing in vivo activity of two Gi/o family members, Gi2 and Go (GI84S mutation), alters thermal homeostasis and the thermal response to psychoactive drug exposure. While the GI84S mutation has not been found in human subjects, this system serves as a model that should phenocopy SNPs that result in gain of function within the system. Data thus far indicates that GoGI84S mice lack the normal hypothermic response to acute baclofen and to the serotonin agonist 8-OH-DPAT while Gi2GI84S mutant mice retain a normal response. Furthermore, GoGI84S mice show parallels to NMS patients in having lower levels of the dopamine metabolite homovanillic acid. Further understanding Go-dependent signaling in thermal side-effects through the aims of this study will allow for more rational design of hyperthermia treatments and should provide a foundation for future pharmacogenomic studies within the human population.

Mary Puckett

Emory University "Interception of Cell Death Signaling by the ASK1/IKK Complex"

Many diseases involve an imbalance of cell survival and cell death. Some, like neurodegenerative disorders are characterized by too much cell death, while others, like cancer, are characterized by too much survival. Many proteins inside



cells interact to control this balance and keep them functioning properly. One critical regulator of this balance is the Apoptosis Signal-regulating Kinase I (ASKI). Under stress conditions, ASKI can induce cell death, while under survival conditions, ASKI function can be inhibited. ASKI is known to play roles in inflam-

Mary Puckett

mation, neurodegenerative diseases, diabetes, heart disease, and cancer. Because of its ability to respond to pro-survival or pro-death signals inside and outside of cells, other proteins interact with ASKI to regulate when it is turned "on" and "off." This project aims to understand the relationship between ASKI and a newly identified interacting partner, the Inhibitor of Kappa b Kinase (IKK). While IKK has known roles in responding to cellular signals and promoting cell survival, recent evidence revealed a new function of IKK-it can modify ASKI by adding a phosphate to a specific site, an event known to alter protein function. This specific modification can impair ASKI activity. However, the details of how these two proteins interact remain unclear. Understanding this interaction could lead to the development of new therapies for the treatment of diseases that have an imbalance of cell survival and cell death, as wide ranging as neurological disorders and cancer.

Adele Stewart

University of Iowa "Molecular Mechanisms of RGS6 Modulation of GIRK Channel Activity"

Greater than 1% of the genes in the mammalian genome encode G protein coupled receptors (GPCRs) making it the largest family of cell surface receptors. These proteins

participate in signaling pathways

involved in numerous physiological

processes from the senses of smell,

vision, and taste to the cellular responses to hormones, neuro-

transmitters, and chemokines.

Unsurprisingly, it is estimated

that more than half of currently

marketed and prescribed pharma-

ceuticals target GPCRs. Elucida-



Adele Stewart

tion of regulatory mechanisms involved in modulating GPCR signaling is, therefore, of great importance to expanding our knowledge of drug action and human physiology. The prototypic role of <u>Regulator</u> of <u>G</u> Protein <u>Signaling</u> (RGS) proteins is negative regulation of G protein signaling. Indeed, RGS proteins determine both the magnitude and duration of the cellular response to GPCR stimulation. Activation of G protein-activated Inwardly Rectifying K+ (GIRK) channels by $G_{\beta\gamma}$ plays an important role in suppressing membrane excitability in neuronal, cardiac, and endocrine cell types. The project recently demonstrated that RGS6 is an essential modulator of parasympathetic stimulation of the heart where it acts to sequester $G_{\beta\gamma}$, released by acetylcholine activation of muscarinic M2 receptors, and attenuate IKAch current effectively preventing parasympathetic override and severe bradycardia. In light of the role of RGS6 in modulating GIRK channel activity in heart and robust expression of RGS6 in the cerebellar granule cell layer of the brain, the project hypothesizes that RGS6 might perform a similar role in this cell population known to exhibit a robust GIRK current activated by $G_{\beta\gamma}$ released from G protein coupled GABA_B receptors. More recently, the research has discovered novel RGS6 isoforms specifically expressed in tissues of the central nervous system, one of which is a phosphorylated form. The nature and function of these species has yet to be investigated. Considering the large diversity of RGS6 isoforms present in brain and the possibility of discovering

new mechanisms involved in RGS6 regulation, elucidation of the specific functions of the various molecular species of RGS6 is of paramount importance. The goal of this work is to identify the mechanism of RGS6 mediated GIRK channel modulation in brain and heart. Comprehensive understanding of these processes could lead to the development of novel treatment strategies for a number of neuronal and cardiac pathologies involving arrhythmias and conduction defects resulting from unchecked parasympathetic signaling and motor deficits involving aberrant neurotransmitter signaling in the brain.

Elizabeth M. Chislock

Duke University "Role of the Abl Kinases in Vascular Function and Angiogenesis"

The process of angiogenesis, in which new blood vessels grow from pre-existing vessels, has a crucial role both in normal vascular development and in diverse pathological conditions. During angiogenesis, the endothelial cells lining blood vessels are stimulated to form new vessels, through the coordinated action of a variety of circulating proteins known as growth factors. Upon binding to receptors on the endothelial



Elizabeth M. Chislock

cell surface, these growth factors regulate endothelial cell responses including proliferation, migration, and survival, all of which are required for blood vessel formation. Angiogenesis is an essential process in cancer progression, allowing for tumor growth beyond the limits of oxygen and nutrient diffusion.

Anti-angiogenic therapies including those targeting vascular endothelial growth factor (VEGF), a prominent pro-angiogenic growth factor, have demonstrated promising activity in both in vitro and in vivo cancer models. However, the clinical benefits of angiogenesis inhibitors targeting the VEGF signaling pathway have only been transient, with eventual continued tumor growth and progression, in part due to the acquisition of resistance by increased production of other pro-angiogenic growth factors. The current project has demonstrated a novel role for the Abl non-receptor tyrosine kinases in endothelial cell function. The Abl kinases, Abl and Arg, have roles in the regulation of a variety of cellular processes, including cytoskeletal remodeling, adhesion, survival and migration. Interestingly, the Abl kinases are activated when endothelial cells are stimulated with specific pro-angiogenic growth factors, and inhibition of Abl kinase activity impaired the ability of endothelial cells to respond to these growth factors. Studies using conditional knockout mice lacking expression of the Abl kinases in endothelial cells have confirmed a crucial role for these kinases in vascular function. The proposed research will examine the role of the endothelial Abl kinases in tumor angiogenesis using these conditional Abl knockout mice, as well as evaluating the efficacy of pharmacological inhibitors of the Abl kinases in the treatment of pathological angiogenesis. These studies aim to provide insights into the molecular mechanisms regulating angiogenesis and evaluate whether the Abl kinases, or their signaling targets, may represent entry points for pharmacological intervention for cancer or other disorders involving deregulated angiogenesis.

Robert R. Lavieri

Vanderbilt University "Defining the Roles of Phospholipase D Isoforms in Cancer via Isoform-Selective Inhibitors"

Phospholipase D (PLD) catalyzes the production of the lipid second messenger phosphatidic acid (PtdOH). PLD expression and/or enzymatic activity are both elevated in a



Robert R. Lavieri

variety of human cancers. Inhibition of PLD enzymatic activity, via genetic or biochemical methods, leads to decreased cancer cell invasion and decreased cancer cell survival. The aforementioned evidence provided the impetus for our medicinal chemistry project focused on the development of isoform-selective PLD inhibitors.

A group from Novartis published a report in 2007 disclosing halopemide as a hit from a high throughput screen for PLD inhibitors. The project initiated iterative analog synthesis with halopemide and has explored a broad chemical space through the synthesis of over 600 compounds. This effort has yielded the most potent, isoform-selective PLD inhibitors ever described. While halopemide inhibits both PLD isoforms relatively equally VU0359595 inhibits PLDI 1,700 times more potently than PLD2, and VU0364739 inhibits PLD2 75 times more potently than PLDI. The study is now poised to answer fundamental questions, both in vitro and in vivo, about how the two mammalian isoforms of PLD affect oncogenic processes such as the suppression of apoptosis, cell invasion and metastasis. This project will both enhance our understanding of cancer cell signaling and directly contribute to the development of new strategies for the treatment of cancer.

Valerie Jacobs

Dartmouth Medical School

"Propentofylline, a Glial Modulating Agent, Targets Microglial Cells in the Tumor Microenvironment Decreasing Glioblastoma Tumor Growth"

Glioblastoma Multiforme (GBM) is the most common and aggressive type of primary brain tumor in humans. It is highly resistant to conventional anti-tumor therapy with a



high recurrence rate, making it a crucial target for alternative therapies. The GBM tumor microenvironment is increasingly being recognized as an important determinant of tumor progression. Propentofylline (PPF), a glial modulating agent with well tolerable side effects, has been extensively studied as a potential

Valerie Jacobs

chronic pain therapy. Mechanisms of action in chronic pain rodent models include: inhibition of microglial activation/ proliferation, migration and decrease in the expression of proinflammatory cytokines. The study hypothesizes that PPF inhibits GBM growth by inhibiting microglia from entering the tumor microenvironment, decreasing TNF- α release and the down-stream targets of TNF- α signaling (i.e., MMP-9, VEGF). CNS-I cell line was used as a model of glioblastoma due to its invasive characteristics similar to human gliomas. *In vivo* work was conducted to determine PPF's effect on tumor volume. Lewis Rats were injected intracranially with 10^5 CNS-I cells and given daily i.p. injections of 50mg/kg PPF or saline starting on day 0. *In vivo* results indicate a four-fold reduction (p=0.03) in tumor growth with propentofylline treatment. No direct change in apoptosis or proliferation of CNS-I cells was observed with PPF treatment in vitro. To confirm that PPF acts only on the tumor microenvironment, CNS-I tumor cells were grown external from the CNS. Lewis Rats were injected with 10^5 CNS-I cells in the right flank and received daily i.p. injections of 50mg/kg PPF or saline starting on day 0. No change in tumor growth was observed. However, *in vitro* transwell migration demonstrated that PPF significantly (p<0.000I) decreased microglial migration in response to CNS-I tumor cells. The results indicate that propentofylline significantly decreases GBM tumor volume in a rat model by a novel mechanism involving inhibition of microglial migration within the tumor microenvironment.

Kirsten Bryant

Cornell University

"Electrostatic Protein-Lipid Interactions in Plasma Membrane Biogenesis and Cellular Signaling Regulation"

Biosynthetic trafficking of receptors and other integral membrane proteins from the endoplasmic reticulum (ER) to the plasma membrane (PM) underlies the capacity of these proteins to participate in crucial cellular functions.



Kirsten Bryant

Elucidating the mechanisms of the trafficking process is fundamental to understanding and intervening with the cellular responses that they regulate. The epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase that plays an important role in cell differentiation, proliferation and epithelial organogenesis. Proper

regulation of the EGFR is essential for normal cell development, and changes in its expression have been linked to tumor progression, making it a common target for cancer therapies. Structurally, the EGF receptor contains several intrinsic sorting signals that have been mapped to its 50-residue juxtamembrane (JX) domain, including residues that have been shown to modulate receptor tyrosine kinase activity and to interact with acidic phospholipids. Evidence from previous studies suggests a role for a polybasic JX region of EGFR in signaling at the plasma membrane (PM) due to interactions with acidic phospholipids such as phosphatdylinositol bisphosphate (PIP₂). Based on previous literature

and our own experimental results, this project will test the hypothesis that negatively charged phospholipids, particularly phosphatidylinositol-4-phosphate (PI4P), play a role in protein export from the endoplasmic reticulum (ER) and subsequent trafficking to the PM. Site-specific mutagenesis results indicate that basic residues in the JX region of the EGFR are important for ER to PM trafficking: reduction in the net charge of this JX region from +8 to +3 results in complete ER retention of this normally PM-associated protein. Additionally, treatment with an inhibitor of the ER-localized PI4P kinase III < results in similar ER retention of wild-type EGFR. These observations suggest a role for electrostatic interactions in biosynthetic trafficking, and the pharmacologic results suggest that a key contributor of this charge in the ER membrane is PI4P. At the PM, it has been suggested that the JX and protein kinase domains of the EGFR bind electrostatically to PIP₂ or other acidic lipids, restricting access of the kinase domain to substrate tyrosines. This project will assess the activity of ER-retained mutant receptors lacking JX basic residues within cells. Thus far, project results confirm that cell lines stably expressing the ER-retained EGFR mutants are capable of anchor independent growth in soft agar, an extremely reliable indicator of malignant transformation. In the proposed research, strategies to perturb both protein structure and phospholipid availability will be utilized to characterize the roles of polybasic amino acid sequences and negatively charged phospholipids in ER-to-PM trafficking. These efforts will be further focused on determining the specific lipid species important for this process. In addition, efforts to illuminate the signaling and transforming capabilities of the ER-retained EGF receptor mutants could result in a new understanding of the plasticity of the signaling platforms emanating from this well-characterized receptor.

Krishna Tobon

University of Medicine and Dentistry of New Jersey "The Role of D1 Dopamine Receptor Post-Transcriptional Regulation in Cocaine-Induced Sensitization"

Based on recent epidemiological data the National Institute of Drug Abuse estimates that over 5 million Americans abuse cocaine each year. The complex molecular mechanisms underlying cocaine addiction are not well understood and there are no FDA approved treatments for cocaine addiction. The DI dopamine receptor is one of several contributing factors involved in various addictive behaviors. Studies in animal models suggest that the DI dopamine receptor is



Krishna Tobon

essential in mediating the psychomotor effects of cocaine. Various studies in different brain regions indicate that cocaine induces DI receptor mRNA expression without a concomitant increase in DI receptor protein expression, suggesting post-transcriptional regulation of the receptor. However, the mechanisms

mediating post-transcriptional regulation of the DI dopamine receptor have not been determined. Thus the goal of this project will be to examine the regulation of DI dopamine receptor expression in cocaine addiction. Preliminary data using a novel reporter transgenic mice model subjected to two different cocaine administration regimens confirms that the DI receptor is post-transcriptionally

regulated in the caudate putamen. Having ruled out mRNA and protein stability as potential mechanisms, this project aims to test the novel hypothesis that DI receptor posttranscriptional regulation is mediated by microRNAs (miRNAs). miRNAs suppress protein translation by interacting with the 3' untranslated region (3'UTR) of the target mRNA. This project will combine the use of genome-wide quantitative expression profiling of miRNAs, bioinformatics, molecular biology, and behavior assays to identify the miRNA(s) necessary and sufficient for post-transcriptional regulation of DI receptors. This study will employ the use of an in vitro cell system and in vivo binge or chronic cocaine treated animal models to directly determine the role of the newly identified miRNA(s) in mediating the psychomotor effect of cocaine. The long-term goal of this project will be to investigate the role of the newly identified miRNA(s) in cocaine abuse and withdrawal with the expectation that it might represent a potentially novel pharmaceutical target for treatment of cocaine addiction.



Namandje Bumpus, Ph.D., John Hopkins University School of Medicine, was presented a 2011 Research Starter Grant in Pharmacology/ Toxicology at the ASPET annual meeting on April 9th in Washington, DC. Dr. Bumpus is pictured with Eileen Cannon and Dr. Terry Bowlin.

Post Doctoral Fellowship in Pharmacology/Toxicology

The PhRMA Foundation Post Doctoral program in Pharmacology/Toxicology provides support for individuals engaged in a multidisciplinary research training program that will create or extend their credentials in pharmacology or toxicology.

The intent of this program is to support post doctoral career development activities of individuals preparing to engage in research that integrates information on the effect of an agent in the intact organism. Recent graduates from pharmacology Ph.D. programs interested in post-doctoral experience that integrates pharmacology with a morphologic specialty (cell biology/anatomy/pathology) are also eligible to apply for this fellowship. It is anticipated that this research training will be accomplished in academic and/or industrial laboratory settings in which multidisciplinary teams are organized to integrate informatics, molecular, cell and systems biology with pharmacology/toxicology research.

The post-doctoral award consists of a \$40,000 annual stipend for up to two years. The second year of this award is contingent upon a progress report approved by the Foundation and submission of a financial report. The award is intended solely as a stipend and may not be used otherwise.

2011 Post Doctoral Fellowship in Pharmacology/Toxicology

Megan Montgomery, Ph.D.

University of California, San Francisco "Cardiac Alpha-1 Adrenergic Receptors: Novel Agonist Drug Targets for Heart Failure"

Cardiovascular diseases are a major health concern worldwide, and high morbidity and mortality rates associated with these diseases highlight the need for new, improved treatments. During heart failure (HF), excess stimulation of beta-adren-



Megan Montgomery, Ph.D.

ergic receptors (ARs) results in cell death, fibrosis and pathological changes in the structure of the heart. Consequently, beta-blockers have become a standard of care in HF therapy, resulting in reduced morbidity and mortality. Alpha-I-ARs in the heart, namely the alpha-IA and alpha-IB subtypes, mediate physiologic growth and

cell survival, providing an adaptive response to pathologic stress. Blocking this beneficial signaling might explain the increased mortality and risk of HF in clinical trials of alpha-I-blockers. Recent studies in our laboratory suggest that the alpha-IA subtype-selective agonist A6I603 has cardioprotective signaling without altering blood pressure, a

vascular alpha-I-AR effect, and prevents and rescues cardiomyopathy in mouse models. Altogether, these studies suggest that alpha-I-agonist therapy might be a new pharmacological treatment for HF. This project will test the hypothesis that alpha-I-AR agonists, at low doses, elicit beneficial cardiac-specific effects by targeting alpha-IA and alpha-IB subtypes, and have potential as new therapeutics for heart failure. The roles of alpha-IA and alpha-IB receptors in signaling pathways associated with cardioprotection and physiological hypertrophy will be determined in a cardiac myocyte cell culture model and in intact mice, using alpha-I agonists with various affinities for the two subtypes and mice with a genetic knock-out (KO) of the alpha-IA, alpha-IB, or both receptors. A61603, the alpha-IA-selective agonist, will also be tested in mouse models of cardiomyopathy to see if it can prevent and rescue disease in the presence of beta-blockade, a standard of care for HF. Cellular and molecular responses in cardiac myocytes and overall cardiac and physiologic effects in mice will be determined using wild type mice and those with KO of the alpha-IA, alpha-IB, or both. Successful completion of this project may advance the cardiovascular field by challenging the classic theory that sustained sympathetic activation is entirely detrimental when, in fact, alpha-I-AR stimulation might be beneficial. In addition, characterizing the effects of the alpha-I-AR subtypes would be advantageous for developing new, cardiac-specific alpha-I-agonists.

Ditte Lovatt, Ph.D.

University of Pennsylvania "TIVA (Transcription In Vivo Analysis): A Novel Tool for Studying Global Gene Expression in Single Cells In Vivo"

The pharmacological effect of a drug on the brain *in vivo* is often a complex task to decipher. In drug screening processes, it is key to establish whether the drug targets the intended



Ditte Lovatt, Ph.D.

cells and whether the intended effect is specific just to these cells. In addition, it is important to know whether other signaling pathways are affected, and whether these changes potentially could be harmful to patients. To address these criteria, the ideal screening model utilizes *in vivo* exploration of the drug's effect on global gene

expression. However, the structural complexity of intact brain tissue compromises exploring a drug's effect selectively on a distinct cell type *in viw* using conventional techniques.

To overcome this technical challenge, a novel approach was developed to identifying the temporal gene expression changes specifically in single neurons while these are still embedded within live, intact tissue. This is facilitated using a custom designed chemical compound called Transcriptome In Vivo Analysis (TIVA) tags that allows tagging and isolation of mRNA for global gene expression profiling in individual cells from live tissue. In the past, gene expression studies have employed whole tissue samples, which are composed of many different cell types, and thus lack cellular resolution. The TIVA approach permits with cellular precision the investigation of how single neurons *in vivo* change their gene expression in response to pharmacological or physiological stimulation. This will provide a unique window into the effects of a drug on the transcriptome.

In these studies TIVA will be used to explore the acute gene expression profile of layer IV neurons from barrel cortex in response glutaminergic stimulation using a model of experience-dependent learning in which glutaminergic sensory input is crucial for learning whisking behavior. Experiencedependent learning is restricted to a critical window during the first three days of postnatal rodent life, and when this window closes new learning becomes impaired with limited plasticity during adulthood. Depriving specific barrels from sensory input during the critical period can be achieved by trimming of the barrel's principal whisker, and results in whisking impairments later in life. Altogether this study will provide novel insight into the *in vivo* signature of single glutaminergic neurons as well as the regulatory mechanisms of experience-dependent learning relative to the critical window.

Research Starter Grant in Pharmacology/Toxicology

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 program provides a research grant of \$60,000 for one year. This program supports individuals beginning independent research careers in academia who do not have other substantial sources of funding. The program is not offered as a means to augment an ongoing research effort.

2011 Research Starter Grant in Pharmacology/Toxicology

Namandje Bumpus, Ph.D. Johns Hopkins University School of Medicine "Role of Drug Metabolism in NNRTI-mediated Toxicity"

Efavirenz, nevirapine and etravirine are non-nucleoside reverse transcriptase inhibitors (NNRTIs) prescribed as part of highly active antiretroviral therapy to treat HIV-I infection. Despite the therapeutic benefits of these drugs there are a number of adverse events associated with NNRTI use



Namandje Bumpus, Ph.D.

tochromes P450 (CYP) catalyze the metabolism of NNRTIs and in certain cases, the toxicities that result from treatment with these drugs have been associated with the formation of reactive metabolites; however, the mechanism(s) by which these metabolites elicit toxicity is currently unknown.

including liver toxicity. The cy-

Compounding this is that fact that efavirenz, nevirapine and etravirine have all been reported to increase the expressions of the CYPs responsible for their metabolism. Thus, prolonged treatment with efavirenz, nevirapine and etravirine has the potential to result in increased formation of toxic metabolites. The specific aims in this proposal seek to gain an understanding of the role of P450-mediated drug metabolism in toxicity resulting from NNRTI-treatment. Aim I will define a role for specific signaling molecules in the modulation of CYP2B6 and CYP3A4 by these NNRTIs; aim 2 tests the hypothesis that metabolism of efavirenz, nevirapine and etravirine underlies the toxicity associated with their use. Further, this aim attempts to systematically examine which metabolites may be involved; and aim 3 tests the hypothesis that metabolites of these drugs cause mitochondrial dysfunction which could result in increased cell death. Successful completion of this project will provide a molecular understanding of the mechanism(s) underlying NNRTImediated liver toxicity.

Jan Williams, Ph.D. University of Mississippi Medical Center "Mechanisms of Matrix Metalloproteinases

in Diabetic Nephropathy"

Diabetes is one of the most common causes of chronic kidney failure and end-stage renal disease (ESRD). The early

stages of diabetes are characterized

with increases in arterial pressure

being transmitted to the kidney leading to increases in a variety of

cytokines and growth factors

(e.g. TGF- β and MMPs) that

development of renal injury.

Despite the magnitude of this

problem, little is known about

are thought to contribute to the



Jan Williams, Ph.D.

the factors underlying the pathogenesis of diabetes-induced nephropathy and the development of new treatments has been hampered due to lack of an appropriate animal model.

Recently, the Type 2 Diabetic Nephropathy (T2DN) rat was developed from a cross between the Goto-Kakizaki (GK) rat, which develops type-2 diabetes but no renal disease, and the Fawn Hooded-Hypertensive (FHH) rat, which develops renal disease but is not diabetic. In preliminary experiments, the project found that MMPs and TGF- β are increased during the development of renal injury in the T2DN rat and inhibitors of these pathways slow the development and may even reverse renal disease. These studies will provide compelling evidence that MMPs play a critical role in the progression of renal injury associated with diabetes and that selective inhibitors of various MMP isoforms may emerge as a treatment for diabetic nephropathy.

Fernanda Laezza, Ph.D.

The University of Texas Medical Branch "Bioluminescence Assays for Voltage-Gated Sodium Channel Drug Discovery"

The voltage-gated Na+ (Nav) channels provide the basis for electrical excitability in the brain. Up or down-regulation of

specific Nav channels is linked to a

human disorders that mostly lack effective and selective therapeutic

options. Emerging evidence indi-

cates that Nav channels operate within a network of intricate

protein:protein interactions and

that this macromolecular complex

plethora of excitability-driven



Fernanda Laezza, Ph.D.

determines the activity, surface expression, membrane localization, and ultimately the function of these channels. The goal of this project is to leverage this reached matrix of intracellular proteins as a new source of highly specific protein interfaces toward the design of safe and selective drugs targeting neuronal Nav channels.

HEALTH OUTCOMES

Pre Doctoral Fellowships in Health Outcomes

The goal of this program is to increase the number of well-trained investigators in Health Outcomes research. This program is designed to encourage and support promising students during their thesis research and is aimed at those candidates who are within two years of completing their research for doctoral dissertations in Health Outcomes.

The fellowship program provides a stipend of \$25,000 annually for up to two years. Up to \$500 a year of the funding may be used for incidentals directly associated with the preparation of the dissertation.

2011 Pre Doctoral Fellowships in Health Outcomes

Kimberly Saverno

University of Arizona "Impact of Medicare Part D on Pharmaceutical and Medical Utilization in Arizona's Dual Eligible Population"

The Medicare Modernization Act of 2003, which established Medicare Part D, was enacted, in part, to provide drug coverage to those Medicare enrollees who did not already



have outpatient prescription drug benefits. However, Medicare beneficiaries who were receiving drug benefits through Medicaid were also impacted by the legislation. These beneficiaries, who are eligible for both Medicare and Medicaid, are commonly referred to as 'dual eligibles.' They constitute an especially vulnerable

Kimberly Saverno

population, characterized by poorer health status, lower incomes, and less education than the average Medicare population. With the implementation of Medicare Part D on January I, 2006, dual eligibles' source of prescription drug coverage shifted from Medicaid to Medicare Part D. This project will evaluate the impact of transitioning prescription drug coverage for Arizona's dual eligibles from Medicaid to Medicare Part D. Findings may benefit policymakers and health care professionals by suggesting whether Arizona's dual eligibles are best served by prescription drug benefits offered under Medicare Part D or Medicaid. Findings may also suggest ways of improving medication access for the dual eligibles under Medicare Part D.

Joshua Roth

University of Washington

"Comparative Effectiveness Approaches to Evaluate Pharmacogenomic Technology: The Cases of CYP2C9/VKORC1 Testing in Warfarin Dosing, ERCC1 Testing in Non-Small Cell Lung Cancer, and Gene-Expression Profiling in Early-Stage Breast Cancer"

The rapid advancement in understanding of genomics over the past decade presents a significant opportunity to "personalize" therapy and improve pharmaceutical outcomes by ascertaining disease prognosis and likelihood of treatment response using genomic technology. However, appropriate translation of genomic technology into clinical practice has been limited by overwhelming amounts of genomic association data, lack of prospective trial evidence, and lack of analytic frameworks to synthesize evidence in a manner that consistently meets the decision-making needs of stakeholders. A number of comparative effectiveness research (CER) approaches have the potential to overcome these limitations,



Joshua Roth

including observational study designs, value of information analysis, and benefit-risk modeling. This project will use these CER approaches to generate additional evidence for three genomic technologies in three distinct case studies. The first case study will evaluate the association between CYP2C9 genetic variants and

serious bleeding in warfarin therapy patients and effect modification by geographic and care setting, using a casecontrol design and a sample of 600 patients from a Seattlebased healthcare system. The second case study will assess the value of additional research to investigate ERCCI expression testing to inform adjuvant chemotherapy decisions in earlystage NSCLC using value of information methods. The third case study will evaluate the comparative health outcomes of gene-expression profiling, clinical-pathological, and combined prognostic strategies to inform adjuvant chemotherapy decisions in early-stage breast cancer using benefit-risk modeling. The results will provide evidence to help facilitate appropriate translation of each genomic technology into clinical practice. Collectively, the case studies will highlight how comparative effectiveness research approaches can be utilized to provide useful information for genomic technology stakeholders.

Post Doctoral Fellowships in Health Outcomes

The PhRMA Foundation Post Doctoral program in Health Outcomes provides stipend support for individuals engaged in a research training program that will create or extend their credentials in health outcomes. The purpose of this program is to support post doctoral career development activities of individuals preparing to engage in research that will strengthen representation of health outcomes in schools of pharmacy, medicine and public health.

To accomplish these goals, support will be provided for a two-year period to selected individuals who are beginning careers in health outcomes research and who give promise of outstanding development as researchers. The award consists of a \$55,000 annual stipend for up to two years.

2011 Post Doctoral Fellowships in Health Outcomes

Rahber Thariani, Ph.D. University of Washington "Value of Information Analyses"

While the area of pharmaceuticals has received considerable attention in comparative effectiveness research (CER), such research conducted on medical devices is in its infancy and represents an engaging opportunity to impact the healthcare

system. Biomarker testing, genomic

tests for personalized medicine

diagnostics will have a dramatic

impact on drug use, effectiveness,

use and point-of-care (POC)

and cost-effectiveness in the

coming decade. This research

research and development, and

comparative-effectiveness (CE)

focuses on prioritization of



Rahber Thariani, Ph.D.

in the area of diagnostic technologies. Specifically, a) using value-of-information (VOI) approaches to aid in the prioritization of diagnostic research, b) assessing the impact of decreasing diagnostic testing costs on evidence thresholds and incentives for research investment, and c) developing a framework to better understand the impact of point-of-care (POC) devices on drug delivery, usage, effective and costeffectiveness. The end result of the research is to provide improved techniques and tools for quantitative decision making, analysis, implementation and development specifically in the area of medical diagnostics, devices and associated therapies.

Tisha Felder, Ph.D., M.S.W. University of South Carolina "Racial and Ethnic Differences in the Use of Oral Anti-Cancer Agents for Breast Cancer Treatment among Medicaid Enrollees"

African Americans and low-income persons, such as Medicaid enrollees, consistently have poor rates of breast



cancer survival. Reasons for poor survival include later stage at diagnosis and differences in treatment. The availability and use of oral anti-cancer agents for breast cancer treatment has been increasing over time. These agents are efficacious, safe, and have the potential to improve the patient quality of life due to their convenience, such as

Tisha Felder, Ph.D., M.S.W.

self-administration and reduced travel to and from cancer treatment centers to receive intravenous chemotherapy. In a state like South Carolina, that is largely rural and where the disparity in breast cancer survival between African American women versus Whites is even higher than national rates, the use of these agents for breast cancer treatment could be an attractive option for patients to consider. Studies have reported racial/ethnic differences in intravenous chemotherapy use, however, it is unknown if these differences exist in the use of oral anti-cancer agents. Using data from the South Carolina Central Cancer Registry linked with South Carolina Medicaid claims, this study will determine if, in an equal access health care system of Medicaid enrollees in South Carolina, there are racial/ethnic differences in the use of oral anti-cancer agents for the treatment of breast cancer. As compliance to oral anti-cancer agents is critical to survival, study findings can help identify patients who may benefit from targeted patient education efforts aimed at promoting safety and compliance to their oral regimen. Long-term goals include informing healthcare insurance coverage policy of oral anti-cancer therapies and exploring adherence to and preferences for oral regimens in racial/ethnic and low-income populations.

Research Starter Grants in Health Outcomes

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 program provides a research grant of \$60,000 for one year. This program supports individuals beginning independent research careers in academia who do not have other substantial sources of funding. The program is not offered as a means to augment an ongoing research effort.

2011 Research Starter Grants in Health Outcomes

Carrie McAdam-Marx, RPh, Ph.D. University of Utah "Clinical and Economic Outcomes Associated with Collaborative Drug Therapy Management in Patients with Type 2 Diabetes"

Maintaining near normal blood glucose levels is important for helping patients with diabetes to avoid diabetes-related



Carrie McAdam-Marx, RPb, Pb.D.

complications such as blindness and renal disease. Recognizing the importance of blood glucose control in diabetes, the University of Utah has implemented a comprehensive diabetes management program for patients with uncontrolled diabetes in three University-owned community clinics. As a part of this program, physicians and pharmacists collaborate

on efforts to initiate insulin when appropriate, as starting insulin therapy is often a difficult step for patients to take. In addition to helping patients learn how to properly take insulin, pharmacists provide diabetes education and monitor

laboratory values for these patients. The goal of this study is to identify how well patients who were started on insulin under this collaborative program manage their blood glucose after insulin is started, as well as the cost of their overall healthcare while in the diabetes management program. To separate the impact of the program from underlying trends in diabetes control and healthcare costs, outcomes for patients treated in the collaborative insulin management program will be compared to patients with diabetes started on insulin but who were treated in a clinic that has not implemented this program. The data generated from this study will provide information to help secure funding for efforts to expand the collaborative diabetes management program to other clinics, including collaborative insulin management, and to provide the opportunity to improve outcomes for a greater number of patients with type 2 diabetes.

Carol Warren, Ph.D.

Florida A & M University

"Impacting Minority Health Outcomes Using Clinical Trials & Patient Registry Data: Provider Capacity Assessment and Potential Internal Rate of Return"

Pharmaceutical clinical trials and patient registries drive genomic and technological innovations that improve patient health outcomes. Providers treating underserved minorities



Carol Warren, Ph.D.

have low participation rates in clinical trials/patient registries. Minority patients will participate in clinical trials when they are invited by their treating providers. Lowered trial and registry participation by providers, considered collectively, can unintentionally negate the promise of genomic advances in personalized medicine

and targeted therapy for underserved minorities. The project goals are better health outcomes from better data from minority serving providers, from a macro perspective of health administration and health policy. The specific aims of the research are to analyze the current baseline capacity for minority-serving providers to participate in clinical trials and patient registries and to calculate what is considered a preferred and sustainable rate of return (IRR) for minorityserving providers to participate in clinical trials and patient registries. The study will describe differentiated strategies implemented by clinical research organizations (CRO) whose organizations support higher numbers of minority serving investigators. Using mixed methods, descriptive cross-sectional quantitative analyses of provider surveys to determine provider capacity and CRO support will be used. Additionally, qualitative analysis of 'solution focused' provider focus groups will be used and the Human Capital neoclassical economic theory will interpret IRR.

PHARMACEUTICS

Pre Doctoral Fellowships in Pharmaceutics

This program has been in effect for 23 years. It assists awardees who have one or two years remaining in the pharmaceutics pre doctoral training—the time during which they are engaged in dissertation research. We provide the funding during the doctoral program after course work has been completed and the remaining training activity is a student's research project.

The fellowship program provides a stipend and funds to cover costs incidental to the training for up to two years. The level of support is \$20,000 per year and up to \$500 a year may be used for incidentals directly associated with the preparation of the dissertation. Five fellowships were granted in 2011.

2011 Pre Doctoral Fellowships in Pharmaceutics

Stacy Sommerfeld Ross University of Iowa "New Insights into Anti-Pseudomonal Aerosols"

Bacterial biofilms are becoming increasingly problematic in medical, dental, food, and manufacturing fields. Biofilms are formed as planktonic bacteria attach to a surface and create a polysaccharide matrix for protection. Biofilms are less susceptible to antibiotics and the immune system, compared to planktonic bacteria. *Pseudomonas aeruginosa* biofilms cause chronic lung infections in cystic fibrosis patients. Current antibiotic treatments are ineffective and can lead to antibiotic resistance. Researchers focusing on different antibiotic combinations are also unable to eradicate the



biofilms. A new approach is to use dispersion compounds that entice the biofilms to release free-swimming bacteria. The major gap in research is the need to optimize antibiotic treatment following this dispersion. The goal for this proposal is to develop dry powder aerosols containing dispersion and antibiotic compounds, which

Stacy Sommerfeld Ross

could be synergistic in breaking up and eradicating the biofilm within the cystic fibrotic lung. Promising compounds will be selected after determining dose-dependence and elucidating when biofilms first react to treatment, have maximum eradication, and adapt to treatment.

22 Fellowships and grants

Justin Thomas University of Kansas "Stabilization of Recombinant Protein Antigens Using Computational Methods"

The physical stability of protein subunit vaccines is critical to ensure efficacy upon administration. If a protein antigen is delivered that is not in its proper three-dimensional fold,



Justin Thomas

the vaccine will not elicit protective antibodies and the individual receiving the vaccination will remain susceptible to the disease or toxin being vaccinated against. A vaccine's stability is particularly important for vaccines that will be stored for long periods of time (i.e., for those stockpiled for biodefense measures) or used to

treat diseases in developing countries since these countries generally lack proper storage capabilities. Currently, the most common way to stabilize vaccines is by adding excipients to the formulation. Excipients are simply molecules that enhance some aspect, such as the stability or solubility, of the pharmaceutically active ingredient to prevent it from changing over the course of its shelf-life. This approach, however, is empirical and does not always lead to sufficient stability. To overcome this limitation, a computational design approach will be undertaken to rationally mutate residues buried in the core of a protein antigen being developed for use in a vaccine against ricin toxin. The mutations will be designed to increase the stability of the antigen. In addition, by only modifying residues in its core, it is believed that the antigen's ability to elicit neutralizing antibodies will not be perturbed. Ricin is an ideal model to test our hypothesis due to its inherent lack of stability and because no antidote is currently available to combat the lethal effects of ricin exposure. Because ricin is one of the world's deadliest toxins and is thought to be a prime candidate for use in bioterrorism attacks, developing a stable antigen that can be used in a vaccine is of paramount importance to the safety of our servicemen and citizens. The method, if successful, will be extended to a protein antigen being developed for use in a vaccine against anthrax, another bioterrorism threat.

Brandon Teska

University of Colorado, Denver "Effect of Phenol and m-Cresol Depletion in Delivery Devices on Therapeutic Insulin Stability"

Insulin is an important protein therapeutic for millions of diabetics worldwide. Due to its challenging formulation stability and rapid depletion from circulation, it is also can be a cumbersome treatment for diabetics. The wearable insulin pump offers a convenient alternative to subcutaneous injection. Current advances in real-time blood glucose



monitoring devices will eventually lead to fully automated insulin pumps giving more patients precise, automated control of their condition. However, long standing issues with insulin stability in contact with the components within the pump limit the pump's utility. Depletion of the antimicrobial agents phenol and m-cresol

Brandon Teska

within the pump decrease insulin's stability and as a result, patients have to replace the entire pump apparatus every two to three days due to catheter occlusions. Not only is an occlusion potentially dangerous for patients, but aggregated, pre-occlusion species may be unknowingly injected by patients before occlusion. This problem is widely recognized, both clinically and scientifically, but still remains unsolved. Only recently has the technology required to characterize insulin's stability in these conditions become available. The goal of this study is to fully characterize the effects of phenol and/or m-cresol depletion on insulin's thermodynamic and kinetic stability within insulin pumps under clinically relevant conditions.

Chester Costales

University of North Carolina at Chapel Hill "The Role of Intestinal Apical Cation-selective Transporters on Oral Absorption and Pharmacology of Metformin in the Diabetic Mouse"

The anti-hyperglycemic agent, metformin, is the most prescribed drug for type II diabetes; yet the mechanism of its intestinal absorption remains unclear. Although the physicochemical properties of this hydrophilic cationic drug would suggest poor oral absorption, its bioavailability is

much higher than expected. As is

indicate that metformin accumulates in the cells, which suggests its

rate-limiting basolateral exit into

ally, modeling data from these

the systemic circulation. Addition-

cell-based studies indicate that the

paracellular route is the predomi-

observed in the clinic, previous

cell-based transport studies



Chester Costales

nant pathway of metformin's transport. This study proposes that the high absorption of metformin in vivo occurs through a transporter-mediated cycling mechanism between the enterocytes and the gut lumen, which increases metformin's residence time in the intestine and its overall absorption by allowing increased access to the paracellular space. This project aims at testing our hypothesis that cation-selective transporters can augment the intestinal absorption of metformin, using a diabetic mouse model. Selective chemical inhibition will be employed to evaluate metformin as a substrate for mouse cation-selective transporters in cells expressing the individual transporters. Metformin's transporters will then be identified in mouse intestinal tissue by Ussing-type diffusion chamber studies. Finally, metformin's absorption as it transits through the gastrointestinal system will be evaluated in vivo in a portal vein cannulated mouse model using selective transporter inhibitors. The changes in metformin's absorption will be related to alterations in systemic glucose levels. These studies will bridge our knowledge of metformin's transport in cell-based assays to its absorption mechanism in an in vivo mouse system. This in vitro-in vivo correlation of metformin's transport mechanism in the mouse will enable us to predict metformin's in vivo behavior in humans from studies conducted in Caco-2 cells and human intestinal tissue.

Randall Logan

University of Kansas "Endosome-to-Cytosol Trafficking of Membrane Impermeable Cargo"

One of the most fundamentally important problems facing contemporary drug delivery scientists is the inability to efficiently deliver therapeutically important, membrane-



impermeable molecules into the cell cytosol. Many of these drugs are considered membrane-impermeable by virtue of their highly charged nature and/or large molecular weight. Such molecules cannot typically enter the cell by passively diffusing across cellular lipid bilayers. Despite this limitation, many membrane-impermeable

Randall Logan

anticancer agents and antibiotics accumulate within cells, enabling them to interact with cytosolic and nuclear targets which ultimately elicits a pharmacological response. For many of these drugs the precise mechanism of their entry into the cell cytosol has been controversial and/or is incompletely understood. This study and others have preliminarily demonstrated that such molecules are efficiently endocytosed and accumulate in late endosomes and lysosomes. From here, these molecules have been shown to accumulate in the endoplasmic reticulum prior to escape into the cell cytosol, although a detailed understanding of these transport steps remain obscure. In this work the project will seek to define the kinetics and substrate specificity of this poorly understood transport pathway. Defining the substrate specificity for this pathway will likely aid in the design of new drugs and/or carriers that will have structural and physiochemical properties that promote cytosolic delivery of these important therapeutic molecules (i.e. anticancer agents, DNA, RNA).

Post Doctoral Fellowship in Pharmaceutics

This 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 and its Pharmaceutics Advisory Committee recognize the critical need for such well-trained scientific investigators. The post doctoral award consists of a \$40,000 annual stipend for up to two years. The second year of this award is contingent upon a progress report approved by the Foundation and submission of a financial report. The award is intended solely as a stipend and may not be used otherwise.

2011 Post Doctoral Fellowship in Pharmaceutics

Mary Krause, Ph.D. University of Kansas

"Development of Bi-Functional, Targeted Anti-Cancer Therapeutics Using a Platinum-Binding Tripeptide Tag"

Metals are playing an increasingly important role in the pharmaceutical industry. Importantly, platinum compounds, such as cisplatin, are effective anti-cancer agents. Although highly potent, these compounds lack specificity and create horrible side effects because uptake by invasive cancer cells is only marginally better than healthy cells. The solution is targeted delivery. The project strategy is to incorporate an inline metal-binding tripeptide tag into proteins that selectively target cancer cells. Adding this modular tag generates a bi-functional, targeted therapeutic. Because metal binding is irreversible at physiological pH, this approach should



dramatically reduce side effects experienced by patients, by reducing both the total dose of platinum administered and exposure to healthy cells, widening the therapeutic window. A unique advantage of this conjugation system is the ability to rationally design and site-specifically encode the tripeptide sequence into any

Mary Krause, Ph.D.

position, allowing complete control over positioning the tag within the protein to generate a homogeneous product. The project goal is to characterize the tagged proteins stability and demonstrate that the tag effectively delivers platinum to cancer cells while reducing damage to normal tissue. This approach will be applied to two model systems to obtain proof-of-concept data, demonstrating the tag may be used in numerous other proteins and applications.



On April 9, 2011, at the ASPET Annual Meeting in Washington, DC, the PhRMA Foundation Pharmacology/Toxicology Pre Doctoral Fellowship Awards were presented. Pictured from left are Eileen Cannon; Krishna Tobon, University of Medicine & Dentistry of New Jersey; Kirsten Bryant, Cornell University; Jason Kehrl, University of Michigan; and Dr. Terry Bowlin.

25 *Fellowships and grants*

Research Starter Grants in Pharmaceutics

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 program provides a research grant of \$60,000 for one year. This program supports individuals beginning independent research careers in academia who do not have other substantial sources of funding. The program is not offered as a means to augment an ongoing research effort.

2011 Research Starter Grants in Pharmaceutics

Bodhisattwa Chaudhuri, Ph.D. University of Connecticut "Experimentally Validated Modeling, Optimization and Scaleup of High Shear Wet Granulation Process"

High shear wet granulation (HSWG) is a particle size enlargement based unit operation, pertinent to the development of the pharmaceutical solids dosage forms (tablets and capsules), which are 80% of the all doses administered. Improper granulation causes problems in down-stream processes such as segregation, caking and poor tableting performance. In spite of its economic importance, widespread use and several decades of research, the process is poorly understood and science based methodology for the design/operation is still missing. The project proposes to

perform research seeking to unravel the complexities of HSWG process, develop an experimentally validated numerical process-model capable to predict the optimal conditions and scale-up criteria. In the first stage of the project, granulation time, patterns and performance of high-shear granulator will be systemically investigated for different vessel size, rotation speed, and filling levels. Once flow/granulation behavior is well understood, the study will establish operating conditions that optimize granulation performance. In the second stage, the improved knowledge of flow/granulation will be used to develop dimensionless scale-up criteria for achieving equivalent performance in granulators of various sizes, aiding large scale manufacturing in the pharmaceutical and associated industries. The knowledge gathered from the project will speed up the development, save rejected batches and reduce the time to market of the pharmaceutical products.



Bryan L. Roth, M.D., Ph.D., Michael Hooker Distinguished Professor, University of North Carolina at Chapel Hill was presented the 2011 Award in Excellence in Pharmacology/Toxicology. Dr. Roth (center) is pictured with Dr. Terry Bowlin and Eileen Cannon at the annual ASPET meeting in Washington, DC. on April 9, 2011.

CLINICAL PHARMACOLOGY

Paul Calabresi Medical Student Fellowship

This program offers students an opportunity to spend up to two years full-time conducting an investigative project in pharmacology-clinical pharmacology. It is hoped that by having students become involved in investigative projects at a point when career choices are still relatively flexible, they will eventually choose research careers in clinical pharmacology.

The minimum period of the fellowships is six months and the maximum is two years, with a maximum stipend of \$18,000. One hundred and seventy two Medical Student Fellowships have been awarded since the program began in 1974. This fellowship has been named in honor of Dr. Paul Calabresi who served the PhRMA Foundation as a committee Chairman and member for 25 years.

2011 Paul Calabresi Medical Student Fellowship

Elizabeth Nguyen Dong Vanderbilt University "Structural Studies of the Interaction between mGlu₅ and Allosteric Modulators"

As technology makes genetic information more readily available, it has been shown that carefully tailoring therapeutic treatments to a patient's genotype can increase drug efficacy and decrease risk of adverse effects. This is because specific



Elizabeth Nguyen Dong

human populations carry different single-nucleotide polymorphisms (SNPs) which can cause protein mutations that influence drug binding or function. With the advent of structure-based drug design, personalized medicine is truly becoming a possibility. Structural representations can be used to understand the interaction

between the protein and a drug, allowing for the possibility of altering drug structures to better bind their protein targets. A G-protein coupled receptor, metabotropic glutamate receptor subtype 5 (mGlu₅), is involved in cognitive function through diverse signaling pathways that influence learning and memory. Modulating the activity of mGlu₅ with positive and negative allosteric modulators could provide novel treatment strategies for disorders causing cognitive dysfunction, such as schizophrenia and fragile X syndrome. Identifying the specific residues on mGlu₅ that contact these compounds will provide a deeper understanding of the binding interaction and aid in the development of therapeutic compounds that treat such disorders. Additionally, this information can be used to identify mutations in patient populations for which these drugs have varying degrees of efficacy. Currently, there is no high resolution structure of the transmembrane region of mGlu₅ to aid in the understanding of this interaction. The project supported by this PhRMA research fellowship focuses on the computational construction of comparative structural models of mGlu₅ with allosteric modulators. Residues of mGlu₅ critical for the binding and function of such compounds can be determined through ligand docking studies informed by site-directed mutagenesis studies. An increased understanding of the interaction between mGlu₅ and its allosteric modulators will aid in the development and application of novel therapeutic agents that specifically target disorders resulting in the disruption of cognitive function.

Jenny Barker

University of Texas Southwestern Medical Center "Zinc-Finger Nuclease Targeted Primary Fibroblasts as Vehicles for Systemic Protein Delivery in a Mouse Model of Hemophilia A"



Hemophilia A is a rare genetic disease caused by mutations in the factor VIII gene resulting in a deficiency of factor VIII and a severe bleeding disorder. Current therapy relies on the infusion of recombinant factor VIII, a strategy that is costly and not entirely effective. Several groups have used the random integration of factor

VIII transgenes in somatic cells to create cells that secrete

factor VIII. While promising, this strategy carries the risk of insertional mutagenesis and has been limited by transgene silencing leading to a decrease in efficacy. To achieve safer and more stable transgene expression, site-specific targeted transgene integration would be more ideal. Toward this end, this project has developed a strategy which uses zinc-finger nucleases (ZFNs), engineered proteins that stimulate homologous recombination (HR) through the generation of site-specific double strand breaks. By this method, if exogenous DNA is used as a template for HR, a transgene can be targeted to a precise genomic location. The study has demonstrated that ZFNs can stimulate transgene targeting in primary mouse fibroblasts 20,000-fold above background. Using this strategy, the project proposes to target the factor VIII gene in the mouse fibroblast genome and determine if transplantation of the genetically modified fibroblasts is therapeutic in a mouse model of hemophilia A. Importantly, this work may be a platform for a personalized pharmacotherapeutic that allows for systemic delivery of proteins from a patient's own cells.

Faculty Development Award in Clinical Pharmacology

Through this program, annual awards are made to medical schools for support for full-time junior faculty members in the field of human clinical pharmacology. The level of support is variable, and is aimed at keeping within the existing salary and fringe benefit structure of the applicant university. The award is for two years.

This program was established by the PhRMA Foundation in 1966 in recognition of the many problems involved in evaluating therapeutic agents. Drug investigation is a demanding task. As in nearly every aspect of the health field, manpower needs are acute. This program is intended to meet some of these workforce needs in the field of clinical pharmacology. The ultimate aim of the awards program is to stimulate teaching, training, and research in clinical pharmacology. It is aimed at providing an opportunity for the development of the research potential of clinical pharmacologists during the years immediately following their formal training programs.

2011 Faculty Development Award in Clinical Pharmacology

Timothy J. Nelson, M.D., Ph.D. Mayo Clinic College of Medicine "Patient-Specific iPS Cells as Cardiovascular Regenerative Biologics"

Regenerative technologies have begun to define a new perspective of future clinical practice. The burden of degenerative diseases creates an ever-growing need for the development strategies able to diagnose, predict, and ultimately repair the underlying regenerative dysfunction and associated pathobiology. Regenerative pharmacology offers a new frontier for medical therapy where patient-specific induced pluripotent stem (iPS) cell-based biologics aim to establish progenitor cells as effective and safe drugs to achieve structural and functional therapeutic repair in practice. Moreover, patient-specific regenerative biologics also offer an unprecedented opportunity for novel diagnostics to quantify the regenerative reserve and identify "druggable" targets for individual patients. Building on the strong track record of



Timothy J. Nelson, M.D., Ph.D.

clinical pharmacology and cardiovascular human genetics, this proposal from Mayo Clinic focuses on novel theranositics for heart failure. Recent recognition that the heart is continuously undergoing rejuvenation provides a paradigm shift in which cardiac performance is dependent on the net balance of tissue turnover and disease reversibility. The

innovative hypothesis of this proposal is that the regenerative potential is imprinted within developmental stem cell signatures, and provides new opportunities to advance clinical pharmacology solutions. The specific objectives of this research plan are to stratify individual cardiogenic capacity in stem cells bioengineered from patients with familial dilated cardiomyopathy, and define innate deficiencies of cardiac repair in order to map therapeutic targets. Central to the success of the project is the production of patient-specific cardiogenesis and quantification of innate regenerative potential within an IRB-approved Mayo Clinic registry of familial dilated cardiomyopathy. The uniqueness of this innovative strategy lies in the ability to reveal the identity of pathways that are inherently corrupted within patient-specific stem cells, independent of confounding and/or compensatory variables including comorbidities and concomitant drug therapies. Defined disease-causing mutations provide the genotype/phenotype specificity needed to validate the diagnostic criteria and therapeutic metrics of functional regeneration. The impact of this PhRMA Foundation Faculty Development Award expands beyond the era of genetic revolution with next generation stem cell-based technology to advance personalized regenerative diagnostics and novel therapeutics, validating a new platform within clinical pharmacology.



At the 2011 Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) on May 24, 2011 in Baltimore, MD, Health Outcomes Advisory Committee Chairman, Dr. Jean Paul Gagnon presented the PhRMA Foundation Health Outcomes awards. Pictured from left are Eileen Cannon; Rahber Thariani, Ph.D., University of Washington; Kimberly Saverno, University of Arizona; Carrie McAdam Marx, Ph.D., University of Utah; Carol Warren, Ph.D., Florida Agricultural and Mechanical University; Tisha Felder, Ph.D., University of South Carolina; and Dr. Gagnon.

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TREASURER'S REPORT

The PhRMA Foundation ended 2010 in solid financial shape despite a financially challenging year. Contributions were down 11% from the previous year, to \$2.35 million. We awarded over \$2.2 million in grants and held down non-grant program and administrative expenses. Total expenditures, at \$2.9 million, were 2% below budget. Net assets at December 31 were \$15.5 million, an 8% increase from \$14.3 million the prior year. The increase in net assets is attributable

to investment gains. For the 12th year in a row, we did not need to transfer net assets to cover payment this year of awards granted in previous years. Financial details are shown in the accompanying Statement of Income and Expenditures.



For 2011, contributions were on track to increase to at least \$3.03 million, and once again we did not transfer net assets to cover our expenses. On behalf of the Board and staff, I give special thanks for the continuing support of our generous contributors, who are listed in this report. We truly appreciate the substantial support of all member companies during these challenging financial times. Our programs represent our industry's commitment to innovation in today's research

as well as to the young investigators of tomorrow.

The Foundation's financial position as of December 31, 2010, has been audited by the accounting firm of Tate and Tryon of Washington, D.C. A full report can be obtained by contacting the Foundation.



GARRY A. NEIL, M.D.



STATEMENT OF INCOME AND EXPENDITURES¹

INCOME		
Contributions	\$	2,351,540
Contributions – in kind from PhRMA	\$	307,728
Interest and Dividends	\$	369,041
(Realized and Unrealized) Gains in Securities	\$	1,102,183
Other Income	\$	46,082
TOTAL INCOME	\$ 4	4,176,574
EXPENDITURES		
Programs		
Awards in Excellence	\$	15,439
Clinical Pharmacology Program	\$	318,000
Health Outcomes Program	\$	401,234
Informatics Program	\$	345,500
Pharmaceutics Program	\$	435,000
Pharmacology Program		520,000
AFPE Fellowship Award	\$	7,500
Other Grants	\$	171,915
Subtotal – Grants	\$2,214,588	
Other		
Committee Meetings, Travel and Honoraria	\$	72,087
Publications and Special Projects	\$	33,437
Subtotal – Other	\$	105,524
PROGRAM TOTAL	\$2,320,112	
Administrative		
Staff, Taxes, Depreciation & Insurance	\$	298,954
Rent & PhRMA Accounting Services ²	\$	307,728
Professional Services and Investment Expenses	\$	47,472
Office Expenses	\$	3,564
Subtotal – Administrative	\$	657,718
TOTAL EXPENDITURES	\$2	2,977,830

¹ For the year ended December 31, 2010

² Rent and Accounting Services are donated by PhRMA

STATEMENT OF INCOME AND EXPENDITURES

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Phrma foundation PROGRAMS FOR 2012

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time					
Health Outcomes Advisory Committee								
Pre Doctoral Fellowships in Health Outcomes (2002)	2 awarded/ I year	\$50,000 total \$25,000 per award per year	February I, 2012 April 15, 2012 July – December					
Post Doctoral Fellowship in Health Outcomes (2002)	2 awarded/ 2 years	\$220,000 total \$55,000 per award per year	February I, 2012 April 15, 2012 July – December					
Research Starter Grants in Health Outcomes (2002)	I awarded/ I year	\$60,000 total \$60,000 per award per year	February I, 2012 April 15, 2012 July I, 2012					
Informatics Advisory Committee								
Pre Doctoral Fellowships in Informatics (2009)	2 awarded/ 2 years	\$80,000 total \$20,000 per award per year	September I, 2011 December 15, 2011 January – August					
Post Doctoral Fellowships in Informatics (2002)	I awarded/ 2 years	\$80,000 total \$40,000 per award per year	September I, 2011 December 15, 2011 January – December					
Research Starter Grants in Informatics (2002)	4 awarded/ I year	\$240,000 total \$60,000 per award per year	September I, 2011 December 15, 2011 January I, 2012					
Basic Pharmacology Advisory Committee								
Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)	I0 awarded/ I or 2 years	\$360,000 total \$20,000 per award per year	September I, 2011 December I5, 2011 January – August					
Post Doctoral Fellowships in Pharmacology/Toxicology (2002)	2 awarded/ 2 years	\$160,000 total \$40,000 per award per year	September I, 2011 December 15, 2011 January – December					

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time						
Sabbatical Fellowship in Pharmacology/Toxicology (2002)	I awarded/ I year	\$40,000 total \$40,000 per award per year	September I, 2011 December 15, 2011 January – December						
Research Starter Grants in Pharmacology/Toxicology (1972)	3 awarded/ I year	\$180,000 total \$60,000 per award per year	September I, 2011 December I5, 2011 January I, 2012						
Clinical Pharmacology Advisory Committee									
Paul Calabresi Medical Student Research Fellowships (1974)	3 awarded/ 6 months up to 2 years	\$54,000 total \$18,000 per award	February I, 2012 April 15, 2012 July I, 2012						
Faculty Development Award in Clinical Pharmacology (1966)	I awarded/ 2 years	\$240,000 total \$120,000 per award per year	February I, 2012 April 15, 2012 July I, 2012						
Pharmaceutics Advisory Commit	Pharmaceutics Advisory Committee								
Pre Doctoral Fellowships in Pharmaceutics (1987)	7 awarded/ I or 2 years	\$240,000 total \$20,000 per award per year	September I, 2011 December I5, 2011 January – August						
Post Doctoral Fellowships in Pharmaceutics	2 budgeted/0 awarded 2 years	\$40,000 per award per year	September I, 2011 December I5, 2011 January – December						
Research Starter Grants in Pharmaceutics (1972)	2 awarded/ I year	\$120,000 total \$60,000 per award per year	September I, 2011 December I5, 2011 January I, 2012						
Comparative Effectiveness									
Center of Excellence Award	2 awarded/ 3 years	\$500,000 total \$83,333 per award per year	September 15, 2011 November I, 2011 December I, 2011						

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

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



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38





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