

## EB'05 ► San Diego

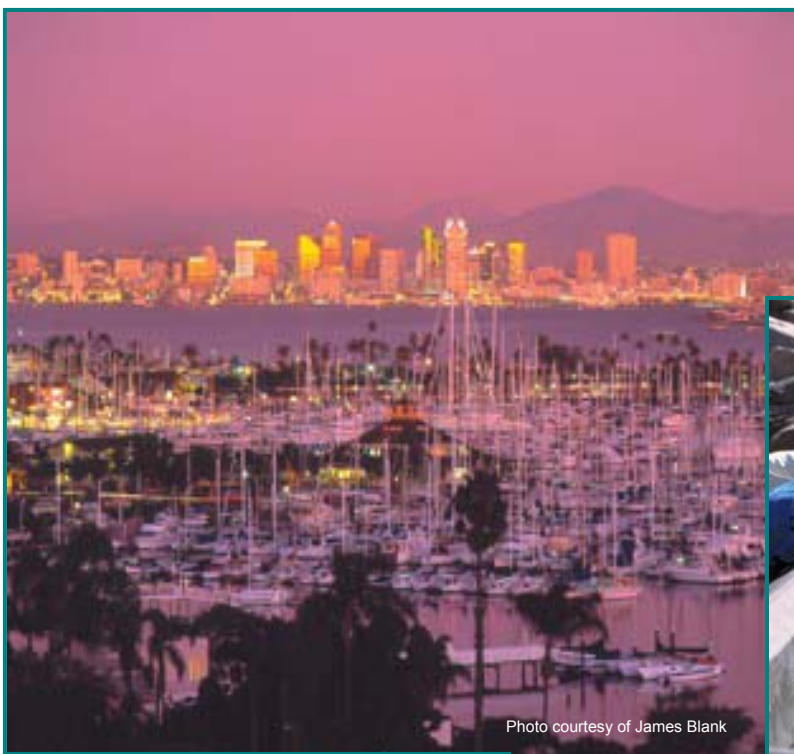


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Photo courtesy of Bill Robinson



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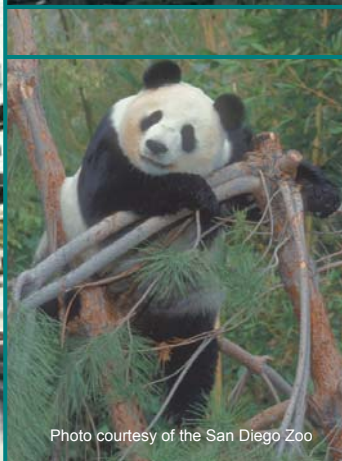


Photo courtesy of the San Diego Zoo

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# The PHARMACOLOGIST

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### A NEW LANDSCAPE

Last year in this spot then-president David Bylund told you about the development of a 5-year plan for guiding ASPET to the next level. That plan has been completed and formally adopted by ASPET's Council. Three important elements of the plan are for ASPET to be the society that all pharmacologists want to join, for ASPET's annual scientific meeting to be the meeting that all pharmacologists want to attend, and for ASPET's journals to be the primary outlets in which pharmacologists choose to publish. Among the several metrics that will be used to gauge progress in achieving those visions are the obvious ones of numbers: number of ASPET members, number of meeting attendees who indicate ASPET as their primary society or interest, and number of manuscripts received. Here is where your help is needed.

The face of pharmacology has changed significantly since I first entered the field. And I'm referring to more than just the replacement of smoked kymographs with electronic physiological monitors and computers. Pharmacologists were easy to identify. They were found mainly in pharmacology departments of academic institutions or pharmaceutical companies, and the members of those departments, more often than not, had received a Ph.D. degree in pharmacology or a medical degree. They studied the effects of drugs in animals or people or in preparations of tissues taken from living organisms. Almost all categorized themselves as pharmacologists.



The landscape today is different. Today's pharmacology departments contain few medical doctors and many scientists whose training is in areas that were almost unknown a few decades ago. Some academic institutions have eliminated separate pharmacology departments and have relocated their faculty into other administrative units. In the dwindling number of major pharmaceutical companies, research groups commonly are organized by disease rather than by basic science discipline; smaller companies are staffed by "research scientists."

Much excellent pharmacology research is carried out by investigators who have never worked with a living subject or its tissues, often in places other than a department of pharmacology, and many pharmacologists conduct drug-research-related activities away from the laboratory bench. It is very likely that many of these scientists do not think of themselves as pharmacologists, even though they are. Clearly, ASPET's constituency has become broader and somewhat amorphous.

ASPET needs to increase its visibility and relevancy to its constituency. Pharmacology is the science of drugs, broadly defined, and those involved in that science are pharmacologists, regardless of their formal training and current departmental or organizational affiliation. The 5-year vision for ASPET provides a good foundation for reaching out in a meaningful way to all pharmacologists, but your help is vital. Let your colleagues who are not members know that ASPET welcomes membership of all scientists who are interested in drug research, regardless of their training or title. Encourage them to publish in ASPET journals, and publish in them yourselves. Let them know about the annual scientific meeting or, better yet, encourage them to submit an abstract or a proposal for a symposium. And promote the merits of involvement with ASPET to students and early-career research scientists. Many will be unaware that ASPET is open to them and, in fact, has programs designed specifically to encourage their participation. Send them a copy of *The Pharmacologist* so that they can see what's happening at ASPET.

Equally important, give us your suggestions as to what you think ASPET should be doing to achieve its vision of the future. After all, ASPET is an organization of members and for members, and your input is important. Contact me or any member of ASPET's Council or ASPET's Executive Officer, Christie Carrico.

Pharmacology continues to be an exciting and essential discipline. ASPET is taking the steps needed to remain out front in the science and in the policy issues that are important to pharmacologists, and to be truly representative of its broad constituency. As a vibrant and dynamic ASPET moves closer to the centennial of its founding, I thank you for allowing me to take its helm for a little while. ♦





**ASPET's Preliminary Program**  
**Experimental Biology 2005**  
**San Diego, CA**  
**April 2-6, 2005**

[WWW.ASPET.ORG/PUBLIC/MEETINGS/EB05.HTML](http://WWW.ASPET.ORG/PUBLIC/MEETINGS/EB05.HTML)

**SYMPOSIA**

**Sunday Morning (9:30 AM - 12:00 PM)**

**Hypocretin (Orexin) and GHB: Molecular Mechanisms to Clinical Therapeutics**

(Sponsored by the Division for Behavioral Pharmacology and the Division for Systems and Integrative Pharmacology)

Chairs: Charles P. France and Luis de Lecea

Hypocretins: Genetic and molecular mechanisms. Masashi Yanagisawa, Univ. of Texas Southwestern Med. Ctr.

Preclinical pharmacology of hypocretin. Emmanuel Mignot, Stanford Univ.

Hypocretin, GHB and narcolepsy: Clinical perspectives. Gert J. Lammers, Leiden Univ. Med. Ctr., Leiden, The Netherlands

Preclinical pharmacology of GHB. Wouter Koek, Univ. of Texas Hlth. Sci. Ctr.

**Glucuronosyl Transferases: Their Role in Drug Interactions and Toxicity**

(Sponsored by the Division for Drug Metabolism, the Division for Pharmacology Education and the Division for Toxicology)

Chairs: Rory P. Remmel and Tim S. Tracy

Drug-drug interactions involving glucuronidation: An unrecognized phenomenon. Rory P. Remmel, Univ. of Minnesota Col. of Pharm.

Regulation of UGT's. Robert H. Tukey, UCSD

Role of UGT polymorphisms in drug effect and toxicity. Chantal Guillemette, Univ. of Laval, Quebec

Acyl glucuronides, covalent adducts and mitochondrial damage. Philip C. Smith, Univ. of North Carolina at Chapel Hill

**Ray Fuller Symposium: Neurotransmitter Transporters: Signaling in Flux**

(Sponsored by the Division for Neuropharmacology)

Chair: Randy D. Blakely

Molecular biophysics of amphetamine action. Aurelio A. Galli, Vanderbilt Univ.

Phosphorylation based regulation of biogenic amine transporters. Sammanda Ramamoorthy, Medical Univ. of South Carolina

Posttranslational control of GABA transport. Michael W. Quick, USC

Regulation of glutamate transport. Michael B. Robinson, Univ. of Pennsylvania

**Sunday Afternoon (3:00 PM - 5:30 PM)**

**Social Structure and Influences on Drug Actions**

(Sponsored by the Division for Behavioral Pharmacology, the Division for Neuropharmacology and the Division for Systems and Integrative Pharmacology)

Chairs: Michael A. Nader and Klaus A. Miczek

Epidemiologically based prevention research on drug abuse. Sheppard G. Kellam, American Inst. for Res., Washington, D.C.  
The physiology of social dominance: Individual differences in the functions of the HPA axis. Robert M. Sapolsky, Stanford Univ. Sch. of Med.

Individual differences in vulnerability and resilience to early stress effects on adult CSF monoamine concentrations, social behavior, and alcohol consumption. Allyson J. Bennett, Wake Forest Univ. Sch. of Med.

Individual differences in dopamine and serotonin receptor function, behavioral and reinforcing effects of drugs in socially housed monkeys. Michael A. Nader, Wake Forest Univ. Sch. of Med.

Aggressive vs. submissive experiences: Differential cocaine self-administration and mesocorticolimbic cellular activation. Klaus A. Miczek, Tufts Univ.

### **HDL Therapy: The New Frontier for the Treatment of Cardiovascular Diseases**

(Sponsored by the Division for Cardiovascular Pharmacology)

Chairs: Charles L. Bisgaier and Roger S. Newton

Structural features and function properties of high density lipoproteins: Relevance to human cardiovascular disease. TBD  
Discovery, history and evolution of ApoA-1Milano: A variant protein with beneficial affects. Cesare R. Sirtori, Univ. of Milan

HDL: A modulator of inflammation and a therapy for cardiovascular diseases. Prediman K. Shah, Cedars-Sinai Med. Ctr.  
Cardioprotective effects of ApoA-1milano/phospholipid (ETC-216) complexes. TBD

Effect of recombinant ApoA-1Milano (ETC-216) on coronary atherosclerosis in patients with acute coronary syndromes. Steven Nissen, Cleveland Clinic Fndn.

### **Protein Modification During Oxidative Injury**

(Sponsored by the Division for Toxicology and the Division for Drug Metabolism)

Chairs: Daniel C. Liebler and Serrine S. Lau

Application of LC-MS methods to identify protein targets of reactive electrophiles generated by lipid peroxidation. Daniel C. Liebler, Vanderbilt Univ. Sch. of Med.

Chemistry of adduction of proteins by the prototypical electrophiles 4-hydroxynonenal and 4-oxononenal. Lawrence M. Sayre, Case Western Res. Univ.

Challenges of sequence-specific mapping of protein modifications from reactive nitrogen species. Steven R. Tannenbaum, MIT

Identification of chemical adduction to target proteins and the impact on biological function. Serrine S. Lau, Univ. of Arizona Col. of Pharm.

### **Functional Selectivity of Receptor Signaling: Epiphenomenon or New Opportunity for Drug Discovery?**

(Sponsored by the Division for Neuropharmacology and the Division for Molecular Pharmacology)

Chair: David R. Sibley

Ligand-specific cellular signaling profiles at the 5-HT<sub>2C</sub> receptor. William P. Clarke, Univ. of Texas Hlth. Sci. Ctr. at San Antonio

Regulation of GPCRs by endocytic membrane trafficking: Novel mechanisms and potential therapeutic targets. Mark von Zastrow, UCSF

What is the molecular basis for functional selectivity of drugs at the 5-HT<sub>2A</sub> receptor? David E. Nichols, Purdue Univ. Sch. Pharm. & Pharmaceut. Sci.

Functional selectivity of dopamine receptor ligands predict novel behavioral effects: Examples from the lab to the clinic. Richard B. Mailman, Univ. of North Carolina at Chapel Hill

Ligand specific conformational changes of GPCRs: Consequences for receptor signaling. Brian K. Kobilka, Stanford Univ. Med. Ctr.

## **Monday Morning (9:30 AM - 12:00 PM)**

### **Role of Neuroinflammation in Neuropathic Pain**

(Sponsored by the Division for Drug Development, Discovery and Regulatory Affairs, the Division for Behavioral Pharmacology and the Division for Neuropharmacology)

Chair: Michael R. Brandt

The increasingly recognized role of neuroinflammation in neuropathic pain; an introduction to the symposium. TBD

Role of CB<sub>2</sub> receptors in conditions of neuropathic pain. T. Philip Malan, Jr., Univ. of Arizona Col. of Med.

Central cytokines as drug targets for the treatment of neuropathic pain. TBD

Modulation of clinical pain by pharmacotherapies that disrupt glial activation. Beata Buzas, NIH

**C-reactive Protein and Cardiovascular Disease: Epiphenomenon or Therapeutic Target?**

(Sponsored by the Division for Cardiovascular Pharmacology)

Chairs: Mark B. Pepys and Ben R. Lucchesi

Structure, function and pathobiology of CRP: A therapeutic target in cardiovascular disease? Mark B. Pepys, Royal Free and Univ. Col. Med. Sch.

CRP and cardiovascular disease: A critical review of the epidemiological evidence. Gordon D.O. Lowe, Glasgow Royal Infirmary, U.K.

CRP is a valuable risk marker for cardiovascular disease. TBD

Role of CRP in pathogenesis of atherosclerosis. Edward T.H. Yeh, Univ. of Texas at Houston

CRP and acute coronary syndromes. Attilio Maseri, Vita-Salute San Raffaele Univ., Milan, Italy

**Role of Xenobiotic Metabolizing Enzymes in the Homeostatic Control of Endogenous Substrates**

(Sponsored by the Division for Drug Metabolism)

Chair: Robert L. Haining

Metabolism of endogenous substrates by xenobiotic metabolizing enzymes. Robert L. Haining, West Virginia Univ. Sch. of Pharmacy

Arachadonic acid metabolism: Bench to bedside. Jorge H. Capdevila, Vanderbilt Univ.

Regulation of cholesterol homeostasis by cytochromes P450. Irina A. Pikuleva, Univ. of Texas Med. Br. at Galveston

Endogenous ligands of the xenobiotic pregnane X receptor. Joyce J. Repa, Univ. of Texas Southwestern Med. Ctr.

**Pathways Illuminated: Visualizing Cell Signaling**

(Sponsored by the Division for Molecular Pharmacology)

Chair: Alexandra C. Newton

Visualizing signaling by kinases B and C in cells. Alexandra C. Newton, UCSD

Microanalytical tools to track cellular signaling. Nancy L. Allbritton, UC-Irvine

The molecular architecture of signal transduction complexes. John D. Scott, Oregon Hlth. & Sci. Univ.

Spatiotemporal dynamics of intracellular signaling. Atsushi Miyawaki, Riken Brain Science Inst., Japan

**How to Talk about Pharmacology to the Public**

(Sponsored by the Division for Pharmacology Education)

Chair: Patangi K. Rangachari

Teaching about drugs in high schools. Nancy Kellogg, Brawley Union High Sch., Brawley, CA

The media's role in disseminating information. Bob Carty, CBC Radio One, Toronto

Out-reach possibilities. Jack W. Strandhoy, Wake Forest Univ. Sch. Med.

**Monday Afternoon (3:00 PM - 5:30 PM)**

**Heterotrimeric G-proteins in Oncogenesis and Metastasis**

(Sponsored by the Division for Molecular Pharmacology)

Chair: Patrick J. Casey

G-12 proteins in tumor progression and metastasis. Patrick J. Casey, Duke Univ. Med. Ctr.

Regulation of MAP kinase signaling networks by G protein-coupled receptors. TBD

Molecular mechanisms of bone metastases: Rationale for targeting the endothelin axis. Theresa A. Guise, Univ. of Virginia

Cellular and biological functions of G12/G13. Stefan Offermanns, Univ. of Heidelberg

**New Pharmacological Targets in Alzheimer's Therapeutics**

(Sponsored by the Division for Neuropharmacology)

Chair: A. Claudio Cuello

Novel therapeutic targets in Alzheimer's disease. A. Claudio Cuello, McGill Univ.

The inhibition of beta-secretase as a therapeutic objective in Alzheimer's disease. Martin Citron, Amgen, Inc.  
The inhibition of gamma-secretase as a therapeutic objective in Alzheimer's disease. Michael S. Wolfe, Brigham and Women's Hosp./Harvard Univ.  
Anti-inflammatories in the experimental treatment of Alzheimer's disease. Sascha B. Weggen, Johannes Gutenberg-Univ., Mainz, Germany  
Vaccination versus passive immunotherapy in the treatment of Alzheimer's. David G. Morgan, Univ. of South Florida

### **Inference of Biological Regulatory Networks**

(Sponsored by the Division for Systems and Integrative Pharmacology, the Division for Molecular Pharmacology and the Division for Toxicology)

Chair: Kenneth S. Ramos

Computational Biology. John J. Quakenbush, Inst. for Genomic Res.  
Genomics. Kenneth S. Ramos, Univ. of Louisville  
Proteomics. Serrine S. Lau, Univ. of Arizona Col. of Pharm.  
Metabolomics. Bruce D. Hammock, UC-Davis  
Systems Biology. TBD

## **Tuesday Morning (9:30 AM - 12:00 PM)**

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### **Developmental Expression of Drug Metabolizing Enzymes and Impact on Pediatric Clinical Pharmacology**

(Sponsored by the Division for Drug Metabolism and the Division for Systems and Integrative Pharmacology)

Chair: Jeffrey C. Stevens

Developmental expression of FMO forms. TBD  
Human CYP3A ontogeny. Jeffrey C. Stevens, Pfizer, Inc., St. Louis  
Clinical implications of clearance alterations during development and pediatric drug trial design. Gregory L. Kearns, Univ. of Missouri, Kansas City  
UGT development. Christian C. Strassburg, Hannover Med. Sch., Germany

### **Pharmacogenomics: Perception and Reality**

(Sponsored by the Women in Pharmacology Committee)

Chairs: Laura K. Nisenbaum and Joan M. Lakoski

Alastair J.J. Wood, Vanderbilt Univ. Sch. of Med.  
Richard B. Kim, Vanderbilt Univ. Sch. of Med.  
Sandra Kirkwood, Eli Lilly and Co.

### **G-protein-coupled Receptor Oligomerization: Biology and Drug Discovery**

(Sponsored by the Division for Molecular Pharmacology)

Chair: Kendall J. Blumer

G-protein-coupled receptor oligomerization and signaling. Kendall J. Blumer, Washington Univ. Sch. of Med.  
Cell biology of G protein-coupled receptor oligomerization. TBD  
Frizzled receptor oligomerization in human disease. Randall T. Moon, Univ. of Washington  
Chemokine receptor oligomerization and lymphocyte recruitment. TBD  
GPCR oligomerization and drug discovery. Susan R. George, Univ. of Toronto

### **Epigenetic Reprogramming of Cancer Cells**

(Sponsored by the Division for Toxicology)

Chair: Bernard W. Futscher

Background and historical perspective of epigenetics and cancer treatment. TBD  
The promise of DNA methylation markers in cancer prognostication. TBD



Tumor specific patterns of aberrant DNA methylation. TBD  
Histone acetylation/deacetylation – Therapeutic opportunities. TBD  
Epigenetic modification – the clinical experience. TBD

**Adolescent Drug Abuse: Long-term Effects of Exposure of the Developing Brain to Drugs of Abuse**

(Sponsored by the Division for Neuropharmacology, the Division for Behavioral Pharmacology and the Division for Systems and Integrative Pharmacology)

Chairs: Robert N. Pechnick and Kathryn A. Cunningham

Overview of concepts and issue in the study of the adolescent brain and drugs of abuse. TBD  
Effects of adolescent exposure to nicotine. Robert N. Pechnick, Cedars-Sinai Med. Ctr.  
Effects of adolescent exposure to opiates. TBD  
Adolescent exposure to stimulants. Michela Marinelli, Rosalind Franklin Univ. of Med. & Sci./Chicago Med. Sch.  
Teenagers and drug abuse. Uma Rao, Univ. of Texas Southwestern Med. Ctr.

**Tuesday Afternoon (3:00 PM - 5:30 PM)**

**Decisions of Benefit vs Risk: QT Interval Prolongation by Non-cardiac Drugs**

(Sponsored by the Division for Drug Discovery, Development and Regulatory Affairs and the Division for Cardiovascular Pharmacology)

Chairs: Alan S. Bass and Peter K. Siegl

Molecular basis for drug-induced torsades de pointes, its relationship to QT prolongation; who is at risk? Dan M. Roden, Vanderbilt Univ. Sch. of Med.  
Strategy for the non-clinical testing of new drugs for the potential of eliciting torsades de pointes arrhythmia. Alan S. Bass, Schering-Plough Res. Inst.  
Strategies for the clinical evaluation of new drugs for the potential eliciting torsades de pointes arrhythmia. TBD  
An integrated risk assessment: Benefit vs. risk of progressing a new drug to the marketplace. Peter K. Siegl, Merck Res. Labs  
Molecular modeling of the rapid delayed rectifier potassium channel: Critical to identifying safe new drugs. Michael C. Sanguinetti, Univ. of Utah

**Wednesday Morning (8:30 AM - 11:00 AM) – NOTE CHANGE IN TIME!**

**Mechanism of Tissue Selective Drug Action in the Cardiovascular System**

(Sponsored by the Division for Systems and Integrative Pharmacology and the Division for Cardiovascular Pharmacology)

Chair: Terry D. Barrett

Mechanism for the selective action of PDE5 inhibition on the corpus cavernosum. Donald H. Maurice, Queen's Univ. at Kingston  
Ischaemia-selective antiarrhythmic drug action and antiarrhythmic efficacy. Michael J.A. Walker, Univ. of British Columbia  
Tissue specific actions of structurally divergent calcium channel blocking agents. David J. Triggle, SUNY at Buffalo Sch. of Pharm. and Pharmaceut. Sci.  
HCN inhibition as a bradycardic mechanism; the importance of absence of other currents in the SA node. TBD

**Lysophosphatidic Acid: From Metabolite to Mediator to Medicine**

(Sponsored by the Division for Molecular Pharmacology and the Division for Systems and Integrative Pharmacology)

Chairs: Myron L. Toews and Kathryn E. Meier

Lysophosphatidic acid: A multi-functional lipid mediator and target for drug development. Wouter Moolenaar, The Netherlands Cancer Inst.  
Agonist and antagonist analogs of LPA with selectivity for LPA1 and LPA3 receptors. Kevin R. Lynch, Univ. of Virginia  
Fatty alcohol phosphates and other analogs targeted at selective regulation of LPA receptors. Gabor J. Tigyi, Univ. of Tennessee, Memphis  
A molecular modeling approach to identify LPA and S1P receptor subtype-selective pharmacophores. Abby A. Parrill, Univ. of Tennessee, Memphis



An autocrine LPA loop in ovarian cancer: Implications for pathology and therapy. Gordon B. Mills, Univ. of Texas Hlth. Sci. Ctr. at Houston

**Novel Insights into Myocardial Preconditioning: From the Clinic to the Proteome**

(Sponsored by the Division for Cardiovascular Pharmacology)

Chairs: Steven P. Jones and G.J. Gross

Clinical evidence for myocardial preconditioning. Roberto Bolli, Univ. of Louisville Sch. of Med.  
Mechanisms of opioid-induced preconditioning. Garrett J. Gross, Med. Col. of Wisconsin  
Proteomic identification of cardioprotective candidate proteins. Jennifer E. van Eyk, Johns Hopkins Univ.  
Two short talks from selected abstracts

**Molecular Library Approaches to CNS Drug Discovery**

(Sponsored by the Division for Neuropharmacology, the Division for Drug Discovery, Development and Regulatory Affairs, and the Division for Molecular Pharmacology)

Chair: Bryan L. Roth

Screening the receptorome reveals validated targets for CNS drug discovery. Bryan L. Roth, Case Western Res. Univ. Med. Sch.  
Allosteric potentiators of GPCRs as novel therapeutic agents for treatment of CNS disorders. Jeffrey Conn, Vanderbilt Univ.  
Targeting protein-protein interactions: Future or folly? Richard R. Neubig, Univ. of Michigan  
Imaging amyloid in humans. William Klunk, Univ. of Pittsburgh

**Drug Metabolism Platform Session and James Gillette Best Manuscript Awards**

**Genetic Susceptibility to Estrogen Carcinogenesis**

(Sponsored by the Division for Toxicology and the Committee on Women in Pharmacology)

Chairs: Judy L. Bolton and Terrence J. Monks

Findings of the Women's Health Initiative. Sylvia Wassertheil-Smoller, Albert Einstein Col. of Med.  
Cytochrome P450 1B1 (CYP1B1) pharmacogenetics: Association of polymorphisms with functional differences in estrogen hydroxylation activity. TBD  
Genetic polymorphism in catechol-O-methyltransferase (COMT) and endogenous catechol estrogen exposure: Role in breast cancer risk? James D. Yager, Johns Hopkins Univ.  
Catechol-O-methyltransferase (COMT) polymorphism in equine estrogen carcinogenesis. Judy L. Bolton, Univ. of Illinois at Chicago Col. of Pharm.

**Pharmacology and Phenotype: Comparing Effects of Drug Antagonists with Gene Knockout *In Vivo***

(Sponsored by the Division for Behavioral Pharmacology and the Division for Neuropharmacology)

Chairs: S. Barak Caine and Linda A. Dykstra

Functional studies with drugs and knockouts: Regulatory systems beyond the cell surface. Laura M. Bohn, Ohio State Univ.  
Drugs and knockouts for 5-HT receptor subtypes: Measures of behavior and neurotransmitter release in vivo. Loren H. Parsons, Scripps Res. Inst.  
Phenotypes of NR1 knockdown mice: Comparison with effects of NMDA antagonists in C57BL/6J mice. Linda A. Dykstra, Univ. of North Carolina  
Drugs and knockouts for dopamine receptor subtypes: Focus on behavioral effects of psychomotor stimulants. S. Barak Caine, McLean Hosp./Harvard Med. Sch.

**DIVISION SESSIONS**

**Monday Afternoon (3:00 PM - 5:30 PM)**

**Division for Behavioral Pharmacology Symposium: Preclinical Assessment of Pain and Analgesic Drugs**

(Also sponsored by the Division for Neuropharmacology)

Chair: S. Steve Negus



Preclinical models of acute pain. Edward J. Bilsky, Univ. of New England  
Preclinical models of inflammatory pain. Todd W. Vanderah, Univ. of Arizona  
Preclinical models of neuropathic pain. Michael R. Brandt, Wyeth Disc. Res., Princeton  
Targeting pain-suppressed behaviors in preclinical models of pain and analgesia. S. Steve Negus, Harvard Med. Sch.  
Use of fMRI for drug development in pain and analgesia. David Barsook, Harvard Med. Sch.

**Division for Cardiovascular Pharmacology Graduate Student and Postdoctoral Scientist Best Abstract Competition**

Chair: John C. Kermode

**Division for Drug Discovery, Development and Regulatory Affairs Symposium: Therapeutic Agent-device Combinations**

Chair: Tom J. Parry

Preclinical development of drug-coated stents. Gregory A. Kopia, Cordis Corp., Warren, NJ  
Clinical development of drug-coated stents. Pedro A. Lemos, Erasmus Med. Ctr., the Netherlands  
Cell-based therapeutics and devices for the treatment of CHF. Emerson C. Perin, Texas Heart Inst., Houston  
Regulation of combination products. Mark D. Kramer, FDA

**Division for Drug Metabolism Session: Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) & the Scientific Community: An Interactive Workshop**

Chairs: Tim S. Tracy and Davis S. Riddick

Navigating PharmGKB: Hands-on experience. Teri E. Klein, Stanford Univ.  
PharmGKB: What can it do for me? Russell B. Altman, Stanford Univ. Med. Ctr.  
Pharmacogenetics of CYP2C9 inhibition and activation. Timothy S. Tracy, Univ. of Minnesota  
Pharmacogenetics of FMO1 and FMO3. Ronald N. Hines, Med. Col. of Wisconsin  
N-acetyltransferase pharmacogenetics and adverse reactions to sulfonamides. Craig K. Svensson, Univ. of Iowa Col. of Pharmacy & Hlth. Sci.

**Tuesday Afternoon (3:00 PM - 5:30 PM)**

**Division for Molecular Pharmacology Postdoctoral Award Finalists**

**Division for Neuropharmacology Symposium: The Ten Commandments of Pharmacology: Does Functional Selectivity/Agonist Trafficking Make Nothing Sacred?**

Chair: Richard B. Mailman

**Division for Systems and Integrative Pharmacology Symposium: 20 Years of Calcium Imaging: A Revolution in Cell Physiology to Dye For**

Chairs: Ismail Laher and Harm J. Knot

Keynote Lecture: Calcium as a master switch. TBD  
Calcium and striated muscle. TBD  
Calcium regulates cell secretion. TBD  
Calcium and smooth muscle contraction. TBD  
Calcium regulates endothelial cell function. TBD

**Division for Toxicology Symposium: The Role of Mitochondria in Toxic Oxidative Stress**

Chair: Marc W. Fariss

**SPECIAL SESSIONS**

**Friday and Saturday**

**Behavioral Pharmacology Society Meeting (6:00 PM Friday - 7:00 PM Saturday)**



(Separate Registration)

For program and registration information, contact Charles P. France

## Saturday Afternoon

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### Graduate Student Colloquium

#### 2005 Teaching Institute: Getting Integrative

(Sponsored by the Division for Pharmacology Education, the Graduate Recruitment and Education Committee and the Committee on Public Affairs)

Chairs: Barbara S. Beckman, Edward J. Bilsky and George J. Christ

## Sunday Morning

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#### Minorities Committee Workshop: Effective Communication to Building Scientific Success

Chairs: Ashiwel S. Undie and Martha I. Davila-Garcia

#### Short Course: Introduction to Cardiovascular Pharmacology: Focus on Pathophysiology and Therapeutic Interventions

Chair: Ben R. Lucchesi

## Monday Morning

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#### ASPET Women in Pharmacology and APS Women in Physiology Committees Workshop: Managing a Laboratory

Chairs: Beth Levant and Joan M. Lakoski

## Tuesday Morning

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#### Short Course: Lipid Signaling: Pathways and Paradigms

Chairs: Kathryn E. Meier and Kevin R. Lynch

Phosphatidylcholine metabolism. Andrew J. Morris, Univ. of North Carolina at Chapel Hill.

## LECTURES

### Ray Fuller Lecture in the Neurosciences

#### Neurotransmitter Transporters on the Rise: Modulation of Synaptic Uptake Systems

Randy D. Blakely  
Vanderbilt University

### Torald Sollmann Award Lecture

TBA

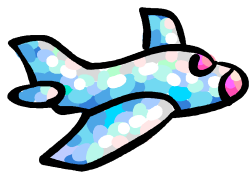
## NOTE:

There will be NO programming on Wednesday afternoon. Wednesday morning sessions will start at 8:30 am and finish by 11:00 am.

For updated program information visit [www.aspet.org/public/meetings/eb05.html](http://www.aspet.org/public/meetings/eb05.html)



ASPET will be making Travel Awards and Best Abstract Awards for Experimental Biology 2005 in San Diego. Information on these awards may be found on the ASPET web site at [http://www.aspet.org/public/awards/awards\\_fellowships.html](http://www.aspet.org/public/awards/awards_fellowships.html)



## TRAVEL AWARDS

**Graduate Student Travel Award** - Full-time students in doctoral programs in pharmacology or engaged in doctoral research in pharmacology who will not have completed their degree requirements by May 1, 2005 may apply.

**Minority Graduate Student Travel Award** - Full-time *underrepresented minority* students in doctoral programs in pharmacology or engaged in doctoral research in pharmacology who will not have completed their degree requirements by May 1, 2005 may apply.

**Young Scientist Travel Award** - Applicant should be in the first 5 years of a research career (as of award deadline). The start of the research career is generally interpreted as the time of completion of the Ph.D. degree or of clinical training.

**Minority Young Scientist Travel Award** - Applicant should be an *underrepresented minority* in the first 5 years of a research career (as of award deadline). The start of the research career is generally interpreted as the time of completion of the Ph.D. degree or of clinical training.

**Summer Undergraduate Research Fellow Travel Award** - Applicant must have been an ASPET SURF Fellow in the summer of 2004. Both Individual and Institutional SURF Fellows are eligible.

**Deadline: December 1, 2004**

## ABSTRACT AWARDS

Presented by ASPET's Divisions



- ★ Graduate Student Best Abstract Award
- ★ Postdoctoral Scientist Award
- ★ Drug Discovery, Development & Regulatory Affairs Young Investigator Award

**Deadline: November 17, 2004**

Applicants for all travel and best abstract awards must:

- ➔ Be ASPET members
- ➔ Be the presenting author of an abstract submitted to EB 2005.
- ➔ Submit applications online.

See the web site for details and online forms.







## Botanical Medicine and Dietary Supplements

The NIH Office of Dietary Supplements has launched a new, improved, Web-accessible International Bibliographic Information on Dietary Supplements (IBIDS) Database. The IBIDS database is available to the public free of charge through a Web interface on the ODS homepage. It currently contains over 730,000 citations on the topic of dietary supplements. Additional information is available at <http://www.nih.gov/news/pr/aug2004/od-18.htm>

The National Center for Complementary and Alternative Medicine will be soliciting public comments for its 2005-2009 Strategic Plan. To view more information, visit: <http://nccam.nih.gov/about/plans/2005/index.htm>. A draft of the strategic plan will be posted on the NCCAM Web site for public comment in October.

## Funding Opportunities

Limited competition for IDeA Networks of Biomedical Research Excellence, National Center for Research Resources. This RFA is open to applicants from the following eligible states: Arkansas, Louisiana, Nevada, New Hampshire, South Carolina, and Vermont. <http://grants.nih.gov/grants/guide/notice-files/NOT-RR-04-010.html>

RFP: Studies to Evaluate the Toxic and Carcinogenic Potential of Test Articles in Laboratory Animals for the National Toxicology Program, RFP NIH-0ES-04-12 (NOT-ES-04-010) <http://grants.nih.gov/grants/guide/notice-files/NOT-ES-04-010.html>

## EB Teaching Institute

The 2005 ASPET Teaching Institute at the Experimental Biology '05 meeting in San Diego will provide opportunities for interested graduate students to hear about job opportunities in industry. Attendees at the **“Let’s Get Integrative”** Teaching Institute will hear from representatives from pharmaceutical companies, biotech, and contract research organizations on how industry is looking for talented scientists trained in integrative whole organ pharmacology. More details to follow in the coming months.

## FASEB’s Breakthroughs Series

The latest in the *Breakthroughs in Bioscience* series is **“Bubbles, Babies and Biology: The Story of Surfactant.”** Written by Dr. Sylvia Wrobel, the article illustrates an excellent example of a problem identified in patients, elucidated in the lab through the cooperation of physicians and scientists and then brought back to bedside for successful treatment. Less than 50 years ago, tens of thousands of premature infants were born each year and died, struggling for breath from some mysterious affliction that left physicians baffled and helpless to intercede. This article traces the path of obscure, unrelated discoveries in physics, lung physiology and pathology that led to the discovery of surfactant and its use in saving lives. The article is available online at <http://www.faseb.org/opar/break/>.

Previous articles: *From Viper’s Venom to Drug Design: Treating Hypertension; Genetic Research: Mining for Medical Treasures; New Weapons to Combat an Ancient Disease: Treating Diabetes; Transplantation: The Challenging Road Ahead; Targeting Leukemia: From Bench to Bedside; Bone Builders: The Discoveries Behind Preventing and Treating Osteoporosis; Making Anesthesia Safer: Unraveling the Malignant Hyperthermia Puzzle.*

### Research!America Quote of the Month

**The challenge to the American scientific community is to rebuild the link not only between science and government but also between science and community.**

Sen. Tom Daschle (SD)  
Senate Minority Leader

Research!America, Membership Matters, June 2004



## Division for Drug Metabolism

### Division Sponsored Symposia and Divisional Programming at Experimental Biology 2005, San Diego, CA April 2-6, 2005

*Developmental Expression of Drug Metabolizing Enzymes and Impact on Pediatric Clinical Pharmacology* (co-sponsored with the Systems and Integrative Pharmacology Division); Chair: Jeffrey C. Stevens.

*Glucuronosyltransferases: Their Role in Drug Interactions and Toxicity* (co-sponsored with the Pharmacology Education Division); Chairs: Rory P. Remmel and Timothy S. Tracy.

*Role of Xenobiotic Metabolizing Enzymes in the Homeostatic Control of Endogenous Substrates*; Chair: Robert L. Haining.

*Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) and the Scientific Community: An Interactive Workshop*; Chairs: Timothy S. Tracy and David S. Riddick.

Division for Drug Metabolism Platform Session: *Biotransformation and Drug Transport* James Gillette Best Paper Awards and selected contributed paper presentations; Chairs: Timothy S. Tracy and David S. Riddick

In addition, the Drug Metabolism Division will co-sponsor a Toxicology Division-sponsored symposium on *Genetic Susceptibility to Estrogen Carcinogenesis*; Chairs: Judy L. Bolton and Terry K. Monks.

Further details for Division sponsored programming will be provided in the December issue of *The Pharmacologist*.

### Best Abstract Competition for Postdoctoral Fellows and Graduate Students

The Division for Drug Metabolism will once again participate in the ASPET Graduate Student Best Paper Award and Post Doctoral Scientist Award competitions to honor graduate students and post doctoral trainees at the upcoming Experimental Biology Meeting in San Diego, CA. As the deadline for abstract submission approaches, please encourage your talented graduate students and post docs to apply for one of these awards. Winners in each competition will receive monetary awards, will be recognized during their poster or oral presentations, and will be presented with certificates at the Division's mixer. In addition, an announcement of the winners will appear in *The Pharmacologist* and on the Division's website.

Applications for a Graduate Student Best Paper Award and a Post Doctoral Scientist Award may be accessed through the ASPET website ([www.aspet.org](http://www.aspet.org)); under Upcoming Meetings, click on EB 2005-Preliminary Program; then click on Best Paper Awards. In order to be eligible for an award, a graduate student or post doc must present a paper at the Experimental Biology meeting and be sponsored by a member of ASPET (see applications for exact eligibility criteria and instructions). The Drug Metabolism Division annually sponsors a platform session, which provides an excellent forum for graduate students and post docs to present their work. However, students and post docs may select either poster or oral as the presentation preference, and this choice will not affect an applicant's chance for receiving an award.

### Requests for proposals for Division-sponsored symposia at Experimental Biology 2006

The Division for Drug Metabolism seeks proposals for Division-sponsored symposia and Divisional programming at Experimental Biology 2006; April 1-5, 2006; San Francisco, CA. Please submit your preliminary ideas and plans to David Riddick [david.riddick@utoronto.ca] as soon as possible so that we can have a list of topics ready for the fall meeting of the ASPET Program Committee. Guidelines and an on-line submission form are available on the Division for Drug Metabolism website: <http://www.aspet.org/public/divisions/drugmetab/meetings.htm>

The final deadline for submission of full symposium proposals is **February 15, 2005**.

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Individuals interested in submitting symposium proposals for EB 2006 in San Francisco to their respective Divisions online may access these forms on the ASPET web site at

[http://www.aspet.org/public/meetings/symp\\_guidelines.html](http://www.aspet.org/public/meetings/symp_guidelines.html)

Deadline for final symposium submission is February 15, 2005.



## MEMBERS IN THE NEWS



Susan G. Amara, Thomas Detre Professor and Chair of the Department of Neurobiology at the University of Pittsburgh, was recently elected to the National Academy of Sciences. Dr. Amara received her B.S. in Biological Sciences from Stanford University and her Ph.D. in Physiology and Pharmacology from the University of California, San Diego, under the mentorship of Dr. Michael G. Rosenfeld. She was on the faculty at Yale University and the Vollum Institute for Advanced Biomedical Research at the Oregon Health Sciences University before moving to Pittsburgh in 2003. Dr. Amara has been active in both ASPET and the Society for Neuroscience. A former winner of ASPET's John J. Abel Award, Dr. Amara has served on the Program Committees for both ASPET and for the XIVth World Congress of Pharmacology. She has served on the Goodman and Gilman Award Committee and currently serves on the John J. Abel Award Committee.

Dr. Alejandro Zaffaroni was recently awarded the American Institute of Chemists' (AIC) Gold Medal, along with Syntex co-founders, Carl Djerassi and George Rosenkranz. The AIC's Gold Medal, the highest award given by the American Institute of Chemists, was first given in 1926 to recognize service to the chemical sciences and to the professions of chemistry and chemical engineering. The same trio was also awarded the Winthrop-Sears Award from the Chemists' Club for their roles in founding Syntex. This award is named after two colonial entrepreneurs and recognizes individuals who, by their entrepreneurial actions, contribute to the vigor of the chemical industry and to improved conditions for mankind. Both awards were presented at the third anniversary Heritage Day of the Chemical Heritage Foundation. Dr. Zaffaroni has been involved in cutting edge research not only in steroids, including the first oral contraceptive, but also in innovative drug delivery systems. He played a key role in establishing not only Syntex, but also ALZA Corporation, Affymetrix, Maxygen and SurroMed.

Dr. Robert R. Ruffolo, Jr., President of Research and Development for Wyeth Research, was named Chief Scientific Officer of the Year at the Third Annual Pharmaceutical Achievement Awards. He shared this honor with Dr. Frank Douglas of Aventis. Prior to moving to Wyeth, Dr. Ruffolo was a Senior Vice President at GlaxoSmithKline. He was elected ASPET's Secretary/Treasurer in 1995 and has subsequently served on the XIVth World Congress Executive Committee and as chair of the Congress' Finance Committee. He is a past recipient of the John J. Abel Award and has served on numerous ASPET committees and editorial boards.



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### **Cinda J. Helke, Ph.D.**

**1951 - 2004**

Cinda Helke, Professor of Pharmacology and Neuroscience, and Associate Dean for Graduate Education at Uniformed Services University of the Health Sciences, died on 13 June 2004. Cinda was a native of Iowa, and retained a midwestern sense of practicality and grounding throughout her life. After graduating from St. Joseph's Academy in Des Moines, she entered Creighton University in Omaha, graduating summa cum laude from the School of Pharmacy in 1974. While at Creighton, she met and married her husband, Joel Helke.

Cinda obtained a Ph.D. in Pharmacology from Georgetown University in Washington, DC in 1978, receiving an award for her outstanding dissertation research on central serotonergic neurons and autonomic function. Her research at Georgetown laid the foundation for her lifelong interest in understanding the structure and function of the autonomic nervous system and its regulation by the central nervous system. She was offered a prestigious PRAT Fellowship for post-doctoral training at the National Institute of Mental Health, where she spent two years in the laboratory of Dr. David Jacobowitz.



Lew Aronow recruited Cinda from NIMH to the Department of Pharmacology in the recently established Uniformed Services University (USU) in 1979, where she rose through the ranks to Professor, playing a major role in developing the teaching programs at USU. Her lectures to medical students were regularly recognized with awards for excellence in teaching. She also quickly established a highly productive research laboratory with continuous funding from NIH over a 22-year period. During this period, she and her coworkers worked extensively on the co-localization of neuropeptides and classical neurotransmitters in autonomic neurons, emphasizing specifically the nodose and petrosal ganglia. Graduate students and post-doctoral fellows from many countries were expertly trained by Cinda; each emerged from the Helke laboratory with a very strong grounding in neuroscience and pharmacology.

Cinda played an important role in the development of graduate education at Uniformed Services University. In 1993 she took over the directorship of the graduate program in Neuroscience, transforming the program into a model for all interdisciplinary graduate programs in medical schools of this size. She was very successful in expanding the recruitment of students to the program and in increasing institutional financial support. Her success with the neuroscience program led to her appointment as Associate Dean for Graduate Education in 2001. The graduate programs flourished under her highly professional leadership, and she pushed vigorously for enhanced support for minorities and women. Her distinguished career in graduate education led to her being awarded the Carol Johns Award, the highest award based on teaching excellence at Uniformed Services University.

Cinda was an active and involved member of the Society for Neuroscience and the American Society for Pharmacology and Experimental Therapeutics (ASPET), serving as the Secretary/Treasurer of ASPET at the time of her death. Both the Uniformed Services University and the larger communities of pharmacology and neuroscience have sustained a significant loss with her untimely death. All will miss her sage advice and counsel.

*Prepared by Brian M. Cox and Linda L. Werling*

### **Niels M. Haugaard, Ph.D.**

**1920 – 2004**

Dr. Niels Haugaard, Emeritus Professor of Pharmacology at the University of Pennsylvania School of Medicine, died on January 15, 2004 from complications associated with lung surgery.

Dr. Haugaard was born in 1920 in Copenhagen, Denmark, and immigrated to the United States in 1940. He received his undergraduate degree from Swarthmore College in 1942 and earned a Ph.D. in Biochemistry from the University of Pennsylvania in 1949.

Along with Dr. William Stadie, Dr. Haugaard was one of the first to conduct a series of studies on oxygen toxicity, which marked the beginning of investigations in this field of research. His subsequent investigative work was concerned with studies of cellular energetics and metabolism and mechanisms of hormone action. In all, Dr. Haugaard published over 100 articles in his more than



Dr. Haugaard's first wife, Ella Schwartzman, also a Professor of Pharmacology at the University of Pennsylvania, participated with her husband in many joint research investigations and co-authored numerous publications. After her death in 1980, he continued working in the laboratory with other collaborators to study the actions of hormones in experimental endocrinopathies. After his official retirement from the Pharmacology Department, Dr. Haugaard joined the laboratory of Dr. Robert Levin, where he investigated the effect of lipoic acid on insulin production and acetyl-choline synthesis. Prestigious honors awarded to Dr. Haugaard include a Guggenheim Fellowship in 1952 and, more recently, a University Research Foundation Award in 2001.

Dr. Haugaard was well known for his ability to tell jokes and often repeated them many times to friends, always with additional embellishment at each re-telling. His interest in politics was avidly maintained and expressed regardless of which political party was in office. He thoroughly enjoyed modern art and worldwide travel in his daily life.

Dr. Haugaard will be remembered as a fine scientist and a kind and gracious gentleman. He is survived by his second wife, Dorothy Hauducoeur Tosi; two children, David and Lisa; three stepchildren, Gregory and Pamela Tosi and Kimberly Patriarca; and two brothers, Erikhis and Dan.

*Prepared by Marilyn E. Hess*

## DEATH NOTICES

ASPET notes with sympathy the passing of the following members:

**Robert C. Anderson**

**Georg E. Cronheim**

**Ruven Greenberg**

**Niels Haugaard**

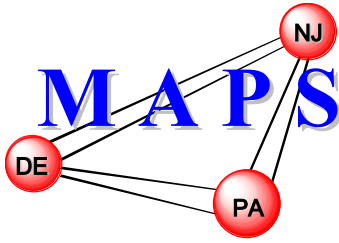
**Cinda J. Helke**

**Clyde G. Huggins**

**James F. Lenney**

**Gilbert J. Mannering**





Mid-Atlantic Pharmacology Society  
2004 Meeting

October 15, 2004  
Wyeth Research  
Collegeville, PA

- 7:45-8:30 Registration, Continental breakfast, Poster set-up
- 8:40-9:00 *Welcome*-Hugo M. Vargas, PhD, President, Mid-Atlantic Pharmacology Society  
*Wyeth Greeting*- Robert R. Ruffolo, Jr., PhD, President, Wyeth Research  
*Introduction to the Program*-Steven Adelman, PhD, Wyeth Research, MAPS Conference organizer
- 9:00-9:45 Overview: Paul Ridker: "The Immune Response in Cardiovascular Disease"
- 9:45-10:30 Arthur Feldman, MD, PhD, Chairman, Dept of Medicine-Jefferson Medical College: "Immune Mechanisms in Heart Failure"
- 10:30-11:00 Break
- 11:00-11:45 Myron Cybulsky, MD, University of Toronto, Toronto General Research Institute: "Initiation of Atherosclerosis: Endothelial Cell Gene Expression and Monocyte Recruitment"
- 11:45-12:15 Douglas Harnish, PhD, Wyeth Research: "Nuclear Receptors in Cardiovascular Disease: Regulation of NFkB, the Immune Response and Atherosclerosis"
- 12:15-1:45 Buffet Lunch, Poster viewing and judging
- 1:45-2:45 *Keynote lecture*- Donald Orlic, PhD, Hematopoiesis Section, Genetics and Molecular Biology Branch, NHGRI/NIH: "Stem Cells and Tissue Repair: State-of-the-Art"
- 2:45-3:00 Koelle Award
- 3:00-3:15 Poster awards
- 3:30-5:00 Reception [Barn]
- 3:30-4:15: Career Workshop

Note: All presentation times include 10 minutes for discussion.

**For meeting information, contact: Jeanne Coughlin (215-707-5227) or Hugo M. Vargas, PhD (215-652-8829)**

**Or visit the MAPS webpage at [http://www.aspet.org/public/chapters/maps\\_chapter.htm](http://www.aspet.org/public/chapters/maps_chapter.htm)**

**Abstract forms: [http://www.aspet.org/public/chapters/maps/MAPS\\_absfrm.pdf](http://www.aspet.org/public/chapters/maps/MAPS_absfrm.pdf)**

**Registration forms: [http://www.aspet.org/public/chapters/maps/maps04\\_regform.pdf](http://www.aspet.org/public/chapters/maps/maps04_regform.pdf)**

**Celebrating 25 Years!**

**25<sup>th</sup> Annual Meeting of the  
Southeastern Pharmacology Society**

Hosted by

**The University of Mississippi  
Department of Pharmacology &  
National Center for Natural Products Research**

**November 4-5, 2004**

**Preliminary Schedule**

**Thursday, November 4, 2004**

**7:00 to 9:00 PM**

**Reception and Registration**

**Friday, November 5, 2004**

**'PHARMACOLOGY in the SOUTHEAST'**

**Morning**

**Symposium – Regional Speakers**

**Afternoon**

**Student Platform and Poster Presentations**

**Evening**

**Banquet, Award Presentations  
'Reflections on 25 Years of SEPS'**

**For more information contact:**

SEPS Meeting 2004  
c/o Larry Walker  
TCRC 1019  
The University of Mississippi  
PO Box 1848  
University, MS 38677

Phone: 662-915-1005

FAX: 662-915-1006

[lwalker@olemiss.edu](mailto:lwalker@olemiss.edu)

Watch for more information on our web page - [http://www.aspet.org/public/chapters/seps\\_chapter.htm](http://www.aspet.org/public/chapters/seps_chapter.htm)



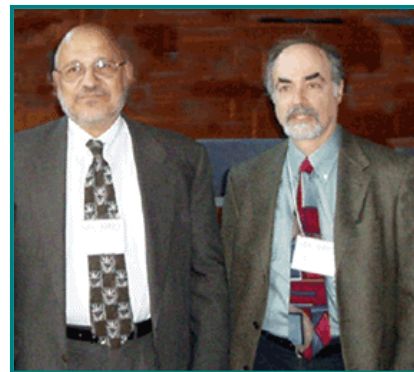
**The Great Lakes Chapter** of ASPET held its annual meeting on June 3, 2004, at the Loyola University Stritch School of Medicine in Maywood, IL. The meeting was attended by over 100 pharmacologists from the greater Chicago area and the surrounding states of Wisconsin, Indiana, and Michigan. In developing the program for the 2004 meeting, the planning committee felt that it would be appropriate to honor Dr. Israel Hanin. Dr. Hanin, who is retiring from the faculty of the Loyola University School of Medicine this year, was one of the founders of GLC-ASPET and has had a long and distinguished record of service to both our regional chapter and the national ASPET organization. As a way of honoring Dr. Hanin, this year's symposium was focused on the theme, "New Frontiers in Neurodegenerative Disease Research: A Tribute to Israel Hanin." This exciting symposium featured an outstanding panel of speakers including: Benjamin Wolozin, Ph.D., of Loyola University, who discussed his work on the "Molecular



Symposium speaker Annette Fleckenstein of the University of Utah with John Goudreau of Michigan State University

and Cellular Biology of Parkinson's Disease;" Annette Fleckenstein, Ph.D., of the University of Utah, who discussed her work on the "Differential Effects of Psychostimulants on Monoaminergic Transporter Function and Implications of Neurotoxicity;" and Elliot Mufson of the Rush University Medical Center who discussed his work on "Cholinergic Neuron Dysfunction During the Progression of Alzheimer's Disease: Potential Drug Targets." The keynote address was presented by Dr. David Holtzman, Professor and Chair of the department of Neurology at

Washington University in St. Louis who spoke about the "Potential Role of Amyloid-Beta Binding Molecules in the Pathogenesis, Diagnosis and Treatment of Alzheimer's



Israel Hanin (Loyola University) and symposium speaker Elliot Mufson (Rush Medical College)

Disease." Along with this outstanding symposium and keynote address, the meeting featured a career workshop, vendor exhibits, a poster session and the annual student and postdoctoral research competitions. The winners of the research competitions were:

### ★ Graduate Students ★

First Place – John Allen, University of Illinois at Chicago, *Adrenergic Receptor Stimulation Promotes Gas Endocytosis from Lipid Rafts*

Second Place – Patrick Osei-Owusu, Loyola University, *5-HT<sub>1A</sub> Receptor Activation Attenuates Lung Neutrophil Infiltration after Hemorrhage/Reperfusion*

Third Place – Michelle Florian-Kujawski, Loyola University, *Effect of Heparins, Oral Anticoagulant, Anti-Xa and Anti IIa Drugs on the Function Levels of Thrombin Activatable Fibrinolytic Inhibitor as Measured by a Chromogenic Substrate Based Assay (Pefakit<sup>®</sup>TAFI): Implications on Endogenous Fibrinolysis*

Third Place – Robert Drolet, Michigan State University, *Sub-Acute and Prolonged Chronic Administration of MPTP in Wild-Type and  $\alpha$ -Synuclein Knock-Out Mice*

### ★ Postdoctoral Fellows ★

First Place – Jing Qiao, Rush University, *Endothelial Expression of a Lysophosphatidylcholine Receptor: Detection by Peptide Antibodies*

Second Place - Fei Huang, Rush University, *Pro-Inflammatory Lysophosphatidylcholine Impairs Endothelial Barrier Function by PDC-Dependent RhoA Activation.*

The GLC-ASPET Executive Committee gratefully acknowledges support for the meeting from Abbott Laboratories; ASPET; Chirality LLC; Indiana University School of Medicine; Northwest Center for Medical Education; Loyola University School of Medicine, Department of Pharmacology; Medical College of Wisconsin, Department of Pharmacology; Midwestern University, Department of Pharmacology; Northwestern University, Feinberg School of Medicine, Department of Molecular Pharmacology and Biological Chemistry; Rosalind Franklin University, Department of Cellular and Molecular Pharmacology; Rush Medical College, Department of Pharmacology; University of Illinois at Chicago, College of Medicine, Department of Pharmacology. In addition, the committee would like to thank the following vendor Exhibitors for their support: AD Instruments, Cambrex, Chemicon and VWR Scientific.





★**ADRENERGIC RECEPTOR STIMULATION PROMOTES *Gas* ENDOCYTOSIS FROM LIPID RAFTS.** J. A. Allen<sup>1</sup>, J. Z. Yu<sup>1</sup>, R. J. Donati<sup>1</sup>, and M.M. Rasenick<sup>1,2</sup>. Univ of Illinois at Chicago.

Upon binding neurotransmitters or drugs, many G protein coupled receptors are internalized leading to receptor recycling, receptor desensitization and down-regulation. Much less understood is whether heterotrimeric G proteins also undergo agonist induced endocytosis. To investigate the intracellular trafficking of *Gas*, we developed a functional *Gas*-GFP fusion protein which can be visualized in living cells (Yu et al, 2002, *Mol Pharm* **61**, 352-359). C6 glioma and MCF-7 epithelial cells expressing *Gas*-GFP were treated with 10 $\mu$ M isoproterenol, and trafficking was assessed with video fluorescence microscopy. Upon isoproterenol stimulation of  $\beta$ -adrenergic receptors, *Gas*-GFP was removed from the plasma membrane and internalized into vesicles. Vesicles containing *Gas*-GFP did not colocalize with markers for early endosomes or late endosomes/lysosomes, revealing that *Gas* does not traffic through common endocytic pathways. Furthermore, *Gas*-GFP did not colocalize with endocytosed  $\beta_2$ -adrenergic receptors, suggesting that *Gas* and receptor are removed from the plasma membrane by distinct pathways. However,  $\beta$ -adrenergic agonist did promote *Gas*-GFP colocalization in vesicles labeled with fluorescent cholera toxin B, a lipid raft marker. Agonist significantly increased *Gas* protein in Triton X-100 insoluble membrane fractions, suggesting that *Gas* moves into lipid rafts/caveolae after activation. Disruption of rafts/caveolae by treatment with cyclodextrin prevented agonist induced internalization of *Gas*-GFP as did overexpression of a dominant negative dynamin. Taken together, these results suggest that receptor activated *Gas* moves into lipid rafts and becomes internalized in vesicles derived from those membrane microdomains. This trafficking phenomenon could enable *Gas* to interact with signaling effectors at multiple cellular sites, so in addition to activation of adenylyl cyclase, *Gas* may participate in intracellular signaling. Supported by: NIMH and NIH T32 HL07692

**DIFFERENTIAL EFFECTS OF METFORMIN ON CONTRACTIONS OF ISOLATED RAT DUODENUM.** Jacob D. Peuler, Ryan N. Chellin, Laura E. Phelps, and Kathy J. LePard. Midwestern University.

Compliance with metformin (MF) is often low due to gastrointestinal (GI) side effects. Taken orally, MF reaches millimolar (mM) levels in GI tissues while only micromolar ( $\mu$ M) levels in plasma. Recently, 30  $\mu$ M MF was reported to release 5-hydroxytryptamine (5HT) from duodenal tissues and 5HT is known to enhance intestinal smooth muscle contractility. However, above 1 mM MF is known to relax arterial smooth muscle. Thus, we examined effects of MF from 30  $\mu$ M to 10 mM on rat duodenum *in vitro* under the following conditions: 1) during amplified recordings of inherent (spontaneous) contractility and 2) after inducing additional contractions (near maximal) with either intestinally-active receptor agonists (5HT and acetylcholine, ACh) or a high, membrane-depolarizing concentration of potassium (K). Low ( $\mu$ M) levels of MF did not alter either spontaneous or induced contractions. However, mM levels exerted contrasting effects, viz. suppression of spontaneous contractions and those induced by either 5HT or K but enhancement of those induced by ACh. In addition, tetrodotoxin failed to influence these differing effects of metformin. Thus, we conclude 1) that MF (at least at mM levels typically found in GI) is capable of both suppressing and enhancing agonist-induced duodenal contractions, 2) that its dominant effect on spontaneous contractility and non-specific, depolarization-induced contractions is suppression, and 3) that all these effects occur independent of intrinsic intestinal nerve traffic. These actions may help explain GI side effects of MF in diabetic patients.

**<sup>3</sup>[H]-A-369508 ([2-[4-(2-CYANOPHENYL)-1-PIPERAZINYL]-N-(3-METHYLPHENYL) ACETAMIDE): AN AGONIST RADIOLIGAND SELECTIVE FOR THE DOPAMINE D<sub>4</sub> RECEPTOR.** R. Chang, R.B. Moreland, M.A. Terranova, M.E. Uchic, M.A. Matulenko, B.W. Surber, A.O. Stewart and J.D. Brioni. Neuroscience Research, Global Pharmaceutical Research & Development, Abbott Laboratories.

Tritiation of the dopamine D<sub>4</sub> receptor agonist A-369508 ([2-[4-(2-cyanophenyl)-1-piperazinyl]-N-(3-methylphenyl) acetamide) has provided a radioligand for the characterization of dopamine D<sub>4</sub> receptors. [<sup>3</sup>H]-A-369508 binds with high affinity to the major human D<sub>4</sub> receptor variants D<sub>4.2</sub>, D<sub>4.4</sub> and D<sub>4.7</sub> (K<sub>d</sub>= 1.7, 4, and 1.2 nM, respectively). It also binds to rat D<sub>4</sub>, (K<sub>d</sub>= 4.4nM), implying similar binding affinity across human and rat receptors. A-369508 shows >400 fold selectivity over D<sub>2L</sub>, >350 fold selectivity over 5-HT<sub>1A</sub> and >700-1000 fold selectivity over all other receptors tested. Agonist activity determined by inhibition of forskolin-induced cAMP in CHO cells transfected with human D<sub>4.4</sub> (EC<sub>50</sub>= 7.5 nM, intrinsic activity = 0.71) indicates that A-369508 is a potent agonist at the human D<sub>4</sub> receptor. Similar data was observed in other functional assays. [<sup>3</sup>H]-A-369508 binds to a single, high affinity site on membranes containing the human D<sub>4.4</sub> receptor. When compared to the D<sub>2</sub>-like antagonist [<sup>3</sup>H]-spiperone, competition binding for agonists like dopamine and apomorphine were 2 to 10-fold more potent with [<sup>3</sup>H]-A-369508, while the antagonists clozapine, haloperidol and L-745870 bind with similar affinity to both ligands. Binding to rat brain regions demonstrated that the most abundant area was cerebral cortex (51.2 fmol/mg protein) followed by hypothalamus, hippocampus, striatum and cerebellum. [<sup>3</sup>H]-A-369508 is

**A ROLE FOR RAS-GRF1 IN PANCREATIC BETA CELLS.** Desma D. Cooley, Marie Tannous, Anjan Kowluru, and Raymond R. Mattingly. Wayne State University School of Medicine.

Ras guanine nucleotide-releasing factor (Ras-GRF), a 140 kD protein, occurs in two isoforms, Ras-GRF1 and Ras-GRF2. Ras-GRF1 is expressed in neuronal tissue while Ras-GRF2 is ubiquitously expressed. Activation of Ras-GRF1 is dependent upon Phosphorylation of serine residues and calcium. The primary function of Ras-GRF is to activate Ras, a small GTP binding protein. The degree of Ras activation depends on the balance between guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs). GEFs promote formation of the active GTP state and GAPs hydrolyze GTP to GDP. Active Ras serves as a molecular switch to activate various effector pathways, including the mitogen activation protein kinase (MAP) cascade. Previous studies in our lab have shown that stimulation via muscarinic receptors or serum, but not calcium, could activate Ras-GRF1 that had been transiently expressed in COS-7 cells. In this study, we use immunoprecipitation and western blot analysis to characterize a new antibody, termed 2152NP, and showed that it selectively recognized Ras-GRF1 that was phosphorylated at Serine 916. Using this phospho-selective antibody, we concluded phosphorylation of Serine 916 correlated with the activation of Ras-GRF1 in neuronal systems. Other investigators have suggested that Ras-GRF1 may also be expressed in pancreatic beta islet cells. Currently our laboratories are investigating the potential expression of Ras-GRF1 in INS and HIT pancreatic cell lines. Preliminary data suggests Ras-GRF1 may be localized in both INS and HIT pancreatic cell lines. The research is supported by IMSD grant# GM 58905-05.

**★SUB-ACUTE AND PROLONGED CHRONIC ADMINISTRATION OF MPTP IN WILD-TYPE AND  $\alpha$ -SYNUCLEIN KNOCK-OUT MICE.** R. Drolet<sup>1</sup>, B. Behrouz<sup>2</sup>, K. Lookingland<sup>1,2,3</sup>, and J. Goudreau<sup>1,2,3</sup>. Neuroscience Program<sup>1</sup>, Dept. of Pharmacology & Toxicology<sup>2</sup>, Dept. of Neurology<sup>3</sup>, Michigan State University.

The functional role of  $\alpha$ -synuclein ( $\alpha$ -Syn) in the pathogenesis of Parkinson's Disease (PD) is not fully understood. One approach is to determine the response of  $\alpha$ -Syn-deficient mice to neurotoxins commonly used in animal models of PD. To this end, wild-type and homozygous  $\alpha$ -Syn knock-out (KO) mice were treated with sub-acute and prolonged, chronic exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). In the sub-acute model, wild-type and  $\alpha$ -Syn KO mice were treated for five consecutive days with MPTP (1-25 mg/kg, s.c.) or vehicle and sacrificed three days following the last injection. The prolonged, chronic model consisted of two injections of MPTP (1-20 mg/kg, s.c.) or vehicle per week for four weeks, with co-administration of probenecid (250mg/kg, i.p.) and animal sacrifice three weeks following the last injection. Dopamine and 3,4-dihydroxyphenylacetic acid (DOPAC) concentrations were measured in the striatum using HPLC-EC. Vesicular monoamine transporter (VMAT-2) protein was measured in the striatum using western blotting techniques. Sub-acute administration of MPTP caused a dramatic, dose-dependent decrease in striatal dopamine concentrations in wild-type mice, while an attenuated response was observed in  $\alpha$ -Syn KO mice. Similar to the sub-acute model, prolonged, chronic administration of MPTP produced a dose-dependent decrease in striatal dopamine and VMAT-2 concentrations in wild-type mice, whereas  $\alpha$ -Syn KO mice had reduced sensitivity to the neurotoxin MPTP. These results suggest that  $\alpha$ -Syn, in part, mediates neurotoxic effects of mitochondrial complex I inhibition in sub-acute and prolonged, chronic animal models of PD. This work was supported by the Michigan State University Foundation

**DIABETES ABOLISHES MORPHINE-INDUCED CARDIOPROTECTION (MIC) VIA AN ALTERATION OF THE GLYCOGEN SYNTHASE KINASE  $\beta$  (GSK) PATHWAY.** Eric R. Gross, Anna K. Hsu, John A. Auchampach, and Garrett J. Gross, Medical College of Wisconsin.

Previously, our laboratory has shown GSK inactivation via phosphorylation is essential for MIC in nondiabetic rats (NDB). However, it is not established whether MIC occurs in diabetics. Therefore, we determined if MIC occurs in diabetic rats (DB) and whether the GSK pathway is altered in DB. Male Sprague-Dawley rats were injected with streptozotocin (65mg/kg) and rats with sustained hyperglycemia (14 days, blood glucose >500mg/dL) were DB. Both NDB and DB rats were subjected to 30 minutes of ischemia and 2 hours of reperfusion, followed by infarct size assessment. Groups of the NDB and DB were administered either vehicle, morphine (MOR, 0.3mg/kg) or the GSK inhibitor, SB216763 (SB21, 0.6mg/kg). All values are reported as mean  $\pm$  SEM%, \* = P < 0.01. MIC was abolished in DB as compared to NDB rats (56  $\pm$  3% vs. 41  $\pm$  1%, respectively). Morphine caused GSK phosphorylation in NDB compared to untreated NDB and DB rats at 5 minutes of reperfusion, however, morphine-induced phosphorylation of GSK did not occur in DB rats (180  $\pm$  9%, 114  $\pm$  13, 134  $\pm$  12, 119  $\pm$  13, RDU, respectively). SB21 also reduced infarct size in NDB and DB compared to untreated NDB and DB rats (39  $\pm$  1%, 42  $\pm$  2%, 57  $\pm$  1, 56  $\pm$  2%, respectively). H9C2 cardiomyocytes were incubated in either a low glucose (LG) or high glucose (HG) DMEM media and stimulated with morphine (1  $\mu$ M) for 0-15 minutes, with results tabulated as a percent change from unstimulated cells. GSK and Akt, an upstream GSK regulator, were both phosphorylated at 15 minutes in LG cells, which did not occur in HG cells (P-GSK: 148  $\pm$  18% vs 87  $\pm$  10%; P-Akt: 177  $\pm$  28% vs 89  $\pm$  16%, respectively, + = P < 0.05). These data suggest diabetes abolishes MIC by altering the GSK signaling pathway.

**HEMODYNAMIC AND ELECTROCARDIOGRAPHIC COMPARISON OF THE ATYPICAL ANTIPSYCHOTIC DRUGS ARIPIPRAZOLE AND OLANZAPINE, AND THE CLASSICAL ANTIPSYCHOTIC, HALOPERIDOL, IN THE ANESTHETIZED CANINE.** Ryan M. Fryer, Lee C. Preusser, Bryan F. Cox, and Glenn A. Reinhart. Integrative Pharmacology, Global Pharmaceutical Research and Development, Abbott Laboratories.

Pharmacotherapy for schizophrenia includes both classical and atypical antipsychotics. However, both may elicit hemodynamic and electrocardiographic perturbations including QT-interval prolongation. Therefore, aripiprazole, olanzapine, and haloperidol were infused in 3 escalating doses in the anesthetized dog targeting supratherapeutic plasma concentrations to provide a comprehensive cardiovascular profile of these compounds. Aripiprazole generally produced a cardiodepressant effect including a steep dose-dependent reduction in MAP (to  $-37 \pm 1$  mmHg), bradycardia ( $-28 \pm 1$  bpm), and a reduction in CO ( $-0.55 \pm 0.02$  L/min) at plasma concentrations greater than 7.7-fold above the clinical  $C_{max}$ . At plasma concentrations 24.7-fold above the clinical  $C_{max}$  aripiprazole also produced a  $-44 \pm 3\%$  reduction in  $dP/dt_{max}$ . Olanzapine produced an immediate and marked reduction in MAP (to  $-25 \pm 2$  mmHg) and elevation in HR ( $17 \pm 1$  bpm) beginning at plasma concentrations approximately 2.6-fold above the clinical  $C_{max}$  and an  $18 \pm 5\%$  increase in  $dP/dt_{max}$  at plasma concentrations  $< 3.3$ -fold. Olanzapine also produced a  $-23.2 \pm 1.1$  mmHg/L/min reduction in SVR concomitant with plasma concentrations 29.1-fold above the clinical  $C_{max}$ . Haloperidol exerted a sustained  $-24 \pm 2$  mmHg reduction in MAP. Haloperidol also produced a modest increase in  $dP/dt_{max}$  immediately upon infusion and a reduction in SVR ( $-16.5 \pm 0.7$  mmHg/L/min) at plasma concentrations 24.8-fold above the  $C_{max}$ . Aripiprazole, olanzapine, and haloperidol all produced a dose-dependent increase in QT-interval corrected for heart rate (maximal effect =  $24 \pm 1$ ,  $21 \pm 1$ , and  $40 \pm 1$  msec above baseline, respectively). These data suggest that aripiprazole, olanzapine, and haloperidol produce hemodynamic and electrocardiographic perturbations in the anesthetized dog at plasma concentrations only modestly above the clinical  $C_{max}$  for the treatment of schizophrenia.

**MECHANISTIC STUDIES ON THE PENILE ERECTION MEDIATED BY CENTRAL DOPAMINE RECEPTORS IN CONSCIOUS RATS.** G.C. Hsieh\*, P.R. Hollingsworth, B. Martino, R. Chang, M.A. Terranova, A.B. O'Neill, L.N. Miller, M. Nakane, D.L. Donnelly-Roberts, R.B. Moreland, and J.D. Brioni. Neuroscience Research, Global Pharmaceutical Research & Development, Abbott Laboratories.

The non-selective dopaminergic agonist apomorphine induces penile erection in conscious rats. While  $D_1$  agonists do not induce penile erection, it is not clear which of the  $D_2$ -like receptors ( $D_2$ ,  $D_3$ , or  $D_4$ ) mediate this process. PNU-95666E is a  $D_2/D_3$  receptor agonist that activates  $D_2$  and  $D_3$  receptors with 92% and 79% efficacy, respectively. When administered subcutaneously, PNU-95666E (0.1 – 3.0  $\mu$ mol/kg) induced non-significant effects on penile erection in conscious rats with maximum efficacy (incidence) of 43%. To examine the role of  $D_4$  receptor activation in penile erection, two selective  $D_4$  agonists PD168077 and CP226269 were investigated. Both compounds exhibited a high degree of selectivity in competition binding assay ( $K_i < 30$  nM,  $D_4$ ;  $K_i > 1$   $\mu$ M for  $D_1$ ,  $D_2$ ,  $D_3$ , and  $D_5$ ) and potent agonist activity determined by FLIPR in  $D_4$ -expressed cells and by GTP $\gamma$ S binding on  $D_4$  membranes ( $EC_{50} < 40$  nM). They fully evoked penile activity whether administered systemically (s.c.) or locally in the brain. PD168077 elicited a maximum incidence of 79% at 0.3  $\mu$ mol/kg s.c. and 80% at 3 nmol/rat i.c.v. Similarly, CP226269 produced a maximum efficacy of 83% at 1  $\mu$ mol/kg s.c. and 100% at 3 nmol/rat i.c.v. These effects were not observed when injected intrathecally, suggesting a supraspinal site of action. Penile erections facilitated by either PD168077 or CP226269 were inhibited by clozapine but not by domperidone (a peripheral  $D_2$ -like antagonist). These results demonstrate that activation of central dopaminergic  $D_4$  receptors leads to facilitation of penile erection in conscious rats and may play an important role for the erectogenic effects of apomorphine. Supported by Abbott Laboratories

**★ PRO-INFLAMMATORY LYSOPHOSPHATIDYLCHOLINE IMPAIRS ENDOTHELIAL BARRIER FUNCTION BY PKC-DEPENDENT RHOA ACTIVATION** Fei Huang<sup>1</sup>, Papasani V. Subbaiah<sup>2</sup>, Oksana Holian<sup>3</sup>, Jihang Zhang<sup>1</sup>, Kwang S. Kim<sup>4</sup>, and Hazel Lum<sup>1</sup>. <sup>1</sup>Department of Pharmacology, Rush University Medical Center, <sup>2</sup>Department of Medicine, University of Illinois, <sup>3</sup>Department of Medicine, John H. Stroger Hospital of Cook County, Chicago, IL, and <sup>4</sup>Department of Pediatrics, The Johns Hopkins University.

We investigated whether the pro-inflammatory lysophosphatidylcholine (LPC) directly impairs barrier dysfunction of vascular endothelial cells and determined the signaling mechanisms of regulation. Stimulation of human dermal and brain microvascular endothelial cells (EC) with LPC (10-50  $\mu$ M) induced rapid decreases (within min) in transendothelial resistance, which were reversible at low concentrations. We investigated whether LPC-induced endothelial barrier dysfunction was regulated by PKC and Rho GTPases, which are believed to be important determinants of endothelial barrier dysfunction. LPC stimulated rapid increases of the membrane-associated PKC phosphotransferase activity, the maximal increase was 1.6-fold over control by 5 min.

Immunofluorescent localization and Western blot analyses of cell fractions indicated that the PKC activation was not accompanied by translocation of PKC $\alpha$  or PKC $\beta$  isoforms to the membrane. LPC also induced rapid increases (by 5 min) of GTP-bound RhoA as determined by affinity-binding analysis. Inhibition of RhoA function with C3 transferase inhibited ~55% LPC-induced resistance decrease. Depletion of PKC $\alpha$  with overnight treatment of PMA or pretreatment with PKC inhibitor GÖ6983 (concentration selective for classic PKCs) prevented ~50% of the LPC-induced resistance decrease. Similarly, the depletion of PKC $\alpha$  or GÖ6983 pretreatment inhibited, respectively 80% and 60% of the LPC-induced GTP-bound RhoA. Results from this study indicated that the pro-inflammatory LPC directly induces barrier dysfunction of human dermal and brain microvascular endothelial cells. LPC also activated RhoA and PKC $\alpha$  signaling mechanisms, of which PKC $\alpha$  appears to be an upstream regulator of RhoA in the regulation of the endothelial barrier dysfunction.

**MUSCARINIC RECEPTOR RECYCLING IN ALZHEIMER'S DISEASE.** N.A. Kalke, C.N. Cook, M.J. Hejna, D.J. Magnuson, S.O. McGuire, and J.M. Lee. Loyola Univ Med Cntr.

In Alzheimer's disease (AD), areas of the brain exhibiting plaques and tangles also demonstrate a loss of high affinity agonist binding of the muscarinic acetylcholine M<sub>1</sub> receptor, which we have previously demonstrated results from an uncoupling of this receptor subtype with its cognate G<sub>q/11</sub> protein. The internalization of the M<sub>1</sub> receptor, which is required for its resensitization, is phosphorylation dependent and secondary to formation of a complex between  $\beta$ -arrestin (cytosolic protein involved in the homologous desensitization of G protein-coupled receptors) and activated Src (non-receptor tyrosine kinase). Using the P2 membrane fraction from human frontal lobe homogenates (BA 10/11/12), immunoprecipitation of  $\beta$ -arrestin followed by subsequent western blotting for the M<sub>1</sub> receptor revealed a five-fold increase in the association of  $\beta$ -arrestin with the M<sub>1</sub> receptor in moderate to severe AD compared to age-matched controls ( $n = 4$ ,  $p < 0.01$ ). Additionally, using western blotting to measure Src protein levels, we found there is no significant change in total Src levels in the frontal cortex, although activated Src is increased three-fold in the P2 membrane fraction of AD tissue ( $n = 8$ ) compared to age-matched controls ( $n = 7$ ;  $p < 0.05$ ). These results suggest that there may be an alteration in the receptor recycling components of the M<sub>1</sub> receptor in AD, leading to a loss of M<sub>1</sub> receptor function which could partially explain the relative small effect of current cholinesterase inhibitors in the symptomatic treatment of AD. (*Supported in part by NIH grant NS 38162 to JML*)

**INHIBITION OF CALCINEURIN IN ALZHEIMER'S DISEASE.** C.N. Cook, M.J. Hejna, D.J. Magnuson, N.A. Kalke, S.O. McGuire, and J.M. Lee. Loyola Univ Med Cntr.

We have previously shown that the activity of protein phosphatase 2B (calcineurin) is decreased in Alzheimer's disease (AD), which may represent a possible mechanism(s) for the hyperphosphorylation of tau and subsequent neurofibrillary tangle (NFT) formation characteristic of the disease. Recently, mRNA expression of DSCR1 (Down's Syndrome Critical Region Gene 1), which encodes the protein calcipressin (identified as an endogenous inhibitor of calcineurin), was found to be upregulated in both Down's Syndrome (DS) and AD (Ermak et al., *J Bio Chem.* 276, 38787-94, 2001). Calcipressin has also been shown to be induced by oxidative stress and A $\beta$  *in vitro*, further establishing a link between this protein and the pathology of both AD and DS. Using Western blotting and immunohistochemistry techniques, we compared temporal lobe calcipressin protein expression in moderate to severe AD with age-matched controls. Although we found no change in AD ( $n=3$ ) compared to age-matched controls ( $n=3$ ) in either total calcipressin protein levels by Western blotting ( $p > 0.05$ ), immunohistochemistry did demonstrate an increase in cellular calcipressin expression ( $t=4.14$ ;  $p=0.0009$ ) in the pyramidal neurons of cell layers III and V in AD ( $n=10$ ) compared to age-matched controls ( $n=7$ ). As these cells are selectively vulnerable to NFT formation, we are currently investigating the neuronal co-expression of calcipressin with neurofibrillary tangles in AD. These data suggest that one of the mechanisms for a decrease in calcineurin activity and increased protein phosphorylation in AD could be altered cellular regulation of calcipressin. (*Supported in part by NIH grant NS38162 to JML*)

**PRESERVATION OF MUSCARINIC M1 RECEPTOR COUPLING IN THE LEWY BODY VARIANT OF ALZHEIMER'S DISEASE.** J.M. Lee, D.J. Magnuson. Loyola Univ Med Cntr.

Previous studies examining the functional status of cortical M<sub>1</sub> muscarinic cholinergic receptors have demonstrated an impairment in receptor-G protein coupling in classic cases of Alzheimer's disease (AD) as measured by the decreased ability of the receptor to form a high affinity agonist binding site. In order to investigate whether this alteration is also found in the Lewy body variant of AD (LBVAD), we compared agonist binding at M<sub>1</sub> receptors in the temporal cortex (Brodmann areas 20, 21, 22) from control ( $n=4-6$ ), moderate to severe AD ( $n=8$ ) and LBVAD cases ( $n=4$ ). We performed competition-binding studies using the M<sub>1</sub> antagonist 3H-pirenzepine (4 nM) in the presence of varying concentrations of the cholinergic agonist carbachol (50 nM to 1 mM). In all membrane



preparations, computer-assisted analysis of antagonist-agonist competition curves revealed that M1 receptor agonist binding fit a two site model with high and low affinity states in all three groups. We found a decrease in the number of receptors in the high affinity state in AD (25%) compared to controls (48%;  $p < 0.05$ ). In contrast, there was an increase in the number of M1 receptors in the LBvAD (70%) compared to controls (54%;  $p < 0.05$ ). These data are consistent with the reported clinical findings of increased effectiveness of acetylcholinesterase inhibitors for the treatment of the LBvAD.

**EVALUATION OF MARINE AND SYNTHETIC MANZAMINES AS INHIBITORS OF MICROGLIA THROMBOXANE B<sub>2</sub> AND SUPEROXIDE ANION GENERATION.** A.M.S. Mayer<sup>1</sup>, M. Hall<sup>1</sup> and M.T. Hamann<sup>2</sup>. <sup>1</sup>Department of Pharmacology, Midwestern University and <sup>2</sup>Department of Pharmacognosy, The University of Mississippi.

We have previously reported that the marine Manzamine A, potently inhibits *E. coli* LPS-activated rat microglia cell superoxide anion (O<sub>2</sub><sup>-</sup>) and thromboxane B<sub>2</sub> (TXB<sub>2</sub>) generation (Mayer et al. Soc. Neurosci. Abstr. 26(2):1346, 2000; U.S. Patents 6,387,916 & 6,602,881). Crystallographic analysis has revealed that apart from the  $\beta$ -carboline substituent, the Manzamine A molecule comprises an array of 5-, 6-, 8-, and 13-membered rings (Hamann et al. The Alkaloids, 60: 207, 2003). The purpose of this investigation was to provide preliminary structure-activity relationship information using several Manzamine A natural and semisynthetic analogs to determine which features of these  $\beta$ -carboline-containing alkaloids determines their anti-inflammatory potency on *E. coli* LPS-activated rat microglia cells. O<sub>2</sub><sup>-</sup> was determined by superoxide dismutase-inhibitable reduction of ferricytochrome C and TXB<sub>2</sub> by EIA. Manzamine marine and synthetic analogs inhibited the release of O<sub>2</sub><sup>-</sup> and TXB<sub>2</sub> with different potency. The structure-activity relationship study revealed that the  $\beta$ -carboline moiety and the 8-membered tertiary amine appear to be essential for the potent O<sub>2</sub><sup>-</sup> and TXB<sub>2</sub> inhibitory activity of Manzamine A. Additional structure-activity relationship studies and lead optimization for the potentially anti-inflammatory manzamines is currently underway in both our laboratories. Supported by Midwestern University and the National Institutes of Health.

**cDNA ARRAY ANALYSIS OF MATRIX METALLOPROTEINASE GENE EXPRESSION IN RAT MICROGLIA EXPOSED TO THE MARINE TOXIN DOMOIC ACID.** A. M. S. Mayer<sup>1</sup>, M. Hall<sup>1</sup>, M. J. Fay<sup>1</sup> and A. M. Romanic<sup>2</sup>.

<sup>1</sup>Pharmacology Dept, Midwestern Univ. and <sup>2</sup>Dept Cardiovascular Pharmacology, Glaxo SmithKline.

Amnesic Shellfish Poisoning, one of the shellfish poisoning syndromes in the United States, is caused by the marine glutamate and kainate analog domoic acid (DOM). Our working hypothesis is that DOM may activate rat neonatal microglia (BM $\Phi$ ), causing generation of matrix metalloproteinases (MMP), and potential toxicity to the central nervous system. We have reported that *in vitro* treatment of BM $\Phi$  with DOM leads to MMP-9 protein release (Mayer et al. BioMedCentral Pharmacology 1:7-19, 2001). The purpose of our study was to investigate MMP gene expression in 4-24 hour DOM [1mM]-treated BM $\Phi$  using a MMP-specific cDNA array (SuperArray Inc, Bethesda, MD). Through side-by-side hybridization with cDNA probes prepared from mRNAs of control or 4, 8, 16 and 24 hour DOM-treated BM $\Phi$ , the expression of 18 MMP and 4 tissue inhibitor of metalloproteinase (TIMP) genes was determined. Control BM $\Phi$  expressed 4 MMP and 2 TIMP genes constitutively *in vitro*: collagenase-like A (MMP-1), MMP-2, -9, -19 and TIMP-2 and -4. Over a 24-hour observation period, DOM *increased* expression of MMP-2, -9, TIMP-2 and -4, by 242, 226, 144 and 163 % of control expression, respectively. Concomitantly, DOM *decreased* expression of MMP- and -19 in a time-dependent manner. Our current data extends our previous observations (Mayer et al. The Toxicologist 72(S1): 346, 2003) by demonstrating the time-dependent nature of DOM's effect on BM $\Phi$  MMP and TIMP gene expression *in vitro*. Supported by grant number R15 ES12654-01 from NIEHS, NIH (to AMM), Midwestern University and Glaxo SmithKline.

**ABT-724, A NOVEL AND SELECTIVE DOPAMINE D<sub>4</sub> RECEPTOR AGONIST, INDUCES PENILE ERECTION IN CONSCIOUS RATS.** J.D. Brioni, R.B. Moreland\*, M. Cowart, G. Hsieh, A. Stewart, P. Hedlund<sup>#</sup>, D. Donnelly-Roberts, M. Nakane, J. Lynch III, T. Kolasa, J. Polakowski, M. Osinski, K. Marsh, K.E. Andersson<sup>#</sup> and J.P. Sullivan. Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories and <sup>#</sup>Department of Clinical Pharmacology, Lund University Hospital, Lund, Sweden.

The physiological role of dopamine D<sub>4</sub> receptors remains unclear. Apomorphine, a non-selective dopamine receptor agonist, facilitates erection in patients with erectile dysfunction acting via a central dopaminergic mechanism but the dopamine receptor subtype/s responsible for the erectogenic effect of apomorphine are not known. The potential role of the D<sub>4</sub> receptor on sexual function was investigated by means of selective D<sub>4</sub> agonist ABT-724. ABT-724 activates human dopamine D<sub>4</sub> receptors with an EC<sub>50</sub> value of 12.4 nM and 61% efficacy. It also activates rat and ferret dopamine D<sub>4</sub> receptors (EC<sub>50</sub>= 14.3 and 23.2 nM, with 70% and 64% efficacy, respectively). In contrast, the compound does not bind dopamine D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, or D<sub>5</sub> receptors. In conscious rats,





subcutaneous injections of ABT-724 facilitate penile erection at 0.03  $\mu\text{mol/kg}$  and this effect is blocked by haloperidol and clozapine (a preferential  $D_4$  antagonist) but not by domperidone (a peripheral antagonist). A pro-erectile effect is also observed after intracerebroventricular administration of ABT-724 but not after intrathecal injections of the compound. Subcutaneous injections of ABT-724 increase intracavernosal pressure in awake freely-moving rats. In the presence of the PDE-5 inhibitor sildenafil, a 10-fold potentiation of the pro-erectile effect of ABT-724 is observed in conscious rats. ABT-724 does not induce nausea or emesis in ferrets and is devoid of cardiovascular effects in rats. The ability of the selective  $D_4$  receptor agonist ABT-724 to facilitate penile erection in preclinical *in vivo* models indicates that the dopamine  $D_4$  receptor plays a unique role in the regulation of penile function in mammals.

**PROTEIN-PROTEIN INTERACTION SITES FOR TUBULIN TRANSACTIVATION OF G PROTEINS.** J. Oh<sup>1</sup>, J.Z. Yu<sup>1</sup>, and M.M. Rasenick<sup>1,2\*</sup>. Physiology and Biophysics, <sup>2</sup>. Psychiatry, University of Illinois at Chicago.

Specific G proteins such as  $G_s$ ,  $G_i$  and  $G_q$  bind to tubulin with high affinity ( $K_d=130\text{nM}$ ) and the hydrolysis-resistant photoaffinity GTP analog (P3 (4-azidoanilido)-P1-5'-GTP, AAGTP) transfers directly from tubulin-AAGTP to the G proteins mentioned above. This process is referred to as transactivation. The mechanism of transactivation, as well as the physiological importance of the interaction between tubulin and  $G_{\alpha 1}$  remain, unknown. The goal in this study, was to determine the precise sites for transactivation on  $G_{\alpha 1}$ . In a previous study (Chen et al., JBC 278: 15285 - 15290, 2003) the 237-270 region of  $G_{\alpha 1}$  was shown to be important for transactivation. That study exploited differences in  $G_{\alpha 1}$ , which binds tubulin with high affinity and transducin, which does not bind tubulin. Therefore, we made 5 mutant constructs in that region of  $G_{\alpha 1}$  to identify the residues responsible for direct nucleotide transfer from tubulin. Each mutant (except W258A) substituted the transducin residue on  $G_{\alpha 1}$  with the analog from transducin. All mutants appeared to be properly folded and functional with the exception of 251/261DM and they also bound to tubulin roughly the same extent as  $G_{\alpha 1}$ . Transactivation was inhibited in D261A and this mutant acted as a dominant-negative to block transactivation of  $G_{\alpha 1}$ . Since previous studies (Roychowdhury et al JBC 274:13485-13490, 1999) suggested that tubulin-G protein interaction stimulates intrinsic tubulin GTPase activity and inhibits microtubule assembly, we tested whether mutant  $G_{\alpha 1}$  constructs alter these properties. Tubulin GTPase was not activated by mutants that had no effect on transactivation and microtubule assembly was not inhibited in the presence of those 3 mutants. These results showed that D261 on  $G_{\alpha 1}$  appears to be an important residue for transactivation from tubulin and residues D251 and W258 for  $G_{\alpha 1}$  activation of tubulin GTPase/ inhibition of microtubule polymerization.

**ATTENUATING EFFECTS OF SILDENAFIL ON VASORELAXANT PROPERTIES OF ORAL ANTIDIABETIC DRUGS.** Jacob D. Peuler, Laura E. Phelps and Jacquelyn M. Smith. Midwestern University.

Diabetic men frequently experience erectile dysfunction for which sildenafil is often recommended. PDE5 inhibitors such as sildenafil are known to enhance the direct vasorelaxant actions of nitrates to the point of causing hypotension. Certain oral antidiabetic drugs (e.g. rosiglitazone, pioglitazone, and metformin) may possess small, delayed but nonetheless direct vasorelaxant properties. Thus, we sought to determine whether sildenafil also enhances the vasorelaxant effects of these three particular agents. Vascular rings from tail arteries of adult male rats were pretreated with therapeutically-relevant concentrations of rosiglitazone (10  $\mu\text{M}$ ), pioglitazone (5  $\mu\text{M}$ ) and metformin (50  $\mu\text{M}$ ), versus their vehicles, in either the absence or presence of 200nM sildenafil (a level found to enhance relaxation of such rings by nitrates in preliminary experiments). After 4 hours, each ring was contracted with norepinephrine. All three antidiabetic agents slightly but significantly relaxed such contractions and sildenafil did not enhance but rather attenuated these relaxations. We conclude that sildenafil may indeed be able to attenuate vasorelaxant actions of certain currently used antidiabetic agents. But these data do not show evidence that sildenafil will interact with these agents (when used to treat diabetic men) to cause hypotension. Support: Viagra Research Grant #91.

★ **5-HT<sub>1A</sub> RECEPTOR ACTIVATION ATTENUATES LUNG NEUTROPHIL INFILTRATION AFTER HEMORRHAGE/REPERFUSION.** P. Osei-Owusu and K.E Scrogin. Dept. of Pharmacology and Experimental Therapeutics and the Center for Serotonin Disorders Research, Loyola Univ. Chicago, Stritch School of Med.

Hemorrhage induces hypotension, bradycardia and eventually circulatory collapse. Previously, we showed that systemic administration of 5-HT<sub>1A</sub>-receptor agonists reverse the hypotensive response to hemorrhage when given immediately after the fall in blood pressure (BP). In this study, we determined whether systemic injection of the selective 5-HT<sub>1A</sub> receptor agonist, 8-OH-DPAT, attenuates reperfusion injury after sustained hypovolemia and subsequent blood re-infusion. Male Sprague-Dawley rats were instrumented with vascular catheters. After 24 hrs they were hemorrhaged to hypotension after which BP was maintained at 50 mmHg for 30 min. 8-OH-DPAT (30 nmol/kg iv, n= 7) or saline (n=7) was then injected and shed blood was re-infused 15 min later (0.53

ml/min/kg, iv). In another group of rats, BP was raised with continuous infusion of phenylephrine (Phen; 1.0  $\mu$ g/ $\mu$ l/min, n=8) after hemorrhage to produce the same pressor response as 8-OH-DPAT injection. In all groups, blood samples were taken before initiation of hemorrhage, 5 min before drug injection, 15 min after injection, and at the end of reperfusion to determine plasma corticosterone levels. The rats were sacrificed 24 hr after blood re-infusion. Tissue malondialdehyde (MDA) levels and myeloperoxidase (MPO) activity were measured to determine lipid peroxidation and neutrophil infiltration respectively in colon, duodenum, kidney, liver and lung. A separate group of rats received a higher dose of 8-OH-DPAT (60 nmol/kg, n=4) to determine the maximum BP and HR responses and MPO activity. 8-OH-DPAT produced significant pressor (59 $\pm$ 4 vs. 80 $\pm$ 2\*\* vs. 75 $\pm$ 5\*\* mmHg for 0, 30 and 60 nmol/kg 8-OH-DPAT 5 min after injection, \*\* $P$ <0.01 vs. saline) and tachycardic (-6  $\pm$ 7 vs. +31 $\pm$ 5\*\* vs. +58 $\pm$ 27\*\* bpm for 0, 30 and 60 nmol/kg 8-OH-DPAT 5 min after injection, \*\* $P$ <0.01 vs. saline) responses. 30 nmol/kg 8-OH-DPAT produced a significant rise in plasma corticosterone level (46 $\pm$ 5 vs. 72 $\pm$ 14\* vs. 30 $\pm$ 6\*.<sup>##</sup> ng/ml for 0, 30 nmol/kg 8-OH-DPAT and Phen 15 min after injection, \* $P$ <0.05 vs. saline; <sup>##</sup> $P$ <0.01 vs. 8-OH-DPAT) and a significant reduction in MPO activity in the lung (1.24 $\pm$ 0.1 vs. 0.79 $\pm$ 0.1\* vs. 1.5 $\pm$ 0.2 vs. 1.24 $\pm$ 0.2 U/mg protein for 0, 30, 60 nmol/kg 8-OH-DPAT and Phen, \* $P$ <0.05 vs. saline). Tissue MDA level was not different between the groups. We conclude that low dose 8-OH-DPAT attenuates reperfusion injury in selected tissues after prolonged hypovolemia and subsequent reperfusion in rats. (Supported by HL 0722354 to KES and AHA 0310026Z to PO)

★ **ENDOTHELIAL EXPRESSION OF A LYSOPHOSPHATIDYLCHOLINE RECEPTOR: DETECTION BY PEPTIDE ANTIBODIES.** Jing Qiao, Taher Mohiuddin, Fei Huang, Yan Xu, and Hazel Lum. Rush University Medical Center, and Cleveland Clinic Foundation.

The orphan G protein-coupled receptors, GPR4 and G2A, are implicated as receptors for lysophosphatidylcholine (LPC) and sphingosylphosphorylcholine (SPC). LPC is a proinflammatory serum phospholipid, which activates endothelial cells. We showed that LPC stimulation of human dermal microvascular endothelial cells induced rapid reversible decreases in resistance, indicating barrier dysfunction. Furthermore, we recently reported that endothelial cells selectively express GPR4 mRNA, but not G2A. *Therefore, we investigated the hypothesis that the LPC-induced endothelial barrier dysfunction is transduced through the specific receptor, GPR4.* We generated a polyclonal anti-GPR4 C-terminus peptide antibody for study. Results indicated that the antibody detected exogenous GPR4 protein overexpressed in COS7 transfected cells and endogenous expression in endothelial cells. Infection of endothelial cells with a retrovirus containing the siRNA-GPR4 knocked-down endogenous GPR4 expression and inhibited the LPC-induced resistance decrease. We conclude that GPR4 transduction mechanisms may be responsible for the inflammatory actions of LPC observed in endothelial cells. This work is supported by a grant from NIH NHLBI 71081 (HL), and postdoctoral fellowship awards from the American Heart Association, Midwest (JQ and FH).

**RHO-GDI IS A DIRECT TARGET OF PHOSPHORYLATION BY CAMP-DEPENDENT PROTEIN KINASE (PKA).** Jing Qiao, Oksana Holian, and Hazel Lum. Rush University Medical Center and Cook County Hospital.

PKA is known to be an important enzyme in promotion of endothelial barrier restrictiveness. Our previous observations indicate that one mechanism of protection is through inhibition of RhoA activation. The accessory protein, Rho-GDP guanine nucleotide dissociation inhibitor (GDI), regulates the activation of Rho GTPases and contains two PKA consensus sequences. Therefore, we investigated the hypothesis that PKA inhibited RhoA activation through direct phosphorylation of GDI. *In vivo* <sup>32</sup>P incorporation studies indicated that PKA enhanced thrombin-induced phosphorylation of GDI in endothelium. *In vitro* phosphorylation studies were made using purified GST-GDI fusion protein and purified PKA catalytic subunit analyzed by Mass Spectrometry. Using Kemptide (a preferred substrate of PKA) as control, we observed a shift of 80 D from 773 D to 853 D, indicating incorporation of one phosphate per molecule of Kemptide. PKA-stimulated phosphorylation of GST-GDI resulted in a shift of 146.33  $\pm$  11.59 (mean  $\pm$  SD) suggesting that two phosphates were incorporated into GST-GDI. These findings suggest that endothelial GDI is a direct target of phosphorylation by PKA, leading to inhibition of RhoA activation and inhibition of endothelial barrier dysfunction. This work is supported by a grant from NIH NHLBI 71081 (HL) and a postdoctoral fellowship award from the American Heart Association, Midwest (JQ).

**HEMODYNAMIC PROFILE OF ABT-870 (IRON OLIGOSACCHARIDE) AND OTHER IRON CONTAINING HEMATINIC AGENTS IN THE ANESTHETIZED BEAGLE DOG.** Lee C. Preusser, R. M. Fryer, A. Gerhardt, L. Delgado-Herrera, L.A. Williams, B.F. Cox, D.R. Kommala, and G. A. Reinhart. Global Pharmaceutical Discovery and Development, Abbott Laboratories.

Iron-deficiency anemia, a common complication of end stage renal disease, is often treated with parenteral iron therapies. However some of these agents have been shown to produce dose-limiting hypotension in patients. ABT-870 [iron (III)-hydroxide oligosaccharide] is comprised of elemental iron complexed with oligosaccharide, a composition that we hypothesized would allow the hypotensive effects of parenteral iron therapy to be overcome. Therefore, MAP and HR were monitored in anesthetized dogs following the infusion of ABT-870, Venofer, and Ferrlecit at doses ranging from 0.5 to 3.5 g human equivalent dose (HEq). A 30-second infusion of ABT-870 at 0.5 g or 1.0 g HEq produced no physiologically relevant effects on MAP and only modest transient increases in HR. Similarly, 10-minute infusion of ABT-870 at 0.5 g and 1.5 g HEq produced little effect on either MAP or HR. Infusion of ABT-870 at 3.5 g HEq produced a modest increase in MAP (6-18% above baseline) with no consistent hypotension concomitant with an increase in HR (28±10% above baseline), an effect that lasted only 15 minutes. A 30-second infusion of Venofer at 0.5 g HEq produced a modest pressor response with no effect on HR. However, 1.0 g HEq exerted variable, biphasic effects on both MAP and HR. Although 10-minute infusion of Venofer at 0.5 g HEq exerted little effect on MAP and HR, 1.5 and 3.5 g HEq elicited a profound dose-dependent decrease in MAP (-21±7 and -64±4% below baseline, respectively) and a pronounced increase in HR (53±14% and 30±12% above baseline, respectively). A 10-minute infusion of Ferrlecit (0.85 or 2.1 g HEq) produced a dose-dependent decrease in MAP (-20±15% and -48±15% below baseline, respectively) and a marked increase in HR (16±11 and 62±21% above baseline). Thus, unlike Venofer and Ferrlecit, high doses of ABT-870 failed to exert consistent hypotensive effects. Therefore, these data suggest that ABT-870 may have a substantially wider therapeutic window as compared to other iron containing hematinic agents.

**CHARACTERIZATION OF THE CARDIOVASCULAR EFFECTS OF A-325100, A DIHYDROPYRIDINE POTASSIUM CHANNEL OPENER, IN THE CONSCIOUS AND ANESTHETIZED CANINE.** Pamela Rakestraw, Ryan M. Fryer, Lee C. Preusser, Murali Gopalakrishnan, Bryan F. Cox, and Glenn A. Reinhart. Integrative Pharmacology, Global Pharmaceutical Research and Development, Abbott Laboratories.

In this study, the cardiovascular effects of the ATP-sensitive K<sup>+</sup> channel opener, (9R)-9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione (A-325100) were investigated in both the comprehensively instrumented pentobarbital-anesthetized dog and telemetry instrumented conscious dog to effectively compare these two models for the determination of drug-induced cardiovascular perturbations *in vivo* relative to efficacy. In the anesthetized dog A-325100 was infused intravenously in three escalating 30-minute infusions producing peak plasma concentrations of 11.9±1.2, 42.0±3.7, and 141±21 ng/mL at the end of each dosing period. At the two highest concentrations, A-325100 produced a dose-dependent reduction in mean arterial pressure to -16±3.3, and -33±3% below baseline, respectively. Although heart rate trended upward in A-325100 treated animals, A-325100 produced no statistically significant changes in heart rate due to intragroup variability. However, a dose-dependent increase in dP/dt<sub>max</sub> was observed concomitant with the fall in MAP (to 21% above baseline). In the conscious, telemetry-instrumented dog, A-325100 was administered in three doses by oral gavage in a randomized fashion and animals were monitored for 6 hours post-dose; peak plasma concentrations achieved were 9.68±1.1, 27.8±2.9, and 68.0±1.6 ng/mL, respectively. At the two lowest doses A-325100 produced no effect on MAP, HR or dP/dt<sub>max</sub>. However, at the highest plasma concentration achieved A-325100 produced a reduction in mean arterial pressure and increase in heart rate that was maintained throughout the 6-hour protocol. Although dP/dt<sub>max</sub> appeared elevated in animals administered the highest dose of A-325100, changes in dP/dt<sub>max</sub> were not statistically significant. In spite of modest differences between the models, the present data demonstrate comparable utility for the conscious and anesthetized dog in assessing the cardiovascular effects of KCOs. However, the anesthetized dog is a more highly controlled and sensitive model that provides a comprehensive characterization of dose-dependent pharmacological effects on cardiovascular and circulatory function.

**INFLUENCE OF D1 OR D2 DOPAMINE AGONIST ADMINISTRATION ON NEONATAL 6OHDA LESION-INDUCED CHANGES IN STRIATAL ENKEPHALIN AND SUBSTANCE P SYSTEMS.** S. P. Sivam. Department of Pharmacology & Toxicology, NWCME, Indiana University School of Medicine.

This study tested whether dopamine (DA) D1 or D2 receptor activation will reverse the neonatal 6OHDA lesion-induced changes on striatal enkephalin and tachykinin systems. The neurotoxin 6-hydroxydopamine (6OHDA) was used to induce DA deficiency in Sprague-Dawley rat pups on the third postnatal day. D1 agonist SKF-38393 (SKF) or D2 agonist LY-171555 (LY) was injected twice daily for 14 days, beginning 24 hr after 6OHDA lesions. The animals were sacrificed at sixty days of age. RIA and HPLC methods determined the changes in DA, Met<sup>5</sup>-enkephalin (ME) and substance P levels. As expected, neonatal 6OHDA induced a severe loss of DA, an increase in ME and a decrease in SP in the striatum. Postnatal administration of SKF significantly reversed the lesion-induced increase in ME and the decrease in SP. LY failed to affect the lesion-induced DA depletion or the changes in ENK or SP. The results indicate that the normal development of striatal SP system is dependent on D1 receptor stimulation during postnatal period. These

studies are relevant to our further understanding of DA deficiency conditions such as Lesch-Nyhan syndrome and Parkinson's disease. (Supported by USPHS grant NS 26063)

**PHOSPHORYLATION OF PDZ-RHOGEF AND ITS ROLE FOR REGULATION OF G12/13 PATHWAY.** S. Tanabe, B. Kreutz, N. Suzuki and T. Kozasa. Univ. of Illinois at Chicago.

Rho guanine nucleotide exchange factor (RhoGEF) activates Rho GTPases, which causes various cellular responses such as cell-cycle progression, chemotaxis and axonal guidance. Three mammalian RhoGEFs which contain an RGS (Regulator of G protein signaling) domain in their amino-terminus (RGS-RhoGEF) have been identified as PDZ-RhoGEF, LARG, and p115 RhoGEF. It has been shown that these RGS-RhoGEFs are direct links between G12/13 proteins and Rho protein. To further understand the mechanism of RhoGEF activation by G12/13, we examined whether these RGS-RhoGEFs are phosphorylated by Src tyrosine kinase, and whether this phosphorylation is involved in their regulation by G12/13. RhoGEFs were co-transfected with Src tyrosine kinase and immunoprecipitated from HEK293 cells. We found that PDZ-RhoGEF and LARG are phosphorylated by Src tyrosine kinase, whereas p115-RhoGEF is not phosphorylated under similar conditions. We also performed in vitro assay using purified G12/13 and Rho proteins from Sf9 cells. Immunoprecipitated RhoGEF was used as one of the components in the assay. It is possible that G12/13 pathway is further regulated by phosphorylation of PDZ-RhoGEF.

**EC 3.4.24.15 (EP 24.15) – STRUCTURAL AND FUNCTIONAL STUDIES.** M. Wang, A. Pabon, V. Grum-Tokars, and M.J. Glucksman. Rosalind Franklin University of Medicine and Science.

The zinc metalloendopeptidase EC 3.4.24.15 (EP 24.15), present in brain, pituitary and gonads, plays an important role in such diverse neurochemical functions as reproduction, nociception, MHCI antigen presentation and cardiovascular homeostasis. EP 24.15 plays a crucial role *in vivo* in the degradation of gonadotropin releasing hormone [GnRH] at the Tyr<sup>5</sup>-Gly<sup>6</sup> bond, which regulates mammalian reproduction. EP 24.15 is involved in the etiology of several diseases including Alzheimer's disease (AD), schizophrenia and prostate cancer. In general, the largest substrates cleaved are 17 residues long, while the minimum length required is 6 residues. In addition, the P1 position can be occupied by any amino acid, although cleavage is favored with Phe, Ala, or Arg. Site-directed mutagenesis and coupled protein expression studies sought to decipher elements crucial in substrate binding and catalytic activity. The kinetic parameters of EP 24.15 mutations compared with wild type were quantitated using a model quenched fluorescent substrate, QFS (7-methoxycoumarin-4-acetyl-Pro-Leu-Gly-Pro-D-Lys-(2,4-dinitrophenyl)) as well as a physiological substrate, GnRH. These studies have been conducted in parallel with the ongoing structural determination of EP 24.15 and are crucial in assessing its catalytic mechanism and role with respect to processing bioactive neuropeptide substrates. Structural models of the active site establishing structure-function correlation by mutated residues were created. (This work was supported by the National Institutes of Health.)

**BIOTECHNOLOGY DERIVED LMW SEMISYNTHETIC SULFAMINOHEPAROSAN AS POTENTIAL ALTERNATE FOR LOW MOLECULAR WEIGHT HEPARIN.** Jyothi Maddenini<sup>1</sup>, Marco Manoni, Ph.D.<sup>2</sup>, Umberto Cornelli, M.D., Ph.D.<sup>3</sup>, Debra Hoppensteadt, Ph.D.<sup>1</sup> and Jawed Fareed, Ph.D.<sup>1</sup> <sup>1</sup> Pathology & Pharmacology, Loyola University Chicago; <sup>2</sup> R.S.M., Montale, Italy, and <sup>3</sup> Corcon, Milano, Italy.

A series of heparin analogues derived from capsular polysaccharide from E.coli, have been developed and found to exhibit similar properties as heparins. A low molecular weight-sulfaminoheparosan (LMW-SAH, Q93C/239, MW=6.1 Kda) compared to a commercially available LMWH, tinzaparin, to determine whether LMW-SAH has similar molecular and pharmacological profile, allowing for the possibility of using this agent as an alternative to LMWHs. Both of these agents produced a concentration dependent effect in the anticoagulant assays, such as APTT, heptest and thrombin time and comparable results were obtained. In anti-Xa and IIa assays, LMW-SAH was weaker than tinzaparin; however, in the protease generation inhibition assays (Xa and IIa) utilizing intrinsic and extrinsic activators, LMW-SAH was found to be 2 to 50 times more potent than tinzaparin. Protamine sulfate neutralization profile of both tinzaparin and LMW-SAH were similar in terms of a complete neutralization of anti-Xa and partial neutralization of anti-IIa actions. In the platelet activation assays both agents produced no effect. Tinzaparin produced a positive screening in HIT assay but LMW-SAH did not produce these effects. This data suggest that LMW-SAH produces the anticoagulant and antiprotease actions which are similar to LMWH. Because of its relative stronger actions on protease generation inhibition this agent may be more effective than LMWHs.





**GENERIC VERSIONS OF COMMERCIALY AVAILABLE LOW MOLECULAR WEIGHT HEPARIN (LMWHs): PRODUCT INDIVIDUALITY IN THERAPEUTIC IMPLICATIONS.** Jyothi Maddenini, Debra Hoppensteadt, Ph.D., Qing Ma, Omer Iqbal, Ph.D., Walter P Jeske, Ph.D., Jeanine M Walenga, Ph.D., Daniel Fareed, Jawed Fareed, Ph.D. and Harry L Messmore, M.D. Loyola University Chicago.

The currently available commercial LMWHs include dalteparin, enoxaparin and tinzaparin in the US and certoparin, reviparin, nadroparin and parnaparin in Europe. Each of these is characterized by a distinct molecular profile and biologic activity in terms of anti-Fxa/IIa ratio. It is now widely accepted that individual LMWHs are chemically unique agents and cannot be interchanged. A generic version of LMWH is required to be chemically and biologically equivalent to the pioneer drug. We used a previously reported approach to compare 3 generic versions of enoxaparin from India and Brazil with the branded enoxaparin from the US. Analysis included molecular and pharmacologic profiling. While the molecular profiles ( $3.93 \pm 1.4$  kD) and anti-FXa potencies ( $90 \pm 4$  U/mg) were comparable for all 4 agents, the generic products showed variations in the global anticoagulant assays. Two generic and the branded enoxaparin were readily digested by heparinase-I, but one generic product resisted digestion. The neutralization profiles of all four agents were similar. While the MW and anti-FXa profiles are similar for all these agents but exhibited assay-based differences and digestion profiles. These studies suggest that there is a need to develop clear step-wise guidelines that will establish equivalency in physicochemical, biochemical, pharmacokinetic, pharmacodynamic and drug interactions for these anticoagulant drugs.

**DOWN REGULATION OF INFLAMMATORY MARKERS AFTER TREATMENT WITH TOPICALLY ADMINISTERED MUCOPOLYSACCHARIDE POLYSULFATE.** Debra Hoppensteadt<sup>1</sup>, Wolfram Raake<sup>2</sup>, Christopher Schultz<sup>1</sup>, Brian Neville<sup>1</sup>, Jawed Fareed<sup>1</sup>. <sup>1</sup>Pathology, Loyola Univ Med Cntr, , <sup>2</sup>Research and Development, Sankyo Pharma GmnH, Munich, Germany.

Mucopolysaccharide polysulfate (MPS) represents a mammalian tracheal preparation, which mimics many of the properties of heparins including its anti-inflammatory actions. MPS is used topically for the treatment of inflammatory disorders. This study was designed to test the hypothesis that topical administration of MPS mobilizes many substances to mediate its therapeutic effects. A group of four non-human primates (*Macaca Mulatta*) were administered 4.5% MPS ointment in a dosage of 45 mg/kg, another four monkeys were administered placebo ointment at a dosage of 0.5 mg/kg for 10 days. Citrated blood samples were drawn at baseline, 2, 4, 8 and 24 hours on days 1, 2, 5, 7 and 10. Markers of inflammation including thrombin activatable fibrinolytic inhibitor (TAFI), C-reactive protein (CRP), CD-40 Ligand (CD-40L), plasminogen activator inhibitor (PAI-1) and monocyte chemotactic protein (MCP-1) utilizing ELISA based methods, were used to measure the anti-inflammatory response. In the MPS treated group, a down regulation of all of these markers was observed over the 10 day period. CRP, CD-40L and MCP-1 showed a 50% decrease in the levels of these markers at day 10 in comparison to baseline. The PAI-1 and TAFI levels showed a slightly lesser effect. These results suggest that the topical administration of MPS leads to a decrease in the markers of inflammation that may result in promotion of the healing of inflammatory lesions.

**PLASMA PROTEIN PROFILING USING SURFACE ENHANCED LASER DESORPTION/IONIZATION (SELDI) IDENTIFICATION OF UNIQUE MOLECULAR COMPONENTS WITH 10 – 12 KDA IN INFLAMMATORY STATE. DIAGNOSTIC AND PROGNOSTIC IMPLICATIONS.** Fareed J, Hussain W, Florian M, Hoppensteadt D, Kahn S, Morgan M, Leva F. Loyola Univ Med Cntr.

Activation of proteases results in the cleavage of various plasmatic and cellular proteins resulting in the formation of protein digestion products of various molecular weights (MW). This study was designed to determine if specific biomarkers are present in the plasma of patients with acute coronary syndrome (ACS) and anti-phospholipid syndrome (APS). ProteinChip technology using the Ciphergen Biosystem (Fremont, CA), a mass-polarization technique was used to obtain the molecular profiles of citrated plasma samples. A strong anion exchange matrix protein chip (SAX-2) was used. Analysis of patient plasma obtained from liver disease (n=37), ACS (n=118) and APS (n=17) revealed the presence of a cluster of unique molecular components in the range of 10–12 kDa. The most prominent peak at a MW of 11.5 kDa was present in many of the patient samples and varied in intensity. It is proposed that these unique components found in pathologic plasma samples represent protease cleavage products with a net negative charge. Surrogate markers of inflammation were also elevated in these groups. The results suggest that ProteinChip Array profiling may identify unique molecular components which can be used as markers of protease activation. These results also suggest that the unique components in three distinct disease states involve inflammatory processes which generate certain mediators involved in this pathologic sequence.



**DIFFERENTIAL DOPAMINE TRANSPORTER-MEDIATED UPTAKE OF NEUROTOXIN IN HYPOTHALAMIC VERSUS NIGROSTRIATAL DOPAMINE NEURONS IN WILD-TYPE AND  $\alpha$ -SYNUCLEIN KNOCK OUT MICE.** Z.L. Zheng, and J.G. Goudreau, Dept of Pharmacology & Toxicology, Dept of Neurology/Ophthalmology, Michigan State University.

Hypothalamic dopamine neurons are relatively spared in Parkinson disease (PD) and are resistant to the neurotoxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). We sought to determine if 1) neurotoxin uptake via the dopamine transporter (DAT) was attenuated in hypothalamic versus substantia nigra dopamine (DA) neurons and 2) if differential neurotoxin uptake in these two regions was altered by expression of  $\alpha$ -synuclein, a key protein in the pathogenesis of PD. Neurons in substantia nigra and hypothalamus were dissociated from neonatal wild-type and  $\alpha$ -synuclein knockout mice. ASP<sup>+</sup> (4-(4-(dimethylamino)styryl)-N-methylpyridinium iodide), an analogue of the MPTP metabolite 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>) was used as a fluorescent substrate for the DAT to allow direct, *in vitro* evaluation of transporter function. Optical section imaging data of active ASP<sup>+</sup> uptake was collected in nigral and hypothalamic neurons of  $\alpha$ -synuclein knockout and wild-type mice using a Leica laser-scanning microscope. ASP<sup>+</sup> uptake was rapid, robust and bi-directional in wild-type nigral DA neurons, while slower and less intense in wild-type hypothalamic DA neurons. The rate and extent of ASP<sup>+</sup> uptake in  $\alpha$ -synuclein knockout nigral neurons was slower and less than ASP<sup>+</sup> uptake observed in wild-type nigral DA neurons. In hypothalamic DA neurons from  $\alpha$ -synuclein knockout mice, there was a dramatic decrease in ASP<sup>+</sup> uptake. These data suggest that: 1) reduced ASP<sup>+</sup> uptake may explain, in part, the resistance of hypothalamic DA neurons to MPTP, 2) decrease toxin uptake cannot explain the MPTP resistance of nigrostriatal DA neurons in  $\alpha$ -synuclein knockout mice, and 3)  $\alpha$ -synuclein mediates toxin transport into hypothalamic DA neurons via the DAT.

**THROMBIN ACTIVATABLE FIBRINOLYTIC INHIBITOR (TAFI) MODULATION BY HEPARIN: THERAPEUTIC IMPLICATIONS.** M. Florian, J. Maddineni, D. Hoppensteadt, M. Janssen, M. Wilmer, R. Bick, O. Iqbal, M. Tobu, and J. Fareed. Loyola Univ Med Cntr and Pentapharm Inc., Basel, Switzerland.

It has been proposed that the observed profibrinolytic effects of heparins are partly mediated by the inhibition of thrombin (T) and its generation. A chromogenic substrate based method measuring TAFI levels (Pefakit<sup>®</sup> TAFI, Pentapharm Ltd., Switzerland) was used to investigate the effect of heparin on TAFI. Results are expressed in terms of % NHP. Samples collected from patients on therapeutic heparinization exhibited varying degrees of TAFI levels ranging from 10-80%. This led to the hypothesis that beside the serpins modulation of T-thrombomodulin (TM) and its activation of TAFI, other factors may be responsible for the variations in TAFI levels. To validate this, samples were collected from 140 healthy, medication free volunteers with normal AT and HC II levels. TAFI levels were measured pre and post heparin (0.25 U/ml). TAFI levels prior to heparin ranged from 22-166 %, while post heparin levels were reduced and ranged from 3-114%. Despite the prolongation of APTT to therapeutic level (> 60 sec) 27 individuals plasma showed levels of functional TAFI >75%. This suggests that additional endogenous factors modulating TAFI or a variant form of TAFI may exist in certain individuals. Thus TAFI is activatable even when the heparin-AT complexes are formed. Furthermore, individual differences in the inhibitory profile of TAFI may also contribute to the observed variations in heparinization responses among patients.

★ **EFFECT OF HEPARINS, ORAL ANTICOAGULANT, ANTI-XA AND ANTI-IIA DRUGS ON THE FUNCTIONAL LEVELS OF THROMBIN ACTIVATABLE FIBRINOLYTIC INHIBITOR AS MEASURED BY A CHROMOGENIC SUBSTRATE BASED ASSAY (PEFAKIT<sup>®</sup> TAFI). IMPLICATIONS ON ENDOGENOUS FIBRINOLYSIS.** M. Florian-Kujawski, D. Hoppensteadt, J. Maddineni, M. Wilmer, H. Ziegler, and J. Fareed. Loyola Univ Med Cntr and Pentapharm Inc., Basel, Switzerland.

TAFI contributes to fibrinolytic deficit by mediating molecular changes in fibrin rendering it resistant to plasmin. A chromogenic substrate based method (Pefakit<sup>®</sup> TAFI, Pentapharm Ltd., Switzerland) was used to evaluate TAFI levels in 140 normal volunteers and were found to be 89.5 ± 20.6 in terms of % NHP. To measure the effect of various drugs heparins, low molecular weight heparins (LMWHs), anti-IIa agents (argatroban, angiomas), anti-Xa agent (DX 9065a) were supplemented in normal human pooled plasma. Compared to the LMWHs, heparin produced a stronger inhibition of TAFI (IC<sub>50</sub>=1.2 µg/ml) and LMWHs (IC<sub>50</sub>= 4-6 µg/ml). Argatroban and angiomas produced inhibition of TAFI resulting in IC<sub>50</sub>s of 1.4 and 12.5 µg/ml. Samples collected from patients on therapeutic heparin (aPTT 60–80 sec) showed variation in the inhibitory profile ranging from 30–90% inhibition. Samples from patients with INR 2–2.5 did not exhibit any decrease in TAFI levels. In patients with higher levels of anticoagulation (ACT >300 sec) a stronger inhibition of TAFI was noted (>80%). This suggests that different anticoagulant drugs produce varying degrees of inhibition of TAFI functionality. Because of the association of the increased TAFI levels with thrombosis and decreased TAFI levels to impaired hemostasis, the monitoring of this important regulator of fibrinolysis is useful in optimizing the safety and efficacy of anticoagulant drugs.



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Paperwork Summary: submit original and **1 copy** of the following:

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\*A letter or e-mail may be sent by the sponsor to the Membership Coordinator (rhipps@aspet.org) in lieu of the sponsor's signature and statement of qualifications of the applicant on the form. Call or e-mail the ASPET Membership Department for additional information: (301) 634-7135 / [rhipps@aspet.org](mailto:rhipps@aspet.org)  
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## Future Meetings

Experimental Biology '05  
San Diego, CA  
Saturday-Wednesday  
April 2-6, 2005  
(AAA, AAI, APS, ASIP, ASBMB, ASNS, ASPET)

Experimental Biology '06  
San Francisco, CA  
Saturday-Wednesday  
April 1-5, 2006  
AAA, APS, ASIP, ASBMB,  
ASNS, ASPET

Experimental Biology '07  
Washington, DC  
Saturday-Wednesday  
April 28-May 2, 2007  
AAA, APS, ASIP, ASBMB,  
ASNS, ASPET

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Mid-Atlantic Pharmacology Society  
2004 Meeting  
October 15, 2004  
Wyeth Research  
Collegeville, PA

Southeastern Pharmacology Society  
25<sup>th</sup> Annual Meeting  
November 4-5, 2004  
University of Mississippi  
University, MS