

Welcome to ASPET!



**New ASPET Executive
Officer Judith Siuciak**

In this issue:

- Introduction to new Executive Officer *Judith A. Siuciak, Ph.D.*
- Message from new President *Richard R. Neubig, M.D., Ph.D.*
- Information for ASPET Annual Meeting at EB 2014
- ASPET membership survey results
- The Case of Elizabeth Hughes: Juvenile Diabetes at the Dawn of Insulin by *Rebecca J. Anderson, Ph.D.*
- MAPS Annual Meeting program information
- Great Lakes Chapter Meeting abstracts (online only)

Contents

NEWS

President's Corner	135
Message from the New Executive Officer	136
ASPET Annual Meeting at EB 2014	137
Important Information	137
Annual Meeting Program	137
Travel Award Information	148
GI Club and IUPHAR GI Section at EB 2013	148
Membership Survey Results	150
Bylaws Change Approved	152
ASPET Committees 2013-2014	153

FEATURE

The Case of Elizabeth Hughes: Juvenile Diabetes at the Dawn of Insulin <i>by Rebecca J. Anderson, Ph.D.</i>	156
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DEPARTMENTS

Career Center	161
Journals	162
Science Policy	165
Postdoc Corner <i>by Joanna K. Sandilos Rega, Ph.D. and Uyen B. Chu, Ph.D.</i>	166
Social Media	168
Book Review: <i>Hallucinations</i> , <i>reviewed by Christine K. Carrico, Ph.D.</i>	169
In the Spotlight: Interviews with ASPET Members	170
Members in the News	173
Staff News	175
New ASPET Members	176
In Sympathy	178
Obituary: Toshio Narahashi <i>prepared by Bill Atchison, Ph.D.</i>	178
Obituary: William L. Woolverton	179
Division News and Committee Lists	
Behavioral Pharmacology	180
Cardiovascular Pharmacology	181
Drug Discovery and Development	182
Drug Metabolism	182
Integrative Systems, Translational and Clinical Pharmacology	182
Molecular Pharmacology	184
Neuropharmacology	184
Pharmacology Education	185
Toxicology	186
Chapter News	
Mid-Atlantic Pharmacology Society	187
Upstate New York Pharmacology Society	188
Great Lakes Chapter	188
Membership Information	191
Membership Application	192
<u>APPENDIX (ONLINE ONLY)</u>	
GLC 2013 Annual Meeting Abstracts	C-1

The Pharmacologist is published and distributed by the American Society for Pharmacology and Experimental Therapeutics.

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The Pharmacologist (ISSN 0031-7004) is published quarterly in March, June, September, and December by the American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, MD 20814-3995. Annual subscription rates: \$20.00 for ASPET members; \$45.00 for U.S. nonmembers and institutions; \$70.00 for nonmembers and institutions outside the U.S. Single copy: \$20.00. Copyright © 2013 by the American Society for Pharmacology and Experimental Therapeutics Inc. All rights reserved. Periodicals postage paid at Bethesda, MD. GST number for Canadian subscribers: BN:13489 2330 RT.

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Deadlines for submission of material for publication: Issue 1, February 15; Issue 2, May 8; Issue 3, August 6; and Issue 4, November 5.

Postmaster: Send address changes to: *The Pharmacologist*, ASPET, 9650 Rockville Pike, Bethesda, MD 20814-3995.



Comings and Goings

Dear ASPET members,

It is truly an honor to serve as ASPET's 82nd president. I thank you for the faith that you have put in me to lead our organization. One great thing about ASPET is the teamwork among its leaders. John Lazo, Past President; Annette Fleckenstein, President-Elect; and I have been working closely together on several initiatives. The rest of Council has provided great support and insights to help move ASPET forward.

One major milestone for ASPET that is happening now is the transition to a new Executive Officer. We are all grateful to Christie Carrico for her outstanding service to ASPET over the past 16 years. She has provided wisdom and an important institutional memory that has kept ASPET on an even keel and in great financial shape. Thank you Christie! We are also delighted to welcome Judy Siuciak as the incoming Executive Officer. She has worked with Christie from mid-August through early September to provide a smooth transition. Judy comes with expertise in the pharma and non-profit sectors as well as in neuropharmacology and biomarkers. We look forward to her input on reaching out to pharmacologists of all stripes.

At the same time, many of us in ASPET Leadership see this as an opportunity to think hard about what we want ASPET to be over the next decade. As you have heard from me in my election candidacy materials and blog and from John Lazo in his messages, it is clear that the landscape for pharmacology is in flux. Research, both through NIH and in the commercial sector, has undergone major changes. The educational mission of medical school pharmacology has also changed with integrated and organ system curricula. At our fall Council meeting, we will have a strategic planning focus to develop an action plan for ASPET to respond to these opportunities and to engage all individuals involved in the study of pharmacology and experimental therapeutics broadly defined. Looking as well to educational opportunities in undergraduate, allied health, and even public arenas should be explored.

To help Council and me best shape ASPET for the years to come, please let us know your thoughts on how we can best serve you and the society. I will continue to communicate through my blog (<http://www.aspet.org/Blog.aspx?blogid=11889>) on the ASPET website. Please give feedback to me or any member of Council by email or via blog comments. Conversation among members is welcome. We need your insights as we move forward.

There are exciting opportunities in understanding complex diseases and mechanisms of drug action, resistance, and toxicity that are driven by new data-intensive methodologies. We must ensure that the next generations of pharmacologists fully understand and can efficiently use these powerful tools. Also, the range of viable drug targets as well as therapeutic modalities (biologics, siRNA, cellular therapy, etc.) is rapidly expanding. Engaging the best minds who are pushing the boundaries of pharmacology and experimental therapeutics will be critical to our society. Reaching out beyond the confines of the U.S. will also strengthen ASPET. The outstanding joint meeting this year with the British and Canadian pharmacology societies and next year's joint meeting with the Chinese (CNPHARS) at EB 2014 in San Diego are great examples.

The program of the EB 2014 meeting also illustrates such new opportunities with symposia on: "Drug discovery in China," "Therapeutic potential of targeting oxidative stress pathways," "Fetal programming in adult cardiovascular disease," "Emerging integrative approaches to predicting host response to antimicrobials," "Chemical biology in drug discovery," and "Targeted/individualized therapy: Approaches for the future translational pharmacologist."

I encourage all of you to take full advantage of these opportunities as well as to very actively engage with ASPET through leadership roles and also by making your ideas known to me and other ASPET leaders. I look forward to a very exciting 2013 – 2014 year with ASPET and all of you in our society.

Sincerely,



Rick Neubig

2014 Dues Notices

Please check your email inbox for your 2014 Dues notice. You can mail your payment or renew online at <https://www.aspet.org/login.aspx>, no later than January 1, 2014.

Message from the New Executive Officer



Dear ASPET Members,

I am delighted to have taken up my duties as the new Executive Officer of ASPET. It is an honor to be associated with an organization that for over 100 years has done much to promote basic and clinical pharmacological research. With a strong Council committed to our mission, a highly professional and dedicated staff, and our diverse membership, ASPET is well-positioned for the future.

As a pharmacologist, familiar with ASPET and its mission, I was immediately attracted to the Executive Officer position. I was also looking for a challenging opportunity that would utilize my scientific and administrative experience from the academic, industry, and non-profit sectors.

A brief bit about my background. I received my B.S. in biology from the Illinois Institute of Technology (IIT) in Chicago. This is where I first became aware of pharmacology as a field, since IIT offered undergraduates the opportunity to take graduate level courses. Upon receiving my degree, I worked as a laboratory technician in the Anatomy Department at Rush Medical College. After a few years of assisting with research efforts, I was certain I wanted to pursue a graduate degree and enrolled in the Ph.D. program in the Pharmacology Department at the University of Illinois College of Medicine. Under the direction of Dr. Claire Advokat, my thesis work investigated the spinal versus supraspinal actions of morphine-induced analgesia and tolerance. I then received an NRSA Postdoctoral Fellowship to work with Dr. Margarita Dubocovich at Northwestern University, my research exploring the localization and characterization of melatonin receptors. After completing my postdoc at Northwestern, the opportunity arose to join Regeneron, a startup company pursuing neurotrophic factors for the treatment of neurological diseases. Although I wasn't sure I wanted to leave academia, I thought Regeneron was doing interesting work and felt that completing a postdoc at a small biotech would offer valuable experience, yet not close the door on a return to academia. It turned out the small biotech atmosphere appealed to me, I particularly appreciated the energy and excitement of a collaborative team, and I stayed at Regeneron a few years past that initial postdoc. My laboratory investigated the neurochemical and behavioral effects of neurotrophic factors, and I had the opportunity to conduct some exciting research linking BDNF and depression. Of course, Regeneron has evolved from that little startup company focused on neurological diseases (if only I had kept my stock!). I subsequently made the leap from small biotech to large pharma when I joined the Neuroscience Department at Pfizer in Groton, CT. My laboratory at Pfizer worked on developing novel therapies for neuropsychiatric diseases and much of my research involved phosphodiesterases, such as PDE10A. It was an exciting time, as Pfizer was at the forefront of this area, and paths forward for novel therapeutic targets were yet to be defined. I came not only to appreciate the importance of the multidisciplinary team approach for drug discovery and development but also the tremendous challenges faced in getting CNS drugs to the market.

In 2008, I noticed an advertisement for a job at the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium. FNIH is a non-profit, 501(c)(3) organization established by the United States Congress to support the mission of the National Institutes of Health (NIH). The Biomarkers Consortium is a public-private biomedical research partnership aimed at developing, validating, and/or qualifying biomarkers. This job offered a slightly different career path, permitting me to gain experience in a unique non-profit setting involved in creating and managing pre-competitive research partnerships to advance scientific goals. The Biomarkers Consortium was in the early stages, and it was a unique opportunity for me to learn and contribute as it evolved. For almost five years at the Biomarkers Consortium, I managed a diverse portfolio of neuroscience and infectious disease projects and also worked on other FNIH projects such as the Alzheimer's Disease Neuroimaging Initiative (ADNI). My time there allowed me to participate in some truly exciting and groundbreaking scientific projects, and to work with remarkable people representing a diverse group of stakeholders from academia, industry, government, and non-profit sectors. As a result of my experience, I developed an appreciation for the important role that precompetitive collaborations play in tackling difficult problems that are beyond the scope of individual companies or institutions.

Looking back at my scientific career, moving from academia to small biotech to large pharma to public-private consortia efforts has been an eye opening and rewarding experience. Every step along the way has been a learning experience. I appreciate the value of a pharmacology degree, the diversity of the scientific community, and the importance of being part of team to get things accomplished. It is my hope that my experience can bring new insights and add value to the ASPET team.

On a personal note, I am a Chicago native, but my husband is from Maryland, so we were thrilled to relocate to this area five years ago and be closer to family. Since moving here, we have made many new friends and enjoyed having old friends visit. The Washington, DC metro area is a great place to live, there are a great many sites to see, museums to visit, and restaurants to explore.

Finally, I really must take a moment to thank Christie Carrico. I have had the chance to overlap with her for the past few weeks and gain insight from her 16 years of experience at ASPET. I appreciate her efforts to make this a smooth transition, and I have truly enjoyed the opportunity to work with her, even briefly.

I am very excited to be associated with ASPET and look forward to working with the ASPET Council, staff, and membership in the future.

With best wishes,

Judy Siuciak

Annual Meeting




Joint Annual Meeting of ASPET & the Chinese Pharmacological Society
April 26 - 30, 2014, San Diego, CA

Important Annual Meeting Information

Abstract Submission Deadline: Friday, November 8, 2013

Call for Abstracts [PDF]: <http://experimentalbiology.org/PDFS/2014/EB-2014-Call-for-Abstracts-FINAL.aspx>

The abstract submission site is open. Submit your abstract for the Annual Meeting:

<http://www.abstractsonline.com/submit/login.asp?mkey=%7B5B9D1EBB%2D5EEF%2D4E8E%2D9FFA%2D641686838541%7D>

Deadline for Discounted Registration: Friday, February 21, 2014

Registration for the ASPET Annual Meeting at EB 2014 is now open: <https://www.xpressreg.net/register/exbi044/reginfo.asp?dt=9%2F9%2F2013+10%3A24%3A42+AM>

Visit the EB 2014 Registration Resource Center: <https://www.xpressreg.net/register/exbi044/xpresstoolkit/login.asp>

A list of registration fees, meeting materials, and the cancellation policy can be accessed at: <http://experimentalbiology.org/2014/Attendees/Registration.aspx>

Housing Deadline: Friday, March 21, 2014

Housing information: <http://experimentalbiology.org/2014/Attendees/Housing.aspx>

Online hotel reservations for EB 2014: <http://registration3.experientevent.com/showEXB141/>

CAMP EB Child Care welcomes children ages 6 months – 17 years. Children participate in age-appropriate activities including arts and crafts projects, active games and much more in a safe, nurturing environment. Meals are not included in the camp fees. Parents can send or bring lunch to the center. Register for Camp EB at <http://www.accentregister.com/register/eb2014>.

Follow ASPET's tweets and Facebook posts about the meeting. On Twitter, our program-related posts will have the hashtag #EB2014. We encourage you to use #EB2014 and #ASPET on Twitter in your discussions about the ASPET Annual Meeting at EB 2014.

For more information, visit www.aspet.org/EB2014 or www.experimentalbiology.org.

2014 Program

Friday, April 25

Day of Service at the ASPET Annual Meeting at EB 2014

The Behavioral Pharmacology Division of ASPET will sponsor a volunteer opportunity at EB 2014 in San Diego. On Friday April 25, 2014, we will spend the day at St. Vincent de Paul Village, doing whatever we can to help the dedicated people at Father Joe's Villages provide assistance to San Diegans. If you plan to join us, please contact Charles P. France at france@uthscsa.edu, 210-567-6969 (voice), or 210-567-0104 (fax) at your earliest convenience. Further details will follow to those who express an interest in volunteering.

Saturday, April 26

Behavioral Pharmacology Society Meeting

Marriott Marquis & Marina, Room TBD; 8:00 AM – 6:00 PM

2014 Teaching Institute: Practical technologies for effective teaching

San Diego Convention Center, Room 3; 12:00 PM – 2:30 PM

Chairs: Renee L. Hayslett, Mercer Univ. and Catherine M. Davis, Johns Hopkins Univ. School of Med.

Introduction to E-learning (pros and cons, dos and don'ts)

Jorge G. Ruiz, Univ. of Miami Miller Sch. of Med.

Animated teaching: A simple way to make educational animations

Danton H. O'Day, Univ. of Toronto

"The games we play": Incorporating gaming into pharmacology teaching

A. Laurel Gorman, Univ. of Central Florida Col. of Med.

Using camtasia (and related technologies) to create student-centered learning modules

Robert B. Stephenson, Michigan State Univ.

Q & A session

Graduate Student-Postdoctoral Colloquium: TBD

San Diego Convention Center, Room 2; 2:45 PM – 5:15 PM

Chair: TBD

ASPET Business Meeting

San Diego Convention Center, Ballroom 20BC; 6:00 PM – 7:30 PM

ASPET Opening and Awards Reception

San Diego Convention Center, Center Terrace; 7:30 PM – 9:30 PM

Sunday, April 27

Diversity Mentoring Breakfast

Marriott Marquis & Marina, Room TBD; 7:30 AM – 9:30 AM

JULIUS AXELROD AWARD LECTURE

San Diego Convention Center, Room 2; 8:30 AM – 9:20 AM

Lee E. Limbird, Fisk University

Seasons of the lives of scientists: The journey from training to careers in discovery to service for society

JULIUS AXELROD SYMPOSIUM: Surprises at the synapse

Supported by the John V. Croker Fund

San Diego Convention Center, Room 2; 9:30 AM – 12:00 PM

Chair: Lee E. Limbird, Fisk University

Animal models of polydrug abuse

San Diego Convention Center, Room 4; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Behavioral Pharmacology; Neuropharmacology; & Toxicology

Chairs: Paul W. Czoty, Wake Forest Univ. Sch. of Med. and Richard De La Garza, Baylor Col. of Med.

Although laboratory animal models have been extremely useful in characterizing the abuse liability of drugs, less success has been achieved in developing widely effective pharmacotherapies for addiction. Whereas the behavior of addicted individuals is largely characterized by the use of multiple licit and illicit drugs, subjects in preclinical animal and human studies are almost invariably exposed to a single substance. This symposium will highlight current efforts to develop animal models of polydrug exposure. The key presenters will describe their studies involving interactions of many abused drugs including cocaine, nicotine, alcohol, and constituents of marijuana.

Polysubstance abuse in humans necessitates appropriate animal models

Richard De La Garza, Baylor Col. of Med

Nicotine + cocaine self-administration: A polydrug model

Nancy K. Mello, McLean Hosp./Harvard Med Sch.

A nonhuman primate model of cocaine/alcohol co-abuse

Paul W. Czoty, Wake Forest Sch. of Med.

Effects of THC exposure on nicotine reward

Steven R. Goldberg, NIDA/NIH/DHHS

Age differences in the reinforcing effects of nicotine-alcohol combinations

Francis M. Leslie, Univ. of California - Irvine

Career opportunities beyond the bench: Education as a viable path

San Diego Convention Center, Room 5A; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Pharmacology Education; Behavioral Pharmacology; Cardiovascular Pharmacology; Drug Discovery and Development; Integrative Systems, Translational and Clinical Pharmacology; Molecular Pharmacology; Neuropharmacology; & Toxicology

Chairs: Jayne S. Reuben, Univ. of South Carolina School of Med-Greenville and Karen Marcdante, Medical Col. of Wisconsin and Children's Hospital of Wisconsin

Postdoc pharmacologists in various endeavors beyond bench research with a particular focus on education as a viable career path. There are more than 15 new medical schools that have been inaugurated within the last couple of years. In addition, there are many osteopathic, pharmacy, nursing and allied health schools that are being established as well. These new developments create an immediate need for content experts in the area of all basic sciences, including pharmacology, to teach the medical students. Participants will be exposed to the means by which they can identify, explore, and target these opportunities.

Drug discovery against protozoal pathogens

San Diego Convention Center, Room 5B; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Drug Discovery and Development & Molecular Pharmacology

Chair: Margaret A. Phillips, Univ. of Texas Southwestern Med. Ctr.

The protozoal parasites such as *Plasmodium falciparum* (malaria), *Trypanosoma brucei* (African sleeping sickness), *Trypanosoma cruzi* (Chagas' disease), and *Leishmania* cause significant morbidity and mortality throughout the world with the poorest and most vulnerable populations most at risk. Vaccines are not available to treat these diseases, and current drug therapy suffers from issues of resistance or toxicity. Significant effort is underway to identify new drugs against these diseases involving collaborations between academia, industry, and not-for-profit organizations. This symposium will focus on a number of new compounds for the treatment of these diseases that are entering the clinics or are in the drug discovery pipeline.

Targeting malarial dihydroorotate dehydrogenase

Margaret A. Phillips, Univ. of Texas Southwestern Med. Ctr.

Hit-to-lead drug discovery around novel scaffolds for human African trypanosomiasis

Michael H. Gelb, Univ. of Washington

Designing selective inhibitors for calcium-dependent protein kinases in apicomplexans

L. David Sibley, Univ. of Washington at St. Louis

Epigenetic gene regulation as an antimalarial drug targeting opportunity

Junior Speaker: Nicholas A. Malmquist, Institut Pasteur

Discovering molecules to probe and treat malaria

Junior Speaker: Emily R. Derbyshire, Harvard Med. Sch.

Therapeutic potential of targeting oxidative stress pathways

San Diego Convention Center, Room 3; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Toxicology; Cardiovascular Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; & Molecular Pharmacology

Chairs: Philip R. Mayeux, Univ. of Arkansas for Medical Sciences and Chunfu Wu, Shenyang Pharmaceutical Univ

Oxidative stress is a major mechanism for various toxicities. The symposium will address mechanisms of oxidative stress important in toxicity, physiological responses to oxidative stress, and novel therapeutic approaches to alleviate oxidative stress.

Targeting mitochondrial oxidant generation in sepsis-induced renal injury

Philip R. Mayeux, Univ. of Arkansas for Medical Sciences

Function and therapeutic potential of the Keap1-Nrf2-ARE pathway

Curtis D. Klaassen, Univ. of Kansas Medical Center

Biological activities and potential medical uses of resveratrol

Chunfu Wu, Shenyang Pharmaceutical Univ.

Design of metal-targeting and antioxidant small molecules for the use in neurodegenerative disorders

Kayla Green, Texas Christian Univ.

CNPHARS LECTURE

San Diego Convention Center, Room 5A; 2:00 PM – 2:50 PM

TBN

Drug discovery in China

San Diego Convention Center, Room 5A; 3:00 PM – 5:30 PM

Sponsored by the Chinese Pharmacological Society & the ASPET Division for Drug Discovery and Development

Chairs: Guanhua Du, Inst. of Materia Medica, Chinese Academy of Med. Sciences & Peking Union Med. Col. and John Glowa, NIH/NCCAM

Because the 2014 meeting is a joint meeting with the Chinese Pharmacological Society, this session will be devoted to presentations on the state of drug discovery in China. Drugs will be discussed which are under development for the treatment of stroke, hypertension, and inflammation.

Emerging technologies in neuropeptide research: Identification and validation of neuropeptide systems as therapeutic targets

San Diego Convention Center, Room 4; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Neuropharmacology; Drug Discovery and Development; Integrative Systems, Translational and Clinical Pharmacology; & Molecular Pharmacology

Chair: Stewart D. Clark, Univ. at Buffalo, SUNY

Neuropsychiatric and other neurological disorders have a devastating impact on individuals, families, and society, and present pharmacological treatments do not fully ameliorate or even treat the full spectrum of symptoms. One class of molecules that shows great promise in this regard is neuropeptides. Neuropeptides, only a fraction of which have been discovered, have powerful and long-lasting effects on brain function. In addition, neuropeptides' target receptors are G protein-coupled receptors which have repeatedly been exploited as drug targets. The proposed symposium will highlight areas in which there have been methodological advances in the study of neuropeptides that will pave the way for the development of improved drugs for a spectrum of neurological disorders.

Neuropeptidomics: Approaches for the discovery of new neuropeptides and their functions

Jonathan V. Sweedler, Univ. of Illinois at Urbana-Champaign

The voltammetric detection and characterization of met-enkephalin fluctuations in live brain tissue

Leslie A. Sombers, North Carolina State Univ.

Fusions of diphtheria toxin and neuropeptides to selectively remove neurons

Stewart D. Clark, Univ. at Buffalo, SUNY

Optogenetic dissection of neural circuits and GPCR signaling in stress-induced behavior

Michael R. Bruchas, Washington Univ. Sch. of Med.

New insights derived from cell specific knockout of heterotrimeric G-alpha proteins

San Diego Convention Center, Room 2; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Molecular Pharmacology; Cardiovascular Pharmacology; Drug Discovery and Development; & Integrative Systems, Translational and Clinical Pharmacology

Chairs: Fiona Murray, Univ. of California-San Diego and Paul Insel, Univ. of California-San Diego

Heterotrimeric G proteins transduce signals from G protein-coupled receptors (GPCRs) to effector proteins to modulate cellular function. G protein signaling constitutes a fundamental mechanism of intercellular communication used by all eukaryotes. Whole body knockouts of G proteins can be embryonic lethal and difficult to interpret, however much progress has been made of cell specific knockout of individual G-alpha proteins. This symposium aims to highlight the physiological role of heterotrimeric G-alpha proteins and recent advances in G protein function and signaling that have been made by cell-targeted knockout studies in mice.

New preclinical and clinical perspectives for smoking cessation

San Diego Convention Center, Room 3; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Behavioral Pharmacology; Cardiovascular Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; Neuropharmacology; & Toxicology

Chairs: Rajeev I. Desai, McLean Hosp./Harvard Med. Sch. and Dorothy K. Hatsukami, Univ. of Minnesota

Tobacco smoking is the leading cause of preventable disease and premature death in the world (approximately 5 million annual deaths). Although behavioral and medication-based smoking cessation approaches are available, there is still a high degree of relapse among individuals who want to quit. This symposium will discuss current smoking cessation approaches and their limitations, and present new evidence from genetic (molecular), pharmacological, immunological, and behavioral studies across different species on novel potential smoking cessation treatments.

Orexin-1 receptors as targets for the development of novel smoking cessation agents

Paul J. Kenny, Scripps Research Institute

Small molecule alpha-conotoxin MII surrogates for the treatment of nicotine addiction

Linda P. Dwoskin, Univ. of Kentucky

Anti-nicotine vaccines and nicotinic partial agonists for smoking cessation

Rajeev I. Desai, McLean Hosp./Harvard Med Sch.

Behavioral interventions for smoking cessation

Stephen T. Higgins, Univ. of Vermont

Targeting smoking cessation: Current approaches and their limitations and future perspectives

Dorothy K. Hatsukami, Univ. of Minnesota

Pharmacology Education Division Programming: Addressing prescribing errors through medical student education and assessment

San Diego Convention Center, Room 5B; 3:00 PM – 5:30 PM

Chairs: Senthil K. Rajasekaran, Oakland Univ. William Beaumont Sch. of Med. and David W. Nierenberg, Dartmouth-Hitchcock Med. Ctr.

Medication errors are estimated to cost \$37 billion and result in 7,000 annual deaths, with a majority of these errors due to improper dosing, wrong drug, or wrong duration. However, in most medical schools, pharmacology training is limited to the early basic science years. The ability to prescribe commonly used drugs safely and effectively should be a core competency of the newly qualified doctor. Given that prescribing is such a fundamental part of medical practice, it is important to develop appropriate and acceptable curricula and assessments to ensure that medical students are gaining these skills before they graduate and move on to their PGY I positions. This symposium will give the audience an opportunity to learn about such an assessment tool created in the UK and will provide tools to implement a curriculum to teach this competency to medical students.

Education in safe and effective prescribing practices

David W. Nierenberg, Dartmouth-Hitchcock Med. Center

Assessing prescribing competence of senior medical students: A UK perspective

Simon Maxwell, Univ. of Edinburgh

A four-year longitudinal curricular model to teach prescribing skills to medical students

Senthil K. Rajasekaran, Oakland Univ. William Beaumont Sch. of Med.

Student/Postdoc Best Abstract Competition

Location TBD; 6:30 PM – 8:30 PM

Student/Postdoc Mixer

Location TBD; 9:00 PM – 11:30 PM

Monday, April 28

JOHN J. ABEL AWARD LECTURE

San Diego Convention Center, Room 2; 8:30 AM – 9:20 AM

TBN

Collaborative role of pharmacology in education of healthcare professions

San Diego Convention Center, Room 5A; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Pharmacology Education; Behavioral Pharmacology; Cardiovascular Pharmacology; Drug Discovery and Development; Drug Metabolism; Integrative Systems, Translational and Clinical Pharmacology; Molecular Pharmacology; Neuropharmacology; & Toxicology

Chairs: Sandra Carlin Andrieu, LSUHSC New Orleans Sch of Dentistry and Robert J. Theobald, Jr., Kirksville Coll. of Osteopathic Med.

It is well known that interprofessional collaborative practice is key to the safe, high quality, accessible, patient-centered care desired by all. Achieving that vision for the future requires moving beyond profession-specific educational efforts to engage students of different professions in interactive learning with each other so that they enter the workforce ready to practice effective teamwork and team-based care. This symposium will address some of the core principles of integrative curricula and will provide participants with specific guidance on the role of pharmacology in both foundational sciences and organ system courses, including the interface with other professions and disciplines in healthcare and health science.

Introduction

Robert J. Theobald, Jr., Kirksville Coll. of Osteopathic Med.

Overview of interprofessional education: Where does pharmacology fit in this venue?

Sandra Carlin Andrieu, LSUHSC New Orleans Sch. of Dentistry

Incorporating pharmacology in interprofessional education at the Medical University of South Carolina

Yiannis Koutalos, Med. Univ. of South Carolina

Nurses as the nation's largest health professions workforce – Responding to the clarion call for interprofessional collaborative practice and education

Jane Marie Kirschling, Univ. of Maryland Sch. of Nursing

Creating successful interprofessional pharmacology education for healthcare students by avoiding the pitfalls

Lynn Wecker, Univ. South Florida Coll. of Med.

Panel discussion

Robert J. Theobald, Jr., Kirksville Coll. of Osteopathic Med.

Drug-induced idiosyncratic reactions and immunotoxicity

San Diego Convention Center, Room 5B; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Toxicology; Drug Discovery and Development; Drug Metabolism; Integrative Systems, Translational and Clinical Pharmacology; & Molecular Pharmacology

Chair: Jack Uetrecht, Univ. of Toronto

The immune system is the therapeutic target of many new drugs, but drugs can also cause immune-mediated adverse reactions, unrelated to the therapeutic effects of the drugs. Idiosyncratic drug reactions are a special problem for drug development because they are often not detected until the drug has been marketed. Biological drugs that target the immune system can cause paradoxical immunotoxicity as is the case with autoimmune hepatitis caused by immunosuppressants such as anti-TNF α antibodies. This symposium will discuss research that has provided important clues to the mechanisms underlying such idiosyncratic drug reactions.

Role of the adaptive immune system in idiosyncratic drug reactions

Jack Uetrecht, Univ. of Toronto

Idiosyncratic drug sensitivity reactions affecting blood cells

Richard Aster, Blood Center of Wisconsin

Unexpected and idiosyncratic effects of biotherapeutics on peripheral blood cells

Nancy Everds, Amgen, Inc.

Preclinical tools for risk assessing immune-mediated adverse drug reactions

Jessica Whritenour, Pfizer, Inc.

Fetal programming of adult cardiovascular disease

San Diego Convention Center, Room 4; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology; Cardiovascular Pharmacology; & Toxicology

Chairs: Mark C. Chappell, Wake Forest Baptist Med. Center and Allyson C. Marshall, Wake Forest Baptist Med. Center

The fetal programming hypothesis is the concept that alterations in the fetal environment may result in developmental adaptations that predispose offspring to cardiovascular (hypertension) and metabolic (diabetes) diseases later in life. Potential effectors of fetal programming include nutrient and growth restriction, environmental stressors, and administration of drugs during pregnancy, as well as sex, fetal age, duration, and severity of exposure. While the original programming insults are diverse, studies reveal specific pathways that are particularly vulnerable to alteration from programming events, including the renin-angiotensin system (RAS), the sympathetic nervous system, and hypothalamic-pituitary-adrenal (HPA) axis. The focus of this symposium is to identify pathways vulnerable to insult by fetal programming and possible sites of pharmacological intervention to correct the programming effects.

Brief introduction

Mark C. Chappell, Wake Forest Baptist Med. Center and Allyson C. Marshall, Wake Forest Baptist Med. Center

Prenatal programming of hypertension: Renal mechanisms and interventions

Michel Baum, Univ of Texas Southwestern Med Ctr.

Hyperglycemia and sex specific cardiovascular programming

Jeffrey Segar, Univ. of Iowa Carver Coll. of Med.

Betamethasone induced programming of the brain renin-angiotensin system

Junior Speaker: Hossam A. Shaltout, Wake Forest Univ. Sch. of Med.

Fetal programming of the hypothalamic-pituitary-adrenal axis

Stephen G. Matthews, Univ. of Toronto

Nuclear receptors as therapeutic targets

San Diego Convention Center, Room 2; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Molecular Pharmacology; Drug Metabolism; Integrative Systems, Translational and Clinical Pharmacology; & Toxicology

Chairs: Donald P. McDonnell, Duke Univ. Med. Center and David Mangelsdorf, Univ. of Texas Southwestern Med. Center

The nuclear receptor (NR) superfamily of ligand-regulated transcription factors has been exploited in the development of a large number of drugs that target a wide range of endocrinopathies and cancers. Whereas most of the currently available therapeutics were developed empirically, it is clear that there may be more useful ways to manipulate NR function in various diseases. The assembled group of speakers are leaders in this field and will provide an exciting update of emerging strategies that target this superfamily of transcriptional regulators.

Sleep disruptions associated with neuropsychiatric and degenerative disorders: Implications, preclinical models and development of novel pharmacotherapies

San Diego Convention Center, Room 3; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Behavioral Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; Neuropharmacology; & Toxicology

Chairs: Robert W. Gould, Vanderbilt Univ. Med. Sch. and Carrie K. Jones, Vanderbilt Univ. Med. Sch.

Current drug treatments for neuropsychiatric and degenerative disorders aim to alleviate primary clinical symptoms without sufficiently treating sleep disturbances such as restlessness, insomnia, sleep apnea, reduced rapid eye movement (REM) sleep, and excessive daytime sleepiness. Insomnia is now recognized not as a consequence of, but a predictor for and often mainstay throughout many neuropsychiatric conditions. Further, sleep disturbances are linked to cognitive deficits, another untreated symptom associated with many neuropsychiatric and degenerative conditions. This symposium will describe sleep disturbances across a range of clinical conditions, effects of current treatments on sleep, and translational preclinical models employed to understand causes and develop novel treatments for sleep disturbances.

Sleep disturbances associated with neuropsychiatric disorders: A brief overview

Carrie K. Jones, Vanderbilt Univ. Med. Sch.

In utero exposure to valproic acid changes sleep patterns in juvenile rats: A potential preclinical model for studying sleep disturbances in autism spectrum disorders

Jessica Mong, Univ. of Maryland Sch. of Med.

Hypothalamic-pituitary-adrenal axis dysfunctions associated with sleep disturbances in post-traumatic stress disorder

Eric Vermetten, Leiden Univ. Med. Ctr. and Univ. Med. Ctr. Utrecht

Muscarinic acetylcholine receptor modulation of sleep/wake architecture for the treatment of psychiatric disorders

Robert W. Gould, Vanderbilt Univ. Med. Sch.

Robert Goeder, Univ. Hosp. Schleswig-Holstein

B.B. BRODIE AWARD LECTURE IN DRUG METABOLISM

San Diego Convention Center, Room 5A; 2:00 PM – 2:50 PM

TBN

Drug Metabolism Division James Gillette Award and Platform Session

San Diego Convention Center, Room 5A; 3:00 PM – 5:30 PM

P.B. DEWS AWARD LECTURE IN BEHAVIORAL PHARMACOLOGY

San Diego Convention Center, Room 4; 2:00 PM – 2:50 PM

TBN

Behavioral Pharmacology Division Symposium: Making the right choice: Translational use of choice procedures in understanding the neurobiology and development of pharmacotherapies for drug addiction

San Diego Convention Center, Room 4; 3:00 PM – 5:30 PM

Chairs: Matthew L. Banks, Virginia Commonwealth Univ. and Michael A. Nader, Wake Forest Univ.

Choice procedures are perhaps the most homologous model in which to study behavior. Although choice procedures are almost exclusively used in human laboratory studies of substance abuse, there is a small but growing body of literature in both rodent and nonhuman primate models of substance abuse that are employing choice procedures. This symposium will discuss the utility of choice procedures to provide insight into novel biological targets and potential pharmacological strategies for substance abuse. The discussions will involve theoretical considerations, experimental design issues for studies involving humans and animals, and how this baseline can inform researchers about the neurobiology and pharmacology of drug abuse.

Gender difference in drug vs. food choice behaviors

Tod Kippin, Univ. of California – Santa Barbara

The use of choice procedures to understand drug mixtures

Junior Speaker: Kevin Freeman, Univ. of Mississippi Med. Center

Utility of choice procedures for medication development for drug dependence in preclinical studies

Matthew L. Banks, Virginia Commonwealth Univ.

Utility of choice procedures in human drug abuse laboratory studies

William W. Stoops, Univ of Kentucky Coll. of Med.

Psychophysiological prediction of drug choice

Junior Speaker: Scott J. Moeller, Icahn Sch. of Med. At Mount Sinai

Mitochondrial fragments: A novel mediator between inflammation and cardiovascular disease

San Diego Convention Center, Room 3; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Cardiovascular Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; and Toxicology

Chairs: R. Clinton Webb, Georgia Regents Univ. and Camilla Ferreira Wenceslau, Georgia Regents Univ.

This symposium will deal with emerging data providing insight in the role of mitochondrial constituents and mitochondrial dysfunction in the genesis of cardiovascular diseases. The pro-inflammatory actions of fragmented mitochondria in the extracellular space comprise a newly discovered area of investigation, first described in 2010. This interaction between mitochondrial constituents and the immune system has been recently associated with cardiovascular diseases (e.g., heart failure, preeclampsia, and diabetes). Further, signaling mechanisms associated with mitochondrial biogenesis and bioenergetics have been found in conditions such as hypertension and the metabolic syndrome. Potential therapeutic targets related to mitophagy, mitochondrial biogenesis, and energetics will be addressed and discussed.

Circulating mitochondrial fragments as a novel signaling mechanism that induces systemic inflammation

Kiyoshi Itagaki, Beth Israel Deaconess Med. Ctr and Harvard Med. Sch.

Mitochondrial dysfunction and myocardial ischemia/reperfusion

Charles L. Hoppel, Case Western Res. Univ.

Mitochondrial dysfunction in atherosclerosis

Marschall S. Runge, Univ. of North Carolina

Evolutionary selection and mitochondrial genetics: Implications on cardiovascular disease susceptibility

Scott Ballinger, Univ. of Alabama

The role of placenta-derived mitochondrial fragments in the development of preeclampsia

Styliani Goulopoulou, Georgia Regents Univ.

Molecular Pharmacology Division Postdoctoral Award Finalists

San Diego Convention Center, Room 5B; 3:00 PM – 5:30 PM

Neuropharmacology Division Postdoctoral Scientist Award Finalists

San Diego Convention Center, Room 2; 3:00 PM – 5:30 PM

Tuesday, April 29

12-lipoxygenase and disease: New insights into regulation and inhibition of a critical enzyme

San Diego Convention Center, Room 2; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology; Cardiovascular Pharmacology; Drug Discovery and Development; & Molecular Pharmacology

Chair: Michael Holinstat, Thomas Jefferson Univ.

The enzyme 12-lipoxygenase is known to affect a number of disease conditions including thrombosis, diabetes mellitus, and cardiovascular disease. Understanding the mechanism by which this enzyme and its bioactive lipid products regulate these systems is crucial in order to develop viable therapeutic strategies while minimizing off-target effects. This symposium focuses on the evolution of this field and highlights 12-lipoxygenase as a preferred therapeutic target for treatment of these pathophysiological conditions.

12-lipoxygenase-mediated fatty acid regulation of hemostasis and thrombosis

Michael A. Holinostat, Thomas Jefferson Univ.

Development of novel inhibitors to human lipoxygenases

Theodore R. Holman, Univ. of California Santa Cruz

12-lipoxygenase regulation of diabetes mellitus

Jerry L. Nadler, Eastern Virginia Med School

12-lipoxygenase polymorphisms and disease

Jerzy Jankun, Medical Col. of Ohio

Emerging integrative approaches to predicting host response to antimicrobials

San Diego Convention Center, Room 5B; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology; Drug Metabolism; & Toxicology

Chair: Namandjé Bumpus, Johns Hopkins Univ. School of Med.

Therapeutic responses to antiviral drugs can be challenging to predict due, in part, to the fact that robust *in vitro* models of viral replication and animal models that are susceptible to certain human viruses are largely lacking. The purpose of this symposium is to bring together researchers who will share their progress in investigating host responses to antiviral therapy against a wide range of viruses through application of systems biology, metabolomics, and novel modeling approaches based upon the use of innovative *in vitro* and *in vivo* systems.

Not just a glue: Pharmacology, physiology and pathology of transglutaminases

San Diego Convention Center, Room 3; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Cardiovascular Pharmacology & Molecular Pharmacology

Chairs: Stephanie Watts, Michigan State Univ. and Erik Bakker, Univ. of Amsterdam

The focus of this symposium will be on the novel and compelling functions of the transglutaminase (TG) family of enzymes in the cardiovascular system, an untapped area of research relative to TG function. TGs typically carry out a protein-protein bond, but recent evidence suggests that TGs attach primary amines – 5-HT, NE, DA and E – to a protein via a covalent modification that can change the function of the protein. Classic receptor activation does not appear to be necessary for this function, so this adds a new and exciting layer of complexity for how amines signal, not only in the cardiovascular system, but elsewhere.

Inhibition of transglutaminase

Jeffrey W. Keillor, Univ. of Ottawa.

Transglutaminase in systemic hypertension: Function and remodeling

Erik Bakker, Univ. of Amsterdam

Transglutaminase-mediated amidation of proteins by monoamines

Kyle B. Johnson, Concordia Univ.

Vascular aging and transglutaminase

Lakshmi Santhanam, Johns Hopkins Univ.

Role of (drug) transporters in imaging in health and disease

San Diego Convention Center, Room 5A; 9:30 AM – 12:00 PM

Sponsored by the Division for Drug Metabolism

Chairs: Bruno Stieger, Univ. Hospital Zurich and Yuichi Sugiyama, RIKEN Innovation Center Res. Cluster for Innovation

The role of transporters in drug development is now widely recognized but the role of transporters in diagnosis is less appreciated. Since many of the widely used imaging probe substances need transporters to enter cells, it is important to understand how transporters function in disease states. Several groups are now working on developing imaging methodology and in particular imaging probes in conjunction with microdosing. This session will highlight the role of transporters in clinical diagnosis with a focus on imaging and the development of new tools for the application of microdosing in drug development.

The role of transporters for diagnostic probes

Bruno Stieger, Univ. Hospital Zurich

Application of novel PET substrates for microdosing studies for assessing transporter functions in drug development

Yuichi Sugiyama, RIKEN Innovation Center Res. Cluster for Innovation

Quantification of drug transporters to understand interindividual variability in drug disposition and drug response

Jashvant Unadkat, Univ. of Washington

PET imaging of ABC efflux transporters at the blood-brain barrier in humans and animal models

Oliver Langer, Med. Univ. of Vienna

Role of genetic polymorphisms in gadoxetic acid enhanced liver imaging

Junior Speaker: Jens P. Kühn, Ernst Moritz Arndt Univ. Greifswald

Transporters in glial cells as new therapeutic targets

San Diego Convention Center, Room 4; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Neuropharmacology; Cardiovascular Pharmacology; Drug Discovery and Development; & Molecular Pharmacology

Chair: Lucio Annunziato, Federico II Univ. of Naples Sch. of Med.

Glial cells constitute the large majority of cells in the nervous system and account for the majority of cells in the human brain. During recent years, a large number of studies have critically attributed to glia a new role which no longer reflects the long-held view that glia constitute solely a silent and passive supportive scaffolding for brain cells but credits them with a much more active role in brain function. Glial transporters, responsible for maintaining intragial ionic homeostasis in ischemic brain injury, are potential candidates in stroke intervention. This symposium will discuss how targeting these transporters may make it possible to modulate regenerative processes occurring after stroke and in other neurodegenerative disorders.

NCX expression and activity in microglia and oligodendrocytes after stroke

Lucio Annunziato, Federico II Univ. of Naples Sch. of Med.

Protective role of microglia and its mechanism under stroke: Na⁺/Ca²⁺ exchange dependent microglial migration

Mami Noda, Kyushu Univ.

Microglia activation in neurodegenerative disorders depends on NHE-mediated H⁺ homeostasis

Dandan Sun, Univ. of Pittsburgh Med. Sch.

The Sur1-Trpm4 channel in glial cells in CNS injury

J. Marc Simard, Univ. of Maryland Sch. of Med.

Cardiovascular Pharmacology Division Trainee Showcase

San Diego Convention Center, Room 3; 2:30 PM – 4:30 PM

PAUL M. VANHOUTTE AWARD LECTURE IN VASCULAR PHARMACOLOGY

San Diego Convention Center, Room 3; 4:30 PM – 5:30 PM

TBN

Drug Discovery and Development Division Symposium: TBD

San Diego Convention Center, Room 4; 3:00 PM – 5:30 PM

Chairs: TBD

Inhibitory G protein-coupled receptors as therapeutic targets for obesity and type 2 diabetes

San Diego Convention Center, Room 2; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Molecular Pharmacology; Cardiovascular Pharmacology; Drug Discovery and Development; & Integrative Systems, Translational and Clinical Pharmacology

Chair: Michelle E. Kimple, Univ. of Wisconsin-Madison

Obesity and the potential for insulin resistance are the biggest risk factors for type 2 diabetes (T2D). Thus, there is a pressing need for more effective treatments for type 2 diabetes, as well as those that might halt or reverse obesity itself. Current T2D therapeutics that act via beta-cell GPCRs mainly target the glucagon-like peptide 1 (GLP-1) receptor, which is coupled to G_s and stimulates cyclic AMP accumulation. These drugs have been used clinically for the past decade and are effective anti-hyperglycemic agents in many individuals. Yet, there exists a subset of individuals that remain resistant to the effects of these drugs. The existence of endogenous signaling pathways that are dysfunctionally up-regulated in T2D and act to inhibit cAMP accumulation might explain the lack of response in certain individuals, as well as provide a new physiological target for T2D. This program will summarize the current state of research in Gi-coupled GPCRs as therapeutic targets for type 2 diabetes and obesity.

Introduction

The Gz-coupled EP3 receptor as a therapeutic target for diabetic beta-cell dysfunction

Michelle E. Kimple, Univ. of Wisconsin-Madison

The PGE2 EP3 receptor in metabolic syndrome: The good, the bad, and the ugly

Richard Breyer, Vanderbilt Univ. Med. Ctr.

TBD

Erik Renström, Skåne Univ. Hosp. Malmö

Peripheral CB1 receptors as emerging therapeutic targets in diabetes and obesity

George Kunos, NIAAA/NIH

Wrap-up

Integrative Systems, Translational and Clinical Pharmacology Division Young Investigator Awards Platform Session

San Diego Convention Center, Room 5A; 3:00 PM – 5:30 PM

Toxicology Division Symposium: Macrophages and tissue injury: Agents of defense or destruction?

San Diego Convention Center, Room 5B; 3:00 PM – 5:30 PM

Chair: Debra Laskin, Rutgers Univ.

Wednesday, April 30

RAY FULLER AWARD LECTURE

San Diego Convention Center, Room 2; 8:30 AM – 9:20 AM

Jeffrey M. Witkin, Lilly Research Labs

AMPA receptor potentiation: Implications for the discovery of medicines for treatment-resistant depression

RAY FULLER SYMPOSIUM: Treatment-resistant depression (TRD): Biological bases and treatments

San Diego Convention Center, Room 2; 9:30 AM – 12:00 PM

Chair: Jeffrey M. Witkin, Lilly Research Labs

The Ray Fuller symposium will complement the Ray Fuller Lecture by addressing new approaches to attacking the problem of treatment resistance depression by focusing on both novel clinical approaches as well as new developments in preclinical modeling.

Introduction

Jeffrey M. Witkin, Lilly Research Labs

Neurostimulation

Paul E. Holtzhiemer, Dartmouth Hitchcock Med. Ctr.

The glutamate hypothesis

Phil Skolnick, NIDA

The cholinergic hypothesis

Christian C. Felder, Lilly Research Labs

Kappa opioid receptors

Irwin Lucki, Univ. of Pennsylvania

Arginase as an emerging therapeutic target

San Diego Convention Center, Room 5B; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Drug Discovery and Development; Cardiovascular Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; & Molecular Pharmacology

Chair: R. William Caldwell, Med. Coll. of Georgia, Georgia Regents Univ.

While part of the hepatic urea cycle, arginase is widely distributed and is expressed in many non-hepatic cell types that lack urea cycle function. Overactive arginase has been implicated in neurovascular injury, abnormal vascular growth and remodeling, tissue fibrosis during vascular disease and tumor growth. This symposium will cover the various cellular and molecular effects of elevated arginase activity and the implications for the development of novel therapeutic interventions.

Recent advances in arginine metabolism: Role and regulation of arginase isoforms

Sidney M. Morris, Jr., Univ. of Pittsburgh Sch. of Med.

Role of arginase in retinovascular disease

Ruth B. Caldwell, Med. Coll. of Georgia, Georgia Regents Univ.

Role of arginases in atherosclerotic vascular disease and age-related vascular dysfunction

Dan E. Berkowitz, Johns Hopkins Univ. Sch. of Med.

Involvement of arginase in cancer biology

Augusto Ochoa, LSUHSC, New Orleans

Chemical biology in drug discovery

San Diego Convention Center, Room 4; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Molecular Pharmacology & Drug Discovery and Development

Chairs: Haiyan Fu, Emory Univ. and Hongzhan Chen, Shanghai Jiaotong Univ. Sch. of Med. (SJTUSM)

Recent NIH initiatives and an expanding number of academic chemical biology centers have fueled the rapid discovery of small molecule modulators for many therapeutically associated molecular pathways and the large scale profiling of therapeutic agents for their efficacy as well as toxicity. All together, these activities enhance our understanding of the mechanism of actions and toxicity of currently used therapeutic agents, accelerate the discovery of new leads for therapeutic development, and bridge the pharmacology discipline with a broad field of chemical biology, genomics, and systems biology. This session will highlight recent research activities in the broad area of chemical biology field that enhance the discovery and development of therapeutic agents and how these two fields merge to generate a synergistic impact on the development of the next generation of therapeutic agents to improve human health. Major goals of some national initiatives will also be presented.

Brief introduction

Haiyan Fu, Emory Univ.

Interrogating protein-protein interactions in cancer

Haiyan Fu, Emory Univ.

Chemical biology of chemical biology of methyl lysine readers

Stephen Frye, Univ. of North Carolina at Chapel Hill

Discovery of new ligands based on the cholinergic modulation in neurodegenerative diseases

Hongzhan Chen, Shanghai Jiaotong Univ. Sch. of Med.

Systems and target-based ligand discovery for GPCRs

Brian K. Schoichet, Univ. of California San Francisco

Scientists versus street chemists: The toxicity of designer marijuana

San Diego Convention Center, Room 3; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Toxicology; Behavioral Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; & Neuropharmacology

Chairs: Laura P. James, Arkansas Children's Hosp. and Jeffery H. Moran, Univ. of Arkansas for Med. Sciences

K2, also known as Spice, is the most common term for "synthetic marijuana" products being sold in the US. These preparations typically contain high-efficacy synthetic cannabinoids, making them much more powerful than marijuana itself. Recent clinical and forensic reports demonstrate that some of the constituents of these synthetic marijuana preparations have unique toxicity, and morbidity and mortality reports are increasingly being associated with K2 use. Cardiac, neurologic, and psychiatric complications are common with K2 exposure, and metabolic, behavioral, and pharmacological studies are beginning to unravel the underlying mechanisms for these adverse effects. This symposium will review the known pharmacology and toxicology of K2 including perspectives of scientists that are working in the areas of public health, chemical analysis, receptor signaling, behavioral effects, and clinical case collection.

An analytical chemist's approach to public health problems

Jeffery H. Moran, Arkansas Dept. of Health

Atypical in vitro pharmacodynamic and metabolic characteristics of K2 synthetic cannabinoids: Keys to toxicity?

Paul L. Prather, Univ. of Arkansas for Med. Sciences

Pharmacodynamic and pharmacokinetic factors impacting the in vivo pharmacology and toxicology of K2 synthetic marijuana

William E. Fantegrossi, Univ. of Arkansas for Med. Sciences

Clinical and unexplained idiosyncratic toxicity of K2 exposure

Genevieve L. Buser, Oregon Hlth. Authority

"Target-site" drug metabolism and transport

San Diego Convention Center, Room 5A; 9:30 AM – 12:00 PM

Sponsored by the Divisions for Drug Metabolism; Drug Discovery and Development; Integrative Systems, Translational and Clinical Pharmacology; & Toxicology

Chair: Robert S. Foti, Amgen

Therapeutic entities from systemic circulation, emerging evidence has highlighted the importance of drug metabolizing enzymes and transporters at the site of therapeutic action. Target-site drug metabolism can affect the efficacy, safety, and metabolic properties of a therapeutic drug, with potential outcomes including altered dosing regimens, stricter exclusion criteria, or even the failure of a new chemical entity in clinical trials. This proposed session will focus on the contribution of drug metabolizing enzymes and transporters at the site of action to the overall therapeutic properties of a given drug.

Pulmonary metabolism of Resveratrol: In vitro and in vivo evidence

Swati Nagar, Temple Univ. Sch. of Pharmacy

The SLC22 transporter family: Impact on drug efficacy, drug-drug interactions and pathophysiology

Douglas H. Sweet, Virginia Commonwealth Univ.

Drug metabolism within the brain changes drug response in vivo

Rachel F. Tyndale, Univ. of Toronto

Tumor metabolism of antibody-drug conjugates: Effect on pharmacokinetics and efficacy

Dan A. Rock, Amgen, Inc.

Future therapies for chronic pain: Focus on novel non-opioid targets

San Diego Convention Center, Room 4; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Neuropharmacology; Behavioral Pharmacology; Cardiovascular Pharmacology; Drug Discovery and Development; Integrative Systems, Translational and Clinical Pharmacology; & Molecular Pharmacology

Chair: Beverley Greenwood-Van Meerveld, Oklahoma Univ. Health Sci Center.

Chronic pain represents a significant health burden estimated to affect 40% of all adults in the United States. While previous ASPET symposia have focused on opioid-related therapies through discussing novel targets for G-protein coupled opioid receptors and peripheral mechanisms of opioid analgesia, this symposium will seek to expand the repertoire of potential treatments for chronic pain by highlighting cutting-edge research on non-opioid targets for neuropathic and visceral pain.

Hydrogen sulfide: From physiological messenger to pharmacological target

San Diego Convention Center, Room 2; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Cardiovascular Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; Molecular Pharmacology; & Toxicology

Chairs: Nancy L. Kanagy, Univ. of New Mexico Sch. of Med. and Utpal Sen, Univ. of Louisville Sch. of Med.

Hydrogen sulfide (H₂S), a gas with a foul odor known for its toxicity, has recently been recognized, along with nitric oxide (NO) and carbon monoxide (CO), as a novel regulator of cardiovascular function. Many tissues produce H₂S in the body, and it is now apparent that it regulates a wide array of physiological processes including angiogenesis, ion-channel activity, glucose metabolism, cell proliferation, and apoptosis as well as ameliorating pathophysiological conditions such as inflammation, ischemic cardiac disease, neurodegeneration, and hypertension. The intent of this symposium is to bring together scientists from diverse backgrounds to share, discuss, and disseminate new findings on the interactions of H₂S with other mediators, mechanisms of H₂S regulation of cellular function, and mechanisms for its protective effects in diabetes and other diseases.

Hydrogen sulfide: Overview of its production and function

Hideo Kimura, National Inst. of Neuroscience.

Hydrogen sulfide: A novel endothelium-dependent dilator

Nancy L. Kanagy, Univ. of New Mexico Sch. of Med.

Hydrogen sulfide: A novel mediator of diabetic renovascular remodeling

Utpal Sen, Univ. of Louisville Sch. of Med.

Hydrogen sulfide as a novel therapeutic agent

Christopher G. Kevil, Louisiana State Univ.

Improving maternal therapeutics: Drug metabolism and transport during pregnancy and lactation

San Diego Convention Center, Room 3; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Drug Discovery and Development; Drug Metabolism; & Integrative Systems, Translational and Clinical Pharmacology

Chairs: Nina Isoherranen, Univ. of Washington; Hollie Swanson, Univ. of Kentucky Med. Center; and Donald Mattison, Risk Sciences Inst.

Use of prescription and over the counter drugs is very common during pregnancy, but due to changes in drug metabolism and transport during pregnancy, the dosing of drugs cannot be directly extrapolated from non-pregnant women or men. Increased scrutiny by the FDA and NIH on therapy of pregnant women has resulted in a considerable increase in the amount of research generated in the area of drug disposition during pregnancy. This symposium is designed to cover the area of drug disposition during pregnancy and highlight the breadth of tools that are currently used to investigate drug disposition during pregnancy.

General overview

Nina Isoherranen, Univ. of Washington

Prediction of drug disposition during pregnancy by PBPK modeling and simulation

Jashvant Unadkat, Univ. of Washington

Mechanisms of CYP2D6 regulation during pregnancy

Junior Speaker: Young Jeong, Univ. of Illinois - Chicago

Regulation of MRP2 during pregnancy in human placenta and liver

Mary Vore, Univ. of Kentucky

Addressing pregnancy-associated changes in pharmacodynamics and pharmacokinetics of anti-malaria drugs

Joel Tarning, Mahidol Univ.

Panel discussion

Donald Mattison, Risk Sciences Inst.

Targeted/individualized therapy: Approaches for the future translational pharmacologist

San Diego Convention Center, Room 5A; 3:00 PM – 5:30 PM

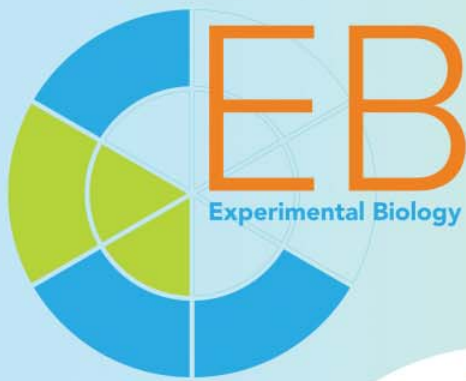
Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology; Cardiovascular Pharmacology; Drug Discovery and Development; Molecular Pharmacology; & Toxicology

Chair: Jeffrey Paul, Astellas

Personalized medicine, described as giving the right drug, at the right dose, to the right person, requires certain tools and approaches to deal with the heterogeneity of human disease. The use of various -omic platforms, including genomics, transcriptomics, proteomics, and metabolomics are some of the approaches used to evaluate individualized molecular interventions. The need for bioinformatics and disease pathway identification are necessary tools to interpret the results of the -omics laboratory and to assign translational/therapeutic relevance. The purpose of this symposium is to introduce molecular approaches available to the pharmacologist and to provide current tools for integration with translational bioinformatics, using examples from oncology targeted therapeutics.

ASPET Closing Reception

San Diego Marriott Marquis & Marina, Room TBD; 6:00 PM – 8:00 PM



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ASPET Travel Awards

Travel Awards for the ASPET Annual Meeting at EB 2014

Students and postdocs are invited to apply for a Travel Award to attend the ASPET Annual Meeting at EB 2014. Student Travel Awards, Minority Graduate Student Travel Awards, Summer Undergraduate Research Fellowship Travel Awards, Young Scientist and Minority Young Scientist Travel Awards consist of a fixed sum of \$600, registration (at the early registration rate), plus up to \$400 in travel reimbursement with receipts after the meeting. All travel awards are inclusive of registration and are given to partially defray the costs of travel and housing. The check for the award and an award certificate will be presented at the ASPET Business Meeting at the Annual Meeting. Applicants must be members of ASPET in good standing. The application deadline for ASPET Travel Awards is December 11, 2013. To apply for a Travel Award, please visit:

Graduate Student Travel Awards: <http://www.aspet.org/awards/travel/grad-student/>

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Minority Young Scientist Travel Awards: <http://www.aspet.org/awards/travel/minority-young-scientist/>

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ASPET Division for Pharmacology Education: Travel Award for Pharmacology Educators:

<http://www.aspet.org/Education/Pharmacology-Educators-Travel-Award/>

Submission Deadline: January 6, 2014

GI Club and IUPHAR GI Section at Experimental Biology 2013

contributed by Sandor Szabo, M.D., Ph.D.

The GI Club, established in 2012 at the EB meeting in San Diego, held its first business and scientific meeting during the EB conference in April in Boston, MA. The meeting took place at the Harvard Club of Boston in the evening hours of Monday, April 22, 2013. It was attended by most of the GI Club Executive Committee and 90% of its International Board, as well as numerous other junior and senior members of the gastrointestinal pharmacology community, altogether about 50 members. After a short social hour and modest buffet dinner, a business meeting was held to discuss the goals, outreach, plans for future meetings, as well as the proposed organizational chart and organizational framework for the GI Club. Our members were very pleased to hear that ASPET invited us to submit symposium proposals for the San Diego EB meeting in 2014, and our Executive Committee has submitted eight symposia and workshop proposals to the World Congress of Pharmacology (WCP) in Cape Town, South Africa in 2014. Two leaders of WCP, Professors T. Brink and D. Olivier, attended our business meeting and made short presentations about WCP, highlighting the attractiveness of Cape Town and South Africa. This was followed by a brief presentation of Professor K. Gyires, former chair of the Department of Pharmacology at Semmelweis Medical University in Budapest, Hungary, who will organize the 8th International Symposium on Cell/Tissue Injury & Cytoprotection/Organoprotection, with focus on the GI tract, in Budapest, in September 2014. These symposia are now the official scientific forum of the IUPHAR GI Section. Since the GI Club also had a broad appeal to the international GI pharmacology community (e.g., about 20 new members, GI pharmacology investigators and educators, joined ASPET last year from various countries of the world, especially, from Japan, Korea, and the E.U.). A proposal from these countries was submitted at the business meeting to modify the name of the Club to "Global GI Club," where "global" would indicate both the broad scope of GI pharmacology to include molecular GI physiology, pathology, and clinical pharmacology, as well as its international appeal and representation. The name change was enthusiastically approved by a large majority of members present.



Attendees at the Business Meeting and Scientific Session of the GI Club and IUPHAR GI Section, held at the Harvard Club of Boston during the ASPET Annual Meeting at EB 2013.

Following the business meeting, a scientific session was held where about 15 internationally known senior GI investigators were asked to make 10-minute presentations on "The Best of My Research: The Last 10 Years." This was followed by a lively group discussion where some of the students & younger coworkers of senior GI investigators asked appropriate and challenging questions. The proceedings of this session will be published as short mini-reviews in the upcoming issues of the *Journal of Physiology & Pharmacology*.



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Late Breaker Abstracts Close

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Travel Awards for the 17th World Congress of Basic & Clinical Pharmacology

The International Union of Basic and Clinical Pharmacology (IUPHAR) will hold its 17th World Congress in Cape Town, South Africa, July 13 – 18, 2014. The meeting is organized and hosted by the South African Society for Basic and Clinical Pharmacology (SASBCP). For more information, please visit <http://www.wcp2014.org/>.

ASPET will be offering travel awards to attend the WCP2014 for graduate student and young scientist members of ASPET in good standing to present a paper at the meeting. Applicants must already be a member to apply. More information for these awards will be available in October.

Annual Membership Survey

by Suzie Thompson

We would like to thank everyone who took the time to participate in the 2013 ASPET Annual Membership Survey. Our survey was designed to look at many of the different services we provide and get your input on how we are doing, how we can improve, and what we need to expand on. Although we are not able to implement every suggestion, we do take every comment seriously, and we are happy to share the results of the survey here.

General Membership

We had 663 members take the survey, with representation from all categories of membership from regular membership to undergraduate student membership. Our survey respondents also produced a good mix of newer members (40% have been members for 0 – 5 years) to long-time members (40% have been members for over 20 years).

We are happy to report that when asked to rate on a scale of 1-10 how satisfied members were with ASPET's programs, we found that 80% of survey respondents were either satisfied or very satisfied with their overall ASPET membership. Respondents also indicated that they were either satisfied or very satisfied with ASPET's benefits, Annual Meeting programming, Annual Meeting social events, networking opportunities, science policy efforts, leadership, and communications efforts. These all scored in the 70th percentile or higher.

In looking deeper at our membership benefits, we found that the top ranking benefits we offer are free full-text online access to ASPET journals, reduced registration fees to attend the ASPET Annual Meeting, and reduced publication fees and no submission fee to publish in the ASPET journals. Our lowest ranking benefits were reduced rates for posting jobs on the ASPET Career Center and bi-monthly public affairs updates by email. As we continue to work to improve our Career Center and our eNewsletter updates, we hope that members will find them more useful in the future.

Journals

ASPET's journals provide a number of content awareness services and while 62% of survey respondents do not use any content awareness services at the moment, we are starting to grow the number of users who are using ASPET's Facebook and Twitter accounts to become aware of new content in the journals. If you would like to be alerted to new content in any of ASPET's journals, there are a number of ways to do this. You can set up email alerts, follow our journals on Facebook or Twitter, or subscribe to our RSS feeds. For more information on how to set up alerts visit <http://www.aspetjournals.org>. Be sure to sign up for at least one of these services so you don't miss out on any new or interesting content.

The Pharmacologist

Over the last year, we have been working hard to improve the quality of *The Pharmacologist*, ASPET's quarterly newsletter. We have changed the look slightly and added new features. We are very happy to report that most of our respondents do read the newsletter, and most seem to be enjoying the new features. If you haven't had a chance to check out our newest features, be sure to find them online at http://www.aspet.org/The_Pharmacologist.aspx. New features include an article on "AZT: A Rational Drug Ahead of its Time" (March 2013) an article on "Hitchings and Elion: Perfect Together" (June 2013), book reviews, and interviews with ASPET members. We will continue to bring you more interesting news and articles through *The Pharmacologist*.

Social Media

In an effort to find out what social media platforms our members are using either professionally or personally, we asked how often people are using the different platforms available. The top three platforms that respondents are using on a regular basis are YouTube, LinkedIn, and Facebook. We are happy to report that ASPET is on all three social media platforms and we are working to improve the content we provide on each of these daily. When asked specifically about our social media postings, respondents had very neutral opinions. We asked if our social media posts were relevant, informative, and interesting, and most respondents had no opinion of them. Currently on Facebook and Twitter, we post a lot of ASPET news and announcements. We are also trying to post more fun facts and interesting items related to pharmacology. If you have any other suggestions on how to improve our postings, please feel free to contact our Social Media Manager, **Gary Axelrod** at gaxelrod@aspnet.org. On LinkedIn, we post our job openings from our Career Center, but we would love to have more interactions with our members and get conversations started about pharmacology and science careers. Again, if you have any suggestions or comments, please contact Gary Axelrod.

Website

We recently updated the homepage of our website to make it more user-friendly and aesthetically interesting. We added many more pictures and graphics and better navigation tools, as well as more content, including a new President's Blog. Unfortunately, many of the survey respondents had not noticed the changes or improvements. We hope that you will take the time to visit us online at <http://www.aspet.org> to view the changes and look at the new content we are providing.

ASPET Annual Meeting

We are happy to report that 33% of survey respondents are definitely planning to attend the ASPET Annual Meeting at Experimental Biology 2014 in San Diego. Another 36% are not yet sure. For those who have not quite made up your mind, please take the time to visit our meeting page, <http://www.aspet.org/EB2014>, and check out our preliminary program. We had record attendance last year and are already planning another fantastic meeting for 2014. With excellent science, great networking opportunities and fun social events in sunny San Diego, it will be a meeting not to be missed. We hope to see everyone there!

Career Center

We asked members a series of questions about our Career Center and whether they have used any of the services on our Career Center. As our Career Center continues to grow, we are seeing a slightly increased number of respondents who have visited our site, uploaded their CVs, applied for jobs, and used our Career Center resources such as career tips and resume writing services. As we continue to grow our Career Center, we hope that you will keep us in mind for all of your job search and posting needs. Visit our Career Center at <http://careers.aspet.org>. And as always, if you have suggestions for improving our site, please contact **Suzie Thompson** at sthompson@aspnet.org.

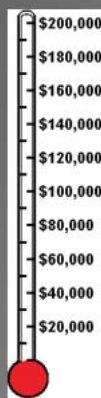
Entrepreneurial Activities

We asked members if they have been involved in an entrepreneurial activity as it relates to the life sciences. 26% of respondents said yes. Of those people, 57% have patents filed, 31% have licensed their technologies, and 35% have started a company. Most of the companies started were in drug discovery and development. A vast majority of our survey respondents agreed that entrepreneurship and technology commercialization topics should be a component of pharmacology education and training. And about 60% of respondents would like to see ASPET organizing focused conference sessions or resources related to technology development. These findings will be passed on to the leadership of ASPET.

A Final Note

Once again, we want to thank you for your valuable input and support for the Society. As expected, there was a mixed bag of comments and suggestions, and these will be made available to the ASPET Council this fall for further discussions. Please feel free to contact us with any further comments to **Suzie Thompson** at sthompson@aspnet.org. We hope to continue to serve you in all your membership needs.

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Thank you for your support!

Bylaws Change Approved

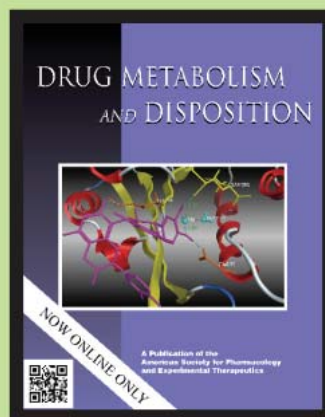
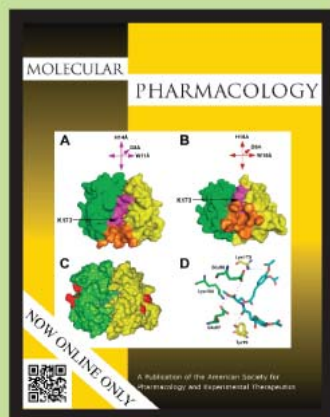
This summer, the membership passed, by an overwhelming vote, a significant change to the bylaws related to becoming a member of ASPET. The membership voted to eliminate the requirement for a member to sponsor applicants for Regular, Affiliate, and Postdoctoral Membership in ASPET. While the other requirements for membership have not changed, individuals wishing to belong to ASPET now need only submit their CV. The CV will be reviewed by staff to see that the qualifications for membership have been met for the category of membership requested. This will speed up both the membership application and approval processes and remove at least one barrier for individuals who wish to become members of ASPET.

Student applicants must still have a statement from a member, or their mentor, or their department chair attesting to their student and research status. Upon completion of their graduate studies and receipt of a degree, students need only submit an updated CV and bibliography for upgrade to Postdoctoral membership status.

Thank you to the many Division Chairs who have reviewed CVs and served as sponsors for members unable to identify an ASPET member at their institution.

ASPET Journals

Why publish with ASPET?



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- If you have any questions about this program, please contact the membership department at membership@aspnet.org or call (301) 634-7060

By helping us recruit new members, you will be contributing to the growth and sustainability of ASPET. A growing ASPET means great recognition for the field of pharmacology, more resources and support for our members, and a louder voice with policy makers.

For more program details, visit:

<https://www.aspet.org/membership/member-get-a-member/>

The Case of Elizabeth Evans Hughes: Juvenile Diabetes at the Dawn of Insulin

by Rebecca J. Anderson, Ph.D.

One day in the fall of 1918, eleven-year-old Elizabeth Evans Hughes came home from a birthday party, where she had eaten cake and ice cream—treats that her parents rarely served. She drank glass after glass of water, unable to satisfy her ravenous thirst. Over the next few months, Elizabeth, who had always been a lively child, was often weak and tired. Sometimes, she drank quarts of water, accompanied by excessive urination. By April 1919, it was clear that her symptoms were getting worse, not better.

Elizabeth's parents took her to see Dr. Frederick Allen, whose Madison Avenue office was within walking distance of the Hughes home in midtown Manhattan. To Allen, Elizabeth's symptoms were all-too familiar. She was suffering from a vicious metabolic cycle. Elizabeth was unable to absorb carbohydrates, and the unmetabolized sugars spilled into her urine, increasing its osmolarity and causing excessive urination. Because she was losing fluids, she was constantly thirsty. Unable to access carbohydrates from her food for energy, her body was burning its stores of fat, and she was losing weight. The excessive lipid metabolism generated ketones, which caused ketoacidosis: a pH shift and edema of vital organs. Elizabeth had juvenile diabetes (now called type 1 diabetes), and in 1919, children with this type of diabetes lived only a few years. Even with the best medical care, Elizabeth would suffer muscle breakdown, her kidneys and other vital organs would eventually fail, and she would sink into a coma, followed by death a few hours later.



Figure 1. Elizabeth Hughes with her mother Antoinette in Rye, New York, in the summer of 1918. (Courtesy of the Thomas Fisher Rare Book Library, University of Toronto)

The Allen Plan

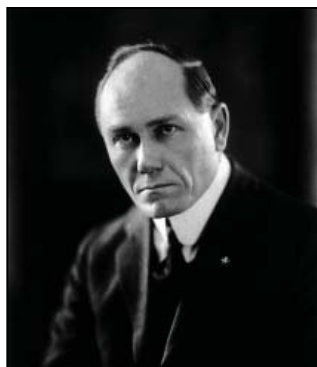


Figure 2. Frederick Allen (Courtesy of the National Library of Medicine)

Frederick Allen was one of America's leading diabetes experts. At the Rockefeller Institute, he had studied carbohydrate metabolism and cared for hundreds of diabetic patients. Based on his astute observations, he formulated the Allen Plan, considered the most successful treatment yet devised for diabetes. Allen's strategy restricted his patients' diet, allowing them to eat only as much food as their bodies could efficiently metabolize, however little that was. After titrating a patient's carbohydrate tolerance, he initiated a maintenance diet that was low in carbohydrates and fixed the total caloric intake just below the point where sugar spilled into the urine. His dietary restrictions reduced ketoacidosis, which relieved the distress of otherwise inevitable organ failure, and that prolonged patients' lives. Allen also advocated daily exercise, claiming it would help patients burn more calories and increase their strength. Patients with type 2 diabetes could lead a normal healthy life by following the Allen Plan. However, children with type 1 diabetes had extremely low carbohydrate tolerance, and many people called his plan the "starvation treatment." In the worst cases of diabetes, the Allen Plan prolonged life by only a few months; the caloric restrictions were so severe that the patients died from starvation rather than from diabetes.

To Allen's critics, his therapy seemed hard-hearted—a treatment so severe in cases of extreme carbohydrate intolerance that many patients could not or would not follow it faithfully. But Allen, a stern, cold, tireless scientist, was utterly convinced of the validity of his approach. His meticulous experimental and clinical observations convinced him that total dietary regulation was the *only* way to prolong the lives of diabetic patients. Nobody had a better solution. Elizabeth's parents accepted Allen's plan but never told their daughter how serious her condition was. They simply explained that to treat her illness, she had to stay on Dr. Allen's diet.

At the onset of diabetes, Elizabeth was four feet, 11-½ inches tall and weighed 75 pounds. She spent several weeks at Allen's Manhattan clinic, which to her was a horrible place. She disliked Allen, a square-faced, jowly man who never smiled and seemed intimidating. She also disliked the diet Allen imposed. During her first few days at the clinic, she was allowed no food at all and felt a raging hunger. Then, slowly, she was given small amounts of certain foods in a careful mix of protein, fat, and carbohydrates, until traces of sugar spilled into her urine. That marked her carbohydrate tolerance and established the caloric limit of her new daily diet. For several weeks, Allen prescribed a very low diet of 400 to 600 calories per day (with one day's fasting every week), then raised it to 834 calories per day. Her weight dropped to 55 pounds, and then he allowed Elizabeth to gain weight to the low 60s on a diet that went as high as 1250 calories, with one "near-fast" day of 350 calories each week.

Many diabetic children remained at the clinic under Allen's care, because the iron-willed discipline required for his diet to work was far too strict for the children and their parents to follow on their own. Even at the clinic, some patients took extreme measures to sneak in food and satisfy their unrelenting hunger. One twelve-year-old boy, whose diabetes had already caused blindness, was so weak that he could scarcely leave his bed. Allen was puzzled at finding sugar in the boy's urine, despite the most stringent monitoring of food intake and considering the boy's limited mobility. After further investigations, the boy finally admitted to eating toothpaste and birdseed from the cage of a pet canary he had requested for company.

Elizabeth's parents, knowing she was unhappy, wanted to care for her at home, and they hired Blanche Burgess, a nurse specially trained by Elliott Joslin, to prepare Elizabeth's meals, administer her urine tests, and monitor her adherence to the Allen Plan in the Hugheses' home. Other than Allen, Joslin was the most prominent American specialist in diabetes. Trained at Harvard and Yale, he had established a thriving diabetes clinic at New England Deaconess Hospital in Boston. Joslin was a strong supporter of Allen's plan and established a program in Boston to train nurses to supervise the rigorous diet program. A prolific writer, he had documented more than a thousand diabetes cases and published the first diabetes patient handbook, a best seller. Elizabeth liked Joslin, whose warm and optimistic manner contrasted sharply with Allen's stern personality. Both Allen and Joslin encouraged her to follow her diet faithfully. Starvation, hard as it was, represented the best hope for survival. However, they were under no illusion that the Allen Plan would permit a long life. They were merely buying time. They knew researchers around the world were closing in on an agent in the pancreas that seemed to regulate carbohydrate metabolism and might lead to a breakthrough in diabetes treatment.



Figure 3. Elliott Joslin (Courtesy of the Thomas Fisher Rare Book Library, University of Toronto)

Starving to Live

Elizabeth returned home at the end of April 1919 and relied on her own willpower and self-control, along with monitoring by her mother and Blanche, to manage her treatment. Allen and Joslin both knew that patients were more likely to comply with the Allen Plan when they took responsibility for their disease management, a novel concept in medical practice at the time. Actively participating in their care gave patients a sense of control over their lives. Elizabeth diligently kept her own log book, entering every morsel of food by category and calorie count, logging the results of her twice-daily urine analysis, and noting her body's general response to her diet. She soon learned that when traces of sugar appeared in her urine, she had to cut back her food intake.

For an eleven-year-old girl, 2,000 calories per day are recommended, about 2.5 times what Elizabeth was permitted. Her daily staples consisted of oatmeal, an occasional lamb cutlet or egg, a few fruits, leafy green vegetables, and an occasional glass of milk. The tasteless vegetables were boiled three times to eliminate all traces of carbohydrates. And every gram of food she ate was weighed beforehand. No sweets or bread allowed. Elizabeth was an obedient little Spartan, kept to her diet perfectly, and rarely showed sugar in her urine. Just once, at Thanksgiving, she sneaked into the kitchen for a piece of turkey skin. Blanche caught her and issued a stern reprimand. Elizabeth never cheated on her diet again.

She overcame the daily hunger that gnawed at her by practicing standards of discipline and determination that were characteristic of the Hughes family. Elizabeth's mother, Antoinette Carter Hughes, was the daughter of a prosperous New York lawyer and could trace her lineage back to the *Mayflower*. Elizabeth's father, Charles Evans Hughes, although from humble origins, had managed a meteoric rise to fame and amassed a modest fortune. A successful lawyer, Hughes had served as governor of New York, was appointed justice to the United States Supreme Court in 1910, stepped down in 1916 to run for president against Woodrow Wilson, and then returned to his father-in-law's New York City law firm to argue cases before his former Supreme Court colleagues. The family had a public reputation for hard work, discipline, and unimpeachable integrity. Privately, they were loving and playful, but they carefully balanced private needs with public duty.

In the summer of 1919, Elizabeth accompanied her mother to Glens Falls, NY, where her oldest sister, Helen, was convalescing from tuberculosis in the fresh, dry air. For the next ten months, Mrs. Hughes nursed her eldest and youngest daughters and watched them slowly waste away: Elizabeth was always hungry but was not allowed to eat, and Helen had no appetite for the food she desperately needed to fight tuberculosis. At the end of March 1920, as Helen lay near death, Elizabeth came down with tonsillitis. The first week of April, Elizabeth consistently showed traces of sugar in her urine, and her food consumption dropped dramatically to an average of only 400 calories per day. The next week, continuing to show traces of sugar, her food allowance decreased to 250 calories per day, and it moved only slightly above that for the next month. Monitoring her daily log, Elizabeth realized that both illness and the emotional stress of losing Helen, who died on April 28, affected her glucose tolerance levels.

By Christmas 1920, Elizabeth weighed 62¼ pounds. At the end of March 1921, she was down to 52 pounds. Her daily diet in April 1921 averaged 405 calories. Allen got her back up to 700 to 900 calories, but her weight was now at a new low plateau, between 52 and 54 pounds. At 13, Elizabeth was a semi-invalid.

To escape the oppressive summertime heat and humidity in Washington, DC, where her father was now President Harding's newly appointed Secretary of State, Elizabeth and her nurse spent the summer of 1921 in the Adirondacks of upstate New York. Elizabeth carefully planned her activities around her diet and limited physical strength. She had breakfast in bed and spent the mornings writing letters or reading, conserving all her energy for well-planned excursions or a stroll to the lake in the afternoons. Her cheerful letters to her mother never betrayed her poor health and constant hunger. She lightheartedly speculated about getting married and what she would do for her 21st birthday.

In December 1921, her parents sent Elizabeth and her nurse to Bermuda to enjoy the climate. By now, Elizabeth and Blanche had settled into a companion-like relationship. Blanche was no longer the disciplinarian or the only expert on Elizabeth's treatment. They worked as a team, adjusting her diet based on internal and external factors. To recover from the stress imposed by Washington's weather and the ocean voyage, they decided Elizabeth should eat only 400 calories during the first few days after her arrival. She then settled into an average diet of about 700 calories. The soothing Bermuda climate worked its magic, and Elizabeth gradually worked up to 800 calories, adding some variety to her diet with celery and spinach.

In March 1922, Elizabeth developed an eye infection and a cough that kept her up at night. Although she was reluctant to stay home and rest, she realized that she was weaker and spent more time reading. She was 14 and her intellect and interests had matured, but physically, her years of starvation dieting had delayed puberty. And at a scant 53 pounds, she was increasingly susceptible to infection.

In May 1922, she contracted diarrhea, an epidemic that was spreading throughout the island. Her fever spiked above 101°F, and she remained very ill for three weeks, recovering only slowly. Her weight and glucose tolerance slipped further. From May 19 to June 2, 1922, Elizabeth consumed less than 300 calories per day. Fully clothed, she weighed less than 50 pounds. After recovering from the bout of diarrhea, Elizabeth's carbohydrate tolerance improved and she was able to eat a little more. Her diet now included an occasional grapefruit, strawberry, or piece of fish, but not on the same day. Nevertheless, she grew progressively weaker and spent more and more time resting. She fought the lassitude and despair that overtook most diabetics in the final stages of sickness, and with her indomitable spirit, she continued to exercise every day. Although she was unable to stand up from a chair without help, she insisted on walking up the ramp to the ship that brought her home from Bermuda in late June.

The contrast between Elizabeth's upbeat letters and her shocking appearance when she arrived home on July 1, 1922, moved Antoinette to action. Mrs. Hughes had clipped an article that appeared in the local papers in May announcing a diabetes breakthrough at the University of Toronto. For years, both Allen and Joslin had written scathing critiques of the quack medicines (including opium and a ham and lettuce diet) that claimed to cure diabetes. But Allen assured Mrs. Hughes that this time the newspapers were right; he knew about the Toronto team's work. On July 3, she wrote to the Toronto investigator, Frederick Banting, explaining that despite the best care, her daughter was "pitifully depleted and reduced." Consistent with her high moral standards, Mrs. Hughes did not ask for any special consideration—stating only the facts of Elizabeth's poor health and assuring Banting that her daughter was a model patient. But she composed her handwritten letter on U.S. State Department stationery.

From Bench to Bedside



Since presenting their first human results with the crude insulin extract at the Association of American Physicians meeting on May 3, 1922, the Toronto team had been inundated with requests. Diabetic patients were literally camping at the doors of their laboratory trying to get insulin. Banting's reply to Mrs. Hughes on July 10 was the same standard reply he sent to all inquirers: insulin was still experimental, supplies were severely limited, and he would inform her when the situation changed. The Hugheses' only option was to try and keep Elizabeth going until insulin was beyond the experimental stage. Meanwhile, they watched their daughter, who now weighed only 48¼ pounds fully dressed, drift closer to death from starvation. Elizabeth had already lived with diabetes longer than anyone had predicted.

Following their discovery of insulin in the summer of 1921, Banting and his young assistant, Charles Best, had considerable difficulty reproducing their results. By early 1922, biochemist Bert Collip had made some improvements in the extraction procedure, and the team administered the partially purified substance to their first patient with encouraging, but temporary, success. Through a collaboration with Eli Lilly & Company, the Toronto team was able to obtain batches of higher purity and improved consistency, but the production of insulin, which was extracted from pancreases obtained at local slaughterhouses, was laborious and still experimental. Lilly's scaled up batches initially had lower potency than Collip's laboratory extract.

By August 1922, Lilly was making sufficient quantities with an optimized method so that the investigators could begin clinical trials. Because Banting and his colleagues had collected only limited preclinical data on the safety and efficacy of their extract and they knew an overdose could be fatal, Banting in Toronto and George Clowes at Lilly hand-picked a small group of diabetes specialists who had the skill and experience to study the experimental substance under systematic,

controlled conditions. In addition to Allen, Joslin, and a few physicians at Toronto General Hospital, this group of clinical investigators included Rawle Geyelin in New York City and John Williams in Rochester, NY.

Elizabeth's Final Journey

In Boston, Joslin gave the first shot to his first patients on August 6. On August 8, Allen met with Banting in Toronto to share his experiences with the Allen Plan and to obtain his allotment of insulin. Allen's most desperately ill patient was Elizabeth Hughes, who still clung to life but was going downhill fast. Through July, Elizabeth had been on a diet of 789 calories, but Allen had then added an extra 100 calories of fat daily, probably to hold off death from starvation until she could begin treatment with this new experimental compound. Although he could have treated her at his diabetes clinic, Allen convinced Banting to add Elizabeth to his list of private patients in Toronto, where supplies of the extract were more plentiful. He told Banting, "You will find Elizabeth a model patient in all respects...Elizabeth herself has a thorough knowledge of all details of the diet," emphasizing that the teenager had earned a rightful place in the queue through her self-discipline and determination, "in addition to any consideration due on account of her family." Allen returned to his clinic and gave his first patients the insulin extract

on August 10. In parallel, a flurry of telegrams bounced between Banting and the Hugheses, and within a few days Elizabeth was on her way to Toronto, accompanied by her mother and Blanche.

On August 16, three days before Elizabeth's fifteenth birthday, Banting examined his new patient and wrote in her chart, "wt. 45 lbs. height 5 ft. patient extremely emaciated, slight edema of ankles, skin dry & scaly, hair brittle & thin, abdomen prommt [sic], shoulders drooped, muscles extremely wasted, subcutaneous tissues almost completely absorbed. She was scarcely able to walk on account of weakness."

Banting began insulin treatment immediately. The first injections, one milliliter of the extract twice a day, cleared the sugar from Elizabeth's urine. For the first ten days, Banting cautiously increased her diet to between 1,100 and 1,200 calories per day, more than she had eaten since her diagnosis. Elizabeth found herself awakening from her nightmare of diabetes, diet, and starvation. While the diabetes experts kept their clinical trial patients on a conservative dietary regimen—not knowing how much a diabetic patient taking insulin could or should eat—Banting, a surgeon with limited clinical endocrinology expertise, thought the most important thing for a girl who weighed 45 pounds was to gain weight. He had access to plenty of insulin, so he prescribed a more liberal diet and gave Elizabeth enough insulin to match the food she ate. She gained seven pounds and enjoyed a larger variety of vegetables and fruits: plentiful amounts of tomatoes, peaches, eggplant, and cauliflower. On August 25, she started eating 2,000 calories per day. Seeing his patient continue to improve, Banting increased her food intake to 2,500 calories. One day for breakfast she ate two peaches, shredded wheat with heavy cream, an egg, bacon, and a slice of toast with lots of butter and cream cheese.

When Banting ordered her to have bread and potato, Elizabeth and Blanche thought he was joking. Elizabeth was delighted, but Blanche was so skeptical that she did separate urine tests each time Elizabeth urinated for 24 hours and could scarcely believe that there was no sugar. Elizabeth continued her meticulous daily records, logging her first piece of white bread in over three years (August 25), the first corn for supper (August 29), and the reintroduction of macaroni and cheese (September 7). Despite these additions, Banting kept Elizabeth's diet low in carbohydrates and supplied extra calories with fats, mostly through a daily pint of heavy cream. Elizabeth was now regularly eating liver, veal, chicken, salmon, orange juice, melons, grapes, potatoes—and more cream. Every day, she ate something that she had not tasted for over three years and wrote to her mother, who had returned to Washington, DC, "You don't know how good it seems and how much I appreciate every morsel I eat." In the first six weeks, she grew half an inch and gained ten pounds. Through the fall of 1922, Elizabeth's health returned and she continued to gain about two pounds per week. She did not recognize herself in the mirror.

Trial and error

But insulin was still experimental, and Elizabeth was an experimental subject, though a very special one. Impurities in the extract caused pain, abscesses, and swelling, and Elizabeth's hips were a mass of swollen lumps. Also, every batch of extract had a different potency. One batch was so weak that Elizabeth had to take five milliliters: three sequential injections with her 2 ml syringe. Her whole leg was numb until she walked it off, but she would endure anything for the sake of her new diet. Insulin was "simply too wonderful for words."

Although insulin had solved one problem (hyperglycemia), physicians, including Banting, were still struggling to understand insulin-induced hypoglycemia. They knew they had to balance the patient's diet with the right amount of insulin, but they did not have the technology to calculate this exactly. Because of the variability in batch potency, investigators had no option but to adjust the dosage of each new batch by trial and error, and patients inevitably experienced insulin overdoses. The symptoms resulting from low blood sugar could be unpleasant, even frightening. Patients felt a sensation of imminent disaster, like "standing in front of an oncoming train," followed by a variety of symptoms including profuse sweating, trembling muscles, sudden hunger, impaired coordination, accelerated heart rate, and dilated pupils. At first, these episodes frightened Elizabeth. Banting supplied her with molasses hard candies, which she used to elevate her blood sugar when she felt the onset of a hypoglycemic attack. As she learned to recognize the symptoms and gained confidence in dealing with insulin overdosing, the episodes became fewer and further apart.

Some experts hoped that insulin might cure diabetes, allowing the pancreas to rest and regenerate islet cells. In November 1922, Banting temporarily took Elizabeth off insulin to reassess her carbohydrate tolerance. Without insulin, she could handle only 933 calories before sugar spilled into her urine, the same as her old diet. Insulin could reverse a despairing patient's psychological outlook and permit a normal diet, but it did not correct the underlying metabolic impairment.

Later in November, the physicians who were leading the insulin clinical trials gathered in Toronto for a conference to discuss their results, coordinate their publications, and advise the manufacturers on dosage and manufacturing standards. Between meetings, Banting took a half dozen of them, including Allen, Joslin, and Best, to see Elizabeth. Her arrival in Toronto in August, as the daughter of the U.S. Secretary of State, had generated front page headlines in the local press and made her a minor celebrity. But Elizabeth hated publicity, kept a low profile during her treatment, and asked her family not to speak to reporters. She did not want to be the poster child for insulin. Now, she dreaded facing this tough group of clinical visitors, remembering the intimidating Allen. Instead, Allen and Joslin simply did not recognize the healthy teenager, who had gained 30 pounds under Banting's care. When Banting introduced her, Allen's jaw dropped and he was speechless. Joslin said he "never saw anybody with diabetes look so well."

Banting taught Elizabeth to give herself the shots of insulin, and she no longer needed a nurse to monitor her diet and treatment. She could now cook her own food, weigh and figure the quantities, and test her urine with Benedict's test. Four days after the meeting with the visiting clinicians, Elizabeth returned to Washington, DC, to celebrate Thanksgiving with her family. Her parents, who had not seen her for three months, greeted a daughter they barely recognized. Although the energetic fifteen-year-old was still short for her age, she had shining hair, bright eyes, and weighed 75 pounds.

Through the 1920s, Elizabeth continued her education and matured. By January 1923, she weighed 92 pounds and employed a strenuous exercise routine to work off some of her calories. She also found that she could manage by approximating her food portions and stopped weighing her food—another liberating step in her recovery. In college, she played sports, took up smoking, indulged in an occasional cocktail, and had an active social life, but she struggled to find a comfortable weight. When she reached 158 pounds, she decided that was too much for her 5 foot, 3 inch frame. She eventually dropped back to slightly below normal weight and gave up smoking, finding a balance between eating, exercise, and insulin in a daily routine that she maintained for the rest of her life.

Elizabeth graduated from Barnard College in 1929 and married William Gossett, a talented young lawyer, the following year. That same year, her father was appointed chief justice of the U.S. Supreme Court. While she was on the Allen Plan, Elizabeth never complained and her letters were always cheery, but the starvation treatment had been a "nightmare" and once she began taking insulin, she actively took steps to put those dreadful years behind her. She wanted no reminders of that terrible existence. Before donating her father's papers to the Library of Congress, she removed everything that referred to her diabetes and destroyed all photos of herself during her illness. With characteristic determination, she moved on with her life, telling no one of her diabetes or insulin dependence. Even Gossett did not learn her secret until a week after their engagement. (Before insulin, diabetic women were usually unable to carry pregnancies to term, and they had only rarely been successful in the few years since.) He needed to know that it might not be possible for them to have a family.

With the help of her physician and her well-honed discipline, Elizabeth gave birth to three healthy children, each delivered by cesarean section, and she miscarried only once. She led an active life, editing her father's papers, founding the Supreme Court Historical Society, and supporting various charitable causes. Regardless of her activities and frequent travel, she always kept disciplined eating habits, regular mealtimes, and a strict regimen of daily exercise. And twice a day, she discretely took her insulin shots. The first one was part of her morning routine. At 5:00 p.m., she went to her bedroom and took the second shot behind a closed door. Her children saw nothing unusual and did not know about her condition until they were adults.

Elizabeth Hughes Gossett died at the age of 73 on April 25, 1981, of a sudden heart attack, perhaps exacerbated by the lifelong challenges of diabetes. To the end of her life, she was slim, attractive, husky-voiced, and somewhat wizened but free of the debilities of legs and eyes that often plague diabetic patients in old age. She remained mentally alert and more intellectually supple than many people half her age. In 58 years, she had taken more than 43,000 injections of insulin, and at the time of her death, she was the longest known surviving patient with type 1 diabetes.

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Rebecca J. Anderson, Ph.D., holds a B.A. in chemistry from Coe College and earned her doctorate in pharmacology from Georgetown University. After several industry positions in pharmaceutical research and development, she now works as a technical writer and is the author of *Career Opportunities in Clinical Drug Research*. Email rebeccanderson@msn.com.

Benedict's urine test

Benedict's test is a simple procedure that allows diabetic patients to detect the presence or absence of glucose in their urine. Benedict's solution includes copper(II) sulfate, sodium carbonate, and sodium citrate. Blue copper(II) ions are reduced by monosaccharides to produce copper(I) ions, which are precipitated as red copper(I) oxide. A color change indicates the presence of glucose:

- clear blue, sugar absent
- opaque green, 0.5% sugar
- opaque yellow, 1% sugar
- opaque orange, 1.5% sugar
- opaque brick red, 2% or more sugar

Career Center

by Suzie Thompson

New Employer Interface

In an effort to keep the ASPET Career Center relevant, attractive, and user friendly, we are happy to announce new enhancements to the Employer Interface. Now, when employers visit our career center, they will see a more modern layout, better organized content, and easier access to post a job or find employer product pricing. Visit the Career Center at <http://careers.aspet.org/employers/> to view the changes and post a job!

Talent Blast

Also new for employers, the ASPET Career Center is offering a new *job posting enhancement* called "Talent Blast." When you post your job with our career center, you can add "Talent Blast" to your job posting package to gain increased exposure for your job. Talent Blast combines sophisticated posting optimization (SEO) and targeted ad campaign management (SEM) to hundreds of additional job sites, providing ultimate exposure and performance that result in more qualified applicants for your job. By adding "Talent Blast" to your job posting:

- Your job posting is optimized (SEO) to rank higher in search results for better visibility on job aggregator sites and job search engines
- Your job posting is distributed to hundreds of additional relevant job boards including vertical sites, regional sites, diversity sites, and even social networks as part of paid ad campaigns (SEM)
- SEO and SEM ad campaigns are monitored and adjusted real-time to achieve the best performance possible
- Your posting is sent to passive job seekers from a national database who match your requirements

We are introducing this new feature at just \$99. This special price is only available until October 1, 2013. To take advantage of this new feature and to post a job, visit us at: <http://careers.aspet.org/employers/>.

Responsive Design

We are also happy to let you know that the ASPET Career Center has incorporated responsive design elements to both the "Employer" and "Job Seeker" pages. This allows users to have an enhanced viewing experience by automatically shifting and re-sizing the career center pages based on the type and orientation of the mobile device you are using.

As always, we continue to look for ways to improve our Career Center for both employers and job seekers. If you have any suggestions or comments about how we can make your user experience better, please feel free to contact Suzie Thompson, sthompson@aspnet.org.

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Journals

by Rich Dodenhoff



Mary Vore to Be Next BPT Chair

Dr. Mary E. Vore was approved by ASPET's Council to serve as the next chair of the Board of Publications Trustees. Dr. Vore will succeed **Dr. James E. Barrett** at the end of this year when his six-year term ends.

Dr. Vore is the Director of the Graduate Center for Toxicology at the University of Kentucky College of Medicine. She has been an ASPET member since 1975 and is very active in the Society. Her service to ASPET includes two terms as Secretary-Treasurer, Chair of the Division for Toxicology, two terms on the Program Committee, and service as a member or chair of the following: Board of Publications Trustees, Bernard B. Brodie Award Committee, Executive Council for the Drug Metabolism Division, Subcommittee on Public Information, the SOT-ASPET Liaison Program Committee for the 1982 joint meeting, and the Membership Committee.



Mary E. Vore, Ph.D.

Dr. Vore has also been active in the Society of Toxicology, serving on its Board of Publications, the SOT Awards Committee, and the Mechanisms Section, for which she filled the positions of Vice President and Councilor.

Her editorial experience includes serving as an associate editor for *Molecular Pharmacology* and membership on the editorial boards of *Drug Metabolism and Disposition*, *Molecular Interventions*, the *American Journal of Physiology: Gastrointestinal and Liver*, *Toxicology*, *Toxicology and Applied Pharmacology*, *Trends in Pharmacological Sciences*, and *Environmental Health Perspectives*. She is an ad hoc reviewer for over a dozen other journals.

Beyond her service to professional societies and peer-reviewed journals, a sampling of Dr. Vore's activities include serving as a member or chair of NIH Study Sections, the NIH National Advisory Environmental Health Sciences Council, the Applied Pharmacology Task Force of the National Board of Medical Examiners, the National Research Council's Committee on Toxicology, and the Board of Scientific Counselors and Technical Reports Review Subcommittee of the National Toxicology Program.

ASPET's Board of Publications Trustees was formed by a constitutional amendment on March 16, 1948 "with authority and responsibility delegated by the Council to control and manage, both editorially and financially, the Society's journals and nonserial publications" (from ASPET's bylaws). Dr. Vore will be the 15th person to lead the BPT. In addition to Dr. Barrett, counted among the previous BPT chairs are Otto Krayer, Karl Beyer, Walter F. Riker, Jr., James A. Bain, Norman Weiner, William W. Fleming, Joel G. Hardman, Kenneth E. Moore, T. Kendall Harden, and Brian M. Cox.

Concatenated PDFs

ASPET's journals have a new feature: for articles with data supplements, readers can now print a single PDF file that includes the formatted article *plus* any printable data supplements. These "concatenated" PDFs are available from a "PDF + Data Supplement" link. Separate PDFs for the article itself and its data supplements continue to be available.

This brings good news to those who objected to the journal's name running down the left side of every PDF page. The stripe now appears on only the first page of each article. A line of text identifying the journal's URL and the date of the download appears on the right side of the first page. If an article is downloaded at an institution or organization that can be identified by our subscription system, the name of that entity will also be included in that line.

Concatenated PDFs first appeared on July 25.

Continuous Publication for All ASPET Journals

Effective with the January 2014 issues, all ASPET journals will be published continuously. Fully formatted articles will be posted online as soon as they are ready rather than being held to release the content of an entire issue at one time. *Pharmacological Reviews* has been published this way since January 2013. *Drug Metabolism and Disposition*, *JPET*, and *Molecular Pharmacology* will move to continuous publication with the first January articles appearing as soon as possible once the December issues close in November.

Under monthly publication, issues go online approximately two weeks before the month on the cover. With continuous publication, each issue will close on the first business day of the cover month. For example, the January issues will be completed on January 2, the February issues on February 3, the March issues on March 3, and so on.

ASPET publishes the manuscript version of articles for *DMD*, *JPET*, and *MOL* as soon as they are accepted. Continuous publication will allow the formatted version to appear up to a month sooner than under monthly publication.

Articles that are best published as a group such as a pair of companion papers or the papers in a special section may be posted on the same day, at the editor's discretion.

Readers will have the option of receiving an email message each time new content is posted or of only getting an email with the complete table of contents when an issue closes. Content alerts for "Fast Forward" (publish ahead of an issue) articles and keyword/author alerts will continue to be available. Initially all recipients of tables of contents alerts will receive the new content alerts. No more than one content alert per journal will be sent each day. Look for an email message in November after the December issues go online explaining how to adjust your alert settings.

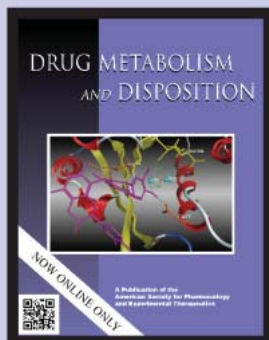
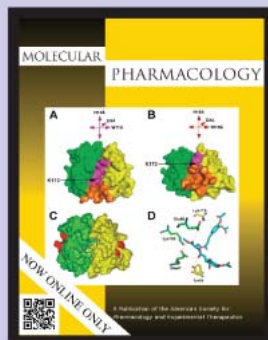
New Editorial Board Members

Pharmacological Reviews welcomed two new Associate Editors recently. **Dr. Jeffrey M. Witkin** is with the Psychiatric Drug Discovery Department at Lilly Research Labs, Eli Lilly and Company. He is also an Adjunct Professor with the Department of Psychology, Indiana University-Purdue University Indianapolis and serves on the graduate school faculty at Purdue University. **Dr. MacDonald (Mac) Christie** is a Professor of Pharmacology at the University of Sydney. He is also a Senior Principal Research Fellow with the National Health and Medical Research Council and Associate Dean Research for the Sydney Medical School.

Dr. Donald E. Mager joined the *JPET* Editorial Board as an Associate Editor. Dr. Mager is an Associate Professor of Pharmaceutical Sciences at the University at Buffalo, The State University of New York.

The Board of Publications Trustees appreciates the commitment of these researchers to *Pharmacological Reviews* and *JPET* and is grateful for their service.

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Science Policy

by Jim Bernstein



Congress Returns Facing Difficult Choices

After a five-week hiatus, Congress returned September 9. Among many policy issues to address, legislators will have to confront wildly divergent spending bills that fund government programs and agencies, including the NIH. From this date to the end of the fiscal year, September 30, there is virtually (absolutely) no chance an agreement could be in place for the start of FY 2014 on October 1.

The Senate budget is \$91 billion higher than the House budget. The Senate also replaces the sequestration for 2014. However, the House budget includes sequestration and is based on spending cap levels well below those mandated by the 2011 Budget Control Act. The House and Senate budgets are top line numbers and as a result each chamber is producing appropriation bills so far apart they cannot be reconciled. Another reason why cuts are so incredibly severe in the House is that House Republicans passed defense and veteran's appropriation bills at higher levels than allowed under sequestration. By restoring defense funding, spending caps were breached and additional cuts had to come from non-defense discretionary programs such as the NIH.

In late August, the House/Labor/HHS appropriations subcommittee (that funds the NIH) was scheduled to "mark-up" its spending bill. The mark-up was cancelled, largely because the reductions in their bill are over 18% less than FY 2013 and almost 26% lower than the Senate. Assuming that the subcommittee applied these cuts equally to all programs under its jurisdiction, the NIH would receive a cut of over \$5 billion, putting its FY 2014 budget at just over \$23 billion. Members of Congress are finding it difficult to actually cut or gut programs that have already been reduced by this year's sequester. So, rather than mark-up its bill, the subcommittee simply did not consider it. Unlike the House Labor/HHS spending bill that has not been acted upon, the Senate Appropriations Committee approved the FY 2014 Labor/HHS spending bill by restoring funding for medical research to pre-sequestration levels. The Senate bill provides NIH a \$1.8 billion increase (just over 6%) above the current FY 2013 pre-sequestration level for a FY 2014 NIH budget of \$30.9 billion.

Congress will have to pass a Continuing Resolution (CR) to fund the government beginning October 1. The terms of the CR would have to be negotiated and there is no guarantee what that outcome might be. Typically, a CR splits the difference. In this scenario, a CR splitting the difference between the House and Senate bills would still mean that NIH would bear the brunt of a budget cut for FY 2014.

The politics of these negotiations is difficult, particularly for Republicans. Having earlier in the year accepted the broad budget cuts outlined in House Budget Committee Chair Paul Ryan's (R-WI) proposal, Republicans now realize that, when the rubber hits the road, they simply can't pass spending bills with cuts this deep. Besides not marking-up the Labor/HHS bill, this proved true when Republicans stopped consideration of an appropriations bill funding transportation and housing programs. The votes simply were not there.

But Tea Party politics are greatly influencing the debate. Before adjourning in early August, House Speaker John Boehner (R-OH) warned, "Sequestration is going to remain in effect until the President agrees to cuts and reforms that will allow us to remove it." And Senate Minority Leader Mitch McConnell (R-KY) is facing a potentially difficult primary challenge, making him move farther away from seeking any possible solution and compromise with Democrats. But there may be some shift and moderation among some conservative Republicans. Appropriations Committee Chair Harold Rogers (R-KY) noted that, "sequestration and its unrealistic and ill-conceived discretionary cuts must be brought to an end." Senator Lindsey Graham (R-SC) artfully stated that, "We screwed ourselves here," referring to the 2011 Budget Control Act that triggered sequestration.

Ahead are the upcoming debt ceiling negotiations that will also impact final spending decisions.

The overriding question facing legislators is how to stop sequestration, and at this moment, there does not seem any way to get from here to there. If there is a sequestration, it would be implemented after January 1. The one thing we can be certain of is that no one really knows how all these moving parts will play out and what the outcome will be for NIH. But the threat of sequestration persists. It remains critical that you contact your Congressional representatives to inform them of the threats to your institution and the research enterprise. For information on how to contact your Congressional representatives, visit the ASPET advocacy Web page: <http://www.aspet.org/Advocacy/Grassroots/>.

ASPET Washington Fellows Publish Op-Eds in Support of Increased Funding for NIH

Several ASPET members of the 2013 class of ASPET Washington Fellows published letters and opinion pieces in their local papers that make a strong case for increasing federal support for the NIH. ASPET Washington Fellows **Matthew Robson** (currently a postdoc at Vanderbilt University), **Abigail Schindler** (postdoc at University of Washington), and **Tricia Smith** (postdoc at Virginia Commonwealth University) make a compelling case for increasing funding for the NIH. Their articles appeared in the Morgantown, WV; Seattle, WA; and Richmond, VA newspapers respectively this summer and can be found by visiting the ASPET website at <http://www.aspet.org/Advocacy/Grassroots/>.



Abigail Schindler, Ph.D. Matthew Robson, Ph.D. Tricia Smith, Ph.D.

The application deadline for 2014 ASPET Washington Fellows Program closed September 1. Those applicants selected will be notified by the end of this month.

Postdoc Corner

by Joanna K. Sandilos Rega, Ph.D. and Uyen B. Chu, Ph.D.

In an effort to reach out to postdoctoral and graduate student members of ASPET, two of our postdoc members, Joanna Sandilos Rega and Uyen Chu, have undertaken the effort to start a blog on the ASPET website geared towards the population of young scientists. Below, you will find introductions to Drs. Rega and Chu and their thoughts about the direction in which they are hoping to take the blog. Visit <http://www.aspet.org/Blog.aspx?blogid=400>.

Joanna Sandilos Rega

Introduction

My name is **Joanna Sandilos Rega**, and I am a postdoc at Fox Chase Cancer Center in Philadelphia, PA. I graduated in 2007 with my B.S. in biology from Penn State University and earned a Ph.D. in pharmacology from The University of Virginia in 2012. My graduate research was focused on molecular mechanisms of ion channel regulation in the context of apoptosis and cell clearance, with an emphasis on GPCR and caspase-dependent pathways. As a postdoc, I am studying a relatively novel macromolecular complex that is involved in nucleotide synthesis (cytoophidia). Specifically, I am interested in understanding the molecular mechanisms that underlie the assembly and disassembly of these structures, as well as their functional role(s) in normal physiology and cancer biology. I hope to gain experience in cancer cell signaling as well as high throughput assay development during my postdoc in order to expand my experimental skill-set.



Joanna Sandilos Rega, Ph.D.

Blogging on Leadership and Management

The National Postdoctoral Association defines a set of "core competencies" that a well-rounded postdoc should strive to develop. I will be focusing my blog entries on the core competency of leadership and management.

Some people are naturally blessed with innate people skills and project management skills, but many scientists find themselves in a managerial position (in industry, government, or as an assistant professor) while having little to no experience with the issues that come along with this type of role. The educational pipeline (undergraduate --> graduate school --> postdoc) is designed to train a good experimentalist, but many programs overlook the necessity to develop, or even address the issues of management and leadership skills.

The good news is that, as postdocs, we come across opportunities to hone our managerial skills every day, but often times they are overlooked and not taken advantage of. In this current funding and job climate, it is even more important to develop not only as a fantastic experimentalist but also as a team player, leader, and well-rounded project manager.

Uyen Chu

Introduction



Uyen Chu, Ph.D.

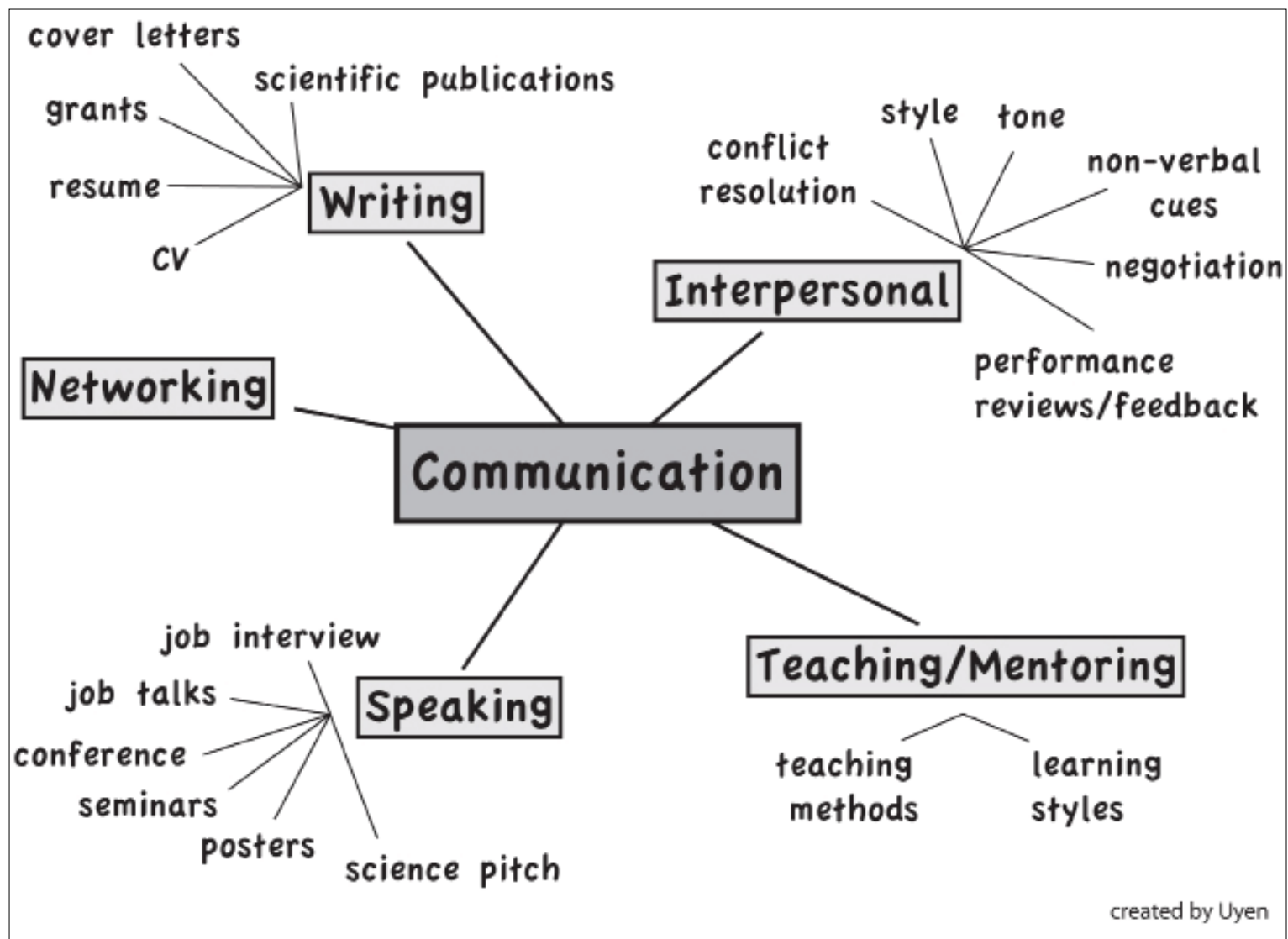
My name is **Uyen Chu**, and I am a postdoc in the Department of Neuroscience at the University of Wisconsin – Madison (UW-Madison). I obtained a Bachelor of Science degree in chemistry and biochemistry at the University of Nebraska – Lincoln (UNL) in 2005 and a Ph.D. in pharmacology at UW-Madison in 2011. My graduate research focused on the synthesis and characterization of drug binding site(s) on the sigma-1 receptor, a membrane chaperone implicated in neuroprotection specifically during the propagation of neurodegenerative diseases. My current postdoctoral research is aimed at unraveling the cellular signaling pathways leading to statin-associated muscle myopathy with a goal of identifying small molecules that mimic the beneficial pleiotropic effects statins but are devoid of the toxicity with long-term statin use. I am a pharmacologist at heart and my overall scientific interests span the areas of drug discovery to determination of the mechanism of drug action and toxicity.

Blogging on Communication

My goal for this blog is to use it as a platform for me to learn and tweak some of the communication skills that are deemed important by the National Postdoctoral Association (NPA) but that I felt is lacking from my formal graduate training. Plus, I have always believed that the best way to learn something is to write about it and get some feedback.

If you're a postdoc, I bet you have sat through seminars where the science was so interesting and relevant to your work, but the presentations were so awful that instead of focusing on the research results, you wondered how the speakers have made it this far in their career. Or you have read journal articles where you could understand the figures but not the writing. I think it's a misconception to think that those with Ph.D.'s are good at communication. While graduate schools provide ample opportunities to develop speaking and writing skills, the training is not systematic. And in my opinion, the current graduate education system emphasizes heavily on some aspects of communication while leaving others underdeveloped such as communicating science to the lay audience. Fortunately, as postdocs it is not too late to hone in on some of these skills.

So below is a diagram that I created of specific communication skills – it is a modification of those listed on the NPA Core Competency web-page. I will use this diagram as a roadmap for my blog on communication – hopefully this will be as fun of a challenge as I imagined.



ASPET

On The Web



Join the conversation Online!



Creating and Maintaining a Social Media Presence: Articles of Interest

For those of you who have embraced social media, we have compiled a handful of tips, tricks, and other helpful information to maximize your experience with these tools.

Facebook introduces embeddable posts

<http://mashable.com/2013/07/31/facebook-embeddable-posts/>

Want to capture a previous Facebook post and embed it into a blog or another Web page? This article gives you the rundown on Facebook's new embedding feature.

Facebook photo sharing tricks

<http://news.yahoo.com/blogs/upgrade-your-life/facebook-photo-sharing-tricks-152534860.html?vp=1>

Have you ever seen a photo on someone's Facebook page that you absolutely loved and wanted to download? This article tells you how to capture that memory and save it so that you no longer have to rely on Facebook to see it.

How to delete your Facebook search history

<http://mashable.com/2013/06/08/facebook-search-history/>

This step-by-step slideshow shows you how to clear your Facebook cache.

Facebook just launched a new feature: Here's how to protect your profile from unwanted searches

<http://finance.yahoo.com/news/facebook-just-launched-a-new-feature--here-s-how-to-protect-your-profile-from-unwanted-searches-185253200.html?page=all>

Here is another detailed "How-To" that you'll want to pay close attention to in order to maximize your privacy on Facebook.

How to lock down Facebook privacy

<http://mashable.com/2013/07/09/facebook-privacy-how-to/>

Need the latest tips on how to keep things in your profile private? Read through this in-depth piece. Don't forget to also check out ASPET's document on maintaining your privacy on Facebook: http://www.aspet.org/uploadedFiles/Knowledge_Center/Social_Media_Resources/Privacy%20tips%20for%20Facebook%20061313.pdf

The limits of Facebook's search tool

<http://bits.blogs.nytimes.com/2013/07/08/the-limitations-of-facebooks-new-search-tool/>

Graph Search is a great tool, but it won't tell you if your fellow ASPET members "like" pharmacology unless that is stated in their Facebook profile. For a detailed narrative of Facebook Graph Search in Facebook's words, visit <https://newsroom.fb.com/News/684/Graph-Search-Now-Fully-Launched-in-US-English>.

With new improvements, Facebook brings Graph Search function to all U.S. users

<http://abcnews.go.com/Technology/facebook-graph-search-function-rolls-us-users/story?id=19597958>

Remember when the Facebook search bar changed a couple of months ago? This explains the features of Facebook's new Graph Search feature, which allows you to search for people, pictures, places and things that your friends "like" in an easier manner than you previously could on the site.

Pipe app finally brings file transfer to Facebook

<http://mashable.com/2013/06/04/pipe-app-facebook/>

Need to transfer files on Facebook? There's an app for that. Pipe allows you to send files of up to 25 MB.

Facebook introduces hashtags

<http://news.yahoo.com/facebook-introduces-hashtags-174050349.html>

Hashtags have now made their way over to Facebook. Use them to identify and search for various topics in the same manner you use them on Twitter.

6 things you can do now to be stealthier on the Internet

<http://www.nbcnews.com/technology/6-things-you-can-do-now-be-stealthier-internet-6C10312932>

This article provides tips on things to do to help avoid hackers. There are no 100% foolproof methods. Yet, when you are connected to the Internet, there are some things you can do to increase the chances that your information will be safeguarded.

Why 'to tweet' is lowercase but 'to Google' is not

<http://news.yahoo.com/why-tweet-lowercase-google-not-220907622.html>

For those of you who are grammarphiles, here is a short read and an interesting case of grammar.

More tips on social media and electronic resources can be found online at: <http://www.aspet.org/knowledge/social-media-and-other-electronic-resources>.

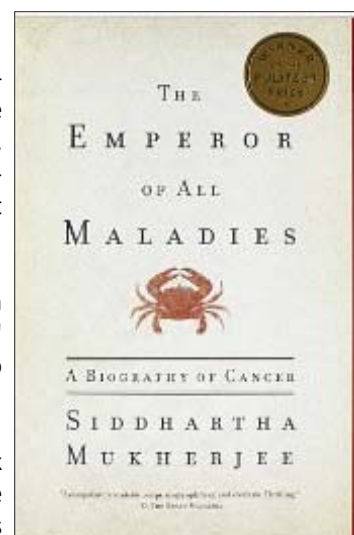
Book Review

by Christine K. Carrico, Ph.D.

The Emperor of All Maladies: A Biography of Cancer, Author: Siddhartha Mukherjee

John Lazo recommended that I read the Emperor of All Maladies. I am grateful for his recommendation, because I thoroughly enjoyed the book, and not only because I was in the cancer research field during a large portion of the time covered in the book. Mukherjee treats cancer, the disease, almost as if it were a person, and the book reads very much like the biography in the title, complete with name dropping of all of the luminaries in the chemotherapy, surgery, and other cancer treatment fields. Treating cancer as an individual isn't an easy task since cancer is not a single disease with a single cause.

Dr. Mukherjee begins the book with the sentence "Cancer begins and ends with people." This book deals with the very human face of cancer. Many of the patients discussed are Dr. Mukherjee's own. Others, like "Jimmy," became a national face for cancer. In all cases, however, the author preserves the dignity of the patients to the extent that he can given that cancer is a disease that robs patients of their dignity.



Breast cancer pink ribbon

Dr. Mukherjee's biography wanders back and forth through time and history, going as far back as Atossa, the Persian queen, who was perhaps the first recorded case of breast cancer. The treatment of breast cancer through the years is chronicled in great detail, from the horrendous disfigurements of the Halstead radical mastectomy through the near miraculous responses to Herceptin. Along the way, Mukherjee meticulously describes the rivalries, professional jealousies, and treatment successes and failures, especially between the surgeons, the chemotherapists, and the preventionists. Leukemia also is covered extensively since it proved to be one of the first pharmacologically responsive cancers. Mukherjee covers in fascinating detail the single-minded alliance between Sydney Farber and Mary Lasker to defeat cancer, culminating with the Congressionally mandated War on Cancer. He follows the struggles among individual investigators such as Emil Frei and Emil Freireich (the two Emilis) and the National Cancer Institute, the euphoria that came from the discovery of the Rous Sarcoma Virus (and the short-lived sense of victory that the cause of cancer had been found), and the evolution of the American Cancer Society from its turgid roots to a dynamic force in research. You feel the excitement when effective drugs such as vincristine from the Madagascar periwinkle are found to be effective, and you cringe with the attempts of oncologists to push multi-drug chemotherapy to the limits of toxicity and beyond in an effort to rid their patients of cancer. All along the way, patient vignettes illustrate and highlight the fact that this isn't a dry medical history, but is the story of individuals.



Madagascar periwinkle, source of vincristine



Cancer virus

Many of you may remember the "Jimmy Fund" which involved red and white tin cans at baseball games, movie theatres, stores, hotels, etc. This fund, the "Children's Cancer Research Fund," was the brain child of Sydney Farber and was designed to raise money to treat childhood leukemia (and build Farber's own research building). It became the official charity of the Boston Red Sox. "Jimmy" was a little boy suffering from leukemia who became famous overnight as the baseball-loving poster child for leukemia. It was a hugely successful fund-raising campaign and took on such a life of its own that people soon forgot the "Jimmy" behind the campaign, assuming he died like virtually all children with leukemia had done. Imagine the shock when the Jimmy Fund development office got a letter in 1998 informing them that "Jimmy" (real name: Einar Gustafson) was still alive fifty years later and living quietly in Maine.

It is a mark of what an interesting story this is and how readable the book is that Ken Burns (*Baseball, The Civil War*) is collaborating with the author to produce a TV documentary due to be released in 2015.

Calling all bookworms!

If you have recently read a pharmacology- or science-related book, fiction or non-fiction, that you found interesting enough to share with your peers, we invite you to write a book review of it for *The Pharmacologist*. For further information, please contact **Gary Axelrod** at gaxelrod@aspet.org or **301-634-7916**.

Interviews with ASPET Members

Our members come from a diverse array of backgrounds, pharmacological interests, and career levels. "In the Spotlight: Interviews with ASPET members" picks three ASPET members from each category of membership (Regular, Postdoc, and Student) to interview for each issue of The Pharmacologist. Get to know your fellow members:

JOANN TREJO, Ph.D.

University of California, San Diego - ASPET Regular Member



Who or what have been your greatest influences in your work/studies?

There are certain scientists that I look up to, learn from and try to emulate. I am particularly influenced by scientists that are not afraid to expose their mistakes, misjudgments, and/or humane flaws.

What do you find most challenging about your work?

The most challenging part of my work is trying to balance the time I spend on my own research versus professional service. I am involved in many education and outreach activities at the University, and I work on advocacy activities for several national societies. I also serve on editorial boards, as an *ad hoc* peer reviewer for many journals, and I am a regular member of an NIH Study Section. While I believe research should be the priority, as scientists, we also have a responsibility to serve the science community and to educate and train scientists. I also strongly believe that as scientists, we must learn to advocate for science, because if we do not convince the public that our work is important for improving the health and lives of Americans, our funding will continue to dwindle away. Therefore, I must find ways to work efficiently and effectively to complete tasks important for my research, education, and outreach activities, and this is a challenge.

What drew you to the University of California, San Diego?

The science. The Department of Pharmacology at University of California, San Diego is one of the best in the country. It has one of the most comprehensive research programs and is renowned for its strengths in signal transduction, computational, and structure-based drug design. Many research efforts focus on the identification of drug targets and therapeutic development for cancer, cardiovascular, inflammatory, and neurological diseases.

Outside of pharmacology, what are some of your other interests or hobbies?

I am interested in the education and career development of the next generation of scientists. As far as hobbies, I like to be outdoors biking, running, and hiking. I especially enjoy backpacking and exploring Yosemite and the Sierra Nevada Mountain Range.

Do you have any suggestions for ASPET regarding anything in the organization in which you would like to see improvement?

I am impressed with the Science Policy Committee. However, I think the Committee will need to develop better efforts to engage the membership in science advocacy, particularly at the local level.

What advice would you offer to aspiring pharmacologists?

I would advise young pharmacologists to follow their passion, find great mentors, seek career advice, and take advantage of opportunities to enhance their career development.

When you leave your lab/office for the final time, what do you hope to have accomplished in your career? Please be as specific as possible.

I hope to have made significant contributions to our understanding of how protease-activated receptors regulate cellular responsiveness. I also hope to make important contributions to science education, training, and increasing the diversity of science.

PRASAD KRISHNAN, Ph.D.

Pennsylvania State University - ASPET Postdoc Member



What sparked your interest in pharmacology?

My initial interest was in becoming a physician and playing a role in the treatment of various diseases, but I soon realized that there are still many diseases without a cure in which even physicians have their hands tied, like cancer. I dream of finding a cure for cancer. It is always nice to have a lofty goal; however, it will be a great service to humanity if I can contribute through my research towards this goal even a bit.

What do you find most challenging about your work?

Deciphering the molecular signaling pathways in my study is both challenging and intriguing as many factors can contribute to a cancer disease pathogenesis. Over the years, this has contributed greatly to my critical thinking and problem solving skills.

Tell us about your most favorite experiment/study with which you have been involved.

I am interested in cancer prevention with natural products. My Ph.D. thesis was on breast cancer prevention with auraptene, a natural compound found in citrus fruits. This was an interesting study in which I saw a significant delay in tumor occurrence with auraptene. Subsequent analysis established for the first time the concentration of auraptene in mammary glands (the target site of action) after its dietary administration. Further mechanistic studies showed the suppression cell cycle machinery with auraptene treatment. This project also gave me the exciting opportunity to analyze human breast cancer specimens to analyze biomarkers of breast cancer.

What might someone be surprised to know about you?

I think my degree in management with specialization in marketing with a couple of years of experience in a consulting firm in India might be surprising!!

How has membership in ASPET benefitted you and your career thus far?

I have been a member of ASPET since I was a graduate student. ASPET membership has helped me to attend EB meetings and I have received travel awards from ASPET both as a grad student and as a postdoc. These awards have contributed to improve my visibility among my peers and future employers. The career sessions in EB meetings are very helpful for an early stage scientist like me. In addition, there are a lot of scientific sessions and social events to network with other pharmacologists and ASPET leaders.

What do you see in store for the future of pharmacology? How do you see the science advancing?

Pharmacology has been the backbone of modern medicine, and it will remain so. The various aspects of pharmacology including dose-response, clinical therapeutic effectiveness, safety, and toxicity form the underlying basis of drug discovery. Pharmacology blends with the developments in the fields of genetics, molecular biology, biochemistry, etc. In the future, pharmacologists will keep playing an important role in ensuring the safety and effectiveness of individualized medicine, which is the future of therapeutics.

MOLLY K. ALTMAN, B.S.

Univ of Georgia College of Pharmacy - ASPET Graduate Student Member



What sparked your interest in pharmacology?

I graduated from the University of Florida with my bachelor's degree in psychology and neuroscience. While at UF, I worked in the lab of Dr. Edwin Meyer in the Department of Pharmacology at UF's Medical College as a student researcher. In addition, I was doing research in the Movement Disorder Clinic at the McKnight Brain Institute at UF. During my time in these two labs, I studied the mechanisms behind Alzheimer's disease and Parkinson's disease and how researchers can target these mechanisms to create drug therapies for patients. I was fascinated by the process of drug development and the science innovation behind pushing something forward from the bench to the bedside.

What drew you to the University of Georgia?

My family was stationed in the Navy at NAS JAX in Jacksonville, FL where I grew up. I started going to the Florida/Georgia football games when I was in high school. Although I went to Georgia's rival the University of Florida for my undergrad, I was interested in going to Georgia. Once I made the decision to start searching for graduate programs in pharmacology all across the country, my search led me to discover the University of Georgia's program in Pharmaceutical and Biomedical Sciences. I researched it further and discovered the program had a number of top-notch faculty and the department was growing, so I decided to apply. The Department of Pharmaceutical and Biomedical Sciences at UGA is a very collaborative and interdisciplinary environment for researchers and students. Nearly five years later and close to graduating, I'm very happy with my decision to pursue my doctoral degree at UGA!

How would the people in your program describe you?

People in my program would describe me as very involved, people oriented, and dedicated; once I start something I will see it through to completion! Since starting my program in January of 2009, I have been involved in departmental and campus-wide leadership as UGA's student chapter president of AAPS (2010 - 2011), and I am currently president of the Graduate Students and Post-Docs in Science organization at the University of Georgia.

What do you like to do for fun?

I really enjoy playing music! I've been a member of UGA's Philharmonic orchestra for all four years that I have been in graduate school. I also love being outdoors. Most weekends you will find me either running, cycling, or playing intramural soccer with other graduate students at UGA. My fiancé and I have just adopted our first dog, and we enjoy taking him for walks together.

How are you hoping that membership in ASPET will benefit your career and interest in pharmacology?

My membership in ASPET has already benefitted my career development tremendously, and it has continued to feed my passion for pharmacology. ASPET has provided great opportunities to travel to conferences and to meet senior accomplished researchers in the field, young faculty, and graduate students all pushing the interface of pharmacology and medicine. I feel like I'm a part of a close-knit community of pharmacologists. As a member, I've also been able to advocate for NIH and science funding as part of ASPET's Washington Fellows Program.

What are your career goals or aspirations in pharmacology?

In the future, I would love to be a professor teaching pharmacology at a medical school or college of pharmacy while conducting research. I really enjoy interacting with students. I feel I really benefitted from the mentorship of my professors, and I'd like the chance to give back to other students. Also, I really enjoyed the collaborations with pharmaceutical and chemical companies that I was able to work on while conducting research at UF and UGA. I'd like to foster these types of collaborations in my own future research.

ASPET

Early Career Pharmacologists

Resources Available for Undergraduates,
Graduate Students, and Postdoctoral Fellows

- * Awards & Fellowships
- * Information on Graduate Studies in Pharmacology
- * Graduate Programs
- * Career Resources
- * Discussion Forums
- * Social Networking Resources:
 - ~ Facebook
 - ~ LinkedIn
 - ~ Twitter
- * ASPET Membership Information



Find us at:

<http://www.aspet.org/knowledge/early-career/>

We welcome your feedback! Is there something you'd like to see on our Early Career Pharmacologists page? Email us at gaxelrod@aspnet.org.



Members in the News

Arthur Brown

The Safety Pharmacology Society (SPS) announced that **Arthur "Buzz" Brown, M.D., Ph.D.**, CEO, President, and Founder of ChanTest, will receive the SPS Distinguished Service Award at the 13th SPS Annual Meeting in Rotterdam, The Netherlands. Dr. Brown is being recognized for his "significant scientific contributions to many areas of Safety Pharmacology, most notably contributions to ion channels and their relationship to human disease." <http://www.sacbee.com/2013/07/24/5591282/chantest-ceo-named-distinguished.html>

Iain L.O. Buxton



Iain L.O. Buxton, D.Pharm., an ASPET member since 1984, was named Foundation Professor by the University of Nevada and inducted into the University's Honor Court. Known for discovery in the field of cyclic nucleotide compartmentation, Professor Buxton was cited for his work on causes of preterm labor and efforts to advance the development of effective tocolytics. Dr. Buxton joined the faculty in the Department of Pharmacology at the University of Nevada School of Medicine in 1985 and is currently Professor and Chair.

<http://www.rgj.com/article/20130605/LIV/306050025/Three-UNR-Foundation-professors-honored>

Lynette Daws



A group of researchers along with Neuropharmacology Division Past Chair **Lynette Daws, Ph.D.**, Professor in the Department of Physiology at the University of Texas Health Science Center at San Antonio, were among the first to show that backup cleaners for serotonin curb "the ability of selective serotonin reuptake inhibitors (SSRIs) to increase serotonin signaling in the brain." Dr. Daws was quoted extensively in a Neuroscience News article regarding the study about the compound decynium-22 enhancing the effect of SSRI antidepressants in mice.

<http://neurosciencenews.com/neuropharmacology-decynium-22-ssri-serotonin-248/>

Margarita Dubocovich and Rajendram Rajnarayanan



Left to right: Dubocovich and Rajnarayanan

ASPET members **Margarita Dubocovich, Ph.D.**, and **Rajendram Rajnarayanan, Ph.D.**, both of the University at Buffalo, presented at a July 7 - 12, 2013 FASEB Science Research Conference on melatonin, held in Niagara Falls, NY. Dr. Dubocovich, gave the opening presentation, entitled "The molecule of darkness: From discovery to its target receptors." Dr. Rajnarayanan's talk was titled, "Probing melatonin receptor conformational dynamics using human computer interfaces."

http://medicine.buffalo.edu/news_and_events/research-news.host.html/content/shared/smb/news/2013/07/pharmacology_melatonin_3045.detail.html

Perry Halushka



Dr. Perry Halushka stepped down from his post as dean of the MUSC College of Graduate Studies on August 1, 2013. He has been affiliated with the Medical University of South Carolina since 1974, when he started there as an Assistant Professor of pharmacology and medicine. Dr. Halushka, who remains at MUSC as a Distinguished University Professor, had been Dean of the MUSC College of Graduate Studies since 2000. His contributions to research and training spurred growth on the campus. Due to the efforts of Dr. Halushka and his faculty and staff, the number of people applying to the College of Graduate Studies nearly doubled during his tenure as dean.

Craig W. Lindsley

In March 2013, the American Chemical Society (ACS) Division of Medicinal Chemistry and the *Journal of Medicinal Chemistry* announced that **Craig W. Lindsley, Ph.D.**, director of Medicinal Chemistry in the Vanderbilt Center for Neuroscience Drug Discovery, has been awarded the 4th Annual Philip S. Portoghesi Medicinal Chemistry Lectureship Award, honoring his contributions to medicinal chemistry research. Dr. Lindsley "has discovered and developed high quality novel compounds in multiple therapeutic areas...and pioneered the medicinal chemistry of allosteric modulation."

<http://news.vanderbilt.edu/2013/03/lindsley-honored-for-impact-on-medicinal-chemistry-field/>

<http://www.acsmedchem.org/nlw2013.pdf> (page 5)

John McNeil



A member of ASPET since 1970, **Dr. John McNeill**, Professor and Dean Emeritus, Faculty of Pharmaceutical Sciences, University of British Columbia has been awarded the Canadian Society for Pharmaceutical Sciences Lifetime Achievement Award. This award has only been presented three other times and recognizes Dr. McNeill's significant contributions to pharmaceutical sciences research. Dr. McNeill joined the Faculty of Pharmaceutical Sciences in 1971, and served as Dean from 1985 to 1996. He is the author of more than 500 manuscripts and review articles, over 500 abstracts and has edited five books. He has received numerous awards for teaching and research over the course of his career. He has been elected to the Royal Society of Canada and to the Canadian Academy of Health Sciences. To read Dr. McNeill's full biography, please visit <http://pharmacy.ubc.ca/research/researchers/john-mcneill>.

James M. O'Donnell



The University at Buffalo School of Pharmacy and Pharmaceutical Sciences announced on July 2 that **James M. O'Donnell, Ph.D.** has been named the school's next Dean. Dr. O'Donnell currently serves as the Assistant Dean for Research at the West Virginia University Health Sciences School of Medicine, a title he has held since July 2005. He will likely assume his new post at UB by November 1, 2013. <http://www.buffalo.edu/news/releases/2013/07/004.html>

Jill M. Siegfried



Jill M. Siegfried, Ph.D., has been named the next head of the Department of Pharmacology and Frederick and Alice Stark Endowed Chair at the University of Minnesota School of Medicine. She will assume this role and also serve as Associate Director for Experimental Therapeutics at the Masonic Cancer Center starting in September 2013. Dr. Siegfried is currently a Professor in the Department of Pharmacology and Chemical Biology at the University of Pittsburgh.

<http://news.med.umn.edu/content/jill-m-siegfried-phd-named-head-department-pharmacology-and-associate-director-experimental>

Palmer Taylor



The University of California, San Diego recently announced that **Palmer Taylor, Ph.D.**, dean of the Skaggs School of Pharmacy and Pharmaceutical Sciences, has been awarded "Chevalier dans l'Ordre national de la Légion d'Honneur" (Knight in the National Order of the Legion of Honour). This honor was bestowed upon Dr. Taylor by French President François Hollande. This highly prestigious national award given by France recognizes distinguished persons who have made a significant contribution "to the development of relationships with France." According to professor of molecular neurobiology Jean Pierre Changeux at the Collège de France and the Institut Pasteur, Dr. Taylor received this high honor for his work on cholinergic systems, dedication to "teaching and training in the pharmaceutical sciences...and [his] cooperation and friendship with French Scientists." Dr. Taylor served as ASPET President in 1995-96.

http://ucsdnews.ucsd.edu/pressreleases/uc_san_diegos_palmer_taylor_awarded_frances_legion_of_honour

Raymond L. Woosley



Biopharmaceutical company ARCA biopharma, Inc. announced that **Raymond L. Woosley, M.D., Ph.D.**, has been appointed to the Company's Board of Directors. Dr. Woosley will serve on the Compensation and Nominating and Corporate Governance Committees of the Board of Directors. He is currently President of AZCERT, Inc. Dr. Woosley also serves as President, Emeritus, of the Critical Path Institute, a non-profit, public-private partnership with the FDA. He founded the Critical Path Institute in 2005 and has served as President, CEO, and Chairman of the Board from 2005 – 2011.

<http://online.wsj.com/article/PR-CO-20130730-908921.html>

Staff News

Judith Siuciak



Judy Siuciak, Ph.D. joined ASPET as the Executive Officer in August, 2013. Judy comes to ASPET with experience from the academic, industry, and non-profit sectors and most recently worked at the Foundation for the National Institutes of Health Biomarkers Consortium. Judy is a Chicago native and received her Ph.D. in neuropharmacology from the University of Illinois, College of Medicine. She and her husband, John, a scientist at NIH, now live in Potomac, MD.

Christine K. Carrico

Christie Carrico, ASPET's Executive Officer for the past 16 years, retired September 6. While she has no immediate plans for travel, she does plan to get more involved in some of her already existing volunteer activities. Mostly she is looking forward to sleeping later, reading the paper over coffee in the morning, going out for lunch without having to keep one eye on the clock, and not having to deal with deadlines. Her cat was quoted as saying, "I hope she doesn't expect me to hang around and entertain her all day."

Photos at right: Left, top: Christie with balloons at her retirement party. Left, bottom: ASPET staff with Christie at her party. Right, top: Christie with American Association of Medical Colleges Senior Director of Scientific Affairs Tony Mazzaschi. Right, bottom: At an Executive Officers Advisory Committee (EOAC) meeting, FASEB Executive Director Guy Fogleman presents Christie with a plaque from the EOAC in honor of her retirement.



Matthew Hilliker



On June 5, the ASPET staff gathered in the conference room at the ASPET office to wish Chief Financial Officer **Matthew Hilliker** and his then fiancée, Laura, congratulations on their upcoming wedding. Matthew and Laura were married in front of their friends and family in Williamsburg, VA on June 8, 2013, where they met while attending the College of William & Mary. They spent their honeymoon in Bar Harbor, ME, observing the wildlife, such as whales and puffins, and relaxing in the beautiful harbor town.

At left: Matthew Hilliker came to a staff meeting expecting to talk about financials. Instead, he found his fiancée (now wife) and was treated to a surprise wedding shower. Here, Matthew and Laura open up a picnic basket full of goodies.

Cassandra Wood



On July 16, the ASPET staff threw a baby shower for Editorial Coordinator **Cassie Wood** as she prepared to welcome a baby boy. Cassie's son Samuel was born on Saturday, August 17 at 1:57 a.m., weighing 6lbs, 12oz. Both are doing well.

Cassie Wood cuts the cake (left) and opens gifts (right) at a baby shower thrown by the ASPET staff.



New ASPET Members

Regular Members

Stephane Allouche, UFR Medecine, France
Tagreed S. Altaei, Hawler Medical Univ, Iraq
Olaf S. Andersen, Weill Cornell Medical College
Bardia Askari, Touro College of Pharmacy
Soo Kyung Bae, The Catholic Univ of Korea, South Korea
Ting Chen, Brigham and Women's Hospital
Ganesh Cherala, Oregon State Univ
Cristina Clement, Albert Einstein Coll of Med
Laura Conforti, Univ of Cincinnati
Thurl E. Harris, University of Virginia
Joel W. Hockensmith, Univ of Virginia School of Medicine
Jeffrey H. Hurst, NHLBI/NIH
Jeremy J. Johnson, Univ of Illinois-Chicago
Stephen G. Kerr, MCPHS Univ
Sandeep Khurana, Univ of Maryland School of Medicine
Dong Hyun Kim, Inje Univ College of Medicine, South Korea
Felix J. Kim, Drexel University
Barry Kreutz, Univ of Illinois College of Medicine
Paul A. Kroon, Institute of Food Research, United Kingdom
Ambrish Kumar, Univ of South Carolina School of Medicine
Harley T. Kurata, Univ of British Columbia, Canada
Ebba U. Kurz, Univ of Calgary, Canada
Woojin Lee, Univ of Kentucky
Changlu Liu, Janssen Research & Development, LLC
Naila M. Mamoon, Millsaps College

Xinliang Mao, Soochow Univ, China
Husnia I. Marrif, Princess Noura Univ, Canada
Wandikayi C. Matowe, American Univ of The Caribbean School of Medicine, Netherlands Antilles
Donald P. McDonnell, Duke Univ Medical Center
Gerald A. Meininger, Univ of Missouri - Dalton Cardiovascular Research Center
David Meredith, Oxford Brookes Univ, United Kingdom
Jeffery H. Moran, Univ of Arkansas for Medical Sciences
Hany Ahmed Mostafa Mostafa Omar, Beni-Suef Univ - Faculty of Pharmacy, Egypt
Nilberto Nascimento, Ceara State Univ, Brazil
Ndubuisi N. Nwobodo, Ebonyi State Univ, Nigeria
Jason N. Peart, Griffith Univ, Australia
Sudarshan Rajagopal, Duke Univ
Predrag Sikiric, Univ of Zagreb Medical Faculty, Croatia
Murali Subramanian, Syngene International, India
Steven J. Tavalin, University of Tennessee HSC
Jill R. Turner, Univ of Pennsylvania
Manthena V. Varma, Pfizer Inc
Paul Whiteaker, Barrow Neurological Institute
Andrew J. Wiemer, Univ of Connecticut
Han-Gang Yu, West Virginia Univ
Shengjun Zhang, The First Affiliated Hospital of Zhengzhou Univ, China
Yuhong Zou, Indiana University-Purdue Univ

Affiliate Members

Fawaz F. Alasmari, King Saud Univ, Saudi Arabia
Endang Darmawan, Ahmad Dahlan Univ Faculty of Pharmacy, Indonesia
Harry Hartmann, MB Labs, Canada

Manu Kumar, Vardhman Mahavir Medical College & SafdarJung Hospital, India
Aleksandr V. Samorodov, Bashkirian State Medical Univ, Russia

Postdoctoral Members

Katherine V. Bricceno, National Institutes of Health
Jessica Finlay-Schultz, Univ of Colorado Anschutz Medical Campus
Ryan S. Funk, Children's Mercy Hospital
Akhil Hegde, Duke Univ
Hongwei Jin, Tufts Medical Center

Aleksandar Krbanjevic, Univ of Illinois-Chicago
Gurdeep Singh A. Marwarha, Case Western Reserve Univ
James J. O'Donnell, Univ of Chicago
Nirmala Parajuli, Univ of Arkansas for Medical Sciences

Graduate Student Members

Sherry E. Adesina, Emory Univ
Rashiqua Adnan, University of Hertfordshire, United Kingdom
Thamer Alqurashi, MCPHS
Yusuf S. Althobaiti, University of Toledo
Kristin L. Bater, Vanderbilt Univ
Adam A. Behensky, Univ of South Florida
Dhaval P. Bhatt, Univ of North Dakota School of Medicine
Samantha M. Carlisle, Univ of Louisville
Annabelle L. Chambers, Univ of Nottingham - Queens Med School, United Kingdom
Thomas F. Gamage, Virginia Commonwealth Univ
Martha Graham, Mercer Univ
Ryan A. Gregg, Temple Univ - School of Medicine
MD Zubayer Hossain Saad, The University of Toledo, Coll of Pharmacy and Pharmaceutical Sci

Dylan P. Kennedy, Univ of Virginia
Mohit Koladia, North Dakota State Univ
Nicholas J. Lodato, Boston Univ
Reynold C. Ly, Mayo Graduate School
Srikrishnan Mallipeddi, Northeastern Univ
Garrett R. Mullins, Univ of Virginia
Kevin M. Nash, University of Toledo
Amarnath Pispapati, Univ of Manitoba, Canada
Solmaz Pourgonabadi, Mashhad Univ of Medical Sciences, Vakilabad, Iran
Alexander C. Ross, Univ of Cincinnati
Katarina R. Savic Vujovic, University of Belgrade, Yugoslavia
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Promotions, Appointments, Awards, and other Achievements...



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In Sympathy

ASPET Notes with Sympathy the Passing of the Following Members:



Carmine Paul Bianchi

Allan H. Conney

John C. Kermode

Toshio Narahashi

Joan B. Carloff

William L. Woolberton



Obituaries

Toshio Narahashi (1927 – 2013), Founding Father of Neurotoxicology, Leader in Cellular Neuropharmacology



Toshio Narahashi, widely considered one of the founding fathers of neurotoxicology and a leader in cellular neuropharmacology, died at his Chicago home on April 21, 2013, of complications associated with colon cancer. He was 86. Over a career spanning more than 50 years, Dr. Narahashi was highly decorated from many scientific societies. He was the 2000 Otto Kraye awardee by ASPET, won the K.S. Cole Award from the Biophysical Society, and a Jacob Javits Award. He was especially recognized for his work in neurotoxicology, and he was the first to be awarded the Distinguished Investigator Lifetime Achievement Award in Neurotoxicology in 2001 from the Neurotoxicology Specialty Section of the Society of Toxicology (SOT), the Distinguished Toxicology Scholar Award from the SOT in 2008, and the prestigious Merit Award in 1991.

Dr. Narahashi graduated from the University of Tokyo Faculty of Agriculture with the DVM equivalent in 1948. His scientific career began with studies on the mechanisms of action of insecticides in the Laboratory of Applied Entomology. Already well ahead of his time, Dr. Narahashi used electrical recordings of neuronal and muscle activity to delineate the mechanisms by which chemicals produced their insecticidal action. His findings led to such pivotal observations as the negative temperature-dependence of DDT for its insecticidal action, and the development of knockdown resistance to insecticides ("KDR"). Dr. Narahashi attained international prominence in 1964 when, as a visiting researcher at Duke, he made the pivotal discovery that tetrodotoxin, the pufferfish toxin, acted specifically on voltage-gated sodium channels to block nerve conduction. Always maintaining a great sense of humor and perspective, he enlivened his description of the mechanism of action of TTX by recounting the famous confrontation between Agent 007 – James Bond and a Russian agent who poisoned him with TTX from a knife blade in her boot (Ian Fleming, *From Russia with Love*). Moreover, he would occasionally dine on the delicacy, and desiccated, preserved puffer fish that decorated his office at Northwestern University's Feinberg School of Medicine. Dr. Narahashi also described in detail ion channel modulation by other toxins including batrachotoxin, grayanotoxin, and sea anemone toxins, popularizing their use as highly specific chemical tools to study ion channel function. In defining the highly selective mechanism of action of TTX, he elevated the study of toxins and the associated science of toxinology from one of mere biological curiosity to one of such prominence, that biological toxins are now mainstays of experimental studies of excitable cells and signaling processes, and have even become accepted therapeutic agents for treatment of intractable neuropathic pain (omega conotoxin GVIA- Ziconide®) or muscle spasticity (Botulinum toxin A).

Dr. Narahashi also made seminal contributions to our understanding of the role ion channels played in therapeutics. His work with the isolated squid axon at Woods Hole Marine Biological Station demonstrated that local anesthetics act from the inside of the axon after first gaining intraneuronal access in the uncharged form. This information is taught as fact in any introductory pharmacology lectures on mechanisms of local anesthesia. Moreover, his work on squid axon also laid the foundation for the potassium channel blocking action of 4-aminopyridine, a drug FDA approved for treatment in multiple sclerosis and its derivatives, 3,4-diaminopyridine, an orphan drug used in paraneoplastic neuromuscular disorders. His more recent work pointed to ion channel specific actions of general anesthetics and ethanol.

Dr. Narahashi was awarded a Ph.D. in neurotoxicology in 1960 from the University of Tokyo in the old European model of degree conferral based on his 26 full-length publications at the time.

After coming to the U.S., Dr. Narahashi held faculty positions at Duke, rising to vice chairman of the Department of Physiology and Pharmacology before moving to Northwestern University Medical School as chair of pharmacology in 1977. He remained at Northwestern until his death and held the John Evans Professorship in Pharmacology, the highest award at the institution. Not content to rest on his many scientific laurels, Dr. Narahashi oversaw development and rebuilding of a Department of Pharmacology at Northwestern, attracting the best and brightest from around the world. In his last four years as department chair, the Northwestern University Pharmacology Department was ranked #1 in the U.S. out of 100 federally-funded departments for citations/publication, a true statement of his impact as an administrator.

While his work with biological toxins earned him world renown, his research with insecticide neurotoxicity has had an equal or greater societal impact. Dr. Narahashi's work with insecticides was pivotal to identifying the ion channel basis of insecticidal action of DDT, pyrethroids, dieldren, and others, making him a world leader of insecticide toxicology.

During his scientific career, Dr. Narahashi trained an estimated 140 graduate students and other professionals. These individuals went on to prestigious jobs in academia as well as in the chemical industry at DuPont and BASF, and themselves oversaw the development of newer more biologically safe insecticides. He published 324 papers and 148 chapters and reviews, and edited 11 books. Dr. Narahashi maintained an active teaching profile during his time as department chair, and continued even after the onset of his cancer. In the winter of 2012, he presented the course "Molecular Basis of Drug Action," a treatise on excitable cell physiology biophysics and pharmacology.

He is survived by his wife of 58 years, Kyoko; a son, Taro; a daughter, Keiko; two grandchildren; five brothers; and one sister.

prepared by Bill Atchison, Ph.D.

William L. Woolverton (1950 – 2013), Leader in Neuropharmacology of Drug Abuse Involving Animal Models

William Woolverton died on June 13, 2013 after a brief illness. He is considered one of the leaders in the neuropharmacology of drug abuse involving animal models. Woolverton, an Alabama native, graduated Phi Beta Kappa from the University of the South in Sewanee, TN in 1972 with a bachelor's degree in biology. He earned his Ph.D. in pharmacology at the University of Chicago under the mentorship of Charles (Bob) Schuster in 1977 and conducted his post-doctoral training at Virginia Commonwealth University under the guidance of Robert L. Balster before returning to the University of Chicago in 1980. In 1993, Woolverton moved to the University of Mississippi Medical Center (UMMC) as Professor and Vice Chair for Research in the Department of Psychiatry and Human Behavior (DPHB) and Director of the Division of Neurobiology and Behavior Research. In 2010, Woolverton was awarded the Billy S. Guyton Distinguished Professorship, the highest honor that is bestowed upon researchers at UMMC. Woolverton was an active member of several professional societies including the Behavioral Pharmacology Society since 1979 and the American Society for Pharmacology and Experimental Therapeutics (ASPET) since 1982. His research covered a broad range of pharmacology from stimulants such as cocaine and amphetamine, to PCP, benzodiazepines, local anesthetics and histamine. His behavioral paradigms focused on models of drug self-administration primarily using drug choice and progressive-ratio schedules of reinforcement. There have been several excellent obituaries written to honor Woolverton's research excellence (Balster et al., 2013; Bergman and Coffey, 2013; Johanson and Rowlett, 2013). He is survived by his wife Candy, his son Christopher, and his daughter Lucy.



References

1. Balster RL, Nader MA, Freeman KB. Obituary: William L. Woolverton. *Psychopharmacology*, 2013.
2. Bergman J, Coffey SF. Obituary: William L. Woolverton. *Behavioural Pharmacology*, 2013.
3. Johanson CE, Rowlett J. Obituary: William L. Woolverton. *Drug and Alcohol Dependence*, 2013.

Division News

Behavioral Pharmacology Division

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News

Awards

P.B. Dews Lifetime Achievement Award for Research in Behavioral Pharmacology. The Behavioral Pharmacology Division will present the P.B. Dews Award at EB 2014 to recognize outstanding lifetime achievements in research, teaching, and professional service in the field of behavioral pharmacology and to honor Peter Dews for his seminal contributions to the development of behavioral pharmacology as a discipline. Please see <http://www.aspet.org/Behavioral-Pharmacology/Dews-Award/> for more information. Previous Recipients of the P. B. Dews Award in Behavioral Pharmacology: 2002 William H. Morse; 2004 Joseph V. Brady; 2006 Leonard Cook; 2008 Charles R. Schuster; 2010 Donald E. McMillan; 2012 James E. Barrett.

Prakash Srinivasan won second place in Postdoctoral Posters presentation in the Graduate Research Day event held on May 3, 2013, at LSU Health Sciences Center, Shreveport.

Scientific Advances

Modification of cocaine self-administration by buspirone (Buspar®): Potential involvement of dopamine D3 and D4 receptors.

Bergman J, Rebecca A, Roof RA, Furman CA, Conroy JL, Mello NK, Sibley DR, Skolnick P.

Int J Neuropsychopharmacology 2013, **16**(2):445-458. PMID:22827916. Buspirone is most widely known as a 5HT1A partial agonist, with mixed clinical success as an anxiolytic drug. The work in this paper shows that buspirone, also known to have dopamine antagonist actions, has high affinity for D3 and D4 subtypes of dopamine receptor and can markedly reduce IV cocaine self-administration in nonhuman primates. In conjunction with other data, these findings have led to an ongoing evaluation in man of the possible benefits of buspirone as an anti-cocaine medication.

Analysis of tolerance and behavioral/physical dependence during chronic CB1 agonist treatment: Effects of CB1 agonists, antagonists, and non-cannabinoid drugs.

Desai RI, Thakur GA, Vemuri VK, Bajaj S, Makriyannis A, Bergman J

J Pharmacol Exp Ther 2013, **344**(2):319-328. PMID: 23197773. This study provides a quantitative evaluation of changes in the dose-related effects of ligands on schedule-controlled behavior to disclose possible differences in efficacy among CB1 ligands and to explore mechanistic interactions between CB1 and dopamine or mu opioid ligands.

Repeated acquisition and discrimination reversal in the squirrel monkey (*Saimiri sciureus*).

Kangas BD, Bergman J

Animal Cognition (in press) 2013. This paper reports systematic studies in a novel touchscreen procedure to, first, document the development of learning sets for acquisition of a novel stimulus discrimination and subsequently, its reversal, and, second, to explore the determinants of this type of learning in nonhuman primates.

Cannabinoid discrimination and antagonism by CB1 neutral and inverse agonist antagonists.

Kangas BD, Delatte MS, Vemuri K, Thakur GA, Nikas SP, Subramanian KV, Shukla VG, Makriyannis A, Bergman J

J Pharmacol Exp Ther 2013, **344**:561-567. PMID: 2328770. The CB1 antagonist, rimonabant, originally hailed as an important new anti-obesity drug, has effects on mood that led to its withdrawal from the market. This paper first establishes the discriminative-stimulus effects of a novel CB1 ligand AM 4054 in squirrel monkeys, and subsequently provides a comparison of the CB1 antagonist effects of rimonabant and AM 4113, a novel CB1 antagonist proposed to have a diminished side-effect profile.

Delay discounting of food and remifentanyl in rhesus monkeys.

Maguire DR, Gerak LR, France CP

David Maguire is a postdoctoral scientist in this lab from the University of Texas Health Sciences Center, San Antonio lab who published this new paper in *Psychopharmacology* (Berl). 2013 May 2. [Epub ahead of print]

Oné Pagán recently got a paper accepted that he is excited about. He noted that "I work on planarians as animal models in pharmacology. Our most recent published paper deals with the behavioral effects of cocaine or nicotine and how it relates to regeneration. I believe that this is the first paper

ever to relate regeneration with abused drug effects at least in this organism. Also, we made the cover of the journal!" [Planarians require an intact brain to behaviorally react to cocaine, but not to react to nicotine. Pagán OR, Deats S, Baker D, Montgomery E, Wilk G, Tenaglia M, Semon J. *Neuroscience*. 2013 Aug 29; **246**:265-70. doi: 10.1016/j.neuroscience.2013.05.010. Epub 2013 May 14.

Behavioral Pharmacologists in the News

Susan K. Wood of the University of South Carolina was highlighted by ASPET, *Medical News Today*, *Science Daily*, and *Red Orbit* in response to her work on stress/depression and cardiovascular interactions she presented at the 2013 Experimental Biology meeting: "Social Stress and the Inflamed Brain: Inflammatory Factors in the Brain May Hold the Key to Depression-cardiovascular Disease Comorbidity."

Richard De La Garza was recently promoted to professor with tenure at the Baylor College of Medicine in the Departments of Psychiatry, Neuroscience and Pharmacology.

Claire Advokat (LSU) and colleagues (James Swanson and Martha Farrah) were interviewed in *The Wall Street Journal* article "ADHD Drugs Don't Boost Kids' Grades, Studies Find," about stimulants and ADHD. The work of Dr. Advokat was mentioned, as well as that of James Swanson (and Martha Farrah). This article was an outcome of the work that was presented in our symposium last April at the ASPET conference. They are appreciative of the opportunity that ASPET provided for that presentation.

Sheldon Sparber, Ph.D. gave seven hours of lectures to medical students at the University of Milan, where he has maintained a visiting professorship since his first sabbatical there in 1991. The lectures included the relationship between structures of various drugs and their activities at receptors for various endogenous transmitters. Additionally, students were introduced to concepts such as drugs as reinforcers, after presenting operant behavior analysis methodology, schedules of reinforcement, non-drug primary, and conditioned reinforcement, etc. Dr. Sparber was initially asked to give a three-hour lecture on January 7 and was asked by the department chairperson that evening if he would continue the following day for an additional two hours because the students requested that he do so in order to discuss the similarity between our old demonstrations showing single, low dose opiate dependence using suppression of food reinforcement operant behavior after naloxone and similar effects in human subjects by other groups. This was the first time these medical students were exposed to such data, concepts, and integration of pharmacology and behavioral neuroscience.

Upcoming Meetings and Activities

Behavioral Pharmacology Society Meeting: This annual meeting is held during the Experimental Biology 2014 meeting time frame – announcements will be sent to society members at a later date.

The ASPET Annual Meeting at Experimental Biology 2014 has several symposia sponsored by the Behavioral Pharmacology Division. These include "Animal models of polydrug abuse," chaired by **Paul W. Czoty** (Wake Forest Univ. Sch. of Med.) and **Richard De La Garza** (Baylor Coll. of Med.), co-sponsored by the Neuropharmacology Division; "Sleep disruptions associated with neuropsychiatric and degenerative disorders: Implications, preclinical models and development of novel pharmacotherapies," chaired by **Robert W. Gould** (Vanderbilt Univ. Med. Sch.) and **Carrie K. Jones** (Vanderbilt Univ. Med. Sch.), co-sponsored by the ISTCP and Neuropharmacology Divisions; "New preclinical and clinical perspectives for smoking cessation," chaired by **Rajeev I. Desai** (McLean Hosp./Harvard Med. Sch.) and **Dorothy K. Hatsukami** (Univ. of Minnesota), co-sponsored by the ISTCP, Toxicology, and Cardiovascular Pharmacology Divisions; "Making the right choice: Translational use of choice procedures in understanding the neurobiology and development of pharmacotherapies for drug addiction," chaired by **Matthew L. Banks** (Virginia Commonwealth Univ.) and **Michael A. Nader** (Wake Forest Univ); and the Ray Fuller Lecture, which will be given by **Jeff Witkin** of Lilly Research Laboratories in Indianapolis, titled "AMPA receptor potentiation: Implications for the discovery of medicines for treatment-resistant depression."

More information can be found starting on page 137 about the ASPET Annual Meeting at EB 2014 symposia and the Volunteer Day of Service at EB that are sponsored by the Behavioral Pharmacology Division this coming April in San Diego, CA.

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News

Be Part of the Trainee Showcase

Each year, the Cardiovascular Pharmacology Division hosts a Trainee Showcase. On April 29, 2014, at 2:00 p.m. at the ASPET Annual Meeting at EB 2014, we will host graduate students and postdocs in presentations of their work. To apply for this, send an abstract to ASPET and an application for the Best Abstract Award in ASPET (graduate students: <http://www.aspet.org/awards/grad-student-abstract/>; postdocs: <http://www.aspet.org/awards/postdoctoral-scientist/>). Not only do you have the opportunity to share your work with peers and colleagues, you have the opportunity to win money!

Attend our Symposia at the ASPET Annual Meeting at EB 2014

The Cardiovascular Pharmacology Division is proud to present new, cutting edge pharmacological symposia that should enrich all who attend. While the focus of most of our symposia offered for EB 2014 is cardiovascular, all of our symposia cross pharmacology divisions and disciplines. Come listen to work on mitochondrial fragments, inflammation, and cardiovascular disease; how the enzymes transglutaminases work more than just as enzymes that link two proteins together, and exciting new work on a messenger that is receiving attention in all physiological systems, hydrogen sulfide. These three symposia are sponsored by the Cardiovascular Pharmacology Division, but we do a whole lot more. We join with the other Divisions of ASPET in support of symposia that benefit us all. An example is a symposium on understanding cell specific knockouts of G proteins, arginase as a target, "Fetal programming of adult cardiovascular disease," and many others.

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News

Drug Metabolism Division at the ASPET Annual Meeting at Experimental Biology 2014

Robert S. Foti (Amgen) will chair a symposium titled "Target-Site Drug Metabolism and Transport." **Nina Isoherranen** (Univ. of Washington), **Hollie Swanson** (Univ. of Kentucky Med. Center), and **Don Mattison** (Risk Sciences Inst.) will co-chair a symposium titled "Improving Maternal Therapeutics: Drug Metabolism and Transport during Pregnancy and Lactation." **Bruno Stieger** (Univ. Hospital Zurich) and **Yuichi Sugiyama** (RIKEN Innovation Center Res. Cluster for Innovation) will co-chair a symposium titled "Role of (Drug) Transporters in Imaging in Health and Disease."

In addition, Drug Metabolism will present the 2014 B.B. Brodie Award in Drug Metabolism to recognize outstanding original research contributions in drug metabolism and disposition, particularly those having a major impact on future research in the field. The B. B. Brodie Award in Drug Metabolism has been established to honor the fundamental contributions of Bernard B. Brodie in the field of drug metabolism and disposition. The Award is presented biennially in even years. Please visit <http://www.aspet.org/Drug-Metabolism/Brodie-Award/> for more information.

Integrative Systems, Translational and Clinical Pharmacology Division

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News

The Division for Integrative Systems, Translational and Clinical Pharmacology (ISTCP) welcomes scientists at all levels that share the goals of creative integration of molecular, cellular, and organ systems pharmacology that spans investigation of the development and application of model disease systems and the clinical environment. The Division lists 266 primary and 944 secondary members and welcomes new membership from graduate

students, postdoctoral fellows, and junior and senior faculty members. The Division embraces active interaction with basic and clinical scientists from the pharmaceutical industry.

The richness of the mandate of the Division will be broadened by its renewed mandate to:

1. Increase the active role (e.g. at the Executive and Programming Committee levels) of all members with a focus on inclusiveness of graduate student and postdoctoral fellows.
2. Promote and support translational and clinical pharmacology as career goals.
3. Develop approaches for integrating across biological systems, species, and experimental models.
4. Develop new therapeutics and models useful for testing experimental therapeutics and for treating human disease.

For additional information (and membership information) please visit <http://www.aspet.org/ISTCP/Home/>.

ISTCP Division at the ASPET Annual Meeting at Experimental Biology

The "Hot Topics" Symposium at EB 2013 was warmly received and the session titled "A (r)evolution in drug discovery & therapy: From organs on a chip and 3D biomimetics to regenerative pharmacology" was led by **George Christ** (Wake Forest School of Medicine) and **Sitta Sittampalam** (NIH Centre for Translational Therapeutics). There will be another "Hot Topics" Symposium at EB 2014, and ISTCP proposes to make this a regular feature at each EB meeting.

Michael Holinstat and **Jeffrey Paul** attended the June 2013 Program Committee Meeting. Following the Business Meeting in April, where symposia preparation were discussed, the Division received a number of proposals. Four ISTCP-sponsored symposia were accepted for the ASPET Annual Meeting at EB 2014. These are:

"Fetal programming of adult cardiovascular disease," chaired by **Allyson Marshall, B.S.** (Wake Forest Baptist Med. Center) and **Mark Chappell, Ph.D.** (Wake Forest Baptist Med. Center). Allyson is a third-year graduate student and an active member of ISTCP and Mark Chappell is on faculty at Wake Forest University Baptist Medical Center, Hypertension and Vascular Research Center.

"12-lipoxygenase and disease: New insights into regulation and inhibition of a critical enzyme," chaired by **Michael Holinstat, Ph.D.** (Thomas Jefferson University). Michael is a faculty member in the Dept. of Medicine, Cardeza Foundation of Hematologic Research of Thomas Jefferson University and currently the Secretary/Treasurer of ISTCP Division.

"Emerging integrative approaches to predicting host response to antimicrobials," chaired by **Namandjé N. Bumpus, Ph.D.** (Johns Hopkins University School of Medicine). Namandjé is on faculty in the Dept. of Pharmacology and Molecular Sciences of Johns Hopkins University School of Medicine.

"Targeted/individualized therapy: Approaches for the future translational pharmacologist," chaired by **Jeffrey Paul, Ph.D.** (Astellas Pharmaceuticals). Jeffrey is a member of the Dept. of Global Clinical Pharmacology and Exploratory Development of Astellas Pharmaceuticals and past Secretary/Treasurer of ISTCP.

In addition, the ISTCP Division is very pleased to co-sponsor the following symposia at EB 2014:

- "Career opportunities beyond the bench: Education as a viable path" (J. Reuben, K. Marcdante)
- "Nuclear receptors as therapeutic targets" (D. McDonnell, D. Mangelsdorf)
- "Collaborative role of pharmacology in education of health care professionals" (S. Andrieu, R. Theobald)
- "Target-site' drug metabolism and transport" (R. Foti)
- "Future therapies for chronic pain: Focus on novel non-opioid targets" (B. Greenwood-Van Meerveld)
- "New insights derived from cell specific knockout of heterotrimeric G-alpha proteins" (F. Murray, P. Insel)
- "Emerging technologies in neuropeptide research: Identification and validation of neuropeptide systems as therapeutic targets" (S. Clark)
- "Hydrogen sulfide: From physiological messenger to pharmacological target" (N. Kanagy, U. Sen)
- "Therapeutic potential of targeting oxidative stress pathways" (P. Mayeux, C. Wu)
- "Idiosyncratic drug-induced toxicity" (J. Uetrecht)
- "Sleep disruptions associated with neuropsychiatric and degenerative disorders: Implications, preclinical models & development of novel pharmacotherapies" (R. Gould, C. Jones)
- "Mitochondrial fragments: A novel mediator between inflammation and cardiovascular disease" (R. Webb, C. Wenceslau)
- "Inhibitory GPCRs as therapeutic targets for obesity and type 2 diabetes" (M. Kimple)
- "Arginase as an emerging therapeutic target" (R. Caldwell)

ISTCP Members in the News

Andrea Gaedigk contributed two chapters to the text "Pharmacogenomics: An introduction and Clinical Perspective" (edited by J.S. Bertino Jr. et al., 2013). This collection of chapters by internationally acclaimed experts in pharmacogenomics covers topics ranging from molecular aspects to systematic diseases and also critical evaluations of the latest technology, ethical and regulatory matters. The two chapters by Andrea are: "Genetic concepts of pharmacogenomics: Basic review of DNA, genes, polymorphisms, haplotypes and nomenclature" and "Analytical methods to identify genetic variations and bioinformatics" (co-authored with Xia Yang).



Andrea Gaedigk



George Christ

George Christ and his collaborator Karl-Erik Andersson recently co-authored "Regenerative Pharmacology" (2013), a book that uniquely addresses the important role of pharmacology in better appreciating future therapies based on regenerative medicine (repair or replacement of damaged cells, tissues, and organs). There are 15 chapters that detail a number of important topics in foundational and clinical sciences applicable to various body systems. This is the first book to critically evaluate this rapidly evolving field of research and is aimed at both experts and novices in tissue engineering.

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News

Molecular Pharmacology Division at the ASPET Annual Meeting at Experimental Biology 2014

The Molecular Pharmacology Division is pleased to sponsor six different symposia at the ASPET Annual Meeting at Experimental Biology 2014 meeting in San Diego. The first session, entitled "New insights derived from cell specific knockout of heterotrimeric G α proteins," will be chaired by **Dr. Fiona Murray** (Univ. of California-San Diego) and **Dr. Paul Insel** (Univ. of California-San Diego) and will highlight the physiological role of heterotrimeric G α proteins and recent advances in G protein function and signaling that have been made by cell-targeted knockout studies in mice. The second session is devoted to "Nuclear receptors as therapeutic targets" and is co-chaired by **Dr. Donald P. McDonnell** (Duke Univ. Med. Center) and **Dr. David Mangelsdorf** (Univ. of Texas Southwestern Med. Center). This symposium will explore efforts made by leaders in the field to develop drugs that target this superfamily of transcriptional regulators to treat a wide range of endocrinopathies and cancers. The third session, "Inhibitory G protein coupled receptors as therapeutic targets for obesity and type 2 diabetes," is chaired by **Dr. Michelle E. Kimple** (Univ. of Wisconsin-Madison) and will explore the current state of research in prostaglandin E₂, α_{2A} , and type 1 cannabinoid receptors as therapeutic targets for the control of cyclic AMP levels in the pancreas. In the fourth session, we seek to showcase studies that employ chemical biological approaches to address problems in pharmacology with a symposium entitled "Chemical biology in drug discovery," chaired by **Dr. Haiyan Fu** (Emory Univ.) and **Dr. Hongzhan Chen** (Shanghai Jiaotong Univ. Sch. of Med.), one of two sessions sponsored jointly with the Division for Drug Discovery and Development. In the second of these jointly sponsored sessions, **Dr. Margaret A. Phillips** (Univ. of Texas Southwestern Med. Ctr.) will chair "Drug discovery against protozoal pathogens," which will highlight both academic and industrial efforts to identify small molecule therapeutics for the treatment of malaria, African sleeping sickness, and Chagas' disease. The session will span early discovery work to the identification of clinical candidates. Finally, **Dr. Michael Holinstat** (Thomas Jefferson Univ.) will chair the session "12-lipoxygenase and disease: New insights into Regulation and inhibition of a critical enzyme." 12-lipoxygenase is known to affect a number of disease conditions including thrombosis, diabetes mellitus, and cardiovascular disease, and this symposium focuses on the evolution of this field and highlights this enzyme as a preferred therapeutic target. This symposium is jointly sponsored with Division for Integrative Systems, Translational and Clinical Pharmacology.

Gordon Research Conferences

The Division would also like to announce several future Gordon Research Conferences of relevance to the molecular pharmacology community. The first is the **2014 Gordon Research Conference on Plasminogen Activation and Extracellular Proteolysis**, chaired by **Katerina Akassoglou**. The meeting will be held from February 9 - 14 at the Four Points Sheraton/Holiday Inn Express in Ventura, CA. The second is the **2014 Gordon Research Conference on Phosphorylation & G-Protein Mediated Signaling Networks**, chaired by **Melanie Cobb**, to be held June 15 - 20 at the University of New England in Biddeford, ME.

Neuropharmacology Division

2013 – 2014 Executive Committee

Laura M. Bohn, Chair
Lynette C. Daws, Past Chair
Lakshmi A. Devi, Secretary/Treasurer
Eric L. Barker, Past Secretary/Treasurer
Susan L. Ingram
Charles D. Nichols
Dennis Paul
Misty D. Smith

Rita J. Valentino
Michael W. Wood
Deana M. Apple, Student Representative
Loc V. Thang, Student Representative
Christopher Cottingham, Postdoctoral Representative
Vikas V. Dukhande, Postdoctoral Representative
Charles France, ASPET Council Liaison
Judith A. Siuciak, Staff Liaison

News

Neuropharmacology Division at the ASPET Annual Meeting at Experimental Biology 2014

The Neuropharmacology Division will offer new awards for trainees! In addition to the prizes offered at the graduate student poster competition and postdoc speaker competition, the Division will offer 12 new travel awards this year. Our hope is to help lessen the burden of the high cost of travel and encourage trainees to participate in the Neuropharmacology Division competitions. These incentive awards will be in the form of up to \$300 in reimbursed travel expenses, and winners will be notified before the meeting. In order to qualify for these awards, you must apply for either a Graduate Student or Postdoctoral Scientist Best Abstract Award in the Neuropharmacology Division. Please see the Neuropharmacology Division ASPET website for more information and to access links to the Best Abstract application portals: <http://www.aspet.org/awards/grad-student-abstract/> or <http://www.aspet.org/awards/postdoctoral-scientist/>.

The Neuropharmacology Division will sponsor three symposia and co-sponsor six symposia at the ASPET Annual Meeting at EB 2014. They are as follows:

The following symposia are sponsored by the Neuropharmacology Division: "Emerging technologies in neuropeptide research: Identification and validation of neuropeptide systems as therapeutic targets," chaired by **Stewart D. Clark** (Univ. at Buffalo, SUNY); "Transporters in glial cells as new therapeutic targets," chaired by **Lucio Annunziato** (Frederico II University of Naples, Italy); and "Future therapies for chronic pain: Focus on novel non-opioid targets," chaired by Beverley Greenwood-Van Meerveld (Oklahoma Univ. Health Sci Center).

The following symposia are co-sponsored by the Neuropharmacology Division: "Animal models of polydrug abuse" (Chairs: P. Czoty, R. De La Garza); "Collaborative role of pharmacology in education of health care professionals" (Chairs: S. Andrieu, R. Theobald); "New preclinical and clinical perspectives for smoking cessation" (Chairs: R. Desai, D. Hatsukami); "Career opportunities beyond the bench: Education as a viable path" (Chairs: J. Reuben, K. Marcdante); "Sleep disruptions associated with neuropsychiatric and degenerative disorders: Implications, preclinical models and development of novel pharmacotherapies" (Chairs: R. Gould, C. Jones); and "Scientists vs. street chemists: The toxicity of designer marijuana" (Chairs: L. James, J. Moran).

Society for Neuroscience 2013 Annual Meeting

The Neuropharmacology Division will be recruiting at the Society for Neuroscience 2013 Annual Meeting, November 9 –13, in San Diego, CA! Come by and visit ASPET's booth, #3817, and learn about how you can make a difference in determining future programming at the ASPET meeting! We will also be hosting a reception at SfN at the Hilton San Diego Bayfront, Room Aqua 304 on Sunday, November 11 from 6:30 – 8:30 p.m. Please contact **Laura Bohn** (lbohn@scripps.edu) or **Lakshmi Devi** (lakshmi.devi@mssm.edu) if you would be interested in helping with this outreach effort.

Election Nominations

ELECTIONS! Please consider nominating yourself or another Neuropharmacology Division member for the positions of Chair-elect (2014 – 2015) or Secretary/Treasurer-elect (2014 – 2015). For details, see the Executive Committee Charge on our website, which is linked to http://www.aspet.org/Neuropharmacology/Executive_Committee/. Nominations should be made to the current committee chair by September 25, 2013: **Laura Bohn** (lbohn@scripps.edu).

Pharmacology Education Division

2013 – 2014 Executive Committee

Carol L. Beck, Chair
Lynn M. Crespo, Past Chair
Robert J. Theobald, Secretary/Treasurer
Rajasekaran Senthil S. Kumar, Past Secretary/Treasurer
Loraine S. Dieckmann, Councilor
Mark M. Knuepfer, Councilor
Kathryn K. McMahon, Councilor
Shafiqur Rahman, Councilor

Helmut Gottlieb
Jayne S. Reuben, Program Committee Representative
Patricia B. Williams
Brian M. Cox, Council Liaison
Kelly Karpa, ex officio
John L. Szarek, Outside Liaison
Judith A. Siuciak, Staff Liaison

News

New Division Officers Announced

Dr. Carol Beck, Assistant Professor, Department of Pharmacology and Experimental Therapeutics, Jefferson Medical College/Thomas Jefferson University, is the new Chair for the Division for Pharmacology Education. **Dr. Robert Theobald, Jr.**, Professor and Chair, Department of Pharmacology, A.T. Still University of Health Sciences, is the new Secretary/Treasurer for the Division. Drs. Beck and Theobald began their new roles as division officers on July 1, 2013.

DPE extends thanks to the Past Chair, **Dr. Lynne Crespo** and Past Secretary-Treasurer, **Dr. Senthil Rajasekaran** for their service to the division. Special thanks to Senthil for stepping in for Lynne at the annual meeting when she was unable to attend.

Division for Pharmacology Education Symposia at the ASPET Annual Meeting at Experimental Biology 2014

Robert J. Theobald, Jr. (Kirkville Coll. of Osteopathic Med.) and **Sandra Carlin Andrieu** (LSUHSC New Orleans Sch of Dentistry) are co-chairing a session on "Collaborative role of pharmacology in the education of healthcare professions." This session brings together pharmacologists involved in a

wide variety of healthcare training settings describing how pharmacology can be part of integrated teaching in different healthcare disciplines. Hear how they experienced problems, created solutions, and managed assessment. The session concludes with an interactive problem-solving workshop to help participants apply some of the concepts discussed. (Monday, April 28, 9:30 a.m. – 12:00 p.m.)

Jayne S. Reuben (Univ. of South Carolina School of Med-Greenville) and **Karen Marcante** (Medical Col. of Wisconsin and Children's Hospital of Wisconsin) will co-chair a session on "Career opportunities beyond the bench: Education as a viable path." This session offers nuts, bolts, and networking information for pharmacologists (at all career stages) who are looking for ways to expand their career options via involvement in pharmacology education. (Sunday, April 27, 9:30 a.m. – 12:00 p.m.)

Senthil K. Rajasekaran (Oakland Univ. William Beaumont Sch. of Med.) and **David W. Nierenberg** (Dartmouth-Hitchcock Med. Ctr.) will chair the DPE Division Symposium on "Addressing Prescribing Errors through Medical Student Education and Assessment." How can we better educate our medical students to avoid prescribing errors — hear about some novel approaches. (Sunday, April 27, 3:00 – 5:00 p.m.)

Save the Dates:

Deadline for Travel Award for Pharmacology Educators applications for the ASPET Annual Meeting at EB 2014: Monday, January 6, 2014

Academy of Pharmacology Educators applications due: Monday, January 6, 2014

DPE Executive Committee Meeting: Sunday, April 27, 7:30 – 9:30 a.m.

DPE Scientific Programming Meeting: Sunday, April 27, 5:45 – 7:30 p.m.

DPE/DDD/ISTCP Mixer: Monday, April 28, 7:30 – 9:30 p.m.

Did you Know?

The DPE site now has a link to the 2012 edition of *Knowledge Objectives In Medical Pharmacology*. Did you ever wonder what pharmacology experts consider the "teaching points" about the drugs you were asked to teach? Or how much time you should REALLY be spending (compared to what others are spending)? Here it is: http://www.aspet.org/uploadedFiles/Divisions_and_Chapters/ASPET_Divisions/Pharmacology_Education/Content/Educational_Assets/Knowledge%20Objectives%202012%20Edition%20Final.pdf. Thanks to Association of Medical School Pharmacology Chairs, Dr. Carl Feingold and Dr. Mary-Ann Bjornsti for permission to post on the DPE website.

Thanks to **Dr. Ryan A. Schneider**, Assistant Professor of Pharmaceutical Sciences, The University of Findlay College of Pharmacy for representing DPE on the ASPET Branding Taskforce.

Join and participate in our new **LinkedIn group** for interesting discussions about Pharmacology Education:

<http://www.linkedin.com/groups/ASPET-Pharmacology-Education-Division-5033126>

Toxicology Division

2013 – 2014 Executive Committee

Rick G. Schnellmann, Chair

Debra Laskin, Chair-elect

Jack A. Hinson, Past Chair

Laura James, Secretary/Treasurer

Heather E. Kleiner, Secretary/Treasurer-elect

Monica Valentovic, Past Secretary/Treasurer

Jessica A. Morgan, Student Representative

John D. Schuetz, Council Liaison

Judith A. Siuciak, ASPET Staff Liaison

News

Toxicology Division at the ASPET Annual Meeting at Experimental Biology 2014

The Division for Toxicology will sponsor four primary symposia at the ASPET Annual Meeting at EB 2014. Our chair-elect, **Debra Laskin** (Rutgers Univ.), will chair a symposium entitled "Macrophages and tissue injury: Agents of defense or destruction?" Also, we have a symposium that will be co-chaired by **Philip R. Mayeux** (Univ. of Arkansas for Medical Sciences) and **Chunfu Wu** (Shenyang Pharmaceutical Univ.). Dr. Chenfu is from the Chinese Pharmacological Society. The title of this symposium will be "Therapeutic potential of targeting oxidative stress pathways." A symposium will be chaired by **Jack Uetrecht** (Univ. of Toronto) entitled "Drug-induced idiosyncratic reactions and immunotoxicity." On Wednesday, April 30, we will have a symposium on K2 entitled "Scientists vs. street chemists: The toxicity of designer marijuana," chaired by **Laura P. James** (Arkansas Children's Hosp.) and **Jeffery H. Moran** (Univ. of Arkansas for Med. Sciences). Additionally, we will be co-sponsoring a number of symposia with other divisions.

The Division for Toxicology has received approval from ASPET Council for development the Donald J. Reed Award and Lectureship in Mechanistic Toxicology. The Reed Lectureship will be a biennial event and will be awarded to a young investigator (less than 45 years of age). Marc Fariss, former Chair of the Division for Toxicology, is chairing the committee to develop this award.

The Division for Toxicology is requesting symposia on timely topics for the EB 2015 meeting. The symposia should be organized following ASPET guidelines, http://www.aspet.org/Meeting_guidelines/#Symposium-Guidelines, and sent to Jack Hinson or any member of the Toxicology Division Executive Committee. Dr. Hinson is a member of the Program Committee. The proposed symposia will be discussed at the EB 2014 meeting. Final decisions for the ASPET Annual Meeting at EB 2015 will be made by the Program Committee in June 2014.

Chapter News

Mid-Atlantic Pharmacology Society

Mid-Atlantic Pharmacology Society 2013 Meeting: October 7, 2013

The Mid-Atlantic Pharmacology chapter of ASPET will be holding its 2013 annual meeting on Monday, October 7, 2013 at the University of the Sciences in Philadelphia. Our theme this year is *G Protein-Coupled Receptors: Current Thoughts and New Directions*. The day will include research poster viewing and judging for a trainee poster award in several categories, scientific talks, the Koelle Award presentation, and networking opportunities. This year's keynote address will be given by **Lakshmi Devi, Ph.D.** of the Mount Sinai Schol of Medicine (NY) on the topic of "Big sciences on a modest budget: Lessons from deorphanizing a hypothalamic G protein-coupled receptor involved in body weight reduction." Other invited speakers discussing their work include **Lawrence Brass** (Univ. of Pennsylvania), **J. Silvio Gutkind** (NIH), **Madhu Chintala** (Merck), and **Mary Abood** (Temple) plus two invited 10-minute talks by trainees selected from submitted abstracts. The day will end with an awards and networking reception, wrapping up the day by 4:30 p.m. Titles of the talks and a detailed schedule are posted on the MAPS Annual Meeting website, <http://www.aspet.org/MAPSAnnualMeeting/>.



To register, visit: https://www.aspet.org/cvweb_aspet/cgi-bin/eventsdll.dll/EventInfo?sessionaltcd=MAPS2013

For directions/parking information: http://www.aspet.org/uploadedFiles/Meeting/Chapter_Meetings/MAPS_2013program_flyer080613.docx

Abstract Submission Form: http://www.aspet.org/uploadedFiles/Meeting/Chapter_Meetings/MAPS%20Abstract%20form_2013.doc

ABSTRACT DEADLINE: TUESDAY, SEPTEMBER 24, 2013

Meeting Program

Morning Session

8:00 AM – 8:30 AM

Check-in and Poster Setup

8:30 AM – 9:50 AM

Poster Presentations*, judging and poster viewing

On-site late registration

*MUST BE PRESENT to be eligible for award

10:00 AM – 10:15 AM

MAPS and USciences Welcome

Diane W. Morel, Ph.D., President, MAPS

USciences representative

10:15 AM – 10:45 AM

Lawrence (Skip) Brass, M.D., Ph.D. (U. Penn):

How the platelet signaling network shapes the hemostatic response to injury and contributes to heart attacks and strokes

10:45 AM – 11:15 AM

J. Silvio Gutkind, Ph.D. (NIH):

The mutational landscape of G proteins and GPCRs in cancer: New molecular targeted therapies?

11:15 AM – 11:45 AM

Madhu Chintala, Ph.D. (Merck):

Discovery and development of vorapaxar, a novel PAR-1 antagonist for the treatment of atherothrombosis

11:45 AM – 12:00 PM

Invited Trainee Talk 1

Afternoon Session

12:00 PM – 1:00 PM

Presentation of George B. Koelle Award (by MAPS Councilor)

Lunch, poster viewing

1:00 PM – 2:00 PM

KEYNOTE ADDRESS: Lakshmi Devi, Ph.D. (Mount Sinai Schol of Medicine, NY): *Big science on a modest budget: Lessons from deorphanizing a hypothalamic G protein-coupled receptor involved in body weight regulation*

2:00 PM – 2:30 PM

Mary Abood, Ph.D. (Temple University): *Cannabinoid Receptors: Inside and Out*

2:30 PM – 2:45 PM

Invited Trainee Talk 2

2:45 PM – 3:00 PM

Closing Remarks

3:00 PM – 4:30 PM

Poster Award Ceremony* and Networking Reception

*MUST BE PRESENT to be eligible for award

Upstate New York Pharmacology Society

Chapter News: Election Results



The elections within the Upstate New York Pharmacology Society (UNYPS) Chapter of ASPET have resulted in the following individuals agreeing to serve or continuing to serve the Chapter. Congratulations and thank you!

President-elect – **Gregory G. Tall, Ph.D.** (University of Rochester)
President – **Suzanne G. Laychock, Ph.D.** (University of Buffalo)
Secretary-Treasurer – **Peter G. Bradford, Ph.D.** (University at Buffalo)
Councilor – **Jean M. Bidlack, Ph.D.** (University of Rochester)

Councilor – **Carlos Feleder, M.D., Ph.D.** (Albany College of Pharmacy)
Councilor – **Ji Li, Ph.D.** (University at Buffalo)
Councilor – **Paul J. Kammermeier, Ph.D.** (University of Rochester)
Councilor – **Kim Bernosky-Smith, Ph.D.** (D'Youville College)

Great Lakes Chapter

Summary from the 26th Annual Scientific Meeting

The Great Lakes Chapter of ASPET held its annual meeting on June 14, 2013 at The Searle Conference Center, Rush University Medical Center, in downtown Chicago. Over 100 pharmacologists attended the meeting, including 18 undergraduates and 19 graduate students and post-doctoral fellows. Attendees included researchers from University of Illinois at Chicago, Rush University, Rosalind Franklin University, Midwestern University, Northwestern University, Lake Forest College, Benedictine University, Loyola University Chicago, University of Michigan, The Ohio State University, Wheaton College, Saint Xavier University, Navy Drug Screening Laboratory, Astellas Pharmaceuticals, AbbVie, Baxter Healthcare, Dai Scientific, Promega Corporation, EMD Millipore, VWR International, Cellular Dynamics International, Fischer Scientific, Integrated DNA Technologies, LC Sciences, MIDSCI, and Exiqon.

The 2013 program was the following:

8:30 AM - 10:30 AM: Registration (The Searle Conference Center, Professional Building, 5th Floor). Continental breakfast (Main Lounge)

Poster session (Main Lounge). Twenty-five posters were presented in the poster session. Four posters were presented by undergraduate students, 9 by graduate students, 5 by postdocs, and 7 by faculty members or research scientists at pharmaceutical companies.

8:30 AM – 12:00 PM: Vendor Exhibit (Main Lounge)

10:45 AM – 11:45 AM: Young Investigator Symposium (542 Brainard Room). Welcome and Opening Remarks by **Alejandro Mayer**, Midwestern University, President, GLC-ASPET

10:45 AM – 11:00 AM: **Ya-fang Chang**, Postdoctoral Fellow (University of Chicago): *MicroRNA-30c regulates EMT, drug resistance and breast tumor invasion*

11:00 AM – 11:15 AM: **Fred Kohlhapp**, Postdoctoral Fellow, (Northwestern University): *Reprogramming of the ovarian cancer microenvironment by miRNA*

11:15 AM – 11:30 AM: **Nichole Pohl**, Postdoctoral Fellow (University of Illinois at Chicago): *Micro-RNA-mediated downregulation of Kv channels in pulmonary arterial hypertension*

11:30 AM – 11:45 AM: **Cristina Bardita, M.D.**, Graduate Student, Rush University: *Intersectin-1s deficiency and intercellular transfer of Alk5 by microparticles promote abnormal lung endothelial cell proliferation*

12:00 PM – 1:00 PM: Lunch & Learn Career Workshop (Fenger-Sippy Room). The workshop consisted of four scientists hosting four tables where pharmacology careers in academics (both graduate and undergraduate institutions), biotechnology companies, and large pharmaceutical corporations were discussed.

1:00 PM – 4:15 PM: **Symposium: Functional microRNA in disease: novel opportunities for pharmacology** (542 Brainard Room)

1:00 PM – 1:05 PM: Welcome and Opening Remarks by **Eric Blomme** and **Maria Barbolina**, Symposium Chairs

1:05 PM – 1:30 PM: **Zain Paroo** (University of Illinois at Chicago): *Regulating the microRNA machinery*

1:55 PM – 2:25 PM: **Jonathan Maher** (AbbVie Inc.): *MicroRNAs as biomarkers of safety and efficacy in drug discovery and development*

2:35 PM – 3:05 PM: **Gianpiero Di Leva** (The Ohio State University): *MicroRNA roles in tumorigenesis and chemotherapy resistance*

3:15 PM – 4:15 PM: **Keynote Address, Chunxiang (Kevin) Zhang** (Rush University): *MicroRNAs in Cardiovascular disease: Current progress and challenges*

4:30 PM – 5:00 PM: **Business Meeting and Awards Presentation**: Dr. Alejandro Mayer, GLC ASPET President presented the results of the Great Lake Chapter of ASPET 2013 Executive Committee Election. Three new members were elected as GLC ASPET councilors: **Philip Kopf, Ph.D.**, Assistant Professor, Pharmacology Department, Chicago College of Osteopathic Medicine, Midwestern University; **James J. O'Donnell III, Ph.D.**, Postdoctoral Fellow, Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago; and **Irena Levitan, Ph.D.**, Adjunct Associate Professor of Bioengineering, Department of Medicine, Section of Pulmonary, Critical Care, Sleep and Allergy, University of Illinois at Chicago.

The poster awards presentation was conducted by **Ricardo Monzon**, Senior Poster Judge and GLC ASPET Secretary (2013 – 2014). Cash prizes were given to the top posters in the following categories:



GLC ASPET Conference 2013 Poster Session

Undergraduate Students

First Place: **Maiwase Tembo**, Biology Dept., Lake Forest College, IL, *Evidence for the role of endocytosis in Parkinson's disease: Insights from a budding yeast model.*

Graduate Students

First Place: **Monal Patel**, Rush University Medical Center, Department of Pharmacology, Chicago, IL, *Cleavage of ITSN-1s by granzyme B promotes lung endothelial cell proliferation via p38mapk/erk1 signaling; implications for plexogenic PAH.*

Second Place: **Mary Ellen Molloy**, Department of Biopharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, *Selective estrogen mimics for the treatment of tamoxifen-resistant breast cancer.*

Postdoctoral Fellows

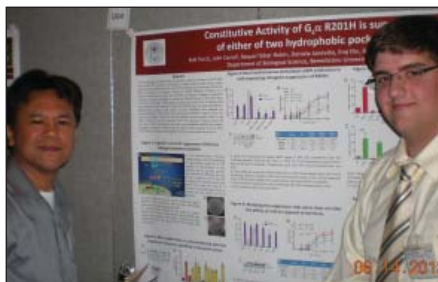
First Place: **Angeline M. Lyon**, Department of Pharmacology, University of Michigan at Ann Arbor. *Molecular mechanisms of PLC β activation.*

Acknowledgements

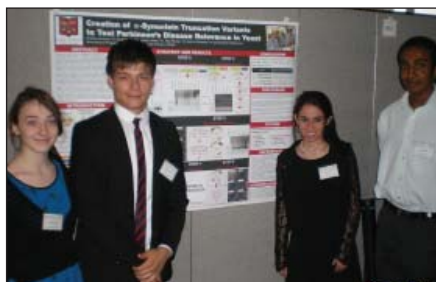
The GLC-ASPET Executive Committee gratefully acknowledges financial support for the meeting from: ASPET, Midwestern University, Loyola University (Department of Pharmacology), The Chicago Medical School at Rosalind Franklin University, College of Pharmacy at Rosalind Franklin University, and Rush University. We also gratefully acknowledge the following in kind contributions: Midwestern University, Chicago College of Osteopathic Medicine, Department of Pharmacology; Dr. Sanda Predescu, Department of Pharmacology, Rush University Medical Center; Dr. Kuei Tseng, Department of Cellular and Molecular Pharmacology, The Chicago Medical School at Rosalind Franklin University; Victoria Sears, Dr. Philip Kopf, and Dr. Walter Prozialeck, Department of Pharmacology, Chicago College of Osteopathic Medicine, Midwestern University.

Support by the following vendor exhibitors is gratefully acknowledged: D.A.I. Scientific Equipment, Exiqon, Fischer Scientific, Integrated DNA Technologies, LC Sciences, MIDSCI, Promega Corporation, EMD Millipore, and Cellular Dynamics International.

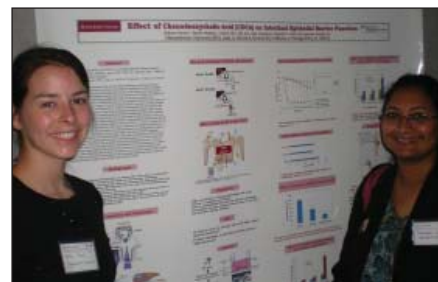
Photo Gallery from the ASPET Great Lakes Chapter 26th Annual Scientific Meeting



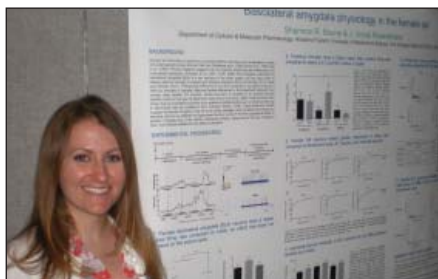
Undergraduate Poster [U04]: Turcic et al.
Benedictine University, Lisle, IL



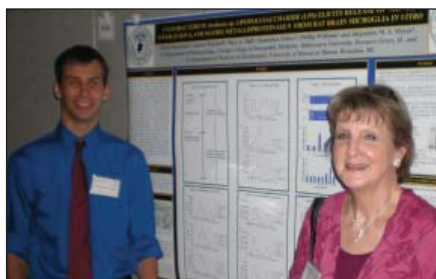
Undergraduate Poster [U01]: Alvarado, et al.,
Lake Forest College, Lake Forest, IL



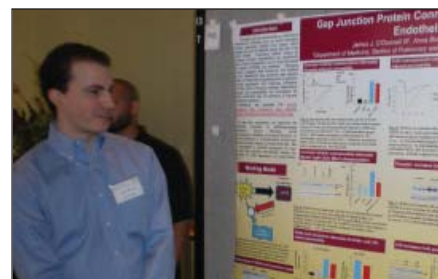
Undergraduate Poster [U02]: French, et al.,
University of Illinois at Chicago, IL



Graduate Poster [G08]: Blume and Rosenkrantz,
Rosalind Franklin University of Medicine and Science, North Chicago, IL



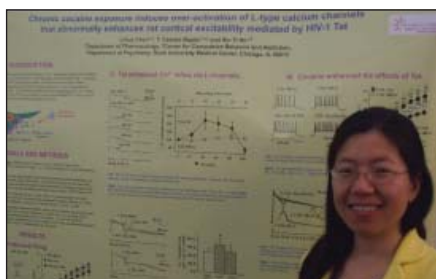
Graduate Poster [G04]: MacAdam, et al.,
Midwestern University, Downers Grove, IL



Postdoctoral Poster [P05]: O'Donnell et al.,
University of Chicago, Chicago, IL



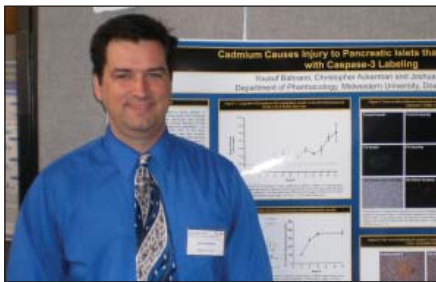
Postdoctoral Poster [P02]: Homan et al.,
University of Michigan, Ann Arbor, MI



Postdoctoral Poster [P01]: Chen et al.,
Rush University Medical Center, Chicago, IL



Faculty Poster [F06]: Peuler et al.,
Midwestern University, Downers Grove, IL



Faculty Poster [F01]: Edwards and Bahrami, Midwestern University, Downers Grove, IL



Faculty Poster [F03]: Gilchrist and Merritt, Midwestern University, Downers Grove, IL



GLC President-elect Sandra Predescu (left) and Cristina Bardita (right)



Left to right: GLC ASPET President Alejandro Mayer, Board member Philip Kopf, Walter Prozialeck, and Joshua Edwards



Gloria Meredith and former GLC ASPET President Walter Prozialeck



Young Investigator Symposia (left to right): Ya-fang Chang, University of Chicago; Fred Kohlhapp, Northwestern University; Nichole Pohl, University of Illinois at Chicago; Cristina Bardita, Rush University



GLC ASPET Symposium speaker: Zain Paroo, University of Illinois at Chicago, Chicago, IL



GLC ASPET Symposium speaker: Jonathan Maher, AbbVie Inc., North Chicago, IL



GLC ASPET Symposium speaker: Gianpero Di Leva, The Ohio State University, Columbus, OH



Symposium keynote speaker: Chunxiang (Kevin) Zhang, Rush University, Chicago, IL



Poster award winners, left to right: 1st place undergraduate Maiwase Tembo, 2nd place graduate Mary Ellen Malloy, 1st place graduate Monal Patel, 1st place postdoc Angeline Lyon



GLC ASPET President Alejandro Mayer presenting a service recognition award to GLC Councilor Maria Barbolina



President Alejandro Mayer presenting a service recognition award to Councilor Geoff Swanson



President Sandra Predescu gives the President's Award to outgoing President Alejandro Mayer.



2013-14 Board, left to right: Alejandro Mayer, Sandra Predescu, Eric Bloome, Kuei Tseng, Ricardo Monzon, Saverio Gentile, Philip Kopf, James O'Donnell, III, and Irena Levitan

Membership Information

Definitions of Categories of ASPET Membership

Regular Members: Any qualified investigator who has conducted and published a meritorious original investigation in pharmacology shall be eligible for membership in the Society. An individual who holds an earned doctoral degree (Ph.D., M.D., or equivalent) is considered a qualified investigator. Exceptions may be made for someone who does not meet the degree requirement but who has made major original research contributions to pharmacology. Applicants for Regular membership will no longer need to be sponsored by an ASPET member.

Postdoctoral Members: Any qualified person who has received their Ph.D. or equivalent degree in pharmacology or a related field within the past five years is eligible for Postdoctoral membership. Postdoctoral members will receive the same benefits as Regular members, including the right to vote in ASPET elections. Individuals may remain in the Postdoctoral Membership category for a maximum of five (5) years from the date of receipt of their Ph.D. (or equivalent) degree after which time they must upgrade to Regular Membership. Applicants for Postdoctoral membership will no longer need to be sponsored by an ASPET member. Please note that the same membership criteria apply for Postdoctoral Members as for Regular Members, including having published a meritorious original investigation in pharmacology.

Affiliate Members: Any qualified person who is engaged in the study of problems in pharmacology but does not meet the requirements for Regular Membership may be eligible for Affiliate Membership, which shall be non-voting. Affiliate members may later be proposed for Regular Membership, upon meeting the requirements. Affiliate Members include representatives in the following careers: faculty members who have made their contribution in teaching; productive research team members who have not published a meritorious original publication; administrators in government, industry, universities, or other organizations who do not have sufficient independent research. Applicants for Affiliate membership will no longer need to be sponsored by an ASPET member.

Student Members: Persons who are enrolled in undergraduate, graduate or professional degree programs, and who have an interest in pharmacology, are eligible for Undergraduate or Graduate Student membership, respectively, which shall be non-voting. Upon completion of their research doctoral degree, student members must upgrade to Postdoctoral Membership. Applicants for Student membership must be sponsored by their mentor, department chair, or ASPET SURF Program Director. (See the sponsor statement instructions at the bottom of the page.)

Regular Member Benefits (Dues \$150):

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Appendix

Abstracts presented at the Great Lakes Chapter 26th Annual Scientific Meeting

GLC-ASPET SYMPOSIUM SPEAKER ABSTRACTS

Regulating the microRNA machinery

Zain Paroo; University of Illinois at Chicago, Department of Biopharmaceutical Sciences, Chicago, IL

Advances in understanding miRNA function are occurring at an accelerated rate. This assigning of biological roles to specific miRNA are revealing new dimensions to cellular pathways and providing novel insights for decoding pathology. In contrast, elucidation of the miRNA machinery has slowed in recent years. A key limitation has been the development of new assays which capture unique biological events in cell-free systems. For example, small RNA-generating assays were required for discovery of Dicer and slicer assays facilitated identification of Argonautes as effectors of small RNA. Establishing de novo biochemical assays will enable discovery of previously unrecognized components of the miRNA pathway and may present new approaches for exploiting miRNA biology for therapeutic development.

MicroRNAs as biomarkers of safety and efficacy in drug discovery and development

Jonathan Maher; Investigative Toxicology and Pathology, Pharmaceutical Research and Development, AbbVie, North Chicago, IL 60064

As the costs and timeframe of developing new pharmaceuticals has risen, the search for new biomarkers to help bring new drugs to market has become increasingly important. There are a multitude of biomarkers utilized for a variety of indications, but biomarkers are used primarily in pharmaceutical discovery and development to evaluate the safety or efficacy of a new chemical or biological entity. Recently the identification of miRNAs that are released into biological matrixes such as serum, plasma or urine and correlate with disease or tissue injury has generated significant excitement in the field. This is due primarily to miRNAs having ideal properties as biomarkers, especially the potential to have high sensitivity and specificity in monitoring biological endpoints of interest. Similarly miRNA assays are: 1) cost-effective, 2) rapidly developed, 3) easy to use, and 4) generally translatable to the clinic. Likewise panels of miRNAs can be multiplexed to monitor multiple endpoints from a single sample. Initial work thus far has focused on miRNA discovery, along with evaluating and qualifying these miRNAs as biomarkers through a variety of internal efforts and through the work of international consortia. A discussion of the current biomarkers utilized will highlight significant gaps that exist within drug safety, with an emphasis to demonstrate the potential use of miRNAs to fulfill key areas of need. In summary it will be demonstrated that miRNAs can perform equivalently or better than traditional gold standard protein biomarkers, and may play an integral role for monitoring disease or injury where no biomarkers currently exist.

MicroRNA roles in tumorigenesis and chemotherapy resistance

Gianpiero Di Leva; Department of Molecular Virology, Immunology and Medical Genetics Comprehensive Cancer Center, The Ohio State University, Columbus, OH 43210

MicroRNAs (miRNAs) represent the major class of small endogenous non-coding RNAs and a steadily growing number of studies have shown that miRNAs have key roles in the regulation of cellular processes. As data have accumulated showing fundamental roles for miRNAs in proliferation, differentiation, survival and apoptosis, it is not surprising that miRNAs were found to be important in tumorigenesis and are considered promising therapeutic targets for novel cancer treatments. Here, we will discuss the recent advances in the involvement of miRNAs in breast and lung tumorigenesis and how dysregulated miRNAs can alter the response to hormonal and tyrosine-kinase directed chemotherapy

MicroRNAs and cardiovascular diseases: From bench to bedside

Chunxiang Zhang, MD, PhD, FACC; Department of Pharmacology, Rush University Medical Center, Rush University, 1735 W Harrison St, Cohn Building, Ste 406, Chicago, IL 60612

MicroRNAs (miRNAs) are a novel class of endogenous, small, noncoding RNAs that regulate gene expression via degradation or translational inhibition of their target mRNAs. As a group, miRNAs are able to directly regulate at least 30% of genes in a cell. In addition, other genes may also be regulated indirectly by miRNAs. It is therefore not surprising that miRNAs could be the pivotal regulators in normal development, physiology, and pathology. Recent studies from us and other groups have demonstrated that miRNAs are highly expressed in cardiovascular system and their expression is dysregulated in diseased hearts and vessels. miRNAs are found to be critical modulators for cardiovascular cell functions such as cell differentiation, contraction, migration, proliferation, and apoptosis. Accordingly, miRNAs are involved in the many cardiovascular diseases such as cardiac hypertrophy and heart failure, atherosclerosis, ischemic heart disease, cardiac arrhythmias, angiogenesis, atherosclerosis and restenosis after angioplasty. Moreover, in contrast to our original thought, miRNAs exist in circulating blood and are relatively stable, thus, they could be proved useful as biomarkers for cardiovascular disease. miRNAs may play important roles in diagnosis, prevention and treatment of cardiovascular disease.

GLC-ASPET YOUNG INVESTIGATOR SYMPOSIUM

MicroRNA-30c regulates EMT, drug resistance, breast tumor invasion

Ya-fang Chang, Postdoctoral Fellow, University of Chicago; Jessica Bockhorn¹, Ya-fang Chang¹, Rachel Dalton¹, Chika Nwachukwu¹, Simo Huang¹, Kathy Yee¹, Aleix Prat², Dezheng Huo¹, Eileen Dolan¹, Charles M. Perou², Olufunmilayo I. Olopade¹, Michael F. Clarke³, Geoffrey Greene¹, Huiping Liu¹; ¹The University of Chicago, Chicago, IL 60637; ²University of North Carolina at Chapel Hill, Chapel Hill, NC 27514; ³Stanford University, Stanford, CA 94305

Metastasis and chemotherapy resistance remain challenging problems in the clinic and the underlying molecular mechanisms are poorly characterized. MicroRNAs have emerged as important epigenetic regulators of various cellular processes during cancer development and progression. We hypothesize that the epithelial-to-mesenchymal transition (EMT) is involved in therapy resistance and cancer progression, but the functional link and signaling pathways need to be elucidated. Our work discovered that miR-30c plays a pivotal role in chemo-resistance and breast cancer cell invasion by directly targeting twinfilin (TWF1), which encodes an actin-binding protein and promotes EMT. TWF1 regulates F-actin formation, a key component of the cellular transition to a more invasive mesenchymal phenotype. We also identified IL-11 as a secondary target of TWF1 in the miR-30c signalling pathway. Identification of a novel miRNA-mediated pathway that regulates chemo-resistance and cancer cell invasion in breast cancer will facilitate the development of novel therapeutic strategies.

Reprogramming of the ovarian cancer microenvironment by miRNA

Fred Kohlhapp; Postdoctoral Fellow, Northwestern University

Surgery and aggressive chemotherapy has a 20% success rate in ovarian cancer (OvCa) meaning new therapies are desperately needed. Ovarian tumors are composed of 7-83% stroma, which drives tumor progression, increases angiogenesis, and promotes metastasis, yet current therapies are aimed at targeting the cancer cells alone. While the tumor stroma consists of a number of cell types, cancer associated fibroblasts (CAFs) are a major constituent. The Lengyel and Peter labs recently reported that in ovarian CAFs, the micro-RNAs (miRNA) miR-31 and miR-214 are downregulated while miR-155 is upregulated when compared to normal or tumor-adjacent fibroblasts. Additionally, it was shown that OvCa cells are sufficient to reprogram normal omental fibroblasts (NOFs) into CAFs through downregulation of miR-214, miR-31, and upregulation of miR-155 during coculture. Mimicking this deregulation by transfecting miRNAs and miRNA inhibitors induced a functional conversion of normal fibroblasts into CAFs as defined by increased

fibroblast motility and promotion of tumor progression both *in vitro* and *in vivo*. Furthermore, the reverse experiment resulted in the reversion of CAFs into normal fibroblasts. The miRNA-reprogrammed normal fibroblasts and patient-derived CAFs shared a large number of upregulated genes highly enriched in chemokines, which are known to be important for CAF function. The most highly upregulated chemokine, CCL5, was found to be a direct target of miR-214. These results indicate that during the process of ovarian cancer progression, NOFs are reprogrammed to become CAFs through the regulation of miRNA expression.

MicroRNA-mediated downregulation of Kv channels in pulmonary arterial hypertension

Nicole M. Pohl, Aya Yamamura, Zaid Patel, Hisao Yamamura, Ayako Makino, and Jason X-J. Yuan. Department of Pharmacology; Department of Medicine, Section of Pulmonary, Critical Care, Sleep and Allergy; Institute for Personalized Respiratory Medicine; Center for Cardiovascular Research, University of Illinois at Chicago, Chicago, IL 60612

Downregulated expression of voltage-gated K⁺ (Kv) channels and decreased Kv currents (IK(V)) in pulmonary artery smooth muscle cells (PASMC) have been implicated in the development of pulmonary vasoconstriction and vascular remodeling in idiopathic pulmonary arterial hypertension (IPAH). It is, however, unclear, why Kv channels are downregulated. microRNAs (miRNAs) are small noncoding RNA that acts as important regulator by post-transcriptionally modulating mRNA and protein expression. In this study, we examined the potential role of miRNAs in the downregulated Kv channel expression and reduced whole-cell IK(V) in IPAH-PASMC. Using a miRNA PCR array approach, we identified 5 miRNAs (miR-15a, -29a, -29b, -138 and -222) that were highly expressed in IPAH-PASMC in comparison to normal PASMC (>2-fold difference). Real-time PCR experiments confirmed the upregulation of miR-29b, miR-138, miR-222 and miR-15a in IPAH-PASMC compared to normal PASMC. Using bioinformatics to predict miRNA targets, we identified multiple potential targets including KCNA5. Overexpression of miR-29b mimic in normal PASMC decreased Kv1.5 protein expression while inhibition of miR-29b in IPAH-PASMC rescued Kv1.5 protein levels, indicating that miR-29b regulates Kv1.5 protein expression. Additionally, luciferase assays reveal that Kv1.5 is a direct target of miR-29b in IPAH-PASMC. Furthermore, patch clamp experiments revealed that whole-cell K⁺ currents are decreased in miR-29b mimic transfected normal human PASMC, indicating that the upregulation of miR-29b may be responsible for the decreased Kv currents observed in IPAH-PASMC. Consistently, transfection of miR-29b inhibitor in IPAH-PASMC rescued whole-cell K⁺ currents. In conclusion, upregulated miR-29b in IPAH-PASMC might be responsible for the inhibited Kv channel expression and function and may therefore provide a new therapeutic target to treat patients with IPAH.

Intersectin-1s deficiency and intercellular transfer of Alk5 by microparticles promote abnormal lung endothelial cell proliferation

Cristina Bardita, Dan N. Predescu, Fei Sha and Sanda A. Predescu; Department of Pharmacology, Rush University, Chicago IL

We have recently shown using an intersectin-1s (ITSN-1s) knockdown mouse (KDITSN) that acute ITSN-1s deficiency induced lung endothelial cell (EC) apoptosis in a process that involved downregulation of Erk1/2 survival signaling. After only 7 days of KDITSN, the remaining ECs exhibited phenotypic changes including hyperproliferation and apoptosis-resistance, leading to repair and remodeling of the injured lungs. Moreover, we found that the apoptotic/activated vascular cells of KDITSN mouse released numerous circulating microparticles (cMPs), comprising Alk5, the broadly expressed transforming growth factor- β (TGF β) type I receptor. A possible involvement of cMPs in regulation of EC phenotype has not been reported yet.

cMPs released in the blood of KDITSN mouse were isolated and fluorescently labeled with Alk5-AlexaFluor594 antibody. Biochemical (Alk5 transfer assays, western blot, immunoprecipitation, density gradient centrifugation, cross-linking, flow cytometry) and morphological (fluorescence and electron microscopy) approaches were used to evaluate the ability of cMPs to interact and transfer Alk5 to ECs, as well as the effects of deficient endocytosis on Alk5 intracellular trafficking and Smad2/3-Erk1/2 signaling. Endocytic deficiency alters Alk5 internalization and enhances its ubiquitination/degradation. cMPs (25 μ g/ml) interact and replenish ECs deficient of ITSN-1s with functional Alk5 receptor, promoting their survival and proliferation. We also demonstrate that a signaling switch from the canonical Smad2/3 to Erk1/2^{MAPK} downstream of TGF β /Alk5, accounts for Erk1/2 activation and upregulation of abnormal proliferative signaling. SB-525334 (Alk5 inhibitor) and annexin-V, (blocker of phosphatidylserine), abolished these effects. Our studies demonstrate a functional relationship between the intercellular transfer of Alk5 via cMPs and ECs survival/proliferation. Furthermore, we define a novel molecular mechanism for TGF β /Alk5-dependent Erk1/2^{MAPK} signaling significant for the abnormal proliferation of pulmonary ECs.

GLC-ASPET ABSTRACTS 2013: FACULTY

F01. Cadmium causes injury to pancreatic islets that is associated with caspase-3 labeling

Yousuf Bahrami and Joshua Edwards, Pharmacology Department; Midwestern University, Downers Grove, IL 60515

Diabetes is a growing worldwide epidemic. There is increasing interest in how environmental contaminants can contribute to the onset of type II diabetes. Impaired insulin release is a hallmark of type I diabetes and is key in the progression of type II diabetes. Multiple epidemiological and experimental studies show that exposure to the metal cadmium (Cd), is associated with diabetes and reduced serum insulin. To examine the cytotoxic effects of Cd within pancreatic islets, male Sprague Dawley rats were injected subcutaneously with either saline (control) or Cd (0.6 mg Cd/kg/day, 5 days per week). After 6, 9 and 12 weeks of Cd treatment, pancreatic tissue samples were removed then fixed in formalin. Pancreata were sectioned and H&E stained to identify islets then examined for changes in islet histology. A trained veterinary pathologist scored each sample for cytoplasmic vacuolization and signs of necrosis and apoptosis. All pancreata from Cd treated animals had elevated scores for signs of vacuolization, apoptosis and necrosis. However, these changes in cell viability did not appear to change with longer Cd exposure times. In another study using the same pancreas samples, tissue was labeled for the apoptosis indicator, active caspase 3. In this study, pancreatic samples were counter stained with hematoxylin so that immuno-labeled islets could be identified. This study resulted in similar findings. Islets from Cd-treated animals had greater caspase-3 labeling and as before, the intensity of labeling appeared to be time independent. These preliminary results show that Cd acts to injury pancreatic islets which may result in diminished insulin release.

F02. Therapeutic potential of miRNA – Identification of miRNAs that play essential roles in disease and may act as novel therapeutics or preventive targets

Xiaochuan Zhou¹, Xiaolin Zhang¹, Nijing Sheng¹, Xiaolian Gao², Chris Hebel², Christoph Eicken²; ¹Atactic Technologies Inc. Houston, TX 77054; ²LC Sciences LLC Houston, TX 77054

MicroRNAs (miRNAs) are effectors of environmental influences on gene expression. Thus miRNAs play an important role in the cellular response to injury, exposure to toxicants, and disease. Insight into the mechanisms through which these small molecules function may lead to development of therapeutics that target miRNA pathways. Identification and quantitation of miRNA expression is an important first step in understanding the potential mechanisms involved in these cellular and molecular responses. Here we present an advanced microfluidic biochip technology that was developed to enable comprehensive miRNA expression profiling. Detection of miRNA using an array offers the opportunity to examine all known and/or predicted miRNA transcripts in a single experiment providing a comprehensive view of all miRNAs that may be involved in the system being investigated. The detection probes are in situ synthesized using PGR (Photo-Generated Reagent) chemistry to afford the high synthesis yield and complete sequence flexibility, and modified nucleotides are incorporated to enhance the binding to short miRNAs without sacrificing specificity. Several key parameters of the biochip technology, including detectivity, specificity, and feature uniformity will be demonstrated. Application examples will be provided to demonstrate how the technology is enabling breakthrough discoveries.

F03. *In vitro* evaluation of pyrrolidine derivatives as CCR1 antagonists for multiple myeloma

Annette Gilchrist¹ and James R. Merritt²; ¹Midwestern University, Chicago College of Pharmacy, Department of Pharmaceutical Sciences Downers Grove, IL 60515; ²Kean University, New Jersey Center for Science, Technology, & Mathematics Union, NJ 07083

Multiple myeloma (MM) is a clonal B-cell disorder characterized by the accumulation of malignant plasma cells in the bone marrow. Studies by other investigators indicate that the chemokine CCL3 and its G protein coupled receptor (GPCR) CCR1 may play a significant role in the disease. Based on a previously disclosed series of CCR1 antagonists, a collection of novel pyrrolidines were synthesized using five related chemotypes. The collection of compounds was initially tested in radioactive binding assays using membranes isolated from human embryonic kidney (HEK) cells overexpressing CCR1, or a MM cell line (RPMI 8226) that endogenously expresses CCR1. Using RPMI 8226 cells

we also examined the compounds for their ability to alter CCL3-induced chemotaxis and CCR1 internalization. Finally, we examined the effects of the compounds on CCL3-mediated (β -arrestin translocation using a PathHunter[®] cell line (DiscoverX). We found that while most of the CCR1 antagonists achieved potent inhibition of ¹²⁵I-CCL3 binding, and many reduced myeloma cell chemotaxis fewer inhibited CCL3-mediate CCR1 internalization or (β -arrestin translocation indicating they may have biased antagonism.

F04. Marine pharmacology and the marine pharmaceuticals pipeline

A.M.S. Mayer^{1,2} and K.B.Glaser^{1,2}; ¹Midwestern University, Department of Pharmacology, CCOM, Downers Grove, IL 60565, and ²AbbVie Laboratories, Abbott Park, IL 60064
As the renaissance in the pharmacology of marine natural products continues (See commentary in Glaser and Mayer, *Biochemical Pharmacology* 78:440-448, 2009), we assessed the status of the clinical marine pharmaceuticals pipeline in 2013. There were five FDA-approved marine-derived drugs in the US market, namely cytarabine for cancer (Cytosar-U[®], Depocyt[®], FDA-approved 1969), ziconotide for pain (Prialt[®], FDA-approved 2004), omega-3-acid ethyl esters for hypertriglyceridemia (Lovaza[®], FDA-approved 2004), eribulin mesylate for cancer (Halaven[®], FDA-approved 2010), and brentuximab vedotin for cancer (Adcertis[®], FDA-approved 2011), while vidarabine as an antiviral (Vira-A[®], FDA-approved 1976) was no longer available, and trabectedin for cancer (Yondelis[®], FDA-orphan drug approval 2005) being EU-registered. In April 2013, the clinical marine pharmaceutical pipeline (Reviewed in Mayer et al. *TIPS* 31:255-265, 2010) consisted of 11 marine-derived compounds in clinical development. Included in the clinical pipeline were three new monoclonal antibodies conjugated to monomethyl auristatin E, a synthetic analog of the marine compound dolastatin, which were in either Phase I, Phase II or Phase III clinical trials. Updated information about the clinical pipeline is available at <http://marinepharmacology.midwestern.edu/clinPipeline.htm>. Furthermore, the preclinical marine pharmacology pipeline remained a global enterprise with researchers from several countries reporting multiple marine chemicals with novel mechanisms of action (Reviewed in Mayer et al. *MARINE DRUGS* 2013, in press). We conclude that both the marine pharmacology preclinical pipeline as well as the clinical pharmaceutical pipeline remained very active in 2013. Supported by Midwestern University.

F05. Aberrant restoration of spines and their synapses in L-dopa-induced dyskinesia: Involvement of corticostriatal but not thalamostriatal synapses

Yiyue Zhang¹, Nasya Mendoza-Elias¹, Kuei-Yuan Tseng¹, Kathy Steece-Collier², Gloria E. Meredith¹; ¹Rosalind Franklin University of Medicine and Science, North Chicago, IL 60064; ²Michigan State University, Grand Rapids, MI 49503
Striatal medium spiny neurons (MSNs) comprise approximately 95% of neurons in the intact striatum. These neurons contain a dense population of spines that are the primary site of excitatory input from cortex and thalamus. This excitatory input is modulated by nigral dopamine (DA) neurons, which synapse onto the neck of the same spines that receive input from the cortex. In the Parkinsonian brain, DA depletion results in significant loss of spines and their excitatory synapses and changes in synaptic plasticity. DA replacement in parkinsonian subjects often result in abnormal involuntary movement known as dyskinesias, however, it is not known whether the induction of L-3,4-dihydroxyphenylalanine (L-dopa)-induced dyskinesias (LIDs) results in structural adaptations of MSNs and their synapses. We examined the structural plasticity of excitatory synapses from corticostriatal and thalamostriatal pathways and their postsynaptic targets (MSNs) in adult Sprague Dawley rats (N = 53) to understand how these striatal circuits change in LIDs. Detailed electron and light microscopic analyses provide new insights in response to LIDs. Our data provide compelling evidence for a dramatic rewiring of the striatum of dyskinetic rats and that this rewiring involves corticostriatal, but not thalamostriatal, contacts onto MSNs. There is a dramatic increase in corticostriatal contacts onto spines and dendrites that appear to be directly linked to dyskinetic behaviors, since they were not seen in the striatum of animals that did not develop dyskinesia. There is also an aberrant increase in spines receiving more than one excitatory contact, i.e. multisynaptic spines, in the dyskinetic animals compared to the 6-hydroxydopamine-treated and control rats. Such alterations could substantially impair the ability of striatal neurons to gate cortically driven signals and contribute to the loss of bidirectional synaptic plasticity present in animal models of LIDs.

F06. Effects of fibrates on contractility of the isolated intact rat duodenum

J.D. Peuler, D. Belisle and L.E. Phelps; Pharmacology Department, Midwestern University, Downers Grove, IL 60515
Fibrates (e.g. gemfibrozil) are a class of lipid-lowering drugs that have been used clinically for over 80 years. But fibrates cause adverse gastrointestinal (GI) side effects, which occur with them all but more frequently with gemfibrozil. Our recent work showed that gemfibrozil could inhibit spontaneous contractility of intact duodenal tissues isolated from female rats. If this occurs in vivo in the form of decreased motility, it would help explain such side effects. In the present work, we found that gemfibrozil can also inhibit spontaneous contractions in duodenum from male rats. Secondly, we found that bezafibrate and fenofibrate can also inhibit spontaneous duodenal contractions but gemfibrozil does so to a greater extent. Thirdly, we found that pretreatment with tetrodotoxin did not affect gemfibrozil's ability to inhibit such contractions. Thus, that ability is not due to an action of gemfibrozil on enteric neuronal activity. Finally, we found that contractions induced by acetylcholine and 5-hydroxytryptamine can be inhibited by gemfibrozil. Thus, gemfibrozil appears to nonspecifically inhibit duodenal smooth muscle contractions induced by at least two known intestinal contractile substances, an action which if present in vivo may help explain its GI side effects and likely those of other fibrates. Support: MWU Masters Program.

F07. Kidney collecting duct specific loss of microRNAs leads to cysts, loss of medullary tissue, and upregulation of the homeodomain protein Cux1

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The processing enzyme Dicer1 is essential for the production of microRNAs (miRNAs). Complete deletion of Dicer1 is embryologically lethal prior to gastrulation indicating the importance of this protein in development. To determine the role of miRNAs in kidney development, we used a conditional allele of Dicer1 to specifically delete miRNA processing in the ureteric bud derivatives. Mice carrying a floxed allele of Dicer1 were crossed with Hoxb7cre mice to generate Dicer1^{CO} mice. Dicer1^{CO} mice were evaluated at postnatal day 21 (P21) and at six weeks of age. Dicer1^{CO} mice exhibited hydronephrosis and cortical cysts. Labeling with DBA lectin and cytokeratin confirmed the collecting duct origin of the cysts and the medullary cavity resulting from hydronephrosis. Renal function was reduced in Dicer1^{CO} mice as assessed by BUN analysis. While cells lining the medullary cavity were highly proliferative, the cells lining the cortical cysts did not label with markers for cell proliferation. Moreover, the homeodomain protein Cux1 was ectopically expressed specifically in the cells in which Dicer1 was deleted. Taken together, our results suggest that Dicer1 is essential for normal kidney development, and that Cux1 is normally regulated by miRNAs.

GLC-ASPET ABSTRACTS 2013: POSTDOCTORAL FELLOWS

P01. Chronic cocaine exposure induces over-activation of L-type calcium channels that abnormally enhances rat cortical excitability mediated by HIV-1 Tat

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Cocaine (COC) abuse enhances deleterious effects of HIV-1 on neurons. HIV-infected cells secrete pathogenic proteins, including the HIV-1 transactivator of transcription (Tat), which can excessively elevate cytosolic calcium (Ca) to excitotoxic levels. The structure and function of the medial prefrontal cortex (mPFC) are altered in both COC-abusing and HIV+ individuals. We show here that chronic COC exposure enhances Tat-mediated abnormal excitation of mPFC pyramidal neurons via over-activating the voltage-gated L-type Ca channels. This finding was electrophysiologically determined in forebrain slices from two rat models, young rats (4-5 weeks) treated with 15mg/kg/day ip COC for 5 days followed by a 3-day withdrawal, and adult rats (~16 weeks) that self-administered COC for 14 days followed by a 3-week withdrawal (see Wayman et al., this meeting). In vitro application of Tat with different concentrations altered firing and voltage-sensitive Ca influx via diltiazem-sensitive L-channels in pyramidal neurons from saline-treated rats of both ages. Baseline firing and Ca influx were evoked in pyramidal neurons from COC-treated rats of both ages. The ability of Tat to promote firing and voltage-sensitive Ca influx was significantly enhanced in COC-exposed rats of both ages. Tat-enhanced mPFC neuronal excitability (i.e., firing) and Ca influx appeared to be greater in adult rats than young rats after chronic COC exposure. The Tat-mediated Ca influx was independent of NMDA receptors and abolished by L-channel blockade. These findings demonstrate

an involvement of the L-channels in the exaggerated effects of Tat on the mPFC after chronic exposure to COC. Such dysregulation may also occur in the brain of HIV+ humans that abuse COC.

Supported by USPHSGs DA033882, DA033206, the Chicago D-CFAR P30A1082151, and the McManus Foundation. We also thank NIH AIDS Reagent Program for providing recombinant Tat for this study.

P02. Kristoff T. Homan¹, Michael Wilson², David M. Thal¹, Emily Wu¹, Scott D. Larsen², and John J. G. Tesmer¹; ¹Departments of Biological Chemistry and Pharmacology, Life Sciences Institute; ²Vahlteich Medicinal Chemistry Core and the Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109

Objective: To develop paroxetine, which selectively inhibits GRK2 over other kinases, into a novel treatment for heart failure.

Methods: Previous high-throughput screening campaigns have identified the selective serotonin reuptake inhibitor (SSRI) paroxetine as a selective inhibitor of G protein coupled-receptor kinase 2 (GRK2). Biochemical analysis of the ability for paroxetine and its derivatives to inhibit AGC family kinases as well inhibit the serotonin transporter have been conducted along with biophysical experiments to elucidate the direct binding interactions of these compounds to the GRKs. Crystal structures of GRKs in complex with inhibitors were determined to validate the mechanism of inhibition and to guide subsequent inhibitor design.

Results: Paroxetine has been identified as an inhibitor of GRK2 ($IC_{50}=20$ mM) that has 50-fold selectivity over other GRK subfamily members and causes increases in contractility in isolated mouse cardiomyocytes as well as whole animal models. The crystal structures of the GRK1•paroxetine and GRK2•paroxetine complexes were used to design a compound that uncouples the SSRI function from kinase inhibition mediated by paroxetine and further increases its potency ($IC_{50}=5$ mM) while decreasing the SSRI by 20-fold. Furthermore this derivative has been crystallized in order to confirm the rational design approach.

Conclusions: GRK•paroxetine complexes have been shown to be an effective platform for subsequent design of increasingly potent GRK2 inhibitors that possess less SSRI function.

Support was provided by NIH grants HL086865, HL071818, and MH089378 and AHA grant N014938.

P03. Downregulation of intersectin-1s contributes to tumorigenesis and lung cancer metastasis

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We have previously shown that intersectin-1s (ITSN-1s), a multidomain protein is downregulated in cultured human lung cancer cells and tumor tissue. Restoring ITSN-1s protein expression by stable transfection of adenocarcinoma lung cancer cells (A549) using myc-ITSN-1s plasmid decreased cell proliferation, colony formation and anchorage-independent growth. ITSN-1s interacts with Cdc42 and inhibits its GAP activity towards Cdc42, a well-known regulator of the cytoskeleton components (actin microfilaments and vimentin intermediate filaments). Long term knockdown of ITSN-1s in mouse lungs downregulates microRNA-200 an upstream regulator of Vimentin. Therefore we hypothesized that ITSN-1s downregulation regulates microRNA-200 and Cdc42, thereby alters the cytoskeleton networks to enhance cell migration and cancer metastasis. To address this hypothesis, we studied A549 cells and ITSN-1s stable-transfected A549 using biochemical and morphological approaches. Immunofluorescence staining with phalloidin showed small/thin filaments of actin in A549, which were converted to thick actin bundles in ITSN-1s stably-transfected cells. Analysis of F-actin/G-actin ratio in both cell types using Western blot and densitometry showed no difference suggesting the structural changes were simply due to polymerization and reorganization of existing actin. Immunofluorescence staining with anti-vimentin antibody showed in A549 cells, a well-organized vimentin network but in ITSN-1s-transfected cells the expression of vimentin was decreased and the vimentin network had collapsed into small clusters of disorganized short filaments near the nucleus. A wound healing assay was performed and cell migration monitored using time-lapse microscopy for 48 hours. Compared to A549 cells in ITSN-1s transfected cells the rate of wound healing was decreased by 43% and the difference was noted starting as early as 3 hours. In conclusion our data suggest the ITSN-1s downregulation in lung cancer promotes cell migration and cancer metastasis.

P04. Molecular mechanisms of PLC β activation

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Phospholipase C b (PLC β) converts the membrane lipid PIP₂ into the second messengers inositol 1,4,5-triphosphate and diacylglycerol, and is activated by extracellular signals via direct interactions with the heterotrimeric G proteins G α_q and G β_γ . However, the molecular mechanisms governing this regulation are only beginning to be understood. Using structural and biochemical studies, we have begun to elucidate how heterotrimeric G proteins relieve autoinhibition of PLC β , leading to dramatic increases in activity. We have also clarified the molecular basis for how the characteristic C-terminal coiled-coil domain of PLC β contributes to membrane association and activation by G α_q . A better understanding of PLC β function is important for developing novel therapeutic approaches to tackle such diverse diseases as cardiac hypertrophy and heart failure. Support for this work was provided by NIH grants HL086865 and HL071818 to J.J.G.T. and an American Heart Association postdoctoral fellowship to A.M.L.

P05. Gap junction protein Connexin 43 (Cx43) functions to exacerbate vascular permeability

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Increased vascular permeability is a hallmark of inflammatory diseases such as acute lung injury (ALI) and sepsis, which account for approximately 75,000 and 300,000 deaths per year in the United States, respectively. Emerging evidence suggests that connexins, the building blocks of dimeric intercellular gap junctions and monomeric hemichannels, may regulate vascular permeability as well as other indices of inflammatory signaling. We investigated the potential impact of connexins on the pathogenesis of inflammatory disease by inhibiting connexin function and altering their expression in human pulmonary artery endothelial cells (HPAECs). We show that gap junction inhibitor carbenoxolone attenuates the thrombin-induced decrease in transendothelial resistance. Carbenoxolone also inhibits thrombin-induced phosphorylation of myosin light chain (MLC), indicating that gap junctions exacerbate thrombin-induced increases in vascular permeability. siRNA knockdown of connexin isotype 43 (Cx43) attenuates the thrombin-induced decrease in transendothelial resistance. Conversely, overexpression of Cx43 through adenovirus exacerbates the thrombin-induced decrease of transendothelial resistance. Therefore, Cx43 exacerbates vascular permeability induced by thrombin. Overall, our data suggests that increased connexin 43 exacerbates vascular permeability and thereby contributes to the pathogenesis of inflammatory disease in vascular endothelium.

GLC-ASPET ABSTRACTS 2013: GRADUATE STUDENTS

G01. Caveolin-2 promoter hypermethylation - a pathogenic mechanism in idiopathic pulmonary fibrosis

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Caveolin-1 and Caveolin-2 (cav1/2) are membrane proteins present in normal lung fibroblasts, whose diminished expression inversely correlates with the fibrogenic characteristics and functions of affected lungs. Since the mechanisms by which cav1/2 genes contribute to the pathogenesis of pulmonary idiopathic fibrosis (IPF) are not clear, we examined the role of epigenetic promoter hypermethylation on silencing cav1/2 expression in IPF. We analyzed the expression of cav1/2 by qPCR and Western blotting in fibroblasts isolated from IPF subjects (F_{IPF}) and normal fibroblasts (F_{normal}), before and after treatment with 5-aza-2'-deoxycytidine and Trichostatin A. Cav1/2 promoter methylation was determined by methylated DNA immunoprecipitation using the anti-methyl-cytosine Ab and by methylation-specific PCR (MS-PCR). The expression of α -Smooth Muscle Actin (α -SMA), Thy-1, collagen I and III was quantified by qRT-PCR. Cav1/2 mRNA stability was investigated using actinomycin D chase experiments, while cav1/2 mRNA levels in F_{normal} and F_{IPF} at different time points after actinomycin D were measured by qRT-PCR. As a functional effect, we investigated the changes in apoptosis-resistance of F_{normal} and F_{IPF} by annexin staining and DNA fragmentation. We found that F_{IPF} show: i) low levels of cav1/2, ii) an unyielding increase in α -SMA, collagen I and III expression, and iii) no changes of Thy-1 protein expression. Moreover, the levels of cav1/2 mRNAs were lower in F_{IPF} . Interestingly, F_{normal} exposed to TGF β , a recognized fibrogenic cytokine, show

decreased cav1 mRNA and increased cav2 mRNA, suggesting a differential regulation of the two genes in response to TGF β . For both cav1/2 mRNAs the degradation rates in F_{IPF} were similar with the ones from F_{normal}, suggesting defective transcription. MS-PCR revealed a CpG island poor promoter with a variable methylation status (without statistical significance) for cav1 and a CpG island, hypermethylated in all FIPF (p < 0.01), in the promoter of cav2 gene. Inhibition of cav1/2 genes expression by specific siRNA (p < 0.05) provoked apoptosis-resistance in F_{normal}. Altogether, our findings show that the reduced expression of cav2 in F_{IPF} is attributable to promoter hypermethylation, while the reduction of cav1 expression involves different epigenetic mechanisms.

*equal contribution to the work

G02. Chenodeoxycholate (CDCA) activates Cl⁻ transport via CF transmembrane conductance regulator in T84 and HEK cells

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The mechanism by which high levels of colonic luminal bile acids (BAs), such as CDCA, cause secretory diarrhea in pathologies like inflammatory bowel disease, is not fully elucidated. We have previously shown that BA act rapidly (in mins) to increase cAMP and activate CFTR in human colonic T84 cells. We hypothesize that BAs act via membrane receptors to stimulate Cl⁻ secretion. T84 cells express protein and transcript for the BA G-protein coupled receptor, TGR5. The multidrug resistant protein (MRP) inhibitor MK571 (20 μ M) enhances the CDCA response in T84 cells 2.6 fold, suggesting the involvement of the cAMP transporter, MRP4. T84 cells express MRP4 transcript. While BA stimulation of colonic proliferation involves M3 muscarinic and epidermal growth factor (EGF) receptors (Biochem Pharm 70:1035,'05), we report that CDCA action in T84 cells is attenuated by the EGFR inhibitor AG1478 (CDCA: Δ lsc 16 \pm 5; +AG1478 (1 μ M): 5.2 \pm 1.2, n>3), but not by atropine (M3 antagonist). CDCA (dose-dependent) or forskolin (FSK) increase Cl⁻ transport [measured by I⁻ efflux] in HEK cells stably transfected with CFTR (HEK-CFTR), but not in untransfected cells. MK571 potentiated this FSK response. HEK-CFTR express MRP4 transcript and possess TGR5 transcript and protein, making them a useful model. These data indicate that membrane proteins, such as EGFR, MRP4 and perhaps TGR5 are involved in CDCA's action in stimulating CFTR. Supported by NIH.

G03. Chronic downregulation of sGC-cGMP signaling pathway as a therapeutic target for Parkinson's disease

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Parkinson's disease (PD) is a common neurodegenerative disorder characterized by the loss of dopamine neurons in the substantia nigra. PD results in detrimental motor symptoms such as resting tremor, rigidity, and bradykinesia. Levodopa is the gold standard for the symptomatic treatment of Parkinson's disease; however, chronic use of levodopa may result in severe motor side effects such as dyskinesias. It is therefore necessary to identify a novel non-dopaminergic mechanisms as therapeutic targets for PD. One promising target is the soluble guanylyl cyclase (sGC) – cGMP signaling cascade. The sGC-cGMP pathway functions as a key cellular intermediary in regulating dopamine and glutamate transmission in the striatum. Interestingly, following dopamine depletion an increase in striatal sGC expression and therefore cGMP synthesis is observed. Research suggests that altered cGMP levels underlie the pathophysiological changes of basal ganglia circuits observed in PD. In agreement with the data, our lab has shown that an acute pharmacological downregulation of the sGC-cGMP signaling pathway results in the reversal of electrophysiological, histochemical, and behavioral abnormalities observed in parkinsonian models. We hypothesize that a chronic pharmacological downregulation of the sGC-cGMP signaling pathway in parkinsonian animals will elicit a lasting decrease in striatal cGMP levels and thus an improvement in motor function. Towards this goal we used the 6-hydroxydopamine (6-OHDA) lesion rat model and utilized the stepping test as an indicator of motor deficits. 6-OHDA lesioned rats were chronically treated with a sGC inhibitor, ODQ (10 mg/kg and 20 mg/kg doses) or vehicle for seven consecutive days. Stepping tests were carried out at different time points during and following ODQ treatment. Our results show that following 3-4 days of ODQ treatment, motor function is restored to approximately 50% of healthy rats. Furthermore improvements in stepping performance persisted after chronic ODQ treatment, suggesting that this treatment may also be disease modifying. No evidence of dyskinesias was observed during and following ODQ treatment. Our results support targeting the sGC-cGMP pathway in the symptomatic treatment of parkinsonian rats.

G04. Effects of cyanobacterium Anabaena LPS on brain microglia generation of classical and alternative activation cytokines and chemokines

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Although environmental and human health may be affected by toxins released by cosmopolitan Gram-negative cyanobacteria such as lipopolysaccharide (LPS), current knowledge of the immunotoxicology of cyanobacterial LPS is limited (Mayer et al., Toxicological Sciences, 121(1): 63-72, 2011). We recently reported that cyanobacterium Anabaena sp. lipopolysaccharide (AnaLPS) elicited release of superoxide anion, thromboxane B2, and matrix metalloproteinase-9 by rat microglia (BMG) in vitro (The Toxicologist CD 132 (S-1), 2013). We hypothesized that BMG treated with cyanobacterium AnaLPS in vitro would in addition generate both classical and alternative activation cytokines and chemokines. AnaLPS was prepared by hot phenol/water extraction. BMG were isolated and treated with 0.1-105 ng/ml AnaLPS for 18 hours at 35.9 °C. Escherichia coli LPS (EclPS) 026:B6 from Difco Lab, Detroit, MI was used as a positive control in all experiments. Cytokines and chemokines were determined using a Milliplex[®] MAP rat cytokine/chemokine multiplex immunoassay technology. EclPS and AnaLPS stimulated BMG to release statistically significant quantities of the following: (a) Pro-inflammatory cytokines: IL-6>IL-1 β >TNF- α (b) Pro-inflammatory chemokines: MIP-2/CXCL2>MIP-1 α /CCL3>MCP-1/CXCL2; and the (c) Anti-inflammatory cytokine: IL-10, at > than 1ng/mL and 104ng/mL, respectively. Although we demonstrated that after an 18 hour in vitro treatment AnaLPS stimulated BMG to release cytokines and chemokines involved in both classical and alternative activation, AnaLPS was considerably less potent than EclPS. Our laboratory continues to characterize the chemistry and immunotoxicology of AnaLPS. AnaLPS isolated by Philip Williams, Ph.D., Department of Chemistry and Biochemistry, University of Hawaii at Manoa, Honolulu, HI and funding by the College of Health Sciences, Midwestern University are gratefully acknowledged.

G05. Cleavage of ITSN-1s by granzyme B promotes lung endothelial cell proliferation via p38MAPK/Elk1 signaling; implications for plexogenic PAH

Monal Patel, Dan Predescu, Rajive Tandon, Cristina Bardita, Jennifer Pogoriler^{*}, Sangeeta Bhorade^x, Minhua Wang, Suzy Comhair⁶, Anna Ryan Hemnes⁵, Jiwang Chen⁶, Roberto Machado⁶, Aliya Husain^{*}, Serpil Erzurum⁶, and Sanda Predescu; Rush University Medical Center, Departments of Pharmacology and Medicine, Vascular Biology Section and Division of Pulmonary and Critical Care Medicine, 60612; ^{*}Department of Pathology, University of Chicago, 60637, ^xCenter for Lung Transplant, University of Chicago, 60637; ⁵Department of Pathobiology, Lerner Research Institute, Cleveland Clinic, 44195; ⁶Vanderbilt University, Division of Allergy, Pulmonary and Critical Care Medicine, 37232; ⁶University of Illinois at Chicago, Section of Pulmonary, Critical Care Medicine, Sleep and Allergy, 60612

Plexiform lesions (PLs), the hallmark of plexogenic pulmonary arterial hypertension (PAH) contain predominantly phenotypically altered, proliferative and dysfunctional endothelial cells (ECs). The cellular and molecular factors that contribute to EC proliferation are poorly understood. We now show that the cytotoxic protease granzyme B (GrB) cleaves intersectin-1s (ITSN-1s), a pro-survival protein of lung ECs and generates two biologically active fragments: an N-terminal fragment (GrB-EH_{ITSN}) with EC proliferative potential and a C-terminal product with dominant negative effects on Ras/Erk1/2 mitogen-activated protein kinase (MAPK) signaling. The proliferative potential of GrB-EH_{ITSN} is mediated via sustained phosphorylation of p38MAPK and Elk-1 transcription factor and abolished by chemical inhibition of p38 kinase. We also show that lung tissue of PAH animal models and human specimens, as well as pulmonary artery ECs isolated from human PAH lungs express lower levels of full-length ITSN-1s compared to controls, and the GrB-EHITSN cleavage product. Moreover, GrB immunoreactivity is associated with PLs in PAH lungs. The concurrent expression of the two cleavage products results in a high p38/Erk1/2MAPK activity ratio, critical for EC proliferation. Overall, our findings indicate that during pulmonary inflammation, GrB-mediated proteolysis of ITSN-1s may provide an advantage for p38MAPK signaling favoring the selection of a proliferative/plexiform EC phenotype.

G05. Cleavage of ITSN-1s by granzyme B promotes lung endothelial cell proliferation via p38MAPK/Elk1 signaling; implications for plexogenic PAH

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G06. Overexpression of protein kinase C alpha differentially activates transcription factors in T47D breast cancer cells in the presence of 17 β -estradiol both in the 2D and 3D environments

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Our lab has previously shown that overexpression of protein kinase C alpha (PKC α) results in a hormone independent, tamoxifen resistant phenotype in the T47D:A18 breast cancer cell line. Moreover, 17 β -estradiol (E2) inhibits colony formation of T47D/PKC α in 3D Matrigel[®] and tumor growth in vivo but not in the 2D environment (Zhang et al 2009). Differential transcriptional activation may account for the phenotypic changes observed in T47D/PKC α cells. In this study, we sought to identify transcription factors (TF) differentially regulated in T47D:A18/neo versus T47D:A18/PKC α grown in 3D Matrigel[®] in the presence and absence of E2, and compare these TFs with those regulated in the 2D environment using a high-throughput screening (HTS) technology. A system for rapid and large scale quantification of TF activity was developed (Weiss et al 2010). Lentiviral reporter constructs contain a TF binding site that precedes a basal promoter to produce firefly luciferase (Fluc). The control construct contained only the basal promoter. T47D/PKC α and T47D/neo cells were infected with lentiviral reporter constructs, and seeded either on top of Matrigel or without Matrigel[®] in 384 well plates in E2-free media. After 3 days, cells were treated with either E2 (10-9M) or vehicle (0.1% ethanol). Fluc activity was assessed at 24, 48 and 72 hours following treatment using Xenogen IVIS Spectrum imaging system. Initial findings showed differential transcriptional activities between the parental T47D/neo and T47D/PKC α cell lines at the basal level in the 2D environment. Specifically, TFs involved in breast cancer tumorigenesis (ETS-1, c-MYC) were more highly activated in T47D/PKC α cells. Furthermore, E2 has a modulating effect on the activities of some TFs in the two cell lines over time; observed both in the 2D and 3D environments. These findings suggest that overexpression of PKC α alters TF activity in T47D breast cancer cells both basally and in response to E2. With this HTS approach, we are now beginning to understand the mechanism whereby PKC α may mediate differential response to E2 dependent on the microenvironment.

G07. Abstinence from cocaine self-administration induces cue reactivity and potentiates excitatory responses of rat cortical neurons to HIV-1 Tat protein

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The medial prefrontal cortex (mPFC) shapes cognition and reward-motivated behavior. Chronic cocaine exposure dysregulates the mPFC, which likely contributes to persistent drug-seeking, craving and relapse to drug-taking during protracted abstinence. Neuropathology of the mPFC occurs in HIV+ individuals and is thought to be exaggerated in the brains of those also afflicted with cocaine addiction. How mPFC neuronal function is altered in the comorbid condition is not known. To address this knowledge gap, we designed a study which revealed that withdrawal from cocaine self-administration (1) induced drug-seeking behavior when rats were re-exposed to the cocaine-paired cues (termed cue reactivity, CR), (2) abnormally increased mPFC neuronal reactivity to depolarizing current pulses), and (3) exacerbated responses of these cells to HIV-1 protein Tat. Briefly describing the study, adult male rats were trained to self-administer cocaine (COC-SA) for 14 days. Presentation of a cue light was paired with successful lever-pressing and cocaine infusions. Control rats received infusions of saline (SAL-yoked) when their COC-SA partners receiving cocaine infusions. The CR was tested 1 day (CR1) and 18-22 days (CR2) after the last operant session. Only COC-SA rats exhibited cocaine seeking during CR1 and the seeking behavior was enhanced during CR2. Brain sections containing the mPFC were harvested one day after CR2, and whole-cell patch-clamp recordings were conducted from mPFC pyramidal neurons. We determined that in COC-SA rats, the resting membrane potential was depolarized and the number of action potentials evoked by depolarizing currents was increased compared to neurons from saline-yoked rats. Bath-applied Tat facilitated membrane depolarization and neuronal firing in both COC-SA and SAL-yoked rats, but Tat-induced changes were significantly more robust after COC-SA. Collectively, these findings demonstrate a persistent mPFC dysregulation that is associated with cocaine-seeking and this brain state augments Tat-induced excitations. Supported by: USPHSGs F31DA033206 & DA033882, P30AI082151, and Daniel F & Ada L Rice Fdn.

G08. Basolateral amygdala physiology in the female rat

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Females are more likely to suffer from an affective disorder in their lifetime, and tend to display differences in their symptomatology compared to males. This difference between males and females may occur as a result of sex differences in limbic function. The basolateral amygdala (BLA) is a limbic structure integral to the generation of emotions and emotional learning. Despite all that is known regarding sex differences in BLA-dependent behaviors in humans and rodents, very little is known about female amygdala physiology. In this study, we examined BLA neuronal activity in urethane anesthetized cycling female and male rats using in vivo extracellular single unit recordings. The estrous cycle was monitored daily for a minimum of 3 weeks before electrophysiological recordings. Females were recorded in the diestrus (low estrogen) or proestrus (high estrogen) phases of the estrous cycle. Our experiments revealed a sex difference in BLA neuronal activity. There was no difference in female BLA activity between diestrus and proestrus phases of the estrous cycle, however, both diestrus and proestrus females showed significantly higher BLA neuronal firing rate compared to males. Neuronal activity in the lateral and basal nuclei of the BLA did not differ between diestrus and proestrus females. However, the basal nucleus was more active in proestrus females compared to the lateral and basal nuclei in males. The number of active neurons per electrode track and the coefficient of variation were similar in both sexes. The relationship between action potential width and BLA neuronal firing rate was more variable in the female BLA compared to males, suggesting that females have more diversity in the population of spontaneously firing neurons. Collectively, our experiments demonstrate that there are sex differences in BLA neuronal physiology and that these differences may render females more vulnerable to affective disorders.

G09. Selective estrogen mimics for the treatment of tamoxifen-resistant breast cancer

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Breast cancer is the most common female malignancy, affecting 1 in 8 women. Resistance to the antiestrogen tamoxifen (TAM), whether de novo or acquired, is a major clinical obstacle. Although recent clinical trials have demonstrated the efficacy of E2 following exhaustive use of antiestrogens, E2 treatment is associated with major side effects such

as an increased risk of other gynecological cancers, deterring the clinical community from adopting it as a treatment strategy. Our lab has previously shown that Protein kinase C alpha (PKC α) overexpression predicts TAM resistance in the clinic and may also predict a positive response to an estrogenic therapy. Further, the ectopic overexpression of PKC α in T47D breast cancer cells, led to a TAM-resistant, E2-inhibited phenotype *in vivo*. The purpose of this study was to identify novel selective estrogen mimics (SEMs), which could achieve the positive therapeutic effects of E2 treatment in TAM-resistant breast cancers, while minimizing the side effects. *In vitro* screening identified two SEMs, BTC and TTC-352, which displayed estrogenic activity in breast cancer cell lines. BTC and TTC-352 treatment resulted in significant tumor regression in two xenograft models of TAM-resistant, PKC α -overexpressing breast cancer. SEM treatment, however, did not result in growth of parental, TAM-sensitive xenograft tumors. Endometrial thickening, caused by both E $_2$ and TAM, is directly associated with gynecological carcinogenesis and uterine cancer. Interestingly, SEM treatment did not increase uterine weight in mice suggesting negligible hormonal stimulation in gynecological tissues. Both BTC and TTC-352 resulted in regression of two TAM-resistant breast cancer models, while displaying enhanced safety compared to E $_2$ and TAM. These data suggest that further development of SEMs targeted to TAM-resistant breast cancer is a feasible therapeutic strategy.

GLC-ASPET ABSTRACTS 2013: UNDERGRADUATE STUDENTS

U01. Creation of α -synuclein truncation variants to test Parkinson's disease relevance in yeast

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Parkinson's disease (PD) is a hypokinetic neurodegenerative disorder characterized by the death of midbrain dopaminergic neurons. This selective cell death is linked to the misfolding and aggregation of the brain protein α -synuclein that accumulates as Lewy bodies. The full-length α -synuclein (140 amino acids long) associates with membranes and its carboxyl-terminus keeps it soluble. In PD, this full-length form is the major component of Lewy bodies, although several carboxyl-terminal truncation variants (α -syn 103, 110, 120, and 123) were also recently found in them (Lewis et al., 2010). While these variants can increase the aggregation of the full-length α -synuclein *in vitro* and enhance toxicity in specialized cell cultures (Li et al., 2005; Liu et al., 2005), the individual properties of each variant towards aggregation, membrane association, and toxicity in free living organisms is not well studied. In this first-year Richter Scholar Project, we sought to test the hypothesis that the larger the truncations, the more the variants would reduce α -synuclein solubility and membrane association, and increase toxicity in organisms. Our goal was to create these four variants of α -synuclein (in both wild-type and two familial PD mutant versions- A30P and A53T) and characterize their properties in a budding yeast (*Saccharomyces cerevisiae*) model for PD. In this poster, we report the successful creation of all twelve variants and their transformation into yeast. The next goal is to evaluate several properties of these variants by comparing them to the full-length form: their cellular localization (GFP imaging), expression/accumulation (Western blotting), and toxicity (serially diluted growth on plates).

U02. Effect of chenodeoxycholic acid (CDCA) on intestinal epithelial barrier function

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Excess bile acids in the intestinal lumen increase fluid secretion via multiple mechanisms resulting in diarrhea. However, the molecular mechanisms mediating the effects of luminal bile acids and the involvement of the tight junctions are not fully understood. Tight junction regulation by bile acids depends on the type and concentration of bile acids and in humans; the colon is exposed to primary and secondary bile acids, both in the unconjugated and conjugated forms. Here we studied the effects of unconjugated primary bile acid, CDCA, on epithelial barrier function.

Human colon carcinoma cells (T84) were grown to form confluent monolayers in collagen-coated Transwells (~20 days) in the research laboratories at BU and UIC. Confluency was presumed when the transepithelial electrical resistance (TER) reached >1000 Ohm cm². TER was measured using an epithelial voltohmmeter. There was a dramatic drop in TER (88%) when the apical (AM), but not basolateral (BLM) membrane of T84 cells were exposed to high dose (0.5mM, 60mins) of CDCA. Time-dependent measurements showed that the drop in resistance was almost instant (75% drop in TER in < 1 min). This drop was not due to cytotoxic cell death as the cells were viable as examined by Trypan blue exclusion. A similar decrease in TER was observed as a result of exposure to pro-inflammatory cytokines (TNF α +IL-1 β +IFN γ ; 50% drop in 24 hrs). Since TER is an indirect method of studying paracellular permeability, we studied the effects of varying concentrations of CDCA on tight junction function by examining the mucosal to serosal movement of a 10-kDa cascade-blue labeled dextran. AM CDCA, but not BLM, caused a time-dependent increase (~2-fold) in dextran flux, which was increased further with pretreatment with proinflammatory cytokines.

These studies suggests that luminal bile acids in the presence of cytokines might alter the integrity of the epithelial barrier to allow basolateral access of luminal contents. Further studies may provide us useful and novel insights into the mechanisms underlying bile acid-induced diarrheas in diseased states such as Crohn's and ulcerative colitis.

U03. Evidence for the role of endocytosis in Parkinson's disease: Insights from a budding yeast model

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Parkinson's disease (PD) is linked to impaired degradation and accumulation of the misfolded protein, alpha-synuclein. Therefore, accelerating degradation of alpha-synuclein is of therapeutic interest. An attractive hypothesis is that endocytosis is a route to alpha-synuclein degradation at the lysosome. Our lab has established genetic evidence that several endocytosis pathway complexes (Pre-ESCRT, ESCRT-I, ESCRT-II, ESCRT-III and post-ESCRT) regulate alpha-synuclein pathology-linked properties in a budding yeast PD model. Most importantly, our lab found that the vascular sorting protein vps28 (a ESCRT-I gene) is a key gene: its absence altered alpha-synuclein localization, increased its accumulation, and enhanced cellular toxicity. Finally we investigated, if increasing the concentration of alpha-synuclein in yeast that lack vps28 further increased alpha-synuclein accumulation and toxicity and we found that it did. Together, these studies illustrate how impaired alpha-synuclein degradation contributes to PD pathology and the growing relevance of endocytosis in this process.

U04. Characterizing novel intragenic suppressors of a constitutively active allele of G $_s$ alpha

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McCune-Albright Syndrome (MAS) is a genetic disorder caused by a mutation in Gs alpha at Arg201 that inhibits GTP hydrolysis, constitutively activating the protein. We developed a yeast model system for MAS in which mutating the homologous residue in the yeast G alpha subunit (R297H) prevents colony formation on media containing 5-fluoro-orotic acid (5-FOA). We constructed a library of 32,000 unique plasmids carrying additional mutations in the constitutively active G alpha gene, and used it to identify 12 mutations at sites homologous to the human Gs protein that were potential intragenic suppressor sites. Three of these sites, when introduced into the human Gs alpha gene, successfully suppressed the MAS mutation's constitutive activity when expressed in HEK293 cells: F142, R231, and L266. Extensive mutagenesis of each of these sites revealed biochemical requirements for suppression at each site. None of the three mutations by themselves caused constitutive activity of the protein or significantly changed cellular responsiveness to hormone, as measured by the ability of a luteinizing hormone receptor agonist to activate cAMP production. Interestingly, these three mutations appear on three different regions of the protein: F142 is on the helical domain, R231 is in the middle of Switch II, and L266 is proximal to Switch III. Intragenic suppressor mutations can be used to model potential sites to which small molecule drugs may be targeted, potentially interacting with the mutant protein in the same way that the mutation did, and reducing or blocking the constitutive activity of the protein. A complete map of the locations and chemical compositions of suppressor mutations for the MAS allele will provide important information to drive rational drug design for the treatment of this disease. This work was supported by NIH grant 1R15ED020190-01