

**Experimental Biology 2009  
 ASPET's Annual Meeting  
 New Orleans, LA  
 April 18 - 22**

**Program Information Inside!!  
 Be sure to join us in the *Big Easy*!!**



All photos courtesy of New Orleans Convention and Visitor's Bureau



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- CPT 2008 Meeting In Review
- ASPET Membership Survey Results
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# The PHARMACOLOGIST

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**2009 DUES NOTICES WILL BE MAILED OUT THIS MONTH. BE SURE TO WATCH YOUR MAILBOX AND SEND IN YOUR DUES BY JANUARY 1, 2009.**

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

Symposia

Sunday, April 19  
9:30 - 12:00 PM

**RAY FULLER SYMPOSIUM: Mechanisms of Nicotine Addiction**

Chair: Henry A. Lester  
Convention Center, Room 206

**Preceded by the Ray Fuller Lecture in the Neurosciences**

Genome-wide association scans and candidate genes in nicotine addiction.

**Laura S. Bierut**, *Washington University*

Signal transduction pathways in nicotine addiction.

**Darlene Brunzell**, *Virginia Commonwealth University*

Proteasome pathway in nicotine addiction.

**Mariella De Biasi**, *Baylor College of Medicine*

Imaging studies of neural substrates in nicotine addiction.

**Edythe D. London**, *UCLA*

**Workshop: Integrating Basic Sciences and Patient Care in a Core Clerkship Curriculum**

Chair: Amy Wilson-Delfosse  
Convention Center, Room 208

Integrating basic and clinical sciences in the post-gateway era.

**Frazier Stevenson**, *UC, Davis*

Building integration in a new medical school: University of Central Florida College of Medicine.

**Lynn M. Crespo**, *University of Central Florida*

Integrating basic sciences and patient care in Western Reserve 2.

**Amy L. Wilson-Delfosse**, *Case Western Reserve University*

Design of an integrative case: Small Group Discussions

Discussants: **Amy Wilson-Delfosse**, *Case Western Reserve University*

**James P. Bruzik**, *Case Western Reserve University*

**Lynn M. Crespo**, *University of Central Florida*

**Frazier Stevenson**, *UC, Davis*

Small group presentations and panel discussion.

**AMPK as a Novel Therapeutic Approach for the Treatment of Metabolic Disorders and Heart Disease**

Chairs: Kenneth B. Walsh and Benoit Viollet  
Convention Center, Room 207

Targeting AMPK as a novel therapeutic approach for the treatment of metabolic disorders.

**Benoit Viollet**, *University of Paris*

Cardioprotective effects of adiponectin are mediated in part through AMPK.

**Kenneth Walsh**, *Boston University School of Medicine*

AMPK activation as a strategy for protecting vascular endothelial function.

**Ming-Hui Zou**, *University of Oklahoma Health Science Center*

AMPK activation projects the failing diabetic heart.

**David J. Lefer**, *Emory University*

**Advances in Down Syndrome Neuroscience Research: Implications for Alzheimer's Disease, Dementias and Other Cognitive Disorders**

Chairs: Tim A. Esbenshade and Alberto Costa  
Convention Center, Room 210

Advances in Down Syndrome research: Human genetics, animal models and cognitive drug therapy.

**Alberto Costa**, *University of Colorado Health Sciences Center*

Human chromosome 21/Down syndrome gene function: Implications for cognitive development and Alzheimer's Disease.

**Kathleen Gardiner**, *University of Denver*

Down syndrome: A genetic disorder in biobehavioral perspective.

**Lynn Nadel**, *University of Arizona*

Structural and functional changes at the synapse associated with Down Syndrome and Alzheimer's Disease.

**Craig C. Garner**, *Stanford University*

### **A Renaissance in Marine Pharmacology: Preclinical Curiosity to Clinical Reality**

Chairs: Keith B. Glaser and Alejandro M. Mayer

Convention Center, Room 209

Marine-sourced secondary metabolites as leads to drugs.

**David J. Newman**, *NCI, Frederick*

The development of marine anticancer derived compounds in the era of molecular medicine.

**Jose Jimeno**, *PharmaMar, Madrid*

*Conus* peptides: How snail compounds can win the race.

**J. Michael McIntosh**, *University of Utah*

Harnessing marine natural products for drug discovery: Pragmatic marine microbiology.

**Guy T. Carter**, *Wyeth Research*

The pseudopterosins – Investigation into their mode of action.

**Claudia E. Moya**, *University of California, Santa Barbara*

The global marine pharmacology pipeline: Compounds with anti-infective, immune, anti-inflammatory and CNS activity.

**Alejandro M. Mayer**, *Midwestern University*

**Sunday, April 19**

**3:00 - 5:30 PM**

### **Metabolomics in the Search for Biomarkers for Human Diseases**

Chairs: Frank J. Gonzalez and Richard B. Kim

Convention Center, Room 207

Metabolomics identifies perturbations in human disorders of propionate metabolism.

**William R. Wikoff**, *The Scripps Research Institute*

Metabolite profiling.

**Oliver Fiehn**, *University of California, Davis*

Metabolomics in biomarker discovery: Future uses for cancer prevention.

**Young Kim**, *NCI, NIH*

From drug metabolism to drug metabolomics.

**Jeffrey R. Idle**, *Charles University, Prague*

### **The Serotonin Transporter: Not Just for Neurons Anymore**

Chair: A. Elizabeth Linder and Stephanie W. Watts

Convention Center, Room 206

Plasma serotonin levels and the platelet serotonin transporter.

**Fusun Kilic**, *University of Arkansas for Medical Sciences*

5-HT and SERT in the pulmonary circulation.

**Barry L. Fanburg**, *Tufts University School of Medicine*

5-HT uptake in the peripheral vasculature: Focus in veins.

**A. Elizabeth Linder**, *Michigan State University*  
A role for 5-HT in the immune response.  
**John Gordon**, *University of Birmingham, United Kingdom*

**Generating Proteomic Diversity in Xenobiotic Biotransformation with Alternative RNA Splicing**

Chair: Curt J. Omiecinski  
Convention Center, Room 208

**Emerging Approaches to Treatment of Alzheimer's Disease**

Chairs: Randy Strong and Greg A. Gerhardt  
Convention Center, Room 210

**Monday, April 20**  
**9:30 - 12:00 PM**

**JULIUS AXELROD SYMPOSIUM: The Neurotransmitter End Game: Structure, Function and Regulation of Neurotransmitter Transport**

Chairs: Randy D. Blakely and Maureen K. Hahn  
Convention Center, Room 206

**Preceded by the Julius Axelrod Lecture**

The end of cannabinoids as we know it: Molecular control of anandamide inactivation.

**Eric L. Barker**, *Purdue School of Pharmacy*

Cocaine (target) trafficking: Dopamine transporters.

**Haley E. Melikian**, *University of Massachusetts Medical School*

Hugging Prozac: How serotonin transporters recognize antidepressants.

**L. Keith Henry**, *University of North Dakota School of Medicine and Health Sciences*

Reading the labels: How phosphorylation modifies serotonin transport.

**Sammanda Ramamoorthy**, *Medical University of South Carolina*

Nothing sweeter than DAT: How insulin controls the dopamine transporter.

**Aurelio Galli**, *Vanderbilt University*

**Regenerative Pharmacology: The New Pharmacology**

Chairs: George J. Christ and Jack W. Strandhoy  
Convention Center, Room 209

Introduction: State of regenerative pharmacology.

**George J. Christ**, *Wake Forest University Baptist Medical Center*

Drug delivery technologies for regenerative pharmacology.

**Grace Lim**, *Kyunpook National University, Korea*

Bio-inductive scaffolds and regenerative nanomaterials for tissue engineering.

**Mark A. Van Dyke**, *Wake Forest University Baptist Medical Center*

Tubular cardiovascular engineering: Developmental pharmacology of muscle, vessel and valves.

**Richard L. Goodwin**, *University of South Carolina*

TBD.

**Tim Bertram**, *Tengion, Inc.*

**MicroRNAs as Biological Effectors and as Pharmacological Targets in the Cardiovascular System**

Chair: J. David Port  
Convention Center, Room 207

**The Role of Nuclear Receptors in Lipid Homeostasis**

Chair: Curt J. Omiecinski  
Convention Center, Room 208

### The Role of Insulin and Leptin in Drug Addiction and Mood

Chairs: Charles P. France and Lynette C. Daws  
Convention Center, Room 210

Insulin, leptin, and food reward.

**Dianne P. Figlewicz Lattemann**, *University of Washington Health Science Center*  
The role of leptin signaling in emotional behavior.

**Xin-Yun Lu**, *University of Texas Health Science Center at San Antonio*

DAT depends on what you eat: Neurochemical and behavioral effects of amphetamine are dependent on insulin status.

**Lynette C. Daws**, *University of Texas Health Science Center at San Antonio*

The role of leptin on human body weight regulation, endocrine function, and neurobehavioral outcomes.

**Julio Licinio**, *University of Miami School of Medicine*

**Tuesday, April 21**  
**9:30 - 12:00 PM**

### All Presidents' Symposium on Integrative Pharmacology

Chair: Dennis C. Marshall and Bill W. Fleming  
Convention Center, Room 206

From integrative to molecular pharmacology and back.

**Elaine Sanders-Bush**, *Vanderbilt University Medical Center*

Integrative pharmacology: The validation of biochemical and molecular findings.

**Sam J. Enna**, *University of Kansas Medical Center*

Experimental basis of integrative pharmacology.

**David B. Bylund**, *University of Nebraska Medical Center*

Integrative pharmacological models in understanding neuroplasticity.

**James E. Barrett**, *Drexel University College of Medicine*

Integrative pharmacology: Oxidative stress, gender and aging.

**Sue P. Duckles**, *University of California-Irvine, College of Medicine*

### Exposure to Environmental Agent Alters Epigenetic Homeostasis

Chairs: Max Costa and Curt J. Omiecinski  
Convention Center, Room 208

Epigenetics: The new genetics of disease susceptibility.

**Randy L. Jirtle**, *Duke University*

Chromatin remodeling by chromium.

**Alvaro Puga**, *University of Cincinnati*

Differentiation of ES cells induced by epigenetic regulation of Pax6.

**Luo Lu**, *UCLA*

Epigenetic effects of nickel exposure.

**Max Costa**, *New York University School of Medicine*

Identifying genome-wide DNA methylation patterns and histone modifications in response to benzo[a]pyrene exposure.

**David I. Rodenhiser**, *University of Western Ontario*

### Discovery and Development of Oligonucleotide Therapeutics

Chair: Tom J. Parry  
Convention Center, Room 207

TBD. **James D. Thompson**, *Quark Pharmaceuticals, Inc.*

Special issues in the discovery and development of siRNA therapeutics.

**Pamela A. Pavco**, *RXi Pharmaceuticals, Inc.*  
TBD. **Christina Gamba-Vitalo**, *Alnylam Pharmaceuticals*  
Pharmacokinetics of oligonucleotide therapeutics.  
**Patrick L. Iversen**, *AVI BioPharma, Inc.*

### Targeting Drug Metabolizing Enzymes for Effective Chemopreventive Approaches

Chairs: Hollie Swanson and Emily E. Scott  
Convention Center, Room 209

### Receptor Signaling and Regulation in Neuropsychiatric Research

Chair: Laura M. Bohn  
Convention Center, Room 210

Fine tuning receptor responsiveness.

**Marc G. Caron**, *Duke University Medical Center*  
When two receptors become three.

**Lakshmi Devi**, *Mount Sinai School of Medicine*  
Serotonin receptor signaling via  $\beta$ -arrestins.

**Laura M. Bohn**, *Ohio State University College of Medicine*  
Dopamine receptor signaling via  $\beta$ -arrestins.

**Martin Beaulieu**, *University of Laval*

**Tuesday, April 21**  
**3:00 - 5:30 PM**

### Neuroplastic and Neurodegenerative Changes Associated with Drug Abuse and Addiction

Chair: Jean Lud Cadet  
Convention Center, Room 210

Transcriptional responses to reinforcing effects of cocaine in the hippocampus and cortex.

**Irina N. Krasnova**, *NIDA, NIH*

Biochemical and molecular consequences of repeated injections of methamphetamine.

**Jean Lud Cadet**, *NIDA, NIH*

Role of microglial activation in drug-induced neurodegeneration.

**Donald M. Kuhn**, *Wayne State University*

Opiates, psychostimulants and adult hippocampal neurogenesis: insight for addiction.

**Amelia Eisch**, *University of Texas Southwestern Medical Center*

**Wednesday, April 22**  
**8:00 - 10:30 AM**

### Virally-encoded G Protein Coupled Receptors as New Drug Targets?

Chair: Rob Leurs  
Convention Center, Room 210

Viral mimicry of G protein coupled receptor signaling.

**Rob Leurs**, *Vrije University, The Netherlands*

HHV-8 encoded GPCR ORF74 and its role in viral oncogenesis.

**J. Silvio Gutkind**, *NIDCR, NIH*

HCMV-encoded GPCR US28 as oncomodulating GPCR.

**Marine J. Smit**, *Vrije University, The Netherlands*

Transgenic mouse models to dissect the role of viral GPCRs in pathogenesis.

**Sergio A. Lira**, *Mount Sinai School of Medicine*

Functional analysis of HCMV-encoded GPCRs using mutant CMN viruses.

**William E. Miller**, *University of Cincinnati College of Medicine*

### Therapeutics in Autoimmunity: Treatment Successes and Side Effects as a Tool of Elucidating Pathogenic Pathways

Chairs: Carol A. Paronis and Cornelia M. Weyand

Convention Center, Room 207

The making and breaking of the immune system in rheumatoid arthritis - going beyond anti-inflammatory therapy.

**Cornelia M. Weyand**, *Emory University School of Medicine*

Mechanisms of action of methotrexate in rheumatoid arthritis - implications for understanding pathogenic pathways in autoimmunity.

**Bruce N. Cronstein**, *New York University School of Medicine*

Treating autoimmune arthritis through selective tyrosine kinase inhibition.

**William H. Robinson**, *Stanford University*

Pharmacogenomics in rheumatoid arthritis - deciphering disease pathways through better understanding of intended drug effects.

**S. Lou Bridges**, *University of Alabama at Birmingham*

### Endothelial Progenitor Cells and Cardiovascular Disease - From Bench to Bedside

Chair: Alex Chen

Convention Center, Room 208

Oxidative stress and EPC dysfunction in salt-sensitive hypertension

**Alex F. Chen**, *Michigan State University College of Human Medicine*

Role of osteopontin in EPC dysfunction in diabetes mellitus.

**Timothy O'Brien**, *National University of Ireland*

EPC and vascular injury.

**Zvonimir S. Katusic**, *Mayo Clinic and Foundation*

EPC therapies for cardiovascular disease – current perspective.

**Douglas W. Losordo**, *Northwestern University*

### Gases as Neuromodulators in Sensing: From Nitric Oxide to Hydrogen Sulfide

Chair: Atsufumi Kawabata

Convention Center, Room 206

Neuronal roles for gasotransmitters.

**Phillip K. Moore**, *King's College London*

Roles for nitric oxide in itching and the development of herpetic and postherpetic neuralgia.

**Yasushi Kuraishi**, *University of Toyama*

Hydrogen sulfide as a neuromodulator in the colon.

**Michael Schemann**, *Technical University Munich*

Hydrogen sulfide and pain

**Atsufumi Kawabata**, *Kinki University of Pharmacy, Higashi-Osaka*

### Regulation of Xenobiotic Metabolizing Enzymes in Humans: Implications for the Propagation of Health and Disease

Chairs: Charles N. Falany and Melissa Runge-Morris

Convention Center, Room 209

Induction of sulfotransferase (SULT2B1b) expression in cystic fibrosis liver disease.

**Charles N. Falany**, *University of Alabama at Birmingham*

Hepatic sterol metabolism: Regulation of human hepatic hydroxysteroid sulfotransferase (SULT2A1) by



nuclear receptor networks.

**Melissa Runge-Morris**, *Wayne State University*

## Division Sessions

**Sunday, April 19**

**3:00 - 5:30 PM**

### **Pharmacology Education Division Workshop: Using Human Patient Simulators to Enhance Pharmacology Education Throughout the Undergraduate Medical Curriculum**

Chair: John L. Szarek

Simulation has been a mainstay in graduate medical education, but only recently has it become more common in undergraduate medical education. This workshop will help pharmacology faculty learn how simulation using patient simulators can be used as part of their repertoire of learning modalities for medical students in the first two years and beyond. The workshop will include didactic and hands-on activities on simulation modalities, the rationale for the use of simulation, simulation as a complement to the basic science curriculum, and scenario construction and debriefing.

Hands on experience using a human patient simulator.

The rationale for the use of simulation as a complement to the basic science curriculum.

**John L. Szarek**, *AT Still University*

Scenario construction and debriefing.

**Susan Pasquale**, *University of Massachusetts Medical School*

Adoption and implementation strategies (and coping strategies for dealing with barriers) that could be used to support using simulation for teaching pharmacology throughout the undergraduate curriculum.

**William B. Jeffries**, *Creighton University School of Medicine*

**Monday, April 20**

**3:00 - 5:30 PM**

### **Molecular Pharmacology Division Postdoctoral Award Finalists**

Convention Center, Room 206

### **Drug Discovery, Development and Regulatory Affairs Division Symposium: New Insights into Pain Signaling Pathways**

Chairs: Anindya Bhattacharya and Mike F. Jarvis

Convention Center, Room 208

Speakers: **Kenneth Mackie**, Indiana University; **Theodore R. Cummins**, Indiana University-Purdue University School of Medicine; **Joyce A. Deleo**, Dartmouth Medical School; **Stefanie Kane**, Merck; **Michael L. Costigan**, Harvard Medical School

### **Cardiovascular Pharmacology Division Junior Scientists' Competition and Benedict R. Lucchesi Distinguished Award Lecture in Cardiac Pharmacology**

Convention Center, Room 210

### **Toxicology Division Symposium: The Nrf2-Keap1 System: An Emerging Key Regulator in the Defense Against Oxidative Stress, Chemical Toxicity and Disease**

Chair: Qiang Ma

Convention Center, Room 209



## EB 2009 PRELIMINARY PROGRAM

Nrf2: Key to defense against oxidants, electrophiles, radiation and inflammation.

**Paul Talalay**, *Johns Hopkins School of Medicine*

Environmental lung disease and the role of Nrf2.

**Steven R. Kleeberger**, *NIEHS, NIH, Research Triangle Park, NC*

Defense against toxic metals and hyperglycemia by Nrf2.

**Qiang Ma**, *NIOSH, CDC*

Nrf1 and Nrf2 interplay in regulation of stress response.

**Jefferson Y. Chan**, *University of California-Irvine, School of Medicine*

**Keynote Address:** Molecular basis for the Nrf2-Keap1 system function.

**Masayuki Yamamoto**, *Tohoku University School of Medicine, Sendai, Japan*

### Behavioral Pharmacology Division Symposium: Pharmacological Imaging in Behavioral Pharmacology and Drug Development

Chairs: Leonard L. Howell and Mike A. Nader

Convention Center, Room 207

Pharmacological MRI in awake rats: application for drug discovery and development.

**Chih-Liang Chin**, *Abbott Laboratories*

Pharmacological MRI studies of the dopaminergic system in rhesus monkeys.

**Zhiming Zhang**, *University of Kentucky*

Functional neuroimaging and cocaine medication development in nonhuman primates.

**Leonard L. Howell**, *Emory University*

PET studies of stimulant drugs in humans.

**Joanna S. Fowler**, *Brookhaven National Laboratories*

**Tuesday, April 21**

**3:00 - 5:30 PM**

### Clinical Pharmacology, Pharmacogenomics & Translational Medicine Division

Convention Center, Room 207

### Systems and Integrative Pharmacology Division Young Investigator Platform

Chairs: David B. Bylund and Dennis C. Marshall

Convention Center, Room 208

### Drug Metabolism Division Early Career Achievement Award Lecture and Platform Session

Convention Center, Room 209

### Neuropharmacology Division Postdoctoral Scientist Award Finalists

Convention Center, Room 206

## Lectures

**Sunday, April 19**

**8:30 - 9:20 AM**

### RAY FULLER LECTURE IN THE NEUROSCIENCES

Convention Center, Room 206

Lecturer: **Henry A. Lester**, *Caltech*

Changes in the Brain During Chronic Exposure to Nicotine

## EB 2009 PRELIMINARY PROGRAM

**Sunday, April 19**  
**2:00 - 2:50 PM**

### **IUPHAR LECTURE**

Convention Center, Room 206  
Lecturer: **Robert Lefkowitz**, *Duke University*

**Monday, April 20**  
**8:30 - 9:20 AM**

### **JULIUS AXELROD AWARD LECTURE**

Convention Center, Room 206



Lecturer: **Randy D. Blakely**, *Vanderbilt University*  
**Miscarriage at the Synapse: Brain Disorder-associated Deficits in Membrane Transport**

**Monday, April 20**  
**3:00 - 3:50 PM**

### **BENEDICT R. LUCCHESI DISTINGUISHED AWARD LECTURE IN CARDIAC PHARMACOLOGY**

Convention Center, Room 210

**Tuesday, April 21**  
**8:30 - 9:20 AM**

### **TORALD SOLMANN AWARD LECTURE**

Convention Center, Room 206

## Special Sessions

**Saturday, April 18**

### **2009 Teaching Institute: Threading New Concepts into Existing Curriculum: Experiences with Genomics**

Chair: George A. Dunaway  
Convention Center, Room 207

### **Diversity Committee Symposium: ASPET Travel Fellows: Lessons Learned Along the Way: Career Choices From Past Travel Awardees**

Chair: Gonzalo E. Torres  
Convention Center, Room 208

The goal of this symposium is to present and discuss career options taken by past fellows and travel awardees. The stories are of scientists who made the decision to either stay in academia or leave academic research and forged paths to alternative career options related to science. These stories will focus on how these scientists got to where they are today and what they have learned along the way. After the talks, there will be an open session with questions and discussion from the audience.



## EB 2009 PRELIMINARY PROGRAM

Career options in science.

**Gonzalo E. Torres**, *University of Pittsburgh*

A career path outside the bench as a medical science liaison.

**Shola Adewale**, *Eisia Inc.*

Scientific regulatory and policy writing in the government: Desktop, an alternative to Benchtop.

**Michelle D. Walker**, *Drug Enforcement Administration*

Career opportunities in biomedical research: The academic perspective.

**Chantal A. Rivera**, *Louisiana State University Health Sciences Center*

### Graduate Student-Postdoctoral Colloquium: Mentoring: It Goes Both Ways

Chair: Sarah H. Lindsey

Convention Center, Room 209

### ASPET's Women in Pharmacology Committee and APS' Women in Physiology Committee Workshop: Pathways to Leadership: Developing Critical Skills

Chairs: Andria Lee del Tredici and Holly Brevig

Location and time: TBD

## Satellite Meetings

FRIDAY & SATURDAY, April 17-18

### G-Protein Targets Colloquium

Room: Convention Center 204 A/B/C

**(Separate, Advance Registration Required)**

Chairs: **Alan V. Smrcka** and **Theresa Filtz**

### Behavioral Pharmacology Society Meeting

Room: Convention Center 201

**(Separate, Advance Registration Required)**

Contact Nancy Ator: ator@jhmi.edu or 410-550-2773

## Public Affairs Sessions

### EB 2008 Public Affairs Session

Monday, April 20

5:00 - 6:30 pm

#### *Evolution of Creationism*

Speakers: Barbara Forrest, Eugenie Scott, Kenneth Miller, Judge John E. Jones (Invited)

**FOR MORE PROGRAM INFORMATION VISIT:**  
**<http://www.aspet.org/public/meetings/eb09.html>**

# G-Protein Targets Colloquium

April 17 – 18, 2009

New Orleans, LA

Organized by Alan V. Smrcka, PhD and Theresa M. Filtz, PhD

This is a satellite meeting to Experimental Biology 2009

## Preliminary Program: Friday, April 17

### Theme I: Effector Structure and Mechanism for Regulation

Session Chair: J. Tesmer

- PLC Beta Structure
- RhoGEF Structure/Function
- Molecular basis for  $K^+$  channel regulation by  $G\beta\gamma$

### Theme II: Novel G Protein Effectors and Regulatory Mechanisms

Session Chair: T.K. Harden

- Novel G13 Effectors
- Regulation of PLC by Small GTP Binding Proteins
- Talk Selected from Abstracts

### Theme III: Effector Scaffolding

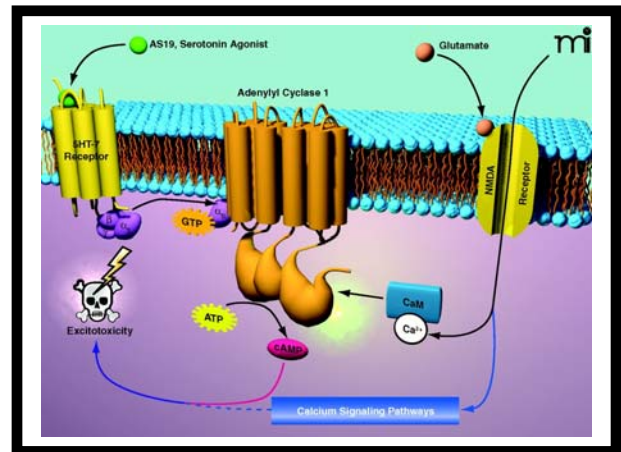
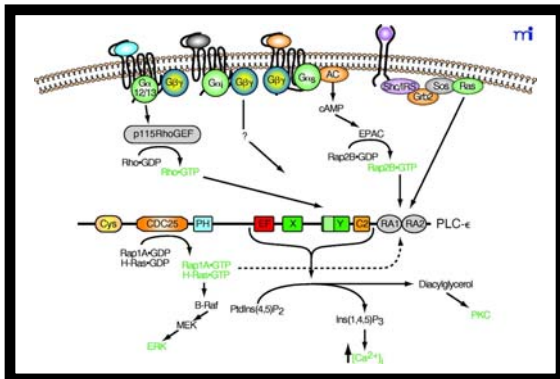
Session Chair: J. Scott

- Adenyl-Cyclase-AKAP Interactions
- Scaffolding of  $K^+$  Channels
- Talk Selected from Abstracts

### Special Lecture on G Protein BRET Methods: Application to G Protein Effectors

Use of BRET to Monitor G Protein Conformational  
Changes

### Poster Session



## Preliminary Program: Saturday, April 18

### Theme IV: Effector Cell Physiology and Pharmacological Targeting

Session Chair: A. Smrcka

- RhoGEF Regulation in Cells
- Epac in cAMP-Dependent Physiology
- Pharmacological Targeting of AC
- Small Molecule Targeting of  $G\beta\gamma$ -Effector Interactions
- Talk Selected from Abstracts

### Theme V: Physiological Roles of G Protein Effector Systems *in vivo*

Session Chair: T. Filtz

- Adenyl Cyclase and Longevity/Physiology
- Physiological Roles of Phospholipase C Epsilon
- PI3Kinase  $\gamma$  in Neutrophil Function

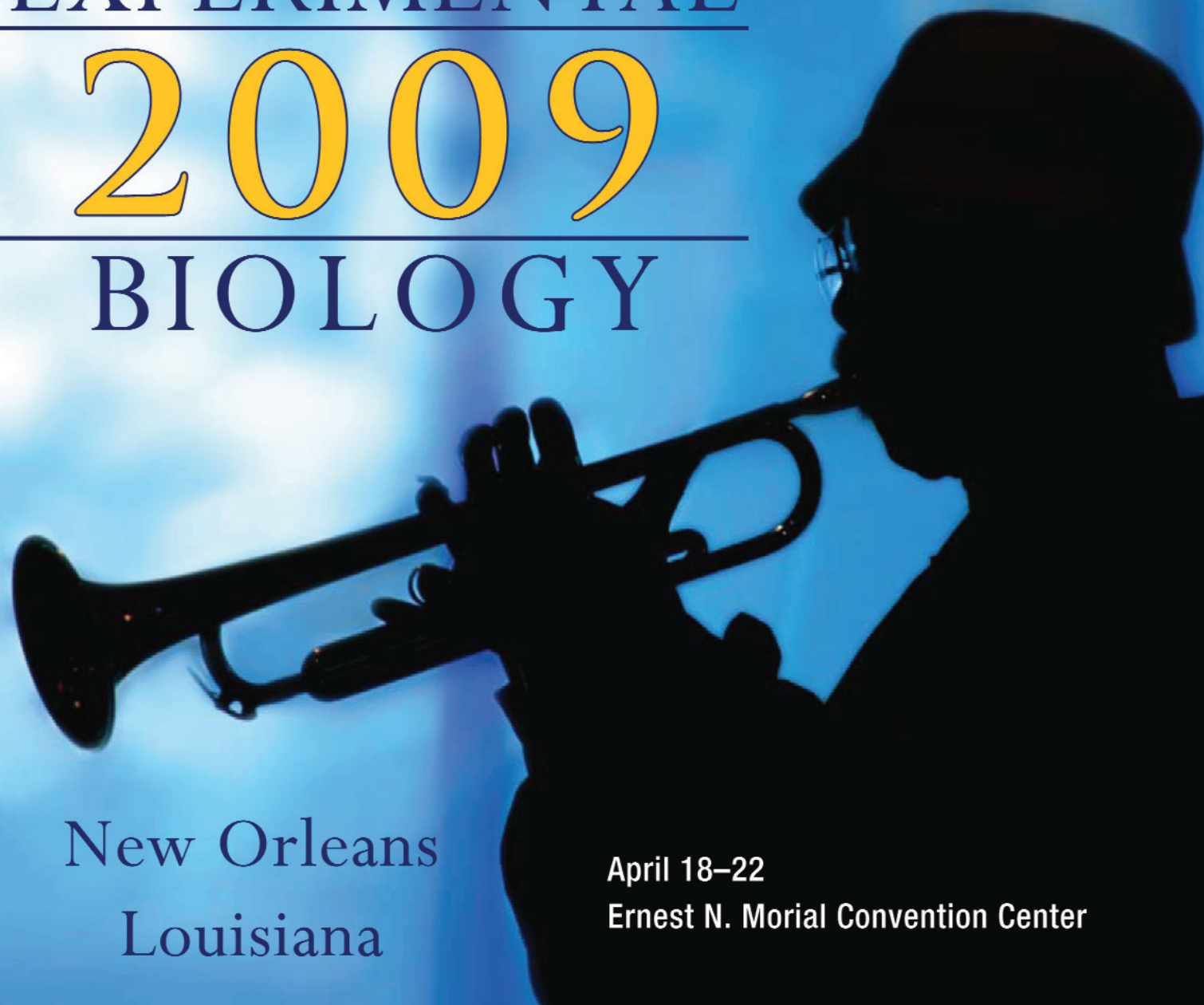
Plenary Lecture:  
Targeting PI3Kinases

For More Information on Programming and to Register:

<http://www.aspet.org/public/meetings/meetings.html>

FOR FURTHER INFORMATION WWW.EB2009.ORG

# EXPERIMENTAL 2009 BIOLOGY



New Orleans  
Louisiana

April 18–22  
Ernest N. Morial Convention Center

## **SPONSORS:**

American Association of Anatomists (AAA)  
The American Physiological Society (APS)  
American Society for Biochemistry and Molecular Biology (ASBMB)  
American Society for Investigative Pathology (ASIP)  
American Society for Nutrition (ASN)  
American Society for Pharmacology and Experimental Therapeutics (ASPET)



## CPT 2009 MEETING REVIEW

ASPET attended the Clinical Pharmacology and Therapeutics 2009 meeting in Quebec, Canada in July. In celebration of ASPET's Centennial, we held a reception in Quebec's Parliament Building. Representing IUPHAR, Dr. Sam Enna, presented ASPET with a plaque honoring ASPET's 100<sup>th</sup> Anniversary. Pictures from the reception are below:



## ASPET MEMBERSHIP SURVEY RESULTS

Thank you to all ASPET members who participated in the 2008 ASPET Membership Survey. The annual survey is designed to give each of our members a voice in the workings of the Society. By offering your opinions, criticisms and suggestions, you are allowing us to examine how we are doing and what we can do to improve your membership experience with ASPET.

### General Membership Questions:

We are happy to report that a very large majority of survey respondents (91.4%) either Agree or Strongly Agree that being a member of ASPET enhances their credibility as a pharmacologist or pharmacology student. 64% of respondents believe that being an ASPET member is expected by their peers and 71% agree that ASPET provides them with good networking opportunities. We are very pleased our members regard ASPET as an important Society to belong to and we hope to continue this trend as we work to bring in new members and grow the society.

ASPET is always looking for new ways to increase our membership. One of the most effective recruitment efforts is to attend non-ASPET meetings to sign up new members. We asked you which meetings ASPET should attend to recruit new members. The three most common suggestions were for the Society for Neuroscience meeting, the Society of Toxicology meeting, and the American Heart Association meeting. We are pleased to let you know that we already attend Society for Neuroscience each year with a booth in the exhibit hall. Also our Division for Neuropharmacology hosts a reception at SFN each year. While we have not attended Society of Toxicology in the recent past, at your suggestion, we are planning to attend in 2009. We do not have plans to attend the American Heart Association; however, this is one meeting we will keep in mind for future planning. Other meetings that were suggested include the College on the Problems of Drug Dependence (we sent ASPET information to be handed out at this meeting in 2008 and will continue to do so in future years), cancer-related meetings, clinical meetings, and other international pharmacology meetings. All of your suggestions are greatly appreciated.

### Public Affairs:

We asked members if they supported increased ASPET involvement in the following public affairs issues:

<b><u>Public Affairs Issues</u></b>	<b><u>Percent of respondents who support increased involvement</u></b>
<i>Increased funding for NIH and NSF supported research</i>	80%
<i>Increased funding for integrated organ system/whole animal research by federal and private research agencies</i>	59%
<i>Increased funding and political support for FDA's role in the regulation of safe and effective drugs</i>	53%
<i>Importance of the basic sciences and pharmacology in medical education</i>	84%
<i>Importance of enhancing basic science education at all levels of education</i>	73%
<i>Support for pro-research-oriented legislation for critical animal research studies</i>	64%

### Scientific Meetings:

The majority of survey respondents attend about 2 meetings a year. When asked if you planned on attending ASPET's Annual meeting at Experimental Biology 2009, taking place in New Orleans in April, 33% said Yes, 33% said No, and 34% said they were undecided. For those of you who are undecided about attending the meeting, we hope that you will take a close look at our exciting program on page 131.

### ASPET Products:

ASPET's newest venture in raising funds for Society activities is our range of ASPET merchandise. Due to popular demand, ASPET sold t-shirts, hats, water bottles, and ornaments at the Centennial meeting in 2008. We were very happy to see that the ASPET merchandise was so popular during the meeting and have decided to continue to sell merchandise on our website as well as at future meetings. From our survey, we saw that most respondents have not yet bought any



## ASPET MEMBERSHIP SURVEY RESULTS

ASPET merchandise. We hope that you will take the time to visit our website at [http://www.aspet.org/public/Products/product\\_main.html](http://www.aspet.org/public/Products/product_main.html) to view the merchandise we have to offer. The ASPET products make great holiday gifts for your lab or colleagues, be sure to check them out! New merchandise will also be available at the ASPET Annual Meeting in 2009. Your purchases go directly to helping ASPET raise funds for future activities. Not to mention, showing your support for ASPET is truly appreciated as we look to grow the Society, recruit more members, and make ASPET the premier Society to belong to.

### **Technology:**

Now that ASPET's 100<sup>th</sup> Anniversary is behind us, we are forging ahead with the future by looking into ways we can improve your membership experience through technology. New technological advances and terms such as Web 2.0 are becoming more and more important, and as technology changes, so must ASPET evolve.

During the Centennial Meeting, ASPET recorded several Centennial symposia and made them available on the ASPET website for downloading and viewing. We asked ASPET members if they had a chance to view these and if they were useful. The majority of respondents had not viewed them; however, of those that did view the podcasts, 99% found them to be very useful. We hope to continue to provide podcasts of our meeting to our members and hope that you will utilize these as they become available.

We also now provide RSS feeds for all ASPET Journals. RSS feeds allow you to set up electronic alerts to inform you when new content becomes available. We asked members if they were making use of these feeds. 17% of respondents are using the feeds, however 83% are not.

We also wanted to gauge our members' understanding and desire for several popular Web 2.0 features such as Podcasts, Blogs, RSS feeds, and Social networking. We asked you which new forms of Web 2.0 communication and technology should ASPET explore and provide for members:

<b><u>Web 2.0 Techology</u></b>	<b><u>% of Respondents that believe ASPET should be providing this service</u></b>
Podcasts	38%
Blogs	21%
Social Networks	19%
RSS Feeds	22%
None of the Above	39%

The percentages for the above table were for the entire membership. When we look at just students who took the survey the percentages are much higher. For student member respondents, 50% want podcasts, 37% want blogs, 47% want an ASPET social network, 18% want RSS feeds and only 12% said none of the above.

We also asked what kinds of specific podcasts, blogs, social networks, and feeds would be useful to ASPET members. These produced a variety of suggestions including podcasts of symposia and lectures from the annual meeting, blogs about pharmacology career paths, RSS feeds on public affairs issues, and an ASPET social networking site for members to connect with each other and network. All of your ideas will be carefully examined as we take steps to explore these new avenues of technology.

### **Other:**

We received several encouraging comments from respondents telling us they were happy with the services we provide. We also received suggestions about getting the younger members of our society more involved, ways to recruit new members, and suggestions for enhancing ASPET's role in the science community. All comments are well received and we would like to thank you once again for your input and support. Without our members, the Society would not exist, so your active involvement is very important to us.

## *The View from the Executive Office— Interviews with ASPET's Executive Officers*

There have been four executive officers throughout ASPET's first 100 years. It's unusual for an organization celebrating its centennial to find all of its executive officers still living. Dr. William L. Dewey, Chair of ASPET's Centennial Committee, began interviewing the executive officers in 2006 to record their memories of the Society and how it changed during each one's tenure. The third in a series of four interviews continues with Kay A. Croker.



**Kay A. Croker**  
*Executive Officer, 1981-1997*

**WLD:** What is the period of time that you served as executive officer of ASPET?

**KAC:** I came to the Society in 1977, and in 1981 I became the executive officer. Prior to that I had served ASPET in several different capacities. I retired in 1997.

**WLD:** So you were there about 16 years?

**KAC:** As executive officer, yes.

**WLD:** And that is almost exactly the same as Dr. Cook. He came in 1961 and left in 1977.

**KAC:** Houston Baker became executive officer in 1977 and left in 1981. I started by producing *The Pharmacologist* with a new word processing program from Xerox called the Smart Program. I provided camera-ready copy for the print shop. I then became the executive assistant and eventually executive officer.

**WLD:** And it was 1981 that you became executive officer?

**KAC:** Right.

**WLD:** Were you a member of the Society before you came in as the executive officer?

**KAC:** No.

**WLD:** Have you become a member?

**KAC:** No.

**WLD:** How familiar were you about the discipline of pharmacology and ASPET and had you been on the Federation campus before joining ASPET?

**KAC:** I worked for Dr. Kimura who was a member of ASPET. He worked for FASEB's Life Sciences Research Office. I did literature retrieval for him and maintained his reprint files. He would suggest that I read *The Pharmacologist* each time it came out. When he left, I had been offered several other jobs on the FASEB campus, but Dr. Kimura insisted I stay with pharmacology.

**WLD:** So you were on the campus for a while before 1977?

**KAC:** I was there for a year. It was an interesting job.

**WLD:** In terms of your memory about the Society, how did it change from 1981 to 1997, in terms of membership? Did it increase much? Was that a big issue?

**KAC:** It did increase, but it didn't increase at the same rate that it had previously; there was a time when the membership would double every year.

**WLD:** Was that in Dr. Cook's time as executive officer?

**KAC:** Yes, and growth started to slow down. We did grow substantially each year, but you can't sustain double growth forever.

## SPECIAL ARTICLE: THE VIEW FROM THE EXECUTIVE OFFICE

**WLD:** So there was some increase in membership, but it was gradual. Now, what about the office staff? Did that grow in relation to the increase in membership and did the number of responsibilities handled by the staff increase as the membership increased?

**KAC:** Actually, the staff had decreased. I thought that we didn't need all that we had, and one of the reasons for that is FASEB. We were able to get through FASEB expert services on a fee-for-service basis. We couldn't afford to hire that same expertise full time in the ASPET office, so it was cost effective to go to FASEB, and we got expert help. FASEB did a lot for me. Of course, I started working on the campus for FASEB, so they knew me.

**WLD:** Now, what about the journals? Did the journals change much during your tenure as executive officer? Did they change in number? Were there any new ones created?

**KAC:** There were no new ones created. We did lose *Rational Drug Therapy*. When Houston was executive officer, he brought that in house. Saunders had been publishing it, and nobody knew anything about its circulation, etc., but once a year we would get a small check. We brought it in house, and we discovered that the actual subscriptions list was about half of what we had been told. There were dead people on the list, and there were people who had not renewed their subscription but still continued to receive it. We still kept it going for awhile, but the number of subscribers continued to decrease and it became more difficult to get good articles. Eventually, we just decided that we could not continue sustaining the loss it produced.

**WLD:** How about in terms of meetings? A very critical thing that happened during your tenure was stopping the fall pharmacology meeting. How about meetings in general? Please talk about changes in the meetings during your term in office.

**KAC:** Meeting attendance started to decrease, and we didn't know why. We had two meetings a year. The spring meeting was with the other FASEB societies and our fall meetings were held on college campuses.

It became increasingly difficult to organize a meeting on campus. It was a lot of work and took a great deal of time. And, it wasn't cost effective. ASPET lost money. The executive office provided money and services requested by the local committee. We lost money in the ASPET office. The local committees found that they were losing money as well because it took a lot of time and effort to put on a meeting. Fewer and fewer proposals came in. Eventually, we decided that people didn't want to stay on a campus and that they wanted to stay in hotels. We still had the August meeting and it was still run by a local committee with considerable support from the ASPET office, and people were not staying on campus any longer. An ASPET Meetings Committee was established, and the ASPET executive office provided the logistical support needed. Attendance and the number of papers submitted dropped. We realized that through our travel awards, other award presentations, and symposium speakers, we were funding more people than were paying to attend. Also, there was increasing competition from a proliferation of specialty meetings. The Society decided to put more of our effort into the spring meeting. At that point, also, we began to develop new small meetings on specific topics organized by individuals or special interest groups of scientists. Sometimes they were associated with our annual meetings as satellites; sometimes they were independent meetings on a university campus or elsewhere. We then dropped the August meeting thinking that these smaller meetings might be a more effective way for the Society to succeed, and for the most part these specialty meetings were quite successful. The fall meeting didn't do well not just because of finances but also because decreased interest caused the attendance to drop way down.

**WLD:** How did the number of people attending these specialty meetings compare to the number of people at the fall meetings?

**KAC:** The specialty meetings were much smaller, 100–200 people.

**WLD:** Much smaller, so the work load was less?

**KAC:** The ASPET office offered whatever support that the organizers asked for. For the most part, they were successful; they didn't make money, but they didn't lose money either. The work load did not decrease, but more of it was done at the local level. It takes almost as much effort to organize a small meeting as it does to organize a large one, but our office did less of the work. There were several of these specialty meetings at various times throughout the year.

**WLD:** I'm sure that it was much easier to do it for 100 people rather than 800 people. Probably that difference of size had an effect.

**KAC:** That was part of it. Sometimes a publication resulted, and that was great. Under the auspices of ASPET, they got together people on a specific topic. I went to one or two of them, and I thought that they were extremely successful. I don't know if they have continued or not.

**WLD:** Did poster presentations start at ASPET meetings during your time as executive officer?

**KAC:** They had poster sessions when I first came to ASPET.

**WLD:** So they had them during Houston Baker's time?

**KAC:** Yes, but there were very few of them. Most people requested platform sessions. Over a period of time, the number of requests for poster sessions steadily increased. The poster sessions were much better attended than the oral

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presentations. People preferred to attend symposiums and special lectures. We continued to schedule platform sessions. Sometimes, the Program Committee thought it would be good to have an oral session on a specific topic, and sometimes people needed to give an oral presentation to get funding for the meeting. We tried to accommodate those needs. The Program Committee tried to do what was best for most of the attendees. The last fall meeting was in San Francisco and that was more successful, partly because the IUPHAR Executive Committee met to plan their international meeting and were there as our guests. That drew a few more people. People used to say that, if you would pick a good site, people would come back; it didn't work. We went to Orlando, and it didn't work. We went to San Diego, and it didn't work.

We had plenary lectures at both meetings. In the spring meeting, the lecturers were invited. At the fall meeting, they were usually award lectures. The Sollmann Award lecture was always successful because of the caliber of people who received the award. It was so successful that over a period of time we added lectures for other Society awards.

**WLD:** How about finances? What happened with or what changed with finances of the Society from 1981 to 1997? There was amazing growth, as I remember.

**KAC:** There was amazing growth. When I became executive officer, the Society had almost no assets. We had an Investment Subcommittee and an investment portfolio that was about \$500,000. We had a bookkeeper on staff and an outside auditing firm. Our auditing fees were very high for a small society. Our auditor fees were higher than larger societies, and the auditors and I agreed to initiate a number of measures to reduce the fees. The publication and general funds were together and the auditor suggested that they be separated. We also moved our accounting to the FASEB accounting office on a fee-for-service basis, and that saved considerable amounts of money. We hired an investment firm to advise us on our investments.

**WLD:** Can you say more about the rate of the growth of the assets of ASPET during your time as executive officer?

**KAC:** I don't remember the timing of it. I remember when I became executive officer we had about \$500,000 or \$600,000, and when I left we had over \$10,000,000. We were in the fortunate position of being able to institute new programs such as Young Investigator Travel Awards and Minority Student Scholarships. We published a new membership brochure and produced a video tape to encourage students to pursue a career in pharmacology. We provided it to schools and colleges who requested it. The Investment Subcommittee contracted with a professional firm to handle our investments.

**WLD:** Would you say that the assets of the Society increased dramatically but unfortunately at the same time the membership's interest in coming to meetings decreased?

**KAC:** Yes, that is right.

**WLD:** Dr. Cook gave an interesting perspective on the issue of membership in the Society. He said that there was a real issue when he was executive officer, and it had to do with two strongly different opinions of many people on the Council, officers, etc., over membership. Some wanted ASPET to be a very elite organization, almost like the National Academy, and you had to be really somebody to get into ASPET. They didn't care about how many members there were, didn't care about finances or reserves. Resources were not even an issue. There was another group that said, no, we want to have 10,000 members, we want to be another AAAS; we want everyone who is interested to become a member. Did that type of differing opinions exist during your tenure?

**KAC:** That existed during my tenure as executive officer. When I became executive officer, there were certain criteria that had to be met before an individual could become a member. Membership in ASPET, once it was achieved, was considered a criterion for professional advancement. It was an important credential to add to your CV. Some institutions wouldn't consider promotion or tenure unless the person belonged to a [FASEB] society. As time went on, that became less and less important, and there were members who said that ASPET should accept all applicants. We had retreats about this and other issues, but the criteria for membership was one of the subjects always discussed.

**WLD:** When did the retreats start?

**KAC:** Sometime in the 1980s, and the size of the membership was always one of the most important topics. Continually, officers reevaluated the criteria for membership. Eventually, they decided that our criteria were too restrictive and that was one of the reasons that our membership wasn't growing faster. The criteria for membership were relaxed and the membership committee ceased to exist.

**WLD:** Isn't it true that for a long time there have been a number of chairmen of pharmacology departments in medical and other professional schools who are not members of ASPET?

**KAC:** Yes, and some presidents and Councils of the Society tried very hard to attract them to the Society.

**WLD:** On a different subject, isn't it true that for a number of years the Federation meeting was held in Atlantic City with an occasional meeting in Chicago but that stopped during your term as executive officer? Why the change?

**KAC:** ASPET had two meetings a year. One in the spring with FASEB in Atlantic City and every third year in Chicago and a fall meeting by ourselves as we said earlier on college campuses. In 1978, Atlantic City added gambling and they became less and less interested in us because we weren't big gamblers. We needed space for scientific sessions, but they

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could make more money using the space for gambling than allocating that space to us. FASEB was pretty much forced to look for other possible sites.

**WLD:** You are saying the main reason, in your mind, why FASEB left Atlantic City was because Atlantic City lost interest in FASEB rather than FASEB losing interest in Atlantic City?

**KAC:** Correct.

**WLD:** How did that affect you as executive officer of ASPET? Would that make your job harder, did it make more work for the ASPET office, or did the FASEB office handle all of those issues?

**KAC:** FASEB handled the meetings, and so as far as the ASPET office was concerned, little changed. Site selection did become a responsibility. When you met in the same place year after year, you became familiar with what was there, and in that respect it was much easier.

**WLD:** Since ASPET is a member of FASEB, how did the FASEB office and our individual Society office work together or was there very little interaction?

**KAC:** There was sustained interaction. I am very grateful to them because when I became executive officer, whenever I needed help there was somebody at FASEB to provide it.

**WLD:** Do you feel that ASPET's members gain anything from having their office on the FASEB campus?

**KAC:** I think because of the interactions with and resources of the FASEB office and our office, the ASPET members get better service from the ASPET office. In addition, the interactions with other societies on campus are beneficial.

**WLD:** Was it less expensive to use FASEB services?

**KAC:** Yes, for the most part, but there is more to it than expense. FASEB provided expertise that you can't put a price on. It saved time, and it saved travel expense to use FASEB services.

**WLD:** Just like you just said about going back to the same city for the meeting, one assumes that going to the same office for services all the time and seeing the same people would also be an asset. Is that correct?

**KAC:** Yes. They became familiar with some of our needs and efficiently satisfied them. They provide an expertise that one society alone could not afford.

**WLD:** Were ASPET's employees also employees of FASEB? The ASPET Council or the president-elect or whoever recommended the salaries to the Council, and they decided the budget for your office. But didn't the ASPET employees also benefit from being with FASEB?

**KAC:** ASPET employees were employed by ASPET, not FASEB. The FASEB member societies all agreed to provide the same benefits, and the details were handled by the FASEB Human Resources Department.

**WLD:** Was that a significant asset?

**KAC:** Oh, yes because we got benefits for our employees that we couldn't have afforded or weren't available due to the small number of employees in our Society.

**WLD:** How about other benefits of being on the campus in addition to being able to use the services, having colleagues work in the service offices, and the better benefits for employees?

**KAC:** Another benefit is the activity of the ASPET executive office to interact with other societies on a frequent basis. It was easy to walk down the hall or across the campus anytime an issue arose and discuss it with someone from another society who had a similar problem. Seldom was an issue unique to any one society. We all had similar issues. We had periodic meetings of the executive officers of the six societies to discuss common issues and FASEB matters, and at any time you could go visit another office.

**WLD:** What was the best part of the job?

**KAC:** I worked with really fantastic people.

**WLD:** The staff?

**KAC:** Yes as well as the ASPET membership and other FASEB societies and members.

**WLD:** So the ASPET members were pretty decent folks?

**KAC:** I thought so. I thought the officers were great. The committees were great to work with. It was a very rewarding experience for me.

**WLD:** Is there any way that the ASPET membership or ASPET as an entity should change the responsibilities or alter the job? How can they improve the job, etc.? Are there any suggestions that you could give to make the executive officer a better job?

**KAC:** The job is a good one. Responsibilities evolved over a period of time and continue to do so. The executive officers should be versatile and acceptable. Every year there is a new Council, new president, and new committee members. The dynamics constantly change.

**WLD:** Was there a structural mechanism that could have made your job better? This could be seen as a tough job because every year you have a different person to whom you report. Another area, which could be difficult, is the relationship between the president and the executive officer. The history of the organization lies with the executive officer

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and staff, yet the president is elected and serves as the president-elect for a year, and then is president and all of a sudden for one year he/she is in charge. They are the ones that have to answer to the membership, but yet, the continuity of the organization lies in the hands of the executive officer. That's a difficult area. Any thoughts on that?

**KAC:** I was fortunate to work with people who, as busy as they were, were always available. They were dedicated to the Society and took their responsibilities very seriously. We worked as a team to further the interests of ASPET and the discipline. Both the president and the executive officer answer to the Council and the membership.

**WLD:** That is interesting because one might think that the executive officer was answerable, really, to the president, president-elect, and the past president, or all of Council.

**KAC:** Well, I felt that the executive officer was answerable to Council, to the president, and to the membership. Anytime a member had a question or a problem and that person called, it was my responsibility to respond.

**WLD:** Did you feel that the presidents really cared a great deal about the Society or were they just doing this because it was an honor? They would be gone in a year, but the executive officer was not.

**KAC:** Every president that I dealt with had a sincere interest in the Society and the discipline. Each one had somewhat different interests and different agendas, but they all took their responsibilities seriously.

**WLD:** And they all treated you well?

**KAC:** Without exception! Now, obviously I had more interactions with some than others. But all, busy as they were with professional responsibilities, were dedicated ASPET members.

**WLD:** Would you give any advice to the ASPET leadership to change the role of the executive officer or the size of the membership? Should it strive to be a smaller elite society as envisioned by some in the beginning or have aspirations to be very large like the Society for Neuroscience?

**KAC:** As I said, at one time I think members thought being a member of ASPET was an honor; that diminished over time.

**WLD:** Has ASPET served its purpose?

**KAC:** I think that ASPET is still very important. There are many other societies now, many with specialized interests. There are many more options now than there once were, but ASPET is still the premier national society that represents and speaks for the entire discipline.

**WLD:** Since ASPET membership is leveling off and there are a lot of chairs of pharmacology departments that don't belong, which may be why many young scientists in pharmacology departments do not become a member, is this something that ASPET should be worried about or is there something that can be done by the Council or executive office to change this?

**KAC:** Has ASPET membership dropped off?

**WLD:** The total membership is now about 4500, but the students and the retired members do not pay dues, which amounts to 1400 out of the 4500. From what you remember, is there anything that you would suggest be done to change the relationship and working arrangement between the executive officer and the membership or leadership?

**KAC:** I can't think of anything that should be done to change the interactions of the executive officer with the presidents, the Councils, or the membership. It was always a good relationship for me, and it is something that should be decided by each leadership group.

Stay tuned for the final interview with  
Christine K. Carrico, PhD, Executive Officer  
from 1997 – present, in the next issue of  
*The Pharmacologist*, December 2008.



## Features Added to Online Journals

Two new features appeared on ASPET's online journals during the summer. Each journal's homepage now has links to the 50 most read and most cited papers. These statistics are recalculated monthly. The most read articles are those that received the largest number of hits, based on full-text HTML and PDF views, during the month reported. The most cited rankings are based on citations to articles on the journal site from articles in journals hosted by HighWire Press. Citations from journals outside of HighWire are not counted, so the rankings do not reflect all scientific literature. However, HighWire Press hosts over 1,100 journals, including most of the leading biomedical research journals.

Enhanced PDFs were introduced in July for articles published in *JPET*, *Pharmacological Reviews*, *Molecular Pharmacology*, and *DMD*. ASPET's logo and the journal title appear in the left margin of the PDF page. The right margin contains the journal's URL, the date on which the PDF was downloaded, and the name of the subscribing institution or individual when accessed by IP address recognition or the reader is signed in. If an erratum was published for an article or an online data supplement exists, its availability is noted at the top or bottom of the page.

This feature appears for articles published in *Molecular Pharmacology* since 1980 and for articles published since 1979 in *JPET*, *Pharmacological Reviews*, and *DMD*. The smaller page sizes of earlier volumes cannot accommodate these enhancements. They were not added to *Molecular Interventions* because the graphics on many pages in that journal run to the edge of the page, leaving no margin.

Enhanced PDFs make it easier to identify the journal in which an article was published. The Society's logo in the left margin "racing stripe" identifies ASPET as the journal's publisher.

## New Look Coming

In the next couple of months, ASPET's online journals will be updated with a new design. The cleaner, less cluttered layout should make the sites easier to navigate. But, this change is for more than navigation and aesthetic reasons. HighWire Press is preparing to support Web2.0 functionality for all of the journals it hosts. The new web site design is the first step in that transition. ASPET's journals will be among the first at HighWire to convert to the new design template. The transition to full Web2.0 will start in 2009 and continue into 2010.

## Subscriptions for 2009

ASPET's Board of Publications Trustees set the Society's 2009 subscription prices in a meeting held by conference call on June 25. ASPET has implemented low to moderate increases whenever prices were raised. Member subscription prices have risen at higher rates in some years because member prices are heavily subsidized. Increases greater than 5% have generally been in response to, or anticipation of, publishing significantly more pages.

In 2009, ASPET's online journal costs will increase for the first time in several years. The cost for Bench>Press, our online peer review system, will also increase. Web 2.0 will present options for new functionality for the online journals, and these will likely incur new costs. Paper and mailing costs have been increasing by double digits and are expected to continue at current rates or higher. Nonmember personal subscriptions have been priced at a loss for many years. Member print subscriptions have been priced at a larger loss.

To address these challenges, the BPT took the following steps. Member print subscription prices will increase by 10% for *JPET*, *Molecular Pharmacology*, and *DMD*; the price for *Pharmacological Reviews* will go up by 5%. The 2009 prices represent only 30–52% of the print manufacturing costs for most of ASPET's journals, so they remain a tremendous bargain for members.

Institutional prices will rise by 6% for *JPET* and *Molecular Pharmacology*, 5% for *PharmRev* and *Molecular Interventions*, and 7% for *DMD*. These increases are below those predicted by industry analysts and anticipated by librarians for 2009. ASPET's institutional subscription prices remain among the lowest for journals in pharmacology and related fields.

Nonmember personal subscriptions will not be available after 2008 except to *Molecular Interventions*. *MI* publishes position available advertisements, and the journal was intended, in part, to reach out to nonmembers who conduct pharmacology research but do not consider themselves to be pharmacologists. *MI* needs individual subscribers for these reasons. (*MI* needs institutional subscriptions as well—have you asked your library to subscribe?)

There are currently only 96 nonmember subscribers across the four other journals. It is likely that many of these orders are used in place of an institutional subscription. Some are purchased by overseas subscription agents and resold to universities and companies at much higher rates.

Nonmember personal subscribers have two options to continue their access to ASPET's journals. Their employers can purchase subscriptions at the institutional rates. Alternatively, these nonmembers can join ASPET and get online access to all five journals as a member benefit. Anyone who reads these journals enough to subscribe should qualify to be an ASPET member, and member dues are less than the 2008 personal subscription rates. Nonmember subscribers have been sent a letter explaining ASPET's new policy, an institutional subscription order form, and a membership application.

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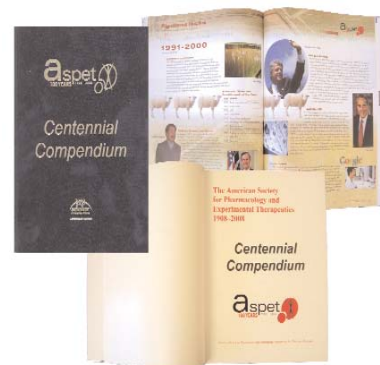
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## Appropriations Update

Congress returned September 8, FY2009 begins October 1, a new president will be elected November 4 and take office January 20, but resolution of the NIH budget might not happen until next spring.

However, there are several moving targets that might mean more money for NIH. At the moment, there still remains talk of a second supplemental that would provide \$500 million additional funds to the agency. ASPET members were informed of this pending action late July but consideration of the supplemental was postponed at the last minute over a variety of procedural issues. An earlier supplemental added \$150 million in FY'08.

There is now the likelihood of a long-term FY 2009 Continuing Resolution (CR) that would provide the funding for all agencies beginning October 1. The terms and duration – possibly through February or March - are not clear and are still being talked about. CR's are typically more short term but it is unlikely that Congress will return for a lame-duck session this fall after a brief three-week work session. And the Democrat-controlled Congress, cautiously anticipating a more friendly Obama administration, will want to wait until after the election since the party is all but assured of picking up even more seats in the House and Senate.

But there remains a possibility that the proposed \$500 million supplemental could be added to the FY 2009 CR. The goal would be for the CR to include the House Labor/HHS subcommittee recommended NIH funding increase of \$1.25 billion (3.9%) and add on the \$500 million proposed in the second supplemental. Senators Harkin and Specter had originally proposed \$5.2 billion to help restore purchasing power at the NIH. Long term, the \$1.25 billion plus \$500 million could be viewed as part of a "down payment" on future increases for NIH in FY 2010.

At the time of this writing, the situation is still fluid and our advocacy message has not been fully formed; ASPET members may already have heard about the need to communicate with Congress to help NIH funding levels.

## FDA

Relative to NIH, the FDA's FY' 09 appropriations situation has been relatively quiet. The Senate committee version of FY 09 Agriculture Appropriations contains an increase of \$325 million dollars over the December 2007/FY 2008 baseline. The House subcommittee version contains a similar amount, both substantial increases for FDA. It is not clear if there would be any supplemental funding for FDA.

The Alliance for a Stronger FDA, of which ASPET is a member, has consistently advocated for the Senate funding level (+\$325million), an appropriation level of \$2.04 billion. However, there is no guarantee this is what the final funding level will be. This increase would be significant, since the increase would be equal to the total increase from FY 03 to FY 08.

## Evolution Symposium at Experimental Biology 2009

"The Evolution of Creationism" is the subject of the EB Public Affairs Symposium to be held at EB'09 in the New Orleans Convention Center on Monday, April 20, 2009 from 5:00-6:30 pm. Confirmed speakers include notable experts on the subject including: Barbara Forrest, Southeastern Louisiana University, author of *Creationism's Trojan Horse*; Ken Miller, Brown University, author of *Finding Darwin's God* and other books on the battle over teaching evolution; Eugenie Scott, Executive Director of the National Center for Science Education, and author of *Evolution versus Creationism* (a second edition of which is soon to be published); and Judge John E. Jones, the Federal Judge who presided at the landmark *Kitzmiller v. Dover, PA* trial in 2005 that was the first direct challenge brought in US federal courts against a school district that required the presentation of intelligent design as an alternative to evolution. The plaintiffs successfully argued that intelligent design is a form of creationism and that the school board policy violated the Establishment Clause of the First Amendment. Judge Jones decision has sparked considerable response from both supporters and critics.

### NIMH Strategic Plan

The National Institute of Mental Health Strategic Plan is now available to review at:  
<http://www.nimh.nih.gov/about/strategic-planning-reports>.

This document represents the culmination of a year-long initiative launched by NIMH to develop a new Strategic Plan that will serve as a guide to the Institute for advancing mental health science over the next 5 years.

### Association of American Medical Colleges Report on Education in Safe and Effective Prescribing Practices

AAMC report addresses the consensus that graduating medical students, residents, and practicing physicians lack fundamental understanding and training in pharmacotherapy and rational prescribing.

View the report at: <http://www.aamc.org/meded/msop>.

### Animal Research Web Sites

The United Kingdom's Research Defense Society allows contributions/materials from scientists worldwide on the contributions of animal research to medical advances. <http://www.animalresearch.info/en/home>. Also, NIH's Office of Extramural Research has launched a new animal research website which includes resources for scientists and institutions, as well as the public. The site offers information and resources for researchers and institutions that have come under attack by animal rights extremists: <http://grants.nih.gov/grants/policy/air/index.htm>.

### ASPET-IOSS Fund Application Guidelines

The ASPET-IOSS Fund was created to provide support for graduate students and post-doctoral researchers seeking training in integrative whole organ systems sciences. The fund is currently supported by Abbott Laboratories, Merck Research Laboratories, Pfizer and Wyeth Research. The goal is to help augment developing programs (see above) that provide training of students in this field.

For application, information, visit: [http://www.aspet.org/public/public\\_affairs/pa\\_ious.html](http://www.aspet.org/public/public_affairs/pa_ious.html).

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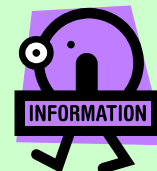
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## CHAPTER NEWS

### **Southeastern Pharmacology Society**

#### **2008 Annual Meeting:**

October 13-14, 2008

Charleston, SC

Hosted by:

Department of Pharmaceutical & Biomedical Sciences and  
Department of Cell & Molecular Pharmacology and Experimental Therapeutics  
Medical University of South Carolina

Topics Include:

Mitochondria Dysfunction, Matrix Remodeling, Tissue Regeneration

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To register visit:

[www.aspet.org/public/chapter/seps\\_chapter.htm](http://www.aspet.org/public/chapter/seps_chapter.htm)

### **Mid-Atlantic Pharmacology Society**

#### **2008 Annual Meeting:**

*“New Horizons in the Pharmacology of Ion Channels”*

Hosted by Robert N. Willette, PhD, GlaxoSmithKline

Thursday, November 6, 2008

GlaxoSmithKline Pharmaceuticals

709 Swedeland Road

King of Prussia, PA 19406

**Keynote Speaker:**

David Julius, PhD, Chairman, Dept of Physiology, University of California San Francisco

*From Peppers to Peppermints: Natural Products as Probes of the Pain Pathway*

**Other Speakers Include:**

Wolfgang Liedtke, Duke University

Donald Gill, Temple University

Sven-Eric Jordt, Yale University

Jon Davis, GlaxoSmithKline (UK)

The meeting will feature the annual poster competition with cash awards for Undergraduates, Graduate Students/Research Associates and Postdoctoral Fellows.

For complete program visit: [www.aspet.org/public/chapters/maps\\_chapter.htm](http://www.aspet.org/public/chapters/maps_chapter.htm)

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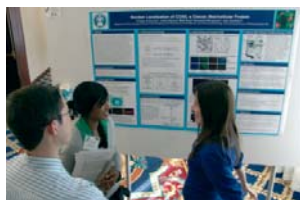
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**New England Chapter  
Summary of the 37<sup>th</sup> Annual New England Pharmacologist Meeting**



Over 105 pharmacologists, graduate students and members of the pharmaceutical industry in the New England region attended this year's 37<sup>th</sup> Annual New England Pharmacologist Meeting, hosted by the Department of Pharmacology of Boston University School of Medicine. The meeting was held on Friday and Saturday, February 29 and March 1, 2008 at the Hilton Hotel in Dedham, MA and featured over 34 poster presentations, 16 oral presentations, and distinguished keynote speakers. Career counseling sessions were provided by representatives from Boston University, Merck Research Laboratories, and Wyeth Research. This marks the third and final year that the New England Pharmacologist Meeting was hosted by the Department of Pharmacology and Experimental Therapeutics at Boston University.



*Kristina Cvitanovic shares her results with Tara Stewart and Conor Smith.*

**Participating schools included:**

- Boston University School of Medicine
- Dartmouth Medical School
- Massachusetts College of Pharmacy and Health Sciences
- Tufts University School of Medicine
- University of Massachusetts Amherst
- University of Vermont College of Medicine



*Emilee Connors discusses her research*

**Keynote Speakers:**



*Dr. Jim Eberwine delivers the Friday afternoon keynote address.*

**James Eberwine, PhD, Elmer Holmes Bobst Professor of Pharmacology and Interim Co- Director of the PENN Genomics Institute at the University of Pennsylvania Medical Center** "Pharmacological Implications from the Genomics Analysis of Single Neurons and Dendrites"



*Dr. Eberwine discusses his research with students, postdocs, and faculty after the keynote address.*



*Dr. Steve Projan presents the after dinner keynote address.*

**Steven J. Projan, PhD, Vice President and Head, Biological Technologies, Wyeth Research,** "The Changes Faces of Drug Discovery and Development"



*Dr. Susan Leeman discusses her neuropeptide research at the Saturday afternoon keynote address.*

**Susan E. Leeman, PhD, Professor, Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine,** "The Peptides Substance P and Neurotensin: Discovery and Some Pharmacological Implications"

**2008 Graduate Student Awards:**



*Drs. Farb & Walsh with the 2008 recipients.*

**Price S. Blair,** Boston University School of Medicine, *Stimulation of Platelet Toll-like Receptor 2 Induces Formation of Platelet-Neutrophil Aggregates in Whole Blood*



*Price Blair receives his award.*

**Min Ding,** Dartmouth Medical School, *Adiponectin Induces Vascular Smooth Muscle Cell Differentiation through AMPK and mTOR Pathway*



*Dr. Carol Walsh congratulates Shruti Kabadi.*

**Shruti V. Kabadi,** Massachusetts College of Pharmacy and Health Sciences, *Uridine Decreases Edema Formation in Various Brain Regions After Traumatic Brain Injury in Rats*



*Dr. Kathleen Martin accepts award on behalf of Min Ding, who was having a baby.*

**Michael B. Tagen,** Tufts University School of Medicine, *Uncoupling Protein 2 Regulates Histamine Production and Mast Cell Activation*



## CHAPTER NEWS



Michael Tagen receives his award.

**Mega A. Doczi**, University of Vermont College of Medicine, *A Possible Role for Golgi Localization of the Kv1.3 Potassium Channel in Postganglionic Sympathetic Neuronal Function*

### **Career Counseling:**

Career Counseling sessions were featured at this year's meeting. Representatives provided counseling on academic career goals as well as information and advice on pursuit of careers in private industry. Merck Research Laboratories and Wyeth Research actively recruited new talent.



James Iannoni, Merck Research Laboratories, shares ideas on career development.



Dr. Susan Leeman discusses academic career development.



Dr. Ruth Gimeno, Wyeth Research, provides career counseling.

### **Meeting Sponsorship:**

The meeting was supported by generous donations from ASPET, Merck, Lilly, Wyeth, ESA Magellan Biosciences, CMA/Microdialysis, Biogen Idec, and Dyax.

Suzie M. Thompson, Member Services and Marketing Manager, presided over the ASPET Booth, providing detailed information on the organization and membership.



### **Future Meeting:**

The 38th New England Pharmacologist Annual Meeting will be held on February 27 and 28, 2009 and will be hosted by the Department of Pharmacology at the University of Vermont College of Medicine.

### **Acknowledgements:**

Dr. Walsh and I would like to thank Sara Johnson for her excellent and devoted attention to detail in running the past three New England Pharmacologist Meetings. We also wish to express our gratitude to Lindsay Ritz, Dmytro Berezhnoy, Erika Langer, Jerry Natowitz, Tricia Smith, Marshall Spriggs, and the students in the NIGMS Biomolecular Pharmacology Training Program at Boston University for their assistance at these meetings.

Respectfully submitted,

David H. Farb, Ph.D.  
President  
New England Chapter of ASPET

Carol T. Walsh, Ph.D.  
Secretary/Treasurer  
New England Chapter of ASPET

**Great Lakes Chapter  
Abstracts from the 2008 Annual Meeting:**

**ANTINEUROINFLAMMATORY POLYKETIDE PLAKORTIDE N FROM THE BRAZILIAN MARINE SPONGE PLAKORTIS ANGULOSPICULATUS.** A.M.S. Mayer, M.H. Kossuga, K. Veloso, A.G. Ferreira, E. Hajdu, and R.G.S. Berlinck. Pharmacology Department, CCOM, Midwestern University, Downers Grove, IL 60565, Instituto de Quimica de São Carlos, Universidade de São Paulo, São Carlos, Brazil, Departamento de Quimica, Universidade Federal de São Carlos, São Carlos, Brazil and Universidade Federal do Rio de Janeiro, Museu Nacional, Rio de Janeiro, Brazil.

The involvement of the inflammatory mediators thromboxane  $\beta_2$  and superoxide anion released by activated brain microglia in neuroinflammatory conditions has been previously hypothesized (Mayer AMS, *MEDICINA* 58:377, 1998; Mayer AMS et al., *SHOCK* 11: 180, 1999). Recently we have identified several marine chemicals as potential leads for the development of antineuroinflammatory agents (Mayer et al. *BioMedCentral Pharmacology* 5:6, 2005) using *Escherichia coli* lipopolysaccharide (LPS)-activated rat microglia as our in vitro discovery model (Mayer AMS et al., *SHOCK* 11:180, 1999). The purpose of this investigation was to determine the effect of several polyketides isolated from the Brazilian marine sponge *Plakortis angulospiculatus* on phorbol ester (PMA)-stimulated thromboxane B<sub>2</sub> and superoxide anion generation from *E. coli* LPS-activated rat microglia. Superoxide anion was determined by superoxide dismutase-inhibitable reduction of ferricytochrome C and thromboxane  $\beta_2$  using commercially available immunoassays. Only plakortide N potently inhibited thromboxane B<sub>2</sub> (IC<sub>50</sub>=0.93 $\mu$ M) but not superoxide (IC<sub>50</sub> >10 $\mu$ M), with low lactic dehydrogenase release (LDH<sub>50</sub>>10 $\mu$ M). Because LDH release was low, our current data suggests that the significant inhibitory effect of plakortide N on LPS-activated microglia thromboxane  $\beta_2$  release was pharmacologic rather than toxic in nature, although the molecular mechanism of inhibition by plakortide N remains undetermined at this time. (Supported by American Society of Pharmacognosy 1998 Research Starter Grant, NIH grant CA 67786 and FAPESP grants 01/03095-0 and 05/60175-2 to RGSB and Midwestern University to AMSM).

**UNBIASED GENOME-WIDE MODEL TO IDENTIFY GENETIC VARIANTS ASSOCIATED WITH CARBOPLATIN-INDUCED CYTOTOXICITY IN LYMPHOBLASTOID CELL LINES FROM INDIVIDUALS OF AFRICAN DESCENT.** R. S. Huang, S. Duan, E. O. Kistner, and M. E. Dolan. Department of Medicine and Department of Health Studies, University of Chicago, Chicago, IL 60637.

Carboplatin, a platinating agent commonly used in treating several cancers, is associated with myelosuppression hindering its utility. To gain a better understanding of the genetic variants associated with carboplatin induced toxicity in African descent, we present a step-wise approach integrating genotypes, gene expression and sensitivity of HapMap cell lines to carboplatin. Cell lines derived from 30 trios of African descent (YRI) were utilized to develop a preclinical model to identify genetic variants and gene expression that contribute to carboplatin induced cytotoxicity. Cytotoxicity was determined as cell growth inhibition at increasing concentrations of carboplatin for 72 h. Gene expression on 89 HapMap YRI cell lines was determined using the Affymetrix GeneChip® Human Exon 1.0 ST Array. SNP genotype and the percent survival at different treatment concentrations along with carboplatin IC<sub>50</sub> (concentration required to inhibit 50% cell growth) were linked through whole genome association. A second association test was performed between SNP genotype and gene expression, and linear regression was then utilized to evaluate the correlation between gene expression and drug sensitivity phenotypes. This approach allows us to identify genetic variants that significantly associate with sensitivity to the cytotoxic effects of carboplatin through differences in gene expression. We found genes (eg: GPC5) whose expression are important in all carboplatin treatment concentrations as well as genes unique to either low or high concentrations of drug (eg: MAPK1, BRAF, MYC, BCL2L1). Our whole genome approach enables us to evaluate genetic and expression contribution to a wide range of cellular phenotypes and could be utilized to integrate pharmacokinetics, pharmacodynamics and pharmacogenetics to construct a more comprehensive map for sensitivity to drugs.

Acknowledgments: This Pharmacogenetics of Anticancer Agents Research (PAAR) Group (<http://pharmacogenetics.org>) study was supported by NIH/NIGMS grant UO1GM61393 and UO1GM61374 (<http://pharmgkb.org/>). Dr. RSH receives support from NIH grant 5 T32 GM 007019-30.

**IN VIVO ADMINISTRATION OF KCNQ CHANNEL MODULATORS INFLUENCES BLOOD PRESSURE AND MESENTERIC VASCULAR RESISTANCE IN RATS.** A.R. Mackie, E.J. Formeister, R. Tiniakov, K.E. Scrogin, and K.L. Byron. Department of Pharmacology and Experimental Therapeutics Loyola University Chicago, Maywood, IL 60153.

Recent work from our laboratory has shown that KCNQ channels are expressed in vascular smooth muscle cells where

they contribute to vasopressin-induced  $\text{Ca}^{2+}$  signaling. Suppression of KCNQ currents by vasopressin or pharmacological agents leads to membrane depolarization and activation of L-type  $\text{Ca}^{2+}$  channels. To determine whether inhibition or activation of vascular KCNQ channels influences mesenteric vascular resistance (MVR) and mean arterial pressure (MAP) in vivo, adult Sprague-Dawley rats were anesthetized with thiobutabarbital (125 mg/kg) and instrumented with femoral venous and arterial catheters for drug administration and arterial pressure determination. A perivascular blood flow probe was placed around the superior mesenteric artery. The KCNQ channel activator (flupirtine) or the inhibitor (linopirdine) was then administered in increasing concentrations (0.01 – 3.0 mg/kg i.v.). Flupirtine produced significant dose-dependent decreases in MAP and MVR. Flupirtine (3.0 mg/kg) caused a  $28.9 \pm 1.2$  mmHg decrease in MAP and a 33.5% decrease in MVR. In contrast, linopirdine produced dose-dependent increases in MAP and MVR. A maximally effective concentration of linopirdine (1.0 mg/kg) produced a  $9.9 \pm 1.3$  mmHg increase in MAP and a 19.2% increase in MVR. Flupirtine (3.0 mg/kg) also caused a modest, but significant decrease in HR of  $26.3 \pm 3.7$  beat/min. Our results indicate that KCNQ channels contribute to tonic modulation of mesenteric vascular resistance and blood pressure. This work was supported by the NHLBI (R01 HL070670 to KLB) and the AHA (0715618Z to ARM). *FASEB J.* (2008). 22:912.34.

**EVIDENCE OF A POSSIBLE DIRECT VASODILATORY ACTION OF THE FIBRATE GEMFIBROZIL.** Jacob D. Peuler and Laura E. Phelps. Pharmacology Dept., Midwestern University, Downers Grove, IL 60515.

Knocking out the gene for peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ) was recently reported to abolish hypertension associated with an overactive human renin-angiotensin-aldosterone system (RAAS) transgenically expressed in mice (*Hyper* 50:945-51, 2007). Thus, attention is now focused on whether fibrates (PPAR $\alpha$  agonists often used to lower plasma triglycerides) are capable of aggravating related forms of hypertension in humans (*Hyper* 50:847-50, 2007). We recently reported acute relaxant effects of high concentrations of gemfibrozil (e.g. 500 micromolar) on various smooth muscle preparations from female rats, including ventral tail arteries pre-contracted with either arginine-vasopressin (AVP) or serotonin (*FASEB J* 21:A1162, 2007). In the present work, we found that 3-4 hour exposure of the same arterial tissue to a much lower but more therapeutically-relevant concentration of gemfibrozil (50 micromolar) also relaxes AVP- and serotonin-induced contractions. The same exposure also relaxes contractions induced by angiotensin II, norepinephrine and a high membrane-depolarizing level of extracellular potassium. Thus, we suspect that fibrates exert a delayed but nonetheless direct and nonspecific vasodilatory action which could offset any potential they have to exert a PPAR $\alpha$ -dependent, RAAS-mediated hypertension. Supported by Midwestern University.

**MINIMIZING PHARMACOTHERAPY DURING WITHDRAWAL AND INITIAL TREATMENT AT CROSSROADS CENTRE BY MONITORING AUTONOMIC CONTROL OF THE HEART.** J.A. Dellinger. University of Wisconsin, Milwaukee, WI 53201.

Background: Substance abuse withdrawal and early treatment protocols requires clinical indications of withdrawal assessment (CIWA) and/or clinical opiate withdrawal syndrome (COWS) scores to assisting health care professionals in administering appropriate withdrawal pharmacotherapy. As the patient advances farther into treatment, the drug therapy becomes more difficult to ascertain and a non-subjective assessment independent of patient input would be helpful. The autonomic control of the heart as reflected by respiratory sinus arrhythmia is studied in the current protocol. Methods: At Crossroads Centre in Antigua, 52 client patients and 18 staff controls were monitored up to three times using electrocardiogram (EKG) and respiration recordings for up to 18 minutes. Each recording included 5 min prone, 5 min sitting, and 5 min standing plus a 2 min "vagal relaxation response"™ (Vrr) task to assess autonomic function. Changes in inter-beat-interval (R-wave peak to R-wave peak) determined using an UFI SC2000 recorder were visually inspected to study the respiratory sinus arrhythmia component and to assess parasympathetic "relaxation." Results: 36 clients completed three EKG recordings (week 1, week 2, and week 4) and concluded with a Vrr session to study baseline autonomic control in three primary withdrawal situations (alcohol, opiates, and cocaine withdrawals). 20 controls from the staff completed the same protocol. 16 clients completed two EKG recordings with a Vrr in each to measure changes in peak parasympathetic tone. Conclusion: The preliminary visual assessments are very encouraging and will be subsequently analyzed using the Porges and Bohrer methods for estimating vagal tone and to more precisely quantify the apparent relaxation monitoring.

Acknowledgement: Thanks to the clients and the staff at Crossroads Centre in Antigua who voluntarily consented to participate in this IRB approved research.

**RECEPTOR FOR ACTIVATED C KINASE 1 (RACK1) BINDS WITH G BETA 1 AND RESTRICTS FOCAL ADHESION KINASE (FAK) ACTIVATION AND RESTORATION OF ENDOTHELIAL BARRIER FUNCTION.** Nebojsa Knezevic, Vidisha Kini, Asrar B. Malik, and Dolly Mehta. Center for Lung and Vascular Biology, Department of Pharmacology, University of Illinois, Chicago.

Thrombin, a serine protease released during vascular injury, rapidly increases endothelial monolayer permeability. Interestingly, the increase in permeability is followed by a recovery period, during which basal barrier function is restored. Although mechanisms increasing endothelial permeability have been well described, the role of endogenous mechanisms mediating barrier repair following increase in endothelial permeability by inflammatory mediators remain unclear.

Gβ1 and receptor for activated C kinase (RACK1) belong to large family of WD40 repeat proteins and act as scaffold to orchestrate downstream signaling events. We therefore investigated the contribution of RACK1 and Gβ1 in promoting recovery of endothelial barrier function. We showed that inhibiting endogenous expression of Gβ1 had no effect on thrombin-induced increase in endothelial permeability but impaired recovery of barrier function post thrombin challenge. In contrast, knock down of RACK1 decreased thrombin-induced endothelial permeability and potentiated endothelial barrier recovery. Since, sustained activation of focal adhesion kinase (FAK) was shown to be required for reversing the increase in endothelial permeability induced by thrombin, we addressed the possibility that Gβ1-RACK1 signaling complex alters barrier function by modulating FAK activation. We also addressed the role of Fyn, a kinase that binds RACK1 and phosphorylates FAK, in the mechanism of barrier recovery. We showed that knock down of Gβ1 inhibited FAK phosphorylation, whereas knock down of RACK1 increased basal FAK phosphorylation. We observed that RACK1 is associated with Gβ1 and Fyn in untreated cells. Thrombin induced a time-dependent reversible dissociation of RACK1 from Gβ1 and promoted the interaction of Gβ1 with Fyn and FAK. Fyn was FAK activation since suppressing endogenous expression of Fyn required for Gβ1 prevented Gβ1 interaction with FAK and FAK activation and also barrier recovery post thrombin challenge. Thus, these data demonstrate that RACK1 prevents the access of Gβ1 from forming a complex with Fyn and FAK, which is required.

**UPREGULATION OF GLYCERALDEHYDE 3 PHOSPHATE DEHYDROGENASE (GAPDH) AND GLUCOSE 6 PHOSPHATE DEHYDROGENASE (G6PDH) DURING THE EARLY STAGES OF CADMIUM-INDUCED RENAL INJURY.** J. R. Edwards, P. C. Lamar, and W. C. Prozialek. Department of Pharmacology, Midwestern University, Downers Grove, IL 60515.

Exposure to cadmium (Cd) results in injury to proximal tubule epithelial. Although some of the generalized cellular responses to Cd-induced injury are well documented, other cellular responses are just now being elucidated. In this study, we examined if G6PDH and GAPDH become up-regulated in a sub-chronic animal model of Cd-induced nephrotoxicity. Male Sprague/Dawley rats were given daily subcutaneous injections of 0.6 mg/kg of Cd in the form of CdCl<sub>2</sub> for up to 12 weeks. After 3, 6 and 12 weeks, representative animals were sacrificed and samples of kidney were analyzed for oxidative stress (TBARS) and expression of GAPDH and G6PDH by Western blot analysis. After 3 weeks of Cd treatment, there were no apparent differences in expression of G6PDH or GAPDH, but at 6 weeks, expression of renal GAPDH and G6PDH was increased by approximately 2 fold. There was no significant change in TBARS at 6 weeks of Cd exposure. At 12 weeks, the increase in GAPDH and G6PDH expression was even more pronounced; there was also a significant increase in TBARS at this time point. GAPDH and G6PDH produce NADH and NADPH, respectively, and play key roles in cellular thiol metabolism. The fact that these enzymes were up-regulated at a time point before the onset of overt signs of oxidative stress, may indicate that they are "sentinel" proteins and part of an early cellular defense and/or stress response. Supported by Grant RO1-ES006478 from the NIEHS.

**AN INDISPENSABLE ROLE OF TRPC6-MEDIATED CA<sup>2+</sup> ENTRY IN INCREASING LUNG MICROVASCULAR PERMEABILITY AND ACUTE LUNG INJURY.** Mohammad Tauseef<sup>1</sup>, Vidisha Kini<sup>1</sup>, Nebojsa Knezevic<sup>1</sup>, Stephen Vogel<sup>1</sup>, Alexander Dietrich<sup>2</sup>, Asrar B. Malik<sup>1</sup>, Lutz Brinbaumer<sup>2</sup> and Dolly Mehta<sup>1</sup>. <sup>1</sup>Department of Pharmacology, College of Medicine, University of Illinois, Chicago, IL and <sup>2</sup>Division of Intramural Research, NIH, Bethesda, NC.

Studies have shown that transient receptor potential cation channels (TRPC) form the principal mechanism to increase intracellular Ca<sup>2+</sup> in several cell types including endothelial cells. We showed that thrombin by binding to its receptor PAR-1 activates transient receptor potential channel 6 (TRPC6), a receptor-operated Ca<sup>2+</sup> channel (ROC), which in turn regulates RhoA-induced endothelial contraction. In the present study, we have investigated microvascular permeability response and lung edema formation in the TRPC6<sup>-/-</sup> mice. We isolated lungs from wild type (WT) mice and determined

the filtration co-efficient (K<sub>fc</sub>), a measure of hydraulic conductivity across endothelial exchange barrier in response to oleoyl-2-acetyl-sn glycerol (OAG), a cell-membrane permeable analog of diacylglycerol (DAG). We show that direct activation of ROC by OAG increased lung microvascular permeability at the concentration of 100  $\mu$ M. To assess whether TRPC6 is required for ROC-mediated increase in lung microvascular permeability, we isolated lungs from TRPC6<sup>-/-</sup> mice and strain-matched WT mice and measured OAG-induced increase in K<sub>fc</sub>. We also used PAR-1 agonist peptide and determined the effect of deletion of TRPC6 in PAR-1 induced increase in lung microvascular permeability. OAG and PAR-1 agonist increased K<sub>fc</sub> in lungs from WT mice whereas they failed to increase K<sub>fc</sub> in lungs isolated from TRPC6<sup>-/-</sup> mice. TRPC6 transcript expression was detected in lungs from WT mice but not from TRPC6<sup>-/-</sup> mouse. Expression of TRPC3, another ROC or TRPC1/4, the SOC were not altered in TRPC6<sup>-/-</sup> mice lungs. We also determined the role of TRPC6 in inducing acute lung injury (ALI) in response to PAR-1 activating peptide and endotoxin LPS by determining lung wet-dry weight ratio and albumin permeability across the lung microcirculation. We observed that PAR-1 peptide as well as LPS increased lung wet-dry ratio and microvascular protein permeability in WT mice while this measure of lung injury was not observed in TRPC6<sup>-/-</sup> mice lungs. Histopathology also showed normal architecture and lack of neutrophil infiltration following LPS challenge in TRPC6<sup>-/-</sup> mice lungs. These intriguing findings suggest that TRPC6 activity is essentially required for increasing lung microvascular permeability and ALI. Thus, TRPC6 offers a novel therapeutic strategy for controlling the loss of endothelial barrier functions and thereby Acute Lung Injury.

**YEASTS SHED LIGHT ON  $\alpha$ -SYNUCLEIN HYDROPHOBICITY: ALANINE-76 REGULATES AGGREGATION & PLASMA MEMBRANE BINDING.** Michael Fiske, Stephanie Valtierra, Michael White, Michael Zorniak, and Shubhik DebBurman. Biology Department, Lake Forest College, Lake Forest, IL 60045.

Parkinson's disease (PD) is a devastating and incurable neurodegenerative disorder that afflicts over one million Americans. The universal PD pathology is the presence of aggregated  $\alpha$ -synuclein within dying midbrain substantia nigra neurons. The role these  $\alpha$ -synuclein aggregates play in cell death is unclear, but debate rages about whether these aggregates are neuroprotective or harmful to cells.  $\alpha$ -Synuclein also binds phospholipids, but how that contributes to function or disease is also unclear. Previously, alanine-76 within  $\alpha$ -synuclein's middle hydrophobic domain (aa70-82) was shown to regulate its aggregation in vitro (Giasson et al., 2001). Here, we specifically tested the hypothesis that alanine-76 contributes to  $\alpha$ -synuclein aggregation and plasma membrane phospholipid association. By mutating alanine-76 to glutamic acid (A76E), we asked if this mutant was less able to aggregate and/or bind phospholipids in live cells. In support of this hypothesis, using a budding yeast model that recapitulates  $\alpha$ -synuclein membrane binding, we found that significantly less A76E localized to plasma membrane. Furthermore, using a fission yeast model that recapitulates  $\alpha$ -synuclein aggregation, we found that less A76E was aggregated in live cells. In both models, more A76E was found cytoplasmically diffuse. We also evaluated any potential effects this mutant had on yeast growth. To our surprise, in neither model system did A76E significantly induce or reduce toxicity, suggesting that yeasts are particularly adept at buffering against the toxic effects of  $\alpha$ -synuclein. Our studies demonstrate that yeasts are powerful model organisms to investigate the molecular regulation of  $\alpha$ -synuclein.

**MUTAGENESIS SCREEN IN C. ELEGANS SUGGESTS ROLE OF MOR GENES IN PHARYNGEAL DEVELOPMENT.** A.R. Ferrier and P.A. Smith. Lake Forest College, Dept. of Biology, Lake Forest, IL, 60045.

The development of an organ is achieved through increasingly restrictive genetic programs, requiring temporal activation and deactivation of genes. Our lab's aim is to elucidate novel genes involved in *C. elegans* pharyngeal development, an organ essential for the grinding and ingestion of food. In the present study we conducted a mutagenesis screen using a *C. elegans* pharyngeal muscle protein, myosin-2, tagged with green fluorescent protein as a visual assay. The screen produced over 200 pharyngeal mutant lines. Interestingly, 20 mutants manifested short and wide blunt pharynges, suggesting that genes required for embryonic elongation were mutated. Some blunt mutants were viable, while others died at the L1 stage, which may reflect the degree of defective elongation. To locate the alleles responsible for disrupting the elongation process we performed single nucleotide polymorphism (SNP) mapping. Thus far, we successfully linked 10 different mutant phenotypes to chromosomal regions. The gene, *mor-1*, which results in a shortened, rounded pharynx, was mapped to chromosome III. Furthermore, we found another 14 similar phenotypes, which may represent at least two other genes, *mor-2* and *mor-3*. The *mor-2* gene, which is mapped to chromosome IV, has been shown to yield similar phenotypes as *mor-1*. The *mor-3* gene, a calcium/calmodulin dependent protein kinase, may also be ascribed a role in abnormal pharynx development. Finally, *sma-1*, which is required for proper pharyngeal elongation, shares phenotypic similarity with some of our blunt mutants. We believe that these *mor* genes share the same molecular pathway and the remaining blunt phenotypes may be a result of defective morphogenesis. Understanding the pathway in which the *mor* genes work will yield a greater comprehension of pharyngeal morphogenesis.

**RAPID IMPROVEMENT OF PROTEIN STABILITY BY THERMAL PROFILING.** K.M. Comess, W.J. Chiou, L. Traphagen, U. Warrior, S.C. Galasinski, and D.J. Burns. Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064.

Buffer conditions are critical to protein folding, stability, and the ability to successfully concentrate, crystallize, and store proteins. Testing a variety of conditions (pH, buffer type, ionic strength, and stabilizing additives) can be a very tedious process and typically consumes large amounts of protein. We describe here a two-step strategy that can be used to screen buffers and additives in a high-throughput fashion using 384-well plates. Protein stability is assessed by the midpoint of thermal denaturation ( $T_m$ ), and stabilizing or destabilizing conditions can be detected by deviations that increase or decrease the  $T_m$  respectively. The  $T_m$  is determined by gradually heating the protein; as the denatured protein unfolds it exposes hydrophobic regions that can be bound by an environmentally sensitive dye. Dye binding results in enhanced fluorescence, which can be detected in a fluorescence plate reader at EX/EM=465nm/590nm. In the first step, conditions comprising a buffer (10-50 mM, pH of 5.5-8.5), a salt (2-98 mM), an additive, and in some cases, a detergent were assembled in a matrix of 384 buffer conditions using an incomplete factorial mixing algorithm. In the second step, 96 additives commonly used for protein crystallization were screened against the four best buffer conditions identified in the first step. Data are shown here for two E. Coli-expressed human Aurora-B kinase constructs and demonstrate  $T_m$  stabilization of as much as 18°C. The pH of the buffer correlated as the dominant factor determining stability. The cofactor screen revealed expected stabilizing interactions, e.g., ATP, as well as stabilization by several multivalent metal ions. The protein consumption in this study was 10  $\mu$ L at 2.5  $\mu$ M for each buffer condition. In conclusion, we report here a two-step screening strategy that can rapidly and significantly improve protein stability and consumes less than 1 mg of protein.

**EVALUATING THE ROLE OF THE MULTI-VESICULAR BODY/VACUOLE PATHWAY IN THE REGULATION OF  $\alpha$  – SYNUCLEIN AGGREGATION AND TOXICITY IN BUDDING YEAST.** A. Ayala, M. Vahedi, M. White, J. Price and S. Deb Burman. Dept. of Biology, Lake Forest, IL 60045.

$\alpha$ -Synuclein is implicated in the pathogenesis of Parkinson's disease, a neurodegenerative illness that destroys midbrain dopaminergic neurons. The misfolding and subsequent aggregation of this protein is the likely cause of cell death. A major hypothesis in the field is that increasing  $\alpha$ -synuclein's rate of degradation may prevent its aggregation and toxicity. Until recently, the proteasome has been the prevalent model for  $\alpha$ -synuclein degradation and malfunctions in this pathway have been shown to increase  $\alpha$ -synuclein accumulation and toxicity. However, increasing pharmacological evidence suggests that the lysosome may also be a site for  $\alpha$ -synuclein degradation. To test this latter hypothesis, we employed a budding yeast model for  $\alpha$ -synuclein aggregation and toxicity to genetically evaluate the role of multivesicular body (MVB) pathway, a major route used by proteins to target the yeast vacuole (its lysosome) for degradation. We asked if  $\alpha$ -synuclein would accumulate and increase toxicity in yeast that lacked one of a battery of MVB proteins, including vps27, vps28, vps34, vps4, mvb12, and doa4. We demonstrate that the absence of vps28 (an ESCRT-1 component) altered wildtype, A53T, and E46K $\alpha$ -synuclein localization. Specifically, a significant proportion shifted from a predominant plasma membrane location to diffuse and aggregated compartments within the cytoplasm. On the other hand, the absence of vps34, a PI 3-kinase acting upstream of ESCRT-1, was extremely toxic to the presence of several foreign proteins, including  $\alpha$ -synuclein. Future research will examine several other lysosomal pathway factors in mediating  $\alpha$ -synuclein toxicity.

**HISTAMINE RECEPTOR SUBTYPES: EVALUATION OF TISSUE DISTRIBUTION AND INTERACTIONS WITH HISTAMINERGIC LIGANDS.** A.M. Manelli, M.I. Strakhova, B. Yao, K.M. Krueger, J.L. Baranowski, T.L. Carr, T.R. Miller, D. Witte, J.D. Brioni, and T.A. Esbenshade. Neuroscience Research, Global Pharmaceutical Research Division, Abbott Laboratories, Abbott Park, IL 60064.

Histamine elicits a wide variety of physiological effects through activation of four different histamine receptor (HR) subtypes (H1, H2, H3, H4). Histamine binds these human HRs with different potencies (H3R > H4R > H1R > H2R) and respective pKi (8.5, 7.7, 5.0 and 4.5) values. However, the rank order of agonist potency for histamine at HR subtypes varies according to the signaling pathway being activated. Functionally, when examining the mobilization of intracellular calcium as measured by the Fluorometric Imaging Plate Reader (FLIPR), the rank order of potency is H1R > H4R > H3R > H2R with respective pEC50 values of 7.9, 7.4, 6.6, and 6.1, reflecting efficient native coupling of the H1R to G $\alpha$ q compared to the less efficient, artificial coupling to promiscuous G $\alpha$ q5 for the H3R and H4R and endogenous G $\alpha$ q for the H2R. In contrast, in a cAMP assay measuring the activation of H2R through its native coupling to G $\alpha$ s, histamine is quite

potent with a pEC<sub>50</sub> of 9.3, whereas histamine is much less potent in inducing cAMP formation at the H<sub>1</sub>R, with a pEC<sub>50</sub> of 4.8. These in vitro studies demonstrate the markedly different potencies of histamine for binding and activating histamine receptor subtypes. Another means by which histamine mediates such varied physiological processes may be explained by the specific location of HR subtypes. mRNA expression profiles for the HR subtypes were determined in rat tissues by RT-PCR to demonstrate the differences in distribution and/or relative levels of the HR subtypes. The differential H<sub>1</sub>-, H<sub>2</sub>-, H<sub>3</sub>-, and H<sub>4</sub> receptor pharmacology, coupled with the tissue expression pattern, may contribute to the selectivity of histamine responses in vivo.

**GENETIC ASSOCIATION OF CANNABINOID RECEPTOR 1 (CNR1) WITH OBESITY AND OBESITY-RELATED TRAITS.** Tesfaye M. Baye<sup>1</sup>, Yi Zhang<sup>1</sup>, Edward Smith<sup>1</sup>, Cecilia J. Hillard<sup>2</sup>, Jennifer Gunnell<sup>1,3</sup>, Joel Myklebust<sup>4</sup>, Roland James<sup>3,4</sup>, Ahmed H. Kissebah<sup>3,4</sup>, Michael Olivier<sup>1,4,5</sup>, and Russell A. Wilke<sup>1,2,3,4</sup>. <sup>1</sup>Human and Molecular Genetics Center, <sup>2</sup>Department of Pharmacology and Toxicology, <sup>3</sup>Department of Medicine, <sup>4</sup>TOPS Center for Obesity and Metabolic Research, <sup>5</sup>Department of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226.

Since the isolation of  $\alpha_9$ -tetrahydrocannabinol (THC) from the marijuana plant in the 1960s, the mechanisms by which cannabinoids affect the human body have been the subject of considerable research efforts. In this report we investigate whether genetic variation in endocannabinoid receptor function (CNR1) is associated with anthropometric measures of human obesity and obesity-related metabolic disorders. Six tagSNPs were selected for the CNR1 gene based on HapMap: two promoter SNPs, three exonic SNPs, and a single SNP within the 3'-UTR. Under a dominant model, family-based association tests revealed significant evidence for association between CNR1 tagSNPs and obesity related traits in subjects participating in the Take Off Pounds Sensibly research program. A common CNR1 haplotype (H<sub>4</sub>; prevalence 0.132) was associated with multiple clinical parameters used to define the metabolic syndrome, and single SNP association revealed several relationships between lipids and CNR1 that are independent of body mass index.

**GENETIC VARIATION IN FATTY ACID AMIDE HYDROLASE (FAAH) IS ASSOCIATED WITH ALTERED LIPID HOMEOSTASIS IN AN OBESE COHORT.** Y. Zhang<sup>1</sup>, E.M. Smith<sup>1</sup>, T. M. Baye<sup>1</sup>, J. Gunnell<sup>1</sup>, A. DelaForest<sup>3</sup>, C.J. Hillard<sup>3</sup>, A.H. Kissebah<sup>1,4</sup>, M. Olivier<sup>1,2</sup>, and R.A. Wilke<sup>1,3,4</sup>. <sup>1</sup>HMGC, <sup>2</sup>Department of Physiology, <sup>3</sup>Dept of Pharmacology, <sup>4</sup>Dept of Medicine, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226.

For centuries, marijuana (*Cannabis sativa*) has been an intriguing subject for its psychoactive and medicinal effects in humans. Recent studies have revealed a complicated network of endogenous cannabinoid (eCB) signaling pathways in which, both exogenous and endogenous ligands act on a selective group of receptors, CB<sub>1</sub> and CB<sub>2</sub> receptors. Two endogenous ligands, e.g. N-arachidonyl ethanolamine (AEA) and 2-arachidonylglycerol (2-AG), have been identified for the CB<sub>1</sub> receptor. Because these lipid transmitters are not found to be kept in storage, but rather synthesized "on demand", fine-tuning of their levels relies on regulated turnover by two key enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGLL).

Alterations in the eCB system are related to a variety of complex diseases including the metabolic syndrome. Genetic and pharmacologic evidence support the hypothesis that increased eCB/CB<sub>1</sub> signaling over-rides the normal satiety signals to stimulate inappropriate food consumption. Very recently, our group conducted association tests in a family-based cohort using tag single nucleotide polymorphisms (tagSNPs) in the CB<sub>1</sub> receptor gene (CNR1) (see poster by Mersha et al.). The tests revealed several relationships between lipids and CNR1. CNR1 tagSNPs influence lipids directly, independent of obesity.

In the current study, the contribution of FAAH gene to obesity-related lipid traits is being characterized using a similar approach. Five FAAH tagSNPs representing linkage disequilibrium within the entire FAAH gene region have been selected using the human HapMap. We present here the preliminary data from one of these tagSNPs, a coding SNP (cSNP; rs324420). As shown previously (Sipe 2005), we observed that this FAAH variant is associated with body mass index (BMI). We also extend these observations, now demonstrating that this cSNP is also associated with obesity-related lipid traits defining the metabolic syndrome, i.e., high triglycerides and low HDL cholesterol.

**SYSTEMIC AND SITE INJECTIONS OF A NOVEL NAV1.8 SODIUM CHANNEL BLOCKER, A-803467, ATTENUATE SPINAL WDR NEURON ACTIVITY IN NEUROPATHIC RATS.** MgGarughty, S., Chu, K., Scania. M.J.C., Kort, Michael E., Faltynek, C.R., and Jarvis, M.F. Abbott Laboratories, Abbott Park, IL 600640.

We have recently reported that systemic delivery of A-803467, a potent and selective Nav1.8 sodium channel blocker, is antinociceptive in rat models of chronic inflammatory and neuropathic pain. In an effort to further evaluate and understand the role of Nav1.8 sodium channels in nociceptive transmission, the effects of systemic, intra-spinal, and intra-DRG A-803467 on WDR evoked and spontaneous firing were measured in neuropathic (SNL) rats. Systemic A-803467 attenuated both evoked (10 g von Frey hair, ED<sub>50</sub> = 20 mg/kg, iv) and spontaneous (ED<sub>50</sub> = 15 mg/kg, iv) WDR activity. These effects were not altered by spinal transection or by systemic pre-treatment with the TRPV1 receptor agonist, RTX (at a desensitization dose). A-803467 (30-100 nmol in 1 ml) injected onto the uninjured L4 DRG reduced evoked but not spontaneous WDR firing. In contrast, intra-spinal (50-150 nmol in 0.5 ml) injection of A-803467 decreased both evoked and spontaneous discharges of WDR neurons. Thus, A-803467 acted at both spinal and peripheral (DRG) sites to affect WDR activity. It also appears, that Nav1.8-related modulation of nociceptive input does not involve fibers containing the TRPV1 receptor. Supported by Abbott Labs.

**C-FOS EXPRESSION IN RESPONSE TO FEEDING IN DIABETIC MICE.** M.Pasek and K.J. LePard. Biomedical Science Program and Dept. of Physiology, College of Health Science, Midwestern University, Downers Grove, IL 60515.

c-Fos is a useful marker of enteric neuronal activation that can undergo alterations in expression with changes in digestive state. FOS expression was evaluated in a Type I and Type II diabetic mouse model under three conditions: freely feeding (free access to food and water), cephalic (fasted for 24 hours with no access to food, only free access to water; then followed by 1 hour of visual exposure to food and free access to water), and fasting (24 hours of free access to water and no food and no visual exposure). c-Fos was examined in both diabetic and control mice using immunohistochemistry and Western blotting techniques. The final body weight and the final reading of blood glucose of the NOD diabetic vs. the NOD control were significantly different. The initial and final body weights of the Agouti diabetic vs. the Agouti control were significantly different as well. No significant differences were observed between diabetic and control NOD and Agouti mice in regard to the expression of c-Fos in freely fed, cephalic, and fasted mice. The expression of FOS can be induced by both vagal and enteric components. Stimuli other than neuronal activation may contribute to FOS expression in enteric neurons. This can be a reason why FOS expression was observed in all of the conditions that were examined, yielding no significant findings.

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**EFFECTS OF MUSCARINIC AGONIST AND ANTAGONISTS ON GASTRIC MOTILITY IN TYPE 2 DIABETIC MICE.** K. Szydlo and K. J. LePard. Biomedical Sciences Program and Department of Physiology, College of Health Sciences College of Osteopathic Medicine at Midwestern University, Downers Grove, IL 60515.

**Background:** Diabetic patients often experience nausea associated with abnormal rate of gastric emptying. Autonomic neurons modulate the rate of gastric emptying by releasing acetylcholine which activates muscarinic receptors on smooth muscle to produce contractions. Cholinergic motility of stomach regions was investigated in type 2 diabetic and control mice by directly activating muscarinic receptors using the muscarinic receptor agonist bethanechol and promoting release of endogenous acetylcholine from autonomic neurons using tegaserod, a 5-HT<sub>4</sub> receptor agonist. **Methods:** In a tissue bath, fundus and antrum from control and diabetic mice were treated with bethanechol or tegaserod. The ability of the muscarinic antagonist 4-DAMP to reduce the bethanechol or tegaserod-induced contractions was determined. The concentration of choline in the tissue bath before and after tegaserod treatment was determined by enzymatic assay. **Results:** Peak contractions to bethanechol in antrum of diabetics were decreased when compared to controls. 4-DAMP was less effective in diabetics to reduce peak contraction of the bethanechol response in fundus compared to controls. The area under curve of the tegaserod response in fundus was greater in diabetics than controls and 4-DAMP's ability to reduce the area of the tegaserod response was greater in diabetics compared to controls. Using fundus from control or diabetic animals, the concentration of choline in the tissue bath was similar and no increase was observed after tegaserod treatment. **Conclusion:** Cholinergic contractions due to direct muscarinic receptor activation by bethanechol were weaker in antrum, but not fundus, suggesting impaired signal transduction in antrum from diabetic mice. In contrast, cholinergic contractions evoked after tegaserod treatment were stronger in fundus, but not antrum, from diabetic mice suggesting enhanced cholinergic receptor activation by endogenous acetylcholine in fundus from diabetic mice. These regional differences in cholinergic motility may contribute to abnormal gastric emptying in diabetic animals.

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**APPLICATION OF A MULTIPARAMETRIC HCS CYTOTOXICITY ASSAY FOR PRIORITIZATION OF COMPOUNDS BASED ON HUMAN HEPATOTOXICITY POTENTIAL.** V. C. Abraham, D. L. Towne, U. Warrior, J. Waring, and D. J. Burns. Lead Discovery, Abbott Laboratories, Abbott Park, IL 60064.

Compound prioritization based on human hepatotoxicity potential has been identified as an unmet need in drug discovery, as it can be a significant hurdle for lead compounds at later stages of drug discovery. We report the validation and application of a high content multiparametric cytotoxicity assay based on simultaneous measurement of four key cell health parameters - nuclear morphology, plasma membrane integrity, mitochondrial function and cell proliferation. Compounds can be prioritized by (a) computing an in vitro safety margin using the minimum cytotoxic concentration (IC<sub>20</sub>) across all measured parameters and cell based efficacy data and (b) using the minimal cytotoxic concentration alone to take into account possible tissue concentration effects. Feasibility data using selected compounds including quinolone antibiotics, thiazolidinediones and statins suggests the viability of this approach. To increase overall throughput of compound prioritization, we have identified the higher throughput, plate reader based CyQUANT assay as a format that is similar to the HCS assay with regards to sensitivity of measuring inhibition of cell proliferation. We expect that the phenotypic output from the multiparametric HCS assay in combination with other highly sensitive approaches such as microarray based expression analysis of toxic signatures will contribute to a better understanding and predictivity of human hepatotoxicity potential.

**CLONING AND CHARACTERIZATION OF CNS EXPRESSION, LIGAND BINDING, AND FUNCTIONAL PROPERTIES OF MULTIPLE MONKEY H3 RECEPTOR ISOFORMS.** M.I. Strakhova, G.B. Fox, T.L. Carr, D.G. Witte, B.B. Yao, A.M. Manelli, T.A. Vortherms, T.R. Miller, J.D. Brioni, and T.A. Esbenshade. Neuroscience Research, Abbott Laboratories, Abbott Park, IL 60064.

We have recently identified three splice isoforms of the histamine H<sub>3</sub> receptor in multiple brain regions of cynomolgus monkey (*Macaca fascicularis*). Two of the novel isoforms displayed a deletion in the third intracellular loop (mkH<sub>3</sub>(413) and mkH<sub>3</sub>(410)), the third isoform displayed a complete deletion of the putative fifth transmembrane domain (mkH<sub>3</sub>(335)). We have confirmed by RT-PCR the expression of full-length mkH<sub>3</sub>(445) mRNA as well as mkH<sub>3</sub>(413), mkH<sub>3</sub>(410), and mkH<sub>3</sub>(335) splice isoform mRNA in multiple monkey brain regions including the frontal, parietal and occipital cortex, parahippocampal gyrus, hippocampus, amygdala, caudate nucleus, putamen, thalamus, hypothalamus, and cerebellum. The full-length isoform mkH<sub>3</sub>(445) was predominant in all of the regions tested, followed by mkH<sub>3</sub>(335), with the mkH<sub>3</sub>(413) and mkH<sub>3</sub>(410) isoforms being of low abundance. When expressed in C6 cells, mkH<sub>3</sub>(445), mkH<sub>3</sub>(413), and mkH<sub>3</sub>(410) exhibit high affinity binding to the agonist ligand [<sup>3</sup>H]-N-a-methylhistamine (NAMH) with respective pK<sub>d</sub> values of 9.7, 9.7, and 9.6. As expected, the mkH<sub>3</sub>(335) isoform did not display any saturable binding with NAMH. In order to determine if these isoforms functionally couple to signaling events, the receptors were co-expressed with the chimeric Gaq15-protein and tested for their ability to couple to calcium mobilization as determined by FLIPR. The H<sub>3</sub> receptor agonist R-a-methylhistamine activated calcium mobilization in cells expressing the mkH<sub>3</sub>(445), mkH<sub>3</sub>(413), mkH<sub>3</sub>(410) with respective pEC<sub>50</sub> values of 8.5, 8.9, and 8.6. No response was elicited in cells expressing the mkH<sub>3</sub>(335) isoform. The existence of multiple H<sub>3</sub> receptor splice isoforms across species raises the possibility that isoform specific properties including ligand affinity, signal transduction coupling, and brain localization may differentially contribute to observed in vivo effects of H<sub>3</sub> receptor antagonists.

**PHOSPHORYLATION OF CAVEOLIN-1 CONTRIBUTES TO THE MECHANISM OF OXIDANT-INDUCED ENDOTHELIAL HYPERPERMEABILITY.** Yu Sun<sup>1,4</sup>, Richard D. Minshall<sup>1,2,3</sup>, David J. Visintine<sup>1,2,3</sup>, Maricela Castellon<sup>1,2,3</sup>, Asrar B. Malik<sup>1,3</sup>, Guochang Hu<sup>1,3</sup>. Departments of Pharmacology<sup>1</sup> & Anesthesiology<sup>2</sup>, & Center for Lung and Vascular Biology<sup>3</sup>, University of Illinois at Chicago, IL, USA; Dept. of Pharmacology<sup>4</sup>, Shandong University, Jinan, Shandong, People's Republic of China.

Oxidants are thought to increase endothelial permeability by opening interendothelial junctions. Here, we tested whether H<sub>2</sub>O<sub>2</sub>-induced phosphorylation of caveolin-1 (Cav-1) stimulates caveolae-mediated transcellular albumin transport and whether this process contributes to an increase in paracellular permeability and protein-rich pulmonary edema accumulation. In rat lung microvascular endothelial cells (RLMVECs), H<sub>2</sub>O<sub>2</sub> (100 fM ~ 1.0 mM) induced a concentration-dependent increase in the uptake (1.5 ~ 2.7-fold) and transendothelial transport of 125I-albumin (1.8~4.5-fold) as well as activation of Src and Src-dependent phosphorylation of Cav-1. Furthermore, H<sub>2</sub>O<sub>2</sub>-induced increases in both albumin permeability and uptake were blocked by methyl- $\beta$ -cyclodextrin and Cav-1 siRNA. Only with very high concentrations of H<sub>2</sub>O<sub>2</sub> ( $\geq$ 5 mM) was there an observable decrease in transendothelial electrical resistance (TER) and

disruption of adherens junctions. To address further the role of Cav-1 phosphorylation in the H<sub>2</sub>O<sub>2</sub>-induced increase in albumin permeability, we compared the effects of H<sub>2</sub>O<sub>2</sub> in wide-type (WT) Cav-1 and non-phosphorylatable Cav-1 mutant (Y14F-Cav-1) overexpressing RLMVECs. H<sub>2</sub>O<sub>2</sub>-induced increase in endocytosis and transendothelial transport of 125I-albumin in WT-Cav-1 expressing cells was abolished in Y14F-Cav-1 expressing cells. Compared to normal RLMVECs, exogenous expression of WT-Cav-1 also reduced the concentration of H<sub>2</sub>O<sub>2</sub> needed to cause a decrease in TER. However, this H<sub>2</sub>O<sub>2</sub>-induced decrease in TER in WT-Cav-1 expressing endothelial cells was abolished in Y14F-Cav-1 expressing cells. These data suggest that phosphorylation of Cav-1 mediates H<sub>2</sub>O<sub>2</sub>-induced increase in transcellular and paracellular permeability. In the isolated WT mouse lung, vascular perfusion of H<sub>2</sub>O<sub>2</sub> induced Cav-1 phosphorylation and lung edema formation, which were abolished in Cav-1 null lungs. Rescue of Cav-1 expression resulted in H<sub>2</sub>O<sub>2</sub>-induced lung edema formation, whereas lungs expressing Y14F-Cav-1 remained protected. Thus, H<sub>2</sub>O<sub>2</sub> induces caveolae-mediated vascular albumin hyperpermeability, paracellular permeability, and pulmonary edema formation through enhanced phosphorylation of Cav-1. Src phosphorylation of Cav-1 may therefore be a therapeutic target for treatment of oxidant-induced acute lung injury.

**MODULATION OF TRPV1 AND TTX-R SODIUM CHANNEL ACTIVITY IN DRG NEURONS FOLLOWING NERVE INJURY OR TISSUE INFLAMMATION.** W. Niforatos, X. F. Zhang, C. Zhong, P. Han, T. Neelands, P. Honore, M. F. Jarvis, C. Surowy, V. Scott, C. Faltynek, C.-C. Shieh. Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064.

Pain as a result of tissue or nerve injury is modulated by a number of different ion channels. Modification in expression of certain ion channels can cause changes in neuronal excitability leading to peripheral and central sensitization. However, the underlying mechanisms of pain pathophysiology are not fully understood. We have examined TRPV1 and TTX-R responses in both a rat model of neuropathic pain (spinal nerve ligation, SNL) and a rat model of complete Freund's adjuvant-induced inflammatory pain (CFA). Two weeks following SNL, L5 and L6 dorsal root ganglion (DRG) were acutely dissociated from both neuropathic and control animals. For the CFA model, L4 and L5 DRGs were acutely dissociated 48h post-injection from both inflamed and control animals. Whole-cell patch-clamp recordings were obtained from either small (15 - 30  $\mu$ m) or medium diameter (31 - 40  $\mu$ m) neurons. Following SNL, capsaicin-evoked currents were greatly attenuated in both small- and medium-diameter neurons with only 7% of all rat DRG neurons tested responding to capsaicin compared to 68% of neurons from control animals. However, capsaicin-evoked currents in uninjured L4 DRG neurons remained similar to control rats. In addition, SNL produced a significant increase in TTX-R currents in L4 uninjured DRG neurons compared to controls, but decreased in injured L5 DRG neurons (Zhang et al., 2004). In contrast, after CFA treatment, capsaicin-sensitive current density in small diameter L4 and L5 DRG neurons was up-regulated compared to control. CFA treatment did not alter TTX-resistant or TTX-sensitive Na<sup>+</sup> channel current density in small diameter DRG neurons. Collectively, these data demonstrate that TRPV1 and TTX-R are differentially modulated in neuropathic and inflammatory pain states.

**DESIGN, SYNTHESIS, AND SAR OF A SERIES OF NON-IMIDAZOLE HISTAMINE H<sub>3</sub> ANTAGONIST CONTAINING A VARIETY OF 6:6 BICYCLIC HETEROARYL CORES.** Huaqing Liu, Robert Altenbach, Yiyin Ku, Yu-Ming Pu, Sou-Jen Chang, Ramin Faghih, Kirill A Lukin, Michael Curtis, Thomas R. Miller, Timothy A. Esbenshade, Arthur A. Hancock, and Marlon Cowart. Abbott Laboratories, R4MN/AP9A/221, 100 Abbott Park Road, Abbott Park, IL 60064-6123.

Histamine H<sub>3</sub> receptors have been shown to be autoreceptors controlling the release of histamine from histaminergic neurons in the central nervous system (CNS). They also act as heteroreceptors modulating the release of other neurotransmitters including acetylcholine, noradrenaline, serotonin and dopamine. It is widely believed that H<sub>3</sub> receptor antagonists have the potential to serve as therapeutics for memory and learning deficits, Alzheimer's disease, epilepsy, and ADHD. We have recently found a series of nitrogen containing 6:6 bicyclic heteroaryl compounds that are highly potent antagonists at rat H<sub>3</sub> (K<sub>i</sub> 0.4  $\pm$  C10 nM) and human (K<sub>i</sub> 0.4  $\pm$  C10 nM) H<sub>3</sub> receptors. The synthesis of the various 6:6 cores and in vitro properties of these compounds will be described.

**[<sup>3</sup>H]A-804598: A POTENT AND SELECTIVE RADIOLIGAND FOR P2X<sub>7</sub> RECEPTORS.** D. L. Donnelly-Roberts, M.T. Namovic, and M.F. Jarvis. Neuroscience Research, R4PM, Abbott Laboratories, 100 Abbott Park, IL 60064-3500.

A-804598 is a potent and selective P2X<sub>7</sub> receptor antagonist with IC<sub>50</sub> values of 10 nM at the rat P2X<sub>7</sub> and 5 nM at the human subtype, respectively, based on a functional assay that utilizes calcium influx in 1321 cells expressing the recombinant P2X<sub>7</sub> receptors. In contrast, A-804598 did not activate cells expressing recombinant P2X<sub>2/3</sub>, P2X<sub>3</sub>, P2X<sub>4</sub>, or P2Y<sub>2</sub> receptors. A-804598 potently blocked the release of IL-1 $\beta$  from THP-1 cells that endogenously express the human

P2X7 receptors. The present studies characterize the ability of [3H]-A-804598 to bind to recombinant rat P2X7 receptors. Using a membrane preparation from cells expressing rat P2X7, [3H]-A-804598 bound to a high affinity site with a KD of 2.7 nM and a Bmax of 1.11 pmol/mg; no specific binding was observed in 1321 cells not expressing P2X7. The pharmacological profile for P2X antagonists to inhibit [3H]A-804598 binding to P2X7 receptors correlated with functional inhibition ( $r= 0.72$ ,  $P<0.05$ ). Two recently characterized P2X7 receptor antagonists, A-740003 and A-438079, potently competed with [3H]-A-804598 binding to rat P2X7 receptors. Taken together, these data demonstrate that A-804598 is not only a potent P2X7 antagonist but [3H]A-804598 is a useful tool for the study of P2X7 receptor pharmacology.

**THE ROLE OF FOCAL ADHESION KINASE IN SPHINGOSINE-1-PHOSPHATE INDUCED ENDOTHELIAL BARRIER STRENGTHENING.** T.L. Thennes and D. Mehta. Department of Pharmacology University of Illinois at Chicago, Chicago, IL 60612.

Dynamic interactions between adherens junctions and cell-matrix adhesions mediated by the actin cytoskeleton regulate endothelial barrier function. Sphingosine-1-phosphate (S1P), a bioactive sphingolipid, by binding its S1P receptor-1 (S1P-1) on the endothelial cell surface promotes endothelial monolayer integrity by stabilizing intercellular junctions and by promoting cell-matrix adhesions at focal adhesion complexes (FACs). Focal adhesion kinase (FAK) regulates cell-matrix adhesive contacts at focal adhesion sites. We address the possibility that FAK is required for S1P-1 signaling to strengthen the endothelial barrier. Inhibition of FAK by transduction of dominant negative FAK mutant (DN-FAK) in human pulmonary artery endothelial (HPAE) cells markedly increased basal endothelial permeability as measured by transendothelial monolayer resistance and S1P could not strengthen it to the level seen in control cells. Over-expression of DN-FAK prevented junctional annealing as determined by cell surface expression of VE-cadherin. Moreover, in endothelial cells isolated from lungs (MLMVECs) of FAK floxed mice, conditional FAK knock down using Cre-adenovirus perturbed junction resealing mediated by S1P. Importantly, we show that inhibition of FAK in HPAE and MLVME cells decreased S1P-1 expression at the cell surface. These findings suggest a novel role for FAK in regulating S1P-1 surface expression, and thus S1P-induced strengthening of cell-cell interactions to promote endothelial barrier enhancement.

**IN VIVO APOPTOSIS AND COMPENSATORY CELL PROLIFERATION IN HIPPOCAMPAL DENTATE GYRUS PRODUCED BY THE CASPASE-9 ACTIVATOR PETCM: STUDIES IN ADULT AND NEONATE-TREATED ANIMALS.** R.S. Bitner, A.L. Nikkel, S.L. Otte, K.B. Gallagher, A.M. Basso, D.A. Katz, M.W. Decker, and L.E. Rueter. Abbott Laboratories, Neuroscience Research, Abbott Park, IL 60064-3500.

The small molecule *a*-(trichloromethyl)-4-pyridineethanol (PETCM) has been shown in vitro to promote apoptosome formation and caspase-9 activation, an essential early step in Apaf-1-mediated apoptosis. Genetic and biochemical results from the Abbott-Myriad collaboration suggest that a gain-of function mutation in the APAF1 (Dep-1) gene may be an etiological factor in major depression. In establishing proof-of-principle animal studies, PETCM may have utility as a pharmacological tool to induce Apaf-1 mediated apoptosis in vivo. As reported here, studies involving systemic PETCM administration were conducted to determine changes in apoptosis and cell proliferation in the hippocampal dentate gyrus (DG), a site of neurogenesis. PETCM (100 mg/kg i.p.) increased the number of TUNEL-positive cells, a measure of apoptotic cell death, in the DG of adult mice and rats by > 250% as compared to vehicle-treated controls 24-later. In addition, increased activated caspase-9 expression was observed in PETCM-treated rats, the maximal increase observed between 2-4 hrs (> 300% vs control) and returning near control levels within 24-hrs. When examined 3-days following PETCM treatment, increased DG cell proliferation was observed, measured by BrdU incorporation and Ki67 expression. Given recent reports of neurogenesis involvement in antidepressant action, the ability of PETCM to stimulate neurogenesis may argue against utility as a tool to induce a pro-depressant phenotype. However, the "compensatory" increase in DG cell proliferation was not observed in adult treated rats previously treated with PETCM as neonates. In conclusion, preliminary studies with PETCM indicate that this small molecule may have utility in studying Apaf-1-mediated apoptosis in vivo. Moreover, these results may provide preliminary evidence that PETCM treatment in neonate versus adult rats produces differential changes in DG cell proliferation, perhaps implying an ontogenetic role of aberrant apoptosis in depression etiology.

**THE REGULATION OF NEURONAL OUTGROWTH BY SEROTONIN RECEPTOR 5-HT7.** Aleksandar Krbanjevic, Guoquan Liu, Elena Strelakova, Jasmina Profirovic, and Tatyana Voyno-Yasenetskaya. Dept. of Pharmacology, University of Illinois at Chicago, Chicago, IL 60612.

Serotonin [5-hydroxytryptamine (5-HT)] is critical in memory formation. The serotonin receptor 7 (5-HT7R) is a novel G-protein coupled receptor that directly regulates morphology of neurons. We showed that 5-HT7R induced neurite

outgrowth in the hippocampal neurons. Importantly, these studies showed that 5-HT<sub>7</sub>R was coupled to G<sub>α</sub>s and G<sub>α</sub>12 proteins. Our preliminary data indicate that 5-HT<sub>7</sub>R-G<sub>α</sub>s pathway induces phosphorylation of the serine/threonine kinase, LIM-kinase 1 (LIMK1). The phosphorylated form of LIMK1 is important in formation and increase in the length of neurites. As it was shown that phosphorylation of LIMK1 promotes formation and increase in the neurite length, we hypothesize that activation of LIMK1 mediates neurite outgrowth induced by 5-HT<sub>7</sub>R.

**SEROTONIN INNERVATION OF THE NUCLEUS TRACTUS SOLITARIUS (NTS) AUGMENTS SYMPATHETIC AND VENTILATORY RESPONSES TO HYPOXIA.** L.Kung and K.E.Scroggin. Neuroscience Program and Department of Pharmacology & Experimental Therapeutics, Loyola University Chicago, 2160 S. First Ave., Maywood, IL 60153.

Previously, we found that hindbrain serotonin nuclei positively modulate sympathetic responses to central chemoreflex stimulation. Here, we tested whether serotonin projections to the NTS positively modulate sympathetic responses to peripheral chemoreflex activation. Blood pressure (BP), heart rate (HR), sympathetic and ventilatory responses to increasing doses of KCN (3, 10, 30, 100 µg/kg, i.v.) were measured in conscious male Sprague-Dawley rats subjected to selective (n = 9-6) or sham (n= 6-5) destruction of serotonin nerve terminals in the NTS. Selective and sham lesions were made under sodium pentobarbital anesthesia (65 mg/kg, i.p.) using bilateral injections of the serotonin neurotoxin, 5,7-dihydroxytryptamine or ascorbic acid vehicle (0.01%) respectively within regions of the NTS that receive cardiovascular afferents. Six days later, rats were implanted with vascular catheters and recording electrodes for measurement of renal sympathetic- and diaphragmatic EMG activity. The next day, BP, HR, renal sympathetic nerve activity (RSNA) and diaphragmatic EMG were recorded during peripheral chemoreflex activation with KCN. Lesioned rats showed an attenuated pressor response ( $6.4 \pm 4.9$  vs.  $29.0 \pm 5.3$  ΔmmHg,  $P < 0.01$ ) at the 100µg/kg KCN dose. RSNA responses to 10 ( $135.4 \pm 38.6$  vs.  $336.4 \pm 60.8$  Δ% baseline,  $P < 0.05$ ), 30 ( $187.3 \pm 48.3$  vs.  $389.6 \pm 61.4$  Δ % baseline,  $P < 0.05$ ), and 100 ( $259.8 \pm 29.4$  vs.  $588.9 \pm 93.18$  Δ % baseline,  $P < 0.01$ ) µg/kg KCN were reduced in lesioned rats. Tidal volume ( $499.2 \pm 134.2$  vs.  $2095.4 \pm 680.5$  Δ% baseline,  $P < 0.05$ ) and minute ventilation ( $364.4 \pm 105.5$  vs.  $1994.0 \pm 869.6$  Δ% baseline,  $P < 0.05$ ) were also reduced at the highest dose in lesioned rats. Neither the bradycardia or tachypnic responses to KCN differed between groups. In conclusion, serotonin projections to the NTS were found to augment the sympathetic and ventilatory components of the peripheral chemoreflex in conscious rats.

**BIOASSAY GUIDED ISOLATION OF ANTIMICROBIAL COMPOUNDS FROM AXINELLA CORRUGATA.** J.E. Vantrease and A.E. Wright. Dept. of Biology, Augustana College, Rock Island, IL 61201 and Harbor Branch Oceanographic Institution, Fort Pierce, FL 34946.

The goal of this project was to perform an extraction on the sponge *Axinella corrugata* and use disc diffusion biological assays to follow the purification of compounds with antimicrobial activity. Several separation techniques such as solvent partitioning and various types of chromatography that use polarity of the molecules were used to further purify the active compounds. After each separation, biological assays were used to confirm activity while HPLC was used to determine purity. Once the active compound was purified, an assortment of NMR experiments, coupled with the data collected from LCMS were used to elucidate the structure. From this information it was determined that one of the compounds in *Axinella corrugata* that was active against MRSA was most likely (-)-7-N-methyldibromophakellin or an analog of it. Based on LCMS and proton NMR data combined with literature, one of the other active fractions separated was assumed to be Stevensine, a previously characterized compound with anti-tumor properties. These results are significant because Stevensine and its analogs have never before been shown to have antimicrobial activity against MRSA and further investigation could yield a compound with pharmaceutical potential.

**MOLECULAR MECHANISM FOR THE CONTROL OF STARCH PRODUCTION IN PLANTS.** Christine Falaschetti, Misty Kuhn, and Miguel A. Ballicora. Department of Chemistry, Loyola University Chicago, Chicago, IL 60626.

Starch provides for a storage of energy, and its production involves a multi-step mechanism. This project focuses on the catalytic properties of ADP-Glucose Pyrophosphorylase (ADP-Glc PPase), a regulatory enzyme in the synthesis of starch, for the potato tuber. The enzyme is a heterotetramer consisting of two small and two large subunits. Normally, the small subunit acts serves in catalysis while the large subunit acts as a regulator. In order to study the mechanism of allosteric control, we have mutated the homologous amino acids Tryptophan and Glutamine in the enzyme from Potato Tuber, which is activated by 3-phosphoglycerate (3-PGA). Interestingly, neither of these mutations is in the allosteric binding site. We transformed the mutant and wild type genes into *E.Coli* and expressed the protein in all its combinations. After purifying the protein, kinetic analysis with enable us to determine whether the enzyme will be unable to be activated by 3-

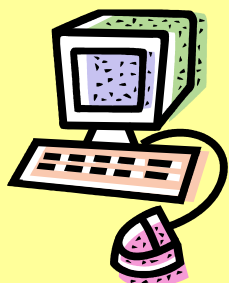
PGA but still bind 3-PGA. This should indicate that the triggering mechanism is common between bacteria and plant ADP-Glc PPases.

**FLUOXETINE LOWERS INDEXES OF SYMPATHETIC CONTROL OF HEART RATE VARIABILITY IN RATS WITH HEART FAILURE.** Marcus Henze<sup>1</sup>, Andrea Engel<sup>1</sup>, Ruslan Tiniakov<sup>1</sup>, Kyle Henderson<sup>2</sup>, John Barakat<sup>2</sup>, Allen Samarel<sup>2</sup> and Karie E. Scrogin<sup>1</sup>. <sup>1</sup>Department of Pharmacology and <sup>2</sup>Cardiovascular Institute, Loyola University Chicago, Stritch School of Medicine, Maywood, IL 60153.

We tested if treatment with the selective serotonin reuptake inhibitor, fluoxetine (FLX), restores heart rate variability (HRV) in rats with heart failure. Male Sprague-Dawley rats were subjected to coronary artery ligation (CAL) under ketamine/xylazine anesthesia (100 mg/kg + 7 mg/kg, im). CAL rats (n=20) with low fractional shortening (<25%) and sham rats (n=16) were fit with telemetric probes for ECG recording. Each group was given FLX (20 mg/kg, sc) or vehicle, once daily for 5 wks. Power spectral density of HRV was determined in the low frequency (LF, 0.06-0.6 Hz) and high frequency domains (HF, 0.6-3.0 Hz) before and after propranolol (4 mg/kg) and atropine (2 mg/kg). Compared to sham rats, CAL rats had lower total power ( $12.6 \pm 3.0$  vs.  $37.1 \pm 9.0$  ms<sup>2</sup>,  $P < 0.01$ ) due to a decrease in both LF ( $1.3 \pm 0.2$  vs.  $4.7 \pm 0.8$  ms<sup>2</sup>,  $P < 0.01$ ) and HF ( $2.2 \pm 0.6$  vs.  $4.1 \pm 0.7$  ms<sup>2</sup>,  $P < 0.05$ ). FLX lowered LF in sham ( $2.4 \pm 0.4$  vs.  $4.7 \pm 0.8$  ms<sup>2</sup>,  $P < 0.01$ ) and CAL rats ( $0.4 \pm 0.1$  vs.  $1.3 \pm 0.2$  ms<sup>2</sup>,  $P < 0.01$ ). FLX reduced the effect of propranolol on LF in CAL ( $-0.01 \pm 0.06$  vs.  $0.79 \pm 0.15$  ms<sup>2</sup>,  $P < 0.05$ ), and sham ( $1.59 \pm 0.42$  vs.  $3.65 \pm 0.65$  ms<sup>2</sup>,  $P < 0.05$ ) rats. Atropine lowered HF in sham-vehicle ( $-60.8 \pm 10.6\%$ ,  $P < 0.01$ ), but not in CAL or FLX-treated rats. CAL and FLX-treatment decreased the inotropic ( $P < 0.01$ ,  $P < 0.01$ ) and chronotropic responses ( $P < 0.01$ ,  $P < 0.01$ ) to vagal nerve stimulation. CAL rats had an increased EC<sub>50</sub> for isoproterenol's inotropic ( $P < 0.01$ ) and chronotropic effect ( $P < 0.01$ ). FLX-treatment lowered the E<sub>max</sub> for the chronotropic response to isoproterenol with no effect on the inotropic response. These data indicate that FLX lowers HRV in the LF and HF domains, due, in part, to a decrease in the sensitivity of cardiac autonomic receptors.

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## MEMBERS IN THE NEWS



Congratulations to **Robert J. Lefkowitz, PhD**, Professor of Medicine and Biochemistry at Duke University, who will be awarded a National Medal of Science by President George W. Bush in a White House ceremony on September 29, 2008.

**Robert R. Ruffolo, Jr, PhD**, senior vice president of Wyeth and president of R&D for Wyeth Pharmaceuticals, is the winner of the 2008 David Perlman Memorial Lectureship – an award presented by the ACS Division of Biochemical Technology (BIOT). The award, sponsored by Genzyme, honors the contributions of the late Perlman, a professor at the University of Wisconsin, Madison. Ruffolo was cited for his achievements in leading the discovery and development of a number of pharmaceuticals including dobutamine (Dobutrex) for congestive heart failure, ropinole (Requip) for Parkinson's disease, and eprosartan (Teveten) for hypertension.

*(This announcement was originally published in [www.cen-online.org](http://www.cen-online.org))*

**Lakshmi A. Devi, PhD** has been named Associated Dean for Academic Enhancement and Mentoring at Mount Sinai School of Medicine. Dr. Devi will continue in her role as Faculty Director of the Office of Postdoctoral Affairs, <http://www.mountsinai.org/?citype=News&ciid=08282008>



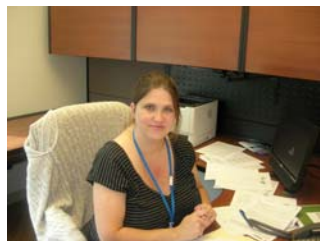
**Jordan E. Warnick, PhD**, professor, Department of Pharmacology & Experimental Therapeutics and assistant dean for Student Education & Research at the University of Maryland School of Medicine, has been inducted into the Pass and Susel Academy of Educational Excellence.

Generous alumni Carolyn Pass, MD, clinical assistant professor, Department of Dermatology, and Richard Susel, MD, clinical assistant professor, Department of Ophthalmology, a husband and wife team from the Class of 1966, have established the Academy of Education Excellence at the University of Maryland School of Medicine. The goal of the academy is to create an environment that enhances the status of teachers as medical educators and promotes and rewards superlative teacher. Dr. Warnick was one of the five first members to be inducted.

"The School of Medicine has had few ways to recognize the select few who truly excel at pedagogy and cherish the opportunity to teach, mentor and mold the next generation of physicians, scientists and allied health professionals," said Dean E. Albert Reece, MD, PhD, MBA. "The academy is designed to recognize faculty members who demonstrate excellence in bedside, classroom and/or innovative medical and graduate education. Honorees are exemplary role models to students, embody the highest ideals of the medical profession and display uncommon commitment to students' best interests."

*(This announcement was originally published in SOMnews, the University of Maryland School of Medicine newsletter)*

## STAFF NEWS



**Crystal Ledger** joins ASPET as the newest member of staff. Crystal is the new Subscriptions Manager and is responsible for running the Subscriptions and Fulfillment Department. She was previously employed with the Endocrine Society, another constituent society of FASEB, where she worked in Subscriptions and Customer Service for the past seven years. Crystal is married and has two children with another one on the way! In her spare time, she enjoys reading, making greeting cards, scrap-booking, and spending time with her family. The ASPET family welcomes Crystal in her new role.

## ASPET WELCOMES THE FOLLOWING NEW MEMBERS:

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**Lori Fitz, PhD**, Wyeth  
**Jian Guo, PhD**, AstraZeneca Pharmaceuticals  
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**Maaïke Hum**, Queen's Univ  
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**Deepika R Laddu**, Univ of Arizona  
**John D Laughlin, BS**, Univ of Colorado-Denver  
**Jason E Maas, BS**, Medical College of Wisconsin  
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*ASPET notes with sympathy the passing of the following members:*

*William A. Creasey*

*Alfred Gellhorn*

*Harold F. Hardman*

*Jason D. Morrow*

*Frank M. Sturtevant*

*Henry I. Yamamura*



### Harold F. Hardman, MD, PhD

Hardman, Harold Frances, MD, PhD, August 2, 1927 – July 14, 2008, Age 80, of Eden Prairie, MN, a native of Bloomfield, NJ, and long term resident of Brookfield, WI. Dr. Hardman served as Professor and Chairman of the Department of Pharmacology at the Medical College of Wisconsin for 30 years, until his retirement in 1992. Author or co-author of nearly 100 scientific publications and recipient of numerous awards and honors, he was an internationally recognized scholar in the field of cardiovascular pharmacology. Dr. Hardman received his BS degree in Pharmacy from Rutgers University in 1949, his MS degree in Pharmacology from the University of Illinois in 1951, and his PhD and MD degrees from the University of Michigan in 1954 and 1958. He is survived by his wife of 58 years, Jean, of Eden Prairie, MN; his sons, David, of Chapel Hill, NC; Tim, of Allenton, PA; John, of Rosemount, MN; daughter, Susan Hardman-Conklin, of Eden Prairie, MN; his 4 grandchildren, Chris and Kayla Conklin, also of Eden Prairie, MN; and Christine and Kimberly Hardman, of Chapel Hill, NC.

*Published in the Star Tribune*

### Jason Morrow, MD

Jason Morrow, MD, chief of the Division of Clinical Pharmacology in Vanderbilt Medical Center's Department of Medicine, was remembered last week [originally published on July 18, 2008] as a gifted scientist and generous friend.

Dr. Morrow, 51, died on July 8. Six hundred people attended his funeral on July 11 at Congregation Micah in Brentwood.

"Jason was an inspired and inspiring leader of our scientific endeavors," said John Oates, MD, founder of the Division of Clinical Pharmacology, who helped launch Morrow's career. "He knew excellence and had an infectious enthusiasm for discovery. We have lost a colleague and leader who held our affection and profound respect."

"Jason Morrow was an extraordinary scientist, a valued colleague and a wonderful and warm human being," added Harry Jacobson, MD, vice chancellor for Health Affairs.

Dr. Morrow received his bachelor's degree from Vanderbilt University and his MD from Washington University in St. Louis, his hometown. He served his medical internship and residency at Vanderbilt, and was chief medical resident from 1987 to 1988, when he joined the Division of Clinical Pharmacology as a research fellow.

In 1990, he and Jackson Roberts, MD, discovered a series of compounds called isoprostanes that help researchers reliably detect and monitor free radical damage.

Also called "oxidative stress," this damage has been implicated in the development of atherosclerosis, age-related macular degeneration and neurodegenerative diseases.

Dr. Morrow joined the Vanderbilt faculty in 1994, and later was named the F. Tremaine Billings Professor of Medicine and professor of Pharmacology. In 2005, he became the forth chief of the Division of Clinical Pharmacology, which currently has 190 employees and a \$33 million annual budget.

Co-author of more than 200 scientific papers, Dr. Morrow also contributed to current understanding of the potential of antioxidant vitamins C and E to protect against heart disease. He was a vigorous advocate for government regulation and oversight of over-the-counter dietary supplements.

Dr. Morrow is survived by his wife, Lisa, their children Jeremy and Stephanie, his mother Vera Morrow, a sister, Leigh Shalloway, and an extended family.

*Prepared by Bill Snyder and published in The Reporter, Vanderbilt Medical Center*



## **Henry I. Yamamura, PhD**

Henry Ichiro "Hank" Yamamura passed away at his home in Tucson, AZ September 4, 2008 after a long, valiant battle with cancer. Even while battling cancer he continued his research and scholarly activities. He is survived by his wife Susan and son Mark.

Hank was born in Seattle in 1940. He obtained a B.S. and M.S in Pharmacy at the University of Washington, continuing on for a Ph.D. in Pharmacology with Aki Horita in 1969. He served as a Captain in the Army Medical Service Corps from 1970 to 1973 after which he Post-Doc'd with Sol Snyder at Johns Hopkins University in Baltimore, MD.

He joined the Pharmacology Department at the University of Arizona College of Medicine in 1975 as an Assistant Professor, spending the remainder of his career there. He was promoted to Associate Professor in 1977 and to Professor in 1980. He also held joint appointments as Professor of Psychiatry and of Biochemistry. In 1997 he was named Regents Professor in the University of Arizona College of Medicine.

Hank pioneered radioligand binding assays, contributing valuable knowledge about neurotransmitter transporters and muscarinic, opioid and other G-protein-coupled receptors, publishing more than 600 articles and editing 10 books over 40 years. He ranked among the top 100 most-cited scientists in the country with his work being cited more than 19,000 times in the scientific literature. He trained and mentored more than 100 students, fellows, and visiting faculty, including 57 post-docs and 18 Ph.D. students. He taught Medical Pharmacology and Neuroscience. He served many committees of professional societies and was President of the Western Pharmacology Society, 1987-1988. He served on the editorial boards of several journals, including the *Journal of Pharmacology and Experimental Therapeutics*. He was Associate Editor of *Life Sciences* (1975-1989), Editor (1990-1992) and Executive Editor-in-Chief (2002-2005).

Hank received numerous awards including the prestigious American Society for Pharmacology and Experimental Therapeutics (ASPET) Award for Experimental Therapeutics in 1995. He was named the University of Washington's Distinguished Alumnus of the year in 2004.

Despite his fame, Hank was a humble person who fondly quoted Walt Disney: "If you can dream it you can do it, it all started with a mouse."

Above all Hank was a great humanitarian who was loved by his students, fellows and colleagues, who were always his highest priority. "He was always there for you." said long-time collaborator Victor Hruby, Regents Professor of Chemistry at the University of Arizona. "He was fun to work with because things got done. He had a habit of always doing the right thing."

"Hank was a great mentor and friend," said Lin Mei, Ph.D. 1989, Georgia Eminent Scholar in Neuroscience and Professor at the Institute of Molecular Medicine and Genetics at the Medical College of Georgia. "I was in a complete cultural shock when I arrived from China. He was very patient with me and always positive. Encouragement from him was almost guaranteed. I really learned a lot in his lab, not just science, but how to do it and how to be a mentor years later."

"Hank always had a wonderful rapport with students both in the classroom and as mentor," said Josephine Lai, a 1988-1990 post-doc, now a Professor of Pharmacology at the University of Arizona, College of Medicine. "He treasured every one of them. You can see that by his collection of hundreds of photos of people who joined his lab over the decades, pinned up layers upon layers of time."

"I measure my life before and after Hank Yamamura," said Bob Speth, an early post doc (1976-1979), Professor of Pharmacology at the University of Mississippi. "I trace all the successes in my career back to the inspirational guidance Hank gave me."

"He generously shared ideas, insights, and credit with collaborators and associates to an extent seldom seen in this competitive environment." said Sam Enna, who co-edited several books with Hank. "While Hank will be greatly missed by his many friends and associates around the world, his greatest legacy is the devotion of his students and their continuing contributions to medical research."

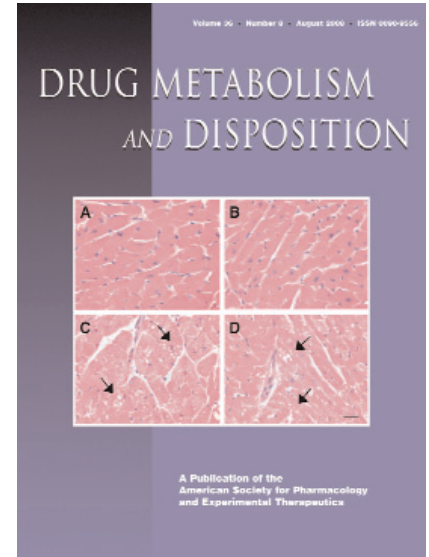
"The Hank Yamamura Endowed Fellowship in Pharmacology" to support Graduate Student training in Pharmacology at the University of Arizona has been established. Gifts can be made to: UAF/Yamamura Endowment, UA College of Medicine, Development Office, P.O. Box 245018, Tucson, AZ, 85724-5018 or by contacting the Office of Development, 520-626-2827, [health@email.arizona.edu](mailto:health@email.arizona.edu).

**Prepared by Robert C. Speth, PhD, University of Mississippi**

*A memorial service for Dr. Yamamura will be held on Friday, September 26. A live webcast of the event can be viewed at:*

<http://streaming.biocom.arizona.edu>

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- Best abstract awards for young scientists at the ASPET meeting
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- Membership in multiple ASPET Divisions for no additional dues.

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- Must have their papers at Society meetings sponsored by a member.
- May not vote in Society elections nor hold an elected office in the Society.

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- *Drug Metabolism and Disposition* (Monthly) - \$102/year
- *Molecular Pharmacology* (Monthly) - \$138/year
- *Molecular Interventions* (Bimonthly) – included with dues

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Submit the completed Application for Membership form or use the online application form on the ASPET web site at <http://www.aspet.org/public/membership/membership.html>. Submit a current *curriculum vitae* including bibliography for Regular and Affiliate Membership. You may e-mail the CV to the ASPET Membership Coordinator, Robert Phipps, [rphipps@aspet.org](mailto:rphipps@aspet.org).

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- Affiliate Membership
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### Section 2: Source

How did you hear about ASPET:

- Meeting \_\_\_\_\_
- ASPET Journal \_\_\_\_\_
- Mentor \_\_\_\_\_
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### Section 3: Personal Information

Name:

Telephone:

Institution:

Fax:

Address:

E-mail:

Date of Birth (optional):

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Name, address and email of your sponsor(s): (2 sponsors required for regular membership & 1 sponsor for student and affiliate membership)

*Please have your sponsor(s) send us a brief letter or e-mail outlining your qualifications for Membership in ASPET to the Membership Coordinator, Robert Phipps, ([rphipps@aspnet.org](mailto:rphipps@aspnet.org)).*

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- |   |  |
|---|--|
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