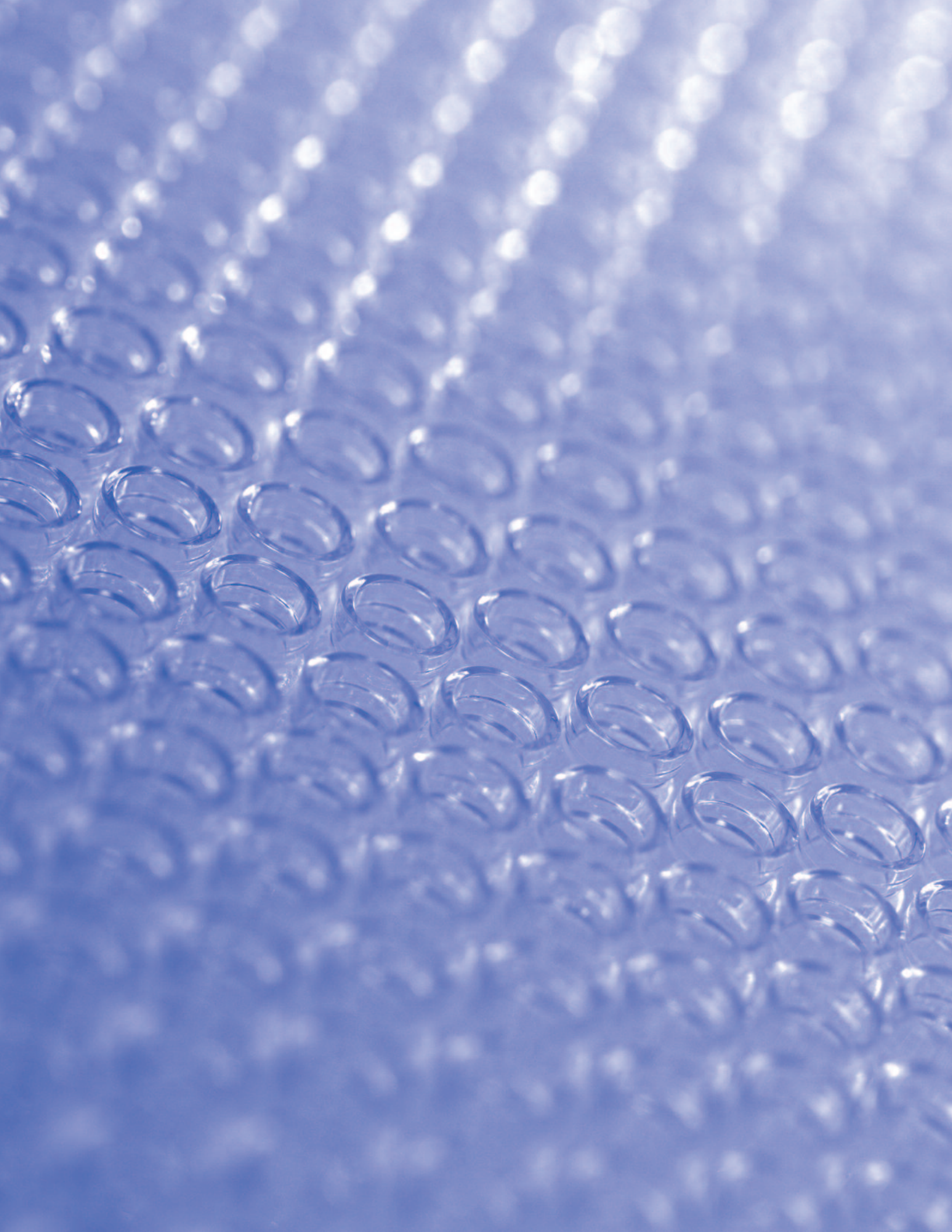


PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA FOUNDATION

Annual Report





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Mission Statement

The mission of the PhRMA Foundation is to support young scientists in disciplines important to the pharmaceutical industry by awarding them competitive research fellowships and grants at a critical decision point at the outset of their careers.

The aim is to encourage young scientists who will be the leaders of tomorrow to pursue careers in research and education related to drug discovery.

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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.

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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.

MESSAGE FROM THE Chairman



For more than 40 years, the cornerstone of the P/RMA Foundation has been its strong support of training, research, and career opportunities for young investigators. We have established a distinguished reputation on par with prestigious institutions and organizations throughout academia, industry, and government. To further strengthen this reputation, we hold our advisory committees and award programs to the highest standards, constantly seeking out new ways to stay competitive and promote the cutting-edge science that sustains pharmaceutical research.

While our priority remains the Foundation's core program, we are also an organization that understands the importance of growth. For this reason, we are committed to forming solid partnerships, expanding our offerings, and implementing new programs.

In 2005, the Board of Directors began to explore initiatives that could strategically leverage the Foundation. Because we firmly believe that scientific advances are often facilitated through collaboration, each of these proposals is rooted in the development of partnerships across the biomedical industry. Using partnership as a platform, we will pursue ways to support R&D-based educational programs, fund joint efforts with universities and non-profit organizations, and strengthen our presence in areas such as pre-competitive research. The focus of these shared endeavors could range from developing new training grants to public awareness campaigns that foster P/RMA's Safe and Innovative Medicines Program.

To bring such large-scale projects to fruition, the Foundation aims to centralize the resources and expertise of its member companies. Together we will promote a meaningful and consistent message that demonstrates the potential of partnership within our

organization and beyond.

The P/RMA Foundation fully supports the mission of the NIH, and in 2008, we launched a new partnership with the Institutes and the NIH Foundation to enhance the nationally offered Clinical Pharmacology course. Through our financial support, we envision a broader reach for the NIH Clinical

Center, greater opportunities for scientific progress, and stronger cooperative efforts among universities, industry, and non-profit scientific and medical organizations.

As part of an ongoing effort to demonstrate the importance of financial support in a young investigator's career, the Foundation will expand its public relations campaigns, incorporating the stories of past award recipients who have changed and improved the field of biomedical science.

We also wish to further connect with the public through educational and outreach efforts that demonstrate how our industry has helped so many patients throughout the world. Altering the public's perception of an industry often associated with its commercial aspects—manufacturers, marketing, brands, and stock prices—is achievable only through the joint efforts of industry representatives, pharmaceutical companies, and organizations like the P/RMA Foundation, whose longstanding investment in exceptional science and history of good works have earned considerable recognition.

As an organization that has strived always to ensure the future success of our discipline, we firmly believe that collaboration across the biomedical industry is essential, not only for achieving our own objectives, but to advance the field as a whole. The P/RMA Foundation will continue to focus on common concerns and pursue new avenues for cooperation to fulfill its greater mission as part of an industry that promotes and protects public health.

A handwritten signature in dark ink, reading "John M. Leonard". The signature is fluid and cursive, with a large loop at the beginning.

JOHN M. LEONARD, M.D.

MESSAGE FROM THE President

As the P/RMA Foundation celebrates its 43rd year in operation, I am proud to report that our core program is as strong and successful as ever.

With a focus on the future of clinical pharmacology and the young investigators pursuing a career in the field, we have fortified our Clinical Pharmacology program and partnered with the NIH to broaden the reach of its Clinical Pharmacology course. In this year's Annual Report, the benefits and challenges of a career in clinical pharmacology are explored through the eyes of experts in academia, industry, and government. The Foundation's Clinical Pharmacology program has had a substantial impact on the industry, and we will continue our efforts to support the careers of clinical pharmacologists, who play such a vital role in the safe and effective use of medicine.

While we are proud that our awards have facilitated the careers of more than 2,000 young scientists, our commitment to providing competitive grants and fellowships requires ongoing assessment. The prestigious Faculty Development Award, presented to more than 100 junior faculty members since its initiation in 1967, will be offered in July 2009 after a seven-year hiatus. New to our awards in 2009 is a Pre-Doctoral Fellowship in Informatics, a program that provides two years of stipend funding. In 2010, we will expand the size of our three available Health Outcomes fellowships. As always, the Foundation continues to pursue opportunities to assist scientific researchers as they embark on their careers.



The grants and fellowships provided by the Foundation have helped sustain the careers of those leading the biomedical field today. We never tire of the success stories our past award recipients have to tell, and have been fortunate enough to maintain relationships with many of these individuals. In the coming years, we intend to build upon our rapport

with former awardees to establish new initiatives and programs that strengthen the field as a whole.

As part of our strategic initiatives for 2009 and beyond, the Foundation will identify and pursue potential partnerships with government agencies, including the FDA and HHS. We will seek out collaborative projects with organizations that specialize in comparative effectiveness and safe prescribing. Working together with representatives and institutions across academia, industry, and government, we hope to generate a wealth of new opportunities for advancing biomedical research and for the scientists we support.

The future leaders of drug discovery and development are at the core of every program that we offer, and it is our mission to help them along their career paths however we can. Our awards are often a springboard for additional funding and, subsequently, for continued research. We strive to make a difference in the lives of young investigators, and while providing grants and fellowships may be a calculable benefit to some, our support assists the scientists and physicians who will one day improve the lives of patients—a benefit that is by our standards, invaluable.

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

DEL PERSINGER

AWARDS IN Excellence

The annual P/RMA 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 P/RMA 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 2008 exemplify the very best in their chosen fields of clinical pharmacology and pharmacology/toxicology. The P/RMA 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.

2008 Award in Excellence in Clinical Pharmacology

DAVID W. NIERENBERG, M.D.

Senior Associate Dean for Medical Education—
Dartmouth Medical School
Professor of Medicine and Pharmacology & Toxicology
Section Chief, Clinical Pharmacology
Dartmouth-Hitchcock Medical Center

Dr. David Nierenberg trained at Harvard College, Oxford University, and then Harvard Medical School, where he was elected to AOA. After graduation, he trained in internal medicine at the Beth Israel Hospital in Boston, and then did a two-year fellowship in clinical pharmacology at UCSF under Howard Morrelli and Ken Melmon. The following year, Ken Melmon invited him to Stanford to be the chief medical resident.

In 1981, Dr. Nierenberg was recruited to Dartmouth Medical School to establish a new Division of Clinical Pharmacology. At Dartmouth, Dr. Nierenberg developed an intensive, required fourth year course in clinical pharmacology, which is now the capstone course of the fourth year, and which has served as a model for similar courses at several other schools. He also built a comprehensive curriculum for the medicine residents in clinical pharmacology, which has also served as a national model. Dr. Nierenberg has assembled a small but very active Division, with two full-time faculty members (one being his colleague Dr. Lionel Lewis), and a new fellow coming on board every two years to be the second member. Their Division at Dartmouth consults on or admits more than 100 patients per year; is one of only seven fully accredited fellowship programs in the country; and is very active in Phase I studies of the clinical pharmacology of new



Dr. David Nierenberg was presented with the 2008 Award in Excellence in Clinical Pharmacology by Del Persinger of the PhRMA Foundation at the Annual Meeting of The American Society for Clinical Pharmacology and Therapeutics (ASCPT) in Orlando, Florida.

anticancer agents.

Dr. Nierenberg's personal research for many years focused in the areas of the clinical pharmacology of antitumor drugs with a focus on methotrexate, and the clinical pharmacology of antioxidant vitamins that were being evaluated in several NIH-sponsored chemoprevention trials. One of his first extramural grants was from the P/RMA Foundation, to help him establish his career, and study drug interactions with methotrexate. He received our Faculty Award in Clinical Pharmacology in 1983. For many years, he directed the Clinical Pharmacology Shared Service of their comprehensive cancer center.

Over the past 18 years, Dr. Nierenberg has been spending increasing amounts of time on his teaching and academic administrative duties. He continues to direct his required fourth-year course; has written or helped edit three textbooks

in clinical pharmacology; was named director of the Year 2 Pathophysiology program; and, since 1995, has served as the Associate Dean (and now Senior Associate Dean) for Medical Education.

Dr. Nierenberg has earned numerous teaching awards while at Dartmouth. In 2008 the graduating seniors elected Dr. Nierenberg to receive their award given to the best teacher of clinical sciences (the third time he has received this award from the graduating class), and he was also elected by the second year students to receive their awards for their most distinguished educator, and most distinguished small group and conference leader. Dr. Nierenberg has served on a number of boards and committees of national societies and organizations. He has actively represented the needs and interests of clinical pharmacology on the APCR, and now in the AAMC

and its Council of Academic Societies. He served on the USMLE Step III committee, maintaining clinical pharmacology perspectives in their new computer-based clinical case modules, and is on his second rotation on the American Board of Clinical Pharmacology. Most recently, he has chaired an ad hoc group organized by the AAMC as part of their Medical Schools Objectives Project to produce recommendations for how all medical schools can improve their training of medical students to become safe and effective prescribers. Their final report is due out later this spring.

Locally, he serves in a variety of service and leadership positions for his local church, his local free clinic, and his local residential shelter for patients recovering from substance abuse.

Dr. Nierenberg received a Faculty Award in Clinical Pharmacology in 1983 from the PhRMA Foundation.

2008 Award in Excellence in Pharmacology/Toxicology

P. JEFFREY CONN, Ph.D.

Lee E. Limbird Professor of Pharmacology
Director, Vanderbilt Program in Drug Discovery
Department of Pharmacology
Vanderbilt University Medical Center

Dr. Conn is Professor of Pharmacology, and Director of the VICB Program in Drug Discovery at Vanderbilt Medical Center. Dr. Conn received his Ph.D. degree in Pharmacology from Vanderbilt University in 1986 and pursued postdoctoral studies in the Department of Pharmacology at Yale University. Dr. Conn joined the faculty of the Department of Pharmacology at Emory University in 1988 where he rose to the rank of Full Professor and established himself as a leader in studies of neurotransmitter receptors and their roles in regulating brain function in circuits involved in psychiatric and neurological disorders. In 2000, Dr. Conn moved to Merck and Company to assume the position of Senior Director and Head of the Department of Neuroscience at Merck's site in West Point, PA. Dr. Conn moved to Vanderbilt University in 2003 to start a new Program in Drug Discovery, with a primary mission of facilitating translation of recent advances in basic science to novel therapeutics. Dr. Conn is Editor in Chief of Molecular Pharmacology, Regional Editor (North America) of Current Neuropharmacology and serves on the editorial boards of 6 other international journals. Dr. Conn serves on the Scientific Advisory Boards of Addex Pharmaceuticals, Prescient NeuroPharma, Invitrogen Life Technologies, Seaside Therapeutics, Cephalon Inc., AstraZeneca US, Michael J. Fox Foundation, and the Dystonia Medical Research Foundation.



Dr. Jeff Conn received the 2008 Award in Excellence in Pharmacology /Toxicology at the 2008 Annual Meeting of The American Society for Pharmacology and Experimental Therapeutics (ASPET) Meeting in San Diego, California.

He is the Chair Elect of the Neuropharmacology Division of the American Society for Pharmacology and Experimental Therapeutics (ASPET). He has received numerous awards and honors, including the NARSAD Essel Investigator Distinguished Investigator Award and was named as an ISI Most-Cited Scientists in Pharmacology & Toxicology. He serves on several national and international committees, including International Union of Pharmacology (IUPHAR) subcommittee on receptor nomenclature, the American Society for Pharmacology and Therapeutics (ASPET) Publications Board of Trust, Pharmacia-ASPET Award Committee for Experimental Therapeutics, and is an Expert Consultant, Compound Selection Committee, Treatment Units for Research on Neurocognition and Schizophrenia (TURNS). He is also the Chair elect of the Neuropharmacology Division of ASPET. Dr. Conn's current research is focused on development of novel treatment strategies for schizophrenia, Parkinson's disease, and other brain disorders.

Dr. Conn received a Research Starter Grant in Pharmacology /Toxicology in 1989 from the PhRMA Foundation.

THE PATH TO SUCCESS

Pursuing a Career in Clinical Pharmacology

It's an exciting time to be a clinical pharmacologist. As the pharmaceutical industry continues to grow on a global scale, expectations for research and development, safe importation, and regulatory oversight will heighten the need for qualified clinical scientists. The next generation of clinical pharmacologists is essential to the continuation and progression of the discipline.

Within the three main branches of clinical pharmacology—academia, industry, and government—clinical pharmacologists contribute to the safe and effective use of medicine. Educators impart the principles of clinical pharmacology relevant to every branch of the discipline. Industry leaders stand at the forefront of drug research and development. And at government institutions, regulatory officials ensure the safety and efficacy of medicines as they move from labs and clinical trials to the marketplace.

As scientists continue to identify sources of patient variability, the concept of individualized care is becoming a mainstay of clinical pharmacology. Just how much personalized medicine will affect drug development and, as a result, patient care, hinges in part on the next generation of investigators.

Not unlike most professions, young scientists often feel overwhelmed as they face the road ahead. What does the future hold for academia? Will I be able to help patients while working in a corporate environment? How does one secure a career with a government agency? Choosing the right track is a difficult decision, and even with a clear path forward, a career in clinical pharmacology may change subtly or dramatically along its course.

Today's teachers, corporate managers, and regulators are the leaders and mentors of tomorrow's clinical pharmacologists. Their invaluable perspectives portray the everyday expectations and responsibilities, joys, and challenges of a profession rooted in the protection of public health. Clinical pharmacology programs convey both a broad and specific understanding of the discipline—broad in the teaching of basic principles, and specifically designed to address topics ranging from drug

metabolism and pharmacokinetics to genetics and rational prescribing. Post-doctorate programs offer an even more specialized curriculum, preparing students to pursue careers in industry, academia, or public health. Starter grants and fellowships, such as those awarded by the P/RMA Foundation, facilitate independent research and foster careers in all branches of the discipline.

The future of clinical pharmacology and the success of those who choose a career in the discipline rely heavily on academic institutions and training programs. Pharmacokinetics, statistics, and rational therapeutics must be supported and taught as fundamental elements of a clinical pharmacology education. The ability to assess efficacy and determine proper dosing are skills invaluable to early drug development. Furthermore, how and where the tenets of clinical pharmacology are taught are just as important. Clinical fellowships are often based in the lab, with only one month each year spent in the clinic. A clear understanding of broad-based care is achieved not only in a research environment, but as a result of time spent in a clinical setting.

A growing number of women are pursuing an education in clinical pharmacology, but just as important as recruiting women to the discipline is the ability to retain these students—potential professors, government officials, and corporate executives. This requires a certain level of transparency, not only as students complete undergraduate training, but throughout their Post-doctoral studies and early careers. For young investigators, a well-defined career path, particularly in the academic sector, is a picture of what lies ahead. The lab and classroom is where mentoring begins, but it is by no means where it ends. An awareness of career progression and opportunities for growth are of the utmost importance, as is long-term mentorship. Academic faculty who serve as mentors are invaluable not only for their contributions to the careers of budding scientists, but for the support and encouragement they provide, sharing unique experiences and broadening their students' perspectives.

Industry

Some of the most exciting aspects of a career in industry are the fast-paced, corporate environment and diverse workforce. Although work intensity fluctuates and responsibilities vary from company to company, a day in the life of an industry professional can involve everything from conducting clinical trials, to report review, to strategic planning. At a small company, teams of medical specialists, engineers, and technicians may focus on promising drug candidates or expanding formulations, whereas large-scale research and development and integration of risk/benefit strategies are more common at major pharmaceutical companies.

A typical day for Steven Ryder, M.D., President of Astellas Pharma Global Development Inc., focuses on the development of new products, a process that involves multiple disciplines and extensive collaboration. "Clinical pharmacology is at the very core," says Dr. Ryder. To design a clinical program, Dr. Ryder works with investigators and their staff, analyzing product data and reviewing the impact of the results. Communication is essential among the teams responsible for testing new drugs before they enter the marketplace. "It really is about the patient," says Dr. Ryder. "Every day, multiple times a day, you ask how does this aspect have relevance to the patient?"

"The value of the clinical pharmacologist is that he sees the big picture."

ANDREW BEELEN

Senior Director, Clinical Research, Myriad Pharmaceuticals

Using cutting-edge science to solve a medical problem, thinking about real patients with real needs, and seeing people benefit in real time are the best parts of the job for Dr. Ryder.

The tools and principles of clinical pharmacology are incredibly useful in a global pharmaceutical company, says Peter Honig, M.D., MPH, Executive Vice President of Merck's Worldwide Regulatory Affairs and Product Safety. "You need to have a strong understanding of clinical pharmacology to rise to management in an organization," he says.

In addition to his clinical regulatory responsibilities, Dr. Honig chairs Merck's late development review committee and oversees regulatory reviews. But what he most enjoys about his work is applying the principles of clinical pharmacology to an identified mechanism. "Selecting the right principles for phase III and translating them to a label that can be used by



Steven Ryder



Andrew Beelen

physicians to prescribe is incredibly rewarding," he says.

Training programs designed to prepare medical school graduates for a career in industry incorporate a diverse curriculum where clinical research, regulatory and medical affairs, and market analysis address the fundamental components of a corporate environment. Understanding and applying science to determine the appropriate dose must be taught in medical school as well as how to critically break down medical literature, says Dr. Honig. Looking ahead, he envisions the clinical pharmacologist at the center of personalized medicine, but predicts the application of individualized care will pose challenges to the discipline.

"Getting the dose right and labeling the drug is really the heart of the tenet," he says. Bridging "bench to bedside" isn't systematically taught in training programs, but according to Dr. Honig, the ability to connect basic scientific discoveries to clinical applications is essential.

For many, a career in industry seems inseparable from a massive corporate environment, but small company settings are challenging this misconception. Andrew Beelen, M.D., came to Myriad Pharmaceuticals after five and a half years at GlaxoSmithKline. There are only 200 employees at Myriad, a fraction of GSK's 110,000. The difference for Dr. Beelen is a greater investment in the entire preclinical pipeline. "I'm involved with the whole development time line," he says, expressing his preference for the company's small scale. "You have more input and I like the small company environment."

Dr. Beelen is responsible for the overall strategy and direction of clinical development in the infectious disease field. Although his job responsibilities are well defined—identifying safety parameters and primary endpoints for clinical studies—no two workdays are the same. "I'm constantly learning," he says, having changed his focus from cancer to malaria to HIV. "I've been fortunate to work in HIV and oncology, where new drugs are desperately needed, and to help bring drugs to market that provide some efficacy to these patients."

As technologies and health care needs change, so will the discipline of clinical pharmacology. Dr. Beelen believes the future holds a great demand for skilled pharmacologists. "We must define our role as more critical in the future," he says. "The value of the clinical pharmacologist is that he sees the big picture."

Academia



Deanna Kroetz

A professor's morning may begin with grant writing, shift to teaching by noon, and end in the lab, but similar to a career in industry, no day is typical in the academic field. For many educators, the dynamics of teaching is one of the most satisfying aspects of the career, second only to the ability to guide the future generation of clinical pharmacologists.



Scott Waldman

Few other positions in clinical pharmacology share the opportunities of an academic career. In both clinical and educational settings, teachers are uniquely positioned to impact patient care while shaping their students' research and career choices.

In the field of academia, one is freer to pursue personal research interests. The observational studies, epidemiological surveys, trials, and reviews of teaching physicians are among the many areas in which educators have influenced patient care.

Managing the demands of a career in academia requires a delicate balance between teaching, laboratory research, and for academic general practitioners, even time with patients. For some, achieving this balance is indicative of a successful career. For others, success culminates in professional advancement and recognition from the scientific community. And most educators find satisfaction through the growth and accomplishments of their students.

There is no single pathway or entry point into an academic career, a reality that may discourage medical students from considering the profession. A position in academic medicine and medical research often begins with an academic clinical fellowship, where students receive theoretical, practical, and medical training. These programs equip budding investigators not only with an understanding of study design, but also with the skills needed to succeed as a professional researcher. A well-rounded curriculum includes training in grant writing, medical publishing, data presentation, and career planning.

Professor Deanna Kroetz, Ph.D., works closely with fellows in her lab at the University of California, San Francisco (UCSF). Developing her students' research techniques and encouraging them to hone their scientific interests are what

she most enjoys. "The satisfying thing about being in academia is training people and developing their strengths—focusing on where they should be," she says.

Like others in the academic domain, Dr. Kroetz is as much a mentor to students as she is an instructor. By their last year of training, her students' strengths are more apparent, at which point the question becomes how and where they can best apply the skills they have learned.

Improving health care is at the core of research programs. Naturally, the research projects Dr. Kroetz pursues impact patient care. The UCSF lab has studied new treatment approaches for inflammation, and how toxicity in a certain population can be avoided with preliminary screening. "Some of this information will be used in clinical decision making," says Dr. Kroetz.

**"What you do in the lab is applied
to the patient's benefit."**

SCOTT WALDMAN

Professor, Jefferson Medical College

"My research interests are in the translational area—the clinical and molecular side—where there is potential of actually seeing something," says Dr. Kroetz. "I really like how science has evolved and bridged with the clinical in the last five or six years."

Collaboration, whether with students or investigators from across the country, is a fundamental part of an educational department's clinical efforts. Discussing research logistics and exchanging ideas with other scientists inspire educators to pursue their own medical interests while working with others.

Administrative work is yet another aspect of a career in academia. Spending some part of the week in an office or on the phone is a necessary part of maintaining and expanding a research program. Says Scott Waldman, M.D., Ph.D., FCP, a professor at Jefferson Medical College, "I spend a lot of time in my office engaged in administration. It's the only way forward to grow your research program."

Dr. Waldman, who began his career as a Ph.D. scientist in anatomy, took an early interest in molecular biology and pharmacology. Accepting a post-doctorate appointment in clinical pharmacology, he has since been fascinated with the integration of molecules to man. "What you do in the lab is applied to the patient's benefit," says Dr. Waldman, who appreciates the dichotomy of laboratory research and clinical care within an academic setting as an inextricable part of public health.

For Dr. Waldman, mentoring is the best part of the day. A mentor can do more than foster an appreciation for science throughout the long and challenging process of becoming an investigator. Understanding which hypotheses to explore and reducing the unknowns are integral to the success of a research project, but having someone to first discuss these issues with may be even more valuable. “Investigators need someone to bounce questions off of,” says Dr. Waldman. “Is [the research] realistic? Is it worthwhile? Is it going to change the face of science? We do this every single day, sitting down with trainees to discuss career paths and fellowships.”

A career in clinical pharmacology education is not without challenges. Funding is a critical element of a research program’s potential success and many programs are facing a decline in the number of interested faculty members. Moreover, the opportunity to practice clinical research in an industry setting may be more enticing to recent graduates. Academicians sustain a demanding work schedule, and maintaining a teaching career along with personal life is a delicate balance that often comes only with time.

Once that balance is achieved, however, the personal and professional rewards of a career in academia are long-lived and very sustainable. In his 35 years as a professor and advisor, Terrence Blaschke, M.D., says his work is as dynamic today as it was when he first joined the Stanford University faculty.

Most satisfying to Dr. Blaschke is the opportunity to teach and train promising pharmacologists “that have come and left the program and been successful in their own careers.” Throughout his career, Dr. Blaschke has worked as a clinical scientist and mentor with students, fellows, and residents, encouraging them to think carefully about the drugs they test. Critical thinking facilitates a deeper appreciation for questioning and understanding, he says.

Government

Government employees express a deep sense of satisfaction about their contributions to public health. Embracing the challenges that accompany the enormous responsibility of protecting consumer safety is crucial in the public health sector, a high-pressure, fast-paced environment. These individuals are part of an intricate network of skilled specialists, and have a sincere appreciation for the constant stream of ideas and information that flows between some of the field’s best and brightest.

Don Mattison, M.D., Capt., USPHS, Senior Advisor to the Directors of the National Institute of Child Health &



Shiew-Mei Huang

Human Development and Chief of the Obstetric and Pediatric Pharmacology Branch in the Center for Research for Mothers and Children, prefers a collaborative approach to improving healthcare. “I value the people that I work with, the investigators, my colleagues, and the idea that we’re interacting on a daily basis with some of the brightest in

pediatrics and obstetrics,” he says.

Dr. Mattison and his colleagues have developed training grants, secured funding for pediatric pharmacological networks, and directed pre-clinical and clinical studies focused on pediatrics and obstetrics. “The drugs that we’re looking at are typically taken by children, and women during pregnancy, but they’re used without dosing information,” says Dr. Mattison. “In a way, we’re focusing on how to appropriately treat two special populations where data from adults may be meaningless.”

On a day-to-day basis, Dr. Mattison corresponds with principal investigators and study leaders to assess and advance the progress of clinical trials. Determining a trial’s progress and which issues must be addressed to move forward, he also aims to gauge the interest of young investigators. “We often act in a mentoring role,” says Dr. Mattison. “We ask ourselves how we can help applicants to improve grant submissions.”

“The environment is mentally stimulating. You have the opportunity to work alongside people that you admire.”

SHIEW-MEI HUANG

Deputy Director in the Office of Clinical Pharmacology, CDER

From time to time, NIH is consulted about the potential safety signals of drugs they are not necessarily testing, but which pose considerable implications for public health. In 2005, Dr. Mattison and his colleagues conducted a study sponsored by the National Institute of Environmental Health Sciences to assess the genetic damage of Ritalin in adolescents.

Shiew-Mei Huang, Deputy Director in the Office of Clinical Pharmacology at the Center for Drug Evaluation and Research, devotes much of her time to regulatory briefings and meetings with advisory committees and working groups, developing guidances and discussing how to appropriately categorize patients and best summarize trial findings. A great

deal of preparation and review precedes the proposal and approval of an FDA-issued guidance or regulation. Proposed FDA regulations are announced in the Federal Register, notifying the public about the rule and allowing an opportunity to comment. The FDA also publishes guidance documents to help organizations comply with agency regulations.

Dr. Huang also leads internal training and educational efforts, presenting lectures to third-year students and preparing reviewers. “The environment is mentally stimulating,” she says. “You have the opportunity to work alongside people that you admire.”

Initially intrigued by how a drug affects the body and in turn, what the body does to the drug, Dr. Huang is a staunch believer that the principles of clinical pharmacology are some of the most useful tools available for understanding patient variability. Proper dosing is a crucial element of patient care, and depends in part on a patient’s race, age, and gender. “Clinical pharmacology is a critical issue in labeling,” says Dr. Huang.

For Kathleen Uhl, who served as an officer in the US Army and completed a fellowship at the Walter Reed Army Institute of Research, joining the FDA was a seamless transition. In her 11 years at the FDA, Dr. Uhl has advanced from



Kathleen Uhl

Medical Officer to Director in the Office of Women’s Health. “Clinical pharmacology is hugely important to drug development,” says Dr. Uhl. “It’s relevant to the entire drug development process.”

Dr. Uhl and her colleagues are devoted to the protection and advancement of women’s health. In addition to guidance and regulatory development, they work with awareness groups to disseminate consumer health information. “There’s no place in the world that does what FDA does; it’s a great place to work and you’re doing something for the public good,” she says.

Today, there is a great need for highly trained scientists who can apply their skills in an academic, industry, or government setting. As an integral part of mainstream medicine, pharmacologists pave the way for safe and effective medical treatments that contribute to longer, healthier, and more dynamic lives for their patients. Now more than ever, a career in clinical pharmacology is full of promise.

Fellowships AND Grants

INFORMATICS

Post Doctoral Fellowships in Informatics

The P/RMA 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.

2008 POST DOCTORAL FELLOWSHIP IN INFORMATICS

SUSAN T. MASHIYAMA, Ph.D.

University of California, San Francisco

"A Computational Atlas of the Trypanosoma Brucei Degradome as a Guide to Drug Discovery: Sequence, Structure, and Active Site Comparisons with Human Proteases."

The parasite *Trypanosoma brucei* causes African sleeping sickness in 300,000–500,000 people per year, mostly affecting the poorest rural populations of Central Africa. The few existing treatments exhibit serious side effects and research is urgently needed to develop new drugs. Proteases are enzymes that cleave proteins, and are of interest in disease research because they have been proven to be druggable targets: protease inhibitors are being used or developed to treat several diseases including parasite infection. Although predicted protein sequences are available from the entire *T. brucei*



Jeffrey Chuang, Ph.D., Assistant Professor of Biology at Boston College. Dr. Chuang is a recipient of a 2008 Research Start Grant in Informatics.

genome, these data have not been analyzed extensively. This study proposes an in-depth computational analysis of all the proteases in the *T. brucei* genome (called the “degradome”) to produce network-based views that contain and utilize information on similarities of sequence, structure, and active-site motifs of the *T. brucei* proteases. Such an ‘atlas’ of the degradome of this pathogen will in itself be a valuable resource for future research involving comparisons of other species to *T. brucei*. The resulting network views will be compared to human proteases and used to identify proteases that are specific to *T. brucei* and are thereby likely to be good drug targets, as lack of similar proteases in humans would minimize detrimental effects from drugs that might inadvertently affect human proteases. Inhibitors for putative *T. brucei*-specific proteases will be identified by in-silico screening. Proteases with good potential inhibitors will then be tested in *T. brucei* using RNAi, a technique that “silences” a targeted gene so that its gene product is not made. RNAi results will show if the knocking down of these proteases results in impairment of the parasite and whether these proteases are vital to the parasite. For those targets that result in impaired phenotypes, direct biochemical tests of the putative inhibitors against these *T. brucei* proteases will be performed to see if they inhibit activity.

Research Starter Grants in Informatics

This program supports individuals beginning independent research careers in academia. Applicants must be appointed to an entry-level tenure-track or equivalent permanent position in a department or unit responsible for Informatics activities as part of its core mission.

The program provides a research grant of \$30,000 per year for up to two years. The “starter” aspect of the program strives to assist those individuals who are establishing careers as independent investigators. The program is not offered as a means to augment an ongoing research effort.

2008 RESEARCH STARTER GRANTS IN INFORMATICS

JEFFREY H. CHUANG, Ph. D.

Boston College

**“Deciphering Malaria Gene Regulation through
Comparative Genomics.”**

Malaria is a global health problem that affects 500 million people worldwide, and known treatment strategies have declined in efficacy. A better understanding of the molecular mechanisms of *Plasmodium falciparum*, the most lethal human malaria parasite, will be crucial to the development of novel treatments. The goal of this project is to computationally model and analyze the malaria gene regulation program, which is quite different from that of other eukaryotes but is still poorly understood. First, a sequence conservation analysis will be undertaken to identify intergenic sequences and transcription factor binding sites conserved by natural selection in the genomes of eight *Plasmodium* species that infect primates, birds, and rodents. The evolution of gene regulatory sequences across different malaria species will be analyzed, and specific regulatory sequences in human malaria will be verified with the collaboration of an experimental group. Second, a database of all functional sequence predictions will be built, allowing for gene, motif, and location-based queries. These studies will shed light on what makes malaria gene regulation unique, as well as provide an important data resource to biomedical researchers studying the molecular basis of the disease.



David Klinke II, Ph.D., an Assistant Professor from West Virginia University, received a 2008 Research Starter Grant in Informatics. Dr. Klinke is pictured with Vivian Suarez, a graduate student in Chemical Engineering at West Virginia University.

DAVID J. KLINKE II, Ph.D.

West Virginia University

**“Interrogating Proteomic Profiles of Breast Cancer
Using Reaction Pathway Analysis.”**

One of the triumphs of the genomics revolution was the development of molecularly targeted therapies for cancer. One drug for such therapy, Herceptin, is used to treat a subset of patients with breast cancer by targeting the over expression of a protein involved in cellular signaling: ErbB2, a member of the epidermal growth factor (EGF) receptor family. The emergence of resistance to these targeted therapies is an increasing problem. Understanding the basis for resistance to these molecularly targeted therapies is hindered by the lack of techniques that enable monitoring for such resistance. The long-term goals of the Klinke Lab are to realize such a prognostic technology through multi-disciplinary research that applies advances in engineering, computation, and life science. The objectives of this research are two-fold: 1) to observe complex patterns of protein expression at the single-cell level and 2) to interpret these patterns of protein expression using reaction pathway analysis. The primary goal of reaction pathway analysis is to make predictions using mathematical models: what do we expect to happen in a particular reacting mixture under particular reaction conditions, given our current understanding of molecular interactions? Differences between our expectations and reality provide the opportunity



W. Jim Zheng, Ph.D. is an Assistant Professor in the Department of Biostatistics, Bioinformatics & Epidemiology at the Medical University of South Carolina. He received a 2008 Research Starter Grant in Informatics.

to learn something new. In the field of cancer biology, many of the molecular players in the various signaling pathways are known. However, the roles that individual proteins play at specific points in time and in particular systems are largely unknown. It is precisely in this situation that mathematical models are most helpful. In short, the proposed research provides a novel approach that combines cutting-edge techniques in computational systems biology and proteomics to address the pressing issue of emergent resistance to molecularly targeted therapies in cancer.

SUSAN J. SCHROEDER, Ph.D.

University of Oklahoma

"Computational Advances Towards Predicting Encapsidated Viral RNA Structure"

The conformation of ribonucleic acid (RNA) inside viral particles has remained elusive since the first crystals of viruses were studied more than 50 years ago. Common human pathogens, such as flu and human immunodeficiency viruses, and many plant viruses have RNA genomes that are encapsidated in viral particles before transmission to another host. A better understanding of the structure of encapsidated RNA genomes would guide rational design of small molecule inhibitors or RNA interference strategies to interrupt encapsidation and prevent viral propagation. Studying encapsidated satellite tobacco mosaic virus RNA will provide the foundations necessary for understanding larger human pathogenic viral RNA structure. Encapsidated viral RNA presents a unique challenge to the RNA folding problem. Existing crystallographic data for satellite tobacco mosaic virus (STMV) demonstrates the presence of well-ordered RNA structure within the viral capsid. However, current RNA secondary structure predictions do not produce structures

consistent with the available crystallographic data. Structure prediction methods that integrate more diverse information, such as chemical modification and crystallographic data, can improve predictions, address the problem of how to identify the correct structure from a group of low energy structures, and lead to the next challenge of tertiary structure prediction. The goals of the research project are to explore more possible RNA structures more efficiently through improvements to the Wuchty algorithm; validate the predictions through experimental determination of the RNA structure by chemical modification patterns; and to establish STMV as a model system for testing and improving RNA structure prediction methods.

YU XIA, Ph.D.

Boston University

"Integrated Prediction of Protein Networks in Yeast."



Yu Xia, Ph.D., Assistant Professor Bioinformatics Program, Boston University. Dr. Xia is a recipient of a 2008 Research Starter Grant in Informatics.

In the past few years, significant progress has been made in genome-wide identification of protein networks in various organisms. The impact of such experimental protein network maps is enormous. For molecular biologists, functions of unknown proteins can be predicted and subsequently analyzed based on their locations on these maps. For systems biologists, it is now possible for the first time to

quantitatively study the organization, function, and evolution of biological systems at the level of protein networks. Despite its enormous promise, the nascent field of network biology is ultimately limited by the accuracy and the completeness of the experimental network maps. The objective of the proposed research is to develop computational methods for reconstructing protein networks in yeast by probabilistic integration of a diverse list of genomic features. These computational methods complement nicely with experimental investigations; indeed, preliminary study suggests that both false positive and false negative rates can be reduced when these computational methods are applied to experimental protein network maps. We plan to collaborate with experimentalists to test some of the computational predictions.



At the 2008 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting in Toronto, Canada, several PhRMA Foundation Health Outcomes award recipients were recognized. Pictured from left to right are **Teresa Cavanaugh**, Pharm.D., University of Cincinnati, **Aaron Gibson**, Pharm.D., M.S., University of New Mexico, **Brent Hollenbeck**, M.D., M.S., University of Michigan, **Daniel Kiefer**, M.D., State University of New York, Stony Brook, and PhRMA Foundation Executive Director, **Eileen Cannon**.

W. JIM ZHENG, Ph.D.

Medical University of South Carolina

"Multi-scale Lung Cancer Modeling by an Object-oriented Software Engineering Approach"

The application of information technology and new advances in medicine have generated vast amounts of biomedical information about disease at tissue, organ, individual and population levels, including but not limited to disease classification, pathology, diagnosis, prognosis and treatment. At the same time, advances in technology have dramatically shifted the paradigm of basic biomedical research from data generation to data analysis. The availability of whole genome sequences from many organisms enables basic science researchers to investigate disease mechanisms at whole genome, proteome and lipidome levels, as well as from molecular to cellular levels. The enormous amount of information generated from such large scale investigation creates a tremendous opportunity for bioinformatics. While biomedical informatics and bioinformatics have historically occupied distinct spheres, the need to bridge the gap between them and translate basic research into clinical practice is significant. We propose to adopt a well-defined software engineering approach, first, to integrate biomedical information and molecular mechanisms of lung cancer into a coherent computational model, and second, to develop methods to analyze and infer new knowledge to related clinical information to molecular mechanisms from the constructed model. The proposed research aims at developing scalable methods to integrate ontology and multi-scale information for translational research, and providing new insight into the molecular mechanisms of lung cancer.

HEALTH OUTCOMES

Post Doctoral Fellowship 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 prepared (or 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 \$40,000 annual stipend for up to two years.

2008 POST DOCTORAL FELLOWSHIP IN HEALTH OUTCOMES

TERESA CAVANAUGH, Pharm.D.

University of Cincinnati

"Cost of Acute Rejection in Renal Transplant Patients"

Rising costs in health care demand rigorous study to determine cost-effectiveness. This is especially true in transplantation. It is well known that acute rejection events add to cost of care in renal transplant patients. However, studies done in the U.S. and abroad reporting rejection cost information are limited in terms of comprehensiveness and/or generalizability. Therefore, there is no consistent basis from which to perform cost-effective analyses of modalities that detect, prevent or treat acute rejection events. This project's retrospective, matched case control analysis will quantify the cost of care (diagnosis and management), both inpatient and outpatient, of acute rejection events and associated complications in renal transplant recipients in a real-world US practice setting. Cost will be derived from the hospital based cost accounting system; however, a model of Medicare reimbursement rates and pharmaceutical wholesale cost will be created to approximate a national cost accounting structure. This will enable the information to be utilized nationwide. The results of this study will be used to foster rational decision making in the care of transplant patients.

DANIEL KIEFER, M.D.

State University of New York

"A Randomized, Controlled Trial of Seprafilm® Adhesion Barrier to Reduce Adhesion Formation Following Cesarean Delivery."

Cesarean delivery has become the most common operation in the United States, with over 1.2 million operations performed annually. The consequences of this shifting clinical practice leading to multiple cesarean deliveries during a woman's life-time are just becoming apparent. Of particular concern is the formation of adhesions, making subsequent deliveries more difficult and riskier. The Seprafilm® Adhesion Barrier has been studied in other abdominal and pelvic surgery and shown to be beneficial in reducing adhesion formation. This study seeks to determine (1) the safety, (2) effectiveness, (3) impact on health-related quality of life, and (4) cost-effectiveness of the Seprafilm® Adhesion barrier when used at the time of cesarean delivery.

Research Starter Grants in Health Outcomes

The purpose of the P/RMA Foundation Research Starter Grants is to offer financial support to individuals beginning their independent research careers at the faculty level.

The program provides a research grant of \$30,000 per year for up to two years. 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.

2008 RESEARCH STARTER GRANTS IN HEALTH OUTCOMES

AARON GIBSON, Pharm.D., M.S.

University of New Mexico

"A Comparison of Quetiapine, Trazodone, and Zolpidem for the Treatment of Insomnia in Schizophrenic Outpatients"

Insomnia is a highly prevalent disorder and has numerous negative effects on sufferers. Epidemiologic studies have reported that at least one-third of adults in the United States have experienced intermittent symptoms of insomnia. In addition, at least 10% of those complaining of insomnia suffer from chronic insomnia (lasting > 30 days). The negative impact on the general population is significant, but in patients with schizophrenia, these negative effects are magnified.

In patients suffering from schizophrenia, there is a direct correlation between complaints of insomnia and negative assessments of quality of life. In addition to decreased quality of life, it is known that severe insomnia is a predicting factor for psychotic decompensation or relapse following the discontinuation of antipsychotic medications. Preventing relapse of symptoms and maintaining function are two of the primary goals for the treatment of this schizophrenia. As severe insomnia has been shown to be a predictor of relapse, maintaining a healthy sleep cycle in these patients may be one of the keys to preventing relapses.

Currently there are several medications that are used to treat symptoms of insomnia in the schizophrenic population. Three of the most common medications used to treat insomnia in this population include Quetiapine, Trazodone, and Zolpidem. Low doses of the antipsychotic Quetiapine are frequently used off-label to help alleviate sleep disturbances. This practice appears to be efficacious, but is often criticized because of its high cost and lack of an FDA indication for this use. Trazodone, an antidepressant with sedating properties, is also used off-label in this population to help with insomnia. It is a much cheaper alternative to Quetiapine. Finally, Zolpidem, a sedative hypnotic is used in this population as well. It has an FDA approved indication for the treatment of insomnia, but has not specifically been studied in schizophrenic patients. Unfortunately, there is no evidence supporting the use of any of the medications mentioned earlier in the schizophrenic population. Clinicians are forced to make treatment decisions regarding insomnia in this population without the benefit of any research evidence proving efficacy.

Since the improvement of symptoms of insomnia is often tantamount to the successful treatment of schizophrenia, the purpose of this study is to compare the effectiveness of these three medications in the schizophrenic population. The study will be a double blind trial comparing the three medications, and the outcomes will be measured both objectively and subjectively. Objectively, the patients sleep cycle will be monitored by actigraph devices which will provide us with the patients' total sleep time. Subjective measures include the Pittsburgh Insomnia Rating Scale (PIRS) and the SF-36 Quality of Life Scale. The goal of the trial is to elucidate any differences in efficacy between these agents, and ultimately to improve the clinician's ability to effectively treat insomnia in schizophrenic patients.



Brent Hollenbeck, M.D., M.S., an Assistant Professor in the Department of Urology at the University of Michigan, received a 2008 Research Starter Grant in Health Outcomes.

BRENT HOLLENBECK, M.D., M.S.

University of Michigan

"Medical Expulsive Therapy for Urolithiasis: Practice Patterns and Clinical Effectiveness"

Nearly one in seven Americans will suffer from urinary stone disease. Many patients seek medical care because of pain related to their urinary stones, and over 60% of these patients will eventually require surgical treatment. Further, over half of all first-time urinary stone formers will have at least one other stone episode during their lifetime, and 3% of patients will develop chronic kidney disease because of their urinary stones. As such, urinary stone disease represents a significant public health concern. Clinical trials suggest that many patients with urinary stones in their ureters can be successfully treated with either a calcium channel blocker or an alpha blocker, thereby avoiding the expense and potential risk of surgery. These medications, used commonly to treat hypertension and benign prostatic enlargement, are collectively called medical expulsive therapy. While clinical trials suggest that medical expulsive therapy is superior to traditional conservative measures (i.e., hydration and pain management, alone), the extent to which physicians are actually using this treatment modality is unknown. This project will aim to better understand the use of medical expulsive therapy in the United States. Time trends will be measured in the use of medical expulsive therapy in U.S. emergency rooms, outpatient departments, and physician offices, employing data from two national cross-sectional surveys. These data will be used to clarify those patient and physician attributes that are associated with medical expulsive therapy use. Additionally

medical claims data from a sample of several million Americans with employer-sponsored health insurance will be analyzed to better understand how medical expulsive therapy affects the natural history of patients with urinary stones and obviates their need for surgery.

DOUGLAS STEINKE, Ph.D.

University of Kentucky

"Gender Disparities in Type 2 Diabetes Medication Utilization: A Population-Based Study Using Medicaid Data"

Type 2 diabetes or adult onset diabetes, is prevalent in the American population and increasing at an alarming rate. Physicians normally prescribe diet and exercise as a first line of treatment, however, in time, type 2 diabetes will progress to where tablets will be needed to control blood sugar levels in the body. Some studies in other chronic diseases have suggested that when prescribing medications, differences may occur between the genders. That is, male patients with diabetes may be treated more aggressively than female patients. This may occur if the physician believes that there are protective factors because of the hormone estrogen or some other factors. This study will use a large population-based database to identify the pattern of use of antidiabetic medications and characterize any differences that exist between the genders. Other variables that will be collected and analyzed include rurality and comorbidities. We will also calculate the rate that patients adhere to their prescribed medication. We will use data from the Kentucky Medicaid population from 1998 to 2006. The results from this health services research could be used to inform primary care providers of gender disparities in disease management and to give a better understanding of possible factors that influence gender disparities and prescribing in the management of type 2 diabetes mellitus.

PHARMACOLOGY

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 thirty four fellowships have been awarded under this program since it began in 1978 including the seven fellows awarded in 2008.

2008 PRE DOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY

BROOKS B. BRODRICK

University of Virginia

"Implications of Fibroblast Growth Factor Receptor 3 in Intestinal Epithelial Cell Development"

The goal of intestinal stem cell research is to understand how epithelial stem cells and/or undifferentiated progenitors maintain residency in their niche, how they avoid replicative senescence, and how they respond to genotoxic insults. Cell-matrix interactions and signals originating from mesenchymal cells below the basement membrane are likely to be important in determining and maintaining stem cell populations in the intestine. Fibroblast growth factors (FGFs) are one such family of mesenchymally derived peptide growth factors essential for normal embryonic development and a variety of morphogenic events. FGFs bind to and activate members of the fibroblast growth factor receptor (FGFR) family. It has become increasingly evident that one family member in particular, FGFR3, is important in regulating intestinal epithelial cell fate. FGFR3 is expressed on the basolateral surface of undifferentiated crypt epithelial cells during normal crypt morphogenesis in the developing mouse intestine. Mice lacking FGFR3 develop fewer intestinal crypts and have reduced crypt survival following radiation-injury suggesting that these mice have fewer clonogenic stem cells. Tcf-4/ β -catenin signaling is

known to regulate stem cell proliferation in intestinal crypts. Crypt epithelial cells in mice lacking FGFR3 show decreased levels of b-catenin protein and reduced transcription of some Tcf-4/ β -catenin target genes. These findings strongly suggest that during intestinal epithelial cell development FGFR3 regulates intracellular signaling pathways that govern cell cycle progression and cell fate determination of pluripotent stem cells and/or undifferentiated progenitors. The current project investigates how FGFR3 mediated signaling regulates morphogenic events in undifferentiated intestinal epithelial cells. The research will specifically address the signaling pathways linking FGFR3 activation to modulation of Tcf-4/ β -catenin mediated transcription in intestinal epithelial cells. These studies will provide insight into regulatory mechanisms controlling intestinal stem cell homeostasis, which will be helpful in the pursuit of new therapies for gastrointestinal diseases and intestinal injury due to other physical or chemical insults to the gut, including chemotherapies.

LAURA L. CHENEY

Stony Brook University

"Interactions Between HIV-1 and Epstein-Barr Virus Mechanisms of Abnormal Immune Activation: Implications for an HIV Vaccine and Antiretroviral Therapy"

With approximately 40 million people worldwide infected with the human immunodeficiency virus type I (HIV-1), it remains one of the most devastating epidemics recorded in human history. Much of the notoriety of HIV is derived from the immune destruction it causes. However, HIV also invokes prolonged generalized immune system activation that persists throughout the course of the disease. This is manifest in particular by production of excess inflammatory mediators and their downstream effectors. Though antiretroviral therapy (ART) has substantially improved HIV disease outcome, immune activation and inflammation remain recalcitrant to antiretroviral treatment and true immune restoration elusive. One potential factor influencing immune activation and subverting therapy is concomitant infection with Epstein-Barr virus (EBV), a ubiquitous pathogen that is best known for causing Infectious Mononucleosis. Research has shown that HIV-infected people have more EBV DNA in their blood than HIV-negative people, and higher circulating EBV-specific antibodies. In addition, in HIV-infected people the incidence and severity of EBV-associated malignancies such as Burkitt's Lymphoma—a malignancy that responds poorly to antiretroviral treatment—is higher. The current project investigates the potential interactions between HIV and EBV in concomitantly infected people. We will determine the



Brooks Broderick, University of Virginia and Stephen Fuhs, University of California, San Diego, received their 2008 Pre Doctoral Fellowship Award during the ASPET Annual Meeting in San Diego, California in April 2008.

frequency of EBV-infected B-cells and non-B cells that may be EBV reservoirs, and the balance between EBV lytically replicating and EBV lying dormant, utilizing cells isolated from three distinct HIV-positive cohorts. We will also investigate whether HIV, in particular the non-structural protein Tat, enhances EBV infectivity and EBV reactivation and replication. In turn, we will also evaluate EBV's ability to enhance HIV replication, specifically examining the role of a candidate EBV gene product and potential drug target, BRLF1. This project is also concerned with the effects their relationship may have on abnormal immune activation and inflammation. We will investigate how well the HIV-affected immune system bolstered by ART can respond to EBV antigens. In addition, we will examine how EBV-induced production of human Interleukin-10 (IL-10) or of virally-produced homologue of IL-10 may negatively influence the immune system's ability to respond to HIV and subvert the goal of complete immune restoration by ART or therapeutic immunization. Understanding how the two viruses interact and contribute to abnormal immune function can help elucidate new pathways for optimizing patient care, developing new therapeutic strategies against HIV and EBV, and an effective HIV vaccine.

STEPHEN R. FUHS

University of California at San Diego

"Compartmentation of GPCR Signaling Components in Caveolae."

It is increasingly apparent that many important signaling molecules, such as G-protein-coupled receptors (GPCRs), post-receptor signaling components (G-proteins and their effectors) as well as growth factor receptors are not uniformly expressed throughout the plasma membrane. Rather, they are enriched in membrane raft/caveolar microdomains as signaling complexes. Caveolin, a critical protein component of caveolae, serves as a scaffold for a large number of signaling molecules. This project asks two questions: 1) What is the caveolar expression and stoichiometry of signaling components of a particular pathway (e.g. GPCR-Gq-PLC- β 3)? The answer will define the least abundant (limiting) component in a particular signal transduction cascade and the organization of signaling components in a critical cellular microenvironment. 2) What determines the dynamic nature and extent of localization of signaling components in caveolin/caveolae? Our preliminary data suggest that a novel post-translational modification may play a role in the binding of signaling proteins to caveolin. Studies have been initiated to assess whether modification by SUMO (Small Ubiquitin-related Modifier), which influences protein-protein interactions and cellular localization, contributes to the regulation of caveolin's interactions. Recent evidence shows that caveolae-localized signaling components are regulated by SUMOylation (e.g. GLUT4, PTP-1b and the Type I TGF β -receptor (T β RI)). Our preliminary data shows that; caveolin non-covalently binds SUMO, caveolin co-immunoprecipitates with Ubc9 (SUMO E2 conjugating enzyme) and that caveolin may itself be SUMOylated. A growing body of literature implicates caveolins and caveolae in signal transduction pathways important for many diseases (e.g. certain cancers, diabetes mellitus, Alzheimer's and cardiovascular diseases). Elucidation of factors that regulate the localization and stoichiometry of signaling components in caveolae should have broad application and may aid in identifying novel therapies targeting these signaling pathways for these and other diseases. The studies proposed will assess SUMOylation as a previously unappreciated regulator of the physiologic and pathophysiologic role of caveolins.



Jamie O'Brien, University of Rochester, was a recipient of a 2008 Pre Doctoral Fellowship in Pharmacology/Toxicology.

MARILYN M. MOK

University of California, San Francisco

"Characterization of Sphingosine 1-Phosphate Induced $\alpha v 6$ -mediated TGF- β Activation and its Role in Pulmonary Fibrosis and Acute Lung Injury"

The lungs are among the most vital organs in the human body. Their primary function is to provide our bodies with oxygen by transporting it from the air we breathe into our bloodstream. Pulmonary fibrosis and acute lung injury (ALI) are conditions that disrupt normal lung function and, in many cases, result in death. Approximately 5 million people worldwide are affected by pulmonary fibrosis. Characterized by an accumulation of excessive scar tissue in the lungs, the condition can arise from various factors, including genetic defects and injury to the lungs from environmental toxins and certain drugs. Similarly, ALI can also arise from injury to the lungs by an array of factors. ALI has a mortality rate of 35–40% and is defined by an abundance of protein-rich fluid, which essentially drowns the organ. Unfortunately, both disorders lack effective pharmacological treatments, and the molecular processes that result in the development of these conditions remain poorly understood. Transforming growth factor beta (TGF- β), a multi-functional protein, has been implicated to play a critical role in the development of these disorders. Cells secrete this protein as a latent complex that needs to be activated before it can perform its functions. Previously, our laboratory discovered that integrin $\alpha v 6$, a protein present on the surface of certain cell types, could activate TGF- β . Furthermore, mice lacking functional 6 proteins are protected from pulmonary fibrosis and ALI, presumably, because activation of TGF- β is blocked. This suggests that 6, TGF- β , or signals that stimulate $\alpha v 6$ -mediated TGF- activa-

tion may serve as therapeutic targets for treating pulmonary fibrosis and ALI. However, the physiological and molecular signals that regulate TGF- β activation by $\alpha v 6$ are unclear. Recently, we discovered that the lipid, Sphingosine 1-Phosphate (S1P), stimulates $\alpha v 6$ -mediated TGF- activation. The proposed research aims to determine the mechanism that results in $\alpha v 6$ -mediated TGF- β activation and the role of S1P in the development of pulmonary fibrosis and ALI. The findings that result from this research will likely improve our understanding of the signals that regulate TGF- β and its bioactivity and lead to the development of new therapies to pulmonary fibrosis and ALI.

JAMIE J. O'BRIEN

University of Rochester

"Use of Small Electrophilic Prostaglandins to Enhance Platelet Production"

Bleeding due to thrombocytopenia is a critical problem that occurs during certain diseases and after myeloablative therapy for cancer. Loss of platelets can also occur after radiotherapy prior to bone marrow transplant and following a radiation terror attack. Treatments for platelet loss include platelet transfusions and administration of recombinant human Interleukin (IL)-11. However, these therapies are sometimes insufficient for disease management because of problems with infection and drug administration. Thus, the development of safe, small molecules to enhance platelet production would be advantageous for the treatment of thrombocytopenia. We report that an important lipid mediator called 15-deoxy- $\Delta 12,14$ prostaglandin J₂ (15d-PGJ₂) causes the Meg-01 cells, a human megakaryoblastic cell line, and mouse megakaryocytes, not only to mature, but also to produce more platelets. Although redox shift can regulate the development of the cells, including proliferation, differentiation, and survival, the role of reactive oxygen species in platelet production remains unclear. Many disorders associated with oxidative stress are also associated with elevated platelet number such as type-2 diabetes mellitus and atherosclerosis. We demonstrate that 15d-PGJ₂ induces reactive oxygen species (ROS) and superoxide accumulation and that incubation with glutathione reduced ethyl ester, an antioxidant, attenuates 15d-PGJ₂-induced platelet production. Collectively, these data support the concept that megakaryocyte redox status plays an important role in platelet generation. This information will be important to understanding the platelet changes that occur during chronic inflammatory diseases such as type-2 diabetes and cardiovascular disease. In addition, discovering alternative treatments for increasing platelet number will reduce the risk of life-threatening hemorrhage in thrombocytopenic patients.

JULIE H. OESTREICH, Pharm.D.

University of Kentucky

"Evaluating the Genetic Influence of P2Y12 and GP IIb/IIIa Receptor Polymorphisms on Platelet Response in Healthy Volunteers"

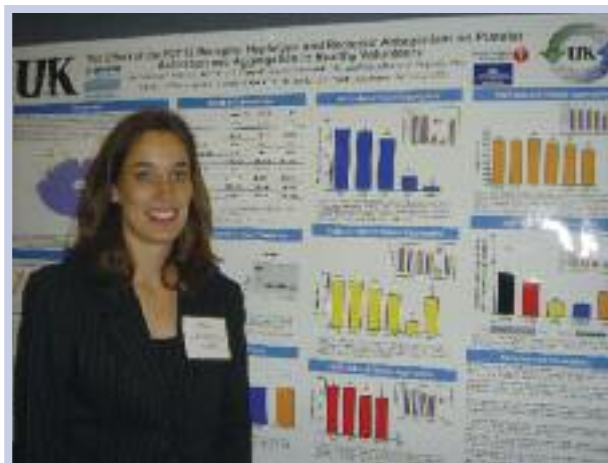
Targeting the P2Y12 receptor in platelets with clopidogrel (Plavix®) is crucial for preventing atherothrombotic events associated with vascular disease and cardiac surgery. Patient responses to clopidogrel, however, are extremely variable, and recent evidence suggests genetic variation in receptor genes may be one important factor. The purpose of our research is to examine the effect of receptor polymorphisms on platelet response in healthy volunteers. Specifically, genetic differences in the P2Y12 receptor and glycoprotein (GP) IIb/IIIa receptor are assessed by comprehensive platelet function testing. Whole blood is collected from individuals of each haplotype or genotype and evaluated for platelet receptor density, intracellular signaling of the adenosine diphosphate (ADP) pathway, platelet activation and aggregation. In addition to the study of genetic variability in healthy volunteers, the long-term research goal determines if genetic testing can be used to predict the effectiveness and safety of drugs that affect platelets, such as aspirin and clopidogrel. We hope to show that personalized genetic testing has the potential to improve medication therapy and decrease the incidence of heart attack and stroke.

MELINDA S. YATES

Johns Hopkins School of Medicine

"Molecular Mechanisms Underlying the Efficacy of a Synthetic Triterpenoid CDDO-Im, as a Cancer Chemopreventive Agent"

Synthetic triterpenoid analogues of oleanolic acid (a natural product found in rosemary and olive leaf extracts) were originally developed as anti-inflammatory agents. Later in vitro studies showed that these triterpenoids are also potent inducers of antioxidative and detoxification enzymes, suggesting that they could be effective cancer chemopreventive agents. Cancer chemoprevention is an approach which uses natural or synthetic agents to block, retard, or reverse the carcinogenic process. Mutagenesis, oxidative stress, and inflammation are important processes in carcinogenesis and are possible targets for cancer chemoprevention. The project has recently shown that the triterpenoid, CDDO-Im, is an extremely potent chemopreventive agent against aflatoxin-induced hepatic tumorigenesis in rats. This protection is achieved in part by inducing cytoprotective genes through the Keap1-Nrf2 signaling pathway. Activation of Keap1-Nrf2



Julie Oestreich, Pharm.D., at the University of Kentucky, was awarded a 2008 Pre Doctoral Fellowship in Pharmacology/Toxicology.

signaling initiates a cytoprotective response that has shown promise in both rodent cancer models and clinical trials. However, recent gene expression studies have indicated that additional signaling pathways beyond Keap1-Nrf2 signaling are also modulated by CDDO-Im treatment and may contribute to the chemopreventive activity of CDDO-Im. Global gene expression analysis using transgenic animal models combined with pharmacologic studies are being used to identify other protective mechanisms which are activated by CDDO-Im treatment. These studies will provide insight into how CDDO-Im may be used most effectively as a cancer chemopreventive agent.

Post Doctoral Fellowships in Pharmacology/Toxicology

The P/RMA 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 purpose (intent) of this program is to support post doctoral career development activities of individuals prepared (or 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.

2008 POST DOCTORAL FELLOWSHIPS IN PHARMACOLOGY/TOXICOLOGY

PAULIANDA J. JONES, Ph.D.

Vanderbilt University Medical Center

"Activation of Group II mGlu Receptors by Agonists and Positive Allosteric Modulators for Anxiety Disorders."

Anxiety disorders affect an estimated 40 million people in the United States each year and are characterized by increased feelings of fear and uncertainty, ultimately leading to a decreased quality of life. Despite the availability of therapeutic agents such as antidepressants, anxiolytics, and beta-blockers to treat anxiety disorders, a considerable proportion of patients suffer from physical dependence, ataxia, withdrawal-induced axiogenic rebound, motor and cognitive impairment, and sedation. Recent anatomical, cellular, molecular, and behavioral studies suggest that activators of group II metabotropic glutamate receptors (mGlu2 and mGlu3) could provide a novel approach for the treatment of anxiety disorders. Consistent with this, new clinical studies reveal efficacy of group II mGlu agonists in treatment of panic attacks and generalized anxiety disorder (GAD). However, group II mGlu agonists activate both mGlu2 and mGlu3, and the relative contributions of these two receptor subtypes to the actions of these drugs are not known. Finally, development of tolerance to direct agonists has the potential of limiting their clinical use. Thus, there is a critical need to build on these exciting advances by determining whether a specific group II mGlu receptor subtype is responsible for these effects and developing novel approaches for activating these receptors. Two groups have now identified two novel structural classes of selective allosteric potentiators of mGlu2, LY487379 and BINA. These small molecules do not activate the mGlu receptors directly but act at an allosteric site on the receptor to potentiate glutamate-induced activation of the receptor. The hypothesis that mGlu2 receptor potentiators will potentiate electrophysiological effects of group II mGlu agonists in the amygdala, a brain region thought to be important for potential anxiolytic effects of these compounds, has not been determined. Furthermore, recent behavioral studies confirm that the effects of mGlu2 potentiators have similar in vivo activity as group II mGlu agonists in classical animal models of anxiety, suggesting that activation of mGlu2 rather than



In San Diego, California during the ASPET Annual Meeting, Paulianda Jones, Ph.D., Vanderbilt University and Karen Kassel, Ph.D., University of North Carolina at Chapel Hill, received their 2008 Post Doctoral Fellowship in Pharmacology/Toxicology Award.

mGlu3 is important for these anxiolytic effects. Also, it is not known whether group II mGlu receptor agonists and mGlu2 potentiators will induce the same level of receptor desensitization and tolerance after chronic administration. This current study utilizes a series of electrophysiological and behavioral techniques to determine the effects of BINA on activation of group II mGlu receptors in the amygdala. This project also aims to determine whether group II mGlu receptor agonists and BINA differ in their propensity to induce desensitization and tolerance after chronic administration in the elevated plus maze and fear potentiated startle models of anxiety.

KAREN M. KASSEL, Ph.D.

University of North Carolina at Chapel Hill

"Effects of Thiazolidinediones on p38 and ERK1/2 Phosphorylation in Cardiac Myocytes"

Diabetes is a disease in which the body either does not produce insulin or does not properly use insulin, and in turn the body is unable to appropriately use sugars and starches from food to provide energy. Approximately 7% of the US population has been diagnosed with diabetes, of which 90% or more have type II diabetes. Thiazolidinediones (TZDs) are used extensively in the treatment of type II diabetes to regulate lipid metabolism and insulin sensitivity. Diabetes is associated with many additional health concerns, including

heart disease and stroke. Some studies have suggested that TZDs may be associated with an increased risk of developing cardiovascular diseases, which is a great concern for diabetic patients already at a higher risk for these diseases. Previous studies have shown that TZDs stimulate stress responses in liver epithelial cells. If TZDs also activate stress responses in other cells, such as cardiac cells, this could contribute to some of the side effects of these drugs. The purpose of this research project is to determine if TZDs stimulate stress responses in cardiac myocytes and to delineate the signaling pathways that are activated in response to TZDs that mediate the stress responses in these cells. The two stress responses that will be investigated are endoplasmic reticulum stress leading to p38 phosphorylation and oxidative stress leading to ERK1/2 phosphorylation. Determining the role of TZDs in activating these stress responses will help us better understand the mechanisms through which TZDs increase cardiac toxicity in diabetic patients.

Research Starter Grants in Pharmacology/Toxicology

The purpose of the P/RMA Foundation Research Starter Grants is to offer financial support to individuals beginning their independent research careers at the faculty level. The program provides a research grant of \$30,000 per year for up to two years. The “starter” aspect of the program strives to assist those individuals who are establishing careers as independent investigators. The program is not offered as a means to augment an ongoing research effort.

The first Research Starter Grant awards were made in 1972; and a total of six hundred and thirteen have been awarded, including the grants beginning on January 1, 2008.

2008 RESEARCH STARTER GRANTS IN PHARMACOLOGY/TOXICOLOGY

ANDREA H. BILD, Ph.D.

University of Utah

“Epigenetic changes in breast cancer phenotypes and potential therapeutic intervention strategies”

One main challenge of cancer research is how to translate the findings obtained with defined cell culture manipulations *in vitro* to the complex behaviors of human cancers *in vivo*. We and other investigators have recently shown a linkage can be established through the common language of a “gene signature” (1–9). This “signature” consists of a set of genes whose expression levels are altered by perturbations *in vitro*

and indicative of an oncogenic state of human cancers *in vivo*. This gene signature can be thought of a “common phenotype” shared by experimental cell culture and patient tumors.

Patients who are most likely to benefit from these targeted therapeutics can then be recognized by high expression of the relevant gene signatures in their tumors. Great synergy and novel biological insight can be obtained by reciprocal flow of information between the *in vitro* and *in vivo* systems. It is this synergy that will be essential in dissecting the genetic and epigenetic aberrations that drive the complexity of breast cancer.

In this proposal we plan to use this conceptual framework to define the epigenetic changes underlying breast cancer phenotypes. While epigenetic changes, like genetic alterations, may arise at any stage of tumor development, it is increasingly apparent that many chromatin-mediated abnormalities appear well before invasive cancer, as well as during tumor progression (10–14). These studies highlight the contribution of epigenetic changes to tumorigenesis, and places epigenetic changes as possible seminal events for tumor initiation, and precursors for specific tumor phenotypes. Specifically, DNA methylation and histone deacetylation have been shown to be central to the aberrant epigenetics of cancer (10–13, 15, 16). *We hypothesize that epigenetic processes underlie the heterogeneity of breast cancer sub-phenotypes.* In this proposal, we plan to use gene expression signatures of histone deacetylase (HDAC) and DNA methyltransferase (DMNT) pathways to uncover their role in driving breast cancer phenotypes. Further, we will use this information to identify relevant small molecule therapies targeting HDAC and DMNT pathways and link them to individual subsets of patients.

PIETER C. J. DORRESTEIN, Ph.D.

University of California, San Diego

“Unraveling the Therapeutic Potential of Marine Organisms”

Large proportions of today’s commercial drugs have origins in natural products (60–75%) and therefore represent an important class of molecules. Penicillin, Vancomycin (antibiotics) and the immunosuppressant agent Rapamycin are just a few examples of such natural products. From sequenced microbial genomes it has become evident that as much as 90% of genes that may produce these natural products are orphan. This suggests that these organisms have the metabolic potential to produce additional natural products with good therapeutic properties. We currently do not have many good strategies to harvest this biotherapeutic potential. The Dorrestein lab will utilize mass spectrometry, including proteomic approaches and MALDI-imaging based tools to begin elucidating the functions of a subset of orphan gene



Dr. Pieter Dorrestein from the University of California, San Diego, was awarded a Research Starter Grant in Pharmacology/Toxicology at the ASPET Annual Meeting in April 2008.

clusters from marine microorganisms (called actinomycetes). This approach emphasizes the discovery of the natural products encoded by orphan non-ribosomal peptides synthetase (NRPS) gene clusters that produce serine or cysteine protease inhibitors. Based on bioinformatic analysis, it is anticipated that these clusters isolated from actinomycetes will produce natural products that are related to aldehyde peptide inhibitors. To date, every aldehyde peptide isolated from natural sources has proven to be an inhibitor of important cellular pathways and a good lead compound in drug discovery programs. Such inhibitors have been shown to inhibit therapeutically important targets such as the proteasome, cathepsins or caspases. This project aims to use novel mass spectrometric approaches to discover a new set of aldehyde containing peptides that are predicted to be encoded by orphan NRPS gene clusters. Once a new inhibitor has been identified and synthesized semi-synthetically using a combination of chemical and enzymatic approaches, they will be screened for anti-tumor, anti-microbial and related therapeutic properties. In addition to harvesting these orphan

gene clusters for their therapeutic potential, the aim is to identify the target of these inhibitors using MALDI-imaging and proteomic approaches. The long-term goal is to develop general mass spectrometry based methodologies that can be used to unravel the biotherapeutic potential of most natural product producing orphan genes.

PIYALI DASGUPTA, Ph.D.

Marshall University

" α 7- Nicotinic Receptor Signaling in Non-Small Cell Lung Cancer"

Cigarette smoking is strongly correlated with the onset of lung cancer. About 60% of non-small cell carcinomas (NSCLC) are associated with smoking. Nicotine, an active component of cigarettes, has been found to induce proliferation of lung cancer cell lines. In addition, nicotine can induce angiogenesis and confer resistance to apoptosis. All these events are mediated through the nicotinic acetylcholine receptors (nAChRs), and nAChRs have been detected in a variety of non-neuronal cells, such as lung cancer cells. Studies in the laboratory are focused on signaling pathways recruited by tobacco components like nicotine and NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone] which facilitate the proliferation and progression of NSCLCs. Preliminary studies show that nicotine and NNK interact with nAChRs on lung cancer cells in subunit-specific manner to mediate proliferative versus anti-apoptotic signals. In particular, lab data would implicate the α 7-nAChR in the proliferative and pro-angiogenic activity of nicotine in lung cancer cells. One major project involves studying the effect of chronic nicotine exposure on the expression and signaling of α 7-nAChR. Studies in neuronal systems have shown that exposure to nicotine can upregulate a variety of nAChR subunits, which have been thought to contribute to nicotine dependence and addiction. However, the effect of nicotine exposure on α 7-nAChR expression in NSCLC cells is not known. It is believed that sustained exposure to nicotine upregulates the expression of α 7-nAChR on the tumor, as well on adjoining blood vessels, thereby facilitating the growth and neovascularization of the lung tumors. Such studies are especially relevant to human health because about 30% of lung cancer patients continue to smoke after diagnosis and many others use nicotine-based cessation devices, which could potentially exacerbate the progression of lung cancer in patients. Research will reveal novel mechanisms describing how nicotine and nAChRs affect the growth and the progression of NSCLC, as well as foster the development of new therapies for this disease.



The Paul Calabresi Medical Student Fellowship was presented to Sonya Tang, Johns Hopkins University School of Medicine, at the 2008 ASCPT Annual Meeting in Orlando, Florida, pictured here with Del Persinger.

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 sixty eight 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 P/RMA Foundation as a committee Chairman and member for 25 years.

2008 PAUL CALABRESI MEDICAL STUDENT FELLOWSHIPS

JULIA MCHUGH

Vanderbilt University

"Pressor Effect of Water"

Although physiology textbooks do not mention water ingestion as a pressor stimulus, this phenomena was unexpectedly found to occur under certain circumstances. For example, acute ingestion of 16 ounces of water exerts a robust pressor response in patients with autonomic dysfunction and to a lesser degree in older normal subjects, averaging 40 mmHg with occasional increases of 100 mmHg. Since these initial observations, effects of water ingestion have also been

reported in normal young subjects, in patients with hypertension, and in individuals with neurally mediated syncope. However, little is known about the mechanism by which water exerts this effect. The magnitude of the response suggests that water may be involved in an unrecognized mechanism involving cardiovascular regulation both in health and disease. The physiological basis underlying water's effect, or how glucose and sodium content in water might effect the response is not yet understood. Nor is it known if the response is mediated within the gut, in the portal circulation or in the liver. Murine models often prove to be powerful tools in the study of mammalian physiology. Particularly useful are the many available gene deletions engineered in the mouse. A mouse model has been recently developed that mimics human autonomic dysfunction and will be an important tool in elucidating this unexpected effect of water ingestion. Current studies are aimed at determining the mechanism of water's pressor effect, the location of the response, and the potential therapeutic value of water.

SONYA C. TANG

Johns Hopkins University School of Medicine

"The Search for Topoisomerase Poisons Targeting Trypanosoma brucei"

Human African Trypanosomiasis (HAT) is 100% fatal when left untreated. Caused by the parasite, *Trypanosoma brucei* (T. brucei), HAT affects 300,000-500,000 persons each year in sub-Saharan Africa. Victims of the disease are often not diagnosed until the neurological stage, during which they experience confusion and disturbance of the sleep cycle. There are only four approved treatments for HAT, according to the World Health Organization (WHO) and all of them are antiquated; many of them are currently facing treatment failure and half of them are unable to cross the blood-brain barrier to treat patients whose disease has progressed into the neurological stage. In view of these problems, new drugs against T. brucei are in demand. Topoisomerases, enzymes that cleave and rejoin DNA strands to remove knots, separate interlocked strands or change the tightness of the strands, have already presented themselves as drug targets in cancerous cells, which rely on the enzymes for DNA replication during cell proliferation. The mitochondrial DNA network (kDNA) in T. brucei is a network of interlocked circular DNA molecules that is topologically complex and its replication requires topoisomerases that are specific to the parasites' mitochondria. Having no homologs in human cells, these mitochondrial topoisomerases would be ideal targets for pharmacologic agents. To understand topoisomerases in T. brucei better, the relationship between the seven T. brucei topoisomerases will



David Alonzo from Purdue University was awarded a 2008 Pre Doctoral Fellowship in Pharmaceutics.

be studied using RNA interference. In addition, experiments to determine the mechanism of pentamidine, a drug currently used in the treatment of HAT that acts in accordance with known topoisomerase poisons, will be done. To identify new topoisomerase poisons, drug screens against the *T. brucei* mitochondrial topoisomerase IA (TbTOPIAmt) will be conducted.

PHARMACEUTICS

Pre Doctoral Fellowship in Pharmaceutics

This program has been in effect for 19 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. Seven fellowships were granted in 2008.

2008 PRE DOCTORAL FELLOWSHIPS IN PHARMACEUTICS

DAVID ALONZO

Purdue University

"Crystallization Inhibition of Supersaturated Solutions"

There is an increasingly strong need in the pharmaceutical industry for creative solubilization strategies. This need originates from the fact that many compounds with therapeutic targets lack enough intrinsic solubility to provide adequate bioavailability for therapeutic effectiveness. One way of circumventing solubility challenges is to formulate insoluble compounds as amorphous solid dispersions. The benefit to this strategy is that amorphous materials exist in a higher energy state than their crystalline counterparts and as a result can generate supersaturated solutions for finite periods of time. The downside to this strategy is that this increase in apparent solubility leads to a solution that will be either metastable or unstable. This instability can result in precipitation of the drug to a crystalline form. If this recrystallization happens over a relatively short period of time, the strategy is essentially rendered ineffective. It is well known that the presence of impurities in a solution have the potential to inhibit crystallization. Polymers can have this effect through inhibition of crystal nucleation and/or crystal growth. It is thought that polymers effective at inhibiting crystallization do so through adsorption onto the nuclei or crystal faces. This adsorption process can take place via several possible mechanisms including non specific van der Waals attraction forces as well as specific hydrogen bonding interactions. While it appears that inhibition of crystal growth is the dominant mechanism, nucleation inhibition may also be important. The goal of this project is to obtain an understanding of the fundamental interactions between model compounds and polymers in solution. This knowledge will provide insight into how amorphous solid dispersions can be rationally designed so that the supersaturation generated is maintained long enough to translate into an effective increase in bioavailability. Current studies of model systems include investigations of the influence of polymeric additives on solution concentration-time profiles and crystal growth rates in addition to screening the relative effectiveness of various polymers at inhibiting crystallization. Information from these studies will provide a starting point for further investigation into the specific mechanisms underlying these phenomena.

BROOKE S. BARRETT

University of Kansas

"Development of a Protective Vaccine against *Shigella flexneri*, *Salmonella Typhimurium*, *Burkholderia Pseudomallei*, *Yersinia Enterocolitica*, and *Pseudomonas Aeruginosa*"

The goal of this work is to develop a series of vaccine candidates for a group of severely virulent pathogens including: *Shigella flexneri*, *Salmonella typhimurium*, *Burkholderia pseudomallei*, *Yersinia enterocolitica*, and *Pseudomonas aeruginosa*. These bacteria share a common host invasion mechanism which utilizes a type three secretion system (TTSS). The TTSS is a specialized supramolecular injectosome composed of 25 or more proteins which form basal and extracellular domains, and share gross architectural similarities with bacterial flagella. The extracellular component, commonly referred to as the "needle complex," is primarily composed of 120 copies of a single monomeric subunit organized in a helical array around a central pore which protrudes from the bacterial membranes. This appendage serves as a promising vaccine candidate due to its surface exposure prior to pathogenic infection, and thus, we focus on formulations of the major protein subunit of the needle complex from each of the five bacteria. Work includes a complete biophysical characterization of each of the monomeric proteins, formulation optimization, real time and accelerated stability studies, and immunogenicity testing in mice. Additionally, in an effort to elicit a more immunogenic response, formulations of the oligomerized proteins will also be carried through formulation development and evaluated in mice.

KRISTIN E. COAN

University of California, San Francisco

"Pharmaceutics Pathway Characterization of Promiscuous Small Molecule Aggregates"

High-throughput screening, a dominant method for the discovery of new drugs, is plagued by the presence of false positive hits. These molecules appear promising in initial screens; however, upon further analysis they provide no useful drug candidates, representing a significant waste of time and money. Previous work suggests that a major contributor to this problem is promiscuous inhibition by small molecule aggregation. Here, drug-like molecules aggregate to form particles several hundred nanometers in diameter. These aggregates have the surprising property of non-specifically binding and inhibiting enzymes, causing false positives in inhibitor screens. These "aggregators" are common in screening libraries, and are also found among common biological



On November 16, 2008 at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting in Atlanta, Georgia, the PhRMA Foundation Pharmaceutics Awards were presented. Pictured from left to right are Eileen Cannon, Jennifer Fiegel, Ph.D., University of Iowa, Martin Telko, University of North Carolina at Chapel Hill, and William Proctor, University of North Carolina at Chapel Hill.

reagents and even marketed drugs. Despite their prevalence, little is known about the aggregates themselves or their mechanism of action. This project will explore the physical characteristics and mechanism of inhibition of promiscuous aggregates using standard biochemical techniques as well as light scattering, flow cytometry and mass spectrometry. Initial experiments have suggested that aggregates may be stable in vivo and given the frequent occurrence of these molecules amongst potential and even known drugs, further characterization of these particles is essential for understanding how they might behave in vivo. This proposal aims to investigate the stability, dynamics, structure, and mechanism of these novel particles to determine their relevance to drug delivery as well as drug discovery.

STEPHEN D. GOLDMAN

University of Kansas

"Intracellular Lipid Trafficking Disorders Resulting from Lysosomal Sequestration of Hydrophobic Amines"

The goal of this project is to explore a potentially life-threatening side effect of drugs that may result from competitive interactions between certain drugs and endogenous lysosomal cholesterol for binding with the soluble intra-lysosomal protein Niemann-Pick C2 (NPC2). NPC2 is known to tightly bind endocytosed cholesterol in the lumen of lysosomes and transport it to the limiting organelle membrane where it is transported throughout the cell. Mutations in NPC2 disrupt its ability to efficiently bind and transport cholesterol and are known to cause the rare but deadly lysosomal lipid storage



Stephen Goldman from the University of Kansas received a Pre Doctoral Fellowship in Pharmaceuticals in 2008.

disorder Niemann-Pick type C (NPC) disease. Considering the fact that many hydrophobic amines are known to extensively accumulate in acidic intracellular compartments such as lysosomes by an ion trapping mechanism, it is likely that the concentration of an amine could exceed that of cholesterol by several orders of magnitude. This exceedingly high concentration of amines could allow them to effectively disrupt the cholesterol-NPC2 interaction, even if the amines binding affinity with NPC2 is relatively weak. The work described in this application involves purification of recombinant NPC2 and evaluation of binding affinities with cholesterol and several hydrophobic amine containing drugs. The concentration of such amines in lysosomes following exposure to cells at therapeutically relevant concentrations will also be determined. These results can provide the ability to predict which drug molecules have the highest likelihood of producing the NPC disease phenotype and will provide invaluable insight into a unique and potentially deadly side-effect of drugs.

WILLIAM R. PROCTOR

University of North Carolina at Chapel Hill

"Mechanisms Underlying Saturable Intestinal Absorption of Metformin"

The processes by which many marketed drugs are absorbed across the intestinal epithelium are not well understood. This is particularly true for many hydrophilic cationic drugs whose oral absorption would be predicted to be quite poor based on their physicochemical properties. This discrepancy suggests involvement of transcellular carrier-mediated transport processes and/or facilitated diffusion through the tight junctions and the paracellular space. The work proposed here focuses on the mechanisms of intestinal absorption of one of the most highly prescribed drugs, Metformin. It has been shown in the clinic to have lower oral bioavailability at higher doses, suggesting the involvement of saturable carrier-mediated processes in its intestinal absorption, although the exact mechanism is unknown. Preliminary data the intestinal cell model, Caco-2 cell monolayers, revealed that Metformin traverses the cell monolayers predominantly via the paracellular route, and yet the transport is saturable. The saturable paracellular mechanism is believed to involve facilitative diffusion aided by electrostatic interactions between positively charged Metformin and anionic residues in the extracellular loops of claudins, a protein family responsible for the barrier properties of tight junctions. The hypothesis to be tested is that the intestinal absorption of Metformin is influenced by absorptive uptake and efflux transporters as well as a novel paracellular facilitative diffusion mechanism. The first aim of the proposed work is to ensure that the results on Metformin transport obtained in the Caco-2 cell model represent the transport mechanisms in human intestinal tissue. Secondly, the novel saturable paracellular transport mechanisms will be examined using modified cell lines expressing varying wild-type and mutated claudins. The work proposed here will lead to the elucidation of the mechanisms underlying the intestinal absorption of small hydrophilic cationic drugs such as Metformin, and will allow prediction of the potential drug-drug interactions with Metformin, currently one of the most widely prescribed drugs on the market.



Martin Telko, University of North Carolina at Chapel Hill, received a 2008 Pre Doctoral Fellowship in Pharmaceutics.

KAREEN RIVIERE

University of California, San Francisco

"Targeted Liposomal Delivery of Synergistic Anti-Cancer Drug Combinations"

Combination therapies are essential to treat life-threatening diseases, such as cancer and HIV/AIDS. The underlying principle is that multiple drugs can act against diverse targets to better treat a disease. Drug combinations that "synergize" are especially effective, have the potential to reduce drug toxicity, and can minimize the development of drug resistance. Synergy occurs when the combined effect of two or more drugs is greater than additive. Since synergism is dependent on the ratio of the combined drugs, synergistic drug combinations must be maintained at fixed ratios in order to achieve the maximum therapeutic effect in vivo. This requirement is clinically challenging because it can be difficult to control the pharmacokinetic properties of multiple drugs in a manner

that allows them to reach target cells at the optimal ratio. We hypothesize that targeted liposomes can enhance the efficacy of synergistic anti-cancer drug combinations in vivo by facilitating the intracellular delivery of these agents at their synergistic ratio. The current project aims to: identify synergistic combination of anti-cancer drugs in cancer cell lines that over-express the folate receptor (FR), optimize the in vitro synergism of the drug combinations with liposomes that target specifically to these FR over-expressing cell lines, and determine the therapeutic efficacy of the targeted liposomal drug cocktails in murine models of the FR over-expressing tumors. These studies may illustrate an improved way to translate in vitro synergism results to animal models and humans, and provide an effective approach for delivering synergistic drug combinations to successfully treat cancer and other life-threatening diseases.

MARTIN TELKO

University of North Carolina at Chapel Hill

"Electrostatic Charging Phenomena in Dry Powder Inhalers and Their Effect on Deposition"

Airborne particles are subject to a number of forces of interaction. The behavior of aerosol drug particles has been studied extensively; however, the importance of electrical charge on their behavior and application is poorly investigated and understood. The aims of the research are to evaluate the fundamental charge properties of aerosols and relate them to the effectiveness of delivery which has implications for the treatment of local and systemic disease following pulmonary administration. Particle charging is already being used in a number of industries to bring about specific particle behavior. Charge may be a design advantage for medicinal aerosols as well. It is postulated that charge is a major factor in drug delivery from dry powder inhalers (DPIs) and that its control can be utilized to maximize DPI performance. Furthermore, it is proposed that the charging characteristics of a pharmaceutical material are related to surface free energy and can thus be determined a priori. Using a combination of techniques the charging characteristics of DPI discharge will be investigated, contributors to the phenomenon identified and effects quantified. Charging propensity will be correlated with material surface properties, and the effects on delivery quantified and optimized.

Research Starter Grants in Pharmaceuticals

The purpose of P/RMA Foundation Research Starter Grants is to offer financial support to individuals beginning their independent research careers at the faculty level. The program provides a research grant of \$30,000 per year for up to two years. The “starter” aspect of the program strives to assist those individuals who are establishing careers as independent investigators. The program is not offered as a means to augment an ongoing research effort.

2008 RESEARCH STARTER GRANTS IN PHARMACEUTICS

JENNIFER FIEGEL, Ph.D.

University of Iowa

"Development of Dry Powder Aerosols to Disperse and Eradicate *Pseudomonas Aeruginosa* Infections in the Lungs"

Pseudomonas aeruginosa biofilms, organized bacterial colonies protected by a slimy matrix, form in the respiratory tract of compromised human hosts and cause serious, chronic infections that the immune system and common therapies cannot eradicate. The dispersal of biofilm-forming bacteria from their protected environment may enable the utilization of traditional antibiotics for effective pathogen killing. Therefore, the goal of the proposed research is to develop a novel aerosol drug delivery system that effectively and safely eliminates respiratory biofilms. An inhalable delivery system will be developed that combines an antibiotic treatment with a dispersion compound to break up the biofilm matrix. Dry powder aerosols will be optimized for high dispersibility from



Pieter Dorrestein, Ph.D., in his lab at the University of California, San Diego with his daughter, Tatiana. Dr. Dorrestein was awarded a Research Starter Grant in Pharmacology/Toxicology in 2008.

a simple hand-held inhaler, efficient deposition in the lungs, high drug loading and drug stability. The role of key physico-chemical aerosol properties on the dispersion and viability of bacterial biofilms will be assessed. Upon its completion, this study will have evaluated the ability of these co-delivery systems to improve bacterial killing and the utility of dispersing the bacterial biofilms while delivering antibiotics effective against *P. aeruginosa* suspension cultures. This project will lay the groundwork for clinical development of co-delivery systems for treatment of opportunistic infections of the lungs.

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BELIEF IN A MISSION...

The PhRMA Foundation is lastingly indebted to a cadre of PhRMA Board members who despite uncommon demands on their time through the nature of their jobs have given more than three decades of faithful and sagacious service. They have done so, plainly, because they believed in what the Foundation was doing, and they believed in its potential for even greater performance in an essential mission.



Treasurer's

REPORT



The P/RMA Foundation ended 2007 in sound financial shape and increased the reserve funds. Contributions were down 5% from the previous year, to \$3.2 million. We awarded approximately \$1.81 million in grants and held down non-grant program and administrative expenses. Total expenditures, at \$2.44 million, were \$94,500 below budget. Total net assets at December 31 were \$14.4 million, a 14.3% increase from \$12.6 million the prior year. Of this amount, \$3.1 million represents funds authorized but not yet paid for the future years of grants already awarded. Most of the increase in net assets is attributable to nearly \$772,000 in investment gains and interest income, and \$776,000 in operating surplus. We did not need to transfer funds from reserves (the Future Commitment Fund) to cover payment this year of awards granted in previous years. Financial details are

shown in the accompanying Statement of Income and Expenditures.

For 2008, contributions are estimated at \$2.57 million. 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 need

the 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, 2007, has been audited by the Rosslyn, Virginia, accounting firm of Buchanan & Company. A full report can be obtained by contacting the Foundation.

A handwritten signature in black ink, appearing to read 'G. Neil', written over a light gray background.

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Biochemistry
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Lexington, Kentucky

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Chairman and Professor
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Microbiology and Immunology
University of Medicine &
Dentistry of New Jersey
Robert Wood Johnson Medical School
Piscataway, New Jersey

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Senior Vice President & Franchise Head,
Neuroscience
Merck Research Laboratories
North Wales, Pennsylvania

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Pfizer Global Research & Development
Pfizer Inc
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Rutgers, The State University of New Jersey
Piscataway, New Jersey

PhRMA FOUNDATION

Programs for 2009

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 budgeted/ 2 years	\$80,000 total \$20,000 per award per year	October 1, 2008 December 15, 2008 January–August
Post Doctoral Fellowship in Health Outcomes (2002)	1 budgeted/ 2 years	\$80,000 total \$40,000 per award per year	October 1, 2008 December 15, 2008 January–December
Sabbatical Fellowship in Health Outcomes (2002)	1 budgeted/ 1 year	\$40,000 total \$40,000 per award per year	October 1, 2008 December 15, 2008 January–December
Research Starter Grants in Health Outcomes (2002)	3 budgeted/ 2 years	\$180,000 total \$30,000 per award per year	October 1, 2008 December 15, 2008 January 1, 2009
INFORMATICS ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Informatics (2008)	2 budgeted/ 2 years	\$80,000 total \$20,000 per award per year	September 1, 2008 December 15, 2008 January–August
Post Doctoral Fellowship in Informatics (2002)	1 budgeted/ 2 years	\$80,000 total \$40,000 per award per year	September 1, 2008 December 15, 2008 January–December
Sabbatical Fellowship in Informatics (2002)	1 budgeted/ 1 year	\$40,000 total \$40,000 per award per year	September 1, 2008 December 15, 2008 January–December
Research Starter Grants in Informatics (2002)	3 budgeted/ 2 years	\$180,000 total \$30,000 per award per year	September 1, 2008 December 15, 2008 January 1, 2009
BASIC PHARMACOLOGY ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Pharmacology/Toxicology (1978)	6 budgeted/ 2 years	\$240,000 total \$20,000 per award per year	September 1, 2008 December 15, 2008 January–August
Post Doctoral Fellowships in Pharmacology/Toxicology (2002)	2 budgeted/ 2 years	\$160,000 total \$40,000 per award per year	September 1, 2008 December 15, 2008 January–December
Sabbatical Fellowship in Pharmacology/Toxicology (2002)	1 budgeted/ 1 year	\$40,000 total \$40,000 per award per year	September 1, 2008 December 15, 2008 January–December
Research Starter Grants in Pharmacology/Toxicology (1972)	3 budgeted/ 2 years	\$180,000 total \$30,000 per award per year	September 1, 2008 December 15, 2008 January 1, 2009

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
CLINICAL PHARMACOLOGY ADVISORY COMMITTEE			
Paul Calabresi Medical Student Research Fellowships (1974)	2 budgeted/ 6 months up to 2 years	\$36,000 total \$18,000 per award	September 1, 2008 December 15, 2008 July 1, 2009
Faculty Development Award in Clinical Pharmacology (1966)	2 budgeted/ 2 years	\$240,000 total \$120,000 per award per year	April 1, 2009 June 1, 2009 July 1, 2009
PHARMACEUTICS ADVISORY COMMITTEE			
Pre Doctoral Fellowships in Pharmaceutics (1987)	2 budgeted/ 2 years	\$80,000 total \$20,000 per award per year	October 1, 2008 December 15, 2008 January–August
Post Doctoral Fellowships in Pharmaceutics (1992)	2 budgeted/ 2 years	\$160,000 total \$40,000 per award per year	October 1, 2008 December 15, 2008 January–December
Sabbatical Fellowship in Pharmaceutics (2002)	1 budgeted/ 1 year	\$40,000 total \$40,000 per award per year	October 1, 2008 December 15, 2008 January–December
Research Starter Grants in Pharmaceutics (1972)	2 budgeted/ 2 years	\$120,000 total \$30,000 per award per year	October 1, 2008 December 15, 2008 January 1, 2009

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

STATEMENT OF Income and Expenditures

For the Year Ended December 31, 2007

INCOME

Contributions	\$3,240,886
Contributions – in kind from PhRMA	\$ 158,260
Interest and Dividends	\$ 429,639
(Realized and Unrealized) Gains in Securities	\$ 342,290
Other Income	\$ 46,045
TOTAL INCOME	\$ 4,217,120

EXPENDITURES

Programs

Awards in Excellence	\$ 15,295
Clinical Pharmacology Program	\$ 304,000
Health Outcomes Program	\$ 252,000
Informatics Program	\$ 260,000
Pharmaceutics Program	\$ 235,000
Pharmacology Programs	\$ 736,700
AFPE Fellowship Award	\$ 7,500
Other Grants	\$ 0

<i>Subtotal – Grants</i>	\$ 1,810,495
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Other

Committee Meetings, Travel and Honoraria	\$ 64,684
Publications and Special Projects	\$ 77,212

<i>Subtotal – Other</i>	\$ 141,896
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PROGRAM TOTAL	\$ 1,952,391
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ADMINISTRATIVE

Staff, Taxes, Depreciation & Insurance	\$ 272,097
Rent & PhRMA Accounting Services ¹	\$ 158,260
Professional Services and Investment Expenses	\$ 42,205
Office Expenses	\$ 12,821

TOTAL ADMINISTRATIVE	\$ 485,383
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TOTAL EXPENDITURES	\$2,437,774
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¹ Rent and Accounting Services are donated by PhRMA

PhRMA FOUNDATION

Staff



DEL PERSINGER
President and Chief Executive Officer



EILEEN CANNON
Executive Director



CHARLOTTE LILLARD
Associate

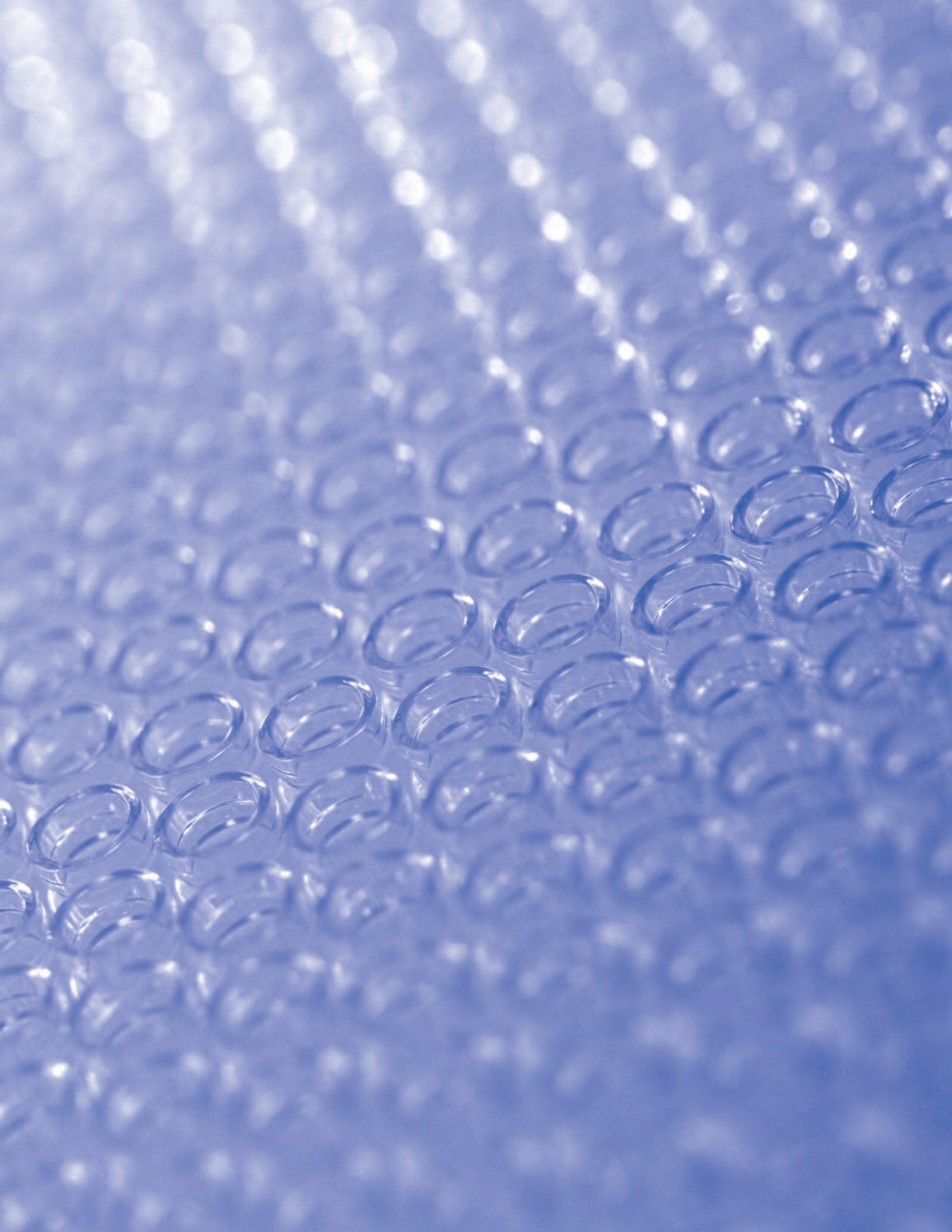
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The *Ph*RMA Foundation owes its success to the pharmaceutical companies that have provided their generous support over the past 43 years. We thank all of you for continuing to invest in the future of pharmaceutical research and the scientists of tomorrow.

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ETHICAL CONSIDERATIONS The Scientific Advisory Committee as well as the program advisory committees of the *Ph*RMA 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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