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March

2011 ASPET Election Results

John S. Lazo
President-Elect

Edward T. Morgan
Secretary/Treasurer-Elect

Kenneth E. Thummel
Councilor

In this year's election, ASPET members chose John S. Lazo as President-Elect, Edward T. Morgan as Secretary/Treasurer, and Kenneth E. Thummel as Councilor.

John S. Lazo, Professor and Associate Dean for Basic Research, Departments of Pharmacology and Chemistry, University of Virginia School of Medicine, will become the President-Elect in July 2011. Dr. Lazo has served as a Councilor and a member of the Board of Publications Trustees. He currently serves as Chair of the *Molecular Interventions* Editorial Advisory Board.

Edward T. Morgan, Professor, Department of Pharmacology, Emory University, will become the Secretary/Treasurer-Elect in July. Among his ASPET activities, Dr. Morgan has served as the Chair-Elect, Chair, and Past Chair of the Division for Drug Metabolism, he has been a member of the Board of Publications Trustees, and was an Associate Editor for *Molecular Pharmacology*. He has been a member of the *Drug Metabolism and Disposition* editorial board since 1994.

Kenneth E. Thummel, Professor and Chair, Department of Pharmaceutics, School of Pharmacy and Adjunct Professor, Department of Environmental and Occupational Health Science, University of Washington, will become a Councilor in July. Dr. Thummel is the immediate Past Chair of the Division for Drug Metabolism and has served on the Program Committee. He has served as an Associate Editor of *Drug Metabolism and Disposition* since 2000.

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ASPET Annual Meeting at Experimental Biology 2011
April 9-13
Washington, DC
Don't miss it!

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ASPET AWARD WINNERS FOR 2011

ASPET will present the Society's awards during this year's Annual Meeting/Experimental Biology 2011 in Washington, DC, on Saturday, April 9. This year's awards include the following:

ASPET–Julius Axelrod Award, given annually for significant contributions to understanding the biochemical mechanisms underlying the pharmacological actions of drugs and for contributions to mentoring other pharmacologists;

John J. Abel Award, given annually to an investigator who has not passed his or her 42nd birthday on April 30 of the year of the Award (funded by Pfizer);

Pharmacia–ASPET Award for Experimental Therapeutics, given annually to recognize and stimulate outstanding research in pharmacology and experimental therapeutics—basic laboratory or clinical research that has had, or potentially will have, a major impact on the pharmacological treatment of disease;

ASPET–Torald Sollmann Award in Pharmacology, given biennially for significant contributions over many years to the advancement and extension of knowledge in the field of pharmacology; and

ASPET Epilepsy Research Award for Outstanding Contributions to the Pharmacology of Anti-epileptic Drugs, given biennially.

In addition, the Society will present the **ASPET Graduate Student Travel Award Winners**, the **ASPET Young Scientist Travel Award Winners**, and the **Summer Undergraduate Research Fellow Travel Awards**. All awards will be presented at the ASPET Business Meeting Awards Reception. The PhRMA Foundation's Awards in Pharmacology/Toxicology will also be presented. The Awards Ceremony will take place at the Washington Convention Center in Ballroom A, starting at 7:00 p.m. This year's award recipients are shown below.

Elaine Sanders-Bush, Ph.D.
ASPET-Julius Axelrod Award

Dr. Elaine Sanders-Bush has been named the recipient of the 2011 ASPET-Julius Axelrod Award in Pharmacology by the American Society for Pharmacology and Experimental Therapeutics (ASPET). Dr. Sanders-Bush is Professor Emirta of Pharmacology at Vanderbilt University and former Director of the Vanderbilt Brain Institute. The Julius Axelrod Award is given to recognize outstanding scientific contributions in research and mentoring. The Award was established to honor the memory of the eminent American pharmacologist who shaped the fields of neuroscience, drug metabolism and biochemistry.

Internationally known for her research on serotonin, a key brain chemical involved in normal behavior and brain diseases such as major depression and schizophrenia, Dr. Sanders-Bush arrived at Vanderbilt University in 1962 to pursue graduate training. She earned a Ph.D. in pharmacology and after postdoctoral training in psychopharmacology, she joined Vanderbilt as Assistant Professor of Pharmacology. During her tenure at Vanderbilt she has made seminal contributions to our understanding of serotonin synthesis, metabolism and function. Her research has made a lasting impact on the field and helped shape our understanding of these important research areas.

Dr. Sanders-Bush has also been a leader in the development of neuroscience research and graduate education at Vanderbilt. She led the creation of a new Ph.D. program in Neuroscience and served as its director from its inception in 1997 until 2008. She has always taken a strong interest in training the next generation of neuroscientists, including the establishment of a partnership with Meharry Medical College to develop an innovative program for increasing diversity in scientific research. In recognition of this outstanding commitment, she won Vanderbilt's first Levi Watkins, Jr. Award for Leadership in Diversity in 2002.

The 2011 Julius Axelrod Award Lecture will be given by last year's recipient, **Brian Kobilka, Ph.D.**, of Stanford University. Dr. Kobilka will deliver a lecture, entitled "Structural Insights into the Dynamic Process of GPCR Activism", on Sunday, April 10, from 8:30 to 9:20 a.m. in Room 143A/B of the Washington Convention Center. Dr. Kobilka will also chair the complementary symposium entitled "Structural Approaches to Understanding GPCR Signaling" immediately following his lecture.

Laura M. Bohn, Ph.D.
John J. Abel Award

Laura Bohn, Ph.D., Associate Professor at the Scripps Research Institute Department of Molecular Therapeutics and Department of Neuroscience in Jupiter, Florida, is the recipient of the 2011 John J. Abel Award, sponsored by Pfizer. Dr. Bohn receives the John J. Abel Award as an outstanding young investigator for her contributions that have helped shape the field of pharmacology.

Dr. Bohn received undergraduate degrees in biochemistry and chemistry from Virginia Tech. She received her Ph.D. from St. Louis University School of Medicine and began post doctoral training at Duke University Medical Center where she was promoted to assistant research professor. Following Duke, she accepted a position at the Ohio State University College of Medicine in the Department of Pharmacology, established her own laboratory, secured NIH funding, and was promoted with tenure. In 2009, she accepted a tenured associate professor position at Scripps in the Department of Molecular Therapeutics.

Dr. Bohn is recognized for her expertise in the regulation of G protein coupled receptor signaling and how it relates to drug responsiveness *in vivo*. She is particularly known for her work on serotonergic and opioid functions.

Dr. Bohn has received recognition research awards from Ohio State and has been named the Joseph Cochin Young Investigator Awardee by the College on the Problems of Drug Dependence in recognition of her contributions to the field of drug abuse and addiction research. She currently serves on the executive committee of the Neuropharmacology Division of ASPET, serves as an ad hoc reviewer of minority NRSA fellowships, and is a standing member of the Molecular Neuropharmacology and Signaling Study Section. She is the current mini-review editor for *Molecular Pharmacology*. Dr. Bohn is also active in community outreach to inform the public about her science and serves as mentor in the Kenan Scholars program that provides research experience to high school and undergraduate students in Palm Beach County, Florida.

Jan Balzarini, Ph.D.
Pharmacia-ASPET Award for Experimental Therapeutics

Dr. Jan Balzarini, of the Rega Institute for Medical Research at The Katholieke Universiteit Leuven in Belgium is the recipient of the 2011 Pharmacia–ASPET Award for Experimental Therapeutics. The Pharmacia–ASPET Award for Experimental Therapeutics is given annually to recognize and stimulate outstanding research in pharmacology and experimental therapeutics—basic laboratory or clinical research that has had, or potentially will have, a major impact on the pharmacological treatment of disease. This award is funded by an endowment from Pharmacia (now Pfizer) and by ASPET.

Dr. Balzarini received his Master in Biological Sciences, Master in Bioscience Engineering, and Doctorate in Bioscience Engineering from the Katholieke Universiteit in Leuven. He is recipient of the Pharmacia–ASPET Award for his outstanding contributions to the discovery, development and molecular understanding of the pharmacology of antiviral and anticancer nucleoside and non-nucleoside agents. He is internationally recognized as an expert in antiviral drug development and has identified new chemotherapeutic targets for antiviral and anticancer therapy. Dr. Balzarini has been at the forefront of, and directly involved in, the discovery and eventual preclinical development of a variety of entirely new and innovative therapeutic leads and concepts.

Dr. Balzarini has received national and international awards including two international UNESCO prizes and the prestigious Rene Descartes Prize of the European Commission for Scientific and Technological Excellence in European Collaborative Research.

Marcus M. Reidenberg, M.D.
ASPET-Torald Sollmann Award in Pharmacology

Marcus M. Reidenberg, M.D., Professor of Pharmacology, Medicine, and Public Health at the Weill Cornell Medical College is the recipient of the 2011 Torald Sollmann Award. The Award was established to commemorate the pioneering work in America of Dr. Torald Sollmann in the fields of pharmacological investigation and education. Dr. Reidenberg was selected for this Award because of his outstanding and productive research career, his significant contributions to medicine utilizing education, research, and service and his unparalleled service to ASPET and the discipline it represents.

Dr. Reidenberg majored in botany at Cornell University and received his M.D. from Temple University. After his internship, he was a postdoctoral fellow in pharmacology at Temple and in general practice while in the U.S. Navy. Following his service, he returned to Temple as an Instructor in Pharmacology and Resident in Medicine. He joined the faculty and would remain at Temple until 1975 when he moved to Cornell with faculty appointments in Pharmacology and Medicine. He has been Assistant Dean since 1988, and received an appointment in the Department of Public Health in 2003.

Dr. Reidenberg's research has been in the area of clinical pharmacology. His work has focused on reasons for individual differences in response to medications. Dr. Reidenberg promoted the principle of proper controls to study adverse drug reactions and reported that patients with renal failure metabolized some nonexcreted drugs differently than patients with normal kidney function. His report of impaired plasma protein binding of organic acids proved essential for proper interpretation of drug levels in patients, and his data for phenytoin binding is in clinical use today. He recognized that individual differences in dose-response could be used to improve therapeutics, and he moved the concept of individualized drug therapy into the mainstream. Dr. Reidenberg raised the banner of addressing control of symptoms in 1982, and over the past 25 years the broad concept of symptom control has gained mainstream acceptance in medicine. More recently, treatment of chronic pain and the pharmacology of gossypol for reproductive health and cancer have been subjects of his 50-year research career.

Over many years, Dr. Reidenberg has provided exemplary leadership to the discipline of pharmacology, including roles in ASPET, IUPHAR, ASCPT, and advisory service to the FDA and NIH. He has worked extensively with the World Health Organization and its Essential Medicines Program and is a member of the WHO Expert Panel on the Selection and Use of Essential Drugs. Dr. Reidenberg served as WHO advisor to the Ministry of Health of the People's Republic of China in 1993 and is currently active in the Essential Medicines activities of WHO.

Dr. Reidenberg's Torald Sollman lecture is entitled "Drug Discontinuation Effects are Part of the Pharmacology of a Drug: Cardiovascular Drug Discontinuations" and will be presented on Tuesday, April 12, from 8:30 to 9:20 a.m. in Room 143A/B of the Washington Convention Center.

Asla Pitkanen, M.D., Ph.D., DSc.
ASPET Epilepsy Research Award for Outstanding Contributions to the Pharmacology of Antiepileptic Drugs

Dr. Asla Pitkanen, Professor of Neurobiology, University of Eastern Finland is the recipient of the 2011 ASPET–Epilepsy Award. The Award is sponsored by ASPET and the International League Against Epilepsy. The award is to recognize and stimulate outstanding research leading to better clinical control of epileptic seizures.

Dr. Pitkanen received her Masters in Biochemistry and Medical Degree from the University of Kuopio in Finland. She began her career in neuroscience as a first year medical student, working with patients with multiple sclerosis and then Alzheimer's disease. She began her research career in epilepsy by investigating GABA-A receptors in cortical cobalt model of epilepsy in the rat.

Among Dr. Pitkanen's many contributions to the study of epilepsy are her seminal contributions to our understanding of the molecular mechanisms of epileptogenesis, the process by which an injured brain becomes epileptic. She has developed novel models of epilepsy induced by brain trauma and stroke. She has pioneered the use of magnetic resonance imaging in charactering these and other models. These models provide a valuable framework for assessing the efficacy of novel therapeutics aimed at prevention of epilepsy.

Dr. Pitkanen is also active internationally in increasing the visibility of epilepsy research. She was one of the organizers of a 2008 workshop on "Research Priorities in Epilepsy for the Next Decade." This workshop detailed epilepsy research priorities that should be investigated and funded in Europe. She has served as Secretary General of the Federation of European Neuroscience Societies, Member of the Commission of the European Affairs of the International League Against Epilepsy, Vice President of the Epilepsy Society of Finland, and as a Member of the Scientific Advisory Board of the European Epileptology Meeting in Finland.

Graduate Student Travel Award Winners to EB 2011

Ahmad Al Tarifi, *Virginia Commonwealth Univ.*
Russell Amato, *Louisiana State Univ. Hlth. Sci. Ctr.*
Shinichi Asano, *West Virginia Univ.*
Farnaz Bakhshi, *Univ. of Illinois at Chicago*
Sri Nagarjun Batchu, *Univ. of Alberta*
Kevin Bigham, *Medical Univ. of South Carolina*
Emily Bisen-Hersh, *Temple Univ.*
Andrea Boyd Tressler, *Case Western Reserve Univ.*
Remy Brim, *Univ. of Michigan, Ann Arbor*
Paula Brock, *Univ. of Utah*
Loren Brown, *Univ. of California, San Diego*
Isabel Canto, *Univ. of California, San Diego*
Noel Yan-Ki Chan, *Weill Cornell Medical Col.*
Pui Yee Chan, *Univ. of Rochester*
Ketul Chaudhary, *Univ. of Alberta*
Alejandra Chavez, *Univ. of Illinois at Chicago*
Hyehun Choi, *Medical Col. of Georgia*
Ian Cook, *Univ. of Alabama, Birmingham*
Lisa Cortez, *Univ. of Arkansas for Medical Sciences*
Tyechia Culmer, *Univ. of North Carolina, Chapel Hill*
Robert Davis, *Michigan State Univ.*
Colins Eno, *Univ. of Louisville*
Rheaclare Fraser, *Univ. of Michigan, Ann Arbor*
Meital Gabay, *Univ. of Rochester*
Jenna Gallops, *Medical Col. of Georgia*
Ashley Guillory, *Univ. of Houston*
Adam Goodwill, *West Virginia Univ*.
Robert Gould, *Wake Forest Univ. Hlth. Sci.*
Brendan Harmon, *Northeastern Univ.*
Sairam Jabba, *Creighton Univ.*
Olan Jackson-Weaver, *Univ. of New Mexico*
Andrew Johnson, *Univ. of Iowa*
Wei Kan, *Univ. of Rochester Medical Ctr*.
Jason Kehrl, *Univ. of Michigan, Ann Arbor*
Cesar Kenaan, *Univ. of Michigan, Ann Arbor*
James Kleinedler, *Louisiana State Univ. Hlth. Sci. Ctr., Shreveport*
Christopher Kuhlman, *Univ. of Arizona*
Hicham Labazi, *Medical Col. of Georgia*
Wenjun Li, *Univ. of Florida*
Yanan Liu, *Univ. of Hong Kong*
Wanshu Ma, *Auburn Univ*.
Duncan Mackie, *Univ. of Iowa*
Rohit Malik, *Loyola Univ., Chicago*
Daniel Manvich, *Emory Univ*.
Nicholas Mastrandrea, *Univ. of Arizona*
Stephanie Mathews, *Univ. of Louisville*
Marie McGee, *East Carolina Univ*.
Amit Modgil, *North Dakota State Univ*.
Carlos Monroy, *Univ. of Iowa*
Kamalika Mukherjee, *Univ. of Kentucky*
Ram Naikawadi, *Univ. of Illinois, Chicago*
Ozhan Ocal, *Univ. of Texas Southwestern Medical Ctr., Dallas*
Kristen Osterlund, *Univ. of Arizona, Phoenix, Col. of Medicine*
Elina Pathak, *Univ. of Arkansas for Medical Sci.*
Maria Posada, *Univ. of Michigan, Ann Arbor*
Emily Salman, *Univ. of Alabama at Birmingham*
Praveen Shukla, *North Dakota State Univ*.
Antonio Soto, *Univ. of California, San Diego*
Meera Sridharan, *Saint Louis Univ*.
Christina Swan, *Vanderbilt Univ*.
Manish Taneja, *Univ. of Houston*
Arunkumar Thangaraju, *Oklahoma State Univ. Ctr. for Hlth. Sci.*
Tracy Thennes, *Univ. of Illinois, Chicago*
Shanthi Vadali, *Univ. of Arkansas for Medical Sci.*
Ajit Vikram, *Nat. Inst. of Pharmaceutical Education & Res.*
Hideaki Yano, *Columbia Univ.*
Jennifer Yeung, *Thomas Jefferson Univ*.
Lianghui Zhang, *Univ. of Rochester Medical Ctr*.

Young Scientist Travel Award Winners to EB 2011

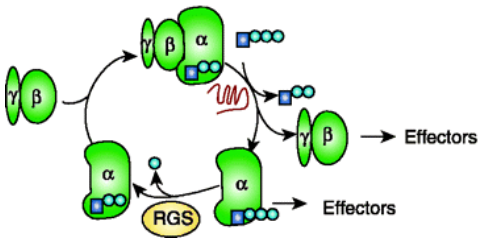
Rayna Bauzo, *Univ. of Florida*
Cecilea Clayton, *Oregon Hlth. & Sci. Univ.*
Ross Corriden, *Univ. of Nottingham*
Mikel Garcia-Marcos, *Univ. of California, San Diego*
Fernanda Giachini, *Medical Col. of Georgia*
Lindsey Hamilton, *U.S. Army Medical Res. Inst. of Chemical Defense*
Eileen Kennedy, *Univ. of Georgia*
Abdul Khan, *Medical Col. of Wisconsin*
Steven Kinsey, *Virginia Commonwealth Univ.*
Angeline Lyon, *Univ. of Michigan, Ann Arbor*
Kevin Murnane, *Emory Univ.*
Hua Pan, *Washington Univ. Schl. of Med.*
Yuzhuo Pan, *State Univ. of New York, Buffalo*
Kirsten Raehal, *The Scripps Res. Inst., Florida*
Silvia Romano, *Univ. of California, San Diego*
Aaron Runkle, *Pennsylvania State Univ.*
Gilandra Russell, *Univ. of Louisville*
Kosuke Saito, *National Inst. of Environmental Hlth. Sci.*
Jacqueline Sayyah, *Univ. of California, San Diego*
Benita Sjogren, *Univ. of Michigan, Ann Arbor*
Tricia Smith, *Virginia Commonwealth Univ.*
Swapnil Sonkusare, *Univ. of Vermont*
John Streicher, *The Scripps Res. Inst., Florida*
Mohammad Tauseef, *Univ. of Illinois, Chicago*
Michael Tranter, *Univ. of Cincinnati Col. of Med.*
Andy Wang, *The Scripps Res. Inst., Florida*
Zhican Wang, *Univ. of Washington*
Sunny Xiang, *Univ. of California, San Deigo*
Lin Yao, *Medical Col. of Georgia*
Yueh-Chiao Yeh, *Graduate Inst. of Natural Healing Sci.*

Summer Undergraduate Research Fellow Travel Awards

Emma Darios, *Michigan State Univ.*
Jordan Faloon, *Univ. of New England*
Molly MacDonald, *Michigan State Univ.*
Anna McNally, *Middlebury Col.*
Robert Helsley, *Univ. of Cincinnati*
Hamzat Feshitan, *Univ. at Buffalo*
Jillian Pattison, *Kenyon Col.*

Plan to attend the ASPET Colloquium:

RGS and AGS Proteins in Physiology and Disease



Sponsored by the Division for Molecular Pharmacology

Organized by John R. Hepler, Emory University, and Venetia Zachariou, University of Crete

This day-and-a-half colloquium will held in conjunction with **Experimental Biology 2011** and will begin on Wednesday afternoon, April 13, and continue through Thursday, April 14.

Registration is separate from the EB meeting.

See www.aspet.org/Meetings/RGS_AGS_Proteins for more information.

American Society for Pharmacology & Experimental Therapeutics at Experimental Biology 2011
Washington, DC

All rooms listed are in the Washington Convention Center unless otherwise noted.

ASPET Booths 1203 & 1205 — Exhibits 9:00 AM–4:00 PM, Sunday–Tuesday

Saturday April 9	Sunday AM April 10	Sunday PM April 10	Monday AM April 11	Monday PM April 11	Tuesday AM April 12	Tuesday PM April 12	Wednesday AM April 13	Wednesday PM April 13
Behavioral Pharmacology Meeting 8:00 AM – 6:00 PM Room 143A/B *Separate, pre-registration required*	**WIP Into Shape Walk** 7:00 AM – 8:30 AM Hyatt Meet at Concierge Desk **Diversity Committee Mentoring Breakfast** 7:30 AM – 9:00 AM Hyatt, Burnham DM, ISTCP, TOX Drug metabolism and action in pathophysiological conditions *R. Ghose, E.T. Morgan* 9:30 AM – 12:00 PM Room 143C	ISTCP, CVP, DDDRA, DPE, TOX Systems biology of oxidative stress and therapeutic implications *I. Laher* 3:00 PM – 5:30 PM Room 140B	NEU, BEH, DDDRA, DM, ISTCP Role of neuroinflammation in psychiatric disease *J.E. Clark* 9:30 AM – 12:00 PM Room 140A	EDUCATION DIVISION What happens to drugs in the body? A pharmacokinetics refresher course *J.S. Fedan, J.S. Leeder* 3:00 PM – 5:30 PM Hyatt, Independence H/I	MP, CVP, NEU Novel regulation, physiological roles, and pharmacological intervention of GPCR-adenylyl cyclase signaling systems *C.W. Dessauer, V.J. Watts* 9:30 AM – 12:00 PM Room 143A/B	DDDRA, MP G_{α} subtype-selective signaling by GPCRs as a substrate for functional selectivity *R. Neubig* 3:00 PM – 5:30 PM Room 143A/B	**NORMAN WEINER LECTURE:** Seven transmembrane receptors: something old, something new *Robert J. Lefkowitz* 8:30 AM – 9:20 AM Room 143A/B MP, ISTCP New roles for arrestins in signaling, trafficking and disease *J.L. Benovic* 9:30 AM – 12:00 PM Room 143A/B	DDDRA, DM, ISTCP, MP Recent developments in the understanding of the biology and physiology of the JAK family of tyrosine kinases *M.A. Sills* 3:00 PM – 5:30 PM Room 140A
Graduate Student Colloquium: Science, Scientist, Advocate: Making the Case for Increased Funding for Biomedical Research *J.S. Fedan, J.V. Barnett* 1:30 PM – 4:30 PM Room 140A	BEH, ISTCP The neurobiology of post traumatic stress disorder (PTSD) and implications for treatment *M. Davis, L.L. Howell* 9:30 AM – 12:00 PM Room 140A	BEH, DDDRA, ISTCP The biological "specifics" of the "non-specific" placebo response *J.D. Roache* 3:00 PM – 5:30 PM Room 140A	BEH, ISTCP, NEU Too much or too little: behavioral models and pharmacotherapies for eating disorders *M.L. Banks* 9:30 AM – 12:00 PM Room 143A/B	BEHAVIORAL PHARMACOLOGY DIVISION Pharmacokinetic approaches to the treatment of drug abuse *G.T. Collins, C.R. Schuster* 3:00 PM – 5:30 PM Room 140A	BEH, ISTCP, NEU Autism and PDD: neuropathology, pharmacotherapies, and new directions *E.A. Walker* 9:30 AM – 12:00 PM Room 140A	NEUROPHARMACOLOGY DIVISION Postdoctoral Award Finalists 3:00 PM – 5:30 PM Room 140A	Joint, NEU and DPE; BEH, ISTCP Chronobiology in the modern curriculum – addressing disease linkage and pharmacological approaches *M.W. Wood, S. Tischkau* 9:30 AM – 12:00 PM Room 143C	CVP, DDDRA, ISTCP Therapeutic angiogenesis *S. Sengupta, R. Sinha Roy* 3:00 PM – 5:30 PM Room 141
2011 Teaching Institute: Creating Educational Partnerships from High School to Graduate School *J.V. Barnett, G.A. Dunaway* 2:00 PM – 5:00PM Room 140B	**JULIUS AXELROD AWARD LECTURE** Structural insights into the dynamic process of GPCR activation *Brian Kobilka* 8:30 AM – 9:20 AM Room 143A/B **Julius Axelrod Symposium:** Structural approaches to understanding GPCR signaling *B. Kobilka* 9:30 AM – 12:00 PM Room 143A/B	MP, CVP, DDDRA, ISTCP, DPE G-protein coupled receptor signaling in stem cell biology *A. Pébay, S. Hooks* 3:00 PM – 5:30 PM Room 143A/B	CVP, ISTCP, WIP Advances in estrogen receptor signaling: potential implications for women's health *A. Cignarella, R.D. Feldman, V.M.Miller* 9:30 AM – 12:00 PM Room 140B	CARDIOVASCULAR PHARMACOLOGY DIVISION Trainee Showcase 2:30 PM – 4:30 PM Room 140B **BENEDICT LUCCHESI DISTINGUISHED LECTURE** Hydrogen sulfide and the cardiovascular system: deadly toxin or promising therapeutic *D. Lefer* 4:30 PM – 5:30 PM Room 140B	ISTCP, CVP Regenerative pharmacology and translational therapies for repair of nerve and muscle diseases/disorders *F.C. Barone, G.J. Christ* 9:30 AM – 12:00 PM Room 140B	DRUG METABOLISM DIVISION Early Career Achievement Award Lecture: (CYP)2B, or not 2B: that is the question *Emily Scott* 2:00 PM – 2:50 PM Room 140B DRUG METABOLISM DIVISION Platform Session & James A. Gillette Best Paper Award *S. Leeder, H. Swanson* 3:00 PM – 5:30 PM Room 140B	CVP, DDDRA, ISTCP, MP Cardiovascular KCNQ (Kv7) potassium channels: physiological regulators & targets for therapeutic intervention *K.L. Byron, D.L. Kunze* 9:30 AM – 12:00 PM Room 140B	TOX, DDDRA, ISTCP Pharmacogenomics to address adverse drug events *D.L. Mendrick, P.B. Watkins* 3:00 PM – 5:30 PM Room 143A/B

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	ISTCP, CVP, DM, TOX Therapeutic peptides: novel approaches in drug development *S. Alagarsamy, M.A. Holinstat* 9:30 AM – 12:00 PM Room 140B	DM, MP, TOX MicroRNA controlled regulation of drug metabolism and disposition *T.Yokoi, A. Yu* 3:00 PM – 5:30 PM Room 143C	PUBLIC AFFAIRS WORKSHOP Promise & partnership: FDA'S critical path initiative and its intersection with pharmacology *M.F. Jarvis* 9:30 AM – 12:00 PM Room 141	TOXICOLOGY DIVISION Hypoxia, hypoxia-inducible factor 1α, and toxic responses *P.E. Ganey* 3:00 PM – 5:30 PM Room 143C	TOX, DM Idiosyncratic drug reactions *C. Ju* 9:30 AM – 12:00 PM Room 141	INTEGRATIVE SYSTEMS, TRANSLATIONAL & CLINICAL PHARMACOLOGY DIVISION Young Investigator Platform Awards Session *A. Gaedigk, D. Marshall* 3:00 PM – 5:30 PM Room 141	ISTCP, CVP, DM, TOX Pharmacogenomics and personalized medicine *A. Gaedigk, J. Paul* 9:30 AM – 12:00 PM Room 140A	Joint, NEU and MP, BEH, ISTCP Physiology and pharmacology of trace amine associated receptors *R.R. Gainetdinov, K.A. Neve, S. Holtzman* 3:00 PM – 5:30 PM Room 143C
ASPET Business Meeting & Awards Ceremony 6:00 PM – 7:30 PM Hyatt, Independence Ballrooms F/G/H/ I	DPE, CVP, ISTCP Pharmacology for healthcare professionals: a thirst for knowledge *L. Wecker* 9:30 AM – 12:00 PM Hyatt, Independence H/I	DPE, CVP Creating effective questions for assessment and as aids in learning in today's pharmacology programs *J.L. Szarek* 3:00 PM – 5:30 PM Hyatt, Independence H/I	MOLECULAR PHARMACOLOGY DIVISION Postdoctoral Award Finalists *Keynote: P.A. Insel* 9:30 AM – 12:00 PM Room 143C	DRUG DISCOVERY, DEVELOPMENT & REGULATROY AFFAIRS DIVISION High impact pharmacologic screening in academia *J.S. Lazo* 3:00 PM – 5:30 PM Room 143A/B	TORALD SOLLMANN AWARD LECTURE Drug discontinuation effects are part of the pharmacology of a drug: cardiovascular drug discontinuations *Marcus M. Reidenberg* 8:30AM – 9:20 AM Room 143A/B CVP, MP Therapeutic targeting of epoxyeicosanoids *J.D. Imig, C. Lee* 9:30 AM – 12:00 PM Room 143C	TOX, DM, ISTCP Organ-specific toxicities caused by novel metabolic pathways *K. Skordos, D. Zhang* 3:00 PM – 5:30 PM Room 143C		Festschrift Symposium Celebrating More than Three Decades of Mentorship by Dr. Paul Insel *Session I: K. Meier and J. R. Jasper* *Session II: H. Motulsky and M. C. Michel* 1:00 PM – 5:00 PM Room 140B
Opening Reception 7:30 PM – 9:00 PM Hyatt, Constitution A		Graduate Student - Postdoc Best Abstract Competition 6:30 PM – 8:30 PM Hyatt, Independence Ballroom BCDE				WIP Career Roundtable 1:00 PM – 3:00 PM Room 142		Colloquium: RGS and AGS proteins in physiology and disease – Day 1 *J.R. Hepler, V. Zachariou* 2:00 PM – 5:00 PM Hyatt, Independence Ballrooms H/I

Posters will be displayed 7:30 AM – 6:00 PM on Sunday and Monday, 7:30 AM – 4:00 PM on Tuesday, and 7:30 AM – 3:30 PM on Wednesday. AUTHORS MUST BE PRESENT AT THEIR BOARDS FROM 12:30 PM UNTIL 2:45 PM.

Sunday Poster Sessions
Behavioral pharmacology – General 1
Drugs of abuse – Opioids
Drugs of abuse – Stimulants
Chemotherapy – Target-based diagnostics & therapeutics
Chemotherapy – Natural products & derivatives
Chemotherapy – Nucleic acid-based approaches to therapy
Drug discovery, development & regulatory affairs
Nuclear hormone receptor signaling
Cell surface receptors
GPCR – Ligand binding pharmacology
GPCR – Dimerization
GPCR – Desensitization/Trafficking
GPCR – Activation mechanisms
Endothelial cells – Oxidative stress
Endothelial cells – Regulation

Monday Poster Sessions
Behavioral pharmacology – General II
Drugs of abuse – Cannabinoids & ethanol
Memory/Cognition/Learning
Nicotine pharmacology
Neuropharmacology – Lipid
Neuropharmacology – General
GPCR – High throughput screening
RGS proteins – Pharmacological targeting
RGS proteins in physiology
Non-receptor α subunit regulators: molecular mechanisms
Diabetes
Pharmacology and women's health
GI pharmacology I
Vascular smooth muscle I
Vascular pharmacology – Endothelial kinases
Vascular pharmacology – Endothelial nitric oxide and guanyl cyclase
Immunopharmacology
Drug metabolism – Phase 1
Drug metabolism – Phase 2

Tuesday Poster Sessions
Neurogenesis and neuroplasticity
Neurotoxicity and neuroprotection
Neuropharmacology – Parkinson's
Neuropsychiatric disorders
Signal transduction – General
Cell signaling pathways
GPCR – Signaling pathways
G Protein alpha subunit signaling
G Protein beta/gamma subunit signaling
GPCR – Local signaling mechanisms
Kinases/Phosphatases
Drug metabolizing enzymes: expression/regulation
Drug transporters
Toxicology of oil dispersant exposure
Pulmonary pharmacology/toxicology
GI pharmacology II
Skeletal muscle pharmacology/toxicology
Smooth muscle pharmacology/toxicology
Vascular smooth muscle II

Wednesday Poster Sessions
Ion channels
TRP vanilloid channel
Neurotransmitter transporters
Autonomic regulation – Cardiovascular function
Cardiovascular protection
Cardiac injury response and mechanisms of protection
Mechanism of renal toxicity/protection
Renin-angiotensis system – Angiotensin receptors
Thrombosis/platelet aggregation
Gene regulation/expression

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2011 DIVISION ELECTION RESULTS

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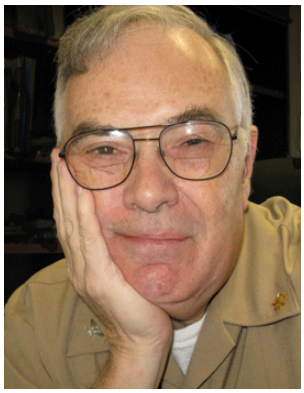

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Division Awards

During ASPET's Annual Meeting at Experimental Biology 2011, the Division for Drug Metabolism will present its Drug Metabolism Early Career Achievement Award to Dr. Emily E. Scott and the Division for Cardiovascular Pharmacology will present the Benedict Lucchesi Award in Cardiac Pharmacology to Dr. David Lefer. Information about each award and the recipients are given below. Each award presentation will be made at the recipient's lecture.

Emily E. Scott, Ph.D.
Drug Metabolism Early Career Achievement Award

Dr. Emily Scott, Associate Professor in the Department of Medicinal Chemistry at the University of Kansas is the recipient of the 2011 Drug Metabolism Early Career Achievement Award, established by ASPET's Division for Drug Metabolism to recognize excellent original research by early career investigators in the area of drug metabolism and disposition.

After graduating with a degree in Marine Biology from Texas A&M University in Galveston, Dr. Scott would earn her Ph.D. from Rice University. In 2004, following postdoctoral work at Rice and the University of Texas Medical Branch in Galveston, Dr. Scott accepted a faculty position as Assistant Professor at the University of Kansas.

Dr. Scott has made important contributions to the field of drug metabolism by publishing a series of pioneering papers on cytochrome P450 structure-function relationships. She has firmly established herself as one of the leading figures in P450 structure and mechanism studies. Her work has had a tremendous impact not only on the field of drug metabolism, but also on a number of other related research related areas of significant clinical and public health concerns, such as lung cancer chemoprevention and mechanisms of chemical toxicity.

Dr. Scott is also actively involved in the professional aspects of the drug metabolism field, serving as Councilor of ASPET's Drug Metabolism Division and having organized several symposia. She also actively participates in teaching at the University of Kansas and serves as Course Coordinator for several classes. Additionally, Dr. Scott directs Masters and Ph.D. research of several students at Kansas.

Dr. Scott's lecture, titled "(CYP)2B or Not 2B: That Is the Question," will be presented on Tuesday, April 12, from 2:00 to 2:50 p.m. in Room 140B of the Washington Convention Center.

David J. Lefer, Ph.D.
Benedict Lucchesi Distinguished Lectureship in Cardiac Pharmacology

Dr. David J. Lefer, Professor of Surgery and Director of the Cardiothoracic Surgery Research Laboratories at the Emory University School of Medicine, is the recipient of the 2011 Benedict Lucchesi Award in Cardiac Pharmacology. The biennial award was established to honor Dr. Lucchesi's lifelong scientific contributions to our better understanding and appreciation of the pharmacological treatment and prevention of cardiovascular disease and for his mentoring of many cardiovascular pharmacologists. Dr. Lefer was selected for this award in recognition of his scientific leadership in the field of ischemia/reperfusion (heart attacks) and cardio-protection and his commitment to mentoring the next generation of cardiovascular scientists.

Dr. Lefer received his Ph.D. from the Wake Forest University Bowman Gray School of Medicine. Following postdoctoral training at the Johns Hopkins School of Medicine, he received a faculty appointment as Assistant Professor at the Tulane University School of Medicine. Dr. Lefer moved to the LSU Health Science Center in Shreveport where he later became Professor with Tenure. Prior to coming to Emory, he was Professor with Tenure in the Division of Cardiology at the Albert Einstein College of Medicine.

Dr. Lefer is an internationally renowned leader in understanding the role of nitric oxide and other nitrogen oxide-metabolites in ischemia-reperfusion injury to the heart. Recently, his laboratory discovered cardio-protective actions of hydrogen sulfide in the context of acute myocardial ischemia-reperfusion injury and heart failure. His research has huge potential for clinical application in patients with

coronary artery disease. Dr. Lefer also serves as Co-Director of the NIH-funded Consortium for the Evaluation of Cardio-protective Agents that helps translate basic science insights into clinical practice.

Dr. Lefer is actively involved in teaching and mentoring of graduate students, postdoctoral fellows and junior scientists, many of whom have begun to make an impact in cardiovascular research. He has received many awards in recognition of his outstanding research including the ASPET Young Investigators Award in Cardiovascular Pharmacology and the Merck Young Investigators Atherosclerosis Award.

Dr. Lefer's lecture is entitled "Hydrogen Sulfide and the Cardiovascular System: Deadly Toxin or Promising Therapeutic," and will be presented on Monday, April 11, from 4:30 to 5:30 pm in Room 140B of the Washington Convention Center.

RUFFOLO CAREER ACHIEVEMENT AWARD ANNOUNCED

Robert R. Ruffolo Career Achievement Award in Pharmacology

ASPET is pleased to announce the creation of a new award to recognize career achievements in pharmacology at the mid- to late-career stage. The award is made possible through a generous contribution from long-time ASPET member **Dr. Robert Ruffolo**. The award will be presented annually beginning in 2012 and will consist of a medal, a cash award of $2500, and complimentary registration and travel for the winner and spouse to attend the ASPET annual meeting to receive the award.

Nominees for this award must be at the height of their careers (typically mid- to late-career scientists) and have made significant contributions to any area of pharmacology, such that their names are well-known in the community but who are not so senior that all of their scientific contributions are behind them. Nomination information and guidelines will be published in the June issue of *The Pharmacologist* and on the ASPET web site.

STAFF NEWS

ASPET Welcomes Mary Blackwood

Mary Blackwood joined the ASPET staff on March 1 as an Editorial Coordinator. Mary will have primary responsibility for managing the peer review process for *Drug Metabolism and Disposition* and will help Cassie Wood with *JPET*. Mary was formerly a vice president for a printing company where she worked on design, prepress, project management, and accounting. She has also worked in positions involving general ledger accounting, office management, and public relations. Most recently, she was an early intervention instructional therapist where she used one-to-one positive behavioral therapy with children with autism. In addition to working at ASPET, Mary is working toward a graduate degree in Marriage and Family Therapy.

Journals

Journals Archived

ASPET recently joined CLOCKSS. As described by its executive director, Randy S. Kiefer, CLOCKSS is "a nonprofit joint venture between the world's leading scholarly publishers and research libraries whose mission is to build a sustainable, geographically distributed dark archive with which to ensure the long-term survival of Web-based scholarly publications for the benefit of the greater global research community."

CLOCKSS stands for Controlled Lots of Copies Keeps Stuff Safe. In the hard copy world, storing books and journals in multiple libraries assures that they will not be lost forever if some copies are destroyed or damaged. If one library burns down, others have copies of the same content so that content remains available. CLOCKSS electronically duplicates this system with its distributed network of redundant archive nodes located at 12 major research libraries around the world. All of the Society's journals' content is stored at each node. The nodes automatically check each other to assure that the content they store is complete. If any node is missing content, the others restore it.

CLOCKSS will make online content available to the world should that content no longer be available through its usual means. Content becomes available only when a "trigger event" occurs, which is why CLOCKSS is called a dark archive. Trigger events include a publisher going out of business, a journal ceasing publication, or the servers that normally house the content going down long term or permanently.

As a CLOCKSS participant, ASPET is committed to CLOCKSS for preservation of the Society's journals, and ASPET is ensuring that an author's work will be maximally accessible and useful over time. The Society's rich archive of pharmacological knowledge is being preserved so that researchers can continue to build upon it. This is as much a commitment to the future as to the past.

Price Increases

Several publications-related prices have been increased. The Board of Publications Trustees approved increases to the following charges during a conference call meeting on March 1.

The pay-per-view fee for online articles has been increased from $10 per article for *JPET*, *Molecular Pharmacology* and *Molecular Interventions* to $20; the fee for *Drug Metabolism and Disposition* and *Pharmacological Reviews* increased from $15 to $25. The new fees went into effect on March 2. They apply only to content published before 1997 and within the most recent 12 months. All other content is freely accessible, and the manuscript version of articles published in *JPET*, *MOL*, and *DMD* continues to be free as Fast Forward publish-ahead-of-print articles.

The copyright fee for all journals will increase from $20 to $25. This fee applies to photocopies of articles. Classroom photocopying remains free as long as students are charged no more than the cost of making the copies.

The manuscript submission fee will increase from $50 to $75 effective April 15. This fee is charged for submissions to *JPET*, *MOL*, and *DMD*. As before, there is no fee for invited articles such as reviews, minireviews, and perspectives in any ASPET journal.

Page charges for *JPET*, *MOL*, and *DMD* will increase from $80 to $90 per page for nonmembers and from $40 to $50 per page for members. This fee will go into effect for articles appearing in the July issues. Similar to the manuscript submission fee, page charges are not levied against invited articles in any ASPET journal.

The fee to reproduce a figure or table for promotional or advertising purposes will increase from $150 to $200 per use.

ASPET has not raised these fees in several years. The manuscript submission fee and page charge fee represent only a portion of the actual cost of peer review and publication.

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Public Affairs/ Government Relations

NIH Faces Potential for Big Cuts but Funding Situation Still In Flux

At the moment, the funding outlook for NIH remains fluid even though a new Continuing Resolution has finally been approved that funds the government through March 18. The week of February 7, the House Appropriations Committee had provided a partial list of cuts that included a $1.6 billion reduction in the NIH budget that was to be included in an upcoming Continuing Resolution (CR) bill that would have covered the remainder of FY 2011. This proposal would have effectively frozen the agency's budget at the FY 2010 level (the proposed cut was based on the President's FY'11 level that was never enacted). The "new" CR through March 18 keeps the NIH at the current FY'10 level. However, to pass the short term extension through March 18, Democrats and Republicans agreed to cut $4 billion from various programs already targeted by the Administration, but none affecting biomedical research (a possible one-month extension that could include a total of $8 billion or more in cuts had also been discussed). The FY'11 fiscal year ends September 30 and some final agreement must be agreed upon. But until then, another short-term CR is likely although there is growing pressure to finish the FY'11 subjecting Congress and financial markets to these budget negotiations every two weeks. While additional cuts in overall spending may mean further reductions to the NIH budget for FY'11, the agency may be spared from a significant reduction in its funding, although even a freeze at the FY'10 level for the remainder of the FY'11 year is going backwards. ASPET members received our legislative Alert on February 10 asking they contact their Members of Congress and their staff to inform them about the benefits that NIH funded research provides to your community and nation and stating your opposition to the proposed budget cuts to NIH. That alert, background information and talking points on the benefits of NIH funding can be found on the Advocacy link on the ASPET web site.

R Releases 2011 State Law Rankings

The National Association for Biomedical Research (NABR) has released its first annual report ranking all 50 states on the relative strength of their laws designed to protect biomedical research facilities and researchers. Available to NABR members only, the report uses a comparative multifactor approach to analyze each state's laws specifically focusing on the following: laws designed to protect research facilities from break-ins and threats, exemptions for medical and scientific research in animal cruelty laws, exemptions for research records and unpublished research in state open records laws, harassment laws, and various other state-specific laws that can be used to protect researchers and research facilities from threats posed by animal rights extremists. The top five states with the strongest laws related to the protection of research facilities and researchers include: 1. New Jersey, 2. South Dakota, 3. Georgia, 4. Kansas, 5. And Oregon.

These five states each have strong research facility protection laws, comprehensive exemptions for research in their state animal cruelty and public records laws, and harassment laws that criminalize a wide range of tactics used by animal rights extremists to harass biomedical researchers.

FASEB Reports

FASEB has released its annual report to Congress, "Federal Funding for Biomedical & Related Life Sciences Research, FY 2012." The report makes annual funding recommendations for the NIH, NSF, DOE's Office of Science, and the USDA Agriculture and Food Research Initiative. For the NIH, FASEB recommends that the agency receive $35 billion in FY 2012.

FASEB's survey of students and educators who participated in a NIH summer research program funded through the American Recovery and Reinvestment Act (ARRA) reveals how the program helped more than 2,000 participants develop research and laboratory skills, influenced students' decisions to pursue a career in science, and enhanced the work of science educators:

Both reports can be viewed at:

www.aspet.org/PolicyUpdatesNews.aspx?id=2024

RGS & AGS Proteins in Physiology & Disease Colloquium

April 13-14, 2011, Washington, D.C.

Chairs: John R. Hepler, Emory Univ & Venetia Zachariou, Univ of Crete
This is a Satellite Meeting to Experimental Biology 2011

RGS/AGS Proteins in Physiology & Disease

Visual System

R7 RGS Regulation of Class A & Class C GPCR Pathways *(T. Wensel, Baylor College of Medicine)*
AGS/PcP2/Go Signaling in Retina *(N. Vardi, Univ of Pennsylvania)*

Inflammation and Cardiovascular Disease

RGS in Bronchial Smooth Muscle/Asthma *(K. Druey, NIAID/NIH)*
RGS Modulation of Myocyte Stress Responses in Heart Disease *(D. Kass, Johns Hopkins Univ)*
RGS Proteins in Cardiovascular Function *(S. Heximer, Univ of Toronto)*

Cancer and Neoplastic Disease

RGS Proteins in Ovarian Cancer *(S. Hooks, Univ of Georgia)*
AGS3 & Polycystic Kidney Disease *(P. Jackson, Genentech)*
AGS Protein Pins in Asymmetric Cell Division *(C. Johnston, Univ of Oregon)*

CNS Disorders

RGS4 in Bipolar Disorders/Schizophrenia *(A. Hegde, Wake Forest Univ)*
RGS10 in Microglia & CNS Inflammation *(M. Tansey, Emory Univ)*

RGS & AGS Proteins & Their Partners as Drug Targets

The RGS/AGS/G Protein Interface as Drug Targets

RGS Proteins as Drug Targets *(R. Neubig, Univ of Michigan)*
Structure/Function of RGS & AGS Proteins *(D. Siderovski, Univ of North Carolina-Chapel Hill)*

Genetic Systems and Structure/Function

AGS-3 Regulates $G\alpha_o$ Signaling in *C. elegans* to Allow Behavioral Responses to Food Deprivation *(M. Koelle, Yale Univ)*

Structural Analysis of RGS Protein Interactions *(J. Tesmer, Univ of Michigan)*

RGS/AGS Binding Partners and Signaling Complexes

Ric8A Regulation of AGS/G Protein Complexes *(G. Tall, Univ of Rochester)*
Coupling of RGS & AGS Proteins with GPCRs *(J. Blumer, Medical Univ of South Carolina)*

For more information and to register, visit
www.aspet.org/Meetings/RGS_AGS_Proteins

Annual Meeting Report

The Great Lakes Chapter of ASPET held its 23rd Annual Scientific Meeting on June 18, 2010 at the University of Chicago Gleacher Center in downtown Chicago. Over 100 pharmacologists, including 24 undergraduate and 27 graduate students, attended the meeting. The attendees included researchers from the University of Illinois at Chicago, Rush University, Rosalind Franklin University, Midwestern University, Northwestern University, Lake Forest College, Benedictine University, Loyola University, Indiana University School of Medicine, Abbott Laboratories, and Astellas Pharmaceuticals. The focus of the 2010 symposium was "Targeting Apoptotic Pathways in Drug Development" and featured an outstanding panel of both national and local speakers. The keynote address, "How the Cells Die," was delivered by Douglas R. Green of St. Jude Children's Hospital. Other speakers and the titles of their presentations were "Apoptosis Resistant Cells in Pulmonary Arterial Hypertension" by Norbert R. Voelkel, MD, Virginia Commonwealth University; "The Death Receptor CD95/Fas Promotes Tumor Growth" by Marcus E. Peter, PhD, Northwestern University; and "Targeting Cell Death in Cancer" by Vincent L. Cryns, MD, Northwestern University.

In addition to the outstanding speakers, the meeting included a postdoctoral symposium, a career workshop (lunch-and-learn format), vendor exhibits, and a poster session that included 31 posters. Six posters were presented by undergraduate students, 14 by graduate students, 4 by postdocs, and the remaining by faculty members or research scientists at pharmaceutical companies. A panel of judges interacted with the poster presenters and cash prizes were given to the top posters in the following categories:

Keui Tseng at the registration desk.

Undergraduate Students

First Place: Alina Konnikova, Lake Forest College, "Autophagic Regulation of Alpha-Synuclein Pathotoxicity Properties in Budding Yeast Reveals Unexpected Complexities"

Second Place: Ashleigh Porter, Lake Forest College, "Possible New Cancer Treatments: Ribosome Biogenesis as an Unexplored Target"

Third Place: Natalie Simak, Lake Forest College, "Cocaine Experience During Adolescence Selectively Arrests the Maturation of Parvalbumin Positive/GABAergic Fast-Spiking Interneurons in the Prefrontal Cortex"

Graduate Students

First Place: Bethany E. White, University of Illinois at Chicago, "Overexpression of PKCα in Breast Cancer Cells Induces Migration, Invasion and E-cadherin Downregulation"

Second Place: Tui-Ting Ho, University of Illinois at Chicago, "Knockdown of Splicing Factor SRp20 Induces Apoptosis in Ovarian and Breast Cancer Cells"

Third Place: Shannon Blume Rice, Rosalind Franklin University, "Targeting Soluble Guanylyl Cyclase (sGC)-cGiMP Signaling Pathway in Parkinson's Disease"

Dr. Sam Sivam with the winning poster presenters from the graduate student and postdoc categories.

Post-doctoral Fellows

First Place: Madhuchhanda Kundu, University of Illinois at Chicago, "Estradiol Induced Regression of T47D:A18 PKCα Tumor Involves Translocation of Estrogen Receptor Alpha from the Nucleus to the Cytoplasm"

The GLC-ASPET Executive Committee gratefully acknowledges financial support for the meeting from ASPET, Loyola University (Department of Pharmacology), Medical College of Wisconsin (Department of Pharmacology), Rosalind Franklin University of Medicine and Science (Department of Molecular and Cellular Pharmacology), and Rush University (Department of Pharmacology).

Left: Attendees waiting for the afternoon symposium to begin. Right: Walt Prozialeck (left) and Alex Mayer (center) with poster presenters from Abbott Laboratories.

We also gratefully acknowledge the following for their support through in-kind contributions: Midwestern University (Chicago College of Osteopathic Medicine, Department of Pharmacology), Dr. Kuei Tseng (Rosalind Franklin University), and Victoria Sears (Midwestern University, Department of Pharmacology).

In addition, we would like to thank the following vendor exhibitors for their support: Sartorius, Fisher Scientific, Millipore Corp., Promega, Binder, and VWR International, LLC.

Business Meeting

As is our tradition, following the afternoon symposium, a short business meeting was held. The results of the 2010 election were reported, and Dr. Ajay Rana, Professor of Pharmacology at Loyola University, was elected to the office of Treasurer and will be replacing our long serving Treasurer, Dr. Subbiah (Sam) Sivam. Sam will remain part of our organization as a member of the GLC Nominating Committee. Dr. Robin Pals Rylaarsdam, Professor of Biology at Benedictine University, was elected to serve as a Councilor and will be replacing Shubhik DebBurman (Lake Forest College).

Following the reporting of the election results, winners of the poster competition were announced. All participating undergraduate poster presenters were awarded a certificate, which was presented by Dr. Shubhik DebBurman (Lake Forest College). The first place undergraduate poster presenter received a prize of $200, second received $100, and third received $50. The first place poster presenters in the graduate and post-doc categories each received a prize of $300. The presenter of the second place poster at the graduate level received $200 and the third place recipient was awarded $100.

Following the award presentation, the GLC-ASPET Executive Committee and the invited speakers enjoyed a post-meeting dinner at Emilio's Tapas in downtown Chicago.

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Poster Abstracts Presented at the 2010 Annual Meeting of the Great Lakes Chapter

June 18, 2010, University of Chicago, Chicago, IL

Cocaine Experience During Adolescence Selectively Arrests the Maturation of Parvalbumin Positive/GABAergic Fast-Spiking Interneurons in the Prefrontal Cortex. Natalie Simak[1,2]*, Daryn K. Cass[1]*, Shannon Blume[1], and Kuei Y. Tseng[1]; [1]Department of Cellular and Molecular Pharmacology, RFUMS/The Chicago Medical School and [2]The RFUMS-Lake Forest College Research Program, North Chicago, IL 60064. **Contributed equally to this work.*

Experience to a drug of abuse during adolescence significantly increases the risk for addiction. However, the mechanisms underlying the increased susceptibility to drug addiction during the periadolescent transition remain elusive. Our recent study in rodents showed that non-contingent repeated cocaine experience elicited differential changes in prefrontal cortical metabolic activity, an effect that is age dependent. Whereas activity in the prefrontal cortex increased following 3 weeks withdrawal from cocaine injection during adolescence (PD35-40), an overall frontal cortical metabolic inhibition was observed in the adult (PD75-80) group. We therefore hypothesized that such a distinctive age-dependent prefrontal neuroadaptation observed following cocaine exposure could be due to a developmental interference of local/cortical interneuronal maturation/function that typically take place during the periadolescent transition period. Among cortical GABAergic interneurons, the parvalbumin (PV)/fast-spiking cell type is of particular interest due to its role in prefrontal functioning. In the present study, we assessed the impact of repeated cocaine injection and asked whether the age at which the drug exposure takes place plays a role in altering interneuron function in the prefrontal cortex. PV interneurons function was assessed by means of immunohistochemical measures. PV is a calcium binding protein used by fast-spiking interneurons and its immunoreactivity is positively correlated to neuronal activity. We observed that PV-immunoreactivity in the normal prefrontal cortex follows a distinctive developmental trajectory with the lowest activity in juveniles and maximal activity in adulthood. In the cocaine group, we found that such a developmental enhancement of prefrontal PV-immunoreactivity was lacking when repeated cocaine experience occurs during adolescence. Interestingly, cocaine exposure did not affect prefrontal cortical PV staining in the adult group. Our results indicate that exposure to cocaine during adolescence prevents the normal developmental facilitation of fast-spiking interneuron function in the prefrontal cortex. Correlation analyses further indicate that such a developmental dysregulation of prefrontal interneuronal circuits could trigger and sustain a disinhibited prefrontal cortex, a prefrontal state that may contribute to the increased risk for drug abuse in adolescence. Supported by Rosalind Franklin University (KYT) and National Institute of Health Grants DA004093 (KYT) and MH086507 (KYT).

Subchronic Cadmium Exposure Results in Decreased Insulin Secretion and Hyperglycemia Prior to Onset of Renal Dysfunction in Rats. Joshua R. Edwards*, Peter Lamar, and Walter C. Prozialeck; Department of Pharmacology, Midwestern University, Downers Grove, IL 60515

Several recent epidemiological studies have shown significant associations between exposure to the environmental contaminant cadmium (Cd), decreased insulin secretion and the development of diabetes. To further examine the diabetogenic effects of Cd, Sprague/Dawley rats were given subcutaneous injections of Cd in the form of $CdCl_2$ at a dose of 0.6 mg/kg, 5 days per week for 12 weeks. Weekly urine samples and fasting blood glucose data were collected. Significant differences in fasting blood glucose levels from control (vehicle saline injected) vs Cd treated animals were detected several weeks prior to statistically significant changes of overt signs of renal dysfunction such as polyuria. Furthermore, at week 12 the mean fasting insulin value from Cd treated animals was significantly less (~50%) of that of control values. Examination of histological slides showed evidence that Cd caused retraction and separation of pancreatic β-cells. This could be especially significant because others have reported that a loss of cell-cell adhesion in pancreatic β-cells and the relocalization of proteins associated with cell adhesion, specifically E-cadherin, results in decreased insulin release. Results from this study provide additional evidence that Cd exposure may be a contributing environmental factor for the development of diabetes. This study also suggests that disruption of cell-cell adhesion in pancreatic β-cells may be an important mechanism of Cd-induced hyperglycemia and decreased insulin release. Supported in part by RO1ES006478 from the NIEHS.

Periadolescent Facilitation of NMDA-Dependent Synaptic Function in the Prefrontal Cortex: Role of NR2B-Containing Receptors. Pascal Accoh[1,2*], Natalie Simak[1,2*], Lijun Heng[1], and Kuei Y. Tseng[1]; [1]Department of Cellular and Molecular Pharmacology, RFUMS/The Chicago Medical School and [2]The RFUMS-Lake Forest College Research Program, North Chicago, IL 60064.
**Contributed equally to this work.*

Dopamine modulation of prefrontal cortical (PFC) function is critical for working memory and decision-making, functions that become enhanced late in adolescence. However, little is known on the mechanisms that support this facilitation. We hypothesized that maturation of dopamine-dependent actions in the PFC occurs late in adolescence as a result of changes in the dominance of different postsynaptic signaling mechanisms. Here, we investigate how postsynaptic NMDA-dependent synaptic transmission changes during the periadolescent transition by examining the amplitude and duration of evoked excitatory postsynaptic current (EPSC) recorded at -70 and +60 mV in PFC pyramidal neurons. Cells recorded from the late adolescent (PD>42) PFC exhibited NMDA currents significantly longer in duration without apparent changes in amplitude or AMPA EPSC kinetics. We next examine whether a change in the distribution of NMDA receptor subunits accounts to the slower decay kinetic observed. Immuno-

histochemical labeling of NMDA receptor subunits was conducted in PFC sections from pre to postadolescent ages, and relative changes of NR2A and NR2B immunoreactivity were assessed by densitometry measures. We found that across postnatal development, PFC NR2B levels (NR2B/NR2A ratio) were lower in preadolescent rats and increased toward adult levels during late adolescence. Subjacent cortical regions such as the motor, somatosensory, and orbitofrontal cortices follow a different developmental trajectory. Together, these results indicate that the periadolescent facilitation of NMDA function in the PFC is region specific. A relative augmentation of NR2B-containing receptors underlying the enhanced NMDA synaptic transmission may account to maturation of dopamine actions in the PFC during the transition to adulthood. Supported by Rosalind Franklin University (KYT) and National Institute of Health Grants DA004093 (KYT) and MH086507 (KYT).

Knockdown of Splicing Factor SRp20 Induces Apoptosis in Ovarian and Breast Cancer Cells. Tsui-Ting Ho*, Ahmet Dirim Arslan*, Xiaolong He, and William T. Beck; Department of Biopharmaceutical Sciences, College of Pharmacy, and Cancer Center, University of Illinois at Chicago, Chicago, IL 60612

Apoptosis (programmed cell death) is a form of cell death characterized by cell shrinkage and nuclear condensation. Past studies have revealed that programmed cell death is under complex regulation. It has been reported that a number of programmed cell death regulatory genes are expressed as functionally distinct or even antagonistic isoforms as a result of alternative splicing. Many studies have reported cancer-specific alternative splicing as well as aberrant splicing factor expression in tumors. Splicing factor SRp20 belongs to a family of serine–arginine-rich proteins important for a variety of cellular functions surrounding mRNA including constitutive and alternative splicing, transport, translation, and degradation as well as genome stability. Our previous work revealed that the expression of SRp20 was upregulated in epithelial ovarian cancer and immortalized human mammary epithelial cells. To investigate the involvement of SRp20 in ovarian and breast cancer, we established stable cell lines carrying doxycycline (Dox) inducible SRp20shRNA. Knockdown of SRp20 suppressed the cell growth in established sublines. We next asked if SRp20 knockdown effect on growth inhibition was by inducing apoptosis. We found the number of apoptotic cells were remarkably increased after Dox treatment by nuclear staining. We then examined the activation of caspase cascade by Western Blotting analysis, and we showed cleaved caspases and decreased expression levels of Bcl-2. Taken together, our results indicate that SRp20 plays a major role in breast and ovarian cancer cell survival, and it may represents a potential new therapeutic target for the treatment of breast and ovarian cancers.

*Both authors contributed equally to this work.

Inhibition of Lactate-Producing Glycolysis Increases Antidiabetic Drug-Induced Vasorelaxations and Blocks Sildenafil's Attenuation of Them. Jacob D. Peuler* and Laura E. Phelps; Department of Pharmacology, Midwestern University, Downers Grove, IL 60515

Sildenafil is used to treat erectile dysfunction in men with type 2 diabetes (T2D). Hypertension is common in T2D but sildenafil attenuates vasorelaxant actions of metformin, pioglitazone and rosiglitazone: 3 antidiabetic (AD) drugs often used to improve glucose metabolism in T2D. Previously, to assess the glucose dependence of this effect, vascular rings from rat tail arteries were treated with each AD drug ± sildenafil. After 4 hours, all rings were contracted with norepinephrine (NE). With extracellular glucose present, all 3 AD drugs relaxed NE contractions and sildenafil attenuated such relaxations. With glucose omitted, relaxant actions of the AD drugs were notably increased and sildenafil failed to attenuate them. More recently, specific inhibition of only lactate-producing glycolysis pathways with iodoacetate (30 micromolar) exerted similar results. We conclude that, in addition to vascular smooth muscle relaxant mechanisms, these 3 AD drugs also activate contraction-enhancing mechanisms, which are dependent on specific glycolysis pathways and mask the full potential of the relaxant mechanisms. Thus, sildenafil's attenuation of AD drug-induced vasorelaxations may not only involve interference with their relaxant mechanisms but also facilitation of specific glycolysis-dependent contraction-enhancing mechanisms. Support: Midwestern University.

Gene Expression Patterns in Pregnancy-Associated Breast Cancers. Szilard Asztalos[1*], Peter H. Gann[2], Meghan K. Hayes[1], Larisa Nonn[2], Elizabeth L. Wiley[2], Seema A. Khan[3], Barbara Susnik[3], Leslie K. Diaz[4], Nilanjana Banerji[4], Rutu Joshi[1], and Debra A. Tonetti[1]; [1]Biopharmaceutical Sciences, [2]Pathology, University of Illinois at Chicago, Chicago, IL 60612; [3]Northwestern University, Chicago, IL 60611; [4]Abbott Northwestern Hospital, Minneapolis, MN 55407. Work performed at UIC.

Introduction: Epidemiological studies have shown that women of all ages experience a transient increase in the risk of developing breast cancer following pregnancy and that pregnancy-associated breast cancers (PABCs) have a worse prognosis than those detected in nulliparous women (Schedin 2006). One hypothesis suggests that molecular events associated with mammary gland involution stimulate tumor growth and metastasis (Schedin 2006). We previously found evidence for increased expression of inflammation related genes in the human breast following pregnancy (Asztalos et al 2010). In this study we employed a gene set (59 genes) comprised of inflammation, extracellular matrix remodeling, angiogenesis and breast cancer biomarker genes in human breast cancer tissue to investigate the role of these processes in pregnancy-associated breast cancers.

Patients and Methods: Women ≤ 45 years of age with breast cancer were eligible for the study, and were categorized as either nulliparous (N=19), recently pregnant (N=17) or distantly pregnant (N=17). Tumor regions were isolated from formalin-fixed paraffin embedded tissues using Laser Capture Microdissection, followed by RNA extraction and cDNA synthesis. Genes of interest were preamplified linearly, followed by real time PCR. Gene expression between groups was compared using either t-test, or unsupervised hierarchical clustering.

Results: When recent and distant PABCs were combined and compared to the nulliparous group, we observed a number of significantly differentially regulated genes, such as CXCL1, THBS1, ESR1, ELN, TGFB3, ADAM9, IL11 and CDH1. When concerted gene expression was compared by non-supervised hierarchical clustering, we found that PABCs had more frequent associations

with inflammation associated gene-expression patterns than those of nulliparous patients.

Conclusions: This is the first study to address the hypothesis suggesting the role of post-pregnancy events in the etiology and aggressiveness of PABCs by looking at a set of human breast cancers. We show that the cancers of patients detected post-pregnancy are more frequently associated with an inflammation-associated gene expression pattern, than those of nulliparous women. The exact role of inflammation in the aggressiveness of PABCs remains to be further elucidated.

Autophagic Regulation of Alpha-Synuclein Pathotoxicity Properties in Budding Yeast Reveals Unexpected Complexities. A. Konnikova*, D. Sanchez, R. Choi, K. Ahlstrand, P. Sullivan, and S. DebBurman; Lake Forest College, Lake Forest, IL, 60045

Parkinson's disease (PD) is an incurable neurodegenerative disease characterized by the selective loss of dopaminergic neurons in the midbrain. This cell death is likely due to misfolding and aggregation of the protein alpha-synuclein. A prevalent hypothesis is that accelerating the degradation of alpha-synuclein can decrease cellular toxicity. Autophagy is a highly evolutionary conserved catabolic mechanism in eukaryotes used to recycle cell's own components such as damaged proteins. Pharmacological research implicates autophagy-based lysosomal degradation of alpha-synuclein, but genetic evidence is still lacking. We hypothesized that basal autophagy protects cells from alpha-synuclein toxicity and tested it in a budding yeast model in strains deleted for individual genes that control the three steps of autophagy: nucleation, expansion, or fusion. Thus far, we have examined four nucleation genes (Atg11, Atg 17, Atg 13, and Atg1), four expansion genes (Atg18, Atg4, Atg3, and Atg2), and two fusion genes (Vam3 and Vam7). We predicted accumulation of alpha-synuclein, its altered cellular localization, and increased cellular toxicity, in at least some of these strains. In fact, none of the gene deletions induced alpha-synuclein dependent cellular toxicity. However, alpha-synuclein localization showed subtle yet consistent changes when some Atg genes were absent. Specifically, in the absence of Atg11 and Atg2, alpha-synuclein aggregated and did not maintain plasma membrane localization. Without Atg17, alpha-synuclein became more cytoplasmically diffuse and less plasma membrane localized. To further our understanding of authophagy-mediated alpha-synuclein degradation, we will continue analyzing knockout strains for the remaining genes that compromise autophagy.(Supported by APDA, NSF-MRI, NSF-CCLI, & NIH R15)

Duloxetine Relieves Osteoarthritic Pain in a Preclinical Rat Model. Erica J. Wensink*, Anita K. Salyers, Madhavi Pai, La Geisha Lewis, Cenchen Zhan, Michael W. Decker, Peer B. Jacobson, Gin .C. Hsieh, and Jorge D. Brioni; Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064

Duloxetine (Cymbalta), a selective and potent (5-HT) norepinephrine (NE) reuptake inhibitor, has recently been approved for the treatment of neuropathic pain. New clinical data also suggests that patients with osteoarthritis (OA) pain of the knee treated with duloxetine reported significant pain relief when compared to placebo. Although the mechanism of action underlying pain relief with duloxetine is not completely understood, it is thought to be related to its ability to increase NE in the central nervous system. In the present study, the effects of duloxetine were characterized in preclinical models of monoiodoacetate (MIA)-induced OA pain in rats. Orally administered duloxetine at 30 mg/kg produced full efficacy in a rat model of OA pain (ED50 = 10 mg/kg p.o.; plasma level for efficacy at the ED50 = 150 ng/ml) as evaluated by hindlimb grip force. The analgesic efficacy of duloxetine was retained in this model upon twice-daily repeated administration of 1, 3, and 10 mg/kg p.o. for 11 days. Duloxetine produced full efficacy when administered intracerebroventricularly (i.c.v.) to supra-spinal site at 3 µg/rat. As well, the compound was efficacious when injected intrathecally (i.t.) to spinal levels. The systemic analgesic action produced by duloxetine (30 mg/kg p.o.) was blocked by pretreatment with the α-adrenergic antagonist phentolamine (i.p.). However, the systemic effect was only partially blocked by i.t. phentolamine. In contrast, the effect of celecoxib (a clinical NSAID used for OA pain) was not reversed by the pretreatment of phentolamine. These results suggest that the analgesic action of duloxetine in OA rats involves activation of the noradrenergic pathways and its analgesic efficacy is primarily mediated at central sites.

Gastric Vagal Fluorogold Labeled Neurons are Reduced in Obese Diabetic Agouti Mice. R. M. Fullmer*[1], J. Cellini[2], and K.J. LePard[2]; Biomedical Sciences Program, College of Health Sciences[1], Department of Physiology , College of Osteopathic Medicine[2], Midwestern University, Downers Grove, IL

Diabetes can cause gastric emptying and motility dysfunctions. Gastric motility dysfunction can lead to additional health complications. Gastric emptying is controlled by parasympathetic and enteric nerves which innervate the stomach. Research suggests diabetes causes impairment or neuropathy in the autonomic nervous system leading to dysfunction. This study examined the effects of diabetes duration of 8, 16, and 24 weeks on vagal gastric neurons found in the Dorsal Motor nucleus (DMN) in obese type 2 diabetic mice (KK.CgA^{y}/J) and age-matched controls (KK). Fluorogold (FG) dye was used as a retrograde neural tracer to label efferent DMN neurons innervating the ventral fundus of the stomach. Tracer was injected into the fundus under ketamine/xylazine anesthesia. After 5 days, animals were perfused with fixative, the brain removed, and brainstem sectioned. Tracer-labeled neurons were counted in 5 sections caudal and rostral to the area postrema. At 8 and 16, but not 24 weeks, diabetic mice were heavier (43±1*g, 46±1*g, 43±1g) than controls (35±1g, 38±1g, 41±1g) (*p<0.05). Diabetic mice at 8 and 24 weeks had a higher HbA1c (8.0±0.5%*, n=4; 5.9±0.2%*, n=5) as compared to controls (5.0±0.1%, n=5; 5.0±0.1%, n=4; *p<0.05). The number of FG-labeled neurons was decreased in each brainstem section from diabetic animals at 8, 16, and 24 weeks as compared to con-

trols (*p<0.05). The total sum of neurons for all 5 sections was decreased in diabetics (146±4*, n=4; 143±10*, n=4; 133±14*, n=4) as compared to controls (211±5, n=4; 201±8, n=3; 212±9, n=3; *p<0.05). Within control or diabetic group, the total neuron sums were similar at 8, 16, and 24 weeks. Decreased labeling was observed in the diabetics as compared to the controls and was not related to age or duration of diabetes at 8, 16, or 24 weeks of the disease state. At 8 weeks of diabetes, neural differences were already evident and did not progressively deteriorate as diabetes duration increases. Funding supported by College of Health Sciences, Biomedical Masters Program, and ORSP at MWU.

Insight into Parkinson's Disease: Is Alpha-Synuclein Degradated by Endocytosis? M. Senagolage*, J. Perez, A. Ayala, and S. Debburman; Biology Department, Lake Forest College, Lake Forest, IL 60045

Parkinson's disease (PD) is an incurable and fatal neurodegenerative disease linked to the death of midbrain dopaminergic neurons. The accumulation and impaired degradation of the aggregated alpha-synuclein protein is thought to contribute to this cell death. Therefore, to develop the ability to selectively accelerate alpha-synuclein degradation is of therapeutic interest. Increasing evidence points to the lysosome as a site for alpha-synuclein degradation, but the exact route(s) are still being determined. In a budding yeast (*Saccharomyces cerevisiae*) model, we tested the hypothesis that the multivesicular body (MVB)/endosome pathway is a route for degradation of wildtype (WT) and familial mutant E46K alpha-synuclein. Specifically, we evaluated if three PD-related a-synuclein characteristics: cellular localization, accumulation, and toxicity, altered or worsened in yeast strains that were deleted for genes that encode for proteins that form the pre-ESCRT step and the ESCRT-I, -II, and -III complexes of the MVB pathway. We report several findings. First, all thirteen MVB genes that were evaluated affected at least one alpha-synuclein characteristic thus providing genetic evidence for the endosome pathway as a regulator of alpha-synuclein pathobiology. Secondly, these genes regulated each a-synuclein property examined to differing extents. alpha-Synuclein localization was the most widely altered property affected by twelve gene deletions. Its accumulation was enhanced by six gene deletions. Lastly, the lack of two genes (vps24 and vps28) modestly enhanced alpha-synuclein-dependent toxicity. Together, our data suggests that both WT and E46K alpha-synuclein are degraded by the lysosome via the endocytosis route.

The Effect of *Microcystis aeruginosa* Lipopolysaccharide (LPS) on Neonatal Rat Brain Microglia Cytokine and Chemokine Generation. Jonathan A. Clifford[1*], Nikunj Patel[1], Mary L. Hall[1], Keith B. Glaser[1,2], Peer Jacobson[2], John P. Berry[3], and Alejandro M.S. Mayer[1]; [1]Midwestern University, Chicago College of Osteopathic Medicine, Downers Grove, IL 60515; [2]Abbott Laboratories, Abbott Park, IL 60064; [3]Florida International University, Miami, FL

Microcystis aeruginosa (*Ma*) is a cyanobacterium that may contaminate freshwater. Cytokines and chemokines are glycoproteins hypothesized to cause neuroinflammation when released by LPS-stimulated microglia. We hypothesized that *Microcystis aeruginosa* (*Ma*) LPS would cause a dose-dependent release of both cytokines and chemokines from rat microglia *in vitro*. Primary rat neonatal microglia were treated *in vitro* with *Ma*LPS (0.1-100,000 ng/mL) and *E. coli* (*Ec*) LPS (0.1-100 ng/mL) for 17 hours at 35.9^0C. Thereafter protein expression in supernates from control and *Ma*LPS (1×10^5 ng/mL)-treated microglia was investigated by RayBio® biotin label-based rat antibody array technology (RayBiotech, Norcross, GA). Up-regulated cytokines and chemokines were assayed using rat-specific ELISA assays. The RayBio® antibody array revealed that *Ma*LPS caused greater than two-fold up-regulation of several proteins: cytokine TGF-β_2 (7.4), chemokines MIP-1α (6.58) and MCP-1(3.09), and MMP-inhibitor TIMP-1(2.58). ELISA results demonstrated that *Ma*LPS triggered a concentration-dependent release of MIP-1α and MCP-1 with maximal release observed with 100,000 ng/mL *Ma*LPS: MIP-1α: 58,153 ± 24,074.5 pg/mL, n=3, p<0.05, and MCP-1: 539.7 ± 174.7 pg/mL, n=3. In contrast, no significant TGF-β_2 or TIMP-1 release was observed with either *Ma*LPS or *Ec*LPS stimulation. Our data provide partial support for our working hypothesis. Although antibody array technology appeared to determine up-regulation of TGF-β_2, MIP-1α, MCP-1, and TIMP-1 after *Ma*LPS treatment, ELISA assays only confirmed enhanced release of the chemokines MIP-1α and MCP-1, but not the cytokine TGF-β_2 nor the matrix metalloproteinase inhibitor TIMP-1. Furthermore, *Ma*LPS appeared less potent than *Ec*LPS in activating rat microglia *in vitro*. Current work in our laboratory is extending our investigation to other proteins released by *Ma*LPS-treated rat microglia. We acknowledge **f**inancial support by Abbott Laboratories, and the Master in Biomedical Sciences Program, College of Health Sciences, Midwestern University.

Inhibition of Activated Rat Microglia Thromboxane B_2 Release by the Marine Sponge *Hymeniacidon* sp. Metabolites. Saba Chaudhry[1*], Mary L. Hall[1], Edward Áviles[2], Abimael D. Rodríguez[2], and Alejandro M.S. Mayer[1]; [1]Midwestern University, Downers Grove, IL 60515, [2]University of Puerto Rico, Department of Chemistry, San Juan, Puerto Rico 00931

Neuroinflammation has been shown to be associated with release of thromboxane B_2 (TXB_2) and superoxide anion (O_2^-) by activated brain microglia (BMG). The purpose of this investigation was to determine the effect of five marine sponge *Hymeniacidon* sp.-derived amphilectane metabolites and two semi-synthetic analogs on TXB_2 and O_2^- generation from *E. coli* LPS-activated rat BMG. Short and long term viability of BMG was assessed by lactate dehydrogenase (LDH) release (1.5 h), and mitochondrial dehydrogenase (MTH) activity (2.5-18 h), respectively. O_2^- levels were determined via superoxide dismutase-inhibitable reduction of ferricytochrome C and TXB_2 by enzyme-linked immunosorbent assay (ELISA) per manufacturer's instructions. Results: (n=3-4) *Hymeniacidon* sp. diterpenes and derivatives did not appear to affect BMG O_2^- release but in contrast potently inhibited TXB_2 (IC_{50}=0.20-5.69 μM) generation with concomitant low toxicity. Comparison of the IC_{50} of the related amphilectane diterpenes (**1**) (TXB_2 IC_{50}=0.20 μM) and (**2**) (TXB_2 IC_{50}=0.23 μM) supports the notion that TXB_2 inhibition was associated with an isocyanide functionality at C-15, with a second isocyanide moiety within the same amphilectane core further increasing the activity. However, the amphilectane diterpenoid skeleton played a significant role, as suggested by comparison of IC_{50} values of these two compounds and (**6**) (TXB_2 IC_{50}~3.14 μM), where the original isonitriles have been replaced by formamide groups. Thus, among the 7 *Hymeniacidon*

sp. metabolites and derivatives tested, metabolite (**2**) displayed the greatest anti-inflammatory potential against LPS-activated rat BMG as evidenced by potent TXB_2 inhibition, and minimization of short-term and long-term *in vitro* cytotoxicity. We conclude that via their inhibition of TXB_2, the marine *Hymeniacidon* sp. metabolites and derivatives show promise as novel chemical leads for the preclinical pharmaceutical development of novel antineuroinflammatory agents. Supported by Midwestern University, and the RISE and SCORE Programs, University of Puerto Rico at the Río Piedras Campus.

Pharmacological Properties and Procognitive Effects of ABT-288. A Potent and Selective Histamine H3 Receptor Antagonist. Marlon D. Cowart, Timothy A. Esbenshade, Kaitlin E. Browman, Thomas R. Miller, John L. Baranowski, Kathleen M. Krueger, Victoria Komater-Roderwald, Min Zhang, Gerard B. Fox, Lynne Rueter, Holly M. Robb, Richard J. Radek, Karla U. Drescher, Thomas A. Fey, R. Scott Bitner, Kennan Marsh, James S. Polakowski, Chen Zhao, Arthur A. Hancock, James P. Sullivan, and Jorge D. Brioni; Abbott Laboratories, Department of Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Park, Illinois 60064-6123

The histamine H_3 receptor (H_3R) is an attractive target for the treatment of cognitive disorders since blockade of this receptor enhances central neurotransmitter release. The *in vitro* and *in vivo* pharmacological properties of the H_3R antagonist ABT-288 were profiled in our laboratories. ABT-288 is a potent and selective competitive antagonist of human and rat H_3Rs (K_is = 1.9 and 8.2 nM, respectively) that enhances the release of histamine, acetylcholine, and dopamine in rat prefrontal cortex. In cognition studies, ABT-288 improved acquisition of a five-trial, inhibitory avoidance test in rat pups (0.001–0.03 mg/kg), social memory in adult rats (0.03–0.1 mg/kg), and spatial learning and reference memory in a rat water maze test (0.1-1.0 mg/kg). *In vivo* rat brain H_3R receptor occupancy of ABT-288 corresponded to efficacious doses and exposure levels in behavioral models. ABT-288 demonstrates a number of favorable attributes including good pharmacokinetics and oral bioavailability, with a wide CNS and cardiovascular safety margin. Thus, ABT-288 is a selective and potent H_3R antagonist with drug-like properties and broad efficacy across animal cognition models suggesting potential clinical efficacy for cognitive disorders such as Alzheimer's disease, ADHD, and cognitive deficits of schizophrenia.

Overexpression of PKCα in Breast Cancer Cells Induces Migration, Invasion and E-cadherin Downregulation. Bethany E. Perez White* and Debra A. Tonetti; University of Illinois at Chicago, Chicago, IL 60612

A woman's lifetime risk of developing breast cancer is 1 in 8; another 1 in 8 will have an invasive form of the disease. Tamoxifen is one of the most widely prescribed drugs for treatment of breast cancer and resistance is a major clinical problem. We have previously shown that overexpression of PKCα in T47D breast cancer cells (T47D/PKCα) leads to tamoxifen resistance. Further, PKCα is clinically relevant because overexpression in primary breast tumors may predict tamoxifen resistance. There is a clinical correlation between resistance and metastasis in breast cancer. Based on this, we wanted to explore the role of PKCα in metastasis. To study migration and invasion, the Boyden and modified Boyden chamber assays were used with NIH3T3 fibroblast-conditioned media as the chemoattractant. Protein expression levels were determined by western blot of whole cell extracts and transcript levels by RT-qPCR. Results show that T47D/PKCα cells are significantly more migratory and invasive than control cells (T47D/neo). Western blots show that there is significantly lower expression of E-cadherin, β-catenin, and α-E-catenin in T47D/PKCα cells compared to T47D/neo cells. These proteins all are part of adherens junctions whose dissolution is thought to play a primary role in metastasis. E-cadherin is a clinically relevant biomarker and loss of expression indicates a worse prognosis. Transcripts of E-cadherin are expressed at 3-fold higher levels in T47D/PKCα cells compared to T47D/neo cells indicating that a posttranslational mechanism is responsible for the downregulation. Based on our current data, we hypothesize that PKCα overexpression in patients may be indicative of not only tamoxifen resistance but also metastasis. Future mechanistic and clinical studies are needed to determine the full prognostic impact of PKCα tumor overexpression in patients. Ultimately we plan to establish PKCα as diagnostic, therapeutic and prognostic biomarker.

H3 Receptor Antagonism Activates Cellular Signaling Suggestive of Symptomatic and Disease Modifying Efficacy in Alzheimer's Disease. Stella Markosyan, Art Nikkel*, Jorge Brioni, and R. Scott Bitner; Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064

Histamine H3 receptor antagonists enhance cognition in preclinical models and have been proposed as novel therapeutics for cognitive disorders, in particular Alzheimer's disease (AD). Increased neurotransmitter release associated with this pharmacology (e.g. acetylcholine and histamine) may lead to activation of postsynaptic signaling pathways relevant to cognition and neuroprotection, such as increased phosphorylation of CREB, a transcription factor germane to cognitive function, and the inhibitory residue (Ser-9) of GSK3β, a primary tau kinase associated with AD pathology. In the present studies, acute administration of the H3 antagonist ABT-239 (0.01-1.0 mg/kg i.p.) increased cortical CREB and S^9-GSK3β phosphorylation in CD1 mice. Continuous (2-wk) s.c. infusion of ABT-239 (0.7 mg/kg/day) normalized reduced cortical CREB and hippocampal pS^9-GSK3β phosphorylation observed in Tg2576 (APP) AD transgenic mice. In addition, ABT-239 infusion reversed tau hyperphosphorylation in the spinal cord and hippocampus of TAPP (tau X APP) AD transgenic mice. Interestingly, ABT-239 produced signaling changes (pS^9-GSK3β) in α7 nicotinic acetylcholine receptor (nAChR) knockout mice. In contrast to wild-type, these mice do not exhibit α7 nAChR agonist induced phosphorylation, thus suggesting that H3 antagonist-mediated signaling is not dependent on ACh-stimulated α7 nAChR activation. In summary, results of these studies suggest that ABT-239 leads to biochemical signaling that promotes cognitive performance as well as attenuation of tau hyperphosphorylation, raising the intriguing possibility that H3 antagonists have potential for both symptomatic and disease modifying benefit in the treatment of AD.

Estradiol Induced Regression of T47D:A18/PKCα Tumor Involves Translocation of Estrogen Receptor Alpha from the Nucleus to the Cytoplasm. M. Kundu*, Y. Zhang, H. Zhao, and D. Tonetti; Biopharmaceutical Sciences, University of Illinois at Chicago, IL 60612

Background: Resistance to tamoxifen (TAM) is one of the most challenging problems in the treatment of breast cancer. In our laboratory we have developed a PKCα overexpressing T47D:A18 cell line which is TAM resistant and 17β estradiol (E2) independent compared to the E2 dependent T47D:A18/neo cell line. PKCα overexpression is known to be associated with TAM treatment failure in breast cancer. This T47D:A18/PKCα model exhibits E2-induced tumor regression *in vivo* or when grown in matrigel (3D matrix) but not on 2D plastic. Recently we have demonstrated that tumor regression involves participation of estrogen receptor alpha (ERα), Fas/FasL and the extracellular matrix. Interestingly membrane impermeable E2-BSA conjugate mediates growth inhibition of T47D:A18/PKCα colonies in matrigel similar to E2 suggesting a potential role of extranuclear ERα. On the basis of our preliminary data we investigated whether extranuclear ERα may play a critical role in E2-induced tumor regression.

Materials and methods: Four micrometer thick sections were prepared from the paraffin embedded T47D:A18/PKC alpha tumor tissues of control and E2-treated mice and T47D:A18/neo tumors. Fluorescence tagged secondary antibodies were used for immunofluorescence staining.

Results: Immunofluorescence images of T47D:A18/PKCα tumor sections from untreated control mice showed that the ERα was mainly localized in the nucleus. Interestingly, treatment with E2 resulted in significant translocation of ERα from the nucleus to the cytoplasm and the plasma membrane of tumor cells. Immunofluorescence analysis of tumor sections obtained from E2 treated mice indicated that approximately 45% of cells contained ERα localized to the plasma membrane. However in T47D:A18/neo tumors the majority of ERα was found in the nucleus.

Discussion: This is the first time we are reporting that E2-induced T47D:A18/PKC alpha tumor regression is accompanied by translocation of ER alpha to extranuclear sites. E2-induced tumor regression observed in our pre-clinical model suggests E2 or E2-like compound may be a potential treatment option for patients harboring PKC alpha overexpressing tumors. Furthermore the extranuclear ER alpha signaling pathway may be an attractive therapeutic target to treat PKC alpha overexpressing tumors that are refractory to current endocrine therapies.

Mechanism of Enhanced Hyaline Droplet Formation in Male Rats Caused by a Novel Experimental Formulation (VP-dimer). Jie Lai-Zhang*, Kenneth Kowalkowski, Andrew Lisowski, Kennan Marsh, William Bracken, Wayne R. Buck, Eric A.G. Blomme, and Yi Yang; Abbott Laboratories, Abbott Park, Illinois 60064

N-vinylpyrrolidinone dimer (VP-dimer or 1,3-bis(pyrrolidonyl)-butane) is a novel experimental formulation with excellent solubilizing properties intended for pre-clinical toxicology studies. Short-term oral toxicology studies using VP-dimer showed an increase of hyaline droplet accumulation within renal tubules in male Sprague-Dawley (SD) rats, but not in the kidneys of female rats. The purpose of this study was to investigate if the hyaline droplet formation is caused by male rat-specific accumulation of $\alpha_{2\mu}$-globulin. VP-dimer was dosed orally for 5 days in male and female SD rats at 0, 0.3, 1.0, or 3.0 ml/kg/day. D-limonene, a compound known to induce male rat-specific $\alpha_{2\mu}$-globulin nephropathy, was also included as a positive control. Male rat-specific hyaline droplet formation in the kidney was confirmed in rats dosed with VP-dimer or D-limonene by standard histopathological evaluation and by Mallory-Heidenhain stain. The immunohistochemistry and Western immunoblotting analysis indicated that $\alpha_{2\mu}$-globulin protein was present in male rat kidneys exhibiting enhanced hyaline droplet formation. $\alpha_{2\mu}$-globulin protein was not detected in the kidneys of any female rats. There were no significant changes in serum creatinine, blood urea nitrogen, traditional urinalysis parameters, or urinary biomarkers (albumin, lipocalin, osteopontin, and Kim-1) in male rats. Kidney transcriptomic analysis indicated minimal changes at gene expression level. These results confirmed that VP-dimer induced hyaline droplet formation is associated with renal accumulation of $\alpha_{2\mu}$-globulin protein and is a male-rat specific finding. Furthermore, there is no evidence of renal functional changes in rats treated with VP-dimer, at least in short-term studies.

Overexpression of PKCa Alters Gene Expression in T47D Breast Cancer Cells Associated with Hormone-Independent Growth. Huifang Han*, Jonna Frasor, and Debra Tonetti; University of Illinois at Chicago, Chicago, IL 60612

Background: Our lab has previously shown that overexpression of protein kinase C a (PKCa) in T47D breast cancer cells leads to a hormone-independent and Tamoxifen-resistant phenotype. Furthermore, we found that PKCa overexpression correlates with Tamoxifen-resistance and disease recurrence in patients. Taken together, these findings suggest overexpression of PKCa is important in the progression of breast cancer to a hormone-independent and Tamoxifen-resistant phenotype. Methods: To determine the mechanism whereby overexpression of PKCa can mediate this progression, gene expression profiles of T47D:A18/neo and T47D:A18/PKCa cells following treatment with EtOH or 17b-estradiol (E2) were compared utilizing the Affymetrix Human Gene ST 1.0 Array. Data was analyzed using Partek Genomics statistical package (Partek, Inc). ANOVA test was used to calculate significance of the differential expression. Gene Ontology (GO) term enrichment was carried out using the Functional Annotation Clustering tool in DAVID Bioinformatics Database. Results: The basal expression of more than one thousand genes are differently expressed in T47D cells by overexpressing PKCa, including genes related to cell cycle progression, gene expression regulation and metabolic processes. Interestingly, many of the E2-regulated genes in T47D:A18/neo cells have similar expression patterns in T47D:A18/PKCa cells in the absence of E2 treatment. Thirty-six genes are up regulated by E2 in T47D:A18/neo cells and they have higher basal expression levels in T47D:A18/PKCa cells compared with T47D:A18/neo cells, including TFF1, STC2 and MYC. On the other hand, seventy six genes are down regulated by E2 in T47D:A18/neo cells that also have lower basal expression levels in the PKCa-overexpressing cells compared to T47D:A18/neo, including ERBB2, TGFB2 and TGFB3. Furthermore, E2 does not have a great influence on the gene expression levels in T47D:A18/PKCa cells. Conclusion: These results suggest that PKCa overexpression may lead to estrogen-independent activation of ER target genes and result in a pattern of gene ex-

pression similar to that in T47D cells treated with E2. This altered activation of ER by PKCa may lead to a gene expression pattern that mediates the progression to the estrogen-independent growth. Pharmacological inhibition of this progression by inhibiting PKCa may offer treatment options for Tamoxifen-resistant breast cancer.

2-(4-hydroxyphenyl)-benzo[b]thiophen-6-ol, an Estrogen-like Compound, Induces Apoptosis in T47D/PKCα Breast Cancer Cells. ME Molloy*, GRJ Thatcher, JL Bolton, and DA Tonetti; University of Illinois at Chicago, Chicago, IL 60612

Background: Tamoxifen (TAM) treatment failure is a major obstacle encountered in the clinical setting. Our lab has previously shown that constitutive overexpression of PKCα imparts a TAM resistant/ hormone independent phenotype in the T47D:A18 breast cancer cell line. Furthermore 17β-estradiol (E2) inhibits tumor growth *in vivo* as well as inhibits colony formation when cells are grown in 3D Matrigel (Zhang, 2009). Before TAM treatment was introduced, breast cancer patients received high-dose E2 and diesthystilbesterol (DES) treatment. Others have shown that E2 can have inhibitory effects on MCF-7 cells both *in vitro* and *in vivo* (Lewis-Wambi, 2009). Taken together, this suggests an estrogenic compound may be efficacious for TAM-resistant breast cancer. The present study was designed to evaluate the effect of an estrogenic compound, 2-(4-hydroxyphenyl)-benzo[b]thiophen-6-ol (BTC), related to the SERMs raloxifene and arzoxifene, on the T47D:A18/PKCα breast cancer cell line.

Results: T47D:A18/PKCα cells showed a 31-fold induction in ERE-luciferase reporter activity when treated with BTC (10^{-7}M) compared to 7-fold induction when treated with E2 following a 24 hour treatment. In the T47D:A18/Neo parental cell line, BTC induced a 40-fold induction whereas estradiol induced a 96-fold induction. In the Matrigel colony formation assay T47D:A18/PKCα cells formed significantly fewer colonies when treated with BTC for 10 days. Conversely, in the T47D:A18/Neo parental cell line BTC enhanced colony formation. Our results indicate that BTC was able to induce significant apoptosis on day 6 (P= 0.038) as determined by the TUNEL Assay. Therefore BTC acts similarly to estradiol by inhibiting T47D:A18/PKCα colony formation and inducing apoptosis when cells are grown in Matrigel.

Conclusion: These findings suggest that BTC is a potential lead compound in the treatment of PKCα overexpressing breast cancer. Furthermore, BTC was shown to be a potent inducer of the cytoprotective enzyme NQO1 in the Hepa 1c1c7 cell system as well as a strong activator of antioxidant responsive elements (Yu, 2007) indicating it may have the added benefit of chemoprotective effects. Further understanding of the mechanism in which BTC induces apoptosis in the T47D:A18/PKCα cell line may result in a clinical advantage to estradiol treatment including fewer side effects.

Age and Diurnal Rhythm of Locomotor Activity and Cocaine Self-administration in Sprague-Dawley Rats. *WC Wong, KA Ford, NE Tucci, JE McCutcheon, and M Marinelli. Rosalind Franklin University of Medicine and Science/Chicago Medical School, North Chicago, IL 60061

In humans, adolescence may be a period of heightened propensity to develop cocaine addiction. We study cocaine self-administration in rats during adolescence and adulthood to understand this phenomenon. Locomotor activity of rats to novel environment often predicts cocaine addiction liability. Similarly, studies on the diurnal rhythm of rats show that these nocturnal animals self-administer more cocaine during the dark phase of the light/dark cycle when their locomotor activity is highest. As there are reports of adolescents having a shifted diurnal rhythm compared with adults, we hypothesized that this may account, at least in part, for the observed differences in addiction liability. We examined the diurnal rhythm of locomotor activity and cocaine self-administration in separate cohorts of rats. Three age groups were examined: young adolescence, peri-adolescence and adulthood. In the first cohort of rats, locomotor activity of male Sprague-Dawley rats was measured for 8 consecutive days by housing the rats in cages with photobeam axes. A diurnal rhythm of locomotor activity was observed in all age groups, with each group displaying significantly higher total locomotor scores during the dark phase. While there are reports showing a shift of diurnal rhythm between adolescence and adulthood in some physiological measurements, we did not observe a shift in locomotor activity between these groups. Next, we studied the effects of age on the diurnal rhythm of cocaine self-administration in adolescent and adult rats. A second cohort of male Sprague-Dawley rats was allowed unlimited access to cocaine self-administration for 4-5 days. Rats displayed a binge-and-stop intake pattern similar to human cocaine users instead of a diurnal rhythm of intake. While our model mirrored the binging behavior of human cocaine users, discerning a diurnal rhythm using this model may be limited by toxicity from cocaine, and by disruption from placing the rats in self-administration chambers for extended period. In conclusion, we observed a diurnal rhythm of locomotor activity, and a binge-and-stop pattern of cocaine self-administration, but not a shift in the patterns of these activities between adolescents and adults.

The Alpha-7 Agonist ABT-107 Produces Preclinical Cognitive Efficacy and Activation of Neurochemical and Cellular Pathways Suggestive of Symptomatic and Disease Modifying Efficacy in Alzheimer's Disease. R. Scott, Bitner, William Bunnelle, Jerry Buccafusco, Michael W. Decker, Karla Drescher, Kathy Kohlhaas, Stella Markosyan, Arthur L. Nikkel*, Lance Lee, and Murali Gopalakrishnan; Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064

We have previously reported that α7 nicotinic acetylcholine receptor (nAChR) agonism produces efficacy in preclinical cognition models correlating with activation of cognitive and neuroprotective signaling pathways associated with Alzheimer's disease (AD) pathology. In the present studies, the potent and selective α7 nAChR agonist ABT-107, which displays excellent drug-like properties, was evaluated in behavioral assays representing distinct cognitive domains. Further, ABT-107 was examined against a donepezil background in anticipation of clinical testing, evaluated for its pharmacodynamic-pharmacokinetic relationship, and mechanistically assessed for neurochemical and biochemical changes related to AD pathology. Specifically, ABT-107 improved cognitive performance in the monkey delayed matching to sample (DMTS), rat social recognition, and mouse two-trial inhibitory

avoidance. Rats maintained at clinical steady-state levels of donepezil showed improved short-term recognition memory when subsequently tested with ABT-107. In time course studies, ABT-107 continued to enhance cognitive performance in the monkey DMTS and mouse inhibitory avoidance at post-injection times when exposure levels were dramatically reduced. Mechanistically, repeated daily (3-days) dosing of ABT-107 in rats increased extracellular cortical ACh, while acute injections in mice increased cortical ERK and CREB phosphorylation, neurohemical and biochemical events germane to cognitive function. Finally, ABT-107 increased cortical and hippocampal phosphorylation of the inhibitory residue (Ser-9) of GSK3β, a primary tau kinase associated with AD pathology. Moreover, continuous (2-wk) infusion of ABT-107 in tau/APP transgenic AD mice reduced spinal tau hyperphosphorylation. Together, these findings raise the intriguing possibility that α7 nAChR agonists such as ABT-107 may have therapeutic utility for both symptomatic alleviation and disease progression in AD.

Ion Channel Phoshporylopathy. Alexander Donovan and *Saverio Gentile; Loyola University Chicago, Department of Molecular Pharmacology & Therapeutics, 2160 S 1st Ave, Maywood IL 60153

Voltage gated ion channel activities regulate several important physiological events including muscle contraction, brain function and secretion. Mutations that inhibit or up-regulate voltage gated ion channel activities can dramatically interfere with normal organ function and can often lead to unpredictable organ failure, and therefore poor quality of life, or even death. Mutations in the pore loop of an ion channel have been demonstrated to be affecting Ionic conductance or ion selectivity providing a predictable mechanism for ion channel malfunction. However, a great number of genomic variations associated with disease that change amino acids in Ion channels have been found in cytoplasmic domains. These mutations are very often located (or predicted to be) far from the pore loop, leaving a veil of mystery on the mechanism underlying the cause of ion channel malfunction.

We have observed that many amino acid substitutions in cytoplasmic regions of ion channels associated with specific diseases create, disrupt or change consensus sites for kinases. We call these events "PHOSPHORYLOPATHIES". We suggest that aberrant (de)/phosphorylation of these sites can change ion channel kinetic and/or trafficking.

We show here that:

1) A mutation on the L-type calcium channel (Cav1.2) associated with Timothy syndrome creates a consensus site for CAMKII and leads to a change in ion channel behavior.
2) Two mutations of the voltage gated potassium channel Kv11.1 associated with the cardiac arrhythmia Long-QT syndrome create or disrupt consensus sites for specific kinases, and therefore affect ion channel behavior.

We believe that Phosphorylopathies can be a possible mechanism linking human genomic variation to disease therefore understanding Phosphorylopathies is crucial in the process of designing an effective pharmacological anticancer strategy.

Possible New Cancer Treatments: Ribosome Biogenesis as an Unexplored Target. Ashleigh Porter*, Carl C. Correll, and Binal Shah; Rosalind Franklin University of Medicine and Science, 60060 Lake Forest College, Lake Forest, IL 60045

Cancer cells constantly need new proteins and therefore have high need for the protein making machines—ribosomes. Ribosome biogenesis is therefore an attractive target for cancer treatment. Duplex formation between the U3 RNA and precursor ribosomal RNA (pre-rRNA) is a key step in ribosome biogenesis. To achieve the necessary high U3-pre-rRNA duplex yield, two essential proteins (Imp3p and Imp4p) are needed to increase the stability of this duplex. We hypothesize that these proteins stabilize the U3-pre-rRNA duplex by hydrogen bonding to its 2'-hydroxyl groups. I am testing this hypothesis by determining how selective replacement of specific 2'-hydroxyl groups with hydrogen atoms affects duplex stability.

Targeting Soluble Guanylyl Cyclase (sGC)-cGMP Signaling Pathway in Parkinson's Disease. Shannon R Blume[1], Diana J Park[2], Anthony R West[2] and Kuei Y. Tseng[1]; [1]Department of Cellular and Molecular Pharmacology and [2]Department of Neuroscience, RFUMS/The Chicago Medical School, North Chicago, IL 60064

Currently available pharmacotherapies for Parkinson's disease (PD) subdue motor symptoms via activation of striatal dopamine (DA) receptors. However, drugs such as levodopa lose effectiveness with time, which are thought to arise as a result of complicated changes in DA receptor expression and function. On the other hand, alterations in striatal cyclic nucleotide homeostasis are apparent following loss of DA and may contribute to pathophysiological changes observed in basal ganglia circuits in PD. To test this possibility, we examined the utility of the sGC inhibitor [1H-[1,2,4] oxadiazolo-[4,3-a]quinoxalin-1-one] (ODQ) for reversing behavioral and electrophysiological correlates of experimental PD observed in mice chronically treated with MPTP. The MPTP model was chosen because this toxin induces a bilateral DA lesion that reproduces the human PD state more accurately than that obtained with unilateral lesions. We found that a single s.c. injection of ODQ (10 mg/kg) transiently reversed the reduction in forelimb stepping behavior observed in MPTP-lesioned mice in a manner that was similar to outcomes observed with L-DOPA (Blume et al., *Exp Neurol 2009*). We next conducted whole-cell patch clamp recordings of striatal MSNs from adult animals to assess the cellular mechanisms thought to be involved in the reversal effects of sGC inhibition. We observed that bath application of ODQ (50 μM) markedly attenuated the number of current-evoked spikes in MSNs. Analyses of the I-V relationship indicated that this inhibition was associated with a selective attenuation of membrane potential responses to depolarizing current steps without apparent changes in response to hyperpolarization. These results indicate that ODQ-induced attenuation of intrinsic excitability is mediated by facilitation of outward-rectifying K^+ currents. ODQ also decreased synaptic excitability through a presynaptic attenuation of glutamate release, suggesting a multiple site of action for sGC inhibitors to normalize the pathologically-enhanced striatal activity observed following chronic DA depletion. Together, our behavioral and electrophysiological data indicate that pharmacological inhibition of the sGC-cGMP signaling pathway could be powerful approach for restoring the enduring changes in striatal dysfunction induced by chronic DA depletion and for treating motor dysfunction associated with PD.

SSRI Antidepressants Potentiate Ritalin-Induced Gene Regulation in the Striatum: Consequences for Addiction Liability? V. Van Waes*, J. Beverley, M. Marinelli, and H. Steiner; Department of Cellular and Molecular Pharmacology, Rosalind Franklin University of Medicine and Science/The Chicago Medical School, North Chicago, IL 60064

The use of the psychostimulant methylphenidate (Ritalin), both in the treatment of attention-deficit hyperactivity disorder, and as a "cognitive enhancer" in the healthy, has increased dramatically over the past decade. Methylphenidate, like cocaine, acts by blocking the reuptake of dopamine and norepinephrine. However, unlike cocaine, methylphenidate does not affect serotonin reuptake. This may explain why methylphenidate mimics some but not all of the molecular effects of cocaine. We investigated whether serotonin-enhancing medications such as selective serotonin reuptake inhibitors (SSRIs) increase gene regulation and behavioral effects of methylphenidate. The molecular and behavioral effects of concomitant treatment with methylphenidate (2-5 mg/kg, i.p.) and a SSRI widely used to treat depression, fluoxetine (Prozac, 5 mg/kg), were assessed in periadolescent rats. Our results demonstrate that fluoxetine robustly potentiates methylphenidate-induced gene expression (c-fos, zif 268) throughout most of the striatum. Significant but smaller potentiation of gene induction was also seen in selective subregions of the nucleus accumbens (medial core, lateral shell). These effects were confirmed with another SSRI antidepressant, citalopram (5 mg/kg). We also assessed whether the methylphenidate+SSRI combination mimicked cocaine effects in an animal model for relapse to cocaine seeking. Our results show that the methylphenidate+fluoxetine treatment triggers robust reinstatement of cocaine seeking in the cocaine self-administration model. Together, these findings suggest that SSRI antidepressants may potentiate the drug addiction liability of methylphenidate.

Anticancer Effects of the Plant Derived Compound YN-786801. Tao Bai*, Harry H.S. Fong, and Hongjie Zhang; Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago College of Medicine, 833 South Wood Street, Chicago, IL 60612

Cancers are caused by fundamental alterations in the genetic control of cell division. Targeting unrestrained cell proliferation has become an essential therapeutic strategy for cancer treatment. Natural products and their derivatives play a vital role in cancer chemotherapy, comprising more than 50% of today's anticancer drugs. They work on specific stages of the cell cycle and function differently in various types of cancers, serving as DNA-damaging agents, microtubule inhibitors, topoisomerase blockers, or protein kinase regulators.

YN-786801 is a novel natural product isolated from a traditional herbal medicine through bioassay-directed fractionation. Here we show that microgram range of YN-786801 considerably reduces the number of adherent tumor cells in a dose-dependent manner. In vivo hollow fiber mouse model assay further confirms its anti-neoplastic activity, showing a 61 % reduction in percent cell net growth of Col2 (colon) cancer cells in YN-786801-treated samples at IP site compared to the vehicle controls. YN-786801 alone effectively arrests the progression of quiescent cells through G1 and into S phase, consequently suppressing cancer cell proliferation. In addition, the induction of apoptosis by YN-786801 may further interrupt cell growth and decrease tumorigenic toxicity, thus providing less opportunity for acquired drug resistance in cancer therapy.

Taking together, YN-786801 exerts cytotoxicity in cancer cells through two critical mechanisms by blocking the cell cycle and simultaneously activating programmed cell death. This indicates YN-786801 to be a novel potent therapeutic agent for future cancer treatment.

Novel Regulation of NF-YB by miR-485-3p Affects TopoIIα Expression. Cheng-Fen Chen[1], Xiaolong He[2], Yin-Yuan Mo[3], and William T. Beck[1]; [1]Department of Biopharmaceutical Sciences, University of Illinois at Chicago, Chicago, IL, 60612; [2]Department of Biopharmaceutical Sciences, University of Illinois at Rockford, Chicago, IL 61107; [3]Department of Medical Microbiology, Southern Illinois University School of Medicine, Springfield, IL 62794

DNA topoisomerase IIα (TopoIIα) is an essential nuclear enzyme. Our teniposide-resistant human leukemic lymphoblastic cells (CEMNM-I-5) express reduced TopoIIα protein. To determine the role of TopoIIα in drug resistance, we knocked down TopoIIα in parental CEM cells by RNAi. Compared to control cells, CEM-si TopoIIα cells are more resistant to etoposide. Our previous work suggested that the transcription factor NF-YB is a negative regulator of TopoIIα, working through the TopoIIα promoter (Morgan and Beck, MoI.PharmacoI59:203,2001). We have found that NF-YB protein expression is increased in CEMlVM-I-5 cells compared to CEM cells. This suggests that increased NF-YB may be the cause of reduced TopoIIα in CEMNM-1-5 cells. We asked what causes the up-regulation of NF-YB in CEMNM-1-5 cells. MicroRNAs are a recently identified group of non-protein coding RNAs that regulate posttranscriptional gene expression. We found by microRNA profiling that hsa-miR-485-3p, is lower in CEMNM-1-5 cells compared to CEM cells. MicroRNA target prediction programs also reveal that the 3' UTR of NF-YB harbors a putative miR-485-3p binding site. We hypothesized that hsa-miR-485-3p regulates drug resistance by decreasing NF-YB expression, which in turn negatively regulates TopoIIα expression. We overexpressed miR-485-3p in CEMNM-I-5 cells which caused reduced expression of NF-YB and a corresponding upregulation of TopoIIα. To validate the binding ofmiR-485-3p to NF-YB 3'-UTR, present experiments with HEK293TcelIs using luciferase reporters carrying the 3'-UTR of the NF-YB gene are being done to clarify the role of miR-485-3p in this phenomenon. (Supported in part by CA40570 [to WTB] from NCI and in part by UIC.)

Mechanism of L-DOPA-induced Striatonigral ERK1/2 Phosphorylation in a Rat Model of Parkinson's Disease. Cicely Moreno* and Subbiah P. Sivam; Department of Pharmacology and Toxicology, Indiana University School of Medicine-Northwest, Gary, IN 46408

Parkinson's disease (PD) is characterized by the degeneration of nigrostriatal dopaminergic neurons. L-DOPA is the primary drug that alleviates the symptoms of PD, but it leads to dyskinesias as a side effect. Previous studies have indicated that extracellular signal-regulated kinase 1/2 (ERK1/2), a MAP-kinase protein associated with gene expression and neuronal plasticity may play a role in L-DOPA-induced beneficial as well as side effects. In the present study, we determined whether a D1 antagonist will influence the L-DOPA-induced ERK1/2 in the striatum and substantia nigra using a rat model of PD. We unilaterally lesioned rat median

forebrain bundle neurons with the neurotoxin, 6-hydroxydopamine and tested the degree of lesion using apomorphine-induced rotation test. Unilaterally lesioned rats were treated with L-DOPA alone or after pretreatment with SCH23390, a D1 antagonist. Thirty minutes after L-DOPA administration, animals were perfused and their brains were removed, sectioned and used for immunohistochemistry of tyrosine hydroxylase (TH, the rate limiting enzyme of DA synthesis), substance P (SP, a neuropeptide marker), and phospho-ERK1/2. As expected, unilateral dopaminergic lesion produced a severe decrease in TH and a modest decrease in SP in the striatum and substantia nigra. Administration of L-DOPA produced a robust increase in phospho-ERK1/2 in the striatum while pretreatment with SCH23390 completely blocked the L-DOPA induced induction of ERK1/2. We report for the first time that similar changes were observed in the substantia nigra. Our study further contributes for the role of striatonigral D1 receptors in modulation of signal transduction mechanisms that may occur in the pathogenesis and/or treatment of PD.

Identification and Flow Cytometric Quantification of Bcl-2 Family Members that Correlate with Navitoclax (ABT-263) Response in Leukemia/Lymphoma. Morey Smith*, Brenda Chyla, Evelyn McKeegan, Mark Anderson, Saul Rosenberg, Steve Elmore, and Stephen Tahir; Abbott Oncology, Global Pharmaceutical Research & Development, Abbott Laboratories, Abbott Park, IL 60064

Navitoclax (ABT-263) is a novel Bcl-2 family member inhibitor of Bcl-2, Bcl-xL, and Bcl-w, with single-agent pro-apoptotic efficacy in small cell lung carcinoma (SCLC) and leukemia/lymphoma cell lines in vitro and in vivo. It is currently in clinical trials for treating patients with SCLC and various leukemia/lymphomas. Identification of predictive markers for response would benefit the clinical development of ABT-263. By comparing the expression of Bcl-2 family genes and sensitivity to ABT-263 in a panel of 31 leukemia/lymphoma cell lines we have identified Bcl-2 family members that correlate with cellular response to ABT-263. Notably, cells sensitive to ABT-263, the expression of Bcl-2 and Noxa were elevated, while expression of Mcl-1 was higher in resistant cells both at the mRNA and protein levels. Furthermore, expression of A1 was found to be higher in resistant leukemia/lymphoma cells at the mRNA level. We went on to develop a quantitative fluorescence cytometry (QFCM) method to measure the protein levels of Bcl-2 family members. This method is specific, sensitive and can be used to quantify Bcl-2 family members requiring fewer cells when compared to western blot methods. It is particularly useful for quantifying expression levels in a cancer cell population within a heterogeneous population of cells. We first characterized and validated several antibodies to various Bcl-2 family members to confirm their specificity for flow cytometry. To demonstrate that this method can be used to correlate the expression levels of Bcl-2 family members and their response to ABT-263 a panel of leukemia/lymphoma cell lines were treated with varying concentrations of ABT-263 and cell viability was determined The expression of Bcl-2 and Mcl-1 as determined by QFCM in the different cell lines correlated best with their cellular response to ABT-263 such that high expression of Bcl-2 was associated with cells sensitive to ABT-263 and Mcl-1 was high in cells resistant to ABT-263. This method is being used in clinical trials to facilitate the quantification of patient stratification biomarkers.

Dual Blockers of Histamine H_3 Receptors and Norepinephrine Transporter for the Treatment of Pain. Tiffany Runyan Garrison*, Robert Altenbach, Huaqing Liu, Marina Strakhova*, Arlene Manelli, Tracy Carr, Brian Wakefield, Chen Zhao, Larry Black, Madhavi Pai, Erica Wensink, Anita Salyers, Tom Shaughnessy, Marlon Cowart, Tim Esbenshade, Gin Hsieh, and Jorge Brioni; Neuroscience Research, Global Pharmaceutical Research & Development, Abbott Laboratories, Abbott Park, IL 60064

Norepinephrine (NE) has a well recognized role in control of pain, and it has been suggested that H_3 receptor antagonists produce their analgesic effects in preclinical models of nociception through modulation of NE release. We hypothesized that the combination of selective NE transporter (NET) blockade with H_3 antagonism in one molecule could have enhanced utility over the single mechanisms, with either increased efficacy or improved tolerability. Two structurally distinct compounds were developed with high potency (H_3 and NET K_i = 5-40 nM), CNS penetration, and good rat PK. A dual H_3-NET inhibitor has much improved GI tolerability compared to duloxetine. All three are fully efficacious and potent against MIA-induced knee joint pain with ED_{50} 0.3-2 mg/kg. However, probing the scope of efficacy in other pain models found the dual blocker is ineffective. The overall conclusion is that although the dual blocker compounds have good efficacy and potency in the MIA model, they fail to improve the magnitude and breadth of analgesic efficacy compared to single-mechanism agents.

Targeting Synaptic Kainate Receptor Function with novel Marine-Derived Anticonvulsant Compounds. Shanti F. Frausto[1,2], Martin B. Gill[1], Minoru Ikoma[3], Makoto Sasaki[3], Masato Oikawa[3], Ryuichi Sakai[4], and Geoffrey T. Swanson[1]; [1]Department of Molecular Pharmacology and Biological Chemistry, Northwestern University, Feinberg School of Medicine, Chicago, IL 60611; [2]Northwestern University Interdepartmental Neuroscience Program; [3]Graduate School of Life Sciences, Tohoku University, Aoba-ku, Sendai, Japan 041-8611; [4]Graduate School of Fisheries Sciences, Hokkaido University, Minato-cho, Hakodate, Japan 041-8611

Glutamatergic synaptic transmission is mediated through three families of ionotropic glutamate receptors which include AMPA, NMDA, and kainate receptors (KARs). KARs have been implicated in epilepsy disorders, but their precise role has not been determined in part due to a lack of pharmacological compounds that selectively target KARs. Previous studies have shown that MSVIII-19 and 2,4-epi-neoDH, act as selective kainate receptor antagonists in *in vitro* recombinant receptor model systems. MSVIII-19 has selective antagonistic action on the GluR5 KAR subunit, while 2,4-epi-neoDH targets both the GluR5 and GluR6 subunits. IKM-159, a novel DH analog produces catalepsy *in vivo* and has antagonist activity for AMPA/KARs (Ikoma et al., 2008). These novel marine-derived compounds have never been tested on any neuronal system. Here, we assess if these novel pharmacological compounds have antagonistic activity on synaptic kainate receptors and determine their efficacy as anticonvulsants in *in vitro* models of epilepsy. We examined the potency of these novel compounds on kainate receptor synaptic currents using whole-cell patch clamp techniques in hippocampal slice preparations.

In mossy fiber-CA3 pyramidal cell synapses, whose principal KAR subunits include GluR6 and KA2, 100 µM 2,4-epi-neoDH

inhibited kainate receptor mediated excitatory postsynaptic currents (EPSCs) by 34% and had no effect on the paired-pulse ratio (PPR) in hippocampal slice preparations. 10 µM MSVIII-19 failed to inhibit postsynaptic CA3 KAR-EPSCs, likely due to MSVIII-19 selectivity for the GluR5 kainate receptor subunit. IKM-159 did not depress CA3 KAR-EPSCs, but showed a higher selectivity for AMPA-EPSCs. IKM-159 reduced AMPA/KAR-EPSCs evoked by stimulation of Schaffer collateral inputs to CA1 pyramidal neurons in acute slice preparations and also reduced bursts of AMPA/KA receptor mediated EPSCs in voltage clamp recordings from hippocampal neurons in culture. IKM-159 reduced spontaneous reoccurring epileptiform discharge (SRED) action potential firing in an *in vitro* model of stroke-induced epilepsy.

Given the initial characterization of these compounds on synaptic kainate receptor function in hippocampal slice preparations and *in vitro* models of epilepsy, we propose that these selective kainate receptors antagonists can be further pursued as a new generation of selective target anticonvulsant therapies in treating epilepsy and seizure disorders.

Annual Meeting Report

Morning Session

The annual Mid-Atlantic Pharmacology Society (MAPS) conference was held on Friday, December 10, 2010, and hosted by the Fox Chase Cancer Center (FCCC) in Northeast Philadelphia. Dr. Robert Beck, Sr., VP of FCCC, welcomed all participants and Dr. Margie Clapper, Professor and Co-Leader, Cancer Prevention and Control, served as the host for the meeting. The conference was well attended by students, faculty and industrial scientists from the Delaware Valley area. The theme for this year was "Cancer Pharmacogenomics: From Bench to Bedside." The title of the meeting is designed to express the range of pharmacogenomic research beginning at the level of laboratory research and concluding with the clinical aspects to illustrate how basic research can lead to significant advances in clinical medicine. The meeting was officially opened by MAPS president Vincent Aloyo, PhD, Drexel University College of Medicine.

Dr. David Flockhart (left) and Dr. Vince Aloyo.

The keynote lecturer for the meeting was Dr. David Flockhart, Chief, Division of Clinical Pharmacology, Indiana University School of Medicine, who spoke on the topic "Pharmacogenetic Approaches to the treatment of Breast Cancer." Dr. Flockhart is highly regarded for his development of a web-based tool to improve the rational prescribing of drugs, a site that is visited more than 20,000 times per month by physicians and scientists around the world (www.drug-interactions.com).

The next speaker on the program was Dr. Rebecca Suk Heist, Assistant Professor of Medicine at MGH, Harvard Medical School. Her presentation was entitled "Targeting somatic mutations in lung cancer: EGFR and ALK." The next presentation was by Dr. Evgeny Kysnekstiy, Associate Professor of Pharmaceutical Sciences at Temple University School of Pharmacy. The objective of his research is to identify inherited factors which define an individual's response to pharmacotherapy, and to develop genetically based diagnostic tools for "personalized medicine." His lecture was titled "Beyond Thiopurine S-methyltransferase (TPMT): A View from the Bench." This lecture concluded the basic research portion of the program.

George B. Koelle Award

Each year, the organizers of the MAPS meeting honor the memory of the world-renowned and pioneering local pharmacologist, the late George B. Koelle. The society selects one scientist (usually local) who most closely shares Dr. Koelle's enthusiasm for teaching and conducting outstanding research, to receive this coveted Award. The 2011 award was presented to Dr. James Barrett, a past President of ASPET. Dr. Barrett was a former Vice President of Neuroscience Discovery Research at Wyeth-Ayerst Research and then went on to serve as President of Research & Development at Memory Pharmaceuticals and later joined Adolor as Senior Vice President, CSO, and President of Research. In 2006 Dr. Barrett served as the co-host for the MAPS meeting when Adolor, along with Cephalon, Inc. co-sponsored the meeting. Dr. Barrett is currently Professor and Chair, Pharmacology and Physiology, Director, Program in Drug Discovery and Development at Drexel University College of Medicine.

Dr. James Barrett, recipient of the 2010 George B. Koelle Award.

This year's presentation was very unique since Dr. Barrett was unable to be present to receive the award. In order to accomplish this task, MAPS was able to present the award to him via the internet with the aid of a TV monitor brought in for this purpose. Dr. Bob Raffa, Past President of MAPS and former Koelle Award recipient himself, presented the award to Dr. Barrett via the computer internet connection.

Luncheon and Poster Session

The MAPS meeting always allows generous time for the luncheon. Fox Chase provided participants with boxed lunches. Students, guest speakers, and other scientists interacted while enjoying a leisurely lunch followed by viewing and judging of the 24 posters entered in the poster competition. Eleven undergraduate students and thirteen graduate students presented their research to MAPS judges. Three colleges and universities were represented in the undergraduate research division: Temple University, University of the Sciences-Philadelphia, and Ursinus College. Six colleges and universities and one local pharmaceutical company were represented in the graduate student/research associate division: Bucknell

University, Drexel University, Temple University Schools of Pharmacy and Medicine, University of the Sciences/Philadelphia, and Penn State University along with GlaxoSmithKline, Inc.

MAPS Councilors Ellen Walker (Temple Pharmacy School) and Bob Willette (Glaxo SmithKline) organized the poster session and recruited several highly qualified judges so that there was plenty of time for each presenter to discuss his or her poster with the judges. Four prizes were awarded for the top two best poster presentations in each division (see winners below). Each of the poster winners received a cash award.

Poster Award Winners

Undergraduate Division:

First Place: Lauren King, Ursinus College, "Oxidative Stress Induces Neurodegeneration of GABAergic Neurons in Caenorhabditis elegans"

Second Place: Michael David Ramirex, Temple University, "Cannabidiol Prevents the Development of Allodynia in Paclitaxel-treated Female C57B16 Mice"

Graduate Student/Research Associate Division:

First Place: Aravindandham Karpagam, GlaxoSmithKline, "Glucagon-like Peptide-1 Mediated Cardioprotection Involves Metabolic Substrate Switching and Increasing Energy Efficiency in the Rat Heart"

Second Place: Jacqueline Freed, USP/PCP, "Arf6 Regulates CXCR4-mediated Migration and Invasion of Metastatic Breast Cancer Cells"

Michael David Ramirez, Temple University, winner of the Undergraduate Division Second Place Poster Award, with Dr. Ellen Walker. Right: Jacqueline Freed, USP/PCP, winner of the Graduate Student Division Second Place Poster Award, with Dr. Walker.

Afternoon Session

This portion of the program was devoted to two presentations that described the clinical usefulness of pharmacogenomics research in the treatment of cancer. Dr. Paul Billings, of Life Technologies, Inc., in Carlsbad, CA opened the session with his presentation titled "Genomic Medicine: the New Oncology Subspecialty?" It is appropriate that the meeting concluded with a presentation by Dr. Howard McCleod, Distinguished Professor of Pharmacogenomics and Individualized Therapy at the UNC Eschelman School of Pharmacy, Chapel Hill. Dr. McCleod has distinguished himself as an internationally recognized expert in the pharmacogenomic analysis of cancer treatments and is the Principal Investigator for the CREATE Pharmacogenetics Research Network and is Director of the Pharmacogenetics for Every Nation Initiative. His concluding presentation was titled "Using the Genome to Guide Cancer Therapy."

Special Presentations and Installation of New MAPS Officers

The afternoon session wrapped with up two very special and important events. First, our new officers for 2011 were officially recognized. Dr. Carol L. Beck, Assistant Dean, Jefferson College of Graduate Studies and Assistant Professor, Dept. of Pharmacology & Experimental Therapeutics at Thomas Jefferson University will serve as Society President, and Dr. Diane Morel, Associate Professor of Pharmacology and Toxicology and Director, Pharmacology/Toxicology Program at the Philadelphia College of Pharmacy will serve as Vice President. MAPS is fortunate to have Carol and Diane in these leadership roles and wishes them much success in the future.

Finally, Dr. Vince Aloyo was presented with the traditional "gavel plaque" by 2011 MAPS President Carol Beck, as a gesture of appreciation for his three years of service to the society.

Dr. Carol Beck, new President of MAPS (left) and Dr. Diane Morel, new Vice President.

Concluding Remarks

Dr. Margie Clapper, meeting moderator and organizer, ended the conference with some concluding remarks about the optimistic future for these new approaches to the improvement in the quality of cancer treatment.

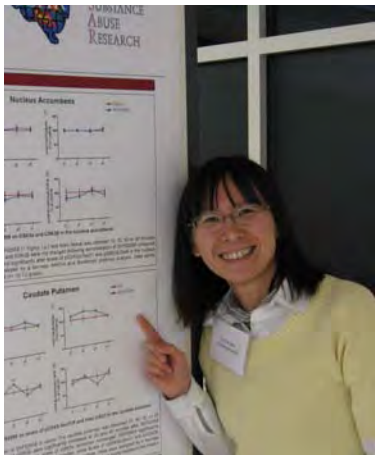
The afternoon was topped off with a reception after all meeting business was completed.

Acknowledgements

The Mid-Atlantic Pharmacology gratefully acknowledges support provided by the following institutions: American Society for Pharmacology and Experimental Therapeutics, Cephalon, GlaxoSmithKline, Johnson & Johnson, and Pfizer. MAPS would like to thank Markus Collins of Fox Chase Cancer Center for serving as the meeting photographer.

Dr. Vince Aloyo receives the "gavel plaque" from 211 MAPS President Dr. Carol Beck.

Left: Dr. Rebecca Suk Heist during her presentation. Center: Dr. Evgeny Kysnekstiy explaining how his research in *TPMT* can play a role in the novel concept of presonalized medicine. Right: Dr. Paul Billings presenting on the use of genomic medicine in oncology.



From left: Dr. Howard McCleod presenting his clinically oriented lecture describing how genomics can successfully guide pharmaceutical therapy. Joshua Ripple of Bucknell University presents his poster. Yi-Ting Chiu, a graduate student in Dr. Ellen Unterwald's laboratory at Temple Medical School, with her poster. Dr. Margie Clapper, Professor and Co-Leader, Cancer Prevention and Control, served as the host for the MAPS meeting.

Poster Abstracts Presented at the 2010 Mid-Atlantic Pharmacology Society Meeting

December 10, 2010, Fox Chase Cancer Center, Philadelphia, PA

Undergraduate Division

Electroencephalographic Investigation of Synesthetic Qualities in Children, Synesthetes and Non-synesthetic Adults. Lauren E. Meeley*, Kacie A. Dougherty, and Joel Bish Ph.D. Ursinus College, Collegeville, PA 19426

This research project was a continuation of an ongoing investigation of grapheme-color synesthesia. Individuals who have grapheme-color synesthesia perceive numbers and letters to be inherently colored despite a lack of color infor-mation. Historically, one of the main hypotheses is that synesthetic processes are the norm for children and through neurodevelopment, neural pruning occurs to reduce the synesthetic experience in typically developing individuals but remains for synesthetes into adulthood. This study investigated this hypothesis by conducting behavioral tests, such as a modified Test of Genuineness and multiple executive function tasks, on children aged three to six. The data from this study did not indicate letter color synesthesia in this younger set of children. However, in older children, aged six to ten, electroencepha-lographic methods as well as behavioral tests show increased synesthetic qualities. These older participants were given a Test of Genuineness and two other grapheme processing tasks. The older children were also given the modified Test of Genuineness used for the younger children. It was found that the older children showed a trend of greater synesthetic experience compared to the younger children. The electroencephalographic data in these older children indicate electrophysiological differences for the children compared to adult controls and adult synesthetes.

PTL-1 as a PAM-1 Target in Single-Cell Embryogenesis in *Caenorhabditis elegans*. George Pellegrino*, Brett Godoy and Rebecca Lyczak; Ursinus College, Collegeville, PA, 19426

It has been recently shown in *Caenorhabditis elegans* that the puromycin-sensitive aminopeptidase, PAM-1 is required for both timely meiotic exit and proper antero-posterior (AP) axis formation. PAM-1 is suggested to possess multiple targets that allow it to regulate diverse cell processes, but none are known to date. In mammals the PAM-1 homolog, PSA is known to target the microtubule-associated protein (MAP), TAU. TAU belongs to the MAP-2/TAU family of structural MAPs involved in microtubule stabilization. PTL-1 (protein with tau-like repeats) is the single MAP-2/TAU family protein in *C. elegans*, however its functions and phenotype in early embryogenesis are poorly classified. Due to PAM-1/ PSA and PTL-1/ TAU homology, PTL-1 is expected to be a PAM-1 target. Reports of robust microtubule bundles in *pam-1* mutants and proposed disruption of dynein-based transport theoretically support this. We hypothesize that a buildup of PTL-1 in the absence of PAM-1 contributes to some of the defects observed in *pam-1* mutants and it is expected that by knocking out *ptl-1* in *pam-1* mutants, the *pam-1* phenotype should be fully or partially recovered. In order to test this we have constructed a *pam-1*/*ptl-1* double knockout mutant strain and have examined single-cell embryonic development. At this time, two possible unique phenotypes have been identified for the double mutant. The first is a novel development following failure to complete cytokinetic cleavage, resulting in single cell embryos progressing directly to a three-cell stage. The second is believed to be partial recovery of *pam-1*, in which embryos release an abnormally large polar body and progress to asymmetric two-cells, following cytokinetic difficulties. Through continued analysis we hope to better classify both the *pam-1* and *ptl-1* phenotypes in early embryogenesis and confirm the validity of those recently observed for the double mutant.

Oxidative Stress Induces Neurodegeneration of GABAergic Neurons in *Caenorhabditis elegans*. Lauren King*, Chris Frymoyer, Alaina Geary, and Rebecca Kohn; Dept. of Biology, Ursinus College, Collegeville, PA, 19426

Oxidative stress damage results when reactive oxygen species (ROS) overwhelm cells' antioxidant capabilities and attack proteins, lipids, and DNA. Chemicals in our environment can cause oxidative stress, including paraquat, which is used as an herbicide. As a result of the damage that oxidative stress causes in neurons, oxidative stress can contribute to progression of human neurodegenerative diseases, such as Alzheimer's Disease and Parkinson's Disease. Studies in rodents have identified genes that confer a neuroprotective effect against oxidative stress in response to neuronal activity. The *unc-13* gene in *Caenorhabditis elegans* codes for proteins that regulate neurotransmitter release and, therefore, play an important role in activity of neurons. Defects in *unc-13* lead to decreased neurotransmitter release and paralysis. As a result of exposure to chemicals that induce oxidative stress, the nematode, *Caenorhabditis elegans*, has a decreased rate of development to adulthood. *unc-13* mutants develop more slowly in response to oxidative stress compared to wild type, a response that may be due to decreased neuronal activity. We hypothesize that exposure of *C. elegans* to paraquat induced oxidative stress would result in neurodegeneration and that *unc-13* mutants would have an elevated rate of neurodegeneration. A *C. elegans* strain in which all GABAergic neurons are labeled with GFP was exposed to oxidative stress by growing worms on plates with the chemical, paraquat. A second strain of worms with labeled GABAergic neurons and a mutation in *unc-13* was tested. Of the 26 labeled GABA neurons, some neurons were visible less frequently following exposure to oxidative stress in both strains tested. Our results suggest that neurodegeneration in the *C. elegans* nervous system is enhanced following oxidative stress, and that decreased *unc-13* activity further affects neurodegeneration of GABAergic neurons. We plan to test strains in which additional subsets of neurons have been labeled with GFP in neurons that utilize dopamine, serotonin, glutamine, or choline.

The Ubiquitin-Proteasome System Modulates Prion Phenotypes in *Saccharomyces cerevisiae.* Alvaro Amor*, Lindsay MacNamara, and Dale M. Cameron; Department of Biology, Ursinus College, Collegeville, PA 19426

Protein quality control systems are an essential feature of all cells. Polypeptides are faithfully synthesized and correctly folded to produce functional proteins, while misfolded or damaged forms are targeted for refolding or degradation to avoid potentially toxic outcomes. Defects in protein quality control underlie various human diseases. In particular, protein misfolding and aggregation are associated with multiple neurodegenerative disorders, including prion diseases. An essential component of protein homeostasis in eukaryotes is the ubiquitin-proteasome system (UPS) whereby polyubiquitinated proteins are selectively targeted for degradation by the proteasome, a large multisubunit protease. Growing evidence suggests that UPS dysfunction contributes to toxicity of protein misfolding; indeed, previous studies have shown that the properties of prions in the yeast *Saccharomyces cerevisiae* are profoundly influenced by the abundance of free ubiquitin[1,2]. However, no clear model has emerged to describe a role for the UPS in prion formation, propagation and toxicity. We have examined UPS influence on the yeast prion *[PSI+]*, a self-propagating aggregated form of the essential translation termination factor Sup35 that is manifested phenotypically as elevated levels of nonsense suppression. We find that chemical or genetic proteasome inhibition reduces the frequency of *[PSI+]* formation and alters the phenotypic strength of the prion. In addition, we show that *[PSI+]* cells are more sensitive to proteasome inhibition than are cells lacking the prion. This sensitivity is not simply due to an inability to degrade the translational readthrough products produced in *[PSI+]* cells and is thus consistent with models in which prion aggregates represent a burden on the UPS. Studies are currently underway to distinguish between a model in which prions are substrates of the proteasome and one where they are indirectly impacted through UPS engagement with other factors.

1. Chernova et al. (2003). *J Biol Chem* 278: 52102-15
2. Allen et al. (2007). *J Biol Chem* 282: 3004-13

The Effects of Estrogen and Bisphenol A on Surface Protein Expression in a Lupus-Prone Murine Model. Matthew Zuber*, Kira Stone*, and Rebecca Roberts; Ursinus College, Collegeville, PA, 19426

Affecting primarily women of childbearing age, Systemic Lupus Erythematosus (SLE) is an autoimmune disease with symptoms that include fatigue, arthritis, and kidney failure. Because female patients with SLE exhibit severe inflammatory symptoms during pregnancy and symptom-regression during menopause, the female-sex hormone estrogen (E2) is hypothesized to play a role in the development and progression of this disorder (Sawai *et al.* 2003). Although the mechanisms governing SLE are currently misunderstood, it is recognized that estrogen binds to estrogen receptors (ERs), and this complex elicits tissue-specific responses via estrogen response elements (EREs) associated with specific genes (Moggs *et al*. 2001). Bisphenol A (BPA), an environmental, endocrine-disrupting chemical found in polycarbonate plastics, mimics estrogen via its ability to bind to estrogen receptors (ERs), and has faced an onslaught of recent criticism for its proposed relationship to a host of detrimental health effects in humans (Alonso-Magdalena *et al*. 2006). Due to its estrogen-like properties, we hypothesize that exposure to BPA may also impact surface protein expression in APCs. Surface expression of B220, MHC-II, CD40, CD80, and CD86 on B cells from control (C57/BL6) and Lupus-prone (NZB/WF1) mice were analyzed via flow cytometry to assess expression intensity following exposure to environmentally relevant doses of E2 and BPA. Preliminary results indicate that B cells from NZB/WF1 mice express lower overall levels of MHC-II, but similar levels of CD40 and CD86 compared to controls, however our data do not yet clarify if BPA or E2 exposure leads to a statistically significant difference in expression of these proteins. Of note, preliminary results show that lupus-prone mice have significantly fewer B cells expressing the CD80 T cell co-stimulatory molecule in comparison to control mice. There is a precedent for similar findings in dendritic cells of older, diseased NZB/WF1 mice and it is currently thought that the disease state reduces levels of CD80 (Colonna *et al* 2006). We propose to confirm our findings and determine if the responses seen are dose-dependent with regards to E2 and BPA. We will also investigate if the CD80 expression is dependent upon disease state by analyzing cell-surface protein expression following E2 or BPA exposure in B cells from older mice displaying the disease state. Determining immune-specific effects of BPA and E2 on surface protein expression in a lupus-prone mice moves medicine one step closer to understanding the mechanism of this autoimmune disease in humans.

The Role of NMDA Receptors in Embryonic Stem Cells with Different Levels of Neurofibromin Differentiation into Neural Cells. Carres Martinez*[1], Dmitri Gourevitch[2], Kate F. Barald[3], Minh Bui[1], and Natalia Coleman[1]*; [1]Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Philadelphia, PA 19104; [2]The Wistar Institute, Philadelphia, PA 19104; 3Department of Cell and Developmental Biology, University of Michigan Medical School, Ann Arbor, Michigan, MI 48109

Genetically engineered embryonic stem (ES) cell-derived neurons and glial cells offer a flexible and potent model to study nervous system development and disease. While it is common knowledge that N-methyl-D-aspartate receptors (NMDARs) are expressed abundantly in the brain and play an important role in regulation of neuronal development, learning and memory, neurodegenerative diseases, and neurogenesis, little is known about NMDR function in ES cell differentiation into neural cells in normal and pathological settings. Since several therapeutic approaches for neurodegenerative diseases are acting through NMDARs, we believe that it is highly imperative to examine if these compounds affect ES cell neural differentiation. We induced differentiation of ES cells (D3) from EB in the presence of NMDA (5μM) for 24 hours and examined the cells 72 hours after stimulation. We also evaluated the addition of NMDA antagonist MK-801 prior to NMDA treatment. Following this protocol we detected the change in the number of β-tubulin type III (Tuj1)-positive cells. NMDA receptor stimulations result in an increase of TUJ1+ cells up to 250% com-

pared to untreated control. Opposite effects were observed after NMDA receptors were blockaded by MK-801 (67%). We are currently studying the effects of this compound on ES cell differentiation *in vitro* using SKO (mouse embryonic cells that have one functional allele for neurofibromin) cell lines that are able to differentiate into to neurons and glial cells. This study will evaluate a potential role for NMDARs on differentiation of ES cells into neural cells of cell types that make different levels of neurofibromin.

Comparison of MTT and BrdU Assays to Examine the Cytotoxic Effects of Doxorubicin on the Human Carcinomas. Paridhi Anand*, Carres Martinez, Kathleen Galm, and Natalia Coleman*; Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Philadelphia, PA 19104

The ability to measure cytotoxicity and cell proliferation is important in cell biology and increasingly important in drug discovery studies. Cell proliferation assays are designed to measure the growth and viability of cells based on a cell's ability to absorb and metabolize a particular reagent. The proper assessment of the potency of chemotherapeutic drugs requires precise and accurate *in vitro* laboratory tests. Therefore, the re-evaluation of the accuracy of cell proliferation assays in cancer drug discovery is important in order to understand and to be aware of the limitations of the methods. It is also important to choose a suitable cytotoxicity assay depending on the supposed cell death mechanism. The aim of the present work is to evaluate several toxicity assays for use on human melanoma (1205Lu), breast (MCF-7), and prostate (DU-145) cancer cell lines. The BrdU assay was compared to the most common assay, MTT, by evaluating the cytotoxicity of doxorubicin. Doxorubicin is a drug used to treat cancers of the ovary, breast, lung, prostate, among others. It is believed to act by intercalating between base pairs during DNA replication.

Effect of 3-(3,5-dichlorophenyl)-2,4-thiazolidinedione (DCPT) on Viability and ATP Content in Human Hepatoma HepG2 Cells. Peter D. Young*, Ruy Tchao, and Peter J. Harvison; University of the Sciences in Philadelphia, Philadelphia, PA, 19104

The thiazolidinedione (TZD) ring appears in a family of drugs known as the glitazones, which are used in the treatment of type II diabetes. Two TZD ring-containing drugs are still on the market and their chronic use has been tentatively linked to hepatic damage. A third TZD containing glitazone, known as troglitazone, was withdrawn from the market due to severe hepatotoxicity in some patients. The mechanism of glitazone-induced toxicity is not well understood, although there is evidence that the TZD ring may be involved. These *in vitro* experiments were therefore designed to explore the potential correlation between cell viability and intracellular ATP levels in the presence of a TZD ring-containing compound. Human hepatoma HepG2 cells were seeded at 20,000 cells per well using 96-stripwell plates. Cells were allowed to grow for 24 hours at 37 °C under 5% CO_2 in DMEM-high glucose media. The cells were washed and were then treated with 250 µM 3-(3,5-dichlorophenyl)-2,4-thiazolidinedione (DCPT) in Hanks' balanced salt solution (HBSS containing up to 0.1% DMSO, v/v) for a maximum of 24 hr. Control groups were similarly treated with HBSS (0.1% DMSO) only. Viability was determined using the CellTiter AQ (MTS) cell proliferation assay (Promega, Madison, WI). Intracellular ATP content was determined using the CellTiter-Glo luminescent assay (Promega, Madison, WI). Viability and luminescent values were converted to ratios (treated/control) for each time point. Following 24 hr of exposure to DCPT, viability had decreased by approximately 50%. In contrast, there was a ca. 90% decrease in intracellular ATP as early as 16 hr. Our results suggest that loss of ATP precedes cell death in HepG2 cells exposed to DCPT. Supported by NIH grant ES012499.

Effect of 5-(3,5-dichlorophenylmethyl)-2,4-thiazolidinedione (5-DCPMT) on Viability and Intracellular ATP Content in Human Hepatoma HepG2 Cells. Ashley Azar*, Ruy Tchao, and Peter J. Harvison; University of the Sciences in Philadelphia, Philadelphia, PA 19104

The glitazones, a group of drugs used in the treatment of type II diabetes, contain the characteristic thiazolidinedione (TZD) ring. These compounds have been associated with liver injury in some patients after chronic use. Although the mechanism leading to hepatic damage has not been fully elucidated, the TZD ring of these drugs may be involved. The purpose of these experiments was to investigate the *in vitro* toxicity of a close structural analogue of the glitazones known as 5-(3,5-dichlorophenylmethyl)-2,4-thiazolidinedione (5-DCPMT). We assessed the effect of 5-DCPMT on viability and cellular ATP content using the human hepatoma HepG2 cell line. Cells were seeded at 20,000 cells/well in 96-well stripwell plates and were allowed to grow for 24 hr at 37 °C under 5% CO_2 in DMEM-high glucose media. The cells were washed and 5-DCPMT (0-25 M) in Hanks' Balanced Salt Solution (HBSS containing up to 0.1% DMSO, v/v) was added to the wells, after which the cells were incubated for 24 hr as above. In control wells, the cells were exposed to HBSS (0.1% DMSO) only. Cell viability was assessed using the CellTiter AQ (MTS) cell proliferation assay (Promega, Madison, WI). 5-DCPMT produced concentration-dependent cytotoxicity with approximately 60% loss of viability at 25 M. A time course study was then conducted to investigate the onset of 5-DCPMT-induced toxicity. The cells were therefore incubated with 25 M 5-DCPMT or HBSS as described above for 0, 1, 2, 4, 16, 18, 20 and 24 hr. Cell viability was again measured using the MTS assay. Intracellular ATP content was determined using the CellTiter-Glo luminescent assay (Promega, Madison, WI). The viability and luminescence data were converted to ratios (treated/control) for each time point. Neither parameter was significantly altered within the first four hours of exposure to 5-DCPMT. However, by 16 hr, both cell viability and intracellular ATP content had dramatically declined compared to the earlier time points. Our results suggest that 5-DCPMT produces a profound effect on the viability of HepG2 cells. The critical period for onset of toxicity appears to be between 4 and 16 hr; however, this will require further investigation. Supported by PHS grant number ES012499.

Cannabidiol Prevents the Development of Allodynia in Paclitaxel-Treated Female C57Bl6 Mice. MD Ramirez,* H Neelakantan, EA Walker, and SJ Ward; Temple University School of Pharmacy, Philadelphia PA 19140

Paclitaxel (PAC) is associated with a chemotherapy-induced neuropathic pain (CINP) state that can lead to the cessation of treatment in late stage breast cancer patients, even in the absence of alternate therapies. Rodent models of CINP-associated allodynia following systemic dosing of PAC are used to investigate underlying mechanisms and potential treatments, but studies are largely restricted in sex and species to male rats, while well-characterized effects of CINP in female mice are lacking. In the present set of experiments, we investigated the effect of a wide range of repeated PAC doses (1.0 – 8.0 x 4 inj IP) on cold (acetone drop test) and mechanical (Von Frey test) allodynia in male and female C57Bl/6 mice. The non-psychoactive *Cannabis* constituent cannabidiol (CBD) has been shown to attenuate other forms of neuropathic pain. Therefore, we also assessed the effect of CBD (5.0-10.0 mg/kg IP) on PAC-induced allodynia in the female mice. Treatment with PAC led to the onset of cold and mechanical allodynia in male and female mice after approximately 10 days post PAC injection. These effects were largely dose-independent, with some effects larger in females versus males. Both doses of CBD prevented the development of PAC-induced cold and mechanical allodynia, and these effects were statistically significant from PAC alone. Therefore, adjunct treatment with CBD during chemotherapy treatment with PAC may be effective in the prevention or attenuation of CINP. (Supported by R01 CA129092.)

Magnetic Resonance Imaging of Isoproterenol-Induced Cardiac Stress Reveals a Reduction in Cardiac Reserve in Heart Failure Mice. Daniel Richards*, Weike Bao, Mary Rambo, and Stephen Lenhard; GlaxoSmithKline, 709 Swedeland Rd, King of Prussia, PA, 19406-0939

Exercise intolerance is defined as the inability of the heart to increase its working capacity during exercise and is one of the most common symptoms of Heart Failure (HF). Animals in this condition can be thought of as having a low cardiac reserve. Isoproterenol, a non selective β_1/β_2 receptor agonist, is used clinically for bradycardia and is also an established inotrope. The aim of this study was to develop an in vivo magnetic resonance imaging (MRI) technique capable of detecting cardiac reserve changes in normal and HF mice. These changes would then be correlated with measured exercise tolerance. It was hypothesized that HF animals would show a reduction in cardiac reserve. Following a baseline Exercise Tolerance Test (ETT), C57BL/6J mice (n=20) were divided into 4 equal groups, then randomly subject to Transverse Aortic Constriction (TAC), Myocardial Infarction (MI) or sham surgery in the subsequent week. 5 of the mice formed an additional non-surgery 'normal' control group. Mice underwent an ETT each week for 4 weeks following surgery. At the end of the 4^{th} week all animals were subject to a baseline cardiac MRI, measuring Ejection Fraction (EF%), End Systolic/Diastolic Volumes (ESV/EDV) and Heart Rate (HR), to calculate Stroke Volume (SV) and Cardiac Output (CO). The MRI was repeated, but with Isoproterenol (1mg/kg BW) injected intraperitoneally immediately prior. ETT duration is significantly reduced in MI/TAC vs. Sham/Normal mice at 1 week post surgery. This difference is lost at further time points. Isoproterenol significantly increases EF% in Sham, TAC and Normal mice ($P<0.01$) and in MI mice ($P<0.05$). Isoproterenol has no effect in MI infarct-only tissues. Absolute EF% increases are significantly less for MI mice than Sham, TAC and Normal, especially in infarct-only tissue regions ($P<0.05$). EDV and ESV are both reduced by Isoproterenol in all mice. HR is increased ($P<0.01$), whilst SV remains constant. CO increases significantly in all but MI mice. These data indicate that when stressed, our HF animal models exhibit some cardiac reserve, but the ability to adapt to stress is significantly reduced in MI mice. This could be the main causal factor of exercise intolerance 1 week post surgery, before the impact of compensatory mechanisms. Future studies will be aimed at determining if cardiac reserve is recovered beyond 4 weeks.

Graduate Student/Research Associate Division

Behavioral and Biochemical Characterization of the Mouse 5-HT$_{2A}$ Receptor. John P. Dougherty* and Vincent J. Aloyo; Drexel University College of Medicine, Philadelphia, PA 19102

Serotonin 2A receptors (5-HT$_{2A}$Rs) modulate learning and memory and are involved in the cognitive deficits present in many disorders. Although often studied in rats and rabbits, 5-HT$_{2A}$R binding properties and the effects of chronic drug treatment on receptor density and 5-HT$_{2A}$R-mediated behaviors are largely unknown in mice. The current study had two goals, determining: 1) binding properties of the mouse 5-HT$_{2A}$R and 2) the effects of chronic drug treatment on mouse behavior and 5-HT$_{2A}$R density. Binding properties were determined via radioligand binding assay using mouse cortex. Effects of chronic drug treatment were determined by treating adult male C57BL/6N mice with 5-HT$_{2A/2C}$R agonist, DOI, or 5-HT$_{2A}$R antagonist, MDL 11939, for eight days. Twenty-four hours after the eighth day of treatment, all mice received an injection of DOI and their behavior was observed. Mice were then sacrificed, their cortices dissected and frozen for later 5-HT$_{2A}$R density determination. Head twitch responses (HTRs), a distinct, 5-HT$_{2A}$R-mediated mouse behavior, are spontaneously-occurring and can be drug-elicited. On select days, DOI-elicited HTRs were counted as a behavioral measure of 5-HT$_{2A}$R activation. Mouse HTRs were consistent with 5-HT$_{2A}$R density in all groups. Similar to rabbits and rats, mice treated with DOI for eight days had reduced cortical 5-HT$_{2A}$R density. In contrast to the 5-HT$_{2A}$R up-regulation observed in rabbits, however, treatment with MDL 11939 for eight days did not alter 5-HT$_{2A}$R density in mice.

The Role of Acute Pain States on Morphine's Antinociceptive and Conditioned Rewarding Effects in C57Bl6 Mice. Harshini Neelakantan*, Joel John, Sara Jane Ward, and Ellen A. Walker; Temple University School of Pharmacy, Department of Pharmaceutical Sciences, Philadelphia, PA, 19140

The prescription opioid morphine functions as a potent analgesic although its rewarding effects, and therefore potential abuse liability, are a concern. Understanding the relationship of analgesia and reward would increase the safe use of this drug for clinical pain management. The purpose of our study was: 1) to define two properties of morphine, antinociception and reward in mice, using

the hot-plate assay and conditioned place preference (CPP) in our laboratory; and, 2) to assess the modulating effect of acute pain states on morphine conditioned reward. The range of antinociceptive effectiveness of morphine was tested using a hot-plate with varying temperatures in Swiss-Webster mice. The latency to hind-paw lick was measured following treatment with morphine (0.32-10 mg/kg, IP). Results showed that middle to high doses of morphine were fully antinociceptive with the effects of morphine being both dose- and temperature-dependent. The influence of acute pain states on morphine reward was assessed using the conditioned place preference (CPP) paradigm using a pseudo-biased design. Mice were either pretreated with 0.4% acetic acid or had hot-plate exposure 4 h prior to saline or morphine conditioning on alternative days for 6 days. The time spent in the morphine-paired side was calculated on the test day for each of these groups and compared. Results demonstrated that while morphine CPP was significantly reduced in the acetic acid treated mice, morphine CPP was enhanced in the mice with hot plate exposure. In conclusion, pain states differentially modulate the rewarding effects of morphine. Understanding of whether pain states protect or predispose patients to prescription opioid abuse has important clinical implications. (Supported by R01 CA129092).

Paclitaxel Impairs Learning and Memory in Mice. Emily B. Bisen-Hersh*[1,2], Christopher S. Tallarida[3], and Ellen A. Walker;[1,3]; Neuroscience Program[1], Department of Psychology[2], and Department of Pharmaceutical Sciences,[3] Temple University, Philadelphia, PA 19140

Cognitive impairment has been self-reported and observed in patients receiving cancer chemotherapy, also termed “chemo-fog,” and is thought to be the result of neurotoxic effects of chemotherapeutic agents. In addition, women receiving adjuvant treatment for breast cancer may be particularly vulnerable. Preclinical research has been useful in directly testing these agents, although studies are generally limited to older chemotherapeutic agents and male rodents. One chemotherapeutic agent commonly used in breast cancer regimens is paclitaxel, a mitotic inhibitor. This agent was tested using both male and female Swiss-Webster mice in a model of learning and memory called autoshaping. On Day 1, mice were pretreated with an injection (i.p.) of vehicle (saline or cremophor) or paclitaxel (4, 8, 12, 16, or 32 mg/kg). Mice were then trained to respond in a recessed hole to earn an Ensure® solution in the presence of an audible tone, presented on a variable-interval schedule, to measure acquisition. This task was repeated on Day 2 to measure retention. Each session lasted 2h or until 20 reinforcers were obtained. On Day 1, dose-dependent deficits in acquisition, reinforced responding, and general activity rate were found in males, whereas only deficits in reinforced responding and general activity rate were found in females. On Day 2, dose-dependent deficits in retention and reinforced responding were found in both males and females. In addition, there was a significant interaction between sex and drug dose on Day 2, with females displaying a lower rate of reinforced responding and taking longer to complete the session. These results suggest that performance on the autoshaping task differs between male and female mice, and this difference is enhanced by higher doses of paclitaxel. (Supported by CA129092 and T32 DA07237).

Continuous Cefriaxone Administration Delays Acquisition of Autoshaped Responding in Mice. Joel S. John*, Scott M. Rawls, and Ellen A. Walker; Department of Pharmaceutical Sciences, Temple University, Philadelphia, PA 19140

Although glutamate transporter subtype 1 (GLT-1) is a promising target for the development of CNS therapies, one potential liability of transporter activation may be effects on learning and memory. Therefore, we studied the effects of ceftriaxone, a beta-lactam antibiotic that activates GLT-1 transporter, on learning and memory in mice. Male C57Bl6 mice were injected i.p. with saline or one of two doses of ceftriaxone (100-200 mg/kg) for 10 days. On Day 11, mice were placed within experimental chambers to measure the acquisition of nose-poke responding in the presence of an audible tone presented on a variable-interval schedule to earn Ensure® solution. On Day 12, mice were placed back into the chambers to measure the retention of the response. The 200 mg/kg cefriaxone treated group showed deficits in acquisition on Day 11, but no deficits in response rates and general activity. No notable deficits were found in acquisition, response rates or general activity for the saline or the 100 mg/kg ceftriaxone group. Although the high dose cefriaxone treatment altered acquisition of learning, there were no noticeable deficits in retention and or response rates on Day 12 for any of the three groups. These results suggest that GLT-1 transporter activation may temporarily impede acquisition without longer term consequences on retention. (Supported by R01CA129092 [EAW] and RC1DA028153 [SMR].)

Effect of Single-Prolonged Stress on Anxiety and Cocaine-Induced Behaviors. Nicole Enman* and Ellen M. Unterwald; Temple University School of Medicine, Dept. of Pharmacology and Center for Substance Abuse Research, Philadelphia, PA 19140

Exposure to severe stress can lead to the development of post-traumatic stress disorder (PTSD) resulting in symptoms such as fear, anxiety, and depression. The occurrence of PTSD is highly comorbid with addiction to drugs of abuse, suggesting that PTSD may facilitate vulnerability to substance abuse. This study examined the effect of single-prolonged stress (SPS), a rodent model of PTSD, on behavioral activity, anxiety-like behavior, and cocaine-induced behaviors. Adult male Sprague-Dawley rats were exposed to a modified single-prolonged stress paradigm consisting of 2 hours of restraint stress, 20 minutes of group swimming, isoflurane exposure until loss of consciousness, and 7 days of isolation. Control animals were handled and weighed daily. Following isolation or control handling, activity was measured for 24 hours. Rats exposed to SPS exhibited significantly less activity than unstressed controls. Anxiety-like behavior was measured with two tests, the defensive burying paradigm and elevated plus maze. For the defensive burying, each rat was placed into a test cage with an electrified shock-probe for 15 minutes, and behavioral responses were scored. Preliminary data show an increase in duration of burying, shock reactivity, freezing behavior, and height of bedding in SPS rats compared to controls, indicating a heightened response to shock threat. In contrast, behavior on the elevated plus maze was not significantly different between groups. To investigate the effect of SPS on acute cocaine-induced locomotion, rats were injected with cocaine (10 mg/kg, i.p.) and locomotor activity was recorded. SPS did not affect acute cocaine-induced locomotion compared to control handling. To assess the development of cocaine-induced sensitization, rats were injected

with cocaine (10 mg/kg, i.p.) once daily for four days, followed by a cocaine challenge 7 days later. SPS and control rats developed significant sensitization to the stimulant effects of cocaine and no difference was observed between groups. A conditioned place preference paradigm was used to determine the effect of SPS on the development of cocaine-conditioned reward. Preliminary results show that control rats spent more time on the drug paired side of the conditioning chamber than rats that underwent SPS, suggesting a reduction in sensitivity to cocaine reward. Data from the present study suggest that SPS enhances anxiety-like behavior, as well as attenuates behavioral activity and the development cocaine conditioned reward. Future studies will examine the effect of single-prolonged stress on stress-induced reinstatement to cocaine seeking.

Role of 5-HT$_{2C}$ Receptors in the Regulation of Cocaine-Induced Behaviors. Caryne Craige* and Ellen Unterwald; Temple University School of Medicine, Department of Pharmacology, Center for Substance Abuse Research, Philadelphia, PA 19140

Previous studies have identified an inhibitory regulatory role of the 5-HT$_{2C}$ receptor in dopamine neurotransmission. Activation of 5-HT$_{2C}$ receptors has been shown to decrease cocaine-induced dopamine release in mesolimbic brain areas associated with reward circuitry. In this context, administration of 5-HT$_{2C}$ agonists prior to cocaine administration elicits an attenuation of cocaine-induced behaviors such as hyperactivity and cocaine self-administration. In this study, the role of 5-HT$_{2C}$ receptors in cocaine-induced, dopamine-mediated behaviors was investigated using C57/Bl6 male mice in the Conditioned Place Preference paradigm. Alterations in cocaine-seeking behavior were assessed using a biased version of this model, in which mice were treated with either a 5-HT$_{2C}$ receptor agonist or antagonist 30 minutes prior to cocaine administration (10 mg/kg, i.p.). Immediately following cocaine administration, mice were placed in the treatment-paired side of the testing chamber. On alternate days, mice were injected with saline and placed in the opposite side. Preference was tested in a drug-free state after 4 days of conditioning. Locomotor activity was assessed on each day while in the testing chambers. Administration of a selective 5-HT$_{2C}$ agonist, RO 60-0175 (1, 3, 10 mg/kg, i.p.), prior to cocaine exposure dose-dependently attenuated conditioned place preference behavior as well as cocaine-evoked hyperactivity. Likewise, administration of a selective 5-HT$_{2C}$ antagonist, SB 242084 (0.3, 1, 3 mg/kg, i.p.), potentiated cocaine-evoked conditioned place preference and cocaine-evoked hyperactivity in a dose-dependent manner. This study supports a role for the 5-HT$_{2C}$ receptor in regulating dopamine-mediated behaviors following cocaine exposure, thus identifying a potential pharmacological therapeutic target in preventing relapse and promoting abstinence in cocaine-dependent individuals.

The Regulation of GSK3 Activity by the Acute Administration of Selective Dopamine Receptor Agonists *In Vivo.* Yi-Ting Chiu*[1] and Ellen Unterwald[1,2]; [1]Department of Pharmacology and [2]Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA 19140

Glycogen synthase kinase-3 (GSK3) is one proposed downstream target of dopamine receptors. Previous studies suggest that GSK3 may participate in dopamine receptor mediated signaling and may be important in conditions associated with dopaminergic dysfunction such as schizophrenia and drug addiction. Indirect evidence suggests that dopamine receptors, particularly D2 receptors, can modulate GSK3 activity in mouse striatum. However, there is no study that directly examined the impact of activation of D1 or D2 receptors by selective agonists on Akt/GSK3 signal pathways in the caudate putamen (dorsal striatum) and the nucleus accumbens (ventral striatum). Here, we used selective D1 and D2 receptor agonists to examine the phosphorylation levels of Akt and GSK3 with western blot. GSK3 is inactivated by phosphorylation at its Ser21 (α isoform) or Ser9 (β isoform) and activated by phosphorylation at its Tyr279 (α isoform) or Tyr216 (β isoform). Akt is an upstream kinase that regulates the phosphorylation of GSK3 and the activity of Akt is increased by phosphorylation. Acute administration of D2 receptor agonist (quinpirole, 2mg/kg) to adult male CD1 mice increased phosphorylation levels of Akt (Thr308) and GSK3 (Ser21 and Ser9), but not pTyr-GSK3 at short time points (15, 30 and 60 minutes) in the caudate putamen and the nucleus accumbens. Acute administration of D1 receptor agonist (SKF82958, 1mg/kg) increased pSer21-GSK3α at 30 minutes and decreased pSer9-GSK3β at 60 minutes in the caudate putamen, but not in the nucleus accumbens. Therefore, D1 and D2 receptors showed different regulation of the activity of GSK3 in the mouse striatum.

Exploration of Doxorubicin as a Chemically Induced Model of Cardiomyopathy in C57BL Mice. Kristeen Maniscalco*, Lisa A. Morgan, Steve C. Lenhard, Meridith Crowell, Victoria L. Ballard, Alan R. Olzinski, and Beat M. Jucker; Heart Failure DPU, Laboratory Animal Sciences, GlaxoSmithKline, King of Prussia, PA 19406

Introduction: Doxorubicin (DOX) is a potent antitumor agent with known cardiotoxic side effects, potentially resulting in unmanageable heart failure. *Purpose:* The purpose of these studies was to comprehensively evaluate DOX as a potential agent that can induce cardiomyopathy and heart failure in mice. *Methods and Results:* All studies were conducted after review by the GSK Institutional Animal Care and Use Committee and in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals. A single dose of DOX (10, 15 or 20 mg/kg, i.p.) was explored in C57Bl mice for up to 14 days. End points included echocardiography, MRI, voluntary running distance, plasma cardiac biomarkers Cardiac Troponin T (cTnT), Cardiac Troponin I (cTnI), Myosin-Like Chain (MLC) and Fatty Acid Binding Protein 3 (FABP3), blood chemistry, body weights, DEXA, heart and skeletal muscle histology. Echocardiography and MRI revealed minimal cardiac performance changes at any dose at day 14. The total distance run was age dependent with older mice running less overall, treatment with DOX decreased running distance in both age groups. There were significant increases in either the 10 and/or15mg groups compared to vehicle in the following biomarkers: cTnT 244% (10mg), cTnI 228% (15mg), MLC 111% (15mg), FABP3 164% & 143% (10 & 15mg, respectively). There were no abnormal changes in blood chemistry profile. At Day 7 the average body weight decreased, compared to vehicle, 17% and 21% in the 10 and 15mg/kg dose groups, respectively. Body fat, total tissue mass and calculated lean muscle mass, were all significant-

ly decreased, as compared to vehicle. Pathology from immunohistochemistry demonstrated cardiac-focal areas of degeneration with minimal cardiac fibrosis and no evidence of any abnormal findings in the skeletal muscle. There was a significant (P=<0.001) decrease in heart weight when normalized to tibia length (16%, 25%) in the 10 and 15mg/kg groups, respectively. *Conclusions:* In doses that were not lethal by day 7 (<20mg/kg), DOX administration resulted in pronounced exercise intolerance, increased biomarkers of cardiac injury results, and reduction in cardiac mass with minimal cardiac performance changes. Therefore while DOX results in whole body and cardiac pathology, it can do so without exhibiting characteristics of decompensated heart failure in the mouse.

Arf6 Regulates CXCR4-Mediated Migration and Invasion of Metastatic Breast Cancer Cells. Jacqueline Freed* and Catherine C. Moore; Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy (PCP), University of the Sciences in Philadelphia (USciences), Philadelphia, PA 19104

The research presented here focuses on novel targets for cancer therapeutics, the G protein-coupled receptor CXCR4, and the monomeric G protein Arf6. CXCR4 is a chemokine receptor essential for neuronal, cardiovascular, and hematopoietic cell migration towards its ligand, SDF, and is now recognized to play a critical role during cancer metastasis. Dysregulation of the SDF-CXCR4 axis on nonmotile primary tumor cells confers an aberrant migratory capacity and promotes metastatic homing of tumor cells to distal SDF-expressing organs. Metastasis is the major cause of mortality in cancer patients, therefore these findings have led to vigorous attempts in identifying the factors that contribute to CXCR4 dysregulation in cancer. We propose a model in which Arf6 contributes to the mechanism of CXCR4 dysregulation in metastasis, and may therefore serve as a potential therapeutic target. Previously we identified Arf6 as a novel regulator of the SDF-CXCR4 axis, whereby it enhances both CXCR4 cell surface levels and CXCR4 signaling to membrane-delineated ERK. Notably, overexpression of an inactive Arf6 mutant or siRNA knockdown of endogenous Arf6 both reduce CXCR4 at the cell surface. Here we addressed the role of Arf6 in CXCR4-mediated migration and invasion of highly invasive breast cancer cells, MDA-MB-231. Specifically, we assessed the effects of siRNA-mediated knockdown of endogenous ARF6 on CXCR4-mediated migration and invasion in response to an SDF gradient, as measured by transwell cell motility assays. Our results demonstrate that in MDA-MB-231 cells, siRNA-mediated knockdown of endogenous Arf6 inhibits both migration and invasion in response to SDF. These results provide novel insight into the role of endogenous Arf6 in regulating CXCR4, and support the model that Arf6 contributes to the mechanism of CXCR4 dysregulation in metastatic cancer cells.

These studies were supported by a New Investigator Program grant from AACP, SS-09 and SS-10 grants and start-up funds from USciences.

Functional Characterization of a Small Molecule Inhibitor, SB431542 Specific for TGF β Type I Receptor Using a UVB Induced Skin Carcinogenesis Model. Anand Ravindran*, Javed Mohammed, and Adam B. Glick; Pennsylvania State University, State College, PA 16802

Small molecule inhibitors are important in demonstrating the role of key signaling pathways in pathological disorders with their potential use as therapeutics especially for pathways, which are activated in disease conditions. TGF β represents an important growth regulatory cytokine with critical roles in modulating tumor formation and progression. Numerous reports have established the dual roles - tumor-protective or tumor-promoting roles of TGF β depending on the specific stage of tumor development. Moreover, up regulated TGF β pathway has been shown to be a common phenotype of advanced stage cancers. A small molecule inhibitor for the TGF β pathway will provide an opportunity to target specifically the tumor-promoting property of TGF β pathway while retaining the anti-tumor function. Here, we studied the role of long term inhibition of TGF β pathway with a small molecule inhibitor, SB431542 specific for the TGF β type I receptor in UVB induced skin carcinogenesis. Topical SB431542 treatment significantly reduced the average number of papillomas upon chronic UVB relative to the vehicle treated group. In order to establish the mechanism for the difference in tumor kinetics, we analyzed the differences in immune responses with SB431542 inhibition. There was a significant loss in the infiltration of CD4+ and CD8+ lymphocytes within the tumors treated with SB431542. In addition, there was also a decrease in the IFNγ secretion by CD4+ and CD8+ cells. Consistent with this, there was a significant reduction in the proliferative response of the skin draining lymph node cells when stimulated in vitro. In summary, the inhibition of TGF β1 pathway with SB431542 provides resistance to the tumor promoting properties of chronic IFNγ presence in the skin microenvironment resulting in decreased number of tumors in UVB skin carcinogenesis.

Prenatal Administration of Melatonin or Melatonin Receptor Antagonist Luzindole Disturbs Adult Behavior and Hippocampal Gene Expression of Male Rats. Joshua A. Ripple, BS* and Kathleen C. Page, PhD; Bucknell University, Lewisburg, PA 17837

Disturbances in melatonin—the neurohormone that indicates darkness—have been implicated in the etiology and pathophysiology of various mental illnesses in humans. Research on developmental outcomes for fetuses of mothers receiving melatonin supplementation or drugs that reduce melatonin signaling during pregnancy is lacking. We hypothesized that administration of melatonin (5 mg/kg) or the melatonin receptor antagonist luzindole (5 mg/kg) to pregnant Sprague-Dawley dams during days 14-18 of gestation would elicit permanent changes in behavior, neuroendocrine function, and hippocampal gene expression in adult offspring. Subjects exposed to melatonin prenatally displayed increased exploratory behavior as evidenced by rearing in the open field test; however, animals administered luzindole prenatally spent more time freezing and grooming in the open field test and showed a trend toward decreased intercept and reduced slope of the learning curve in the Morris water maze. Analysis of relative adult hippocampal gene expression with qRT-PCR revealed increased expression of brain-derived neurotrophic factor (BDNF) with a trend toward increased expression of melatonin 1A receptors (MEL1A) in melatonin-exposed animals compared to controls. Moreover, prenatal treatment increased microtubule-associated protein 2 (MAP2) expression in luzindole-treated ani-

mals compared to controls. These data support our hypothesis that the manipulation of fetal melatonin signaling alters development and leads to physiological and behavioral abnormalities in adult offspring. Furthermore, we designate the term circadioneuroendocrine (CNE) axis to stress the functional interdependence of the hypothalamic-pituitary-adrenal axis and circadian circuit and propose the CNE axis hypothesis of psychopathology.

Captopril Prevents and Reverses Cardiac Hypertrophy in Mice Subjected to Transverse Aortic Constriction (TAC) by Inactivating the Fetal Gene Program and Reducing Fibrosis. John J Upson*, Tao Wang, Lisa A Morgan, Alan R Olzinski, Gerald P McCafferty, Roberta E Bernard, Stephen Lenhard, Shufang Q Zhao, Kristeen Maniscalco, Thimmaiah P Chendrimada, Mark R Harpel, Robert N Willette, and Beat M Jucker; GlaxoSmithKline, Heart Failure DPU, Metabolic Center for Excellence in Drug Discovery, UW2523, King of Prussia, PA 19406

Cardiac hypertrophy in response to pressure overload is initially an adaptive response aimed at maintaining normal cardiac function. However, the prolonged hemodynamic burden ultimately leads to decompensated heart failure. The diverse signaling cascades known to contribute to the development of cardiac hypertrophy are a source for drug discovery targets. In particular, the renin-angiotensin system has been implicated in cardiac hypertrophy, and angiotensin-converting enzyme (ACE) inhibitors have been shown to prevent pathologic cardiac hypertrophy in several animal models. We used a mouse model of left ventricular pressure overload induced by transverse aortic constriction (TAC) and the ACE inhibitor captopril to characterize genetic changes associated with the pathogenesis of cardiac hypertrophy. Transcriptomic profiling of left ventricles from TAC animals (normalized to sham operated groups) were compared following vehicle or captopril treatment for two days, two weeks or six weeks. Unexpectedly, heart weight-to-body weight (HW/BW) ratio was not significantly increased in the vehicle group (6%) at 2 days, but increased significantly in the captopril treated group (17%). In contrast, HW/BW was significantly increased at both two and six weeks in the vehicle group (48% and 69%, respectively), and this increase was repressed by captopril at both time points (18% and 24%, respectively). Gene expression analysis revealed a strong correlation between cardiac hypertrophy and activation of the fetal gene program, upregulation of fibrosis and alterations in metabolism, inflammation, calcium signaling and apoptosis. Captopril treatment exacerbated these gene changes at two days post-TAC, but significantly attenuated them at both two and six weeks. Captopril's ability to reverse hypertrophy was evaluated by beginning treatment regimens two weeks after TAC. TAC resulted in a significant increase in left ventricular mass-to-body weight (LVM/BW) ratio at both two and six weeks (49% and 73%, respectively), and this increase was not only repressed by captopril but reduced below pre-dose values (38%). Gene expression analysis of left ventricle revealed nearly identical expression profiles for six week TAC animals treated with captopril either immediately after surgery or beginning two weeks after surgery. These results demonstrate that TAC-induced cardiac hypertrophy and fibrosis in the mouse can be prevented and reversed by ACE inhibition through inactivation of the fetal gene program.

All studies were conducted after review by the GSK Institutional Animal Care and Use Committee and in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals.

Glucagon-like Peptide-1 Mediated Cardioprotection Involves Metabolic Substrate Switching and Increasing Energy Efficiency in the Rat Heart. Karpagam Aravindhan*, Weike Bao, Mark R. Harpel, Robert N. Willette, John J. Lepore, and Beat M. Jucker; Heart Failure Discovery Performance Unit, Metabolic Pathways CEDD, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406

In animal models, glucagon-like peptide-1 (GLP-1) elicits cardiovascular benefits beyond its role in systemic glycemic control; however, the precise mechanisms remain unresolved. Here we show that GLP-1 plays a direct cardioprotective role in rat by enhancing myocardial glucose utilization and promoting an energetically-favorable metabolic substrate switch only in the non-ischemic region but not in the ischemic region of the heart. *Methods:* In ischemia/reperfusion (I/R) experiments, Sprague Dawley rats were randomized to receive vehicle or GLP-1 during 30 min of cardiac ischemia followed by 3-24 hr of reperfusion. In addition to myocardial infarct size, relative carbohydrate and fatty acid oxidation was measured in both normal and I/R injured hearts after 1-^{13}C glucose clamp and NMR-based isotopomer analysis. Myocardial glucose utilization and lactate production were assessed in normal hearts using [^{3}H]-2-deoxyglucose uptake measurements and Langendorff perfusion, respectively, and O_2 consumption in adult rat ventricular myocytes (ARVM) was assessed using the Seahorse Bioscience XF Analyzer, all following treatment with GLP-1 at maximum effective dose. *Results:* In I/R injured hearts, GLP-1 reduced myocardial infarct size (↓27% of ischemic area, $p<0.05$, N=6) and increased contractility (↑20% of +dP/dt, $p<0.05$, N=6). GLP-1 also induced metabolic substrate switching by increasing the ratio of carbohydrate vs fatty acid oxidation (↑14%, $p<0.01$, N=6) in the LV non-ischemic border zone. No substrate switching occurred in the LV ischemic zone, despite an increase in cAMP (↑106%, $p<0.05$, N=5) and lactate (↑121%, $p<0.01$, N=6). In normal hearts *in vivo*, GLP-1 increased glucose uptake (↑64%, $p<0.05$, N=8), without affecting glycogen levels, and in Langendorff perfused isolated hearts, GLP-1 increased glucose uptake and lactate production by 1.9-fold and 2.6-fold, respectively. In ARVM, GLP-1 decreased O_2 consumption (by 23%, $p<0.05$, N=4), consistent with a switch from fatty acid to carbohydrate oxidation. *Conclusion:* GLP-1 mediates cardioprotection following cardiac I/R injury in rat. Our results show that this benefit may derive from a direct role for GLP-1 on the myocardium. While anaerobic glycolysis may contribute to ischemic cardioprotection, a shift to more energetically favorable carbohydrate oxidation in healthy, non-ischemic myocardium may play a beneficial role in maintaining cardiac contractility.

ASPET WELCOMES THE FOLLOWING NEW MEMBERS

REGULAR MEMBERS

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Adrian Chrastina, PhD, Proteogenomics Res. Inst. for Systems Med.
Maria A. Croyle, PhD, Univ. of Texas at Austin Col. of Pharmacy
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Patrick T. Ronaldson, PhD, Univ. of Arizona

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Oladoja Awofisayo, Univ. of Uyo
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Anil Bhatta, Georgia Health Sciences Univ.
Dustin E. Bosch, Univ. of North Carolina-Chapel Hill Schl. of Med.
Kirsten L. Bryant, Cornell Univ.
Lani S. Chun, NIH/NINDS

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Krishna E. Tobon, New Jersey Med. Schl.- UMDNJ

IN SYMPATHY

ASPET Notes with Sympathy the Passing of the Following Members:

Ivan T. Beck, MD, PhD

Chen-Yuan Lee, MD

Charles (Bob) Schuster, Ph.D.

OBITUARY

Nancy White, ASPET's Meeting Manager from 1996 to 2009, passed away on February 17 after a two and a half year battle with ovarian cancer. Nancy was familiar to anyone who organized or spoke in any session at the ASPET annual meeting as she worked with them extensively prior to the meeting, made sure that everything ran smoothly at the meeting, and followed up with them after the meeting. She was also ASPET's Council Assistant, making all the arrangements for the Council Meetings. Nancy retired in 2009 and was able to spend some time pursuing her long-time interest in antiques.

Definitions of Categories of ASPET Membership

Regular Members: Any doctoral level investigator who has conducted and is the primary author on at least one publication of an original study in the area of pharmacology published in a peer-reviewed journal is eligible for membership in ASPET. Exceptions may be made for someone who does not meet the degree requirement but who has made major research contributions to pharmacology. Dues for regular members are $140/year. Regular members must be nominated by one (1) Regular or Retired ASPET member.

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Sponsors should send an email or letter addressing the applicant's qualifications for ASPET membership directly to the ASPET office (rphipps@aspet.org).

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

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- Sponsor candidates for Student membership only.
- Not sponsor a paper for a non-member at a Society meeting.
- Not vote in Society elections.
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- Pay only $30 annual dues thereafter. Undergraduate student members pay no dues and get their first graduate year free.
- 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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Submit the completed Application for Membership form or use the online application form on the ASPET web site at **http://www.aspet.org/membership/apply/.** 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**.

Sponsor Statements: Submit a statement of qualifications of the applicant from one Regular/Retired Member of ASPET for Regular Membership, Affiliate Membership and Student Membership (Affiliate Members may also sponsor student applicants). In addition to the statement certifying that the applicant is qualified for ASPET membership, sponsors should provide their own current address, phone, fax, and email. It is the responsibility of the applicant to insure that these documents are submitted to the ASPET office.

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Membership Application – TP0311

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Application for:

❑ **Regular Membership**

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❑ **Graduate Student – Expected Date of Graduation:** _____

❑ **Undergraduate Student - Year:** ❑ **Fr** ❑**Soph** ❑**Jr** ❑**Sr**

Section 2: Source

How did you hear about ASPET:

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Name:

Institution:

Address:

Telephone:

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Section 4: Optional Demographics (Not Required)

Date of Birth: _____

Sex: ❑ Female ❑ Male

Ethnicity:

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❑ Black or African American

❑ American Indian or Alaskan Native

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❑ Native Hawaiian or Pacific Islander

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The information in this section will be used by ASPET to collate statistics and will be kept private. Completion of this section is voluntary.

Section 5: Sponsor (Must be an ASPET Member)

Name and email of your sponsor:

Please have your sponsor send us a brief letter or e-mail outlining your qualifications for membership in ASPET to the Membership Coordinator , Robert Phipps, (rphipps@aspet.org).

Section 6: Division Selection

Divisions: *Division membership is a benefit of ASPET membership and there is no additional charge to belong to a division. It is highly recommended that you join a division so that you may take full advantage of Society participation. Joining a division allows you to participate in creating the scientific program for the annual meeting, network with people in your field at mixers and divisional programs, and receive special notices and newsletters about items and activities of interest in your field. Be sure to pick a division!*

Indicate primary (1) and as many secondary (X) divisions to which you wish to belong:

___Division for Behavioral Pharmacology
___Division for Cardiovascular Pharmacology
___Division for Drug Discovery, Development & Regulatory Affairs
___Division for Drug Metabolism
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___Division for Molecular Pharmacology
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Section 7: Curriculum Vitae

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Current Education :

Expected Degree & Date:	School:	City/State/Country:	Major Field:

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