aspet The Pharmacologist
Vol. 54
Number 3
2012
September

ASPET Annual Meeting at Experimental Biology 2013

Joint meeting with the British Pharmacological Society; guest societies include the Canadian Society for Pharmacology and Therapeutics & the Behavioral Pharmacology Society

Saturday, April 20 - Wednesday, April 24

Paul Revere Statue

Skyline from Boston Harbor

Fenway Park

In this issue:

Customs House

Bunker Hill Monument

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

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 subsciption 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.

Periodicals postage paid at Bethesda, MD. GST number for Canadian subscribers: BN:13489 2330 RT.

ASPET assumes no responsibility for the statements and opinions advanced by contributors to *The Pharmacologist*.

Deadlines for submission of material for publication: Issue 1, February 15; Issue 2, May 16; Issue 3, August 15; and Issue 4, November 15.

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

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Message from the President

Dear ASPET Members,

It is a great honor to serve as the 81st President of ASPET, and I would like to thank everyone who helped in my election. I sincerely hope to fulfill expectations of all of ASPET's members and trust you will communicate your thoughts and needs throughout the next year.

This is a truly dynamic time for pharmacology and experimental therapeutics. The confluence of rapidly growing genomic and proteomic databases, disease-associated molecular drug targets, high throughput screening programs, small molecule libraries, sophisticated computational tools for drug target docking, computer assisted drug design, nanotechnology-inspired delivery systems, advance microscopy tools including intravital imaging, and genetically modified animal models has stimulated a broad increase in the strategies to produce and test new potential therapeutics. The success of antibody-based therapies including antibody-drug conjugates adds new dimensions to the ASPET interests. When constructing an election platform, I emphasized the need for ASPET to expand its membership and embrace individuals who identify with these emerging areas. Recognizing that expanding any self-associating professional community requires time, the goal of my administration will be to infuse a spirit of inclusiveness. I have already begun to work with Rick Neubig, ASPET's President-Elect, to ensure there is a continuum of this effort for the next two years. As part of this effort, we plan to co-sponsor a Symposium at Experimental Biology 2013 entitled "Systems Biology Answering Pharmacological Questions." It should be a great program, so I urge you to please try to attend it. One of the main topics at our Council Retreat last October focused on how we can enhance our ability to attract new members. You should see some evidence of how we plan to operationalize these discussions in the coming year.

The dynamic events are not simply in the science of pharmacology. We face serious challenges in the areas of education, scientific publication, and research funding. Our Past President, Lynn Wecker, emphasized the need to provide junior level investigators the resources and mentoring to ensure their future success. This must continue particularly in this period of fiscal restriction and educational reform. The use of electronic and social media and online learning are clearly reshaping the future of how we interact and communicate. The ASPET website has improved dramatically under Lynn's and Christie Carrico's careful leadership, and we have a presence on Facebook, Twitter, and LinkedIn. If you have not visited these sites, I encourage you to do so as they are very informative. ASPET's Education Division, under the leadership of Lynn Crespo, provided a fabulous session at our last annual meeting, and I look forward to additional contributions from this group. ASPET also should focus some attention on ensuring predoctoral funding remains vibrant for our field, which is highly important for the economy of our nations. We must also recognize the needs for postgraduate education of our members who are in private and governmental sectors. It is particularly important that we stay at the forefront of the changes in the teaching of pharmacology at medical schools, which reflect initiatives by the USMLE and LCME.

It is almost impossible to ignore the changes that are occurring in scientific publications. ASPET is rightfully proud of its long tradition in publishing superior peer-reviewed journals. Our journals provide members and others an effective and economical vehicle to present their research findings to the world. We must ensure they continue to fulfill that mission in an era of increased competition, open access, and online publication.

The last several years have been very difficult for individuals seeking NIH grants with funding rates at historical lows. Young members peer out into the future and fear it will be almost impossible to establish an independent laboratory; more senior members worry about not being funded in the future even with worthy proposals. As a member of FASEB, we have been vocal in our call for continued support for NIH funding. Jim Bernstein has been vigilant in providing our members with information about the future of funding. As President, I will endeavor to provide the public and our representatives with the factual information about the importance of our research. We are a national treasure that provides great value to the health and welfare of our society.

The current challenges provide ASPET an unusual opportunity to experiment with new approaches to meet the needs of our membership. I welcome your thoughts at any time and anticipate your engagement in this great adventure.

Sincerely,

John S. Lazo, Ph.D.

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ASPET T-Shirt

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- Tell a friend, colleague or student about the benefits of membership

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-If you have any questions about this program, please contact the membership department at membership@aspet.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:

http://www.aspet.org/membership/member-get-a-member/

Annual Meeting

Joint meeting with the British Pharmacological Society; guest societies include the Canadian Society for Pharmacology and Therapeutics & the Behavioral Pharmacology Society

Saturday, April 20 - Wednesday, April 24
Boston, MA

Important Dates to Remember

Abstract Submission Deadline: Thursday, November 8, 2012

Early Registration Deadline: February 22, 2013

Deadline for Discounted Hotel Reservations: March 22, 2013

Registration is now open. For more information and to register for the ASPET Annual Meeting at Experimental Biology 2013, visit **www.aspet.org/EB2013** or **www.experimentalbiology.org**.

2013 Preliminary Program

Friday, April 19

An annual volunteer opportunity at EB is organized by the Behavioral Pharmacology Division of ASPET. Contact Charles France for details at **france@uthscsa.edu**.

Saturday, April 20

2013 Teaching Institute
Boston Convention Center, Room 108; Noon – 2:30 PM
Chairs: Joey V. Barnett, Vanderbilt Univ. Sch. of Med. and Nicolas J. Goulding, Barts and the London Sch. of Med. and Dentistry

Graduate Student Colloquium: Introducing the Individual Development Plan: A Key to Success
Boston Convention Center, Room 107C; 2:00 PM – 5:00 PM
Chair: Lynn Wecker, Univ. of South Florida

As Yogi Berra once said, "You got to be careful if you don't know where you're going, because you might not get there." Although Yogi was likely not thinking about a scientific career when he made that statement, the concept of the Individual Development Plan (IDP) as a tool to help individuals assess their skills, interests and values, has been used in the business and governmental sectors for some time, and has now permeated academia. Simply put, the IDP is typically used to identify professional goals and objectives, assess one's skill set relative to these goals, and develop a plan (both short-term and long-term) to acquire the skills required to achieve these goals. Most resources would agree that the IDP is currently recognized as the best practice in promoting professional development , and is recognized as an important, valuable and beneficial tool for professionals at all career stages with all types of goals. It also serves as a communications tool, enabling graduate students to communicate their long and short term goals with their mentors. Creating an IDP at the beginning of graduate school can lead to more effective time management and use of resources, and more focused efforts, targeted towards achieving career goals.

This colloquium will begin with a brief overview of ASPET's new mentoring program and will quickly move into a synopsis of the steps used to create an IDP. You will learn how to map out your general career trajectory, match your skills and strengths with your career choices, and identify areas for development that build upon your current strengths. Once the process and steps are presented, attendees will begin to create their own IDP and should expect to have a solid first version by the time they complete the workshop, keeping in mind that the IDP is a 'living document' that continuously evolves throughout one's career.

ASPET Business Meeting
Boston Convention Center, Room 107AB; 6:00 PM – 7:30 PM

ASPET Opening and Awards Reception
Boston Convention Center, SW Lobby; 7:30 PM – 9:30 PM

Sunday, April 21

Diversity Mentoring Breakfast
Westin Boston Waterfront, Room TBD; 7:30 AM – 9:00 AM

Orthostatic intolerance: Insights into pharmacologic, physiologic and gender issues
Boston Convention Center, Room 106; 9:30 AM – Noon
Sponsored by the Divisions for Cardiovascular Pharmacology & Integrative Systems, Translational and Clinical Pharmacology
Chairs: Julian Stewart, New York Med. Col. and Amy Arnold, Vanderbilt Univ. Sch. of Med.

Standing up from a supine or seated position depends on rapid cardiovascular adaptations that are driven by an interplay of autonomic, volume and hormonal mechanisms. The inability of these mechanisms to adequately compensate for changes in posture results in orthostatic intolerance. A growing number of disorders have been associated with orthostatic intolerance and all are more prevalent in women. This symposium will explore the underlying physiologic mechanisms, gender difference and current pharmacologic targets for both acute and chronic forms of orthostatic intolerance, including syncope, fatigue, and postural orthostatic tachycardia syndrome.

Physiologic insights into postural fainting
Roger Hainsworth, Univ. of Leeds

Influence of gender on orthostatic regulation: Why women?
Qi Fu, Texas Healthy Presbyterian Hosp. Dallas

Sympathetic nervous system reactivity in postural syncope and postural orthostatic tachycardia syndrome
Elisabeth Lambert, Human Neurotransmitter Lab.

Orthostatic intolerance and chronic fatigue syndrome
Peter Rowe, Johns Hopkins Children's Ctr.

Novel functions for cyclic nucleotide phosphodiesterases and their implications for pharmacological intervention
Boston Convention Center, Room 107AB; 9:30 AM – Noon
Sponsored by the Divisions for Molecular Pharmacology; Cardiovascular Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; and Neuropharmacology
Chair: Marco Conti, UCSF

Phosphodiesterases (PDEs), the enzymes that degrade and inactivate cyclic nucleotides, are considered critical components in cellular homeostasis, and the design of PDE inhibitors occupies a prime role in pharmacology. The discovery of several new genes and numerous variants has broadened the applications of PDE pharmacology. Genetic models and selective inhibitors have uncovered a host of new functions that can be ascribed to a specific PDE isoform. This session will focus on how the integration of specific PDE variants into macromolecular complexes with receptors, channels and kinases provides novel insights into the generation of signaling microdomains and the specificity of cellular responses to external cues.

Domain structure and interactions in cyclic nucleotide phosphodiesterases: An atomic view of PDE regulation
Jayvardhan Pandit, Pfizer Global R&D, Groton Labs.

Novel insights into the mechanism of action of beta-adrenergic antagonists: Modulation of PDE4-beta-adrenergic receptor complexes
Wito Richter, UCSF

Phosphodiesterases and cyclic nucleotide compartments in the regulation of cardiac
Rodolphe Fischmeister, Univ. de Paris-Sud XI, France

PDE inhibitors and the treatment of airway inflammation
Clive Page, King's College, London

Post translation regulation of PDE10 and the implication in their physiological role in the CNS and in drug discovery
Nicholas Brandon, AstraZeneca, Cambridge, UK

Correlating structure and function of drug metabolizing enzymes: An ongoing challenge
Boston Convention Center, Room 107C; 9:30 AM – Noon
Sponsored by the Divisions for Drug Metabolism & Toxicology
Chairs: Emily Scott, Univ. of Kansas and Eric Johnson, Scripps Res. Inst.

The diversity and flexibility of many of the active sites of human drug metabolizing enzymes with different ligands makes correlations between structure and function an ongoing challenge. The design of specific inhibitors of certain cytochrome P450 enzymes requires knowledge of the enzyme structure and the ability to integrate biophysical and computational approaches to understand function. This symposium will explore the ways that cytochrome P450 enzymes are being used as drug targets by exploring the use of traditional (NMR) and newer (structure-based ADMET) methods to predict metabolism.

Cytochrome P450 Structure: Common themes and variations on the theme
Eric Johnson, Scripps Res. Inst.

Investigations of human cytochrome P450 enzymes with solution NMR
Emily Scott, Univ. of Kansas

Predicting ligand interactions with metabolizing enzymes: An in silico structure-based approach
Maria Miteva, Univ. Paris Diderot

Novel pharmacoenhancer cobicistat: Discovery and development of a CYP3A inhibitor
Lianhong Xu, Gilead Sci., Inc.

Cognitive enhancers for the treatment of neuropsychiatric disorders
Boston Convention Center, Room 108; 9:30 AM – Noon
Sponsored by the Divisions for Behavioral Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; and Neuropharmacology
Chairs: Kathleen M. Kantak, Boston Univ. and Roger D. Spealman, Harvard Med. Sch.

There is a current trend of exploring cognitive-enhancing therapeutic drugs as treatments for a number of neuropsychiatric disorders, including Alzheimer's disease, schizophrenia, anxiety and drug addiction. This session will review novel preclinical research currently being done to discover new drug targets across a spectrum of disorders. Findings show a striking similarity in the drug targets that have been examined across multiple neuropsychiatric disorders and it now seems likely that the discovery of safe and effective cognitive-enhancing therapeutic drugs for one disorder may translate to other disorders with neurocognitive deficits.

Targets for cognitive-enhancing pharmacotherapy
Joseph G. Wettstein, F. Hoffmann-La Roche Ltd.

Translational approaches to cognitive enhancing drugs for neuropsychiatric disorders
Trevor W. Robbins, Univ. of Cambridge

Novel cholinergic-based therapeutic strategies for Alzheimer's disease and age-related memory decline
Alvin V. Terry, Georgia Hlth. Sci. Univ.

Therapeutic uses of cognitive enhancers in rat and monkey models of drug addiction
Bríd Á Nic Dhonnchadha, Boston Univ.

Neuroplasticity in rodent models of fear extinction and use of cognitive enhancers
Gary B. Kaplan, VA Boston Healthcare System

Summary and discussion
Kathleen M. Kantak, Boston Univ. and Roger D. Spealman, Harvard Med. Sch.

Emerging technologies for delivering neurotherapeutics across the blood-brain barrier
Boston Convention Center, Room 109A; 9:30 AM – Noon
Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology; Cardiovascular Pharmacology; Drug Discovery and Development; and Neuropharmacology
Chairs: Nisha Nanaware-Kharade, Univ. of Arkansas for Med. Sci. and Eric C. Peterson, Univ. of Arkansas for Med. Sci.

The blood brain barrier is vital for CNS homeostasis and the preservation of neuronal integrity. It also plays a role in the pathology and progression of a broad spectrum of CNS disorders, including Alzheimer's disease, ALS, Parkinson's disease as well as presenting a challenging barrier to delivering drugs into the CNS. This symposium will highlight some of the new technologies developed for delivering drugs across the BBB, including neurosurgical techniques, chemical-based strategies that modify the physicochemical properties of the drug, and biotechnology-based strategies which "trick" the endogenous BBB transporters.

Anatomy and physiology of the blood brain barrier (BBB) with special emphasis on transport of biologicals across the BBB and insights into the development of in vitro BBB model
Eric Shusta, Univ. of Wisconsin-Madison

Principles and targeting of blood brain barrier/neurovascular unit
Maria Balda, Univ. Col. London, Inst. of Ophthalmology

CNS delivery of therapeutics using the intranasal route of administration
Willam H. Frey, Regions Hosp.

Gene delivery across the blood brain barrier for treating neurological disorders
Brian Kaspar, Nationwide Children's Hosp.

Workshop: Do it right! Writing case-based exam items, interpreting item analysis and designing educational research projects to assess outcomes
Westin Boston Waterfront, Room TBD; 9:30 AM – Noon
Sponsored by the Division for Pharmacology Education
Chairs: Agata P. Butler, Nat'l. Board of Med. Examiners and R. Senthil Kumar, St. Matthew's Univ. Sch. of Med.

Reflecting world-wide shifts toward integrative curricula, this workshop focuses on writing MCQ exams for basic science courses that assess the application of knowledge to clinical situations and interpreting the data obtained from student performance. Following an introduction to the topic, three 60 minute sessions will be conducted to:
1) provide guidance and hands-on training in constructing and critiquing case-based assessment items;
2) help to understand the basics of exam item analysis and the ways one can interpret the results; and
3) discuss hot topics in medical education, including potential teaching and assessment methods for educational research.

Introduction to the workshop: Importance of correct item writing and current trends in recognizing educational research
R. Senthil Kumar, St. Matthew's Univ. Sch. of Med.

Developing High-Quality Multiple-Choice Test Items for Basic Sciences
Agata P. Butler, National Board of Medical Examiners

Setting Pass/Fail Standards: Discussing Item Analysis
Steven Haist, National Board of Medical Examiners

Hot Topics in Medical Education Research
Lynn Crespo, Univ. of South Carolina Sch. of Med., Greenville

JULIUS AXELROD AWARD LECTURE
Boston Convention Center, Room 107AB; 2:00 PM – 2:50 PM
Gavril W. Pasternak, Memorial Sloan-Kettering Cancer Center
No pain, big gain: Truncated mu opioid receptor splice variants as drug targets

JULIUS AXELROD SYMPOSIUM: Expanding the repertoire of G-protein coupled opioid receptor targets
Boston Convention Center, Room 107AB; 3:00 PM – 5:30 PM
Chair: Gavril W. Pasternak, Memorial Sloan-Kettering Cancer Center

Alternative pre-RNA splicing of the mu opioid receptor gene: Insight into complex mu opioid actions
Ying-Xian Pan, Memorial Sloan-Kettering Cancer Center

Opioid receptor heteromers: New pharmacology and new therapeutic possibilities
Lakshmi A. Devi, Mount Sinai Sch. of Med.

Biased agonism and trafficking: Discriminating opioid drug actions by receptor endocytosis
Mark Von Zastrow, UCSF

The genetics of opioid analgesia
Jeffrey Mogil, McGill Univ.

Translating pharmacology into career choices in the pharmaceutical and biotechnology industry
Boston Convention Center, Room 106; 3:00 PM – 5:30 PM
Sponsored by the Divisions for Pharmacology Education; Drug Discovery and Development; and Integrative Systems, Translational and Clinical Pharmacology
Chairs: Janet Clark, Drexel Univ. Col. of Med. and other chair TBD

The integration of pharmacology into the complex fabric of drug discovery and development emphasizes just how critical the discipline is to evaluating a compound, assessing its therapeutic potential, evaluating liabilities and then integrating all of this into making a decision about progression into humans. Leading pharmacologists in the various specialty areas of expertise that contribute to the drug discovery and development process will discuss how their pharmacological specialties contribute to the process and share how they determined their career paths.

Educational initiatives in pharmacology for a career in the pharmaceutical or biotechnology industry
James Barrett, Drexel Univ. Col. of Med.

Pharmacology in target identification and validation
Peter Hutson, Shire Pharmaceut.

Pharmacogenetics in drug discovery and development (30 min)
David Stone, Merck Res. Labs.

Pharmacoepidemiology in drug discovery & development (30 min)
Sean Hennessy, Perelman Sch. of Med. at the Univ. of Pennsylvania

Clinical pharmacology and the development of drugs (30 min)
Darrell Abernethy, FDA, Annapolis

Epigenetic control of drug metabolism and transport
Boston Convention Center, Room 107C; 3:00 PM – 5:30 PM
Sponsored by the Divisions for Drug Metabolism; Drug Discovery and Development; Integrative Systems, Translational and Clinical Pharmacology; Molecular Pharmacology; and Toxicology
Chairs: Aiming Yu, Univ. at Buffalo, SUNY and Yoichi Osawa, Univ. of Michigan

The importance of genetic factors in the control of drug metabolism is well recognized; however there is also increasing evidence that drug-metabolizing enzymes and transporters are regulated by epigenetic factors such as DNA methylation, histone modification, and noncoding RNA mechanisms. This session will introduce new findings on epigenetic regulatory mechanisms in drug metabolism and transport and the impact of epigenetic factors on the pharmacological and toxicological effects of drugs and their implications in therapy.

Overview of genetic and epigenetic mechanisms underlying variable drug metabolism and drug response
Magnus Ingelman-Sundberg, Karolinska Inst., Stockholm

Chromotin modification in control of drug metabolism during liver development
Xiaobo Zhong, Univ. of Kansas Med. Ctr.

Epigenetic mechanisms in differential regulation of CYP1A1 and CYP1B1 genes
Oliver Hankinson, UCLA David Geffen Sch. of Med.

Noncoding RNAs in post-transcriptional control of drug metabolism and transport
Aiming Yu, Univ. at Buffalo, SUNY

Innate immunity and cardiovascular disease: Unfolding the therapeutic potential of toll-like receptors
Boston Convention Center, Room 108; 3:00 PM – 5:30 PM
Sponsored by the Divisions for Cardiovascular Pharmacology & Integrative Systems, Translational and Clinical Pharmacology
Chairs: R. Clinton Webb, Georgia Hlth. Sci. Univ. and Styliana Goulopoulou, Georgia Hlth. Sci. Univ.

Toll-like receptors (TLRs) are pattern recognition receptors that activate the innate immune response. In addition to exogenous infections ligands, TLRs sense certain endogenous molecules that are released during host tissue injury/death. Activation of TLRs leads to the activation of NF-kB and the production of pro-inflammatory cytokines that may have both beneficial (repair) and detrimental (Inflammation) effects on the host. TLRs are expressed not only in immune cells but also in cardiac and vascular tissue, suggesting that TLRs may be a link between innate immunity, inflammation, and cardiovascular disease. This session will address newly discovered TLR-associated molecular pathways that are involved in the genesis of endothelial dysfunction and cardiovascular remodeling characterizing various cardiovascular pathologies. The therapeutic potential of TLR manipulation will be discussed.

TLR signaling: Innate immune sensing and response
Bruce Beutler, Scripps Res. Inst.

"Shall I respond?": DANGERous questions and answers
Polly Matzinger, NIAID, NIH

Doubled-stranded RNA receptors in pregnancy-induced hypertension
Brett Mitchell, Texas A&M Hlth. Sci. Ctr.

TLRs: New therapeutic targets for treating atherosclerosis
Claudia Monaco, Imperial Col. London

Therapeutic approaches for erectile dysfunction and benign prostatic hyperplasia: Present & future
Boston Convention Center, Room 109A; 3:00 PM – 5:30 PM
Sponsored by the British Pharmacological Society; and the ASPET Divisions for Cardiovascular Pharmacology; Drug Discovery and Development; and Integrative Systems, Translational and Clinical Pharmacology
Chair: Selim Cellek, Cranfield Univ., Bedfordshire

Despite the successful pharmacological agents such as PDE5 inhibitors, alpha blockers and 5-alpha reductase inhibitors, erectile dysfunction and benign prostatic hyperplasia remain difficult-to-treat diseases. The aim of this symposium will be to provide an evidence-based overview of the novel pharmacological agents, stem cell, and gene therapy approaches that have recently been developed for the two diseases. In addition, the session will open a debate on the use of PDE5 inhibitors in both erectile dysfunction and benign prostatic hyperplasia as well as their use for other indications.

Pahtophysiological link between ED and BPH
Selim Cellek, Cranfield Univ., Bedfordshire

Soluble guanylate cyclase activators for ED
Peter Sandner, Bayer HealthCare AG, Wuppertal

PDE5 inhibitors for treatment of BPH
Arthur Burnett, Johns Hopkins Hosp.

Novel therapeutic approaches to ED and BPH
Michael O'Leary, Harvard Med. Sch.

Use of PDE5 inhibitors in indications other than ED and BPH
Ian Eardley, Leeds Royal Infirmary

Monday, April 22

JOHN J. ABEL AWARD LECTURE
Boston Convention Center, Room 107C; 8:30 AM – 9:20 AM

Advancing discoveries from the academic laboratory to the market
Boston Convention Center, Room 106; 9:30 AM – Noon
Sponsored by the Divisions for Drug Discovery and Development & Pharmacology Education
Chair: Robert Leadley, Schoolcraft Col.

As pharmaceutical companies continue to merge and downsize their basic research efforts in many therapeutic areas, there is an increasing need and interest for academic investigators to think entrepreneurially about their discoveries. This symposium will help guide investigators through the various steps leading to commercialization of their research by covering topics such as intellectual property protection, private and public funding opportunities, regulatory requirements, and the steps required to move a discovery out of the lab and into the marketplace.

Intellectual property protection: What, when, and how to protect and share your discovery
Weston Gould

Regulatory hurdles from bench to bedside
Ronald L. Dundore, InfaCare Pharmaceut. Corp.

What to know when working with Technology Transfer Offices
Ronald J. Shebuski, Cardiovascular Research Consulting, LLC

Licensing: Do you have what they really want?
Chris Vlahos, Lilly Res. Labs.

Novel dynamics of cAMP: Towards new therapeutic interventions through compartmentalized signaling networks
Boston Convention Center, Room 107AB; 9:30 AM – Noon
Sponsored by the British Pharmacological Society and the ASPET Division for Molecular Pharmacology
Chair: Martina Schmidt, Univ. of Groningen

The discovery of cAMP transformed the understanding of cellular regulation by providing not only the second messenger concept, but also the discovery of G proteins, G protein-coupled receptors (GPCRs), and the conceptual roots of compartmentalized signaling. Spatiotemporal dynamics in the subcellular distribution of cAMP signaling networks likely determine the net outcome of cAMP in chronic disorders. This session will explore the spatiotemporal dynamics of compartmentalized cAMP signaling and the roles of adenylyl cyclases, A-kinase anchoring proteins, G protein-coupled receptors, and protein kinase A as possible drug discovery targets.

Cyclic nucleotide signaling in subcellular compartments
Manuela Zaccolo, Univ. of Glasgow

Adenylylcyclase as orchestrators of cAMP microdomains
Dermot M.F. Cooper, Univ. of Cambridge

Cell signalling in space and time
John. D. Scott, Univ. of Washington

Structure, function and inhibition of G protein-coupled receptor kinases
John Tesmer, Univ. of Michigan

Cell signalling in space and time
John. D. Scott, Univ. of Washington

Structure, function and inhibition of G protein-coupled receptor kinases
John Tesmer, Univ. of Michigan

Dysregulation of cAMP networks in fibrotic lung disease
Marc Peters-Golden, A. Alfred Taubman Hlth. Care Ctr.

New kids on the block: Organic cation transporters and plasma membrane monoamine transporter in neurodegenerative, psychiatric and addictive disorders
Boston Convention Center, Room 107C; 9:30 AM – Noon
Sponsored by the Divisions for Neuropharmacology; Drug Metabolism; Integrative Systems, Translational and Clinical Pharmacology; Molecular Pharmacology; and Toxicology
Chair: Lynnette C. Daws, Univ. of Texas Hlth. Sci. Ctr. at San Antonio

In addition to the traditional high affinity transporters for biogenic amines which are the targets for many CNS drugs, organic cation transporters and plasma membrane monoamine transporters have been recently discovered to transport biogenic amines in the brain as well. This symposium will address the significant role of these "newer" transporters in regulation of biogenic amine neurotransmission as it relates to their
1) distribution and cellular location in brain;
2) ability to transport biogenic amines, even in the presence of the high-affinity transporters for these neurotransmitters;
3) neuroprotective actions;
4) sensitivity to regulation by corticosterone and stress and implications for drug abuse and psychiatric disease; and
5) potential as targets for the development of improved therapeutics to treat psychiatric, addictive and neurodegenerative disorders.

Plasma membrane monoamine transporter: Structure, function, and therapeutic potential for mental illness
Joanne Wang, Univ. of Washington

Neurotoxicity in animal models of Parkinson's disease is mediated by the organic cation transporter-3
Kim Tieu, Univ. of Rochester, Sch. of Med. and Dentistry

Organic cation transporters and the plasma membrane monoamine transporter: Uncovering novel targets to treat depression
Lynette C. Daws, Univ. of Texas Hlth. Sci. Ctr. at San Antonio

Role of organic cation transporter-3 in stress effects on cocaine reinstatement
Paul J. Gasser, Marquette Univ.

Role of the coagulation cascade in tissue injury and disease
Boston Convention Center, Room 108; 9:30 AM – Noon
Sponsored by the Divisions for Toxicology & Integrative Systems, Translational and Clinical Pharmacology
Chair: James P. Luyendyk, Michigan State Univ.

The coagulation cascade comprises a highly regulated network of serine proteases terminating in the generation of the enzyme thrombin. Exposures spanning hepatotoxic drugs to inhaled particles have been shown to cause activation of the coagulation cascade, and coagulation cascade activation is now believed to not merely be the consequence of tissue injury, but a critical mechanism of disease progression and toxicological response. This session will explore various components of the coagulation cascade and the role they play in staph infection, ischemia/reperfusion kidney injury, nephrotoxicity, heart failure and liver disease.

Host prothrombin and fibrinogen are critical determinants of pathogen toxicity and host tissue damage following S. aureus infection
Matthew J. Flick, Cincinnati Children's Hosp.

Fibrinogen: A biomarker and therapeutic candidate in kidney damage
Vishal S. Vaidya, Harvard Med. Sch.

Contribution of coagulation proteases and protease activated receptors to sterile inflammation
Rafal Pawlinski, UNC, Chapel Hill

Liver let die: Coagulation decides
James Luyendyk, Michigan State Univ.

Fatty acid activation of G protein-coupled receptors: Basic and clinical perspectives
Boston Convention Center, Room 109A; 9:30 AM – Noon
Sponsored by the Division for Molecular Pharmacology
Chairs: Graeme Milligan, Univ. of Glasgow and Celia Briscoe, Janssen

This session will review what is known about the expression, function and regulation of members of the G protein-coupled receptor family shown to be receptors for free fatty acids. The speakers will also address the pharmacology and mode of binding, both orthosteric and allosteric, of selected ligands, the state of validation of each receptor as a potential therapeutic target and the progress to date of translating the basic molecular knowledge of these receptors into clinically useful drugs.

Overview of the free fatty acid receptor family. From de-orphanisation to therapeutic potential
Celia Briscoe, Janssen

Developing novel ligands for free fatty acid receptors
Graeme Milligan, Univ. of Glasgow

GPR40 as a potential target for the treatment of type 2 diabetes
Vincent Poitout, Univ. of Montreal

The function and regulation of GPR120
Gozoh Tsujimoto, Kyoto Univ.

CANADIAN SOCIETY FOR PHARMACOLOGY AND THERAPEUTICS TRAINEE PRESENTATIONS AND AWARD LECTURE
Boston Convention Center, Room 109B

DRUG METABOLISM DIVISION EARLY CAREER ACHIEVEMENT AWARD LECTURE
Boston Convention Center, Room 108; 2:00 PM – 2:50 PM

Drug Metabolism Division James Gillette Award & Platform Session
Boston Convention Center, Room 108; 3:00 PM – 5:30 PM

Neuropharmacology Division Postdoctoral Scientist Award Finalists
Boston Convention Center, Room 106; 3:00 PM – 5:30 PM

Molecular Pharmacology Division Postdoctoral Award Finalists
Boston Convention Center, Room 107AB; 3:00 PM – 5:30 PM

Drug Discovery and Development Symposium
Boston Convention Center, Room 107C; 3:00 PM – 5:30 PM
Chairs: TBD

Local Ca2+ signals in the endothelium: Key regulators of vascular function and dysfunction
Boston Convention Center, Room 109A; 3:00 PM – 5:30 PM
Sponsored by the Division for Cardiovascular Pharmacology
Chairs: Mark T. Nelson, Univ. of Vermont and Robert M. Bryan, Jr., Baylor Col. of Med.

Endothelial cell Ca2+ is broadly accepted as a key regulator of endothelial cell-dependent dilation of small arteries. Recent studies using sophisticated Ca2+ imaging techniques have shown that endothelial cells experience local changes in Ca2+ under physiological conditions, the frequency and nature of which determine their effect on endothelial cell function. This session will focus on localized endothelial cell Ca2+ signals mediated by two pathways: Ca2+ influx through Transient Receptor Potential (TRP) channels and inositol trisphosphate (IP3)-medicated Ca2+ release from intracellular stores. Understanding these Ca2+ signaling mechanisms in the endothelium is a critical first step in identifying the cause for endothelial cell dysfunction in vascular disorders such as hypertension.

Conducted vasodilation in resistance arteries: Ca2+ signaling between endothelial cells
Steven S. Segal, Univ. of Missouri

Blood flow mediated dilation in small mesenteric arteries: Role of endothelial Ca2+ signaling
David X. Zhang, Med. Col. of Wisconsin

Differential regulation of SK and IK channels during endothelium dependent hyperpolarization
Kim A. Dora, Univ. of Oxford

Elementary TRPV4 Ca2+ signals regulate endothelium dependent vasodilation
Swapnil K. Sonkusare, Univ. of Vermont

Endothelial Ca2+ wavelets and myoendothelial feedback
Donald G. Welsh, Univ. of Calgary

Tuesday, April 23

Pharmacology Education Division Program: The future of Ph.D. education in biomedicine: U.S. and European perspectives
Westin Boston Waterfront Hotel, Room TBD; 9:30 AM – Noon
Chair: Jane A. Mitchell, Imperial Col. London

PhD training in the USA: present and future
Joey V. Barnett, Vanderbilt Univ. Med. Ctr.

PhD education in the UK: why change?
Nick J. Goulding, Barts and the London Sch. of Med. and Dentistry

Standards of PhD education: the ORPHEUS perspective
Michael Mulvany, Aarhus Univ. Graduate Sch. of Hlth. Scie., Denmark

Research funder perspective: PhD graduate attributes – future needs
TBD

Roundtable discussion

Acetaminophen induced hepatotoxicity: Lessons learned during the last four decades investigating mechanisms of toxicity
Boston Convention Center, Room 106; 9:30 AM – Noon
Sponsored by the Divisions for Toxicology; Drug Discovery and Development; Drug Metabolism; and Pharmacology Education
Chairs: José E. Manautou, Univ. of Connecticut and Hartmut Jaeschke, Univ. of Kansas Med. Ctr.

2013 marks the 40th anniversary of the publication of the pioneering work of Brodie and co-workers in the Journal of Pharmacology and Experimental Therapeutics demonstrating the role of drug metabolism and protein covalent binding in acetaminophen-induced hepatotoxicity. While this work paved the way for toxicological investigations aimed at elucidating the mechanism of acetaminophen toxicity, the precise mechanism of liver toxicity has eluded investigators. This session will highlight what is known 40 years after the initial publication of Brodie's paper, including the role of biotransformation, the role of mitochondria and oxidant stress, the hepatoprotective effects of Vanin-1, the use of acetaminophen plasma protein adducts as diagnostic markers in acetaminophen-induced hepatotoxicity.

Acetaminophen biotransformation and reactive intermediate toxicity: How did we get here?
Steven Cohen, Massachussetts Col. of Pharm. and Toxicol.

Mitochondria – oxidant stress and other signaling events associated with acetaminophen hepatotoxicity in mice and humans
Hartmut Jaeschke, Univ. of Kansas Med. Ctr.

Role of Vanin-1 in acetaminophen hepatotoxicity: Regulation of thiol homeostasis and immune response to liver injury
José E. Manautou, Univ. of Connecticut

Acetaminophen plasma protein adducts: Diagnostic markers and disease mechanisms in mice and humans
Laura James, Univ. of Arkansas for Med. Sci.

A "reductionist" approach to cardiovascular disease: Inorganic nitrate to nitrite to NO
Boston Convention Center, Room 107AB; 9:30 AM – Noon
Sponsored by the British Pharmacological Society
Chairs: Amrita Ahluwalia, Queen Mary Univ. and David Lefer, Emory Univ. Sch. of Med.

While previously considered inactive oxidative metabolites of endogenous nitric oxide (NO) synthesis, inorganic nitrate and nitrite are now known to be reduced back to NO to provide an alternative source of NO under certain conditions. There is growing evidence that this pathway can act as a rescue pathway in situations where the normal healthy endogenous synthesis of NO has been compromised. This session will discuss the therapeutic potential of this pathway and the clinical studies that have translated much of the basic science into therapeutics.

Inorganic nitrite-a metabolite with a mission!
Mark Gladwin, Vascular Medicine Inst.

Nitrite therapy in heart failure: Mechanisms and therapeutic potential
David Lefer, Emory Univ. Sch. of Med.

The red blood cell nitrite reductase: A therapeutic target in hypertension
Amrita Ahluwalia, Queen Mary Univ. of London

Dietary nitrate/nitrite and pulmonary hypertension
Reshma Baliga, Barts & The London Med. Sch., London

Purinergic transmission in visceral function and sensation
Boston Convention Center, Room 107C; 9:30 AM – Noon
Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology & Molecular Pharmacology
Chair: James J. Galligan, Michigan State Univ.

Purines are primary neurotransmitters controlling GI motility, secretion and blood flow as well as contributing to control of bladder sensation and function. They also play an important role in visceral sensation and pain mechanisms. This session explores in detail the various aspects of purine function with a focus on the development of new therapeutic approaches to modulating purine mechanisms as a strategy to treat GI and bladder functional disorders.

Multiple purinergic neurotransmitters in the abdominal viscera
Violeta Mutafova-Yambolieva, Univ. of Nevada

Purinergic control of gastrointestinal secretion
Fivos Christofi, Ohio State Univ.

Purinergic synaptic transmission in the enteric nervous system and control of gut motility
James J. Galligan, Michigan State Univ.

Purinergic signaling in visceral pain mechanisms
Christopher Keating, Univ. of Sheffield

Voltage-gated ion channel blockers as potential analgesic agents
Boston Convention Center, Room 108; 9:30 AM – Noon
Sponsored by the Divisions for Drug Discovery and Development & Neuropharmacology
Chair: Michael F. Jarvis, Abbott Labs.

Voltage-gated ion channels play an integral role in the regulation of membrane ion conductance, neurotransmitter release, and cellular excitability in neurons. Several nonselective sodium channel blocking drugs have reduced chronic pain in human trials. Recently discovered gain and loss of function mutations of one particular sodium channel isoform implicate this channel as a modulator of nociceptive sensitivity. Inhibition of low- voltage activated (T-type) and high-voltage active (N type) calcium channels leads to analgesia through modulation of neuronal membrane excitability and neurotransmitter release. These results will be discussed in the context of developing new small molecule channel modulators as potential analgesic agents lacking the addictive and analgesic tolerance potential of opioids.

Structure and function of voltage-gated sodium channels at atomic level
William A. Catterall, Univ. of Washington

Chasing men on fire: sodium channels and pain
Steve Waxman, Yale Univ. Sch. of Med.

Novel means of targeting T-type calcium channels to treat pain
Gerald Zamponi, Univ. of Calgary

Antinociceptive pharmacology of small molecule sodium channel blockers
Michael F. Jarvis, Abbott Labs.

Structure and function of voltage-gated sodium channels at atomic level
Simon Tate, Convergence Pharmaceut.

Transcription factors as therapeutic drug targets
Boston Convention Center, Room 109A; 9:30 AM – Noon
Sponsored by the Divisions for Molecular Pharmacology; Drug Discovery and Development; and Toxicology
Chairs: Theresa M. Filtz, Oregon State Univ. Col. of Pharmacy and Mark Leid, Oregon State Univ. Col. of Pharmacy

Transcription factors are the proximal regulators of gene expression that control the nature of a cell — what type of cell it is, what it can become, how it responds — as well as the regulators of aberrant responses, growth and proliferation in diseases as varying as neoplastic transformation to cardiac hypertrophy to insulin resistance. Targeting transcription factors in disease should provide a highly selective means to manipulate cell response, function, growth and proliferation, but in general, transcription factors are considered to be difficult drug targets. The discovery that nuclear hormone receptors respond to endogenous small molecules has led to the realization that it might be possible to target transcription factors with small molecules. This session explores varying approaches in interrupting or mimicking the protein-protein and protein-DNA interactions that underlie the basic activity of transcription factor proteins.

Regulating the regulators: Transcription factor control by post-translational modification
Mark Leid, Oregon State Univ.

Activation of p53 tumor suppression by MDM2 antagonists
Lyubomir T. Vassilev, Hoffmann-La Roche, Inc.

Small molecule transcriptional modulators: Structure and mechanism
Anna Mapp, Univ. of Michigan

Synthetic strategies for targeting protein-protein interactions
Paramjit Arora, New York Univ.

Therapeutic applications of zinc finger nucleases
Edward Rebar, Sangamo BioSciences, Inc.

Cardiovascular Pharmacology Division Trainee Showcase
Boston Convention Center, Room 107AB; 2:30 PM – 4:30 PM

BENEDICT R. LUCCHESI DISTINGUISHED AWARD LECTURE IN CARDIAC PHARMACOLOGY
Boston Convention Center, Room 107AB; 4:30 PM – 5:30 PM

Negative symptoms of schizophrenia: Neuronal circuit, translation and future directions
Boston Convention Center, Room 106; 3:00 PM – 5:30 PM
Sponsored by the Divisions for Drug Discovery and Development; Behavioral Pharmacology; and Neuropharmacology
Chairs: Ruggero Galici, Bristol-Myers Squibb and Leslie Jacobsen, Bristol-Myers Squibb

Negative symptoms are a primary cause of disability in schizophrenia, comprising restricted affect, lack of motivation and asociality. These diverse symptoms are not fully explained by the current understanding of the pathophysiology of schizophrenia. This session will bring together preclinical and clinical scientists to summarize the current knowledge on negative symptoms of schizophrenia and to discuss promising treatments and future directors for translational assays and model development.

Negative symptoms: Clinical features and prospects for treatment
Brian Kirkpatrick, Scott & White Healthcare

Emotion and motivation deficits in schizophrenia: The behavioral and neural substrates of negative symptom
Ann Kring, Univ. of California, Berkeley

Emerging pharmacotherapies for negative symptoms of schizophrenia
Leslie Jacobsen, Bristol-Myers Squibb

Modeling negative symptoms of schizophrenia in animals
Athina Markou, UCSD

Integrative Systems, Translational and Clinical Pharmacology Division Young Investigator Awards Platform Session
Boston Convention Center, Room 107C; 3:00 PM – 5:30 PM

Toxicology Division Symposium: The mitochondrion as a toxicological and pharmacological target
Boston Convention Center, Room 108; 3:00 PM – 5:30 PM
Chair: TBD

Behavioral Pharmacology Division Symposium: The opoid-cannabinoid connection: A translational, behavioral perspective
Boston Convention Center, Room 109A; 3:00 PM – 5:30 PM
Chairs: Margaret Haney, Columbia Univ. Col. of Physicians and Surgeons and Ziva D. Cooper, Columbia Univ. Col. of Physicians and Surgeons

Reciprocal modulation of opioid and cannabinoid systems in rodent models of opioid- and cannabinoid-agonist induced physiological dependence
Aron H. Lichtman, Virginia Commonwealth Univ.

Pharmacological and neurobiological studies investigating opioid and endocannabinioid interactions in rodent models of stress-induced analgesia
David Finn, Natl. Univ. of Ireland

Pharmacological evidence for opioid modulation of the reinforcing effects of CB1 receptor agonists in non-human primates
Zuzana Justinova, Univ. of Maryland Sch. of Med.

Naltrexone alters marijuana's analgesic and intoxicating effects in daily marijuana smokers
Ziva D. Cooper, Columbia Univ. Col. of Physicians and Surgeons

The potential clinical efficacy of cannabinoid agonists in treating opioid-dependent patients
Adam Bisaga, NYS Psychiatric Inst.

Wednesday, April 24

NORMAN WEINER LECTURE
Boston Convention Center, Room 107B; 8:30 AM – 9:20 AM
David E. Clapham, Boston Children's Hospital, HHMI

Apolipoprotein E: A protein at the intersection of vascular and neurodegenerative disease biology
Boston Convention Center, Room 106; 9:30 AM – Noon
Sponsored by the Divisions for Neuropharmacology & Cardiovascular Pharmacology
Chairs: Cheryl Wellington, Univ. of British Columbia and Michael Wood, AstraZeneca Pharmaceuticals

Apolipoprotein E (ApoE) isoform variability has been identified as an important risk factor of Alzheimer's disease and as well as shown to influence the risk of cardiovascular disease. ApoE is a multifunctional and polymorphic protein synthesized and secreted by liver, brain, and tissue macrophages. The molecular mechanisms underlying ApoE as a risk factor for disease remain largely unknown. This program will examine evidence for potential ApoE involvement in several disease settings, including atherosclerosis, restenosis, Alzheimer's disease, and traumatic brain injury. A roundtable discussion will conclude the session by examining how the current knowledge of ApoE disease biology can be exploited in the search for new drugs to treat these disorders.

The role of ApoE from macrophages in atherogenesis
Sergio Fazio, Vanderbilt Univ. Med. Ctr.

The role of Apolipoprotein E in restenosis
David Hui, Univ. of Cincinnati

The role of ApoE in determining the fate of Aβ in Alzheimer's disease
Mary Jo LaDu, Univ. of Illinois at Chicago

The role of ApoE in traumatic brain injury
Cheryl Wellington, Univ. of British Columbia

Roundtable Discussion
Michael Wood, AstraZeneca Pharmaceuticals

The 5-HT2C receptor: A new target for multiple therapeutics
Boston Convention Center, Room 107A; 9:30 AM – Noon
Sponsored by the British Pharmacological Society and the ASPET Divisions for Molecular Pharmacology & Neuropharmacology
Chair: Lora Heisler, Univ. of Cambridge

The 5-HT2C receptor is implicated in a wide variety of behaviors and physiological processes via action in the CNS. 5-HT2C receptor activation provides a tonic influence over the release of various neurotransmitters and neuropeptides and has been implicated in depression, anxiety, schizophrenia, reward, glucose homeostasis, and energy balance, to name a few. With the advent of more advanced genetic technology and more selective 5-HT2C receptor compounds, a greater understanding of the functional role and potential therapeutic application of the 5-HT2C receptor has begun to be realized. This session will look at insights into the 6-HT2C receptor, that allow for a better understanding of their potential for the treatment of a number of prevalent conditions, including depression, obsessive-compulsive disorder, schizophrenia, drug addiction, obesity and type 2 diabetes.

5-HT2C receptors and reward
Laurence Tecott, UCSF

The effect of Htr2c post-transcriptional modifcation on 5-HT2C receptor regulated behaviour
Anthony Isles, Cardiff Univ. Sch. of Med.

A novel treatment for obesity: The 5-HT2C receptor agonist lorcaserin
Steven Smith, Florida Hosp.

5-HT2C receptor agonists: A mechanistically new target for type 2 diabetes treatment
Lora Heisler, Univ. of Cambridge

New roles for signaling by G protein beta/gamma subunits
Boston Convention Center, Room 107B; 9:30 AM – Noon
Sponsored by the Divisions for Molecular Pharmacology; Cardiovascular Pharmacology; and Neuropharmacology
Chair: Alan Smrcka, Univ. of Rochester Sch. of Med.

Heterotrimeric G protein beta/gamma subunits were discovered more than 30 years ago as essential components of the GPCR signal transduction machinery. More current studies have shown that instead of (in addition to) serving a scaffolding role, these components of the GPCR complex also play an important role in downstream signaling, implying a potential role as therapeutic targets. This session will explore their potential role in development, angiogenesis, parkinsonism, inflammation, heart failure, subcellular signaling, and neural circuitry.

Pharmacological targeting of Gbg subunits: Mechanisms and outcomes
Alan Smrcka, Univ. of Rochester Sch. of Med.

Translocation of Gbetagamma subunits to subcellular compartments
N. Gautam, Washington Univ. Sch. of Med.

Distinct roles for individual G bg isoforms in neurological signaling circuits
Janet Robishaw, Weis Ctr. for Res.

Scaffolding of Gbg by WD40 repeat proteins
Songhai Chen, Univ. of Iowa

G protein beta gamma subunits in trafficking of signaling complexes
Terry Hébert, McGill Univ.

Pharmacological enhancement of wakefulness
Boston Convention Center, Room 107C; 9:30 AM – Noon
Sponsored by the Divisions for Behavioral Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; and Neuropharmacology
Chair: Jeff Witkin, Eli Lilly and Co.

This symposium will investigate the clinical need for wake promoting agents for the treatment of sleep apnea, shift work and other conditions of fatigue. Both the pharmacological mechanisms that can impact wakefulness, cognitive augmentation, and their side effects, and new pharmacological mechanisms underlying wake-promoting neurobiology will be addressed.

Introduction to wake promotion
Dale M. Edgar, Eli Lilly and Co.

Physiological control systems for wakefulness
Luis De Lecea, Stanford Univ.

Modafanil (Provigil) as a wake-promoting agent
Jeff Vaught, Forme CSO/Executive VP Cephalon

Histamine H3 Receptor Inverse Agonisim
Jean-Charles Schwartz, Bioprojet

Metabotropic glutamate receptors as targets for wake promotion
Keith A. Wafford, Eli Lilly and Co.

Signals activating pancreatic stem cells and beta cell regeneration
Boston Convention Center, Room 108; 9:30 AM – Noon
Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology & Molecular Pharmacology
Chair: Thomas M. Wilkie, UT Southwestern Med. Ctr. at Dallas

Complex physiology drives beta cell expansion in diabetes and pregnancy. Recent discoveries demonstrate the integration of metabolic cues, neural processing and efferent signaling involved in the stimulation of beta cell expansion in diabetes. This session will explore the use of pregnancy as a model for the hormonal stimulation of beta cell expansion, hypothalamic control of islet cell function, the role of RGS proteins in the pancreas as biomarkers of beta cell expansion, and the use of stem cells as human beta cell progenitors.

Serotonin regulates pancreatic beta cell mass during pregnancy
Michael German, UCSF

Mapping the specific neuronal connections between the central nervous system and the endocrine pancreas
Chris Rhodes, Univ. of Chicago

GPCR-signaling biomarkers for pancreas development, cancer and diabetes
Thomas M. Wilkie, UT Southwestern Med. Ctr. at Dallas

Pancreatic stem and progenitor cell niche: Pancreatic organogenesis throughout life
Lola Reid, UNC, Chapel Hill

Small molecules and transcription factors driving beta cell differentiation
Doug Melton, Harvard Univ.

The pharmacology of natural products
Boston Convention Center, Room 109A; 9:30 AM – Noon
Sponsored by the Divisions for Behavioral Pharmacology; Drug Discovery and Development; Drug Metabolism; Integrative Systems, Translational and Clinical Pharmacology; and Toxicology
Chairs: Craig Hopp, NCCAM, NIH and and John Williamson, NCCAM, NIH

The use of natural products by the public for the treatment of illness has steadily increased. Most of these products have not been proven to be clinically efficacious. Recent studies have highlighted pathways involved in the beneficial actions of natural products, involving inflammatory, immunomodulatory, cell proliferative, and antioxidant targets, as well as assorted pharmacokinetic mechanisms. This session will highlight scientifically based studies underlying the efficacy of cranberry juice for the treatment of urinary tract infections, anti-inflammatory mechanisms of omega-3-fatty acids, the pharmacological actions of cocoa extract, the pharmacology of phytoestrogens, and the potential for using tetra-hydro-palmatine to treat drug abuse.

Cranberry: Role in prevention of bacterial adhesion
Amy Howell, Rutgers, the State Univ. of New Jersey

Novel pro-resolving mechanisms and omega-3 fatty acids
Charles Sherhan, Brigham and Women's Hosp. and Harvard Med. Sch.

Natural product's potential for drug abuse treatment
David Y.W. Lee, Harvard Med. Sch.

Pharmacological effects of cacao flavanols: From receptors to clinical endpoints
Francisco Villarreal, UCSD Sch. of Med.

Prevention of estrogen carcinogenesis by botanical dietary supplements for women's health
Judy L. Bolton, Univ. of Illinois at Chicago

Panel Discussion (Questions for Speakers and NCCAM)

Peripheral mechanisms of opioid analgesia
Boston Convention Center, Room 106; 3:00 PM – 5:30 PM
Sponsored by the Divisions for Neuropharmacology; Behavioral Pharmacology; and Molecular Pharmacology
Chair: Kelly A. Berg, Univ. of Texas Hlth. Sci. Ctr.

While opioids are a key drug class for the treatment of pain, their CNS effects with the attendant legal and social issues cause significant drawbacks. One approach to eliminate these drawbacks is to target opioid receptors located on primary sensory neurons that mediate pain neurotransmission in the periphery. This symposium will discuss the roles of peripheral delta opioid receptors (DOR) and kappa opioid receptors (KOR) in the molecular mechanisms involved in pain regulation. The potential role of DOR-KOR heteromizeration and interactions with arrestin in the mechanisms underlying peripherally restricted opioid analgesia will be discussed. Results from in vitro experimental strategies and molecular/computational modeling will be integrated with *ex vivo* and *in vivo* findings in peripheral sensory neurons to generate insight in the significance of opioid receptors in peripheral mechanisms of opioid analgesia.

Current status of pain therapeutics
Ken Hargreaves, Univ. of Texas Hlth. Sci. Ctr. San Antonio

Molecular determinants and thermodynamics of opioid receptor signaling
Marta Filizola, Mount Sinai Sch. of Med.

6'GNTI is a G protein-biased kappa opioid receptor agonist that inhibits arrestin recruitment
Jonathan Javitch, Columbia Univ. Med. Ctr.

DOR-KOR heteromer-mediated signaling and antinociception in primary sensory neurons
William P. Clarke, Univ. of Texas Hlth. Sci. Ctr. San Antonio

Sleep apnea: A sleeping giant in disease pathologies
Boston Convention Center, Room 107C; 3:00 PM – 5:30 PM
Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology; Behavioral Pharmacology; Cardiovascular Pharmacology; and Neuropharmacology
Chairs: Issy Laher, Univ. of British Columbia and Najib Ayas, Univ. of British Columbia

Sleep apnea is a common disease that is characterized by repetitive episodes of asphyxia and is recognized as an independent risk factor for cardiovascular morbidity and mortality. This symposium will summarize the currently available information on the cardiovascular, metabolic and other consequences of sleep apnea, pharmacological and non-pharmacological management strategies for sleep apnea, and the use of different animal models to study sleep apnea.

Sleep apnea for non-experts
Najib Ayas, Univ. of British Columbia

Animal models of sleep apnea
Vsevolod Polotsky, Johns Hopkins Univ.

Sleep apnea and cardiovascular diseases
T. Douglas Bradley, Univ. of Toronto/Mount Sinai Hosp.

Sleep apnea and type 2 diabetes
Esra Tasali, Univ. of Chicago Med. Ctr.

Biomarkers of sleep apnea
Atul Malhotra, Brigham and Women's Hosp. and Harvard Med. Sch.

Stem cells: Pharmacology and therapeutics
Boston Convention Center, Room 108; 3:00 PM – 5:30 PM
Sponsored by the British Pharmacological Society-Young Scientists and the ASPET Divisions for Integrative Systems, Translational and Clinical Pharmacology & Behavioral Pharmacology
Chairs: Daniel Reed, Imperial Col. London and Jane A. Mitchell, Imperial Col. London

The application of stem cells in pharmacology is quickly gathering momentum and pharmacology is of great importance for the optimal use of stem cells in regenerative medicine. This session, organized by the Young Scientists Group of the British Pharmacological Society, will address how and why pharmacology is important in stem cell research and vice versa. Speakers will address how stem cells can be used in cardiovascular pharmacology and the treatment of cardiovascular disease, the pharmacologic mobilization and activation of endogenous stem cells and stem cell progenitors, the role of stem cells in neuroprotection, and the use of stem cell derived cells as model systems for screening.

Stem cells: Pharmacology and therapeutics
Boston Convention Center, Room 108; 3:00 PM – 5:30 PM
Sponsored by the British Pharmacological Society-Young Scientists and the ASPET Divisions for Integrative Systems, Translational and Clinical Pharmacology & Behavioral Pharmacology
Chairs: Daniel Reed, Imperial Col. London and Jane A. Mitchell, Imperial Col. London

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Stem cell based solutions for cardiovascular disease
TBA

Regenerating the lung
TBA

Stem cells and pattern recognition receptors
Daniel Reed, Imperial Col. London

Systems biology answering pharmacological questions
Boston Convention Center, Room 109A;3:00 PM – 5:30 PM
Sponsored by the Divisions for Toxicology & Integrative Systems, Translational and Clinical Pharmacology
Chairs: Rick Neubig, Univ. of Michigan and John Lazo, Univ. of Virginia Sch. of Med.

While the paradigm of one-drug-one-target has lead to important advances in therapeutics, it is becoming clear that the complex interplay of biological systems can greatly influence the response of a drug. Moreover, drugs often exploit multiple targets within an organism. A more complete understanding of all of the interacting elements of a signaling pathway, transcriptional network, or neural circuit may be necessary to accurately predict the response to a given drug. Complex biological interactions such as redundancy and feedback have important implications for both acute responses and the development of resistance. The availability of large data sets of protein structure and interactions, genomic variations, and compound actions permit a more thorough analysis of such questions. Leading researchers in this new and rapidly developing area will discuss how the use of complex systems approaches can be used to explore mechanisms of drug resistance, design novel therapeutic agents, and predict efficacy.

P4 Medicine: How a systems approach will revolutionize medicine
Leroy Hood, Inst. for Systems Biol.

Network models in cancer pharmacology
Dana Pe'er, Columbia Univ.

Practical applications of systems biology in the pharmaceutical industry
Bruce Gomes, Novartis Inst. for BioMedical Res., Inc.

Metabolic network analysis to predict therapeutic responses
Jason Papin, Univ. of Virginia

SIR JAMES BLACK HONORARY LECTURE
Boston Convention Center, Room 107B; 2:00 PM – 2:50 PM
Sponsored by the British Pharmacological Society
Robert J. Lefkowitz, Duke Univ. Med. Ctr.
Molecular mechanisms of biased agonism at 7 transmembrane receptors
Note: This lecture and session are part of a colloquium on G-Protein Coupled Receptors which continues Wednesday evening and Thursday. While this lecture and session are open to any EB registrant, attendance at the poster session, dinner, and remainder of the colloquium Wednesday evening and Thursday requires separate registration.

Colloquium Symposium: Bridging the efficacy divide: Novel molecular insights driving biased ligand drug discovery
Boston Convention Center, Room 107B; 3:00 PM – 5:30 PM
Jointly sponsored by the British Pharmacological Society and the ASPET Divisions of Molecular Pharmacology and Neuropharmacology
Chairs: Arthur Christopoulos, Monash Univ., Victoria and Robert J. Lefkowitz, Duke Univ. Med. Ctr.

Biased ligands: developing better drugs through selective signaling at GPCRs
Jonathan Violin, Tevana Inc.

Ligand-biased signaling under the light of BRET
Michel Bouvier, Univ. de Montréal

Allosteric modulation of endogenous metabolites: Implications for on- and off-target drug action and bias
Patrick M. Sexton, Monash Univ., Victoria

Moving from biased signaling to functional (physiological) bias
Andrew Tobin, Univ. of Leicester

For the remainder of the G-Protein Coupled Receptors Program, see page 154.

ASPET Closing Reception
Westin Boston Waterfront, Room TBD; 6:00 PM – 8:00 PM

Annual Meeting News

At the annual meeting in April, the Council of Division Chairs, the ASPET Council, and the Program Committee discussed the process used to create the symposium portion of the annual meeting and whether there were ways to make it more responsive to the pace of scientific discovery and the needs of our members. The one recurring concern was that almost a year-and-a-half elapses between the time ideas for symposia were identified and the actual symposium occurred. While the approved symposia frequently change during this period to accommodate new research, these groups were still concerned that the time frame was too long. Therefore, with concurrence of the Program Committee, ASPET Council recommended shortening the time from initial idea generation to actual symposium to one year. Where this will be most noticeable for the first time to ASPET members will be at the 2013 annual meeting in Boston where your division representatives will be actively soliciting ideas for symposia for the next year's meeting. There will be discussions at Division Business Meetings. Most likely there will also be discussions in the halls, in the back of session rooms, at mixers, and over drinks in the bar. The Program Committee will meet the last day of the meeting to discuss ideas that the division representatives and at-large members have gathered over the course of the preceding four days, and in the weeks immediately preceding the annual meeting. At this meeting of the Program Committee, the topics for symposia for the 2014 meeting will be decided. Joint divisional sponsorships will be agreed upon. The division representatives to the Program Committee and the at-large members will then go back to the divisions and members and ask them to put together a formal symposium proposal on these topics in the ensuing two months. The Program Committee will then meet again at the end of June to review these formal proposals to make sure that they meet the original goals, that there is scientific breadth in the program, and that the best possible speakers have been identified. From this discussion will emerge the final program of symposia for the 2014 meeting. Organizers will be notified very shortly thereafter if their proposals have been approved as submitted or if there are minor changes that need to be made. We hope that these changes in the programming process will make the annual meeting scientific program more timely and give the members maximum involvement in the process. The Program Committee roster can be found on page 158.

4th GPCR Colloquium

Wednesday, April 24 - Thursday, April 25

Boston Convention and Exhibition Center, Room 107AB, Boston, MA

Organizers: Laura Bohn, PhD, The Scripps Research Institute, Scripps Florida
Roger Sunahara, PhD, University of Michigan Medical School
Graeme Milligan, PhD, University of Glasgow, College of Medical, Veterinary and Life Sciences

Sponsored by the ASPET Divisions for Neuropharmacology, Molecular Pharmacology, Drug Discovery and Development, & Toxicology, and the British Pharmacological Society

Attendees are invited to submit a poster for presentation on Wednesday evening and Thursday morning. Poster titles and abstracts must be emailed to Danielle Jordan at **djordan@aspet.org**, no later than February 25, 2013.

Preliminary Program

Wednesday, April 24:

1:00 PM — Registration open

2:00 PM – 2:05 PM — Welcome and introduction to the 4th GPCR Colloquium and Sir James Black Honorary Lecture

2:05 PM – 2:55 PM — **Sir James Black Honorary Lecture**
Molecular mechanisms of biased agonism at 7 transmembrane receptors
Robert J. Lefkowitz, Duke University

Bridging the efficacy divide: Novel molecular insights driving biased ligand drug discovery
Session Chairs: Arthur Christopoulus and Robert J. Lefkowitz

3:00 PM – 3:25 PM — *Ligand-biased signaling under the light of BRET*
Michel Bouvier, Université de Montréal

3:25 PM – 3:40 PM — COFFEE BREAK

3:40 PM – 4:05 PM — *Allosteric modulation of endogenous metabolites: Implications for on- and off-target drug action and bias*
Patrick M. Sexton, Monash University

4:10 PM – 4:35 PM — *Moving from biased signaling to functional (physiological) bias*
Andrew Tobin, University of Leicester

4:40 PM – 5:05 PM — *Biased allosteric modulators*
Arthur Christopoulus, Monash University

5:10 PM – 5:30 PM — *Bringing receptor bias into clinical development for pain therapeutics*
Jonathan Violin, Trevena, Inc.

Official end of ASPET's Annual Meeting at Experimental Biology 2013.
Attendance at the poster sessions, dinner and remainder of the Colloquium on Wednesday evening and Thursday requires separate registration.

5:30 PM – 8:30 PM — Open Registration; POSTER PRESENTATIONS; DINNER (Buffet- 6:30pm) for GPCR symposium (Poster awards if prizes can be raised; **Sponsorship needed, Please contact Christie Carrico or Laura Bohn**).

Thursday, April 25:

8:00 AM – 8:30 AM — Registration Open, Coffee

8:30 AM – 9:20 AM — **Allosteric modulators: Enhancing the selectivity and potency of current therapeutics**
Allosteric modulators for improving CNS therapeutic targets
Jeff Conn, Vanderbilt University

Report from the MLPCN GPCR probe development
Session Chair: Laura Bohn

9:25 AM – 10:05 AM — *Introduction to the MLPCN and an update on Sphingosine1Phosphate receptor drug development*
Hugh Rosen, The Scripps Research Institute

10:10 AM – 10:35 AM — *The chemistry behind CNS drug development*
Jeff Aubé, University of Kansas

10:40 AM – 11:05 AM — *An industry perspective on GPCR drug discovery*
Chris Felder, Eli Lilly and Company

11:05 AM – 11:20 AM	COFFEE BREAK

Location, location, location: Diverse signaling as a function of context (within the cell)

11:20 AM – 11:55 AM	*Receptor Trafficking Determining Receptor Signaling* Mark von Zastrow, University of California, San Francisco
11:55 AM – 12:20 PM	*Nuclear membrane receptors signaling* Karen O'Malley, Washington University
12:20 PM – 1:30 PM	LUNCH: Provided (box lunches)

Structure and function: Emphasis on context and drug design
Session Chair: Roger Sunahara

1:30 PM – 2:10 PM	*An update on GPCR structure and drug development* Brian Kobilka, Stanford University
2:15 PM – 2:40 PM	*X-ray Structures for the predictive generation of GPCR drugs* Fiona Marshall, Heptares Therapeutics
2:45 PM – 3:05 PM	*Cannabinoid ligands gaining entry* Patricia Reggio, University of North Carolina, Greensboro

Transient or transformative: Receptor oligomerization finds its way

3:10 PM – 3:40 PM	*Receptor oligomerization and ligand directed signaling* Graeme Milligan, University of Glasgow
3:45 PM – 4:10 PM	*5HT2AR-mGluR interactions and implications in schizophrenia* Javier González-Maeso, Mount Sinai School of Medicine
4:15 PM – 4:40 PM	TBD
4:40 PM	Adjournment

Share your news...

Awards,

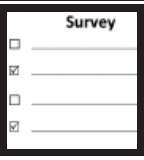
Promotions,

Achievements

Share your accomplishments with *The Pharmacologist* and with the ASPET community.

Send information and pictures to **gaxelrod@aspet.org**.

Annual Membership Survey



Thank you to everyone who participated in the 2012 ASPET Annual Membership Survey. We had 723 members complete the survey. Members were given the opportunity to enter a raffle to win an ASPET T-shirt upon completing the survey. Congratulations to Brittany Speer, Gloria Malpass, and Peter Syapin for winning an ASPET T-shirt!

The membership survey was designed to give each of our members a voice in the Society, and by getting your input, we hope to continue to improve our benefits and develop new programs and initiatives to fit your needs. While 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 with you.

General Membership:

We are happy to report that 71.4% of survey respondents feel that ASPET is successfully meeting their professional needs. 71.5% of respondents agree that ASPET provides useful and important member benefits, and 76.3% agree that ASPET provides good networking opportunities. We are also happy to note that 78.2% of respondents feel that ASPET membership enhances their credibility as a pharmacologist.

In looking deeper at our membership benefits, we found that all of our benefits are considered either very useful or moderately useful. Our most useful benefit is free full-text online access to ASPET journals, with over 92% of respondents finding this benefit useful. Our next few highest rated benefits include free access to all back issues of the ASPET journals, reduced registration fees to attend the ASPET Annual Meeting at Experimental Biology, free membership in the ASPET divisions, and networking opportunities with fellow members and pharmacologists.

Communication:

ASPET strives hard to communicate with our members frequently to make sure they are always up-to-date on the latest ASPET news and Pharmacology news. It is important to us that you are made aware of pertinent information while not bombarding you with too much. We asked members how often you wanted to receive updates and news from ASPET. 50.7% of respondents said monthly, 25.9% said Bi-monthly and 18.7% said weekly. An overwhelming majority of respondents (93%) prefer to receive all their news and updates from ASPET via email. We currently send out a bi-monthly email newsletter, as well as a larger quarterly online newsletter (*The Pharmacologist*), and update our website, Facebook, and Twitter daily.

Website and Other Technologies:

We are also happy to report that 80% of survey respondents use and visit the ASPET website. The most sought out information on the website is the meetings page where we post information about our Annual Meeting at Experimental Biology. Our other popular pages include the publications page (where you can now directly access the ASPET journals using your membership login and password), our membership information page, *The Pharmacologist* newsletter page, and the membership directory page. As we continue to work to improve our website and provide more valuable content to each of our sections, we hope that you will continue to visit us often. If you have any suggestions for improvements or want to help provide content, please contact our Web Manager, Gary Axelrod at **gaxelrod@aspet.org**.

ASPET is also looking into creating online videos of ASPET programs, sessions from the annual meeting, and interviews with members. We asked members how interested they were in viewing this type of media, and about 60% of respondents said they would be interested. In the coming months, we will be looking at ways to incorporate this type of media for our members.

ASPET Annual Meeting:

We asked members a series of questions regarding their attendance of scientific meetings. Most survey respondents attend 2-3 meetings a year. About 75% of respondents attend ASPET's annual meeting every year, every other year, or every few years. When asked if survey respondents are planning to attend the 2013 meeting in Boston, MA, 37.3% responded positively. Another 35.3% were not sure yet. We hope that everyone will make an effort to attend next year's meeting. As we are meeting jointly with the *British Pharmacological Society* and the *Canadian Society of Pharmacology and Therapeutics*, it is sure to be an exciting meeting. The programming is jam-packed and the social activities are sure to be a great time. Check out more information about the 2013 Annual Meeting at Experimental Biology at **http://www.aspet.org/EB2013/**.

ASPET Branding:

Coming out of last Fall's Leadership Retreat, ASPET is examining our current branding and how members view the Society. We want to be the best Society for our members, all the while attracting new members and becoming more relevant in the scientific community and beyond. We have hired a research firm, McKinley Advisors, to help us in this great endeavor, but to get an initial gauge of what our members think, we asked a couple of questions regarding our brand. We asked survey respondents whether they agreed or disagreed with the following statements:

ASPET is influential in the world of pharmacology and bio-medical sciences.

ASPET is an innovative Society.

ASPET is an inclusive Society.

ASPET is relevant in the world of pharmacology and bio-medical sciences.

ASPET connects pharmacologists and those studying drugs.

ASPET is committed to creating leaders in the pharmacology and bio-medical fields.

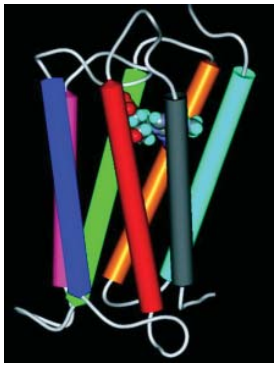
We were very happy to see that a strong majority either agreed or strongly agreed with these statements.

We also asked members if ASPET should aim for a goal of growth to represent anyone who is doing research of any type with drugs, or should it focus more narrowly to be the best possible Society for that group of scientists who identify with pharmacology? 67% feel we should be more broad and 33% felt we should stay narrow.

This is just the beginning of a re-branding effort for ASPET. McKinley Advisors will be working more in depth with members to find out exactly what our members would like to see our Society doing. They will be sending out an all member survey later this year and we hope that you will participate. We will keep you posted on all of our research efforts.

A Final Note:

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



4th GPCR Colloquium

Wednesday, April 24 – Thursday, April 25

aspet

BPS BRITISH PHARMACOLOGICAL SOCIETY

Held in as a satellite meeting to the ASPET Annual Meeting at Experimental Biology 2013
Boston, MA

To register for the meeting:
ASPET Members, login to the Members Only section to register.
Nonmembers, go to the following URL to register:
http://tinyurl.com/4thGPCRregistration.

For updates and more information on the 4th GPCR Colloquium, please visit: **http://www.aspet.org/Meetings/GPCR2013/**.

ASPET Committees 2012-2013

Committees Established by Bylaws

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Lynn Wecker, Past President
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Sandra P. Welch, Secretary/Treasurer-Elect
Mary E. Vore, Past Secretary/Treasurer
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Stephen M. Lanier, Councilor
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James E. Barrett, Ex Officio
Brian M. Cox, Ex Officio; FASEB Board Representative
Scott A. Waldman, MD, Ex Officio
Christine K. Carrico, Ex Officio

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Raymond Dingledine

ASPET Reorganizes Committee Structure

One of the outcomes of the 2011 Long Range Planning Retreat was a mandate to increase ASPET's activities in mentoring and career development. While ASPET has a long history of engaging in career development activities at the annual meeting through the activities of the Women in Pharmacology Committee (WIP), the Diversity Committee, and the Graduate Recruitment and Education Committee (GRE), there was no single focus for our career development activities, and often there was duplication of effort among the three committees. Recognizing that there was no unique focus in many of their activities (the WIP Walk excepted!), the Women in Pharmacology Committee voted to disband in the fall of 2011. In an effort to increase the efficiency of our volunteer and staff efforts, as well as maximize the utility to our members, Council voted at its April meeting to reorganize its key committees. There will now be two committees that will address the areas previously covered by the WIP, GRE, and Diversity Committees.

The Committee on Mentoring and Career Development, co-chaired by Marcus Delatte and Susan Ingram, will focus on providing mentoring and career development sessions to ASPET members, especially our younger scientists. Initially, the committee will:

- Organize the Graduate Student/Postdoc Colloquium on career development topics at the annual meeting;
- Establish and maintain a mentoring program for ASPET's young scientists;
- Plan and participate in the Diversity Mentoring breakfast at the EB meeting;
- Oversee judging for the minority graduate student posters at EB for the Dolores Shockley Award;
- Nominate women and minorities for major ASPET and FASEB awards;
- Organize the WIP Networking walk; and
- Plan other career development and mentoring activities at the annual meeting as appropriate.

The Graduate Recruitment and Education Committee will focus on another critically important aspect of our discipline, facilitating the recruitment, training, and education of students choosing careers in pharmacology. Under the co-chairmanship of Joey Barnett and Kelly Karpa, the Graduate Recruitment Committee will:

- Organize and execute the Teaching Institute at the annual meeting;
- Oversee and coordinate the activities of the SURF Program, including the review of SURF applications;
- Review the SURF and non-MARC Minority Travel Awards to EB;
- Develop means to facilitate recruitment of graduate students into pharmacology, including ensuring that adequate and up-to-date information about the discipline is available;
- Maintain an active program that targets the recruitment of minorities and women into pharmacology, including participation in the SACNAS and ABRCMS meetings;
- Oversee the subcommittee responsible for the National Directors of Graduate Studies in Pharmacology meetings and maintain a communication mechanism for this group of educators; and
- Act as a conduit to provide information to ASPET members and others about issues related to education.

As has always been the case with ASPET committees, these committees will also look for and carry out other opportunities to further the recruitment, education, career development, and mentoring aspect of their missions. The recruitment, care and nurturing of our young scientists should be a primary function of all more established scientists, and with the help of these committees, ASPET hopes to be able to facilitate such a culture.

One additional committee reorganization deserves mention. The Committee on Public Affairs has long been a key committee, working with Jim Bernstein, to identify and provide public comments on policy and funding issues that are important to ASPET members. However, public policy has become an increasingly important part of ASPET's activities and the challenges to which we must respond have become more complex. Therefore, Council decided in April that it was time to give the Committee on Public Affairs a higher profile. The committee has been renamed the Science Policy Committee (SPC), similar to its counterpart in FASEB. Each year, the Past President of ASPET will go onto the committee to serve a three-year term. The ASPET Representative to the FASEB Board will also serve on the SPC during his/her four year term on the FASEB Board. The remainder of the committee will consist, as it does now, of interested members who have demonstrated a commitment to participating in ASPET's public affairs activities. As of July 1, 2012, Dr. Lynn Wecker, current Past President is chairing the SPC, and Dr. Brian Cox participates as ASPET's representative to the FASEB Board. The membership of the Mentoring and Career Development Committee, Graduate Recruitment and Education Committee, and Science Policy Committee can be found on page 159.

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HTTP://CAREERS.ASPET.ORG/

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Journals

by Rich Dodenhoff

FASEB Journal Back Issues Needed

When back issues of *The FASEB Journal* went online, a handful of the copies were damaged during the scanning process, leaving a gap in the journal's online archive. The FASEB Office of Publications is seeking the August through November issues (numbers 11-14) from volume 4, 1990.

The FASEB Journal is also working to digitize the back issues of the EB abstracts, known as *The FASEB Journal Experimental Biology Abstracts*. Abstracts issues for the following years are needed:

1987	1992
1988	1998, part 1, vol. 12, no. 4
1989	1998, part 2, vol. 12, no. 5
1990	2001, part 1, vol. 15, no. 4
1991	2001, part 2, vol. 15, no. 5

If you can contribute a hard copy of any of the issues listed above, please contact Barbara Walker, MLS, Content Licensing and Sales Manager, FASEB Office of Publications at **bwalker@faseb.org** or by telephone at 301-634-7305. Donated copies cannot be returned as they will be de-spined for scanning.

Member Access to ASPET's Journals

ASPET members can now access the Society's four journals by logging on at the ASPET website (**www.aspet.org**) or by going to **www.aspet.org/journalslogin**. Members receive access to the Society's journals as a member benefit. Previously, members had to activate their online journals subscription and maintain a separate user name and password for the journals, which are on servers at HighWire Press and use a separate access system.

Our new access system allows members to reach all journal content via ASPET's website. Three routes will take members to the journals: Log on from the homepage using your ASPET member username and password. Go to the Publications page. Where it says "To access the full text of ASPET's journals online, members must log in here," click on "here." On the page that follows, click on the name or cover of the journal you wish to read. Members can go directly to the Publications page, click on the "here" link, and log in. Or, go directly to **www.aspet.org/journalslogin**.

Members who activated subscriptions at the journals sites can continue to use them with their separate username and password, if they wish. Going to the journals through ASPET's website allows members to use the same username and password that they use to pay dues online, register for meetings, and access content available only to members.

ASPET journal content from 1997 up to the most recent 12 months is freely accessible to all. A subscription is needed for content published prior to 1997 and within the last twelve months.

If you have forgotten your username or password for the ASPET site, please contact **membership@aspet.org**.

Editors to Continue for Second Term

The Board of Publications Trustees is pleased to announce that Dr. Michael Jarvis and Dr. David Sibley will each serve a second three-year term as Editor of *JPET* and *Pharmacological Reviews*, respectively. Each editor of an ASPET journal is appointed for an initial three-year term that can be renewed once. Dr. Jarvis and Dr. Sibley began their current terms at the start of 2010. The BPT unanimously and enthusiastically endorsed their reappointment, and both Editors agreed to continue serving their respective journal and the Society in these important roles through 2015.

The Journal of Pharmacology and Experimental Therapeutics was begun by John J. Abel in 1909. The first issue appeared about six months after ASPET was founded. Dr. Abel served as editor until 1912 and as a coeditor from 1912 until 1932. Dr. Jarvis is the twenty-first person to lead ASPET's flagship journal.

Pharmacological Reviews began publication in 1949 under the editorship of Dr. Louis S. Goodman. Dr. Sibley is the twelfth editor of the Society's highly ranked review journal and second oldest publication.

New Editorial Board Members

Dr. Xiao-bo Zhong joined the *Drug Metabolism and Disposition* Editorial Board in May. Dr. Zhong is an Associate Professor with the Department of Pharmacology, Toxicology, and Therapeutics at the University of Kansas Medical Center.

Dr. Scott Mittelstadt is now the *JPET* Assistant Editor, succeeding Dr. Keith Glaser. Dr. Mittelstadt is a Senior Group Leader, Integrative Pharmacology, at Abbott Laboratories.

The following researchers joined the *JPET* Editorial Board as Associate Editors:

Dr. Shripad Bhagwat, Chief Scientific Officer, Zacharon Pharmaceuticals;
Dr. Brendan Canning, Associate Professor of Medicine, The Johns Hopkins Medical Institutions;
Dr. Beverley Greenwood-Van Meerveld, Professor of Physiology, University of Oklahoma Health Sciences Center;
Dr. Andrea Hohmann, Linda and Jack Gill Chair of Neuroscience and Professor, Department of Psychological and Brain Sciences, Indiana University;
Dr. Gerard Marek, Medical Director, Abbott Laboratories;
Dr. Kathryn Meier, Director/Chair, Program in Nutrition and Exercise Physiology, College of Pharmacy, Washington State University;
Dr. Timothy Ness, Simon Gelman Endowed Professor of Anesthesiology, University of Alabama-Birmingham;
Dr. Jeff Stevens, Senior Director, Pharmacokinetics, Dynamics, and Metabolism, Pfizer; and
Dr. Ellen Walker, Professor, Pharmaceutical Sciences, Temple University.

JPET also added four members to its Editorial Advisory Board:

Dr. Anindya Bhattacharya, Principal Scientist, Jansen R&D;
Dr. Keith Glaser, Abbott Laboratories;
Dr. Jesus (SUSO) Pintor, Full Professor, Department of Biochemistry and Molecular Biology IV, University School of Optics, Universidad Complutense De Madrid; and
Dr. Uwe Rudolf, Associate Professor of Psychiatry, Harvard Medical School.

The Board of Publications Trustees appreciates the commitment of these researchers to ASPET's journals and is grateful for their service.

Science Policy

by Jim Bernstein

Fight Steep Budget Cuts to the NIH

CR Keeps NIH at FY'12 Level Thru March 2013

Upon Congress' return from a five-week summer recess, one of the first working orders of the day is to approve the Continuing Resolution (CR) that House and Senate leadership agreed to in-principle prior to recess. Assuming passage this September, the terms of the CR will keep the government open through the first six months of FY'13, which begins October 1. Federal programs, including the NIH will be frozen at their current FY 2012 level for the duration of the CR which will run through March 2013.

Both parties want to avoid a government shutdown that would result without a final agreement, especially during a contentious election year. But until the CR is formally approved, it is not a done deal. The proposed CR would adopt the $1.047 trillion limit agreed to under last summer's contentious debt raising deal. Conservatives wanted a lower spending cap of $1.028 trillion, $19 billion less than the agreed to CR. The $19 billion difference could become more problematic and threaten passage of the CR if some Members of Congress challenge their leadership over what they view to be excessively high spending levels. Taking into account little or no legislation is done on Monday and Friday (as Members travel to home districts for the weekend), there are only about eight business days remaining until the new fiscal year begins.

Assuming the CR passes, what happens down the road after the CR expires on March 31, 2013? At that time, Congress will be looking at FY'14 spending, ongoing debates regarding revenue and tax reform, and another fight over raising the federal debt limit may be in the works. It is possible Congress would extend the CR through the remaining six months of FY 2013 (effectively freezing FY'13 spending at the FY'12 level). But conservative House Republicans, having conceded on the higher spending cap limit in the CR ($1.047 trillion v $1.028 trillion), may push for further reductions in a year-long extension. And further complicating all this will be the outcome of which party controls the White House and Senate. (The House is expected to remain in Republican control.)

Threat of Sequestration

With NIH funding apparently frozen for the first six months of FY 2013 at the FY'12 level, there remains the potential of sequestration – mandatory across the board cuts – that would cut the NIH budget in a significant way. ASPET members have been informed of this possibility over the past several months and how they might inform members of Congress of sequestration's devastating impact on biomedical research, including a total cut to NIH of $2.4 billion. The Office of Management and Budget (OMB) has estimated that NIH would fund 750 fewer grants in FY'13 than it will award this year. Depending on how the budget cuts would be implemented, the number of grants not funded in FY'13 compared to FY'12 could be significantly higher, upwards of 2,300 fewer grants.

Many members of the biomedical research community assume that Congress would never make such draconian cuts. However it is important to remember that while no Member of Congress wants sequestration to happen, it might. Sequestration was the trigger imposed by Congress to help make certain that $1.2 trillion in deficit reduction would be identified, through a combination of tax increases and spending cuts. Congress failed to do that, and as a result sequestration is now law. It will be implemented in January 2013 unless a clear plan and bipartisan solution prevents that from happening.

There remains a chance that when the CR is approved, it would include legislative language that prevents sequestration from happening. House and Senate leadership have said that they want the CR to be free of other policy considerations. An attempt to remove sequestration could be in the works, but it is not clear if such a plan even materializes that it would succeed.

How ASPET Members Can Help

Contact your Congressional Representatives today. Legislators need to hear from you that the investment in biomedical research should be a national priority. View the following pages in the Advocacy section of the ASPET website for more details on the impact of sequestration, **http://www.aspet.org/PolicyUpdatesNews.aspx**, and for information on how to successfully contract and/or meet with your Congressional delegation, **http://www.aspet.org/Advocacy/Grassroots**.

ASPET members can also take advantage of programs to facilitate grassroots Congressional education efforts. ASPET encourages its members visiting Washington, DC/Bethesda for NIH or other business to make Capitol Hill visits to your Congressional delegation. To aid this effort, ASPET will assume the costs of an extra night hotel stay following the conclusion of your official business. The following day, ASPET will make all Congressional meeting arrangements, provide talking points, etc., and have you well prepared for the day of advocacy. We also encourage you and colleagues to visit your Congressional Representatives if possible in your local Congressional district. These meetings, at home and in Washington, are critical to raise awareness of the impact of sequestration on the NIH and the entire biomedical research enterprise. For additional information or details on how to arrange a Congressional meeting, contact Jim Bernstein at 301-634-7062; **jbernstein@aspet.org**.

And finally, ASPET has also created the Advocacy Outreach Program designed to develop awareness in graduate students, postdocs, and faculty of the need for enhanced biomedical research advocacy. The discussion/presentation provides an overview of the political and economic environment impacting NIH funding and the skills needed to allow scientists-advocates to help influence the debate. There is no financial obligation to your institution or department.

ASPET Washington Fellows Program

Program Mission

The mission of the ASPET Washington Fellows Program is to enable developing and early career scientists interested in science policy to learn about and become more engaged in public policy issues. Fellows will develop an understanding of how public policy decisions made in Washington help shape and impact science policy, such as funding for the National Institutes of Health and other science agencies. Fellows will also learn how to advocate effectively on Capitol Hill and in their home districts. This program will help fellows develop the skills and insights to become future leaders in science.

What Will ASPET Fellows Do?

• Advocate on Capitol Hill: ASPET Fellows will come to Washington, DC to meet with their Congressional delegation to advocate for biomedical research and increased funding for the NIH. Fellows will be well trained by ASPET and prepared with the appropriate message to deliver to Congress. ASPET will cover transportation costs, hotel, and other reasonable expenses that follow ASPET's reimbursement policy.

• Become advocates in their home districts: ASPET Fellows will meet with Members of Congress in their home district, act as a conduit to inform colleagues within their departments/institutions about federal legislative matters, write op-ed pieces to local papers, etc. All these activities will be prepared with the support and advice of ASPET.

• Attend the ASPET Annual Meeting at Experimental Biology '13. ASPET Fellows will attend the ASPET Annual Meeting in Boston in 2013 and any related policy program sessions assigned. They will meet with the ASPET Public Affairs Committee to discuss their experiences as a Fellow. Fellows will receive an ASPET travel award to attend the meeting.

Qualifications

The ASPET Washington Fellows Program is open to any graduate student, postdoctoral trainee, or researcher no more than 4 years past the completion of his/her postdoctoral training. Applicants must be members of ASPET in good standing and have a strong interest in science and its intersection with public policy. Fellows will be selected by the ASPET Public Affairs Committee.

Application Information

ASPET anticipates 5–10 Washington Fellows Program participants in 2013. Fellows serve one-year terms.

All applications must contain the following information and be submitted by October 1, 2012 as a single combined PDF:

• A letter (no more than two pages) from the applicant stating their interest in public policy and why they are interested in the ASPET Washington Fellows Program

• A curriculum vitae

• A letter of support from the candidate's mentor and/or department chair supporting the application. Incomplete applications and/or applications received after October 1, 2012 will not be considered.

Questions? Contact Jim Bernstein, ASPET Government & Public Affairs Director, at tel: 301-634-7062; **jbernstein@aspet.org**.

Integrated and Organ Systems Sciences

New Funding Opportunity

ASPET Graduate & Postdoctoral Award for Integrative Research in Pharmacology

Objective: The major goal of the ASPET Graduate & Postdoctoral Award for Integrative Research in Pharmacology (ASPET-IRP Award) is to provide support for graduate and postdoctoral trainees who are involved in active research projects that involve *in vivo* pharmacology or are focused on organ systems as an integral part of their research efforts.

Eligibility Guidelines: The ASPET-IRP Award will consider applications from research proposals submitted by graduate or postdoctoral students with demonstrated interest in *in vivo* pharmacology. Graduate and postdoctoral candidates must be members of ASPET and must conduct research at a U.S. academic institution. Postdoctoral applicants who have completed three or more years of postdoctoral training are not eligible.

Research Areas of Interest: Awards will be made to support training in *any* research area of interest. Selection of awards will be based on the depth of the *in vivo* component with clear evidence of an integrated, whole organ systems approach that also includes a pharmacological component. Applications without all of these components will not be considered.

Duration: No more than six awards will be made, each of which will be for one year duration. It is anticipated that the first awards will begin January 2013 and end December 2013.

Terms: The awards provide funding payable to the institution. The stipends may be supplemented with institutional funds or other research grants. No indirect costs are provided.

For Postdoctoral Awards:

- $30,000 stipend
- $2,000 supplies

For Graduate Student Awards:

- $20,000 stipend
- $2,000 supplies

Application Guidelines: The application deadline is October 15, 2012. Applicants will be notified by November 15, 2012 and awards will begin January 2013. Awardees will be expected to attend the Experimental Biology Meeting in the year of their award and will be honored at the ASPET Opening Awards Ceremony.

Applications should contain the following materials:

1. A letter from mentor or department chair supporting the candidate's application for the ASPET Graduate & Postdoctoral Award for Integrative Research in Pharmacology. The letter should: a) identify/acknowledge the mentor supervising the candidate's research; and b) identify existing levels of support for ongoing research.
2. If applicable, copies verifying the applicant's active (current for 2013) visa status, e.g., H1B1.
3. The applicant's curriculum vitae.
4. A research proposal no longer than 4 pages. The applicant can attach supplemental data if they wish.

Application materials should be sent (as a PDF or Word file) to **jbernstein@aspet.org**. Applications received after October 15 or incomplete applications will not be considered.

Questions? Contact **Jim Bernstein**: 301-634-7062 or **jbernstein@aspet.org**.

Social Media

by Gary Axelrod

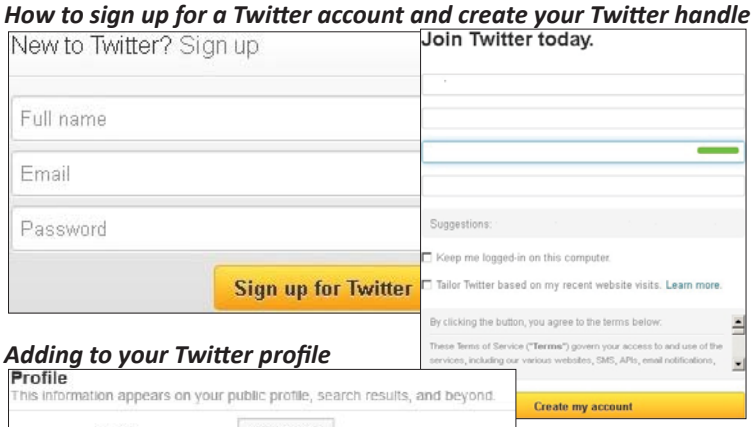
'How To' Tips for Twitter

Follow these tips, and you'll be tweeting in no time!

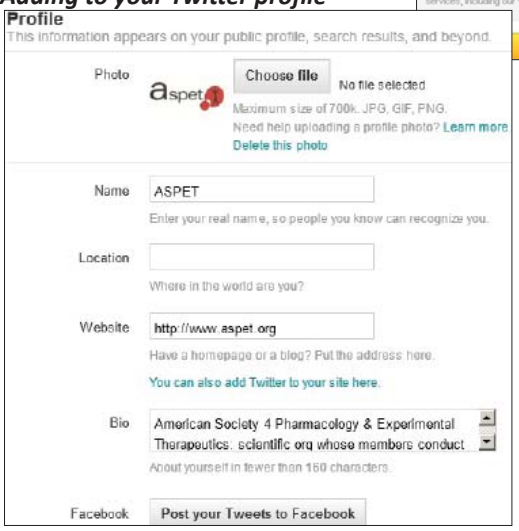
If you are interested in learning a new way to help shape policy matters, staying up-to-date with the news, following the bigwigs, and interacting with ASPET, Twitter is a great way to accomplish all of that. With Twitter, you can actually have a dialogue with newsmakers and newscasters. Below, you will find a step-by-step "how to" guide on Twitter. So, follow along and engage us in the Twitter-verse. For more information, visit **http://www.aspet.org/knowledge/social-media-and-other-electronic-resources/**. Happy tweeting!

The Basics of Twitter:

How to sign up for a Twitter account and create your Twitter handle

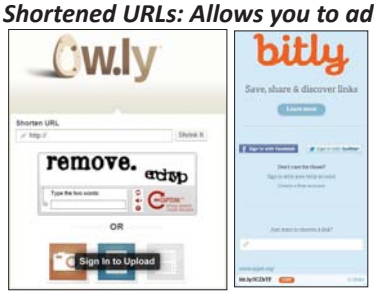


Adding to your Twitter profile



Sending a tweet

Shortened URLs: Allows you to add more text to your tweets.



Hashtags (#): Used for creating searchable topics on Twitter.

Explanations:

The first thing you need to do is head to **www.twitter.com** on the Web. Type in your name, email address and a password on the screen that greets you and click the "sign up" button. Create your password, and follow the prompts on the next screen, "Join Twitter today," to create your **Twitter handle** (a.k.a. account name) and click the yellow button. You will have to confirm your new Twitter account from an automatic email that Twitter will send to you. Twitter then asks you to pick five people/organizations to follow. You can do this or you can skip this step, but we'd love it if you typed "ASPET" in the search box, found our Twitter account "@ASPET," and then clicked on our "Follow" button.

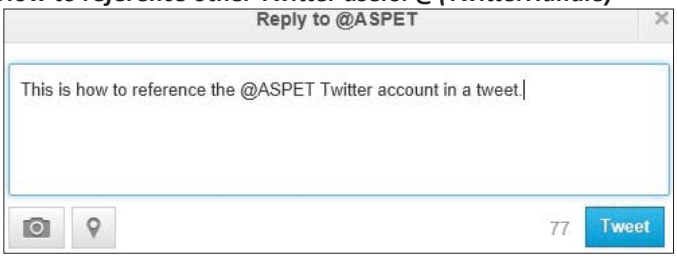
You are basically ready to tweet now. You can spruce up your profile if you so desire, adding a short 160-character biography, your location, your website, and a picture. You can even cross the "great divide" and elect to share your tweets on Facebook. If you are hoping to get better feedback from others on Twitter, it is best to have a filled out bio and profile picture posted. Now, that you're all set up and ready to tweet (to post messages on Twitter), here's the most basic rule: You are only allotted 140 characters per tweet, so in order to get the most out of Twitter, you have to learn the abbreviated lingo.

To create and send a tweet, click on the blue box with the white ink quill in the upper right-hand corner of any Twitter page. Then, you can tweet something simple to engage people. For example, in March 2013, ASPET could release a tweet saying, "#EB2013 is one month away. See you at @expbio www.experimentalbiology.org" Twitter is a great tool for promoting newsworthy items for your organization and engaging others to talk about these happenings, and the ability to link to websites lets you give the reader more information.

The following will help you stay within your 140 characters:
1. A URL is another name for a Web address.
2. Two examples of URL shorteners are ow.ly (**http://ow.ly**) and bit.ly (**https://bitly.com**).
3. Go to one of these websites, type in the full URL, and click the button that says "shorten" or "shrink it."
4. Click the aforementioned tweet-composing button, and copy and paste the shortened URL into your tweet along with a message that fits within the 140 character limit.

The **hashtag** allows your tweet topic to be searched. A hashtag is any Twitter text that follows a "#." The first character must be a letter, but after that, numbers are allowed. Apostrophes, hyphens, and all other symbols cannot be used in hashtags though. Typing "#ASPET" into the search feature atop the page, allows you to see recent comments about ASPET in which the tweeter used that hashtag. You can start topics by creating your own hashtag or add to topics that already exist by using the hashtag for that topic.

How to reference other Twitter users: @(TwitterHandle)



When you want to reference, reply to, or retweet the Twitter handle of another person or group, type the "@" followed by someone else's Twitter handle. If you want to reply to a tweet, move your mouse to the tweet you wish to reply to, and you will see the arrow on the screen become a hand. To type your reply, click the link at the bottom of that tweet that says "reply" and type your message. In your reply, "@(TwitterHandleYouAreReplyingTo)" will show up at the beginning of your tweet.

Using the search function on Twitter

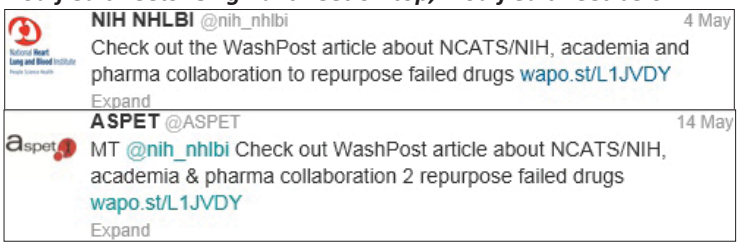
When you type "@" plus a Twitter handle into the site's search feature, you can track recent tweets in which that particular Twitter handle is mentioned. Similarly, when you type "#" plus a topic name that starts with a letter and doesn't have spaces or symbols, you can track recent tweets in which a certain hashtag is mentioned.

Retweets with the retweet button: Original tweet on top, retweet below.

When you **retweet** a message, you are sharing another's tweet with your list of followers on Twitter. There are three common ways to retweet a message. You can find a tweet that you would like to spread to your followers, and even if you are not following that particular Twitter handle or they aren't following you, you can hover your mouse over that particular tweet and hit the retweet button. The post then shows up in your tweets as a retweet with the original tweeter's Twitter handle above it and their profile picture beside it. You can also retweet a message by typing "RT @(TwitterHandle)" plus the content of the message.

Retweets with "RT": Original tweet on top, retweet below.

Modified tweets: Original tweet on top, modified tweet below.



If you want to send a retweet but are modifying the text of the original tweet, you should, out of common courtesy, write "MT @(TwitterHandle)" plus the content of the modified message to signal that you are posting a modification of someone else's tweet. MT signifies the posting of a **modified tweet**.

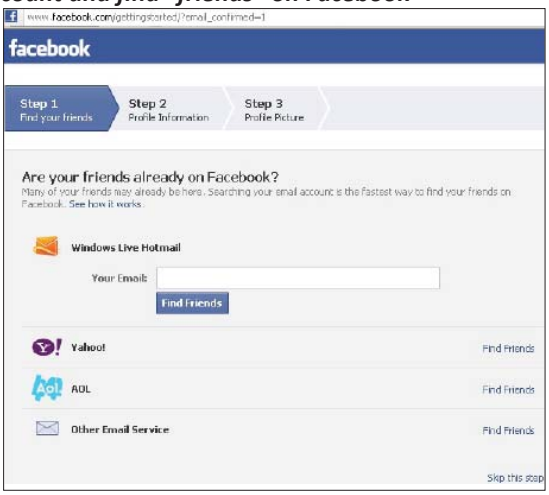
'How To' Tips for Facebook

A quick guide to getting started and connecting with others

If you are interested in learning a new way to connect with others personally and professionally and an additional way to engage with ASPET and see what's happening with organization initiatives, programs, and other members, Facebook can serve as a great interactive forum for you. The following tips will guide you through the sign-up and set-up process and show you how to start using this powerful social networking tool.
For more information, visit **http://www.aspet.org/knowledge/social-media-and-other-electronic-resources/**.

The Basics of Facebook:

How to sign up for a Facebook account and find "friends" on Facebook



Your main page upon logging in

Search for Facebook "friends" or places/ organizations/celebrities to "like."

An example of a Facebook news feed

Explanations:

Go to **www.facebook.com** on the Web. Type in your name, email address, and a password on the screen, in addition to your date of birth. The latter item is needed in order to control what features Facebook allows you to use. Following this, Facebook will probably send you an email to confirm your email address. Once you have clicked on the link in the email, you will be presented with the three-step screen (to the left) and asked if you want to "find friends." A Facebook friend is simply what your connection with another person on Facebook is called. If you choose to click the "Find Friends" button on this screen, Facebook will ask you for the password for your email account to search it for contacts who are on Facebook. Facebook is not able to access the password to your email account, so this is a safe feature. If you choose to skip this step, you will be prompted to go the next screen where you can choose to fill out some elements of your profile information, such as where you went to high school and college and where you work. The final step of signing up for an account asks you to post a picture of yourself.

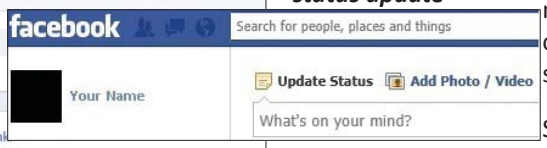
You are now officially on Facebook. Welcome to your news feed page. Once you have connected with friends, as well as the fan pages of organizations, places, and celebrities, you will see updates of information from them taking up most of the space in the center of the screen on this page.

Within the blue header bar atop the page, you will see a white box. Use this box to search for people, celebrities, places, or organizations. When you type something into the white box, Facebook's smart search feature will show results of your search dropping down from the search box. To "friend" another person, go to their Facebook page and click on the button towards the top that says "Add Friend." That person will have to confirm your request. To "like" an organization, place, or celebrity, go to their page and click the "Like" button. In Facebook lingo, the concept of "liking" an organization, place, or celebrity is the equivalent to "friending" a person on Facebook.

Once you have connected with friends and organizations on Facebook, their status updates will appear in the center of your main screen as a "news feed." You can even dictate a parameter by which to sort your news feed content. If you scroll to the top of the page, just above all of the status updates of those you are connected to, you will see the word "Sort." When you click on the word, you have the option to sort your posts by "Most Recent" or "Most Popular." Selecting "Most Recent" shows the most recent posts at the top. Selecting "Most Popular" puts the most liked and responded to posts at the top. The downside of the "Most Popular" sorting method is that you might miss a post that may be important to you but not as important to others. We recommend that you select "Most Recent" to make sure you catch ASPET's Facebook posts in your news feed.

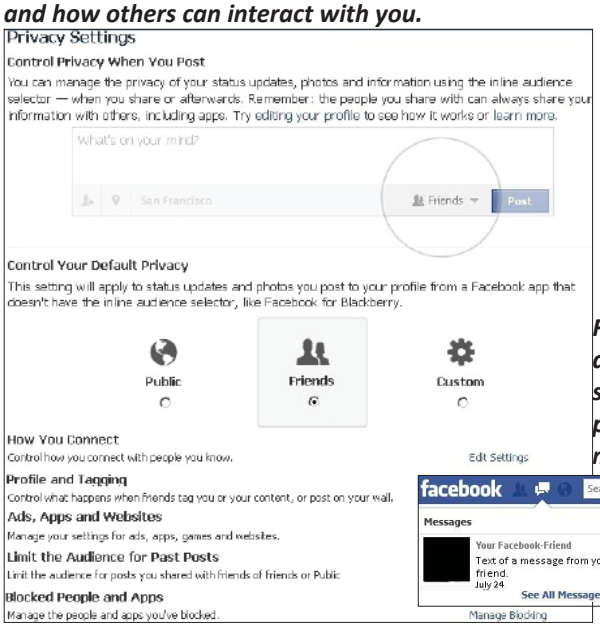
ASPET's Facebook wall

Where to type a status update



The menu to get to and tweak Facebook privacy settings

The privacy settings allow you to control who sees certain items and how others can interact with you.



Finding and sending private messages

ASPET's Facebook page

In addition to following others' news feeds, arguably the best part of Facebook is the "social" media aspect of it. You can engage your peers and organizations such as ASPET by commenting on, sharing, and liking our posts. A post is any sort of message that is written on someone's Facebook wall. A Facebook wall is merely what the space to write comments on and post pictures is called. To "like" someone's Facebook wall post or somebody's comment on a post, all you have to do is click on the word "Like" or the little "thumbs up" graphic at the bottom of the comment or wall post.

Towards the top of any of the pages associated with your Facebook profile, the box that allows you to type in a status update is perhaps the most integral part of connecting with others. To write a post on your Facebook wall, find the area atop your profile that says "Update Status" and type something in the box that reads, "What's on your mind?" You could say that you're tired, you just returned from an amazing vacation, you're looking forward to the next ASPET Annual Meeting at Experimental Biology 2013, or whatever is on your mind. Your status updates will appear on your friends' news feeds, so they can stay up-to-date with what you are posting.

Similarly, you can also post pictures and videos of family, friends, vacations, etc. by clicking on the "Add Photo / Video" link right next to the "Update Status" text. Then, just follow the prompts to upload your masterpieces. You can even upload multiple pictures as a digital photo abum by clicking on the subsequent option "Create Photo Album."

As a Facebook user, you will learn that the one main area you MUST stay on top of is the management of your privacy settings. Facebook tends to change this area somewhat frequently. You will often find news of what you need to update in your privacy settings from news outlets such as **http://news.yahoo.com/social-media/** or **http://mashable.com/social-media/**. In its current set-up, find the arrow in the blue bar at the top of the page on the right-hand side. Click the arrow, and select privacy settings.

You can control who sees your profile and who can post certain items on your profile by clicking on the "How You Connect" and "Profile and Tagging" sections. You can make your profile available to everyone on Facebook, or you can set it so that only friends or other specified groups of people can see it. The "Ads, Apps and Websites" section allows you to keep track of what applications (also known as "apps") you have allowed access to certain information in your Facebook profile. Setting this feature to disallow all applications is the safest option, thereby disallowing third-party access to information in your Facebook profile.

Facebook also allows you to send private messages to other people. Some people set up their profiles to only accept messages from people on their "friends" list, while others have a more liberal policy. To send a private message to a friend or anyone else who you are allowed to write privately, you can go to the blue bar at the top of the page and click on the middle of three icons next to the Facebook logo that appear either dark blue or white, and from that menu (pictured at left), click on the text "Send a New Message." Alternatively, you can go to a person's profile page and click on the button that says "Message."

There are many more things you can do on Facebook, but the best way to figure out the site is to log on and start exploring. Now that you know the basics of Facebook, check out ASPET's page, **https://www.facebook.com/ASPETpage**, and connect with us. After you click the "Like" button, move your mouse away and then hover over the button again without clicking anything. You will see a small menu. Click on "Show in News Feed" to ensure that you receive the latest ASPET updates on policy issues, events, and more.

Members in the News

Rick Neubig

ASPET President-elect **Richard R. Neubig, M.D., Ph.D.**, a Professor of Pharmacology and Associate Professor of Internal Medicine at the University of Michigan, has been named director of U-M's new Center for the Discovery of New Medicines (CDNM). Founded by multiple schools and departments at U-M, the CDNM is a collaborative university-wide effort that supports and funds drug discovery across various disciplines on campus that are involved in biomedical research. Through rapid-access seed grants and twice-yearly pilot grant competitions, the CDNM will fund crucial steps in the drug discovery process while linking facilities that were previously unconnected. This collaboration forges a greater cooperation between academic groups and biotech companies to help discover new transformational medicines. More information is available at **http://cdnm.lsi.umich.edu/**.

Debra Schwinn

On Wednesday, July 18, the University of Iowa named **Debra A. Schwinn, M.D.**, the next Dean of the University of Iowa Roy J. and Lucille A. Carver College of Medicine, effective November 1, 2012, pending approval by the State of Iowa Board of Regents. At present, Dr. Schwinn is Chair of the Department of Anesthesiology and Pain Medicine, the Allan J. Treuer Endowed Professor of Anesthesiology, and Adjunct Professor of Pharmacology and Genome Sciences at the University of Washington in Seattle. Donna Hammond, Ph.D., will continue to serve as Acting Dean of the UI Carver College of Medicine until Dr. Schwinn's appointment begins. Both Drs. Schwinn and Hammond are members of ASPET.

John McNeill

Professor and Dean Emeritus **John McNeill, Ph.D.,** of the University of British Columbia (UBC) Faculty of Pharmaceutical Sciences received an honorary degree from the the Faculty of Pharmaceutical Sciences and Biologics at Université Montpellier 1 in Montpellier, France. The honorary degree was given in recognition for McNeill's accomplishments as an educator, researcher, and administrator. Dr. McNeill has been a member of ASPET since 1970 and of the Faculty of Pharmaceutical Sciences at UBC since 1971.

Margarita Dubocovich

The University at Buffalo School of Medicine and Biomedical Sciences has named **Margarita L. Dubocovich, Ph.D.**, Senior Associate Dean for Inclusion and Cultural Enhancement. She also serves as the Chair of the University at Buffalo's Department of Pharmacology and Toxicology. Dr. Dubocovich is the President of ASPET's Upstate New York Pharmacology Society.

Michael Wood

Michael W. Wood, Ph.D., an External Collaborations Director in Neuroscience at AstraZeneca, coedited *Targets and Emerging Therapies for Schizophrenia* with Jeffrey S. Albert, a book that was just published by John Wiley & Sons, Inc. Wood has concentrated his research on neuroscience drug discovery, leading research efforts on novel therapeutics targeting schizophrenia.

Dennis Paul

On September 1, 2012, *The Baltimore Sun* wrote a feature article about **Dennis Paul, Ph.D.** In addition to his duties as Professor of Pharmacology at the LSU Health Sciences Center in New Orleans, LA, Dr. Paul serves as the starter for American Le Mans Series races. *The Sun* profiled Dr. Paul's advance planning to get to the race in Baltimore on Saturday, September 1, ahead of the Category 1 Hurricane Isaac that loomed over New Orleans. Dennis Paul serves on the Executive Committee of the Division for Neuropharmacology. A link to the article in *The Sun* can be found at **http://www.aspet.org/Page.aspx?id=3907**.

Staff News

Matthew Hilliker

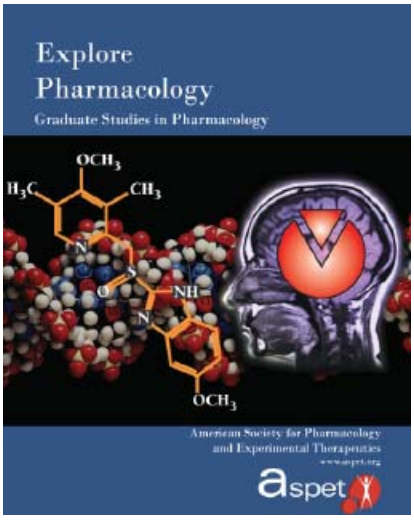
Matthew Hilliker joined ASPET as the Director of Accounting, Membership, & Subscriber Services in July 2012. He manages ASPET's accounting operations and is responsible for all financial activities of ASPET to ensure compliance with generally accepted accounting principles and government regulations. Matt also supervises and works with the Membership and Subscriber Services team. He received his B.S. in Accounting and Finance from the College of William & Mary. Matt has previously in non-profit accounting both for a CPA firm and as Assistant Controller for a non-profit organization. In his free time, he enjoys watching hockey and rooting for the Washington Capitals.

ASPET Staff Bowling Party

On Friday, August 3, the ASPET Staff took time out from the office in favor of a get-together at Bowl America in Gaithersburg, MD. The event served as a fun afternoon of getting to know co-workers better, enjoying conversation, knocking down pins, and eating greasy food.

ASPET Staff pose for a picture after a couple of games at the lanes.

Bowling trophy winners Angelique Raptakis, Jim Bernstein, Crystal Ledger, Rich Dodenhoff, and Matthew Hilliker pose with their prizes.



Order your copy of the 2012 *Explore Pharmacology* brochure

Explore Pharmacology is a great tool to get undergraduates and other students interested in pharmacology. If your academic institution has undergraduate science programs, *Explore Pharmacology* is a great resource to teach them about pharmacology and career opportunities within the field: **http://www.aspet.org/knowledge/pharmacology-resources/#Brochures**. To order multiple copies of Explore Pharmacology, please contact Pat Stoute (**pstoute@aspet.org**) or go to the ASPET Online Store, **http://www.aspet.org/store**.

New ASPET Members

Regular Members

Clement B. Alawa, National Animal Production Research Institute
Shaifali Bhalla, Midwestern Univ. Chicago College of Pharmacy
Rebecca M. Craft, Washington State Univ.
Alexander Dietrich, LMU-Munich
Edward J. Ishac, Virginia Commonwealth Univ.
Takahiro Iwamoto, Fukuoka Univ. Faculty of Medicine
Sarah C. Lummis, Univ. of Cambridge
Jason A. Mears, Case Western Reserve Univ.
Mohamed A. Morsy, Faculty of Medicine - El-Minia Univ.
Prakash S. Nagarkatti, Univ. of South Carolina School of Medicine
Vedavalli Pokala, Pacific Univ.
Brooks B. Pond, East Tennessee State Univ.
Rita Raddatz, Cephalon, Inc.
Amina M. Sallam, Dubai Pharmacy College
William A. Sather, Univ. of Colorado Denver/Anschutz Med. Campus
Rebecca P. Seal, Univ. of Pittsburgh
Natalie J. Serkova, Univ. of Colorado Denver/Anschutz Med. Campus
Jai M. Shin, UCLA
Douglas Sweet, Virginia Commonwealth Univ.
Kevin Thorneloe, GlaxoSmithKline Pharmaceuticals
Bennett Van Houten, Univ. of Pittsburgh
Sandeep S. Vansal, Touro College of Pharmacy
Nigel J. Waters, Novartis Institutes for Biomedical Research
Jennifer L. Whistler, Univ. of California, San Francisco
Shinji Yamazaki, Pfizer, Inc.
Haoming Zhang, Univ. of Michigan
Dafang Zhong, Shanghai Institute of Materia Medica

Affiliate Member

Bibu J. Kariyil, Aruna Natural Extracts Ltd.

Postdoctoral Members

Judith N. Alawa, Ahmadu Bello Univ.
Kathirvel Kandasamy, The Univ. of Tennessee Health Sci. Ctr.
Sai S. Koka, Virginia Commonwealth Univ.
Cibele S. Pinto, Univ. of Kansas Medical Center
Girija Raman, Louisiana State Univ. Hlth. Sci. Ctr.
Manish B. Shah, Univ. of California-San Diego
Elzbieta I. Stolarczyk, Univ. of Kentucky

Graduate Student Members

Ryan C. Bates, Univ. of Colorado Denver/Anschutz Med. Campus
Alex J. Brewer III, Baylor College of Medicine
Colleen M. Carey, Georgia Health Sciences Univ.
Eileen S. Carpenter, SUNY Stony Brook
Lies De Bock, Ghent Univ.
Victoria Fischer, Stony Brook Univ.
Elena N. Hambardjieva, Stony Brook Univ.
Aminu Ishaka, Univ. Putra Malaysia
Christian H. James, GlaxoSmithKline
Mary F. Keith, Philadelphia Coll. of Osteopathic Medicine - Georgia Campus
Ken Lee, Stony Brook Univ.
Carmine S. Leggett, Univ. of Louisville
Cindy V. Leiton, Stony Brook Univ.
Shu Meng, Temple Univ.
Jessica M. Murray, Saint Louis Univ.
Ashleigh E. Pulkoski-Gross, SUNY - Stony Brook Univ.
Katherine E. Ryland, Univ. of Michigan

Undergraduate Student Members

Seemaab Ali, Yale Univ.
Balyssa B. Bell, Grinnell College
Alexandra E. Bellem, Univ. of Kansas Medical Center
Nikki C. Boggess, Univ. of Kansas Medical Center
Kirby K. Bullock, LSUHSC Shreveport
Yashuan Y. Chao, Univ. of Colorado Denver
Yangmin Chen, Rutgers Univ.
Ellen Choi, Rutgers Univ.
Benjamin Cochran, Vanderbilt Univ.
Talia G. Cohen, Univ. of Buffalo
Brianna L. Conley, Brigham Young Univ.
Jordan L. Daugherty, Univ. of Toledo
Allison M. Dugan, The Ohio State Univ.
Jacob Elam, Univ. of Tennessee
Lobna Eldasher, Rutgers Univ.
Gloria Felix, Hunter College
Lindsay Garcia, California State Univ., Stanislaus
Jesus A. Gastelum, San Diego Mesa College
Khushwinder K. Gill, California State Univ. of Bakersfield
Mohan Govindraj, Rutgers Univ.
Matthew Hartzell, DePaul Univ.
Megan A. Hemmrich, Univ. of Kansas Medical Center
Jenna L. Hirsch, Metropolitan State College of Denver
Brittany M. Hollister, Rollins College
Cassie L. Huckabee, Lyon College
Patrick D. Hyatt, Univ. of Kansas Medical Center
William Hyatt, Hendrix College
Daniela Janevska, Benedictine Univ.
Samantha L. Ketcham, Univ. of Texas Hlth. Sci. Ctr. San Antonio
Amanda L. Kleeman, Univ. of Michigan
Vani Kumaran, Rutgers Univ.
Andriy Kuzmov, Rutgers Univ.
Amanda Labuza, Rensselaer Polytechnic Institute
Christopher Lau, Univ. of Kansas Medical Center
Tam M. Le, Univ. of Arizona
Charles Lee, Rutgers Univ.
Xiao Liang, Univ. of Massachusetts at Amherst
Chelsea P. Liebowitz, Univ. of Michigan
Jason Ma, SUNY-Buffalo
Christian R. Marks, Northwestern State Univ. of LA

Raechel E. McKinley, North Carolina Agricultural & Technical St. Univ.
Safia F. Nawaz, Hendrix College
Caitlin A. Nicholson, Dartmouth College
Marissa Nimnual, Rutgers Univ.
Valerie M. Olson, Colorado State Univ.
Abigail Overacre, Univ. of Oklahoma
Okari O. Owate, SUNY at Buffalo
Ji Woong Park, Washington & Jefferson College
Roberto Perez, Rutgers Univ.
Corey S. Post, Univ. of Illinois at Urbana-Champaign
Ashley Press, High Point Univ.
Verma Purnima, Rutgers Univ.
Gregory W. Roloff, Univ. at Buffalo
Julie Safirstein, Rutgers Univ.
Tatiana Shaurova, Univ. at Buffalo
Andrew Shen, Rutgers Univ.
Steven H. Shen, Univ. of Kansas Medical Center
Matthew K. Stern, Univ. of Michigan
Theresa A. Ten Eyck, Univ. of Colorado Denver Anschutz Med. Ctr.
Daniel J. Troup, Univ. of Arizona College of Pharmacy
Qi Wang, Rutgers Univ.
Brittany M. Watson, Univ. of Kansas Medical Center
Brittany D. Weems, Univ. of Texas Health Science Center
Elizabeth S. Williams, Univ. of Michigan
Sarah C. Wyss, Ohio Univ.
Dahea You, Rutgers Univ.
Carolyn V. Zielinski, The Univ. of Toledo
Abebayehu L. Zula, Univ. of Colorado Denver

In Sympathy

ASPET notes with sympathy the passing of the following Members:

Avram Goldstein, M.D.

Dora B. Goldstein, M.D.

Obituary

Avram Goldstein (1919 - 2012), founder of ASPET's *Molecular Pharmacology* journal

Avram Goldstein, 92, an emeritus professor of pharmacology at the Stanford University School of Medicine and one of the discoverers of endorphins in the late 1970s, died June 1 after a long decline.

Among his accomplishments, Goldstein helped orchestrate the medical school's emergence in the 1950s as a powerhouse for medical research by recruiting its faculty and shaping its curriculum, wrote a pharmacology textbook, founded a journal, organized California's first major methadone program and made breakthrough discoveries in his lab about how narcotic drugs work in the brain.

As a 35-year-old assistant professor at Harvard in 1955, Goldstein accepted an offer to chair Stanford's pharmacology department and hire new faculty for a research-oriented medical school that the university planned to build on its sprawling campus in Palo Alto. At that time, the medical school was based in San Francisco and focused training on preparation for medical practice — as did most medical schools of the day. Goldstein recruited other leading scientists to Stanford, notably by telling famed biochemist Arthur Kornberg, MD, that if he liked his current department at Washington University in St. Louis so much, "Fine — bring them all." Stanford's medical school moved to the Palo Alto campus in 1959, and its newly arrived faculty spent decades in the middle of the revolution in molecular biology that followed on the discovery of DNA.

"Stanford Medical School, as we know it today, is the result of Avram Goldstein's leadership and vision," said Dean Philip Pizzo, MD. "He has left an endurable mark on the institution and the generations of individuals he worked with and trained. Of course his name will forever be associated with Stanford because of the professorship in his name — but more so because of the impact he had on individuals and our communities, locally and globally."

Goldstein was born July 3, 1919, in New York City to Israel and Bert Goldstein and had a younger sister, Vivian. Growing up in Manhattan during the skyscraper-building boom and the Great Depression, he attended the progressive Walden School. The son of a prominent rabbi and Zionist, Goldstein became an atheist in childhood and dedicated his life to science. He was admitted to Harvard at age 15 but deferred college for a year and worked on a kibbutz in Palestine (although later, as an adult, he did not participate in Jewish life). After graduating from Harvard in 1940 and Harvard Medical School in 1943, he served in the U.S. Army in Colorado during World War II, treating soldiers returning from Europe. Goldstein's first wife, Naomi Friedman, died in a car accident in 1946. He married Dora (Dody) Benedict, who would become a distinguished pharmacologist and Stanford professor herself, in 1948. During 62 years of marriage, they raised four children, and spent sabbatical years in Edinburgh, Copenhagen and Cambridge, England.

While department chair (1955-70), Goldstein studied the effects of caffeine in human subjects, founded the journal *Molecular Pharmacology* (1965), wrote *Biostatistics* (1967) and co-authored the textbook *Principles of Drug Action* (1968). In 1969, wanting to do socially meaningful work, he began studying opiates such as morphine and heroin at a time when these drugs were ravaging American cities but nobody understood their effects in the brain. Goldstein announced to his lab staff one day, "We're going to switch all the research we're doing, quit the microbial stuff ... and apply for new grants to work on opiates." He developed the methodology for studying how molecules bind to opiate receptors in the brain, a key step in the search for the endorphins.

In the 1970s Goldstein worked doggedly to isolate and identify the chemical structure of an endorphin receptor and then the endorphin itself. At one point his lab spent four years turning tons of pig pituitaries into 2 micrograms of purified endorphin. (He posted on the wall of the lab the sheet music for He Shall Purify from Handel's *Messiah*.) The molecule he thus discovered was one of the major endorphins, which he named dynorphin because of its high potency. However, he lost the friendly competition to discover the first endorphins (the enkephalins).

Simultaneously with his lab research, Goldstein worked directly with heroin addicts in San Jose, where he organized California's first major methadone clinic in the early 1970s. He wanted to learn about the realities of heroin addiction and to measure scientifically the effectiveness of methadone treatment. Over the years, Goldstein advised officials on drug policies, generally advocating a public-health, harm-reduction approach. He helped develop urine tests that identified returning Vietnam veterans addicted to heroin so they could receive treatment before being discharged. Goldstein's book *Addiction* (1994; 2001) explained drug addiction, from biology to government policy, for a broad audience. He consulted for biotech industry in Silicon Valley, serving as scientific advisor to several companies. Thus his work ran the spectrum from basic research to real-world, applied science. These came together in 1974 when Goldstein established the Addiction Research Foundation next door to Stanford, housing lab research, human-subjects research and treatment of heroin addicts.

Biochemist and Nobel laureate Paul Berg, PhD, who was among the faculty who came to Stanford from Washington University with Kornberg, saw Goldstein as a man who acted on what he believed, and persisted even when the going was tough. "He'd never take no for an answer," said Berg, who remembers Goldstein's recruiting visits to St. Louis, including one especially persuasive encounter when he pulled out a floor plan showing one floor was completely open, saying they could do anything they wanted with it.

Goldstein also led the design of the school's new curriculum taking effect in 1959, which aimed to cover the required ground but to remain flexible enough to maximize opportunity for students to do whatever interested them the most. Students were allowed to take a large number of electives, and they were given lab space of their own. And, contrary to the national trend, which was toward reducing the time spent in medical school, Stanford extended the time from the standard four years to five.

"Avram was a tough mentor in the sense that he had high expectations and standards — but he was also exceedingly fair. I regard it as an incredibly lucky stroke that I ended up stumbling into his lab," recalled Charles Weitz, MD, PhD, a professor of neurobiology at Harvard Medical School who from 1984-88 was a graduate student in the Goldstein lab, which was a formal, serious place. "Clearly, being in his lab was the formative thing that influenced how I think about science and how I train people in my lab now."

Weitz said Goldstein taught students how to be objective about their work. "What that really means is you have to disentangle your hopes for a result from what the data were actually telling you. This is more difficult than it sounds."

Goldstein's colleagues remember him as a man who not only spoke out about his convictions, but acted on them.

"He was courageous and was an activist — that was his personality," said Berg. "He was in the forefront of every progressive movement — during the Vietnam War uproars on campus, he led student protests." He also fought hard to set up the methadone clinics, said Berg, which were not welcomed by the community. "He did not just sit back and watch things go by. If he was stymied, he'd fight very hard to get what he thought was right."

Goldstein embraced the California lifestyle, driving a convertible and holding lab meetings at home by his swimming pool. He was passionate about piloting small airplanes — even moonlighting as an instrument flight instructor and writing several books about flying. He loved opera, and was fascinated by southwest American Indian cultures.

He won the Benjamin Franklin Medal in Life Science (1980) and major awards in pharmacology. He was elected to the National Academy of Sciences and its Institute of Medicine. He published more than 360 research articles.

In the 1970s, Goldstein was treated for lymphoma, one of the first patients to receive radiation, and recovered fully. However, he was confined to a wheelchair in his last decade, after a spinal-cord injury, and relied on his longtime caregiver Mara Passi. He is survived by his children, Margaret Wallace of Longmont, Colo., Daniel Goldstein of Port Townsend, Wash., Joshua Goldstein of Amherst, Mass., and Michael Goldstein of San Francisco; and five grandchildren. He was pre-deceased by his sister, Vivian Olum, in 1986, and his wife, Dora, in October 2011.

Both the family and Stanford's medical school are planning memorials.

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Division News

Behavioral Pharmacology Division

2012-2013 Executive Committee

Leonard Howell, Chair
Paul Czoty, Secretary/Treasurer
Lawrence P. Carter, Councilor
Wouter Koek, Councilor
Bruce Mandt, Postdoctoral Representative
James E. Barrett, ASPET Council Liaison
Christine K. Carrico, Staff Liaison

Cardiovascular Pharmacology Division

2012-2013 Executive Committee

Stephanie W. Watts, Chair
John C. Kermode, Past Chair
Nancy L. Kanagy, Secretary/Treasurer
David B. Averill, Secretary/Treasurer-elect
William M. Armstead
Alan Bass
Dayue Duan
Ross D. Feldman
Steven P. Jones
Richard H. Kennedy
Fadi T. Khasawneh
David D. Ku
Benedict R. Lucchesi
Jeffrey R. Martens
Mariana Morris
Carrie A. Northcott
Hemal H. Patel
Nancy J. Rusch
Hossam A. Shaltout
Hugo M. Vargas
Sarah M. Schumacher, Student Representative
Richard R. Neubig, Council Liaison
Christine K. Carrico, Staff Liaison

News

The Awards Committee, Chaired by Nancy Rusch, is pleased to announce that the Paul M. Vanhoutte Distinguished Lectureship in Vascular Pharmacology is now fully endowed. Originated by David Ku, the lectureship is now the first endowed lectureship in ASPET's history. Our thanks to all who donated to this important event. The next Paul M. Vanhoutte Distinguished Lectureship will be in 2014, with applications due in September 2013.

At EB 2012, Fadi Khasawneh spearheaded a special event at the Cardiovascular Pharmacology mixer. He pulled together many of the trainees who have won our Best Abstract Competitions, given that EB 2012 was the 10th year the Division had supported these activities.

Past and present winners of the Cardiovascular Pharmacology Division's Best Abstract Competition celebrate the 10th year anniversary of the Cardiovascular Pharmacology Trainee Showcase.

Cardiovascular Pharmacology Division Programming for the ASPET Annual Meeting at EB 2013

Symposium title: **Orthostatic intolerance: Insights into pharmacologic, physiologic and gender issues**
Submitted by: Julian Stewart, M.D., Ph.D. and Amy Arnold, Ph.D.
Co-chairs: Julian Stewart, M.D., Ph.D. and Amy Arnold, Ph.D.

Talk 1: *Physiologic insights into postural fainting*
Speaker 1: Roger Hainsworth, M.B., Ph.D., D.Sc.

Talk 2: *Influence of gender on orthostatic regulation: Why women?*
Speaker 2: Qi Fu, MD, Ph.D.

Talk 3: *Sympathetic nervous system reactivity in postural syncope and postural orthostatic tachycardia syndrome*
Speaker 3: Elisabeth Lambert

Talk 4: *Orthostatic intolerance and chronic fatigue syndrome*
Speaker 4: Peter Rowe, M.D.

Symposium title: **Innate immunity and cardiovascular disease: Unfolding the therapeutic potential of toll-like receptors**
Submitted by: R. Clinton Webb and Styliani Goulopoulou
Co-chairs: R. Clinton Webb and Styliani Goulopoulou

Talk 1: *TLR signaling: Innate immune sensing and response*
Speaker 1: R. Bruce Beutler, M.D.

Talk 2: *"Shall I respond?": DANGERous questions and answers*
Speaker 2: Q. Polly Matzinger, Ph.D.

Talk 3: *Doubled-stranded RNA receptors in pregnancy-induced hypertension*
Speaker 3: Brett Mitchell, Ph.D.

Talk 4: *TLRs: New therapeutic targets for treating atherosclerosis*
Speaker 4: Claudia Monaco

Symposium title: **Local Ca2+ signals in the endothelium: Key regulators of vascular function and dysfunction**
Submitted by: Swapnil K Sonkusare, Ph.D.
Co-chairs: Mark T. Nelson and Robert M .Bryan, Jr.

Talk 1: *Conducted vasodilation in resistance arteries: Ca2+ signaling between endothelial cells*
Speaker 1: Steven S. Segal, Ph.D.

Talk 2: *Blood flow mediated dilation in small mesenteric arteries: role of endothelial Ca2+ signaling*
Speaker 2: David X. Zhang, Ph.D.

Talk 3: *Differential regulation of SK and IK channels during endothelium dependent hyperpolarization*
Speaker 3: Kim A. Dora, Ph.D.

Talk 4: *Elementary TRPV4 Ca2+ signals regulate endothelium dependent vasodilation*
Speaker 4: Swapnil K. Sonkusare, Ph.D.

Talk 5: *Endothelial Ca2+ wavelets and myoendothelial feedback*
Speaker 5: Donald G. Welsh, Ph.D.

The Cardiovascular Pharmacology Division continues its support of the Best Abstract Competition. Abstracts should be submitted through EB (same deadline), and application information will be available on our website (**http://www.aspet.org/Cardiovascular_Pharmacology/Home/**).

The Cardiovascular Pharmacology Division will have an executive committee meeting, business meeting, and mixer at EB 2013. Once finalized, these dates will be posted on the Division website. Come join us in support of the Division and cardiovascular science.

Looking Ahead and Getting You Involved!

Submit your symposium for consideration for EB 2014! This meeting will be held in San Diego. ASPET has posted online forms that can be used for symposium submission (**http://www.aspet.org/division-info/symposium-sponsorship/guidelines/**). We encourage you to contact our programming committee to discuss tips for a successful submission and consideration of your symposium.

What would be helpful for you to see on the Cardiovascular Pharmacology Division website? Please contact Stephanie Watts (**wattss@msu.edu**) with ideas and comments. We are always looking for ways to improve and serve you better.

Drug Discovery and Development Division

2012-2013 Executive Committee

Kenneth Tew, Chair
Donald Mattison, Chair-elect
Michael Jarvis, Past Chair
Tim Esbenshade, Secretary/Treasurer
Robert Leadley, Secretary/Treasurer-elect
Tom Parry, Past Secretary/Treasurer
Robert Caldwell
Rebecca Roof
Poulomi Acharya, Postdoctoral Representative
Bradford Fischer, Postdoctoral Representative
John Lazo, Council Liaison
Christine K. Carrico, Staff Liaison

News

ASPET Council approved a name change for DDDRA (Drug Discovery, Drug Development and Regulatory Affairs) to DDD (Drug Discovery and Development). This is to simplify and take into account the fact that regulatory affairs are already an integral part of DDD. The focus and approach of the division remain unchanged.

Drug Metabolism Division

2012-2013 Executive Committee

Wayne Backes, Chair
Jeffrey Jones, Chair-elect
Hollie Swanson, Past Chair
Marion Sewer, Secretary/Treasurer
Nina Isoherranen, Secretary/Treasurer-elect
Deepak Dalvie, Past Secretary/Treasurer
Lauren Aleksunes, Councilor
Aiming Yu, Councilor
Kenneth E. Thummel, Council Liaison to the Division
Edward T. Morgan, Ex Officio
Christine K. Carrico, Staff Liaison

Letter to Drug Metabolism Division Members

Colleagues,

There are several events and opportunities in the Drug Metabolism Division that are scheduled for the coming year. These are summarized below. This message has been posted on the Division Website, so that you can use it for reference (**http://www.aspet.org/DrugMetabolismPage.aspx?id=3684**).

1. ASPET Division for Drug Metabolism Early Career Achievement Award – This award was established in 2006 to recognize excellent original research by early career investigators. To be eligible, the nominee needs to have received their final degree after December 31, 1998 (i.e., be within 15 years of their final degree). The nominations will consist of:

a. At least two letters of support
b. A summary describing the importance of the nominee's research contributions (limit 2 pages)
c. A biographical sketch of the candidate
d. Their CV and publication list
e. Copies of the five most significant published papers authored by the candidate.

If you would like to nominate someone for the award, the deadline for submission of the packet is October 5, 2012, and it must be submitted electronically to **awards@aspet.org**. More detailed information can be found at **http://www.aspet.org/Drug-Metabolism/Early-Career-Achievement-Award/** on the Division website.

2. 2012 Election Results – Dr. Jeffrey Jones of Washington State University was elected as the Chair-elect and Dr. Nina Isoherranen of the University of Washington was elected as Secretary/Treasurer-elect. We would like to thank Dr. Steve Leeder, Dr. Emily Scott, and Xiaobo Zhong who have completed their terms as Past-Chair, Past-Secretary/Treasurer, and Councilor. For more information, please visit: **http://www.aspet.org/DrugMetabolismPage.aspx?id=2468**.

3. Summary of EB2012 – EB2012 was very successful, with several Division-sponsored symposia. On behalf of the Executive Committee and the Division membership, we would like to again congratulate **Dr. Yuichi Sugiyama (from the Univ. Tokyo) as the recipient of the B.B. Brodie Award, http://www.aspet.org/DrugMetabolismPage.aspx?id=3690**. We would also like to congratulate **Dr. Kyoung Noh (Seoul National University) as the Gillette Award winner in the area of Drug Metabolism (http://www.aspet.org/DrugMetabolismPage.aspx?id=3692)**, and **Dr. Xuena Lin (Novartis Institutes for Biomedical Research) as the winner in the area of Metabolism and Pharmacokinetics**. Additional information can be found on the Division website: **http://www.aspet.org/Drug_Metabolism/Home/**.

We would also like to acknowledge the winners of the Student and Postdoc Poster Awards (**http://www.aspet.org/DrugMetabolismPage.aspx?id=3703**). The winners for the postdoc competition were: first place – **Manish Shah (University of California, San Diego)** on *Dual Ligand Complexes of Human Cytochrome P450 2B6 and Rabbit Cytochrome P450 2B4 with Amlodipine Reveal Substrate Access Channels into the Active Site*; second place – **Aik Jiang Lau (University of British Columbia)**, *Selective Activation of Human Pregnane X Receptor, Glucocorticoid Receptor, and Constitutive Androstane Receptor by Individual Ginkgolides*; and third place – **Dan Li (University of Kansas Medical Center)**, *RNA-Seq*

identifies novel alternative transcripts of cytochrome P450s in human hepatocytes. The winners of the graduate student competition are as follows: first place – **Kelly Clapp (University of Michigan)**, *Ubiquitination of Neuronal Nitric Oxide Synthase in the P450 Oxygenase and Calmodulin-binding Domain*; second place – **Lei Li (Wadsworth Center, New York State Department of Health)**, *Characterization of a Cyp2a(4/5) bgs-null Mouse Model: Role of CYP2A and CYP2B in Nicotine Metabolism*; and third place – **Yanhui Li (Johns Hopkins University)**, *P450 3A5 is primarily responsible for the formation of the most abundant oxidative metabolite of maraviroc*.

Dr. Lin presented this work at the platform session and accepted the award in pharmacokinetics. Dr. Swanson presented the award.

Drs. Noh and Kim accepted the award in drug metabolism from Dr. Swanson.

The Drug Metabolism/Toxicology Division Mixer during the ASPET Annual Meeting at EB 2012.

Additional information about Drug Metabolism Division events at the ASPET Annual Meeting at EB 2012 can be found on the Drug Metabolism Division website: **http://www.aspet.org/Drug_Metabolism/Home/**.

4. Preview of Division Programming for EB2013 in Boston – The Experimental Biology Meeting for 2013 will be held jointly with the British Pharmacological Society from April 20 – 24, 2013. Several Symposium and Platform Sessions are planned for the meeting, including:

a. *Correlating structure and function of drug metabolizing enzymes: An ongoing challenge: Co-chairs – Emily Scott, University of Kansas and Eric Johnson, Scripps Res. Inst.; Co-sponsoring division: TOXICOLOGY.*

b. *Epigenetic control of drug metabolism and transport: Chairs – Aiming Yu, SUNY-University at Buffalo and Yoichi Osawa, University of Michigan; Co-sponsoring Divisions: DRUG DISCOVERY AND DEVELOPMENT; INTEGRATIVE SYSTEMS, TRANSLATIONAL AND CLINICAL PHARMACOLOGY; TOXICOLOGY.*

c. *The Drug Metabolism Division Platform Session, which will include talks selected from the submitted abstracts as well as the winners of the James R. Gillette Best Paper Awards from the Journal Drug Metabolism and Disposition* **(http://dmd.aspetjournals.org/)**.

d. Additionally, we will be co-sponsoring a symposium with the Divisions for Neuropharmacology; Integrative Systems, Translational and Clinical Pharmacology; Molecular Pharmacology; and Toxicology entitled, “New kids on the block: Organic cation transporters and plasma membrane monoamine transporter in neurodegenerative, psychiatric and addictive disorders."

Additional information on this meeting can be found on the ASPET website **http://www.aspet.org/EB2013/**.

5. Symposia for EB 2014 – EB 2014 will be held in San Diego, CA from April 26 – 30, 2014. Program planning for the annual meeting has been modified in order to identify topics that are hot and more likely to draw a good audience. To accomplish this goal, the Program Committee will meet at the end of the EB 2013 Meeting to discuss ideas for Symposium topics. If you have ideas for a symposium for EB 2014, feel free to contact Dr. Jeff Jones **(jpj@wsu.edu)**, Dr. Hollie Swanson **(hswan@uky.edu)**, Dr. Wayne Backes (e-mail address below) or any of the members of the Executive Committee for the Drug Metabolism Division.

Finally, if you have any comments or suggestions for the division or the website, please feel free to contact us either by email or by phone.

Wayne L. Backes, Ph.D.
Chair, Drug Metabolism Division
ASPET
Phone: (504) 568-6557
wbacke@lsuhsc.edu

Marion Sewer
Secretary/Treasurer, Drug Metabolism Division
ASPET
Phone: (858) 822-5283
msewer@ucsd.edu

Integrative Systems, Translational and Clinical Pharmacology Division

2012-2013 Executive Committee

Hamid I. Akbarali, Chair
Ismail Laher, Chair-elect
Dennis C. Marshall, Past Chair
Jeffrey Paul, Secretary/Treasurer
Michael A. Holinstat, Secretary/Treasurer-elect
Andrea Gaedigk, Past Secretary/Treasurer
Darrell R. Abernethy
Ozhan Ocal, Student Representative
Ross Corriden, Postdoctoral Representative
Stephen M. Lanier, Council Liaison
Christine K. Carrico, Staff Liaison

News

Dr. Dennis Marshall, Past Chair iSTCP was appointed for a three-year term to the FASEB Finance Committee.

ISTCP will introduce a "HOT TOPICS" Symposium on breakthrough technologies at EB 2013: **A (r)evolution in drug discovery & therapy: From Organs on a chip and 3D biomimetics to regenerative pharmacology**. Co-Chairs for the symposium are Dr. George Christ, Wake Forest Institute for Regenerative Medicine at the Wake Forest School of Medicine and Dr. Sitta Sittamplam, NIH Center for Translational Therapeutics.

New technologies and research paradigms are being rapidly applied to the pharmacological arena with the overall goal of increasing both the efficiency of the drug discovery process and the safety and efficacy of the resulting therapeutics. Moreover, the parallel development of novel biomaterials, drug discovery, and drug delivery systems/vehicles is increasing the range of potential therapeutics that can be utilized. This symposium will provide a cutting edge look at these new developments. The goal is to review their implications for developing new insights into drug action, as well as providing improved, potentially curative (regenerative pharmacology), therapies for the treatment of tissue, and end organ disease/dysfunction.

The ISTCP Division is currently seeking members to join the Executive Committee as Councillors. Please contact Dr Hamid I. Akbarali, Virginia Commonwealth University (**hiakbarali@vcu.edu**), if you are interested.

Molecular Pharmacology Division

2012-2013 Executive Committee

James Porter, Chair
John Tesmer, Chair-elect
Randy Hall, Past Chair & Program Committee Representative
David Port, Council of Division Chairs Representative
Val Watts, Secretary/Treasurer
Rennolds Ostrom, Secretary/Treasurer-elect
Carmen Dessauer, Past Secretary/Treasurer
Angeline Lyon, Postdoctoral Representative
Richard R. Neubig, Council Liaison
Joe Blumer
Roger Sunahara
Gregory Tall
Yaping Tu
Qin Wang
Guangyu Wu
Jin Zhang
Christine K. Carrico, Staff Liaison

News

The Molecular Pharmacology Executive Committee would like to remind Division members that applications for EB 2013 Postdoctoral Scientist (**http://www.aspet.org/awards/postdoctoral-scientist/**) and/or Graduate Student Best Abstract Awards (**http://www.aspet.org/awards/grad-student-abstract/**) are due November 14, 2012.

2012 Great Lakes GPCR Retreat

The 2012 Great Lakes GPCR Retreat will be held October 17-19. Registration information can be found here: **http://www.gpcr-retreat.com/**.

Molecular Pharmacology of GPCRs, 2012

The Molecular Pharmacology of GPCRs 2012 meeting will be held December 6-8 in Melbourne, Australia. Further information on the meeting and registration can be found at: **http://www.gpcrmeeting.com**.

Neuropharmacology Division

2012-2013 Executive Committee

Lynette C. Daws, Chair
Laura M. Bohn, Chair-Elect
Margaret E. Gnegy, Past Chair
Eric L. Barker, Secretary/Treasurer
Lakshmi A. Devi, Secretary/Treasurer-elect
Linda Dykstra, 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
Jason M. Kehrl, Student Representative
Vikas V. Dukhande, Postdoctoral Representative
Spring R. Farrell, Postdoctoral Representative
Lynn Wecker, ASPET Council Liaison
Christine K. Carrico, Staff Liaison

Pharmacology Education Division

2012-2013 Executive Committee

Lynn M. Crespo, Chair
George A. Dunaway, Past Chair
Rajasekaran Senthil S. Kumar, Secretary/Treasurer
Loraine S. Dieckmann, Councilor
Kelly Karpa, Councilor
Mark M. Knuepfer, Councilor
Kathryn K. McMahon, Councilor
Shafiqur Rahman, Councilor
Ellen A. Walker, Councilor
Helmut Gottlieb
Patricia B. Williams
Brian M. Cox, Council Liaison
Joey V. Barnett, Ex Officio
John L. Szarek, Outside Liaison
Robert J. Theobald, Outside Liaison
Christine K. Carrico, Staff Liaison

Toxicology Division

2012-2013 Executive Committee

Jack A. Hinson, Chair
Rick G. Schnellmann, Chair-elect
Patricia E. Gainey, Past Chair
Monica Valentovic, Secretary/Treasurer
Laura James, Secretary/Treasurer-elect
Todd D. Porter, Past Secretary/Treasurer
Jessica A. Morgan, Student Representative
Mary E. Vore, Council Liaison
Christine K. Carrico, ASPET Staff Liaison

News

The Chair-elect of the Division of Toxicology is **Rick Schnellmann** from the Medical University of South Charleston. The Secretary/Treasurer-elect is **Laura James** of the University of Arkansas for Medical Sciences.

The program for the EB 2013 meeting is currently being developed, and it appears that our division will co-sponsor two symposia. Also, as Chair-elect Rick Schnellmann is organizing a Division of Toxicology symposium for EB 2013 entitled *The Mitochondrion as a Toxicological and Pharmacological Target*.

On June 26, the division submitted a letter to the membership exploring their interest in a named lectureship to be presented at the Experimental Biology meeting. From that, we received a number of very positive replies. However, it was pointed out by some members that the required $50,000-$100,000 endowment would be difficult to raise in the current economic climate. This issue will continue into the future.

On The Web

Join the conversation online!

ASPET is online! Join us on Facebook, Twitter or LinkedIn for the latest in news, discussions and events. Discuss hot topics with your peers, check out pictures from ASPET events and find resources to help in finding a job or a graduate program.

www.facebook.com/ASPETpage
www.twitter.com/ASPET
www.linkedin.com/groups/American-Society-Pharmacology-Experimental-Therapeutics-3320218

Chapter News

Mid-Atlantic Pharmacology Society

Mid-Atlantic Pharmacology Society 2012 Fall Meeting: October 25, 2012: Epigenetic Targets and Novel Therapeutics

The Mid-Atlantic Pharmacology Society 2012 annual meeting will be on Thursday, October 25, 2012 at the GlaxoSmithKline Upper Providence Research Campus in Collegeville, PA. GlaxoSmithKline will be our host. C. David Allis, Ph.D., Rockefeller University will present the keynote address: "Beyond the Double Helix: Varying the 'Histone Code'. The theme of epigenetics will be continued in the afternoon by the other three guest speakers. The other guest speakers are Johnathan Whetstine, Ph.D., Harvard Medical School/Mass. General Hospital, "Looking Through the Eyes of Histone Demethylases: The Biological Impact of Lysine Methylation"; Victoria Richon, Ph.D., Epizyme, "Targeting Chromatin Modifying Enzymes in Cancer: Lessons Learned and Path Forward"; and Peter Tummino, Ph.D., GlaxoSmith-Kline, "A Second Generation of Epigenetic Agents for Oncology."

The morning session will feature research poster presentations by undergraduate, graduate, and professional students, postdoctoral fellows, and research associates. Members of the MAPS Board of Councilors serve as coordinators and judges. Two trainees will be invited to give 10-minute oral presentations during the symposium. The poster session will be followed by the keynote address and presentation of the Koelle Award. The session after lunch will consist of talks by Drs. Whetstine, Tummino, and Richon. The day will end with an awards ceremony and networking reception.

Online pre-registration and a complete schedule is available on the MAPS/ASPET website. The deadline for abstracts is October 1. Please join us! For additional information, contact MAPS at **MAPharmSociety@gmail.com**.

Great Lakes Chapter of ASPET

Summary from the 25th Annual Scientific Meeting

The Great Lakes Chapter of ASPET held its 25th Annual Scientific Meeting on June 22, 2012 at the Searle Conference Center at Rush University Medical Center in downtown Chicago, IL. Over 100 pharmacologists attended the meeting, as well as eight undergraduates and 26 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, Chicago State University, Loyola University Chicago, Indiana University, University of Wisconsin at Madison, Michigan State University, Iowa State University, Medical College of Wisconsin, Concordia University Wisconsin School of Pharmacy, Marquette University, Purdue University, University of Michigan, Navy Drug Screening Laboratory, AD Instruments Inc., BD Biosciences, Promega Corporation, EMD Millipore, VWR International, Abbott Laboratories, Cellular Dynamics International, Jazz Pharmaceuticals, and Takeda Pharmaceuticals.

The 2012 Program was as follows:
8:30 AM – 10:30 AM: Registration (The Searle Conference Center, Professional Building, 5th Floor), Continental breakfast (Main Lounge)

Poster session (Main Lounge). Thirty-one posters were presented in the poster session. Eight posters were presented by undergraduate students, 19 by graduate students, 3 by postdocs and 8 by faculty members or research scientists at pharmaceutical companies.

8:30 AM – Noon: Vendor Exhibit (Main Lounge)

10:45 AM – 11:45 AM: Young Investigator Symposium (542 Brainard Room)

10:45 AM – 11:45 AM: **Jessica Loweth**, Postdoctoral Fellow, Rosalind Franklin University of Medicine and Science
Cocaine craving and AMPA receptor plasticity: Modulation by metabotropic glutamate receptors

11:05 AM – 11:20 AM: **Karin Ejendal**, Postdoctoral Fellow, Purdue University
The role of Gbetagamma subunits in D2 dopamine receptor-induced sensitization of Ca2+-sensitive adenylyl cyclases

11:25 AM – 11:40 AM: **Abdelhak Belmadani**, Research Assistant Professor, Northwestern University Feinberg School of Medicine
Uncovering new neurogenic niche in the adult mouse brain: Role for the chemokine receptor CXCR4

Noon – 1:00 PM: Lunch (Fenger-Sippy Room)

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

1:00 PM – 4:15 PM: Symposium: *Targeting GPCRs: From Traditional Pharmacology to Allosteric Modulation (542 Brainard Room)*

1:00 PM – 1:15 PM: Welcome & Opening Remarks, **Alejandro Mayer**, Midwestern University, President, GLC-ASPET & Robin Rylaarsdam, Symposium Chair

1:15 PM – 1:45 PM: **Timothy Esbenshade**, Abbott Laboratories
Drug discovery challenges of a GPCR target: Development of histamine H3 antagonists

1:55 PM – 2:25 PM: **Saverio Gentile**, Loyola University Medical Center
G Protein estrogen receptor (GPER) regulates hERG channel activity in ERneg breast cancer cells. Is cancer a channelopathy?

2:35 PM – 3:05 PM: **Annette Gilchrist**, Midwestern University
Evaluation of CCR1 antagonists for multiple myeloma

3:15 PM – 4:15 PM: Keynote Address, **Jeffrey Conn**, Vanderbilt University
Multiple modes of efficacy and stimulus bias of allosteric modulators of GPCRs

4:30 PM – 5:00 PM: Business Meeting & Awards Presentation, Election Results (Alejandro Mayer, GLC ASPET President), Awards (Robin Rylaarsdam, Senior Poster Judge)

A panel of judges interacted with the poster presenters and cash prizes were given to the top posters in the following categories:

Undergraduate Students

First Place: **Sarah Lynch**, Dept. of Pharmacology and Toxicology, Indiana University School of Medicine, *GABA attenuated L-DOPA-induced striatal and nigral ERK1/2 signaling in a rat model of Parkinson's disease*.
Second Place: **Katrina Campbell**, Neuroscience Department, Lake Forest College, *Identifying specific amino acids in Parkinson's disease protein alpha-synuclein that control its toxic properties*.
Third Place: **Daniela Janevska**, Biology Department, Benedictine University, *Finding novel intragenic suppressors of a constitutively active allele of Gs alpha*.

Graduate Students

First Place: **Tracy Thennes Schmidt**, Department of Pharmacology, University of Illinois at Chicago, *Inducible deletion of endothelial FAK triggers acute lung injury through p38 MAPK mediated dysregulation of RhoA and Rac1 activities.*
First Place: **Dan Thomases**, Department of Cellular and Molecular Pharmacology, Rosalind Franklin University of Medicine and Science, *Impact of the GABA-A α1 positive allosteric modulator Indiplon in reversing the abnormal prefrontal disinhibitory state induced by NMDA receptor blockade during adolescence*.
Third Place: **Tsui-Ting Ho**, Department of BioPharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago, *Novel mechanism of drug resistance in leukemia cells associated with changes in HoxA9 and microRNA expression*.

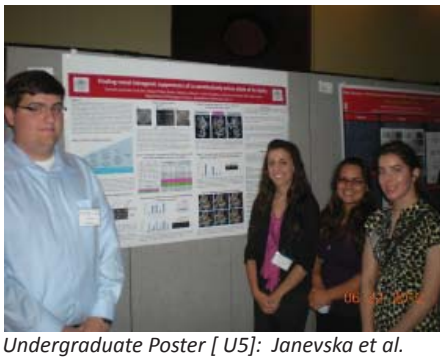
Postdoctoral Fellows

First Place: **Kristoff Homan**, Department of Pharmacology, University of Michigan, Ann Arbor. *New therapeutics targeting heart failure: Development of GRK2 selective inhibitors*.

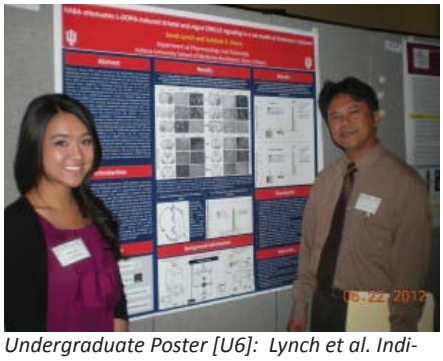
The GLC-ASPET Executive Committee gratefully acknowledges financial support for the meeting from: ASPET, Iowa State University (Department of Biomedical Sciences), Loyola University (Department of Pharmacology), Medical College of Wisconsin, Rosalind Franklin University of Medicine and Science (College of Pharmacy), Northwestern University (Department of Pharmacology), and Takeda Pharmaceuticals USA. We also gratefully acknowledge the following for their support in kind contributions: Midwestern University, Dr. Sanda Predescu, (Rush University Medical Center, Department of Pharmacology), Dr. Kuei Tseng (Rosalind Franklin University of Medicine and Science), Victoria Sears (Midwestern University, Department of Pharmacology), and Dr. Walter Prozialeck (Midwestern University, Chicago College of Osteopathic Medicine, Department of Pharmacology).

Support by the following vendor exhibitors is gratefully acknowledged: AD Instruments Inc., BD Biosciences, Bio Rad, Promega Corporation, EMD Millipore, VWR International, and Cellular Dynamics International.

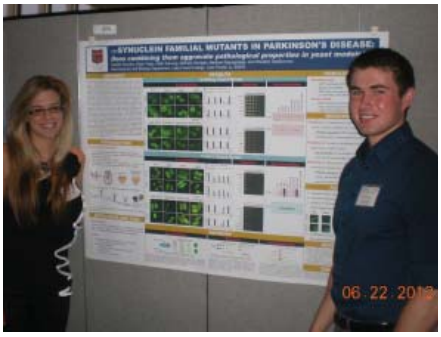
Photos from Great Lakes Chapter Annual Meeting: June 22, 2012



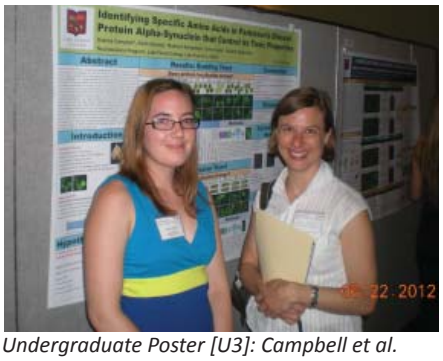
Undergraduate Poster [U5]: Janevska et al. Benedictine University, Lisle, IL



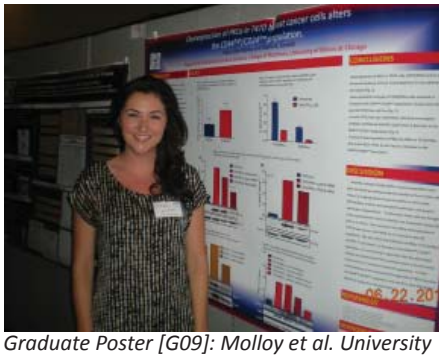
Undergraduate Poster [U6]: Lynch et al. Indiana University School of Medicine, Gary, IN



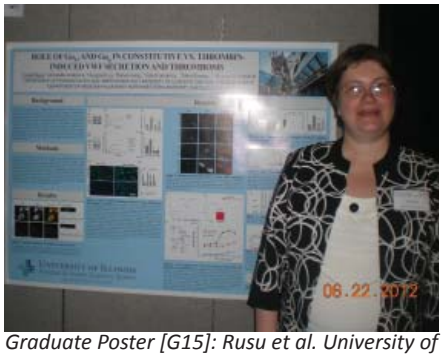
Undergraduate Poster [U4:] Kukulka et al. Lake Forest College, Lake Forest, IL



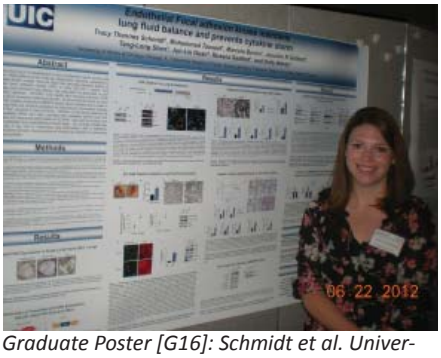
Undergraduate Poster [U3]: Campbell et al. Lake Forest College, Lake Forest, IL



Graduate Poster [G09]: Molloy et al. University of Illinois, Chicago, IL



Graduate Poster [G15]: Rusu et al. University of Illinois and Northwestern University, Chicago, IL



Graduate Poster [G16]: Schmidt et al. University of Illinois and Rush University, Chicago, IL

Faculty Poster [F02]: Bhalla et al. Midwestern University, Downers Grove, IL

Faculty Poster [F08]: Curtis et al. Midwestern University, Downers Grove, IL

Faculty Poster [F06]: Mayer & Glaser Midwestern University, Downers Grove, IL

Young Investigator Symposium: Jessica Loweth, Rosalind Franklin University, North Chicago, IL

Young Investigator Symposium: Karin Ejendal, Purdue University, IN

Young Investigator Symposium: Abdelhak Belmadani, Northwestern University, Chicago, IL

GLC ASPET Symposium participants, please note the smiles and full room!

GLC ASPET Symposium speaker: Timothy Esbenshade, Abbott Laboratories, Chicago, IL

GLC ASPET Symposium speaker: Saverio Gentile, Loyola University Medical Center, Chicago, IL

GLC ASPET Symposium speaker: Annette Gilchrist, Midwestern University, Downers Grove, IL

GLC ASPET Symposium Keynote speaker: Jeffrey Conn, Vanderbilt University Center for Neuroscience & Drug Discovery, Nashville, TN

GLC ASPET Undergraduate Poster 3rd Place: Daniela Janevska, Benedictine University, Lisle, IL presented by Board member Robin Pals-Rylaarsdam

GLC ASPET Undergraduate Poster 2nd Place: Katrina Campbel, Lake Forest College, Lake Forest, IL presented by Board member Robin Pals-Rylaarsdam

GLC ASPET Undergraduate Poster 1st Place: Sara Lynch, Indiana University, IN presented by Board member Robin Pals-Rylaarsdam

GLC ASPET Graduate Poster 3rd Place: Tsui-Ting Ho, University of Illinois, Chicago, IL presented by Board member Robin Pals-Rylaarsdam

GLC ASPET Graduate Poster 1st Place: Dan Thomases, Rosalind Franklin University, North Chicago, IL presented by Board member Robin Pals-Rylaarsdam

GLC ASPET Graduate Poster 1st Place: Tracy Thennes Schmidt, Rush University, Chicago, IL presented by Board member Robin Pals-Rylaarsdam

GLC ASPET Postdoc Poster 1st Place: Kristoff Homan, University of Michigan, Ann Arbor, MI presented by Board member Robin Pals-Rylaarsdam

GLC ASPET Undergraduate, Graduate and Postdoc Award winners presented by Board member Robin Pals-Rylaarsdam

GLC ASPET 2012-2013 Board Members (left to right): Saverio Gentile (Councilor), Kuei Tseng (Treasurer), Alejandro Mayer (President), Eric Blomme (Councilor), Sandra Predescu (Vice-President), Geoffrey Swanson (Secretary), Ricardo Monzon (Councilor), and Maria Barbolina (Councilor)

GLC-ASPET Symposium Speaker Abstracts

G Protein Estrogen Receptor (GPER) Regulates Kv11.1 Ion Channel Activity in ERneg Breast Cancer Cells. Is cancer a channelopathy?

Gentile Saverio, Loyola University Medical Center

Breast cancer is a major cause of death among women worldwide, and novel strategies need to be developed to lessen its morbidity. Clinical heterogeneity of breast cancers indicates new subsets of gene expression that can create novel molecular pathways mediating estrogen's (E2) effects on proliferation. It has been established that in cancer cells displaying an E2 receptor positive (ERpos) or E2 receptor negative (ERneg) phenotype, proliferation can be mediated by an E2-dependent mechanism. Interestingly, recent studies have demonstrated that E2 effects on proliferation of ERneg breast cancer cells can be mediated by the G protein-coupled receptor, GPER. However, very little is known about the biochemical signaling cascade activated by E2 via GPER. The human ether-a-go-go related gene (hERG) encodes the voltage-gated potassium channel Kv11.1, which is primarily expressed in electrically excitable cells. Interestingly, recent translational research in cancer biology has revealed that Kv11.1 is robustly expressed in cancers of varying histogeneses, including breast cancer. Although, it is well established that Kv11.1 plays a major role in neurons or myocytes nothing is known about its role in breast cancer. Our investigation shows that Kv11.1 ion channel activity is stimulated by a non-genomic E2-activated signaling cascade via GPER in ERneg breast cancer cells. Our experiments also show that changes of Kv11.1 activity determine variation of proliferation rate in ERneg breast cancer cells. In addition, stimulation of Kv11.1 activity led to an increase of intracellular calcium. Understanding the role of hormonal regulation of Kv11.1 ion channel will offer a compelling opportunity to better understand the mechanism of breast cancer proliferation and might lead to discovery of a myriad of new potential drug target for cancer treatment.

Evaluation of CCR1 antagonists for multiple myeloma

Gilchrist Annette, Midwestern University

Over the last decade several compounds directed at the G protein coupled receptor (GPCR) CCR1 have been taken into the clinic for rheumatoid arthritis, multiple sclerosis, and chronic obstructive pulmonary disease. Recently, CCR1 and its endogenous ligand CCL3 (MIP-1α), have also been implicated in multiple myeloma (MM), a cancer of B lymphocytes that often leads to bone lesions and skeletal fractures. Patients with MM have a profound increase in CCR1 and CCL3 expression, leading to speculations that CCR1 antagonists might prove beneficial for this disease. We have evaluated several CCR1 antagonists for their ability to inhibit binding of ^{125}I-CCL3 using endogenous receptors on myeloma cells, and compared these results with membranes from HEK cells with overexpressed CCR1. There was a clear difference in the rank order depending on the type of cell being tested. As drugs often have different efficacies depending on the behavior for which they are examined, we then compared the CCR1 antagonists for their ability to inhibit CCL3-mediated translocation of β-arrestin. For these studies we used a PathHunter assay (DiscoveRx) that employs an enzyme fragment complementation approach. Surprisingly we found that while many of the CCR1 antagonists inhibited CCL3 mediated β-arrestin translocation in a dose dependent manner some had very little effect. The results suggest that some of the compounds may provide "biased" inhibition in downstream signaling. Finally, we differentiated peripheral blood mononuclear cells to osteoclast-like cells in the presence or absence of CCR1 antagonists and examined the ability of the conditioned media from these cells to induce chemotaxis of myeloma cells. Our data indicates CCR1 is intimately involved in the interactions between multiple myeloma cells and osteoclasts. Thus, it seems that CCR1 antagonists are worthy of further investigations to determine whether they might provide potential drug therapies for patients with multiple myeloma.

Keynote Address

Multiple modes of efficacy and stimulus bias of allosteric modulators of GPCRs

Conn Jeffrey, Vanderbilt University

Selective activators of specific subtypes of metabotropic glutamate receptors (mGluRs) have exciting potential for development of novel treatment strategies for a variety of psychiatric and neurological disorders. For instance, we have identified mGluR4 as an exciting new target for treatment of Parkinson's disease. Unfortunately, it has been difficult to develop compounds that act as selective orthosteric agonists of specific mGluR4 or other mGluR subtypes that have properties that are likely to be suitable for development of therapeutic agents. We have discovered and chemically optimized selective positive allosteric modulators (PAMs) for mGluR4. These compounds do not activate mGluR4 directly but dramatically potentiate the response of these receptors to glutamate. These allosteric potentiators offer high selectivity for mGluR4 and provide an exciting new approach to development of novel selective activators of this and other GPCR subtypes. Interestingly, highly selective mGluR4 PAMs have robust efficacy in reducing parkinsonian motor symptoms in rodent models. In addition to mGluR4, we have now discovered and optimized highly selective allosteric modulators of multiple other GPCR subtypes. Furthermore, we have performed in vivo studies that reveal that these compounds have robust effects in animal models that have been used to predict efficacy for novel anxiolytics (mGluR2; mGluR5) and antipsychotic agents (mGluR2, mGluR5). In addition to mGluRs, we have discovered novel highly selective allosteric potentiators for M1, M4, and M5 muscarinic receptors. These studies suggest that allosteric modulators provide a viable approach for discovery of selective activators for members of multiple GPCR families. The diversity of allosteric modulators now available is allowing us to develop fundamental new insights into the multiple mechanisms by which these compounds can regulate GPCR function. In addition, our recent studies are providing new insights into the functional impact of different modes of efficacy of allosteric modulators in animal models.

GLC-ASPET Young Investigator Symposium

Cocaine Craving and AMPAR Plasticity: Modulation by Metabotropic Glutamate Receptors

Loweth Jessica, Postdoctoral Fellow, Rosalind Franklin University of Medicine and Science

After prolonged withdrawal from extended-access cocaine self-administration, Ca^{2+}-permeable AMPA receptors (CP-AMPARs) accumulate in the nucleus accumbens (NAc) and mediate the withdrawal-dependent intensification ("incubation") of cueinduced cocaine craving. Our goal is to understand mechanisms that normally restrict CP-AMPARs from NAc synapses in order to develop strategies to reverse or prevent CP-AMPAR accumulation during incubation and thus reduce craving. Using patch-clamp recordings in NAc slices from "incubated rats" (extended-access cocaine self-administration and >40 days of withdrawal), we found that acute bath application of the mGluR1 positive allosteric modulator (PAM) SYN119 (compound Ro 0711401, 1 μM) rapidly removes CP-AMPARs from NAc synapses. In addition, behavioral studies followed by patch clamp recordings found that acute systemic administration of SYN119 (10 mg/kg, i.p.) reduces the expression of incubated cocaine seeking and removes CP-AMPARs from NAc synapses. Based on these findings, we hypothesized that mGluR1 normally exerts inhibitory tone on CP-AMPAR levels in NAc synapses and that loss of mGluR1 tone during cocaine withdrawal enables CPAMPAR accumulation. Indeed, we found that that mGluR1 surface levels decrease slowly in the NAc during withdrawal, just preceding CP-AMPAR accumulation, and that restoring mGluR1 tone during this period by administering repeated, intermittent injections of SYN119 (10 mg/kg, i.p.) attenuates the incubation of cue-induced cocaine seeking. We then measured NAc surface levels of mGluR1 and GluA1 in these animals using biotinylation. Compared to vehicle controls, SYN119-treated rats showed an increase in mGluR1 surface levels, as well as a small but significant reduction in GluA1 surface levels. These findings suggest that repeated mGluR1 PAM injections during a critical period of withdrawal opposes the decrease in surface mGluR1 that normally occurs, thus maintaining the mGluR1-mediated inhibitory control over CP-AMPAR accumulation. Taken together, our results show that mGluR1 negatively regulates CP-AMPAR levels in the NAc and point to a role for mGluR1 PAMs in the treatment of cue-induced cocaine craving and relapse in human addicts. Supported Contributed by: NIH Grants DA009621 (M.E.W. and K.Y.T.), MH086507 (K.Y.T), DA015835 and DA029099 (M.E.W.) and Postdoctoral NRSA F32DA030844 (J.A.L.)

The Role of Gbetagamma Subunits in D2 Dopamine Receptor-Induced Sensitization of Ca2+-Sensitive Adenylyl Cyclases

Ejendal Karin, Postdoctoral Fellow, Purdue University

Chronic dopamine receptor activation is implicated in several central nervous system disorders. Although acute activation of Gαi-coupled D2-dopamine receptors inhibits adenylyl cyclase, persistent activation enhances adenylyl cyclase activity, a phenomenon called heterologous sensitization. Previous work revealed a requirement for $G\alpha_s$ in D_2-induced heterologous sensitization of AC5. To elucidate the mechanism of $G\alpha_s$-dependency, we expressed Gαs mutants in $G\alpha_s$-deficient $Gnas^{E2-/E2-}$cells. Neither Gαs-palmitoylation nor $G\alpha_s$- Gbetagamma interactions were required for sensitization of AC5. To investigate the role of Gβγ in heterologous sensitization of AC5 and the related AC6, we utilized N-terminal deletion mutants of AC5 and AC6, and observed that the lack of this Gβγ regulatory domain correlate with an attenuation of heterologous sensitization. Moreover, we found that co-expressing βARKct-CD8 or Sar1(H79G) blocked heterologous sensitization. These studies are consistent with a role for $G\alpha_s$-AC5 interactions in sensitization, however, Gβγ appears to have an indirect role in heterologous sensitization of AC5, possibly by promoting proper signalosome assembly.

Uncovering New Neurogenic Niche in the Adult Mouse Brain: Role for the Chemokine Receptor CXCR4

Belmadani Abdelhak, Research Assistant Professor Northwestern University Feinberg School of Medicine

It is now well established that neurogenesis is confined to just two regions in the adult mammalian brain, the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus and the subventricular zone (SVZ) of the lateral ventricles. Neural stem/progenitor cells (NSCs) in the SVZ are capable of generating a progeny of neuroblasts that migrate towards the olfactory bulb (OB) along a well-defined migratory route known as the rostral migratory stream (RMS). In the adult hippocampus, NSCs can also be found in the SGZ of the DG and are believed to be the only NSCs that provide new neurons to the adult hippocampus. As the SVZ in adult represents a remnant of the embryonic germinal neuroepithelium, which persists throughout life as an actively mitotic layer in the wall of the lateral ventricles, it was attempting to suggest that it might also continue to provide new neurons to the adult hippocampus. Using a mouse reporter line in which SVZ NSCs could be traced through the expression of enhanced green fluorescent protein (EGFP) we observed for the first time the presence of new pool of EGFP expressing cells that line the medial surface of the hippocampus, and migrate as streams of single cells across the hippocampal fimbria. They then follow the meninges and enter the DG of the hippocampus. In these animals, EGFP was placed under the control of CXCR4 promoter, a key family member of the chemokine receptors, a GPCR that pattern neuronal migration during embryonic morphogenesis. As these cells follow a caudal destination to reach the DG, we termed this path as the caudal migratory stream (CMS). Further characterization of this new population of CXCR4 cells is under way to ensure their identity as true stem cells providing new neurons to the DG in different circumstances.

GLC-ASPET Abstracts 2012: Faculty

F01. Kinase inhibitor profiling using a universal luminescent ADP detection platform with complete Kinase Profiling Systems.

Alves Juliano*, Turri Jacquelyn, Hsiao Kevin, Goueli Said, and Zegzouti, Hicham; Promega Corporation, 2800 Woods Hollow Road, Madison, WI 53711

The advancement of an inhibitor throughout the various stages of the drug development is predicated upon its selectivity toward the target of interest. Thus, profiling the compound against a broad panel of kinases is important for providing a better understanding of its activity against other targets. This requires a robust and universal assay to asses the selectivity and potency of the inhibitor against multiple classes of kinases in a cost-effective manner. The luminescence-based ADP-Glo™ kinase assay is a universal platform that addresses all the needs of kinase screening, mode of action (MOA) studies and inhibitor profiling throughout the drug discovery process. Because it measures kinase activity by quantifying the amount of ADP, the universal product of all kinases (protein and other substrate kinases), this technology provides the required universality for all kinases, and significantly reduces the amount of enzyme needed in kinase assays, making it affordable to generate inhibitor profiles for different kinase families. The ADP-Glo™ assay has been validated for more than hundred kinases and is optimized for use with a large panel of complete Kinase Enzyme Systems (KES) that span different families of the human kinome. Here we demonstrate the profiling of several kinase inhibitors using newly designed kinase strips. Each pair of multiwell strip contains concentrated amounts of kinases from the same family and their corresponding substrates, and the stock volumes were standardized so that all kinases generate 5–10% ATP-to-ADP conversion when diluted into the kinase reaction. We show that using the new kinase profiling strips we could easily generate selectivity profiles using small or large kinase panels, as well as identifying compound promiscuity towards members of a single kinase subfamily or different subfamilies of the kinome. The fact that ADP-Glo™ platform offers so many positive attributes makes it an ideal assay not only for primary and secondary screening but also for profiling compounds in a cost-effective manner using one single platform.

F02. Effects of metformin on bethanechol-induced contractions of the rat bladder.

Curtis J.K., Phelps L.E., and Peuler J.D.; Pharmacology Dept. Midwestern University, Downers Grove, IL 60515

By contracting detrusor smooth muscle, bethanechol can treat urinary retention in patients with diabetic bladder dysfunction. Previously, we reported that millimolar levels of the widely-used antidiabetic drug metformin can markedly inhibit such contractions in the rat bladder. In the present work, we find that levels ≤ 200 micromolar do not do so suggesting that therapeutically-relevant levels of metformin (as seen in plasma of diabetic patients) will not interfere with the ability of bethanechol to contract and thus empty the bladder in patients who need it. The mechanism whereby metformin (at ≥1 millimolar) inhibits bethanechol-induced bladder smooth muscle contractions is unknown. We also found that, at its EC50 of 5 millimolar, metformin's inhibition of bethanechol contractions was significantly antagonized ($p<0.05$) by 4-aminopyridine (4AP) and tetraethylammonium (TEA). Therefore, we suspect that such metformin inhibits bethanechol contractions in bladder by activating potassium (K) efflux through both 4AP-sensitive and TEA-sensitive detrusor smooth muscle K channels. Support: Midwestern University Biomedical Science Masters Program.

F03. Homogenous, Luminescent HTS-formatted Platform Technologies for cAMP- and cGMP-Dependent Phosphodiesterase (PDEs)

Goueli Said A. [1,2] and Hsiao Kevin[1]; [1]Research and Development, Promega Corp. Madison, WI 53711, and [2]University of Wisconsin School of Medicine and Public Health, Madison, WI 53706

Cyclic nucleotide phosphodiesterases (PDEs) represent eleven different gene families of enzymes that are encoded by at least 21 different genes and accounting for at least 55 isoforms. They have been implicated in controlling specific cellular functions including Cardiovascular, pulmonary, and inflammatory diseases and they play potential role as targets for treatment of cancer. Thus, the development of novel isoform-specific inhibitors may be useful for the development of therapeutic agents against cancer. We have devised two novel approaches to monitor the activity of cAMP-PDE and cGMP-PDE and developed two homogenous, luminescent high through-put screening (HTS) assays to screen for novel inhibitors of PDE. The first strategy relies on the activation of cAMP-Dependent Protein Kinase (PKA) in the presence of low concentration of cAMP and also by moderately higher concentration of cGMP. The effect of compounds on the activity of PDE can be monitored by the cAMPdependent activation of PKA and measuring the active PKA using luminescent Kinase assay. The other strategy relies on the conversion of AMP generated in the presence of PDE into ATP and measuring the generated ATP using luminescent Kinase assay. Both strategies have been developed into HTS formatted assays and can be carried out in two simple steps in 384-, and 1536-well formatted plates. The Assays are luminescent and thus they encounter minimal interference from fluorescent compounds and the robustness of the assays are indicated by their remarkably high Z' value (>0.8). In summary, both assays can be used to screen libraries of compounds targeting PDE that might be developed into potential drugs for treatment of cancer.

F04. Retrospective Analysis of the Effect of Multiple Commonly Used Toxicology Formulations on Urinary Biomarkers of Renal Toxicity (Albumin, Lipocalin-2, Osteopontin and Kim-1) in Rats

Lai-Zhang Jie[1], Kowalkowski Kenneth[1], Lisowski Andrew[1], Riendl Susan[2], Buck Wayne[1], Blomme Eric[2], Yang Yi[2]; [1]Cell Molecular and Exploratory Toxicology, Global Pharmaceutical R&D, [2]Investigative Toxicology and Pathology, Global Preclinical Safety, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6048

Urinary proteins can represent sensitive biomarkers of drug-induced nephrotoxicity. Several putative urinary biomarkers have recently been evaluated by the Predictive Safety Testing Consortium (PSTC) and have been successfully qualified by the FDA/EMEA/PMDA as acceptable regulatory tools in rat toxicology studies. To better characterize the utility of these urinary biomarkers in our routine rat toxicology studies, the potential effect of commonly used toxicology formulations on four urinary biomarkers (albumin, lipocalin-2, osteopontin, Kim-1) was determined. A retrospective analysis was conducted using data collected (n=209) in exploratory rat toxicology studies (typically of 5 days duration) performed during the past two years. Seven commonly used toxicology formulations were evaluated including saline, 0.2% HPMC and PEG-400. The four urinary biomarkers were analyzed using Mesoscale Multiplex Rat Kidney Toxicity Panel. Urinary biomarker concentrations were normalized to urinary creatinine levels. None of the commonly used formulations resulted in statistically significant changes in urinary biomarker levels. Overall, these results indicate that these four urinary biomarkers are acceptable for rat toxicology studies and provide further support for the integration of these biomarkers in rat toxicology studies.

F05. Genome-wide trasncriptomic changes induced by lipopolysaccharide in whole blood of rats: Optimization of a novel collection procedure.

Ditewig Amy C.[1], Fricano Meagan M.[2], Liguori Michael J.[1], Blomme Eric A.[3], Jung Paul M.[4], Yang Yi[3]; [1]Cell, Molecular, Exploratory Toxicology, [2]Neuroscience Discovery, [3]Investigative Toxicology and Pathology, 4Nrf2 Biology Abbott Laboratories, Abbott Park, IL 60064

Blood is an easily accessible tissue that can be used to identify biomarkers for a wide range of tissue injuries using transcriptomic profiling. Using blood for transcriptional profiling presents significant technical challenges, particularly because of the presence of large quantities of globin mRNA transcripts that prevent acceptable signal collection. PAXgene™ blood RNA collection tubes have been the traditional method for blood collection. However, they are not ideal for rat toxicology studies because they require large amounts of blood (2.5 ml). We have developed a reproducible method of RNA stabilization and isolation from small quantities of whole blood to be used for transcriptional profiling. To confirm the validity of this technique, male, Sprague-Dawley rats (n=3) were treated with vehicle or 5 mg/kg of lipopolysaccharide (LPS; IV) for 2h, 6h and 24h. Two blood collection methods were used: collection of blood in PAXgene™ tubes, or collection of 500 µl of blood in 2 ml of Qiazol®. Both techniques yielded abundant, high quality RNA. Total RNA (50 ng) was processed using the NuGEN Ovation™ RNA Amplification System, and cDNA was hybridized to Affymetrix Rat RAE230 microarrays. For both techniques, similar genes and pathways were deregulated following LPS treatment. In particular, genes associated with LPS-induced inflammatory response, LPS and IL-1-mediated inhibition of RXR function and IL-10 signaling were differentially expressed. In conclusion, this novel blood preparation technique yielded results similar to the traditional method, but required less blood input and was less costly; this method can be used in preclinical toxicology and pharmacology studies to identify novel biomarkers.

F06. Marine pharmacology and the 2011 marine pharmaceuticals pipeline.

Mayer A.M.S.[1*] and Glaser K.B.[1,2]; [1]Midwestern University, Department of Pharmacology, CCOM, Downers Grove, IL 60565; [2]Abbott Laboratories, Abbott Park, IL 60064

As the renaissance in the pharmacology of marine natural products continues (Glaser and Mayer, Biochemical Pharmacology 78:440-448, 2009), the purpose of this project was to assess the status of the clinical marine pharmaceuticals pipeline in May 2012. Results were the following: 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), 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. The clinical marine pharmaceutical pipeline, recently reviewed (Mayer et al. TIPS 31:255-265, 2010), as of May 2012 consisted of 11 marine-derived compounds in clinical development. These included three new monoclonal antibodies conjugated to synthetic dolastatin derivatives, that were in either Phase I, Phase II or Phase III clinical trials. Finally, the preclinical marine pharmacology pipeline remained a global enterprise with researchers from several countries reporting novel mechanisms of action for multiple marine chemicals (Mayer et al. Comparative Biochemistry and Physiology C 153: 191-222, 2011). We conclude that both marine pharmacology preclinical research as well as the clinical pharmaceutical pipeline remained very active in 2012. *Supported by Midwestern University.*

F07. Cadmium disrupts glucose-stimulated insulin release and alters beta catenin immuno-labeling in islets.

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There is increasing interest in how environmental contaminants can contribute to the onset of diabetes. Multiple epidemiological studies show that exposure to the metal cadmium (Cd), is associated with diabetes and reduced serum insulin. Insulin release is dependent upon normal cell-cell adhesion. The roles of E-cadherin and associated proteins such as beta catenin are especially important in islet cell-cell adhesion. One goal of this study was to examine the acute effects of Cd on insulin release. Islets were isolated from rats then allowed to recover overnight. Individual islets were incubated in physiological buffer for 4 hours containing either low (0.5 mg/ml) or high (3.0 mg/ml) glucose with or without Cd (1000, 100 and 10 nM) present. There was an approximate 20 fold increase in insulin release when control islets not exposed to Cd were incubated in low vs high glucose containing buffers. In the low glucose buffer, Cd caused a nearly two fold increase in insulin release at all concentrations of Cd examined. However, when islets were incubated in high glucose buffer there was a 10 fold decrease in insulin release in islets exposed to 1000 nM Cd. Similar decreases were observed in islets incubated in buffer containing 100 and 10 nM Cd. To further determine the effects of Cd on islet cell biology and function, 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. Later, pancreata were sectioned and immuno-stained for beta catenin. Co-immuno-labeling of insulin was performed to ensure that the changes in beta catenin labeling occurred in islets and not the more ubiquitous acinar cells. Interestingly, all tissue from animals exposed to Cd, at all time points examined, had dramatically increased islet staining for beta catenin. This would indicate that Cd caused a disruption of cell-cell adhesion. The current study shows that the environmental contaminant, Cd, disrupts glucose-stimulated insulin release at very low levels and is associated with increased beta-catenin labeling, a protein associated with cell-cell adhesion.

F08. Potentiation of oxycodone antinociception by agmatine and BMS182874 via an imidazoline I_2 receptor-mediated mechanism.

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Background and Objectives: The potentiation of oxycodone antinociception by BMS182874 (endothelin-A (ET_A) receptor antagonist) and agmatine (imidazoline receptor/α_2-adrenoceptor agonist) is well-documented. It is also known that imidazoline receptors but not α_2-adrenoceptors are involved in potentiation of oxycodone antinociception by agmatine and BMS182874. However, the involvement of specific imidazoline receptor subtypes (I1, I2, or both) in this interaction is not clearly understood. The objectives of the present study were to determine the involvement of imidazoline I1 and I2 receptors in agmatine- and BMS182874-induced potentiation of oxycodone antinociception.
Methods: Male Swiss Webster mice were treated with oxycodone, agmatine, BMS182874, and combined administration of oxycodone with agmatine or BMS182874. Efaroxan (imidazoline I_1 receptor antagonist) and BU224 (imidazoline I_2 receptor ligand) were used to determine the involvement of I_1 and I_2 imidazoline receptors, respectively. Antinociception was determined by the tail flick and hot-plate latency methods. Parameters were measured for 360 min and expressed as Mean±S.E.M. N=6 per group.
Results: Oxycodone produced significant antinociceptive response in mice in both tail flick and hot-plate latency tests which was not affected by efaroxan (P>0.05). Oxycodone antinociception was blocked by BU224 (P<0.05) in both tests. Agmatineinduced potentiation of oxycodone antinociception was blocked by BU224 (P<0.05) but not by efaroxan (P>0.05). BMS182874-induced potentiation of oxycodone antinociception was unaffected by efaroxan (P>0.05) but was significantly blocked by BU224 (P<0.05).

Conclusion and Significance: This is the first report demonstrating that agmatine-induced enhancement of oxycodone antinociception is blocked by BU224 but is not altered by efaroxan. We also found that BMS182874-induced increase in oxycodone antinociception is blocked by BU224 but not affected by efaroxan. We conclude that imidazoline I2 receptors but not imidazoline I_1 receptors are involved in BMS182874- and agmatine-induced potentiation of oxycodone antinociception in mice. Our findings support the hypothesis that I_2 receptor agonists may be useful as combination therapy with oxycodone to improve antinociception and attenuate the development of tolerance.

GLC-ASPET Abstracts 2012: Postdoctoral Fellows

P01. Anti-inflammatory and neuroprotective effects of a novel compound mito-apocynin in a mouse model of Parkinson's disease.

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Parkinson's disease (PD) is one of the most common neurodegenerative disorders marked by a progressive increase in nonmotor and motor deficits. Recent evidences indicate that glial cell activation and its inflammatory response may contribute to the progressive degeneration of dopaminergic neurons in PD. Despite intense investigation, no neuroprotective therapy that successfully intervenes in the progression of the disease is currently available. Apocynin has been shown to possess antiinflammatory and antioxidant properties but the clinical utility of apocynin as a neuroprotective agent is still controversial. In this present study, we investigated whether mito-apocynin, a novel derivative of apocynin, could protect against glial activation and nigrostriatal neurodegeneration in cell culture and animal models of PD. First, we characterized the neuroprotective effect of mito-apocynin in 1-methyl-4-phenyl pyridinium (MPP^+)-treated primary neuronal cultures. Mitoapocynin treatment in primary mesencephalic cultures significantly attenuated MPP^+-induced tyrosine hydroxylase (TH)–positive neuronal cells and neurite loss. Interestingly, mito-apocynin also attenuated MPP^+-induced glial cell proliferation, nitrotyrosine, 4-hydroxynonenol and p65 activation. Next, we evaluated the anti-inflammatory effect of mito-apocynin in the MPTP-induced mouse model of PD by examining glial (both astrocytes and microglia) activation by IBA-1 and GFAP immunohistochemistry, respectively. Oral administration of mito-apocynin significantly attenuated MPTP-induced microglial and astroglial cell activation in substantia nigra. Additionally, MPTP-induced activation of iNOS in the substantia nigra was also attenuated by mito-apocynin. Notably, our histological findings paralleled improved motor function and striatal neurotransmitter levels in MPTP- treated mice that also received mito-apocynin. Importantly, immunohistological analysis of nigral dopaminergic neurons confirmed the neuroprotective effect of mito-apocynin against MPTP-induced nigrostriatal dopaminergic neuronal loss. Collectively, our results demonstrate that mito-apocynin produces distinct anti-inflammatory and antioxidant effects in a well-established neurotoxicity animal model of PD. These data strongly suggest that additional preclinical development of mito-apocynin may yield an effective neuroprotective drug capable of intervening in the progression of Parkinson's disease. (NIH grants NS039958 & NS074443)

P02. New therapeutics targeting heart failure: Development of GRK2 selective inhibitors.

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Heart failure is a leading cause of death in adults throughout the world. One of the defining characteristics of heart failure is dysregulation of G protein-coupled receptor (GPCR) signaling, namely that mediated by the β-adrenergic receptors (βARs). Prolonged stimulation of βARs results in receptor desensitization, which is initiated through phosphorylation by G proteincoupled receptor kinases (GRKs). It has been demonstrated that inhibition of one of these GRKs, GRK2, improves prognosis in heart failure through increased cardiac performance. Given the therapeutic potential of inhibiting GRK2, considerable effort has been devoted towards developing selective inhibitors. In this work, high-throughput screening methods were used to identify potential GRK2 inhibitors. One set of related compounds has been identified as potent inhibitors of GRK2 for which structure-activity relationships are being elucidated. Another inhibitor is a previously approved FDA drug (paroxetine) which demonstrated high selectivity for GRK2 *in vitro* and was efficacious in cellular and ex vivo studies.

P03. Periadolescent facilitation of NMDAR-mediated synaptic plasticity in the prefrontal cortex requires NR2B-containing receptors and postsynaptic PKA signaling.

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Dopamine (DA) regulation of glutamate transmission in the prefrontal cortex (PFC) is critical for sustaining working memory and decision-making, two cognitive processes that become enhanced late in adolescence. However, the mechanisms that support this facilitation remain elusive. We therefore hypothesize that prefrontal maturation occurs late in adolescence as a result of changes in local glutamatergic transmission. We conducted *in vitro* electrophysiological recordings to determine how NMDAR-mediated transmission onto layer V pyramidal neurons changes during the periadolescent transition. We compared the kinetics of evoked excitatory postsynaptic currents (EPSC) from apical vs. basolateral dendrites recorded at -70 and +60 mV. A developmental facilitation of $EPSC_{NMDA}$ was observed only when the evoked response was elicited ~150µm lateral from the apical dendrite. Pyramidal neurons recorded from the PD50-80 age group exhibited $EPSCs_{NMDA}$ significantly longer in duration than those from the PD25-40 group. Bath application of the NR2B antagonist ifenprodil (5µM) markedly reduced the prolonged $EPSCs_{NMDA}$ observed in the PD50-80 group, whereas no reduction in $EPSC_{NMDA}$ duration was found in the PD25-40 group. Similarly, recordings conducted with electrodes containing the PKA inhibitor PKI-[5-24] peptide revealed that PKA signaling is necessary for sustaining $EPSC_{NMDA}$ in the PD50-80 group. These results indicate that the postpubertal facilitation of NMDA-NR2B function in the PFC is input-specific (i.e. apical dendrite) and dependent on postsynaptic PKA. We next determined if such concurrent facilitation of NMDA-NR2B function and PKA signaling during adolescence is associated with enhanced synaptic plasticity in the PFC in vivo. We found that high frequency stimulation of the ventral hippocampus resulted in an NMDA-mediated LTP in the PD50-80 PFC whereas neither LTP nor LTD was observed in the PD25-40 age group. Together, a protracted input-specific developmental facilitation of NMDA-NR2B function could enhance prefrontal plasticity and contribute to the maturation of DA action in the PFC to improve working memory performance through adolescence. *Supported by Rosalind Franklin University (KYT) and NIH Grant R01-MH086507 (KYT).*

GLC-ASPET Abstracts 2012: Graduate Students

G01. The prostaglandin F2alpha/calcineurin-signaling pathway inhibits adipocyte differentiation via an autocrine interleukin-11/gp130-dependent signaling cascade.

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Adipocytes are specialized cells that play a critical role in the regulation of both energy homeostasis and the control of systemic metabolic responses. However, these essential adipocyte functions are disrupted in the setting of obesity leading to the development of insulin resistance, dyslipidemia and type 2 diabetes. Considerable evidence now indicates that defects in adipogenesis likely play an important role in the development of type 2 diabetes. Accordingly, considerable efforts have been focused on understanding the molecular mechanisms underlying the regulation of adipocyte differentiation. In this regard, a number of autocrine and paracrine factors have previously been shown to play important roles in the regulation of adipogenesis, amongst these is prostaglandin F2a (PGF2α), an inflammatory mediator that is known to be a potent endogenous autocrine negative feedback regulator of adipocyte differentiation. Previous work from our laboratory has shown that PGF2a inhibits adipocyte differentiation via the calcium-dependent serine/threonine phosphatase, calcineurin. Activation of this pathway inhibits adipogenesis by preventing the expression of the critical adipogenic transcription factor PPARg. Using a microarray-based strategy, we have now identified a downstream transcriptional target of calcineurin: IL-11, that we believe is likely to be involved in mediating the anti-adipogenic effects of the PGF2α/calcineurin-signaling pathway. IL-11 is a multifunctional cytokine belonging to the IL-6 family of cytokines that has been previously implicated in the inhibition of adipocyte differentiation, although, the precise mechanisms involved have not yet been fully elucidated. IL-11 is known to signal via the common gp130 cytokine receptor signaling subunit to activate the ERK and JAK/STAT signaling pathways. Using a dominant-negative gp130 mutant, we now show that

gp130 signaling plays a critical role in mediating the inhibitory effects of PGF2α on adipogenesis. Moreover, using a panel of chimeric mutant forms of gp130, we demonstrate that the activation of the JAK/STAT, but not the ERK pathway, is necessary and sufficient to block the expression of PPARg and thereby inhibit adipocyte differentiation. Collectively, our results demonstrate that the PGF2α/calcineurin-signaling pathway inhibits adipocyte differentiation via the activation of an autocrine IL-11 signaling pathway that involves the gp130-mediated activation of STAT transcription factors.

G02. Differential effects of repeated stress on neuronal activity in female and male basolateral amygdala.

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Women are more likely to suffer from stress-related affective disorders such as depression, anxiety and post-traumatic stress disorder than men. This disparity may arise from sex differences in amygdala function and its response to stress. The basolateral amygdala (BLA) is a stress sensitive limbic structure integral to the generation of emotions and emotional learning. Sex differences in BLA-dependent behaviors have already been examined and established in humans and rodents. However, much less is known about female amygdala physiology and the mechanism underlying sex differences in the BLA. In this study, the effects of repeated restraint stress on BLA neuronal activity was measured using *in vivo* single unit extracellular physiological recordings in anesthetized female and male rats. Animals were stressed for 7 out of 9 days and recorded 1-3 days post-stressor. Our experiments revealed a sex difference in BLA neuronal activity, and in BLA response to repeated stress. Under control conditions, the BLA of female rats displayed a higher firing rate. Control females had higher BLA activity compared to stressed females. The opposite response pattern was observed in males, where control males had lower BLA activity compared to stressed males. There was no significant difference in female BLA firing rate between the diestrus and proestrus phase of the estrus cycle. The sex difference in BLA activity was also reflected in elevated plus maze (EPM) performance. Stressed females spent more time in the open arms than the closed arms compared to control handled females. Stressed males show the opposite response pattern in the EPM with more time spent in the closed arms and less in the open arms. The sex specific effects of repeated stress in the BLA suggests the female and male amygdalae are functionally distinct, and adapt to stress through different mechanisms.

G03. Molecular cloning and functional characterization of the oxidative-stress sensitive kinase PKD1 gene promoter in a cell culture model of Parkinson's disease

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Oxidative stress is recognized as a common pathophysiological trigger in degenerative processes of many neurological diseases including Parkinson's disease (PD). Recently, we have identified a novel oxidative stress signaling pathway in which protein kinase D1 (PKD1) is activated as an early protective response to oxidative insult. We showed that PKCδ- dependent PKD1 activation loop phosphorylation is critical to the survival of dopaminergic neurons. In the present study, we characterized the transcriptional regulatory mechanisms of PKD1 in a dopaminergic neuronal model of PD. In order to investigate the transcriptional regulation of PKD1, we first cloned the 5'-flanking region (1620 bp) of the mouse PKD1 gene and then subcloned it into a luciferase reporter vector. Progressive 5' and 3' deletion analyses revealed that the -250/+113 promoter region contains the full promoter activity in MN9D dopaminergic neuronal cells and that the noncoding part of exon1 harbors both positive and negative regulatory elements. In silico analysis of the PKD1 promoter indicated the presence of binding sites for key redox transcription factors, including Sp1, Sp3, and NF-kB. Overexpression of Sp1, Sp3, and NF-kB p65 proteins stimulated PKD1 promoter activity, demonstrating that these redox cis-regulatory elements positively regulate PKD1 gene expression. In order to validate the role of the Sp family of transcription factors in PKD1 gene regulation, we used the Sp inhibitor mithramycin A. Treatment of MN9D dopaminergic cells with mithramycin A resulted in significant attenuation of PKD1 promoter activity, PKD1 mRNA and protein expression. Further mechanistic studies revealed that the histone deacetylase inhibitors trichostatin A and sodium butyrate, and the DNA demethylating agent 5-Aza-2'-deoxycytidine, can also upregulate PKD1 mRNA expression. Collectively, our findings demonstrate that the Sp3 binding and epigenetic mechanisms, such as DNA methylation and histone modifications are key regulatory events controlling the expression of the oxidative stress-sensitive, prosurvival kinase PKD1 in dopaminergic neuronal cells.

G04. Acrylamide-induced Neurotoxicity is Associated with Down Regulation of Kappa Opioid Receptors in Juvenile rats

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Acrylamide is a type-2 alkene monomer with established human neurotoxic actions. While the primary source of human exposure to acrylamide is occupational, other exposure sources include food, drinking water, and smoking. Recent reports by the World Health Organization estimate that acrylamide intake is 2-3 times higher in children than in adults. The primary objective of this project was to assess both behavioral effects and gene expression and translational changes induced by acrylamide neurotoxicity in juvenile rats. Three week-old male Wistar rats were administered acrylamide daily (p.o., 30 mg/kg doses, n=6) for twenty one days. Neurobehavioral effects were assessed twice per week using locomotor activity, weight, hindlimb heel splay, forelimb and hindlimb grip strength. Gene expression changes were evaluated in the cerebellum, spinal cord, and sciatic nerve of acrylamide treated rats using GeneChip Rat Genome 230 2.0 array (Affymetrix). Quantitative RT-PCR followed by western blot analyses were conducted to confirm the transcriptional effects. Acrylamide treatment induced significant characteristic neurotoxic symptoms: increased heel splay ($p<0.01$), decrease in hind limb grip strength ($p<0.001$), and decrease in locomotor activity ($p<0.01$). Gene expression changes evaluated in the cerebellum, spinal cord, and sciatic nerve revealed down regulation of fifteen genes among the three tissues. RT-PCR was conducted to validate the microarray data. The identified differentially expressed genes play a role in neuronal development, pain pathways, muscle contraction, and control of motor function. Western blot analyses revealed a significant decrease ($p<0.05$) in expression of kappa opioid receptors (KOR) in motor cortex as well as reduced expression of Nr4a2 protein in the cerebellum. The current study revealed that acrylamide-induced neurotoxicity in juvenile rats is associated with gene expression changes and down regulation of KOR expression in motor cortex. Such an effect might be responsible for the enhanced pain sensation observed in animal studies as well as in workers who have high acrylamide exposure. Current studies are examining the acrylamide effect on other opioid receptors in both central and peripheral nervous systems, as well as on the Nr4a2 pathways.

G05. Human α-synuclein protects against manganese neurotoxic insult during the early stages of exposure in a dopaminergic cell model of Parkinson's disease.

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The role of α-synuclein (α-Syn) aggregation in neurodegeneration is well recognized, but the physiological function of normal α-Syn protein remains unknown. Recently, we demonstrated that α-Syn negatively regulates a proapoptotic kinase Protein Kinase Cδ (PKCδ) and suppresses parkinsonian toxicant MPP^+ induced dopaminergic neurodegeneration. In the current study, we further show that α-Syn exhibits a neuroprotective role against acute manganese (Mn) induced neurotoxicity in a dopaminergic cell model of Parkinson's disease (N27 cells). Stable expression of human wild type α-synuclein at physiological levels in N27 dopaminergic cells significantly attenuated Mn induced neurotoxicity for up to 24 hr of exposure. To further explore the cellular mechanisms, we studied the mitochondrial dependent apoptotic pathway. Western Blot analysis revealed a time-dependent reduction in the levels of cytosolic cytochrome c release following Mn exposure in the α-Syn-expressing cells compared to vector control cells. Further analysis of the caspase cascade suggests that α-Syn significantly attenuated the Mn-induced caspase -3 and -9 activation in a time-dependent manner. Interestingly, the Mn-induced reactive oxygen species (ROS) generation was not affected by stable expression of α-Syn in N27 cells. Stable expression of α-Syn also dramatically reduced Mn induced proteolytic activation of the pro-apoptotic kinase PKCδ. ICP-MS studies revealed no significant differences in intercellular Mn levels in treated vector and α-Syn cells. Analysis of metal transporter DMT1 expression also showed no differences between α-Syn over expressed cells and vector cells, suggesting α-Syn didn't interfere with Mn uptake in the cells. Collectively, these results demonstrate that α-Syn exhibits neuroprotective effects against Mn induced neurotoxicity during early acute toxicity in a dopaminergic neuronal model of PD (NIH grants ES19267, ES10586, NS74443).

G06. Manganese exposure downregulates STAT5b to compromise the cellular protective mechanisms against manganese neurotoxicity.

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Although manganese (Mn) is an essential element found in most tissues, chronic exposure to Mn has been linked to the pathogenesis of manganism, which displays neurological abnormalities somewhat similar to those associated with Parkinson's disease. However, the cellular and molecular mechanisms underlying Mn-induced neurotoxicity are yet to be defined. Recently, we showed that protein kinase C delta is one of the key mediators of Mn-induced apoptosis in neuronal cells. To further characterize the kinase dependent cell death signaling mechanisms, we examined the effect of Mn on several signaling pathways, including signal transducer and activator of transcription (STATs). Interestingly, 300 M Mn exposure in N27 dopaminergic neuronal cells over a 12 hr downregulated STAT5b protein levels in a time dependent manner. However, STAT1 was unaffected during the Mn treatment, indicating the isoform specific effect of Mn on STAT5b. qRT-PCR analysis also showed a reduced level of STAT5b mRNA levels in Mn treatment. Exposure of Mn to primary striatal cultures also reduced STAT5b. Furthermore, Bcl2, one of the downstream targets of STAT5b, was concomitantly reduced with STAT5b downregulation. Also, the downregulation of STAT5b inversely correlated with increase in apoptosis, as measured by caspase-3 proteolytic cleavage. Importantly, knockdown of STAT5b sensitized cells to Mn toxicity, demonstrating a pro-survival role for STAT5b. In order to recapitulate the results of cell studies in an animal model, C57 black mice were treated with 10 and 30mg/kg via oral gavage for 30 days. Analysis of striatal brain tissue showed significantly reduced STAT5b in Mn-treated mice compared to the control group. Taken together, our results suggest that Mn exposure downregulates STAT5b in striatal neurons and that Mn-induced downregulation of STAT5b may compromise the protective signaling pathway to exacerbate neuronal cell death (NIH grants ES10586, ES19267, NS74443).

G07. Novel mechanisms of drug resistance in leukemia cells associated with changes in HoxA9 and microRNA expression.

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The acquisition of resistance to anticancer drugs is a key obstacle to successful cancer therapy. An increasing number of studies have investigated the roles of microRNAs in drug resistance. We previously reported that the upregulation of miR-135b and miR-196b correlated positively with acquired drug resistance in the human T-cell leukemia cell line, CCRF-CEM (CEM), and that the elevation of expression of these two microRNAs in response to the DNA damaging agent etoposide appears to be histiotype-specific. To develop a mechanistic understanding of why these microRNAs are differentially expressed, we have studied miR-196b, which maps between the HoxA9 and HoxA10 genes on chromosome 7p15.2, suggesting that miR-196b and HoxA genes might be co-activated. Indeed, we found upregulation of HoxA9 mRNA after short-term (48 h) exposure of CEM cells to the topoisomerase II inhibitors etoposide and doxorubicin. Of note, we also found that HoxA9 is constitutively overexpressed in multidrug-resistant CEM/VM-1-5 cells. Of interest, we found that HoxA9 is clearly associated with drug resistance, as knockdown of HoxA9 using esiRNA (a heterogeneous mixture of siRNAs that all target the same mRNA) partially sensitized multidrug-resistant CEM/VM-1-5 cells to etoposide. This indicates that the expression of miR-196b is linked to HoxA gene transcription and to drug responsiveness. We subsequently confirmed that the expression of HoxA9 mRNA follows the same pattern in other leukemia cells. For example, both miR-196b and HoxA9 are upregulated in response to short-term etoposide exposure in HL-60 (acute promyelocytic leukemia), but not in solid tumor-derived MCF7 (breast cancer cell line) and its etoposide-resistant subline MCF7/VP, or Rh30 (rhabdomyosarcoma cell line) and its etoposide-resistant subline, Rh30/V1. We are presently assessing the role of HoxA9 in drug resistance in other leukemia cell lines and investigating the mechanistic basis for this effect. In summary, we report here a novel mechanism of anticancer drug resistance in leukemia cells that is associated with HoxA9 and specific changes in microRNA expression. This is the first report that HoxA9 may impact on anticancer drug resistance.

G08. Molecular genetics of pain in Sickle cell disease.

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Pain is a major concern of patients with sickle cell disease (SCD). SCD pain is characterized by episodes of acute pain that are responsible for the majority of acute care visits by SCD patients and persistent chronic pain affecting quality of life in these patients. Pain severity and frequency vary significantly in SCD patients and we hypothesized that genetic polymorphisms would account for some of these variations. In the study, we applied the candidate gene approach to examine the role of single nucleotide polymorphisms (SNPs) in SCD pain. Sickle cell subjects (N=83; mean age=35.58; 67.5% female; 78.3% SS type) were recruited during routine outpatient clinic visits and entered answers to a computerized pain questionnaire (PAINReportIt®), from which composite pain index (CPI) scores were calculated. Blood or buccal swab samples were collected for DNA extraction and genotyping was completed using PCR-RFLP, Taqman and the Sequenom MassArray System. Data were analyzed using Pearson's chi-square or Fisher's exact tests followed by Bonferroni for multiplicity. Several SNPs were significantly associated with CPI scores, acute care visits or opioid equivalent doses. One such association showed a relationship between DRD3 rs6280 and acute care utilization ($P<0.05$, N=83). The odds of homozygous individuals to have ≥1 utilization are 5.344 fold greater than that of heterozygous individuals. DRD3 rs6280 has been implicated in several pain models conferring its role in opioid therapy for pain in humans. These data suggest that genetic polymorphisms may account for some of the pain variations seen in SCD.

G09. Overexpression of PKCα in T47D breast cancer cells alters the $CD44^{high}/CD24^{low}$ population.

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The purpose of this study was to assess the role of protein kinase C alpha (PKCα) in promoting the breast cancer stem cell phenotype. PKCα overexpression in breast cancers is associated with increased proliferation, metastatic growth and drug resistance. Work in our lab demonstrated that stable overexpression of PKCα in T47D breast cancer cells leads to tamoxifen resistance, hormone independent growth (Chisamore, M.J., et al. 2001) and an increase in the invasive and migratory potential of these cells (White, B.P., et al. AACR 102nd Annual Meeting 2011). Furthmore, we have shown that the overexpression of PKCα leads to an increase in Notch4 activity in T47D cells (Yun, J., et al. 29th Annual San Antonio Breast Cancer Symposium. 2006), which recently was shown to play an important role in breast cancer stem cell activity (Harrison, H., et al. 2010). In this study, we investigated the role of PKCα in regulating breast cancer stem cell activity. We find that the overexpression of PKCα in the T47D breast cancer cell line (T47D/PKCα) led to an increased tendency to form mammospheres in non-adherent cell culture. Flow cytometric analysis of T47D/PKCα cells revealed a 3-fold increase in the $CD44^{high}/CD24^{low}$ population compared to the parental cell line. Pharmacological inhibition of PKCα by Gö6976 (1μM) significantly reduced the $CD44^{high}/CD24^{low}$ population within the T47D/PKCα cell line. The $CD44^{high}/CD24^{low}$ population was also reduced by the transient downregulation of PKCα by siRNA. Transient downregulation of PKCα was accompanied by a concurrent downregulation of Notch4 suggesting that Notch4 may play a role in the stem cell phenotype exhibited by the overexpression of PKCα in these cells. These data suggest that PKCα may result in an increase in the breast cancer stem cell population perhaps contributing to the more aggressive phenotype observed in PKCα-overexpressing breast cancers.

G10. Induction of Prokineticin-2 and its neuroprotective effect against neurotoxic insult in dopaminergic neurons.

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Prokineticin-2 (PK2), a recently discovered mammalian protein homolog to mamba snake venom, has been shown to regulate diverse physiological functions in a tissue-specific manner. In the adult brain, PK2 signaling participates in olfactory bulb neurogenesis by directing the migration of subventricular zone progenitor cells, and it also controls circadian rhythms by functioning as an output molecule from the suprachiasmatic nucleus. PK2 expression, however, is undetectable in other regions of the brain. In the present study, we observed a dramatic increase in PK2 gene expression in an MPP^+-treated dopaminergic neuronal cell model, as measured by targeted qPCR pathway

array analysis. Western blot and immunohistochemical analyses of PK2 protein levels further validated the upregulation of PK2 gene expression in MPP^+-treated cells. PK2 expression in nigral dopaminergic neurons also increased in the MPTP model of Parkinson's disease (PD). Importantly, elevated levels of PK2 in nigral samples from postmortem PD patients further supported the clinical relevance of our findings. The PK2 receptors PKR1 and PKR2 were both abundantly expressed in primary dopaminergic neurons. Interestingly, treatment with recombinant PK2 (rPK2) significantly attenuated MPP^+-induced ROS generation, caspase-3 activation and DNA fragmentation, demonstrating its neuroprotective function. Furthermore, rPK2 increased calcium in the dopaminergic neuronal cell line and primary dopaminergic neurons, and the PK2 receptor antagonist PC-7 significantly blocked PK2-induced calcium levels. Moreover, the primary mesencephalic neuronal cultures treated with rPK2 were significantly protected from MPP^+-induced TH positive neuronal loss and dopamine uptake, further confirming the neuroprotective effects of PK2. Taken together, our results from both cell culture and animal models demonstrate a novel neuroprotective role for PK2 signaling against neurotoxic stress in the nigrostriatal dopaminergic system.

G11. Solution structures and models describing the thioredoxin system from mycobacterium tuberculosis.

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Mycobacterium tuberculosis (M. tb) resists the oxidative killing by host macrophages, in part by using its thioredoxin (Trx) system. Trx catalyzes thiol-disulfide exchange reactions using redox active cysteine thiols to reduce disulfides of other essential proteins, including metabolically essential enzymes. Oxidized Trx is then reduced by thioredoxin reductase (TrxR) in an NADPHdependant reaction. The M. tb Trx system consists of three Trx's (TrxA, TrxB, and TrxC) and one Trx reductase (TrxR). TrxB and TrxC are known substrates of TrxR. TrxA, meanwhile, has been reported to not bind to TrxR and to possibly be "cryptic." The M. tb Trx system is dissimilar to the human Trx system (25-35% indentity) such that inhibitor specificity for the M. tb Trx system should be obtainable. Thus, the M. tb Trx system appears to be a viable drug target. The objective of this study was to calculate the NMR solution structures of oxidized and reduced Trx's. Structures have been calculated using standard NMR solution structure experiments. Our studies indicate that TrxA is well- folded in both oxidized and reduced states. Structures of the individual Trx's and binding models of the TrxN(N=A, B, or C)-TrxR, constructed from NMR titrations of each ^{15}N enriched TrxN and unlabeled TrxR, are discussed. These binding models show an empty pocket between the Trx and the TrxR. Design of uncompetitive inhibitors will be discussed targeting this pocket.

G12. Overexpression of protein kinase C alpha differentially activates transcription factors in T47D breast cancer cells in 3D culture in presence of 17β-estradiol.

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Background: 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, 17β-estradiol (E2) inhibits colony formation of T47D/PKCα in 3D Matrigel and tumor growth *in vivo* (Zhang et al, Mol. Cancer Res, 2009). Differential transcriptional activation may account for the phenotypic changes observed in T47D/PKCα cells. In this study, we sought to identify transcription factors differentially activated in T47D:A18/neo versus T47D:A18/PKCα grown in 3D Matrigel in presence and absence of E2. Method: A system for rapid, non-invasive, large scale, dynamic quantification of trancriptional factor (TF) activity was developed (Weiss et al, PLoS ONE, 2010). Reporter constructs were constructed containing TF binding site that preceeds a basal promoter to produce firefly luciferase (Fluc) using a lentiviral backbone. The control construct contained only the basal promoter. T47D/PKCα and T47D/neo cells were infected with lentiviral reporter constructs. Cells were seeded on top of Matrigel in 384 well plates in estrogen-free media. After 3 days, cells were treated with either E2 (10^{-9}M) or EtOH vehicle. Fluc activity was assessed by bioluminescence imaging at 24, 48 and 72 hours following treatment.
Results: There were differential transcriptional activities between the parental T47D/neo and T47D/PKCα cell line at the basal level. Of all TFs tested, many had significantly higher activities in T47D/PKCα cells. Furthermore, E2 has different effects on time dynamics of some TFs in two cell lines. Lastly, some TFs, such as Oct4, ETS1, and Stat5, were modulated by E2 only in T47D/PKCα cells. Conclusion: These findings suggest that overexpression of PKCα alters TF activity in T47D breast cancer cells. Moreover, E2 treatment influences the transcriptional profiles of PKCα overexpressing and parental cell lines differently, providing a better understanding of the mechanism through which PKCα causes changes in cancer phenotype and lead to new approaches to combat breast cancer.

G13. Protein kinase C α overexpression is associated with loss of membrane-associated E-cadherin and β-catenin in T47D xenograft breast tumors.

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Expression of protein kinase C α (PKCα) has been shown to be a clinically relevant indicator of tamoxifen response, recurrence and overall survival in breast cancer. To study this association, we developed a model of PKCα-overexpressing breast cancer by stably transfecting PKCα into T47D breast cancer cells. We have shown PKCα induces a hormone-independent, tamoxifenresistant phenotype *in vitro* and *in vivo*. This model is further characterized *in vitro* by increased migration and invasion, expression of mesenchymal markers and loss of adherens junctions and epithelial proteins. β-Catenin and E-cadherin are components of adherens junctions in normal epithelia and their loss is associated with poor prognosis in breast cancer. Therefore we hypothesized that xenograft tumors derived from T47D/PKCα cells would have loss of membrane-associated β-catenin and E-cadherin. Immunofluorescence staining showed cytoplasmic localization of β-catenin and E-cadherin in T47D/PKCα tumors in sharp contrast to membrane association in T47D/neo tumors. Western blot showed reduction in the level of E-cadherin in T47D/PKCα tumor samples but no change in the level of β-catenin compared to T47D/neo tumors. Based on this, we next wanted evaluate the β-catenin degradation pathway mediated by glycogen synthase kinase-3β (GSK-3β). Cellular extracts show increased levels of the serine 9 inhibitory phosphorylation of GSK-3β in T47D/PKCα cells but no increase in total protein compared to T47D/neo. Treatment with the proteasomal inhibitor MG132 for 2 h did not increase the levels of β-catenin *in vitro* in T47D/PKCα cells. Current data indicate a correlation between PKCα expression and loss of membrane-associated β-catenin and E-cadherin. Further, β-catenin is stabilized in the cytoplasm of T47D/PKCα cells possibly allowing for nuclear localization and downstream gene transcription. Taken together with previous data, PKCα correlates with markers of poor outcome in addition to hormone-independence and tamoxifen-resistance suggesting that PKCα may play a central role in breast cancer progression.

G14. The role of CX3CR1 in resistance of ovarian carcinoma cells to radiation therapy.

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Ovarian carcinoma is a leading cause of death from gynecologic malignancies. The current standard of care, a combination of chemotherapy and radiation, fails to keep patients in remission. Thus, modifications of the therapy and the combinations with the new molecular biological technologies are crucial for the development of the modernized approaches to combat this disease. Previous attempts to use radiotherapy as an additional treatment was not successful mainly due to the dose-related side effects, as well as radioresistance. Therefore, mechanistical understanding of the biology of ovarian carcinoma could offer ways to overcome current problems. Fractalkine receptor (CX3CR1) belongs to a chemokine family of G protein-coupled receptors, the most frequently and successfully drug-targeted group of proteins. Interaction of chemokines with their receptors plays a pivotal role in homing distant metastasis, as well as promoting migration, adhesion, and proliferation in many types of cancer. This project is aimed at understanding the role of CX3CR1 in sensitization of epithelial ovarian cancer cells to radiotherapy. Our data indicate that downregulation of CX3CR1 in ovarian carcinoma cells leads to approximately 50% sensitization to x-ray radiation, as determined by the clonogenic ability assay. Our Western blotting and immunofluorescence analysis data also show that downregulation of CX3CR1 results in accumulation of DNA damage at lower doses. Thus, our data indicate that disruption of the CX3CR1 signaling could sensitize ovarian carcinoma to radiation therapy.

G15. Role of Gα12 and Gαq in constitutive vs. thrombin-induced vWF secretion and thrombosis.

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Thrombosis and embolism in pulmonary blood vessels is a common cause of acute lung injury. An important and yet poorly understood mechanism required for coagulation is von Willebrand Factor (vWF) secretion by endothelial cells (ECs). We used an siRNA approach to distinguish the role of Gα12, Gα13, and Gαq as well as RhoA and αSNAP- a Ca^{2+}-dependent adaptor protein for NSF ATPase in the SNARE exocyst/fusion complex- in basal and thrombin-induced vWF secretion in human lung endothelial cells. αSNAP siRNA completely abolished constitutive, Ca^{2+}-induced, as well as thrombin-induced vWF secretion suggesting vWF secretion is mediated by fusion and exocytosis of WPBs. In addition, siRNA-mediated depletion of Gα12 inhibited both constitutive and thrombin-induced vWF secretion while exogenous expression of a constitutively-activated Gα12 mutant promoted vWF secretion. Interestingly, Gα12 siRNA had no affect on Ca^{2+}-induced vWF secretion. In Gαq- and RhoA siRNA depleted HUVECs, thrombin-induced vWF secretion was reduced by 40% whereas basal vWF secretion was not affected and depletion of Gα13 had no effect on basal or thrombin-induced vWF secretion. Based on our data in cultured human endothelial cells, we hypothesized that G12/13 and Gq/11 deficiency, by affecting availability of vWF, would cause defects in hemostasis and thrombosis in a mouse model of vascular injury. We used EC-Gq/11 dKO, $G11^{-/-}$ and $G12^{-/-}$ knockout mice and measured clotting time, vWF in blood and in lung perfusate. These *in vivo* studies confirmed the important role of Gα12 in basal vWF secretion and revealed complementary roles of G12 and Gq in thrombin-induced vWF secretion. Our research, thus, provides new clues regarding the molecular mechanisms that initiate vascular disease and anticipate that this information will lead to development of novel pharmacological reagents for treatment of thrombotic cardiovascular diseases.

G16. Inducible deletion of endothelial FAK triggers acute lung injury through p38 MAPK mediated dysregulation of RhoA and Rac1 activities.

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Sepsis-induced acute lung injury (ALI) results from inflammatory cell infiltration and protein-rich edema formation. Since focal adhesion kinase (FAK) influences adherens junction formation required for establishing the endothelial barrier, we generated tamoxifen-inducible endothelial (EC) FAK deficient transgenic mice (EC-$FAK^{-/-}$) to address whether FAK controls pulmonary fluid balance and inflammation. EC-FAK deletion severely disrupts the lung vasculature and promotes pro-inflammatory cytokine generation such that EC-$FAK^{-/-}$ mice have increased mortality to endotoxin (LPS). FAK null lung ECs showed actin stress fibers, adherens junction disassembly and increased pro-inflammatory cytokine levels, naming EC-FAK as a central regulator of lung fluid balance and inflammation. Mechanistically, loss of FAK markedly altered the balance of small GTPases RhoA and Rac1; RhoA activity was significantly increased whereas Rac1 was decreased. FAK deletion also amplified p38MAPK activity, which is known to generate cytokines downstream of toll-like receptors. We confirmed these findings using siRNA-mediated FAK suppression in human pulmonary ECs. Moreover, EC-FAK levels were decreased in lungs of patients diagnosed with lung disease and in mice following sepsis. Thus, upregulating endothelial-FAK provides an unexpected mechanism for preventing cytokine storm and ALI.

G17. Impact of the GABA-A α1 positive allosteric modulator Indiplon in reversing the abnormal prefrontal disinhibitory state induced by NMDA receptor blockade during adolescence.

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Developmental disruption of prefrontal cortical (PFC) inhibitory circuits is thought to contribute to the adolescent onset of cognitive deficits observed in schizophrenia. However, the mechanisms underlying such changes remain unclear. At the cellular level, changes in PFC function are dependent on local dopamine-glutamate interaction and the activity of parvalbumin-positive fast-spiking GABAergic interneurons, which exert inhibition over pyramidal output cells and enable synchronous firing in the PFC. Given the crucial role of N-methyl D-aspartate (NMDA) receptors in the regulation of GABAergic transmission in the PFC, we examined how repeated administration of the NMDA antagonist MK-801 during the periadolescent transition period (from postnatal days P35-40) impacts the normal development of local prefrontal GABAergic network function. Electrophysiological analyses of cortical network activity *in vivo* indicate that MK-801-induced developmental disruption of local prefrontal GABAergic circuits is sufficient to elicit a sustained disinhibited PFC state through adulthood (P65-85). Such disinhibition is associated with selective attenuation of high frequency (20, 40 & 100 Hz)-dependent inhibitory control exerted by ventral hippocampal afferents onto the PFC. We next determined the impact of the GABA-A α1 positive allosteric modulator Indiplon in reversing these changes. We found that acute local administration of Indiplon into the PFC normalized the abnormal longlasting prefrontal disinhibitory state induced by adolescent MK-801 exposure. Together, these results indicate that impairments of glutamatergic activation of GABAergic interneurons by NMDA receptors during adolescence can disrupt the normal development of a functional inhibitory tone in the adult PFC and contribute to the onset of prefrontal deficits observed in schizophrenia. Our data also indicate that such a disinhibited frontal cortical state can be pharmacologically rescued by a GABA-A α1 positive allosteric modulator. *Supported by NIH Grant MH086507 and the Brain Research Foundation.*

G18. Sulforaphane restores physiological function to resistance arterioles impaired by type-2 diabetes.

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Increased reactive oxygen species (ROS) and depleted levels of antioxidants such as glutathione (GSH) are hallmarks of diabetes. In the present study, we tested the hypothesis that GSH depletion and elevated ROS increase myogenic tone in type- 2 diabetes. Myogenic regulation, defined as the constriction in response to changes in intraluminal pressure, is an important process regulating capillary pressure and peripheral resistance. In the current study, myogenic tone was monitored in mesenteric arteries from diabetic (db/db) and non-diabetic (db/m) mice. At physiological pressures, myogenic tone was greater in db/db vessels compared to db/m. ROS levels were higher in db/db vessels and associated with increased myogenic tone. NF-E2-related factor (Nrf-2) is a transcription factor that regulates the expression of antioxidant genes. Nrf-2-dependent genes and total GSH were downregulated in db/db arterioles. Sulforaphane, a phytochemical found in cruciferous vegetables such as broccoli sprouts has been identified as an Nrf-2 activator. Incubating db/db vessels overnight with sulforaphane (500 nM) increased mRNA levels of Gclc and Gclm, the subunits required for GSH synthesis. Sulforaphane treatment restored myogenic tone and lowered ROS levels. Although sulforaphane also increased Gclc and Gclm mRNA levels in db/m vessels it did not affect myogenic tone and ROS levels. This suggests that sulforaphane restores vascular function by increasing GSH levels. To confirm this, myogenic tone was assessed after manipulating GSH levels directly. Incubation with cell-permeant GSH reduced myogenic tone in db/db vessels compared to untreated db/db controls. Depletion of GSH levels in db/m vessels with buthionine sulfoximine, a glutathione synthesis inhibitor, increased myogenic tone in db/m compared to untreated controls. In conclusion, type-2 diabetes is associated with downregulation of Nrf-2 genes that results in depleted GSH and a concomitant increase in ROS levels. This imbalance in antioxidant status is critically involved in producing increased myogenic tone in resistance vessels. This likely increases peripheral resistance and could contribute to hypertension seen in these animals and possibly in humans. Importantly, we demonstrate that sulforaphane effectively activates Nrf-2 genes to restore total GSH, ROS levels and myogenic tone, thus identifying sulforaphane as a potential therapeutic to treat diabetic vascular complications.

G19. Structural plasticity of corticostriatal synapses in a model of levodopa-induced dyskinesias

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Levodopa (L-dopa)-induced dyskinesias (LIDs) are among the most common and disabling complications in the treatment of Parkinson's disease. Previous studies in animal models have suggested that changes in glutamate function lead to an aberrant synaptic plasticity. We questioned whether an increase in corticostriatal glutamatergic synapses could underlie LIDs in a rat model. We used stereology to count synapses in the striatum of adult male rats that received sham or 6-hydroxydopamine (6- OHDA) lesions, and were treated with L-dopa or saline for 3 weeks. Abnormal involuntary movements (AIMs) were rated following an injection of L-dopa. Rats were perfused and sections through the dorsal striatum were immunoreacted with vesicular glutamate transporter1 (VGLUT1) antisera to label corticostriatal terminals. Synapses were sampled in a volume of 150-190μm^2 over 4 serial sections in 15 planes using the physical disector. Dopamine depletion significantly reduced the total number of asymmetric (excitatory) inputs from the cortex, especially the number of axospinous but no axodendritic contacts. Treatment with L-dopa alone (sham/L-dopa group) did not alter the total number of excitatory synapses compared to salinetreated controls. The Parkinsonian rats that developed severe AIMs showed a significant increase in the number of VGIUT1-labeled synapses ($p<0.005$), and VGLUT1-labeled axospinous ($p<0.01$) and axodendritic contacts ($p<0.005$). The proportion of contacts on post-synaptic targets also changed. Notably, the severe AIMs rats showed an increase in the proportion of axodendritic to axospinous synapses, suggesting an aberrant redistribution of these terminals. Interestingly, there was a significant decrease in VGLUT1-labeled multisynaptic boutons (MSBs) in the severe AIMs group versus controls ($p<0.05$). Results show that corticostriatal contacts are increased in the dyskinetic striatum, and that these changes are due to sprouting onto dendrites and spines, rather than a remodeling of existing boutons, as suggested by the decrease in MSBs. This study provides data on the role of pathway-specific synaptic changes in striatal circuitry in L-dopa-induced AIMs and enhances our understanding of current limitations of anti-dyskinetic therapies.

GLC-ASPET Abstracts 2012: Undergraduate Students

U01. Determining the status of indoor airborne microbial organisms in the gentilly area post Hurricane Katrina.

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After Hurricane Katrina struck New Orleans, Louisiana, on 29 August 2005, 80% of the city was inundated with water including the Gentilly community. In 2006, studies were conducted by Singleton et al. to establish the types and concentrations of airborne microbes both inside and outside of selected buildings in neighborhoods around the greater New Orleans area. Mold and other contaminants grew inside of the buildings and high concentrations of harmful micro-organisms were found. The purpose of this study is to determine the status of indoor airborne microbial organisms in buildings within the Gentilly area post Hurricane Katrina. Indoor airborne sampling was conducted for 6 hours at 4 buildings within the Gentilly area. Various tests were then conducted on samples to identify the types of microorganisms present. It was found that most bacteria identified were gram positive and cocci in shape and few were bacillus in shape and both gram positive and negative. These bacteria were capable of acid fermentation but did not produce gas. No spores were identified during endospore staining indicating the absence of harmful pathogens. A small number of molds were identified. After 48 hours there was little to no growth of microorganisms as compared to research conducted by Singleton et al. in 2006 in which high concentrations of microbes were identified in buildings samples after 48 hours. This indicates that the concentration of microorganisms was less in these buildings as compared to research conducted in 2006. These results show that there have been improvements in the air quality of the buildings since Hurricane Katrina. This may be as a result of proper refurbishing and remediation of the buildings. Future research includes conducting DNA analysis for further identification of the microorganisms found at the sample sites and determining the concentration and types of microorganisms present outside of the buildings. Future research also includes retesting the sites that were tested by Singleton et al. in order to determine the status of their microbes since the year 2006.

U02. Biochemical requirements for suppressing a constitutively active allele of Gs alpha

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Inappropriate activation of the G_s alpha subunit by mutation of modification of Arg201 is associated with the human diseases of McCune-Albright Syndrome and cholera. Previous work in our laboratory identified Asp223 as a site where substitution to valine could reverse the constitutive activity of an Arg201His mutation. In this study, Asp223 was substituted with a variety of other amino acids, including glutamic acid, asparagine, glutamine, alanine, leucine, isoleucine, and glycine. HEK cells transfected with plasmids carrying the different G_s alpha subunit alleles were used to measure basal levels of cAMP. The Arg201His allele significantly elevates basal cAMP. Substitution of Asp223 with nonpolar residues suppressed the elevation in basal cAMP, while substitution with acidic or polar residues had no effect on the constitutive activity of the Arg201His mutation. This characterization of which amino acids at residue 223 can suppress the Arg201His mutation may provide a foundation for identifying small molecules that can be used as effective therapies against McCune-Albirght Syndrome.

U03. Identifying specific amino acids in Parkinson's disease protein alpha-synuclein that control its toxic properties.

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Parkinson's disease (PD) is a common neurodegenerative disease in which neurons in a specific region of the midbrain die. This loss results in a variety of symptoms including tremors, rigidity, and other motor and cognitive problems. A PD hallmark is the misfolding-induced aggregation of a membrane-associated protein called alpha-synuclein in these dying neurons. Proteins are made of amino acids, and while each amino acid contributes to the overall protein shape and function, certain amino acids are typically more important than others. My research project involves testing, in yeast models, a subset of five specific amino acids recently implicated to be important in alpha-synuclein's shape and inducing PD-related property changes: namely, its ability to accumulate within cells, associate with membrane phospholipids, and induce cellular toxicity. First, we mutated each of the five amino acids (D2, A76, V77, Q79, E83) to a different amino acid to either enhance (A76V, E83A, E83V) or reduce (D2A, A76E, V77E, Q79R) their predicted contributions to the above three pathological characteristics. Then, we have begun assessing each mutant's ability to alter alpha-synuclein 1) association with phospholipid membranes, 2) aggregation, and 3) toxicity to cells in two established PD models, budding yeast and fission yeast. Our accruing data for each of these five amino acids supports their relevance in alpha-synuclein's contributions to PD pathology, strengthening previous predictions in the field and the usefulness of yeasts as model organisms for studying molecular mechanisms underlying the spectrum of protein misfolding diseases.

U04. α-synuclein familial mutants in Parkinson's disease: Does combining them aggravate pathological properties in yeast models?

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Parkinson's disease (PD) is a hypokinetic neurodegenerative disease that arises from the selective death of midbrain dopaminergic neurons. This cell death is linked to misfolding and accumulation of the abundant brain protein, α-synuclein. Genetic mutations account for 10% of familial PD cases and the best studied mutant gene is α-synuclein itself, where the familial point mutants are A53T, A30P and E46K. The PD-linked properties of each α-synuclein familial mutant are widely studied and reported. Our lab too has previously published each familial mutant's pathology-related properties using two types of yeast models (Sharma et al, 2006; Brandis et al, 2006; Fiske et al, 2011), where each mutant distinctively affects α-synuclein's localization, aggregation, and cell survival properties, indicating each amino acid's strategic importance to controlling pathology. In this study, we hypothesized that combining these three familial mutations (evaluated as double or triple mutants) will blend individual mutant's cellular localization and aggregation properties, and they will lead to higher cellular toxicity. We tested our hypothesis in fission yeast (which best models α-synuclein aggregation) and budding yeast (which best models α-synuclein membrane association). Surprisingly, we found one mutant (A30P) dominated over the other two mutants (A53T, E46K) in controlling α-synuclein localization in both organisms, and that the exact pattern of localization depended on the type of yeast. Moreover, the combination of double or triple mutations did increase cellular toxicity over what was achieved by individual mutants in either organism. Our findings illustrate that each of these individual amino acids within

α-synuclein cooperatively exert differential influence over cellular pathology and that organismal context is also a determinant to this pathology. Currently, as our final analysis, we are investigating the single and combinatorial familial mutant properties once again in budding yeast using an eGFP vector system that not only much higher α-synuclein expression, but prominently displays both membrane localization and intracellular aggregation over a time course.

U05. Finding novel intragenic suppressors of a constitutively active allele of Gs alpha.

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McCune-Albright Syndrome (MAS) is a genetic disorder caused by mutations that inhibit GTP hydrolysis in Gsα, permanently activating the protein. We have developed a yeast model system for MAS in which mutations in the yeast Gα subunit homologous to those seen in MAS (R297H) prevent colony formation when the mutant allele is the only Gα gene present in the cells. We then constructed of a library of 32,000 secondary mutations in the constitutively active yeast Gα gene with the goal of identifying intragenic suppressors of the MAS mutation. Nine novel suppressor alleles have been identified and have been mapped to the crystal structure of the Gsαprotein. Suppressor mutations have been identified in the GTP-binding site of the protein, near the βγ-interaction surface, on a potential effector interaction surface, in switch III, and also on regions of the α subunit with no currently characterized function. Ten of the suppressors identified in the yeast model have been studied in the context of the human Gsα protein, expressed in a human cell line. Three of the ten suppress the constitutive elevation in basal cAMP caused by the MAS mutation (R201H). The construction of a detailed map of sites on the surface of Gα which can inactivate the MAS allele can drive rational drug discovery of better treatments for MAS patients.

U06. GABA attenuates L-DOPA-induced striatal and nigral ERK1/2 signaling in a rat model of Parkinson's disease.

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Parkinson's disease (PD) is characterized by the degeneration of nigrostriatal dopaminergic neurons. L-DOPA is the primary drug used to treat PD symptoms, but side effects such as dyskinesias limit its long term use. Previous findings show that LDOPA acts on supersensitive D1 receptors to induce extracellular signal-regulated kinase (ERK1/2), a MAP-kinase protein that may be involved in induction of dyskinesias. Since α-aminobutyric acid (GABA) is known to be intimately involved in basal ganglia function, we investigated whether increasing GABA levels via a GABA-Transaminase (GABA-T) inhibitor affects the LDOPA-induced ERK1/2 phosphorylation in the striatum and substantia nigra (SN) using a rat model of PD. Unilateral dopaminergic lesions of median forebrain bundle neurons were done using the neurotoxin 6-hydroxydopamine. Rats were prescreened for the extent of the lesion by apomorphine-induced rotation test. Lesioned rats were treated with aminooxyacetic acid (AOAA, a GABA-T inhibitor), L-DOPA, or in combination. Immunohistochemistry of tyrosine hydroxylase (TH, a direct indicator of lesion), substance P (SP, an indirect marker that is decreased after lesion), and phospho-ERK1/2 was done using striatum and SN slices. As expected, unilateral dopaminergic lesions produced >90% TH loss and a 30-70% SP loss in the striatum and SN. L-DOPA alone induced a 343% and 330% increase in phospho-ERK1/2 in the striatum and SN, respectively. Pretreatment with AOAA attenuated the L-DOPA induced increase in phospho-ERK1/2 by 62% and 68% in the striatum and SN, respectively. Pretreatment with AOAA also attenuated the L-DOPA induced rotations. AOAA alone did not affect the parameters tested. It has been previously shown that GABAergic compounds are modestly successful in relieving PD symptoms. The present study reveals for the first time that GABAergic drugs, by virtue of attenuating L-DOPA-induced rotations and ERK phosphorylation, may also help counteract the dyskinesia type side effect of L-DOPA.

U07. Osteoblast gene expression in response to changes in cAMP.

Turcic Kyle, Ghanayem Kathryn, Rylaarsdam Robin; Benedictine University, Lisle, IL 60532

McCune-Albright Syndrome (MAS) is a human genetic disease characterized by a classic triad of symptoms: cafe au lait hyperpigmentation of the skin, precocious puberty, and polyostotic fibrous dysplasia of bone. The cause of this disease is a somatic mutation in the heterotrimeric G alpha subunit, Gs. The MAS mutation prevents inactivation of the G-protein, resulting in hormone signaling pathways that are permanently activated in the affected tissues. While the skin pigmentation is largely a cosmetic issue and the precocious puberty can be somewhat controlled by medication, little can be done to treat or prevent the progression of the spongy bone found in the fibrous dysplasia lesions, although surgeries to reduce bone malformations are in use. The goal of this project is to examine the changes in gene expression in bone cells caused by MAS with the aim of identifying potential targets for drugs to treat this aspect of the disease. In our preliminary experiments, 7F2 osteoblastic cells were treated with forskolin for varying amounts of time to mimic the effects of the constitutively active Gs allele seen in MAS. Forskolin directly activates adenylyl cyclase, the effector enzyme of Gs. RNA isolated from these cells was subjected to RT-PCR to measure expression levels of two bone-specific genes, RUNX2 and Bone SialoProtein (BSP). The levels of these transcripts were normalized to RNA levels for the housekeeping gene GAPDH. These experiments will provide the technical foundation for microarray experiments on differentiated human osteoblasts in the future. Genes unregulated by overactive signaling through Gs will be attractive candidates to be inactivated by drugs, leading to better treatments for the bone pathology of MAS.

U08. Effect of season on dendritic spine formation: Using the spinophilin protein as a method of assessing regional neuronal plasticity in the forebrain of the male red-sided garter snake.

Prokop Jennifer, Monzon R., Jurkovic J. & Krohmer R.W.; Saint Xavier University, Chicago IL 60655

Studies have recorded variations of regional morphology in the brains of seasonally breeding vertebrates. Male red-sided garter snakes (Thamnophis sirtalis parietalis) exhibit a disassociated reproductive pattern where mating is initiated at a time when the gonads and steroidogenesis are inactive. The past studies indicate that neural plasticity is correlated with hormonal sex-steroid fluctuations. These changes can be measured by the density and number of dendritic protrusions. Dendritic protrusions, known as dendritic spines, receive much of the incoming excitatory signals from associated contacts with surrounding neurons. In addition, these dendritic spines also appear to be transient and have the ability to mobilize, relocate and emerge from the dendritic shaft enabling a certain level of synaptic plasticity, if conditions are met. One such condition is the concentration of the scaffold protein, spinophilin. Spinophilin is a precursor, cytoskeletal protein that is vital for the proliferation of novel spines and increased density. The current study examined seasonal and hormonal influences on the density and morphology of dendritic spines within regions shown to be critical for the regulation of reproductive behaviors. The study attempted to determine if seasonality was correlated to dendritic spine formation via spinophilin. After spring emergence, collected animals were castrated and analyzed in terms of seasonal differences in brain region spinophilin expression. Tissue samples were also processed using the FD Rapid Golgi stain technique and the spines were counted and analyzed to determine density. In male red-sided garter snakes, dendritic spines and the concentration of spinophilin, within various regions associated with reproductive behaviors are dramatically denser during spring mating than in fall collected nonmating individuals. Also, animals maintained under conditions of low temperature dormancy (LTD) exhibited increasing spine density the longer animals were maintained in LTD. Animals receiving testosterone or estradiol exhibited greater density of dendritic spines than control animals. These results add to the increasing amount of evidence suggesting that testosterone may play a critical, although indirect, role in the regulation of reproductive activity in an animal exhibiting a dissociated reproductive pattern.

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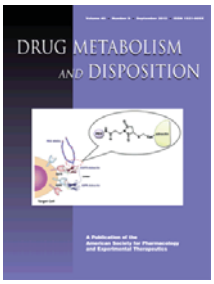

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Membership Application

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Application for:

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Sex: ☐ Female ☐ Male

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