

Kenneth P. Minneman, Annette E. Fleckenstein, and Terrence J. Monks Elected to ASPET Office



Kenneth P. Minneman
President-Elect



Annette E. Fleckenstein
Secretary/Treasurer-Elect



Terrence J. Monks
Councilor

Kenneth P. Minneman, Professor of Pharmacology at Emory University Medical School in Atlanta, Georgia, will assume the duties and responsibilities of President-Elect of ASPET in July 2006. Dr. Minneman has previously served on Council as a Councilor and is the Past Chair of the Division for Molecular Pharmacology. Annette E. Fleckenstein, Associate Professor of Pharmacology and Toxicology at the University of Utah, will become Secretary/Treasurer-Elect in July 2006. She is a past Secretary/Treasurer of the Division for Neuropharmacology. Dr. Terrence J. Monks, Professor and Chair of the Department of Pharmacology and Toxicology at the University of Arizona Health Sciences Center College of Pharmacy, will assume the position of Councilor in July 2006. He has served on the Program Committee and is a Past Chair of the Division for Toxicology.

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The PHARMACOLOGIST

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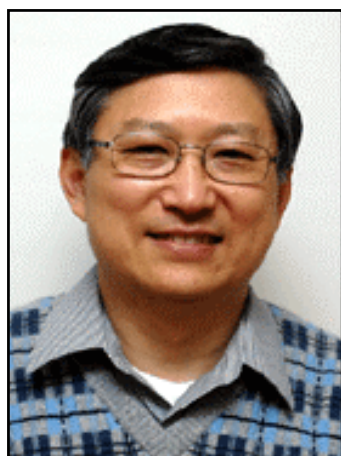
Christopher M. Counter, Ph.D.
John J. Abel Award

Christopher M. Counter, Ph.D., Associate Professor in the Department of Pharmacology and Cancer Biology at Duke University, is the recipient of the 2006 John J. Abel Award, sponsored by Eli Lilly. Dr. Counter receives the John J. Abel Award as an outstanding young investigator for his contributions that have helped shape the field of pharmacology.

Dr. Counter and colleagues' work, the "Role of Telomere Length and Telomerase Activity in Cell Immortalization and Tumorigenesis," is a landmark paper that showed human cells acquire the ability to keep dividing indefinitely by overcoming telomere shortening via activation of the telomerase enzyme. This paper has been cited over 1000 times. Dr. Counter's work on the role of telomerase in initiating cancer as well as his discovery of the RalGEF pathway involvement in tumorigenesis provided the groundwork for a completely novel pharmacologic approach to not only

treating, but preventing cancer. Dr. Counter has expanded his studies of the relationship of telomerase to cancer to include clinical applications.

Dr. Counter completed his doctoral degree at McMaster University in Canada under the mentorship of Silvai Bacchetti and Calvin Harley. He began his research career as a Research Associate with Robert Weinberg at The Whitehead Institute of MIT. In 1998, Dr. Counter moved to Duke University.



John C. Lee, Ph.D.
Pharmacia-ASPET Award in Experimental Therapeutics

John C. Lee, Ph.D., of GlaxoSmithKline is the recipient of the 2006 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.

The research conducted by Dr. Lee and his colleagues led to the discovery of p38MAP Kinase and illustrated its critical role in inflammation signaling and in inflammatory diseases. His discovery of this kinase target and of selective p38MAP Kinase inhibitors and their pharmacology has led to their potential use in the treatment of several important diseases. The work has led to a broader appreciation of this kinase cascade in a variety of biologic processes and has fueled discovery and development projects throughout the pharmaceutical industry. Because of his research, nearly all major pharmaceutical companies have initiated projects around p38 inhibitors and there are now several promising candidate compounds in clinical trials.

After earning a Ph.D. in virology and immunology from the University of Miami School of Medicine, Dr. Lee completed a postdoctoral fellowship at the Oak Ridge National Laboratory. In 1975, he joined the National Cancer Institute at Frederick, Maryland, where he began his investigations in cytokine research. Dr. Lee moved to GlaxoSmithKline in 1982 where he is now site director, Department of High Throughput Biology.





Frank J. Gonzalez, Ph.D.
Bernard B. Brodie Award in Drug Metabolism

Dr. Frank Gonzalez, Chief of the Laboratory of Metabolism at the National Cancer Institute, National Institutes of Health, is the recipient of the 2006 Bernard B. Brodie Award based on his tremendous impact on the field of drug metabolism. The Brodie Award recognizes Dr. Gonzalez's outstanding contributions to our understanding of human drug metabolism and to future research in the field.

Beginning with his initial efforts to clone rodent and human P450 cDNAs and to characterize the functions of the expressed, recombinant enzymes, Dr. Gonzalez has sought to define the enzymatic properties, polymorphic expression and mechanisms of conditional regulation underlying inter-individual variation in human drug metabolism. These studies laid a foundation for the current use of expressed recombinant human drug metabolizing enzymes by the FDA and the pharmaceutical industry to identify the contributions of individual enzymes to drug metabolism. The work of Dr. Gonzalez and his colleagues also led to the characterization of allelic variants of several P450s including CYP2D6, CYP2A6 and CYP2C9 that contribute to inter-individual differences in drug metabolism. His laboratory has led the effort to develop mouse models for the study of drug metabolism. Gene knockouts in mice for both specific P450 enzymes and transcription factors that regulate P450 expression were generated. In vivo models for human drug metabolism, produced using human genomic clones as transgenes, have been of value to study mechanisms governing the tissue-specific and regulated expression of human P450s as well as to predict human drug metabolism and toxicity. These genetically engineered mice provide integrated biological models to study the potential physiological roles of P450s and their regulation. The knockout and humanized mouse models developed by Dr. Gonzalez are also widely used for research in areas that include toxicology, carcinogenesis and the regulation of lipid homeostasis.

Dr. Gonzalez will give the B. B. Brodie Lecture, entitled "Acetaminophen Metabolism and Hepatotoxicity: 35 Years Since B. B. Brodie" on Monday April 3, from 1:30 pm to 2:30 pm in Room 307 of the Moscone Convention Center.



Anthony R. Means, Ph.D.
Goodman and Gilman Award in Receptor Pharmacology

Dr. Anthony R. Means, Nanaline H. Duke Professor and Chairman of the Department of Pharmacology and Cancer Biology at Duke University Medical Center, is recipient of the 2006 ASPET/GlaxoSmithKline Goodman and Gillman Award.

Dr. Means' research at Duke focuses on the study of cell signals that regulate cell proliferation, differentiation or function, and how altering these pathways contributes to the onset of cancer. He hopes that improving the understanding of these pathways will provide clues that may be used to develop new drugs to combat the disease. He is the author of over 350 scholarly publications.

He earned his undergraduate and master's degrees from Oklahoma State University and his Ph.D. in Endocrinology from the University of Texas. Dr. Means completed a postdoctoral fellowship at the University of Melbourne in Australia. He then held faculty positions at Vanderbilt University and Baylor College of Medicine before joining the Duke faculty in 1991, where he has served as Chair of the Department of Pharmacology and Cancer Biology for 15 years.





Leonard Cook, Ph.D.

P. B. Dews Award in Behavioral Pharmacology

Dr. Leonard Cook, retired from the DuPont Merck Pharmaceutical Company, is the winner of the 2006 P.B. Dews Lifetime Achievement Award in Behavioral Pharmacology. The award is given every other year and honors the fundamental contributions of P.B. Dews to behavioral pharmacology.

Dr. Cook is internationally recognized as one of the foremost pioneers in behavioral pharmacology. He has contributed substantially to the discovery and evaluation of psychotherapeutics and to the career development of behavioral pharmacologists, who in their turn, have been leaders in the field.

Dr. Cook has established drug behavioral interactions that are presently taught as classical principles in this field.

Dr. Cook earned his Ph.D. from Yale University School of Medicine and subsequently joined Smith Kline & French Laboratories where he played a dominant role in the discovery of the first drugs for schizophrenia as well as in the early development of their Department of Pharmacology. Dr. Cook later joined Hoffmann-LaRoche where he was appointed Director of Pharmacology and led research in the identification of drugs for treating anxiety. In 1983 he joined DuPont de Nemours as director of their CNS research and expanded their CNS research program to focus on Alzheimer's disease therapy. Throughout his career, Dr. Cook has set the standard for CNS drug discovery programs in industry.

Dr. Cook has held academic posts as Adjunct Professor of Pharmacology at Temple Medical School and in psychiatry at the University of Pennsylvania. He was also Visiting Professor of Pharmacology at Beijing and Shanghai Medical Schools.

Dr. Cook will deliver the P.B. Dews Lecture, entitled "Reflections on My Career in Psychopharmacology," on Monday April 3, from 1:30 pm to 2:30 pm in Room 303 of the Moscone Convention Center.

Award winners will receive their awards at the ASPET Awards Ceremony on Saturday April 1 at 7:00 pm in Room 2002 of the NEW Moscone WEST Building.

A Reception will follow the Awards Ceremony and is open to all attendees at the meeting.



**NOTE
NEW
TIME!**

The ASPET Annual Business Meeting will precede the Awards Ceremony at 6:00 pm in Room 2002.



GRADUATE STUDENT TRAVEL AWARD WINNERS TO EB '06

Jazmin I. Acosta - Arizona State University
Isabel Arrillaga-Romany - Tufts University
John A. Allen - University of Illinois at Chicago
Leah Allen-Klee - University of Kentucky
Immaculate Amunom - University of Louisville
Ningfei An - LSU Health Sciences Center
Noelle C. Anastasio - University of Texas Medical Branch, Galveston
Cordelia Barrick - University of North Carolina
Marcel Bassil - Université de Montréal
Rayna M. Bauzo - Emory University
Jessica A. Bonzo - University of California San Diego
Diptiman Bose - University of the Pacific
Kelly E. Bosse - University of Michigan
Michael R. Braden - Purdue University
James Burston - Virginia Commonwealth University
R. Elaine Cagnina - University of Virginia
Manpreet S. Chahal - Washington State University
Curtis Robert Chong - Johns Hopkins University School of Medicine
Shinjae Chung - University of California, Irvine
Gregory T. Collins - University of Michigan
Tatiana Sousa Cunha - Wright State University
Mary F. Divin - University of Michigan
Nichole Dowdy-Sanders - University of Arkansas for Medical Sciences
Mitra Esfandiarei - University of British Columbia St. Paul's Hosp
Riham Z. Fardoun - University of Houston
Kristina M. Fetalvero - Dartmouth College
Julie R. Field - Vanderbilt University
Shobana Ganesan - University of Mississippi
Frederick Spencer Gaskin - University of Missouri School of Medicine
Alison Goddard - Queen Mary, University of London
Elizabeth Ann Hackler - Vanderbilt University
Ryan E. Hibbs - University of California, San Diego
Kristin L Hillman - University of North Dakota
Alexandra Hlavacova - Michigan State University
Katherine A. Jackman - University of Melbourne
Biny K. Joseph - University of Arkansas for Medical Sciences
Chris Jurgens - University of North Dakota
Karen M. Kassel - University of Nebraska Medical Center
Wu Ke - Medical College of Wuhan University
Gilbert Roland Kinsey - Medical University of South Carolina
Irene K. Klein - University of Illinois-Chicago
Laura M. Kreckler - Medical College of Wisconsin
Laura Leanne Lash - University of Texas Medical Branch, Galveston
Melissa Wei Li - Michigan State University
Susan McQuown - University of California, Irvine
Natavia Middleton - University of South Alabama
Wei Ni - Michigan State University



ASPET AWARD WINNERS FOR 2006

Emily A. Oestreich - University of Rochester
Theresa Operana - University of California, San Diego
Prajakta S. Palkar - University of Louisiana at Monroe
Margaret M. Panning - SUNY Upstate Medical University
Ravi Kumar Pasumarthi - University of South Carolina
Marina Viktoria Pazin - Northwestern University
Jesse Procknow - Saint Louis University
Nicholas M. Radio - Duquesne University
Toni L. Richards - University of Kansas Medical Center
Marcelo Rocha - UMDNJ - Robert Wood Johnson Medical School
Sharif M. Rumjahn - University of Nevada School of Medicine
Sandeep Samudre - Eastern Virginia Medical School
Rana Sawaya - University of Toronto
Rebecca L. Scotland - University of Kentucky
Zabeena P. Shaik - University of Arkansas for Medical Sciences
Aaron D. Smith - East Carolina University
Ryan C. Smith - Creighton University
Dongzhe Song - University of British Columbia
Xiaowei Sun - University of Alabama at Birmingham
Eva Hoi Ching Tang - University of Hong Kong
Jennifer N. Tichenor - University of Nevada School of Medicine
Kori Wallace - University of Virginia
Eric M. Wauson - University of North Carolina
Yan Weng - SUNY at Albany
Matthew R. Whorton - University of Michigan
Kelly S. Williamson - Oklahoma Medical Research Foundation
Kelly M. Witt - Creighton University
Susan K. Wood - University of Michigan
Ruiyu Xie - University of Arizona
Eun-Ja Yoon - Vanderbilt University
Mozow Yusof - University of Missouri-Columbia
Jiejun Zhang - University of Florida College of Medicine

YOUNG SCIENTIST TRAVEL AWARD WINNERS TO EB '06

Sathanandam S. Anand - University of Georgia
Jennifer M. Bomberger - Dartmouth College
Qing Feng - Dartmouth Medical School
Rob H.P. Hilgers - Medical College of Georgia
Michael Holinstat - Vanderbilt University Medical Center
Alireza Hosseini - Eastern Virginia Medical School
Varsha Iyer - Uniformed Services University for the Health Sciences
Archana Jha - State University of New York, Buffalo
Anita Lakatos - Emory University
M. Danet S. Lapiz - University of Texas Health Science Center at San Antonio
Aurea Elizabeth Linder - Medical College of Georgia
Ajaib S. Paintlia - Medical University of South Carolina
Gail Pereira do Carmo - McLean Hospital-Harvard Medical School
Yu Qiu - University of Minnesota
Stacey Reading - University of Vermont



Raudel Sandoval - University of Illinois at Chicago
Jamaluddin Shaikh - University of Mississippi
Hossam A. Shaltout - Wake Forest University
Hirofumi Suzuki - University of Georgia
Jeffery N. Talbot - University of Michigan Medical School
Huda Tawfik - Medical College of Georgia
Yoav E. Timsit - National Institute of Environmental Health Sciences
Trent Volz - University of Utah
Tina C. Wan - Medical College of Wisconsin
Michael P. Wansaw - McLean Hospital/Harvard Medical School
Gregg Ward - North Carolina Central University
Xia Wen - Medical University of South Carolina
M. Keith Wilkerson - University of Vermont College of Medicine

SUMMER UNDERGRADUATE RESEARCH FELLOW TRAVEL AWARDS

Daniel J. Brauner (Sponsor: Kathryn E. Meier, Washington State University)
David Brown (Sponsor: Lee M. Graves, University of North Carolina at Chapel Hill)
A. Kristina Govorovska (Sponsor: Margarita L. Dubocovich, Northwestern University)
Hillery C. Metz (Sponsor: Raymond M. Quock, Washington State University)
Kevin Ogden (Sponsor: Stephanie Watts, Michigan State University)

TRAVEL AWARDS TO 15TH WORLD CONGRESS OF PHARMACOLOGY BEIJING, CHINA July 2006

James A. Bain Young Scientist Travel Awards

Michael Bruchas – University of Washington
Scott Hansen – University of California, San Diego
Liming Jin – Johns Hopkins University
Jing Huang – Verachem LLC
Yuri Karl Peterson – Duke University Medical Center
Evan Riddle – University of Utah
Jianxin Shi – University of California, San Diego

Graduate Student Travel Awards

Jessica Bonzo – University of California, San Diego
Erica Bowton – Vanderbilt University Medical Center
Erin Brace-Sinnokrak – University of California, San Diego
Alex Carrasquer – University of Louisville
Curtis Chong – Johns Hopkins University
Chris Evelyn – University of Michigan
J. Corey Fowler – University of North Carolina, Chapel Hill
Li Gan – Tufts University
Ryan Hibbs – University of California, San Diego
Michelle Marie Jacobs – Vanderbilt University
Karen Kassel – University of Nebraska Medical Center
Yanny Lau – Michigan State University
Abbey Maul – University of Nebraska Medical Center
Michael Morabito – Vanderbilt University
Theresa Operana – University of California, San Diego
Ali Razmara – University of California, Irvine
Carol Rivera-Lopez – University of Virginia
Rebecca Roof – University of Michigan
Gulnar Shahid – University of Houston
Wanyun Sheng – University of Houston



Special Events at EB '06
April 1 - 5, 2006 **San Francisco, California**

NEW TIME**NEW TIME****NEW TIME****NEW TIME**

NOTE: The Annual Business Meeting of the Society will be on Saturday, April 1, at 6:00 pm in Room 2002 of Moscone West. This immediately precedes the Awards Ceremony.

John V. Croker Lecture

Richard M. Weinshilboum, Mayo Medical School
Pharmacogenomics: A Journey from Phenotype to Genotype
 Sunday, April 2, 1:30 – 2:30 pm, Moscone Convention Center, Room 303

Ray Fuller Lecture in the Neurosciences

Marc G. Caron, Duke University Medical School
Novel Signaling Paradigm of Monoamine-mediated Behaviors in Animal Models
 Sunday, April 2, 8:15 – 9:15 am, Moscone Convention Center, Room 303

ASPET-Ray Fuller Seminar

Signal Transduction: Relevance to CNS Disorders & Therapeutic Approaches
 Sunday, April 2, 9:30 am – 12:00 noon, Moscone Convention Center, Room 303

Bernard B. Brodie Award Lecture

Frank J. Gonzalez, National Cancer Institute
Acetaminophen Metabolism and Hepatotoxicity: 35 Years Since B.B. Brodie
 Monday, April 3, 1:30 – 2:30 pm, Moscone Convention Center, Room 307

P.B. Dews Award Lecture

Leonard Cook, Temple University
Reflections on my Career in Psychopharmacology
 Monday, April 3, 1:30 – 2:30 pm, Moscone Convention Center, Room 303

FASEB Excellence in Science Award Lecture

Marilyn G. Farquhar, University of California, San Diego
G Proteins and RGS Proteins: Linking Trafficking and Signaling
 Tuesday, April 4, 2:15 – 3:15 pm, Moscone West, Room 3000/3003

EB Workshop for 2006 Summer Short Courses in Integrative and Organ Systems Science

At the 2006 Experimental Biology meeting in San Francisco, ASPET's Public Affairs Committee will sponsor a workshop on **Monday, April 3, 2006**, to provide information on the National Institute of General Medical Sciences four short summer courses that will provide specialized training for using intact organ system and in vivo animal models in the conduct of research. The summer short courses will be held at University of California at San Diego, Michigan State University, University of Nebraska Medical Center, and the University of North Carolina at Chapel Hill. The EB workshop will be held in room 309 of the Moscone Convention Center from 12:30 pm - 2:00 pm. The purpose of each short course is to introduce graduate students and Ph.Ds to the knowledge and skills needed for integrative studies of organ systems and intact animals, and to the physiological and biochemical responses of these systems to drugs. These critical skills are in short supply. Graduate students and Ph.Ds. with these skills are in great demand in both academic and industrial settings. Attendees at this workshop will hear about the summer courses from the course directors and from students who participated this past summer. For information on this summer's short courses visit:

http://www.aspet.org/public/public_affairs/pa_NIGMS_shortcourse_awards.html



ASPET PROGRAM FOR EXPERIMENTAL BIOLOGY 2006 – SAN FRANCISCO, CA

(All rooms listed are in the North & South Moscone Convention Center buildings unless otherwise noted)

Symposia 9:30 AM – 12:00 PM and 3:00 – 5:30 PM Sunday – Tuesday

Symposia 8:30-11:00 AM Wednesday

Friday March 31	Sunday AM April 2	Sunday PM April 2	Monday AM April 3	Monday PM April 3	Tuesday AM April 4	Tuesday PM April 4	Wednesday AM April 5
<p>Behavioral Pharmacology Society Mtg - Day 1 6:00-9:30 PM Marriott Hotel Separate, pre-registration required Golden Gate A1/A2</p>	<p>Ray Fuller Lecture Novel Signaling Paradigm of Monoamine-mediated Behaviors in Animal Models M.G. Caron 8:15-9:15 AM Room 303</p>	<p>John V. Croker Lecture Pharmacogenomics: A Journey from Phenotype to Genotype R.M. Weinsilboum 1:30-2:30 PM Room 303</p>	<p>ASPET/APS Women's Committees Workshop Mastering the Juggling Act: Laboratory, Life and Leadership Roles A.M. Schreihofer, D.H. Damon, L.K. Nisenbaum 8:00-10:00 AM Room 130</p>	<p>Public Affairs Committee Workshop Training Opportunities for Scientists in Integrative, Whole Organ Pharmacology G.J. Schaefer 12:30-2:00 PM Room 309</p>	<p>CVP (CPTM, SIP) Role of COX-2 in the Regulation of Cardiovascular Function A.L. Hyman, B.R. Lucchesi 9:30 AM-12:00 PM Room 305</p>	<p>FASEB Excellence in Science Award G Proteins & RGS Proteins: Linking Trafficking & Signaling M.G. Farquhar 2:15-3:15</p>	<p>SIP (CPTM, CVP, DDDRA, MP) Mammalian NO Metabolism & Signaling: Physiological & Therapeutic Frontiers D.R. Janero 8:30-11:00 AM Room 303</p>
<p>Saturday April 1</p>							
<p>Behavioral Pharmacology Society Mtg - Day 2 7:30 AM-5:00 PM Marriott Hotel Separate, pre-registration required Yerba Buena 12/13/14</p>	<p>NEU Ray Fuller Symposium Signal Transduction: Relevance to CNS Disorders & Therapeutic Approaches M.G. Caron 9:30 AM-12:00 PM Room 303</p>	<p>DM (TOX) What Regulates the Regulators? Factors that Alter Expression of the Nuclear Receptors which Regulate Drug-Metabolizing Enzymes A.B. Okey, D.S. Riddick 3:00-5:30 PM Room 307</p>	<p>TOX (DM, SIP) Targets of Toxicant Sensitivity in Aging H.M. Mehendale 9:30 AM-12:00 PM Room 303</p>	<p>Bernard B. Brodie Lecture 1:30-2:30 PM Room 307</p>	<p>MP (SIP) New Aspects of Glucocorticoid Signaling P.J. Barnes, J.S. Fedan 9:30 AM-12:00 PM Room 309</p>	<p>Clinical Pharmacology/ Experimental Therapeutics/ Translational Medicine Division Programming Receptor Pharmacogenomics at the Clinical Interface D.A. Flockhart, D.R. Abernethy 3:00-5:00 PM Room 301</p>	<p>MP (DDDRA, NEU) Allosteric Modulation of GPCRs: From Small Molecules to Accessory Proteins A. Christopoulos, B.L. Roth 8:30-11:00 AM Room 305</p>
<p>Teaching Institute How to be a Course Director J.W. Strandhoy 12:30-3:00 PM Room 309</p>	<p>CPTM (DDDRA, SIP) Imaging Modalities that Bridge Preclinical & Clinical Drug Efficacy B.F. Cox, D.R. Abernethy 9:30 AM-12:00 PM Room 301</p>	<p>CPTM (DDDRA, DM, SIP) Pediatric Clinical Pharmacology – Recent Advances & Future Challenges D.G. McCarver, J.S. Leeder 3:00-5:30 PM Room 301</p>	<p>CVP (MP, SIP) Using Genetic Approaches to Define the Role of Adenosine Receptors in the Cardiovascular System J.A. Auchampach 9:30 AM-12:00 PM Room 305</p>	<p>P.B. Dews Award Lecture 1:30-2:30 PM Room 303</p>	<p>DM (DDDRA, SIP) Function, Regulation, and Genetic Polymorphisms of the Cytochrome P450 Reductase X. Ding 9:30 AM-12:00 PM Room 301</p>	<p>DM (CPTM, TOX) Metabolic Considerations in the Action of Herbal Medicines T.K.H. Chang 3:00-5:30 PM Room 303</p>	<p>TOX (SIP) Response to Oxidative Stress by Specific Epithelial Cell Types P.R. Mayeux 8:30-11:00 AM Room 301</p>
<p>Graduate Student Colloquium: Pointers for Getting Your Point Across E.J. Bilsky, M.L. Toews 1:00-3:15 PM Room 305</p>	<p>BEH (CP, DDDRA, NEU, SIP) Metabotropic Glutamate Receptors M.F. O'Neill, N. Moore 9:30 AM-12:00 PM Room 309</p>	<p>BEH (DDDRA, NEU) 5-HT_{2C} Receptors: Pharmacology & Therapeutic Opportunities S. Rosenzweig-Lipson, J. Bergman 3:00-5:30 PM Room 303</p>	<p>BEH (DDDRA, NEU, SIP) Preclinical Models for Cognitive Enhancers: Within Reach or Still Too Great a Stretch? G. Lynch, K.M. Kantak 9:30 AM-12:00 PM Room 309</p>	<p>Behavioral Pharmacology Division Programming Behavioral Pharmacology at 50: A Look at the Future C.A. Paronis, L. Dykstra 3:00-5:30 PM Room 303</p>	<p>NEU (BEH, CPTM, SIP, TOX) Mood Stabilizers & Antidepressants: New Mechanisms for Old Compounds D-M. Chuang 9:30 AM-12:00 PM Room 307</p>	<p>Toxicology Division Programming Therapeutics and Toxicology of COX-2 Inhibitors J.P. Kehrer 3:00-5:30 PM Room 305</p>	<p>NEU (BEH, CPTM, DDDRA, SIP) Multiple Approaches to NGF Antagonism for Novel Pain Drugs F.F. Hefti 8:30-11:00 AM Room 307</p>
<p>Advances in H₃ Receptor Research: Implications for Novel Therapeutics (In memory of Art Hancock) T.A. Esbenshade, M.F. Jarvis, M. Williams 2:00-5:30 PM Marriott Hotel Golden Gate A1/A2</p>	<p>TOX (CP, DDDRA, NEU, SIP) Cellular & Molecular Pathways of Neurotoxicity: Relevance to Neurodegenerative Diseases J.L. Cadet 9:30 AM-12:00 PM Room 307</p>	<p>MP (CVP, CPTM, SIP) Cardiac Stem Cells: Revolutionizing Myocardial Biology & Regenerating the Heart M. Sussman 3:00-5:30 PM Room 305</p>	<p>DM Drug Metabolism Platform Session Biotransformation & Drug Transport <i>James R. Gillette Best Manuscript Winners</i> D.S. Riddick, L.S. Kaminsky 9:30 AM-12:00 PM Room 307</p>	<p>DDDRA Division Programming Innovative Drug Delivery Strategies: Knocking on the Door of Drug Development T.C. Stover 3:00-5:30 PM Room 301</p>	<p>SIP (CVP, DDDRA, EDU) Beginner's Guide to Emerging Technologies in Drug Development S. Sengupta 9:30 AM-12:00 PM Room 303</p>	<p>Neuropharmacology Division Programming Neuroproteomics of the Synapse and Drug Addiction L.A. Devi 3:00-5:30 PM Room 309</p>	<p>DDDRA (CPTM) Monoclonal Antibody & Small Molecule Cancer Therapies – What's the Difference? J. Winkler, L.S. Friedman 8:30-11:00 AM Room 309</p>

Saturday March 31	Sunday AM April 2	Sunday PM April 2	Monday AM April 3	Monday PM April 3	Tuesday AM April 4	Tuesday PM April 4	Wednesday AM April 5
Bridges to Success in Academia: From Undergraduate Student to Professor and Beyond G.E. Torres, M.L. Dubocovich 3:15-5:30 PM Room 307	EDU Best Practices in Pharmacology Education J.E. Warnick 9:30 AM-12:00 PM Room 302	EDU (SIP) Beyond Listening: A Workshop on Strategies that Actively Engage Students in the Classroom W. Jeffries, R.F. Orzechowski 3:00-5:30 PM Room 200/212	Pharmacology Education Division Programming Distance Education in Pharmacology: Promises and Pitfalls P.K. Rangachari 9:30 AM-12:00 PM Room 301	Drug Metabolism Division Programming Metabolomic/ Metabonomic Probes of Drug Metabolism Consequences L.S. Kaminsky 3:00-5:30 PM Room 307		DDDR (CPTM, SIP, EDU) Getting Started in Drug Development: Academics to Industry B.R. Yerxa 3:00-5:30 PM Room 307	ASIP/ASPET Minisymposium Pathobiology of Liver Regeneration & Xenobiotic Metabolism G. Darlington, H. Mehendale 8:30-11:30 AM Room 2001
ASPET Business Meeting 6:00-7:00 PM Moscone West Room 2002	CVP (CPTM, MP, SIP) Embryonic Stem Cell Therapy: From Cardiology to Heart Repair A. Terzic 9:30 AM-12:00 PM Room 305			Systems & Integrated Pharmacology Division Programming Pharmacology of Cytokines in the Cardiovascular System R.C. Webb, M.W. Brands 3:00-5:30 PM Room 305		Molecular Pharmacology Division Programming Postdoctoral Award Finalists B. Kobilka 3:00-5:30 PM Moscone West Room 2008	
Awards Ceremony & Opening Reception 7:00-9:00 PM Moscone West Room 2002	ASPET/AAA Workshop Beyond Academia: Career Options in Industry & Biotech 10:00 AM-12:00 PM Room 123			Cardiovascular Pharmacology Division Programming Graduate Student and Postdoctoral Scientist Best Abstract Competition W.M. Armstead, J. Shen 3:00-5:30 PM Moscone West Room 2008			

Posters displayed 7:30 AM – 4:00 PM, Sunday – Tuesday (Late-Breaking Posters on Wednesday)
Authors Must be Present by their Boards 12:30-2:45 PM

Sunday Posters

Anxiety & Anxiolysis
Depression & Stress
Opioid Dependence
Antinociception
Neurotransmission
Neurotransmitter Receptors
GPCR Signaling I
GPCR Signaling II
Alpha Adrenergic Receptors
RGS Proteins
Hormone & Hormone Receptors
DMD: Gene Expression & Regulation
DMD: Phase I
DMD: Phase II
Clinical Pharmacology & Toxicology
CV Pharmacology: Remodeling

Monday Posters

Monoamines and Behavior
Cognition, Attention & Neurogenesis
Drug Discrimination & Behavioral Methods
Cannabinoids
Neuropharmacology I
Neuropharmacology II
Signal Transduction I
Signal Transduction II
Smooth Muscle Pharmacology & Toxicology
Vascular Pharmacology: General
Endothelium
Pulmonary Pharmacology & Toxicology

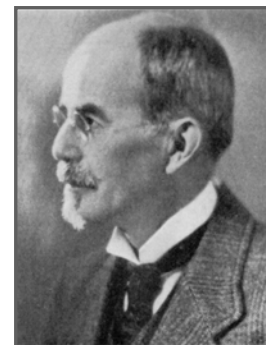
Tuesday Posters

Neurotoxicology & Neuroprotection
Neurodegeneration
Systems Pharmacology & Toxicology
Renal Pharmacology & Toxicology
DMD: Pharmacokinetics/Toxicokinetics
DMD: Reactive Metabolite & Toxicity
DMD: Transporters
Hypertension: Blood Pressure Regulation
Vascular Pharmacology: Coronary
Cardiovascular Pharmacology: Ion Channels
Second Messenger Systems
Allosteric Modulation of GPCRs
Kinases & Phosphatases
Mammalian NO Metabolism & Signaling
Immunopharmacology
Chemotherapy
Natural Products

CALL FOR AWARD NOMINATIONS FOR 2007

JOHN J. ABEL AWARD

The John J. Abel Award in Pharmacology, supported by Eli Lilly and Company, was established to stimulate fundamental research in pharmacology and experimental therapeutics by young investigators. The annual Award consists of \$2,500, a plaque, and travel expenses for the winner and spouse to the award ceremony at the annual meeting of ASPET.



Nominees for this award shall not have passed their **thirty-ninth birthday on April 30** of the year of the Award. The candidate need not be a member of the Society; however, a nomination must be made by an ASPET member, and no member may nominate more than one candidate a year. The Award shall be made for original, outstanding research in the field of pharmacology and/or experimental therapeutics. Independence of thought, originality of approach, clarity and excellence of data presentation are important criteria. Candidates shall not be judged in comparison with the work of more mature and experienced investigators. Quality rather than the number of contributions shall be emphasized. It shall be the responsibility of the sponsor to make clear the contribution of the candidate to any jointly authored reprints and manuscripts and the originality and independence of the candidate's research. Selection will be made by the ASPET Awards Committee, appointed by the President of ASPET.

Nominations shall be accompanied by six (6) copies of each of the following:

1. Summary that describes the importance of the candidate's work.
2. Each of six published articles or manuscripts accepted for publication that are a representation of the candidate's work.
3. Brief biographical sketch of the candidate.
4. Candidate's *curriculum vitae* and bibliography.

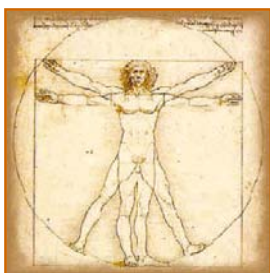
Nominations for this Award must be received no later than **September 15, 2006**, by the Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Maryland 20814-3995.

Winners of the John J. Abel Award

1947	George Sayers	1967	Frank S. LaBella	1987	Lee E. Limbird
1948	J. Garrett Allen	1968	Richard J. Wurtman	1988	Robert R. Ruffolo, Jr.
1949	Mark Nickerson	1969	Ronald Kuntzman	1989	Kenneth P. Minneman
1950	George B. Koelle	1970	Solomon H. Snyder	1990	Alan R. Saltiel
1951	Walter F. Riker, Jr.	1971	Thomas R. Tephly	1991	Terry D. Reisine
1952	David F. Marsh	1972	Pedro Cuatrecasas	1992	Frank J. Gonzalez
1953	Herbert L. Borison	1973	Colin F. Chignell	1993	Susan G. Amara
1954	Eva K. Killam	1974	Philip Needleman	1994	Brian Kobilka
1955	Theodore M. Brody	1975	Alfred G. Gilman	1995	Thomas M. Michel
1956	Fred W. Schueler	1976	Alan P. Poland	1996	John D. Scott
1957	Dixon M. Woodbury	1977	Jerry R. Mitchell	1997	David J. Mangelsdorf
1958	H. George Mandel	1978	Robert J. Lefkowitz	1998	Masashi Yanigasawa
1959	Parkhurst A. Shore	1979	Joseph T. Coyle	1999	Donald P. McDonnell
1960	Jack L. Strominger	1980	Salvatore J. Enna	2000	William C. Sessa
1961	Don W. Esplin	1981	Sydney D. Nelson	2002	Steven A. Kliewer
1962	John P. Long	1982	Theodore A. Slotkin	2003	David S. Brecht
1963	Steven E. Mayer	1983	Richard J. Miller	2004	David P. Siderovski
1964	James R. Fouts	1984	R. Peter Guengerich	2005	Randy Hall
1965	Eugene Braunwald	1985	P. Michael Conn	2006	Christopher M. Counter
1966	Lewis S. Schanker	1986	Gordon M. Ringold		



CALL FOR AWARD NOMINATIONS FOR 2007



THE PHARMACIA-ASPET AWARD IN EXPERIMENTAL THERAPEUTICS

The Pharmacia-ASPET Award in 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. The award is supported in perpetuity by a gift from Pharmacia. The winner will receive a \$2,500 honorarium, a bronze medal, and travel expenses for the winner and spouse to the award ceremony at the ASPET annual meeting.

There are no restrictions on nominees for this award. The Award shall be made on the basis of published reprints, manuscripts ready for publication, and a two-page summary of the candidate's accomplishments and qualifications for the award. Selection will be made by the ASPET Awards Committee, appointed by the President of ASPET.

Nominations shall be accompanied by six (6) copies of each of the following:

1. Two (2)-page summary that details the importance of the candidate's work.
2. Each of six articles published or ready for publication by the candidate that have direct bearing on the Award.
3. Brief biographical sketch of the candidate.
4. Candidate's *curriculum vitae* and bibliography.

Nominations for this Award must be received no later than **September 15, 2006**, by the Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Maryland 20814-3995.

Winners of the ASPET Award for Experimental Therapeutics

1969	John A. Oates	1983	Marcus M. Reidenberg	1997	Michael M. Gottesman
1970	Joseph R. Bertino	1984	Sir James Black	1998	Phil Skolnick
1971	Elliot S. Vesell	1985	Louis Lemberger	1999	Yung-Chi Cheng
1972	Francois M. Abboud	1986	Alan C. Sartorelli	2000	Saloman Z. Langer
1973	Dean T. Mason	1987	Albrecht Fleckenstein	2001	George R. Breese
1974	Leon I. Goldberg	1988	Jean-Francois Borel	Became Pharmacia-ASPET Award in Experimental Therapeutics	
1975	Mackenzie Walser	1989	Benedict R. Lucchesi	2002	Darryle D. Schoepp
1976	Louis Lasagna	1990	Albert Sjoerdsma	2003	William C. DeGroat
1977	Allan H. Conney	1991	Theophile Godfraind	2004	Philip Needleman
1978	Attallah Kappas	1992	James W. Fisher	2005	Donald McDonnell
1979	Sydney Spector	1993	V. Craig Jordan	2006	John C. Lee
1980	Sanford M. Rosenthal	1994	Susan B. Horwitz		
1981	David G. Shand	1995	Henry I. Yamamura		
1982	William H. Prusoff	1996	Robert F. Furchgott		

TORALD SOLLMANN AWARD IN PHARMACOLOGY INVESTIGATION AND EDUCATION

The Torald Sollmann Award in Pharmacology was established to commemorate the pioneer work of Dr. Torald Sollmann in the fields of pharmacological investigation and education. Sponsored by Wyeth Research, the Torald Sollmann Award is presented biennially in odd years for significant contributions over many years to the advancement and extension of knowledge in the field of pharmacology. The award consists of an honorarium of \$3,500, a medal, and travel expenses for the winner and spouse to the annual meeting. The formal presentation of this biennial award and medal will be made at the annual meeting of ASPET. The recipient will be invited by the President of the Society to deliver a Sollmann Oration to the membership that may be published in an appropriate ASPET journal.

There are no restrictions on nominees for this award. However, a nomination must be made by a member of the American Society for Pharmacology and Experimental Therapeutics (ASPET), and no member may nominate more than one candidate in a year. The award



CALL FOR AWARD NOMINATIONS FOR 2007

shall be made on the basis of originality and uniqueness of accomplishments throughout a long career distinguished by sustained, significant contributions to education, research, and service in pharmacology. Selection of the recipient will be made by the ASPET Awards Committee, appointed by the President of ASPET.

Nominations shall be accompanied by six (6) copies of each of the following:

1. **No more than** five letters from nominators describing the contributions to pharmacology of the candidate that make him/her eligible for this Award, listing major contributions.
2. Brief biographical sketch of the candidate.
3. Candidate's *curriculum vitae* and bibliography.

Nominations for the 2007 Award must be received no later than **September 15, 2006**, by the Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Maryland 20814-3995.

Winners of the Torald Sollmann Award

1961	Otto Kraye	1981	Avram Goldstein	1997	Alfred G. Gilman
1963	Bernard B. Brodie	1984	K. K. Chen	1999	William W. Fleming
1966	Arnold D. Welch	1986	Walter K. Riker	2001	Benedict R. Lucchesi
1969	Earl W. Sutherland, Jr.	1988	James A. Bain	2003	Palmer W. Taylor
1973	Julius Axelrod	1990	George B. Koelle	2005	Kenneth E. Moore
1975	Sidney Udenfriend	1992	E. Leong Way		
1978	Karl H. Beyer, Jr.	1995	Theodore M. Brody		

EPILEPSY RESEARCH AWARD FOR OUTSTANDING CONTRIBUTIONS TO THE PHARMACOLOGY OF ANTIEPILEPTIC DRUGS

The Epilepsy Award is sponsored by The International League Against Epilepsy (ILAE) and donated by Pfizer for the purpose of recognizing and stimulating outstanding research leading to better clinical control of epileptic seizures. This research may include the basic screening and testing of new therapeutic agents, studies on mechanisms of action, metabolic disposition, pharmacokinetics, and clinical pharmacology studies. This Award, presented biennially in odd years, consists of an honorarium of \$2,000, a Certification of Citation, and travel expenses to the awards ceremony at the ASPET annual meeting.

Nominees for the 2007 award must be actively engaged in the research for which the Award is made, and primary emphasis will be placed upon work accomplished in the five-year period prior to the Award. Nominations for the Award may be submitted by members of any recognized scientific association, domestic or foreign. Selection of an awardee will be made biennially by the Epilepsy Award Committee appointed by the President of ASPET, with representation of ILAE.

Nominations shall be accompanied by six (6) copies of each of the following:

1. Summary describing the nominee's major achievements.
2. Nominee's six most significant papers, including manuscripts accepted for publication.
3. Brief biographical sketch of the candidate.
4. Nominee's *curriculum vitae* and bibliography.

Nominations for this Award must be received no later than **September 15, 2006**, by the Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Maryland 20814-3995.

Winners of the Epilepsy Award

1978	Alan Richens	1986	Robert L. Macdonald	1995	Karen N. Gale
1979	Paolo L. Morselli	1987	James O. McNamara	1997	Marc A. Dichter
1980	Dixon M. Woodbury	1988	Harvey J. Kupferberg	1999	Robert Sloviter
1981	James A. Ferrendelli	1989	Frank C. Tortella	2001	Wolfgang Löscher
1982	Ewart A. Swinyard	1990	Robert Naquet	2003	Brian S. Meldrum
1983	Arthur Camerman	1991	Raymond Dingledine	2005	J. Victor Nadler
1984	Phillip C. Jobe	1992	O. Carter Snead III		
1985	Robert J. DeLorenzo	1994	Michael A. Rogawski		





**DIVISION FOR DRUG METABOLISM
EARLY CAREER ACHIEVEMENT AWARD**

The ASPET Division for Drug Metabolism Early Career Achievement Award has been established to recognize excellent original research by early career investigators in the area of drug metabolism and disposition.

The award is presented biennially in odd-numbered years. The award consists of \$1,000, a plaque, and complimentary registration plus travel expenses (to a maximum of \$1,000) for the winner to attend the awards ceremony at the ASPET annual meeting. The awardee will deliver a lecture at the annual meeting describing his/her relevant research accomplishments. The awardee will be invited to publish a review article on the subject matter of the award lecture in *Drug Metabolism and Disposition*.

Nominees for this award must have a doctoral degree (e.g. Ph.D., M.D., Pharm. D., D.V.M.) and must be within 15 years of having received their final degree, as of December 31 of the year of the award. There are no restrictions on institutional affiliation, and a candidate need not be a member of ASPET. There is a requirement for two nominators, although more are acceptable. Nominators must be members of ASPET. An individual cannot nominate more than one candidate per award cycle.

Candidates who have made their research contributions in any sector (e.g. academia, industry, government) of the drug metabolism community may be nominated for the award. The primary criterion for the award is the level of excellence and originality of the research conducted by the candidate in the field of drug metabolism and disposition. Independence of thought, originality of approach, clarity of communication, and the impact of the work on the drug metabolism field are important considerations. Candidates shall not be judged in comparison with the work of more experienced investigators. Selection will be made by the Executive Committee of the Division for Drug Metabolism.

Nominations shall consist of the following components:

2. Two or more letters of nomination and support. The signed original and five copies of each letter should be submitted in hard copy format.
3. The five most significant published papers authored by the candidate. A detailed examination of these publications will form a primary basis for evaluation. Six copies of each paper should be submitted in hard-copy format.
4. A summary, limited to two pages, that describes the importance of the candidate's research contributions. This summary must include brief statements regarding the candidate's role in the five published papers and the overall significance and impact of the work. Submit as an email attachment in RTF or PDF format.
5. A brief biographical sketch of the candidate. Submit as an email attachment in RTF or PDF format.
6. The candidate's curriculum vitae and publication list. Submit as an email attachment in RTF or PDF format.

Nominations for this Award must be received no later than **September 15, 2006**, by the Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Maryland 20814-3995. Submit email attachments to carrico@aspet.org.

ASPET to give Julius Axelrod Award in 2007

The Julius Axelrod Award, originated by the Catecholamine Club in 1991, will be administered and awarded by ASPET beginning with the 2007 Annual Meeting. Nominations will be due October 15, 2006, for this award. Watch the next issue of *The Pharmacologist* for nomination procedures.





Making Your NIH-Funded Research Available at PubMed Central

Authors of articles written since May 2005 that resulted from NIH-funded research have been asked to deposit their accepted manuscripts in the NIH's open-access repository, PubMed Central. The policy and process have created much confusion for authors, and many still wonder what should be deposited, when it should be deposited, what impact copyright agreements have on the policy, and who can deposit manuscripts.

For *JPET*, *Molecular Pharmacology*, and *Drug Metabolism and Disposition*, "what" should be deposited is the final, accepted manuscript version. The final accepted manuscript version may be deposited with PubMed Central any time after acceptance by the journal. The NIH would prefer that this be done as soon as possible after acceptance.

ASPET changed its copyright transfer forms prior to implementation of the new policy so that authors of NIH-funded research articles accepted by *JPET*, *Molecular Pharmacology*, and *Drug Metabolism and Disposition* may deposit their manuscripts with PubMed Central. ASPET asks its authors to make their articles freely available at PubMed Central **12 months after publication** in the journal. Authors do not have to track the 12-month window. When depositing at PubMed Central, authors are asked for the length of the embargo period. Select 12 months. The system will calculate the release date from meta data supplied to PubMed when the article is published in a journal issue.

Note that manuscripts are freely accessible immediately at the journal's web site when published as Fast Forward articles (typically 24-48 hours after acceptance). These articles have open access immediately. We provide open access at the journal site instead of at PubMed Central.

We provide open access at the journal site instead of at PubMed Central.

Why are we doing this? We want articles to generate as many hits as possible at the journal site so that we can develop online advertising revenue. Posting on another site takes hits away from the journal site, making it a less attractive place to put a banner ad.

At this time, ASPET authors of NIH-funded research must deposit their manuscripts themselves. Publishers have asked the NIH to develop a system to allow bulk deposits of manuscripts by publishers on behalf of authors. That system is not in place.

This information pertains to *JPET*, *Molecular Pharmacology*, and *Drug Metabolism and Disposition*. If your NIH-funded article has been accepted by another journal, check the journal's author instructions and copyright transfer form. If they do not provide clear answers, check with the publisher before acting.

Participation in the NIH plan has been less than 4%. In a February 8 letter to Elias Zerhouni, Thomas Detre, the Chair of the NIH Board of Regents and the NIH Public Access Policy Working Group, concluded that the NIH Policy should be amended to make manuscript deposits mandatory and that manuscripts should be freely accessible after only six months. According to Dr. Detre, "Since there is evidence that the submission system is relatively easy to use and that the majority of NIH-funded researchers appear to know about the policy, technical difficulties or lack of awareness do not appear to be primary reasons for non-compliance." Confusion over the policy is ignored.

It is hoped that Dr. Zerhouni will begin to work with publishers to increase submissions. A bulk-deposit system would solve the problem. Shortening the embargo period will likely have a negative impact on some and perhaps many journals. Statistics show that online article usage remains high six months after publication. Some journals are likely to lose too many subscriptions to remain financially viable if the embargo is shortened.

JPET Back Issues Now Online

On March 1, HighWire Press notified ASPET that the archival issues of *JPET* would be online within a week. Every issue from 1996 back to 1909 should be available as PDF files from the *JPET* web site by the time this issue of *The Pharmacologist* is published. Articles from 1997 onward are available in full-text HTML and PDF versions.



JOURNALS

The online back issues will include everything that was part of the scanned copies, including covers, editorial boards, advertising (there's an ad for typewriters in an early issue), tables of contents, and other front- and back-matter items. The same was done for the archival issues of *Pharmacological Reviews*, *Molecular Pharmacology*, and *Drug Metabolism and Disposition*.

Articles from 1997 onward are freely available 12 months after publication in their final format. Manuscripts accepted for *JPET*, *MolPharm*, and *DMD* since July 2005 have been freely available immediately upon publication.

The archiving project started in 2003 with the collection of back issues. A number of ASPET members donated copies: Alan Buckpitt, David Bylund, Ken Hardin, Jonathan Katz, Terrence Monks, David Moody, and Richard Neubig. Many thanks are due to them for their help in digitally preserving the Society's journals and wealth of pharmacological knowledge.

When all of the *JPET* issues are online, the complete archive of ASPET journals will be available electronically. Archival issues are included with subscriptions. All ASPET members have access to the Society's five journals, including the archives, as a member benefit.

15TH World Congress of Pharmacology

Beijing, China

July 2-7, 2006

Registration Deadline:

March 31, 2006

www.iuphar2006.org



Photo courtesy of www.Beijingpage.com





NIH Funding

NIH has estimated the Biomedical Research and Development Price Index (BRDPI) will increase by 5.5 percent for FY 2005. The NIH projects the BRDPI to increase by 4.1 percent for FY 2006 and 3.8 percent for FY 2007 and FY 2008. The NIH web site also provides information on the proposed FY'07 budget for each institute and center:

<http://officeofbudget.od.nih.gov/pdf/Press%20info%20final.pdf>. Every NIH institute and center is cut with the exception of NIAID, which receives a \$12 million increase over FY'06 to expand pandemic avian flu research.

ASPET-Industry Meeting

On March 2-3, ASPET convened a meeting of several industry leaders to discuss new mechanisms by which training in integrative, whole organ systems pharmacology can be augmented. The goals for the meeting were to:

1. Look for means to supplement the existing NIGMS funding mechanism (see below); and/or
2. Develop alternative funding sources and mechanisms by which additional training programs might be implemented.
3. Determine commitment of genuine interest to support a U.S. based industrial consortium that would support training for in vivo, integrative biologists.

The meeting was intended to be a small open table discussion. Presenters included Michael Collis, founder and leader of the Integrative Pharmacology Fund that has generated millions of dollars from industrial and government sources to support integrative sciences in UK universities, and Peter Preusch of NIGMS who presented an overview of NIGMS programs in support of integrative training. Following these presentations, a small roundtable discussed what effective mechanisms might be created among industrial partners to support a U.S. based initiative.

ASPET-Merck Postdoctoral Fellowships in Integrative Pharmacology

The ASPET-Merck Postdoctoral Fellowship in Integrative Pharmacology will renew the competition in Cancer Pharmacology. Fellowship term is three years with no less than six months of the Fellowship to be spent at the Merck Research Laboratories in Boston, MA. For eligibility guidelines, research areas of interest, and application information view:

http://www.aspet.org/public/merck_fellowships/guidelines.html. Application deadline is August 31, 2006.

EB Workshop for 2006 Summer Short Courses in Integrative and Organ Systems Science

At the 2006 Experimental Biology meeting in San Francisco, ASPET's Public Affairs Committee will sponsor a workshop on Monday, April 3, 2006 to provide information on the National Institute of General Medical Sciences four short summer courses that will provide specialized training for using intact organ system and in vivo animal models in the conduct of research. The summer short courses will be held at University of California at San Diego, Michigan State University, University of Nebraska Medical Center, and the University of North Carolina at Chapel Hill. The workshop will be held at the Moscone Convention Center from 12:30 pm - 2:00 pm. The purpose of each short course is to introduce graduate students and Ph.Ds to the knowledge and skills needed for integrative studies of organ systems and intact animals, and to the physiological and biochemical responses of these systems to drugs. These critical skills are in short supply. Graduate students and Ph.Ds. with these skills are in great demand in both academic and industrial settings. Attendees at this workshop will hear about the summer courses from the course directors and from students who participated this past summer. For information on this summer's short courses visit:

http://www.aspet.org/public/public_affairs/pa_NIGMS_shortcourse_awards.html

FBI Stop

The FBI has instituted a Science & Technology Outreach program (STOP) to try to get help from the biological research community on issues related to bioterrorism. The FBI is requesting input from the biological science community leaders regarding: 1) bioterrorism concerns and questions; 2) current vulnerabilities within the academic community or industry; 3) further types of outreach that would be valuable; 4) ways to make STOP more effective to the biological science audience; 5) suggested target audiences for the STOP program; and 6) suggestions in approaching the international goal of bioterrorism prevention. Institutional involvement in this effort could help educate the FBI on how scientific research works and could provide great benefit to both science and security. For more information contact Gretchen Lorenzi, Ph.D., STOP coordinator, FBI WMD Countermeasure Unit at Gretchen.lorenzi@ic.fbi.gov or (202) 324-0236.



Division Election Results for 2006

Division for Behavioral Pharmacology



Charles P. France
Chair-Elect



Leonard L. Howell
Secretary/Treasurer-
Elect

Division for Cardiovascular Pharmacology



Debra I. Diz
Chair-Elect



John C. Kermode
Secretary/Treasurer-
Elect

Division for Drug Discovery, Drug Development & Regulatory Affairs



Gary D. Novack
Chair-Elect

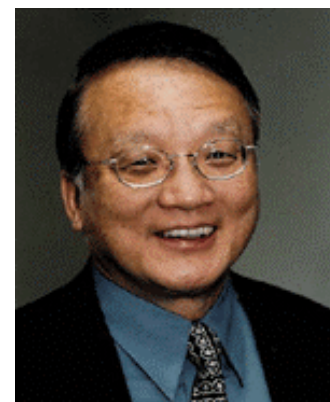


Richard H. Alper
Secretary/Treasurer-
Elect

Division for Drug Metabolism



Kenneth E. Thummel
Chair-Elect



John Y.L. Chang
Secretary/Treasurer-
Elect



Division for Molecular Pharmacology



Robert H. Tukey

Chair-Elect



Theresa M. Filtz

Secretary/Treasurer-Elect

Division for Neuropharmacology



P. Jeffrey Conn

Chair-Elect



Margarita L. Dubocovich

Secretary/Treasurer-Elect

Division for Pharmacology Education



Jack W. Strandhoy
Secretary/Treasurer-Elect

Division for Toxicology



Curtis J. Omiecinski
Chair-Elect

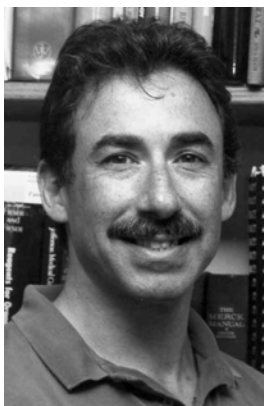


Lawrence R. Curtis
Secretary/Treasurer-Elect

The Division for Drug Metabolism has initiated a new award. The Division for Drug Metabolism Early Career Achievement Award has been established to recognize excellent original research by early career investigators in the area of drug metabolism and disposition. The award will be presented biennially in odd-numbered years and consists of a \$1000 prize, a plaque and travel expenses to attend the annual meeting. See the [official announcement on page 15](#).



MEMBERS IN THE NEWS

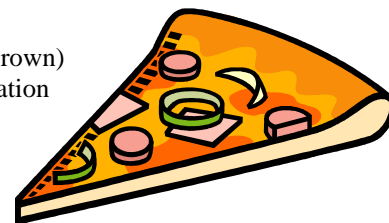


Scott A. Waldman, MD, Ph.D., Samuel MV Hamilton Professor of Medicine and Chair of the Department of Pharmacology and Experimental Therapeutics at Thomas Jefferson University, was recently named the new editor of *Clinical Pharmacology and Therapeutics*, to replace Dr. Michael Stein of Vanderbilt University. His editorial appointment will take effect January 1, 2007. At the same time, publication of *Clinical Pharmacology and Therapeutics* will be assumed by Nature Publishing Group. *Clinical Pharmacology and Therapeutics* is the official journal of the American Society for Clinical Pharmacology and Therapeutics (ASCPT), and for many years APSET and ASCPT shared in the editorial oversight of that journal. Dr. Waldman is a former president of ASCPT and has been active with ASPET's Division for Clinical Pharmacology, Pharmacogenomics and Translational Medicine. Dr. Waldman looks forward to "building on the foundation established by my predecessors " and to "continue to increase the visibility of the journal and the cutting edge science it delivers to the discipline of clinical pharmacology."

STAFF NEWS



Margie Arkin, Meetings Assistant, (wearing the crown) won a pizza party for the ASPET office from radio station MIX 107.3 on Ground Hog Day 2006. The ASPET office got to dine on all-you-can eat pizza and wings and have their picture taken with afternoon drivetime DJ, Chili Amar, seated next to Margie.



Cassandra Zaruba, Editorial Assistant in ASPET's journals office, is a published author. Her first novel, *Liquid Bones*, is a psychological thriller set in North Dakota and told from the perspective of each of the five main characters. Cassie not only wrote the book, but took the cover photograph and designed the book cover as well. A book signing held at the ASPET office on February 2 was well-attended by FASEB campus staff.

Cassie joined ASPET in November 2004 to assist with the manuscript management of *Molecular Pharmacology* and *JPET*.



Regular Members ◆

- Ahmed, Salah-Uddin**, University of Michigan Med Sch, Dept of Internal Medicine/Rheumatology
Aitken, Alison, Emory University, Dept of Pharmacology
Anand, S., University of Georgia College of Pharmacy, Dept of Pharmaceutical & Biomedical Sciences
Boerma, Marjan, University of Arkansas Medical Sciences, Dept of Surgery
Byrnes-Blake, Kelly, Zymogenetics, Inc, Preclinical Development & Pharmacokinetics
Caruso, Thomas, Virginia Tech, VA-MD Regional College of Veterinary Medicine
Chen, Hao, University of Tennessee, Dept of Pharmacology
Chou, Ting-Chao, Memorial Sloan-Kettering Cancer Center, Dept of Preclinical Pharmacology Core
Counter, Christopher, Duke University Med Ctr, Dept of Pharmacology & Cancer Biology
Cox, Helen, King's College, Guy's Campus
Dell'Acqua, Mark, University of Colorado at Denver HSC, Dept of Pharmacology
Dent, Paul, Virginia Commonwealth University, Department of Biochemistry
Du, Yuhong, Emory University, Dept of Pharmacology
Duanmu, Zhengbo, Wayne State University, Institute of Environmental Health Sciences
Feng, Quing, Dartmouth Medical School, Dept of Pharmacology & Toxicology
Gaedigk, Andrea, Children's Mercy Hospitals & Clinics, Dept of Clinical Pharmacology
Garcia-Espinosa, Maria, Wake Forest University Hlth Sci, Hypertension & Cardiovascular Disease Center
Gerdin, Matthew, NIH, Lab of Cell & Molecular Regulation
Guo, Meng, Henry Ford Health System, Eye Care Services
Han, Guichun, Medical College of Georgia
Hansen, Scott, University of California, San Diego, Dept of Pharmacology
Henry, L., Vanderbilt University Medical Center, Dept of Pharmacology
Javors, Martin, University of Texas, HSC, Dept of Psychiatry
Jha, Archana, SUNY, Center for Single Molecule Biophysics, Dept of Physiology & Biophysics
Krueger, Kathleen, Abbott Laboratories, Dept of Neuroscience
Lambert, Nevin, Medical College of Georgia, Dept of Pharmacology & Toxicology
Landskroner, Kyle, Bayer Healthcare, Biological Products Division
Law, Michael, Healthpoint, Ltd
Le Grand, Bruno, Centre De Recherche Pierre Fabre, Division of Cardiovascular Diseases
Lee, John, GlaxoSmithKline, Dept of High Throughput Biology
Llenas, Jesus, Almirall Prodesfarma
Mascelli, Mary, Centocor, Inc., Dept of Clinical Pharmacology & Experimental Medicine
Milicic, Ivan, Abbott Laboratories, Neuroscience Research
Miller, Alyson, University of Melbourne, Dept of Pharmacology
Murillo, Horacio, American Assoc for the Advancement of Science
Peterson, Yuri, Duke University Medical Center, Dept of Pharmacology
Qiu, Yu, University of Minnesota, Dept of Pharmacology
Ralay-Ranaivo, Hantamalala, Northwestern University Feinberg School of Medicine, Dept of Drug Discovery & Chemical Biology
Reading, Stacey, University of Vermont College of Medicine, Dept of Pharmacology
Riddle, Evan, University of Utah, Dept of Pharmacology & Toxicology
Rydel, Russell, Elan Pharmaceuticals, Inc, Pharmacology & Neurobiology
Sandoval, Raudel, University of Illinois, Dept of Pharmacology
Schuetz, Erin, St. Jude Children's Research Hospital, Dept of Pharmaceutical Sciences
Shi, Jianxin, University of California, San Diego, Dept of Pharmacology
Suzuki, Hirofumi, University of Georgia Coll of Vet Med, Dept of Physiology & Pharmacology
Talbot, Jeffery, University of Michigan, Dept of Pharmacology
Tanda, Gianluigi, NIDA
Tawfik, Huda, Medical College of Georgia, Dept of Pharmacology & Toxicology
Wilkerson, M., University of Vermont, Dept of Pharmacology
Williams, Jason, Vanderbilt University Inst of Imaging Sci, Dept of Molecular Physiology & Biophysics
Williams, Noelle, University of Texas Southwestern Med Ctr, Dept of Biochemistry
Yu, Shan, Medical University of South Carolina, Dept of Pharmaceutical Sciences



Affiliate Members ◆

Brown-Bryan, Terry, Loma Linda University, Dept of Physiology & Pharmacology
Huang, Jing, Verachem LLC
Johnson, Inneke, North Carolina Central University, Dept of Neuroscience/Drug Abuse
Lee, Choon-Myung, Emory University School of Medicine, Dept of Pharmacology
Morales, Jose, Emory University School of Medicine, Yerkes Primate Center
Nazef, Naim, Merck Research Laboratories
Romero, Maritza, Medical College of Florida, Dept of Pharmacology & Toxicology
Roy, Upal, Tulane University School of Medicine, Dept of Pharmacology
Wan, Tina, Medical College of Wisconsin, Dept of Pharmacology & Toxicology

Graduate Student Members ◆

Acosta, Jazmin, Arizona State University, Dept of Behavioral Neuroscience
Amunom, Immaculate, University of Louisville, Dept of Biochemistry & Molecular Biology
Andjelic, Cynthia, University of Utah, Dept of Pharmacology & Toxicology
Arrillaga-Romany, Isabel, Tufts University School of Medicine, Dept of Psychiatry
Banerjee, Sugato, University of Nebraska Medical Center, Dept of Pharmacology & Experimental Neurology
Bolte, Craig, University of Cincinnati, Dept of Pharmacology
Bonzo, Jessica, University of California - San Diego, Dept of Biomedical Sciences
Bradaric, Michael, Rush University Medical Center, Dept of Pharmacology
Braden, Michael, Purdue University, Dept of Medicinal Chemistry & Molecular Pharmacology
Brasel, Chris, Oklahoma State University Center for Health Sciences, Dept of Pharmacology
Burkhalter, Rebecca, University of Missouri, Dept of Pharmacology
Carrasquer, Alex, University of Louisville School of Medicine, Dept of Pharmacology & Toxicology
Carruthers, Nick, Wayne State University, Institute of Environmental Hlth Sciences
Chung, John, University of Michigan, Dept of Pharmaceutical Sciences
Coffee, R., Vanderbilt University School of Medicine, Dept of Pharmacology
Dever, Joseph, University of Wisconsin, School of Veterinary Medicine
Dewar, Brian, University of North Carolina, Dept of Biology
Falenski, Katherine, Virginia Commonwealth University, Dept of Pharmacology & Toxicology
Fetalvero, Kristina, Dartmouth College, Dept of Pharmacology & Toxicology
Gan, Lu, Tufts University, Dept of Pharmacology
Ganesan, Shobana, University of Mississippi, Dept of Pharmacology
Gonzalez, Radames, University of Puerto Rico, Dept of Microbiology
Harb, Diala, University of Montreal, Dept of Pharmaceutical Sciences
Israel, Davelene, University of Arizona, Dept of Pharmacology & Toxicology
Jackman, Katherine, University of Melbourne, Dept of Pharmacology
Jacobs, Michelle, Vanderbilt University, Dept of Pharmacology
James, Taryn, University of Missouri, Dept of Medical Physiology & Pharmacology
Joseph, Biny, University of Arkansas Medical Sciences, Dept of Interdisciplinary Toxicology
Kumar, Dinesh, University of Arkansas for Med Sci, Dept of Pharmacology & Toxicology
Labenski, Matt, University of Arizona College of Pharmacy, Dept of Pharmacology & Toxicology
Lawrence, Latondra, Texas Woman's University, Dept of Molecular Biology
Leung, Brenda, DePaul University
Liu, Tongsheng, Ohio State University College of Pharmacy, Dept of Pharmacology
Montgomery, Megan, University of Nebraska Medical Center, Dept of Pharmacology
Moore, Cavonda, Jackson State University, Dept of Biology
Morabito, Michael, Vanderbilt University, Dept of Biology
Najarro, Marcela, Howard University, Dept of Pharmacology
Oldham, William, Vanderbilt University School of Medicine, Dept of Pharmacology
Oliver, Colin, Roswell Park Cancer Institute
Operana, Theresa, University of California - San Diego, Dept of Pharmacological Chemistry



NEW MEMBERS

Parrish, Jason, Purdue University, Dept of Medicinal Chemistry & Molecular Pharmacology
Porter, Gavin, Emory University, Dept of Molecular & Systems Pharmacology
Rivera-Lopez, Carol, University of Virginia, Dept of Pharmacology
Rogge, George, Emory University, Yerkes National Primate Research Center
Roof, Rebecca, University of Michigan, Dept of Pharmacology
Sheng, Wanyun, University of Houston Coll of Pharmacy, Dept of Pharmacological & Pharmaceutical Sciences
Smith, Tarik, Emory University
Snyder, Ashley, University of Virginia, Dept of Biochemistry & Molecular Genetics
Tan, Hendrick, Hospital for Sick Children, Dept of Clinical Pharmacology & Toxicology
Tian, Liantian, NEOUCOM, Dept of Physiology & Pharmacology
Viotti, Manuel, Ramapo College, Dept of Biology
Voss, Bryan, Vanderbilt University School of Medicine, Dept of Pharmacology
Whorton, Matthew, University of Michigan, Dept of Pharmacology
Wu, Ke, Wuhan University Medical College, Dept of Internal Medicine
Xie, Ruiyu, University of Arizona HSC, Dept of Pharmacology & Toxicology
Zhu, Shu, Medical College of Georgia, Dept of Pharmacology & Toxicology

Undergraduate Student Members ◆

Akan, Ekak, University of Houston, Dept of Biology
Benson, Coby, James Madison University, Dept of Chemistry
Bryant, Joseph, Albany State University, Dept of Chemistry
Che, Juvet, Grambling State University, Dept of Biology & Chemistry
Clark, Andrew, University of Maryland, Dept of Biochemistry
Cone, Tiffany, University of Maryland, Dept of Biology
Gillelyen, Jason, Morehouse College, Dept of Biology
Hernandez, Victoria, San Jose State University, Dept of Psychology
Ibarra, Christian, San Francisco State University, Dept of Cell & Molecular Biology
Jackson, Susan, Indiana University, Dept of Biology
Mcfadden, Donnetta, University of Maryland, Dept of Biochemistry



Proceedings from the
**National Meeting of Directors of Graduate Studies in
Pharmacology**
July 21-23, 2005 at Vanderbilt University
now available on the ASPET web site under Meetings.

sponsored by Vanderbilt University, Meharry Medical College, Merck, PhRMA, and
ASPET





Daniel Martin Ziegler

1927-2005

Dr. Daniel Martin Ziegler, Professor of Biochemistry at the University of Texas at Austin, died unexpectedly on Nov. 9, 2005, of a cardiovascular event after recovery from a short hospital stay for renal problems. On Nov. 14, a funeral Mass was held at St. Louis Catholic Church in Austin, TX. Next year, numerous colleagues, students, and friends will celebrate his legacy to the field of biochemistry and drug metabolism with a Symposium in his honor at the American Society for Experimental Pharmacology and Therapeutics Annual Meeting in Washington, DC. Along with the scientific community, we wish to commemorate his life and his accomplishments.

Dan Ziegler was born on a farm in the small town of Quinter, KS, the tenth of thirteen children. He attended Benedictine College in Atchison, KS, where he received his B.S. in Chemistry in 1949. Afterward, he attended the Institute of St. Thomas in Cincinnati and obtained a Masters degree Biochemistry. In 1952, he entered the graduate program at Loyola University in Chicago, and, working under the supervision of Dr. Jacklyn Melchior, earned a Ph.D. in Biochemistry in 1955. His graduate studies included some of the first pioneering efforts on subcellular fractionation of liver, pituitary, and other organs, methods which he held to high standards and personally taught all of his students and postdoctoral fellows. An example of his rigor was the standardization of the biuret protein method with liver microsomes using Kjeldahl nitrogen determinations. He was also one of the first to obtain extremely pure preparations of respiring liver mitochondria, which soon led him to the Enzyme Institute at the University of Wisconsin, where he was initially a National Heart & Lung Institute postdoctoral trainee and was later appointed Assistant Professor (1958-1961) under the directorship of Professor David Green. Here, he was the first to purify several components of the mitochondrial electron transport chain, notably the succinate-cytochrome b complex, and to elucidate their function. He was recruited by Professor Lester Reed at the Clayton Foundation Biochemical Institute of the University of Texas at Austin in 1961 as an Assistant Professor of Biochemistry (in the Department of Chemistry) and began a long and distinguished career. He was quickly promoted to Associate Professor in 1962 and then to Full Professor in 1969. In 1990, he was named the Roger J. Williams Centennial Professor of Biochemistry and then became Professor Emeritus upon his retirement in 1997.

Dan Ziegler's scientific accomplishments were the hallmark of scientific excellence. He was recognized as an Established Investigator of the American Heart Association from 1960-1965 and held a U.S. Public Health Service Career Development Award from 1965-1975. In 1990, he was recognized for his research contributions to the field of drug-metabolizing enzymes by receiving the Bernard B. Brodie Award of the American Society of Pharmacology and Experimental Therapeutics. He received the Alexander von Humboldt Senior Research Award from the German government in 1991. In the same year, the Fifth International Symposium on the Biological Oxidation of Nitrogen in Organic Molecules was dedicated to Dan for his many contributions elucidating the metabolism of aliphatic and aromatic amine drugs and carcinogens. In 1996 on the eve of his retirement, a special Symposium preceding the International Society for the Study of Xenobiotics (ISSX) Meeting was held in honor of his life's work, the discovery and functional characterization of a multi-gene family of enzymes that came to be known as the Flavin-containing Monooxygenases, or FMOs. During the subsequent ISSX meeting, Dan was presented with ISSX's highest honor, an Honorary Life Membership, only the fifth the Society had conferred up to that time. In 2001, Dan Ziegler's alma mater, Benedictine College, conferred upon him an honorary Ph.D. in Chemistry.

Dan Ziegler published over 100 research articles and served as editor and on advisory boards for many journals, serving as an Associate Editor for the *Journal of Biological Chemistry*. As mentioned above, his life work was the FMOs. He began this research when he came to Austin with keen interest in the newly described class of enzymes called monooxygenases, or mixed-function oxidases (as the nomenclature was debated at the time). He used a simple metabolic reaction, the oxidative metabolism of the model compound, *N,N*-dimethylaniline, which formed both an *N*-oxide and an *N*-dealkylated product (formaldehyde and *N*-methylaniline). The latter were catalyzed by cytochrome P450, while the former was a non-P450 reaction. Extensive characterization and purification of this enzyme revealed it to be a FAD-containing monooxygenase that catalyzed the *N*-oxidation of a wide variety of drugs. However, many in the field of drug metabolism were skeptical and believed that this protein was simply some degraded form of the NADPH-P450 reductase. However, in a collaboration that would lead to lifelong friendship, Bettie Sue Masters and Dan Ziegler published a definitive paper in 1971 showing that the two proteins were immunochemically and biochemically distinct. Over the next two decades, he carried out many elegant studies expanding our knowledge on the broad substrate specificity (oxidation of inorganic as well as organic compounds bearing the elements nitrogen, sulfur, selenium, phosphorous or boron), wide tissue and species distribution (including human), and catalytic mechanism of this FMO (utilizing a 4 α -hydroperoxyflavin). He was so far ahead in this



OBITUARY

field that there were few other laboratories engaged in studies of FMO, and most investigators in the field of drug metabolism simply referred to it as “Ziegler’s Enzyme.” During this time, however, Dan developed a number of productive collaborations, trained numerous students and postdoctoral fellows, and showed his colleagues how generous, supportive, and effective he could be as a mentor. With the advent of modern molecular biology in 1990s, a number of laboratories became interested in the FMOs and showed them to be a multi-gene family, as predicted by studies of David Williams, Ziegler, and Masters in the mid-80s that showed that lung and liver FMOs were immunochemically and catalytically distinct. We now know that the FMOs exhibit genetic polymorphisms and are responsible for trimethylaminuria (as featured on the 1999 cover of *Science News*), variations in drug metabolism/toxicity, and perhaps cancer susceptibility.

Dan Ziegler is survived by his wife Mary Alice, whom he married in 1952, and by three sons, one daughter, and eight grandchildren. Although his scientific contributions were substantial, his greatest joy was his family, whom he taught by example, the essential elements of humility, respect, honesty, integrity, fidelity, and love. As a member of St. Louis Catholic Church, he was active in organizing the folk choir, served on the school board, and taught in the church religious education program. The death of Dan Ziegler was an untimely event for his spouse, his family, his students and postdoctoral fellows, and his colleagues and friends in the scientific community. He was a dedicated scientist who inspired us to strive for excellence by his thorough approach to research problems, by his strong determination toward their achievement, and by his constant encouragement and critical thinking. His profound impact on the field of drug metabolism and enzymology is not diminished by his death but is carried on in all of us who in some way have had the good fortune to have been impacted by his character and example.

Prepared by Fred F. Kadlubar, Ph.D. and Russell A. Prough, Ph.D

IN SYMPATHY

ASPET notes with sympathy the passing of the following members:

Kenneth C. Back

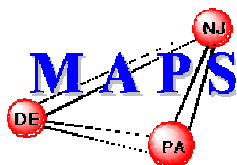
Arthur Furst

Aryeh Hurwitz

Alexander Kandel

Daniel Ziegler





Mid-Atlantic Pharmacology Society Annual Meeting Chemical Biology: New Targeted Approaches to Cancer Therapeutics October 28, 2005

The annual meeting of the Mid-Atlantic Pharmacology Society (MAPS) was held at the historic Wistar Institute in Philadelphia, PA on October 28, 2005. The program for the meeting centered on "**Chemical Biology: New Targeted Approaches to Cancer Therapeutics.**" The theme for this meeting was selected based on new developments in cancer biology and therapy and the growing research interests of the Wistar Institute in the area of chemical biology.

A panel of experts was invited to participate, and Dr. Frank J. Rauscher of Wistar organized an excellent program with a wide range of topics. The morning program started with our MAPS Distinguished Speaker lecture which was delivered by Dr.



Dr. Stuart Schreiber delivering the Keynote Address.

Stuart Schreiber of Harvard. Dr. Schreiber's lecture on "Rethinking the Process of Drug Discovery" was thought provoking because his lab has developed systematic ways to use small molecules (precursors to therapeutic drugs that are used as bioprobes) to explore cell circuitry and disease biology. In addition, he is well known for developing the emerging area of chemical biology. By using this chemical approach, he has discovered principles that underlie information transfer and storage in cells. Thus his lecture educated and prepared the audience for the range of topics covered in the program.

Dr. Scott Strobel (Professor, Yale) presented an excellent lecture titled "Catalysis of Peptide Bond Formation by the Ribosome." Subsequent speakers on the program included Dr. Nick Tonks (Professor, Cold Spring Harbor Labs), Dr. Prem Reddy (Director, Fels Institute for Cancer Research, Temple) and Dr. David Tuveson (Asst Professor, Cancer Biology, U. Pennsylvania). Dr. Tonks gave an interesting talk on "Redox Regulation of Protein Tyrosine Phosphatases and the Control of Signal Transduction." Dr. Reddy delivered a great talk on "Non-ATP Competitive Inhibitors of Kinases for Cancer Therapy" and updated the audience on his research and clinical use of a new targeted anticancer drug. Lastly, Dr. Tuveson's lecture, "Modeling and Manipulating Cancer," addressed the important role of murine models in cancer research and how to bridge this preclinical information to the clinical situation. Each speaker delivered a high quality presentation that was informative and thought-provoking.

The MAPS meeting was attended by approximately 100 scientists, post-doc and graduate students from academic and pharmaceutical institutions in the region. Building on our successful outreach to nearby colleges in 2004, MAPS invited undergraduate students and faculty to attend the 2005 meeting to learn more about the field of pharmacology. MAPS was very pleased to host biology and chemistry undergraduates from Ursinus College (Collegeville, PA), Seton Hall University (South Orange, NJ) and the University of the Sciences in Philadelphia (Philadelphia, PA) at the conference. By providing this opportunity to local colleges, MAPS hopes to raise awareness and provide information to science-oriented undergraduates that might help them choose a career in pharmacology. For the second year in a row, MAPS received very positive feedback from faculty and college students who attended the meeting, which is very encouraging for the future of pharmacology.

New scientific work was presented at the meeting in the form of 31 posters at the Wistar. Of these, 8 posters were presented by undergraduate students (6-Ursinus, 1-Seton Hall University, 1-USIP). All of the



Dr. Russel Kaufman of The Wistar Institute opened the MAPS 2005 meeting with a warm welcome and provided history on the Institute.



MAPS 2005 Poster Competition Award Winners
Bottom Row: Ms. Dana Francis, Ms. Deanah Mitchell, Ms. Caitlin White with Dr. Hugo M. Vargas.
Top Row: Dr. Natalia Riobo, Ms. Jennifer Werkheiser, Dr. Saadet Inan. Not shown: Dr. Karpagam Aravindhan



CHAPTER NEWS

posters were interesting and covered a wide range of topics and several awards were given to acknowledge superb work and oral presentation. MAPS held a poster competition and distributed awards to acknowledge excellent work. In the Post-doctoral category, awards were given to Drs. Natalia Riobo (1st Place, University of Pennsylvania, Dept of Pharmacology) and Karpagam Aravidhan (2nd place, GlaxoSmithKline). In the Graduate student & Research Associate category, awards were given to Jennifer Werkheiser (1st Place, Temple University, Dept of Pharmacology) and Deanah Mitchell (2nd Place, Temple University, Dept of Pharmacology). Undergraduate awards were also presented to Dana Francis (1st Place, Ursinus College, Biology Dept.) and Caitlin White (2nd Place, Seton Hall University, Dept of Biology).

For the fourth year, MAPS offered the ASPET Division of Systems and Integrated Pharmacology (DSIP) poster award to recognize outstanding work in systems and integrated pharmacology. Dr. Saadet Inan (Postdoctoral Fellow, Temple University School of Medicine, Dept of Pharmacology) received this award for her poster entitled "Agmatine-induced stereotyped scratching in mice is antagonized by nalfurafine, a kappa opiod agonist."



Dr. Robert Raffa presents the 2005 George B. Koelle Memorial Award to Dr. Robert Ruffolo (right), President of Wyeth Pharmaceuticals.

Dr. Robert R. Ruffolo (President, Wyeth Research) was the recipient of the 2005 **George B. Koelle Memorial Award**. Dr. Robert Raffa (Councillor, MAPS; Temple Pharmacy School) presented the award. Dr. Ruffolo is a well-recognized and respected leader in the pharmaceutical industry and was given this award to acknowledge his tremendous contributions to pharmacology and drug development. Dr. Ruffolo spoke modestly about his career and was a gracious recipient. Before closing his remarks, he took a moment to encourage the "next generation" of new scientists to feel good about entering the field of pharmacology, because "we" will be needed to drive drug discovery and development in the future.

The 2005 meeting was held for the first time at the Wistar Institute and MAPS sincerely

thanks Dr. Russel Kaufman (President, Wistar) for providing the resources to host the meeting. In addition, MAPS acknowledges the generous contributions of our sponsors that helped make this meeting a success: ASPET; Cephalon, Inc.; GlaxoSmithKline; Hoffman La-Roche; Johnson & Johnson, Inc.; Merck Research Laboratories and Wyeth Research.



The Presidents: Dr. Robert Ruffolo, President of Wyeth (center) with MAPS Presidents, Dr. Hugo Vargas (2003-2005, left) and Dr. Ronald Tallarida (2006-2008, right).



To commemorate a successful meeting, Dr. Stuart Schrieber (Harvard, center) posed with Dr. Frank Rauscher, Deputy Director of the Wistar Institute Cancer Center (meeting organizer, right) and Dr. Hugo Vargas of MAPS.



Students and Faculty at the MAPS 2005 Poster Session



Category: Undergraduate

✿ **IDENTIFICATION OF A MUTATION THAT SUPPRESSES PARALYSIS IN *UNC-13* MUTANTS IN *CAENORHABDITIS ELEGANS***

Dana Francis*, Graciela Gallo, Rebecca Eustance Kohn. Biology Department, Ursinus College, Collegeville, PA 19426

The release of neurotransmitters from neurons is a highly regulated process. In order for these chemicals to be released, several proteins associate together, forming the SNARE complex. One protein involved in this complex is syntaxin. Syntaxin is normally held in a closed conformation by the protein UNC-18; however, when synaptic vesicles come close to the plasma membrane, the protein UNC-13 will open syntaxin and allow for neurotransmitters to be released. When the UNC-13 protein is absent, neurotransmitters cannot be released to signal muscles to contract. In the nematode, *Caenorhabditis elegans*, the absence of this protein results in paralysis. A second genetic mutation can suppress paralysis resulting from *unc-13* mutations in *C. elegans*, resulting in the restoration of movement. Snip-SNP mapping indicates that this second mutation is found on chromosome III. The gene for syntaxin is on chromosome III and previous research has shown that a constitutively open form of syntaxin can bypass the need for the UNC-13 protein (Richmond, 2001). Sequence analysis, however, indicates that the mutation is not in syntaxin. We are continuing our snip-SNP mapping to narrow down the region on chromosome III where the suppressor gene is located.

MATERNAL AND PATERNAL CONTRIBUTIONS OF THE *SCU-1* GENE IN THE *C. ELEGANS* EMBRYO

Tom Group* and Rebecca Lyczak, Ursinus College, Collegeville, PA 19426

Caenorhabditis elegans is a nematode ideal for studying embryonic development. During embryonic development, the entrance of sperm cues important events such as, meiosis completion in the oocyte, eggshell formation, and establishment of the anterior-posterior (A-P) axis. Both the egg and sperm have essential proteins for embryonic development that when absent can cause embryonic lethality or developmental defects. The egg is most important for embryonic development because it holds most of the proteins; the sperm brings in only a few proteins making defects that are both maternal and paternal uncommon. The *scu-1* (sperm *cue* abnormal) gene is one of these uncommon genes. When mutated, *scu-1* embryos demonstrate embryonic lethality as well as the inability to properly establish an A-P axis and meiotic exit defects.

We are trying to determine if *scu-1* is maternal, paternal or both. Studies thus far, have shown both a maternal and paternal requirement for SCU-1 and that each alone is sufficient for development. Crosses of *scu-1* males and normal females have shown complete rescue. Crosses of normal males and *scu-1* females have shown some rescue with about half the worms hatching. DIC microscopy and time lapse photography was used to examine the resulting embryos for defects. Control crosses of normal worms have shown no lethality. Worms heterozygous for *scu-1* develop normally showing no zygotic requirement for *scu-1*.

Tentative conclusions show both a maternal and a paternal requirement for *scu-1* and a strong maternal effect, shown by the 50% mortality rate in crosses with mutant females. This is likely due to the mass of the embryo compared to that of the sperm and its carrying capacity for proteins. In the future, I would like to view dead embryos to see if they look the same as dead embryos laid by *scu-1* hermaphrodites. Through these studies, we can gain a better understanding of embryonic development in *C. elegans* which can be applied to other organisms.

SEX-BASED DIFFERENCES IN THE CONTRACTILE PROPERTIES OF FRESHLY ISOLATED MURINE CARDIAC MYOCYTES

Monica Crary* and Beth A. Bailey. Ursinus College, Collegeville, PA, 19426

Pre-menopausal women exhibit a significantly lower risk of heart disease than do age-matched men. While the role of estrogen in protection from atherosclerosis has been widely studied and accepted, only recently have scientists begun to investigate the direct effects of estrogen on cardiac function. In addition, recent studies suggest that estrogen may not be the only factor contributing to the "protection" seen in female hearts; because the female cardiovascular system must respond to the stresses of pregnancy, perhaps the female heart is better-equipped to deal with a variety of hemodynamic stresses. We hypothesized that basic contractile properties of cardiac muscle cells isolated from male and female hearts might differ, and that this difference would be accentuated in the presence of elevated pacing frequencies. Cardiac myocytes were isolated from hearts excised from male (MM) and female (FM) mice. After excision, the aorta was cannulated, and the heart was retrogradely perfused with a digestion buffer to allow isolation of individual



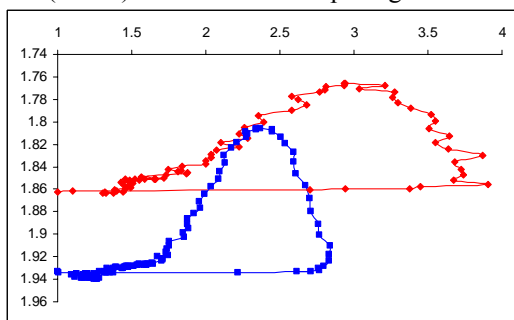
myocytes from the tissue. Freshly isolated myocytes were loaded with the calcium-sensitive fluorescent dye Fluo-3 and placed on a perfusion chamber located on the stage of an inverted fluorescent microscope. Myocytes were perfused with a HEPES buffered solution containing 1.5mM Ca^{2+} and pre-warmed to 37°C and field stimulated at varying frequencies from 0.5–4 Hz. Magnitude of sarcomere shortening, rates of shortening and relengthening, and calcium transients were recorded using data acquisition hardware and software from IonOptix. At all pacing frequencies, Peak Ca (indicated by Fluo-3 fluorescence) was greater in FM than MM, although these data did not reach statistical significance. At low pacing frequencies (0.5, 1 Hz), MM shortened to a significantly greater extent than did FM (10.9 ± 9 vs 7.2 ± 7 and 10.1 ± 9 vs 7.3 ± 8 %RSL, respectively). At higher pacing frequencies, as peak calcium decreases, the differences in sarcomere shortening are no longer apparent. These data demonstrate that MM shorten to a greater extent than FM, but that the intracellular calcium concentrations at the peak of contraction do not differ, thereby suggesting that MM and FM may differ in their myofilament responsiveness to intracellular [Ca].

ARE THERE DIFFERENCES IN INTRACELLULAR CALCIUM HANDLING BETWEEN MALE AND FEMALE MURINE CARDIAC MYOCYTES?

John Dillon* and Beth A. Bailey. Ursinus College, Collegeville, PA 19426

Hearts of males are significantly more prone to ischemia-reperfusion induced Ca^{2+} overload, myocardial dysfunction and myocyte death than their premenopausal female counterparts. Our hypothesis is that fundamental sex-based differences in myocyte Ca^{2+} regulation and/or myofilament Ca^{2+} binding affinity predispose male cardiocytes to Ca-mediated dysfunction. **Methods:** Myocytes were isolated from female (F) and male (M) Swiss Webster mice (9-12 weeks) using collagenase-based perfusion techniques. Sarcomere length (light diffraction) and Ca^{2+} transients (fluo-3) were measured at pacing rates of 0.5-3 Hz and at bath [Ca] of 1.5mM.

Results: Under control conditions (0.5Hz; length was not significantly different in M and F magnitude (% sarcomere length) was M ($10.9 \pm 0.9\%$, n=21) vs F ($7.2 \pm 0.7\%$, n=24) did not differ between M and F (2.17 vs 2.61, were obtained at pacing frequencies from 0.5Hz binding affinity which was determined from the the Ca^{2+} transient (f/f_{rest}) Sarcomere length (□) greater in M ($.087 \pm .04$) vs F ($.028 \pm .004$). See results suggest that myofilament Ca^{2+} binding myocytes and this predisposes them to during periods of high [Ca] stress.



1.5mM Ca^{2+} resting sarcomere (average $1.76 \square$). Contraction significantly greater ($p < .05$) in while Ca transient amplitudes respectively). Similar results to 3Hz. Myofilament Ca^{2+} slope of the terminal portion of relationship, was significantly example. **Conclusion:** These affinity is greater in M versus F hypercontractile damage

COMPARATIVE PHARMACOKINETIC STUDIES OF MEDIUM CHAIN ALKYL ALCOHOLS, ALKYL ALDEHYDES, AND CARBOXYLIC ACIDS

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Previous studies have shown that both alkyl aldehydes (hexanal [C6] – undecanal[C11]) and alkyl alcohols (hexanol – undecanol) are effective central nervous system anesthetics, but the aldehydes are typically 80% less potent than the alcohols. The anesthetic potency of the medium chain carboxylic acids (octanoic acid – decanoic acid) has not yet been examined. In living organisms, these alkyl alcohols are oxidized to the corresponding alkyl aldehydes and may be further oxidized to the carboxylic acid derivative. Aldehydes and carboxylic acids were studied to determine whether the anesthetic affect could be traced to the alcohol, aldehyde, or acid form. The goal of this study is to determine the time course of maximum uptake of all three compounds at varying concentrations and compare the values for both compounds. Weakly electric fish (*Eigenmannia virescens* – Transparent Knife Fish, and *Apteronotus albifrons* – Black Ghost) were used as model organisms to determine dose-response curves for these compounds. Once these curves were obtained, cubic spline analysis was utilized to determine the maximum point of uptake. The time for maximum uptake for the alkyl alcohols was typically during the first minute of drug exposure, corresponding to a first order coefficient of between -3-4. For the alkyl aldehydes, the time for maximum uptake is typically one to three minutes after initial exposure, with a first order coefficient in the range of -1-2. The carboxylic acids took the longest for maximum uptake, typically between minutes 3-5 (first order coefficient less than -1). This demonstrates that these compounds enter the fish’s vascular system at varying rates to produce the anesthetic affect. The flow chart for drug movement is as follows: Bathing Solution → Gill Epithelium → Gill Capillaries → Efferent Brachial Artery → Meninges (Blood-brain barrier) → Brain Stem Neuron. Given this pathway, it is surprising that the anesthetic affects the brain in less than one minute. Data from this study shows that carboxylic acids apparently possess the least anesthetic potency in this

metabolic pathway. The physiological data from this study may assist in the development of safe, fast-acting, and rapidly recoverable anesthetics.

TIME COURSE OF ANESTHETIC ACTION AND RECOVERY OF ALKYL ALCOHOLS AND ALKYL ALDEHYDES

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Alkyl alcohols (hexanol [C6] – undecanol [C11]) and alkyl aldehydes (hexanal – undecanal) at low concentrations (10^{-4} M) are effective central nervous system anesthetics. These compounds produce an anesthetic neuronal depression within one minute following initial exposure and produce 10-40% depression at twenty minutes. Furthermore, recovery from anesthesia is essentially 90% complete in twenty minutes. The goal of this investigation is to determine whether prolonged exposure beyond twenty minutes produces additional depression and whether recovery time is affected. Weakly electric fish (*Eigenmannia virescens* – Transparent Knife Fish) were used as a model organism with thirty minute exposure and recovery times, instead of the typical twenty minute time courses. Results indicate that at lower concentrations of alkyl alcohols ($<5 \times 10^{-5}$ M), minimal additional depression of the electric organ discharge (EOD) occurs. However, at greater concentrations ($\geq 1 \times 10^{-4}$ M), fatalities may occur after twenty-five minutes of exposure. Prolonged recovery produced a minimal increment (1-2%) in overall recovery. Cubic spline analysis for 1×10^{-4} M decanal on the same species of fish yielded first order coefficients of .66 and .36 for the fifth and twentieth minute of recovery, respectively. Comparable values were observed for the first twenty minutes of a thirty minute exposure (.70 and .36). Moreover, the thirtieth minute of data has a spline value of .22, indicating a plateauing effect. Similar experiments were conducted using another species of weakly electric fish (*Apteronotus albifrons* – Black Ghost). The findings of these experiments were consistent with the original findings, except that the sensitivity to these compounds was decreased, which is typical of the species. *A. albifrons* was also exposed to alkyl aldehydes, which again produced similar results and supported previous data of decreased potency of alkyl aldehydes when compared to alkyl alcohols. Results from this study indicate that prolonged time course exposure does not significantly decrease EOD frequency. Additionally, recovery EOD frequency is also not significantly increased. Therefore, twenty minute time course is optimal for exposure and recovery time course. This research also supports previous data that the recovery process is diffusion driven and not enzymatic.

✿ A FLUORESCENCE-BASED SECOND MESSENGER ASSAY TO IDENTIFY SMALL MOLECULE ANTAGONISTS OF SOMATOSTATIN^Φ

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The brain/gut peptide somatostatin (SRIF) is an inhibitory hormone that controls hormone secretion and cell proliferation. All five SRIF receptor subtypes inhibit the production of the second messenger, 3,5' cyclic adenosine monophosphate (cAMP) in a variety of mammalian cells. Synthetic small molecule SRIF mimetics exist for all five plasma membrane receptor subtypes, but small molecule inhibitors of SRIF action remain elusive. We utilized cAMP accumulation as a cell-based assay for SRIF ligands in AtT-20 cells, a murine corticotroph cell line that expresses SRIF receptors. Intracellular cAMP levels were quantified using a *Bridge-It cAMP Designer Fluorescence Assay* (Mediomics, LLC, St Louis, MO), which replaced more conventional radioimmunoassay methods. Four synthetic biphenyl compounds were selected, based on structural similarity to known SRIF synthetic agonists, and tested for the ability to affect SRIF-induced reductions in cellular cAMP. None of the tested compounds inhibited SRIF activity, however one compound class showed a possible positive modulatory effect. This project established a novel fluorescence-based cAMP assay as a functional assay for examining small molecule ligands of SRIF action.

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TOXIC EFFECTS OF TWO NEUROPROTECTIVE COMPOUNDS ON AN MDCK CELL LINE

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Alzheimer's disease (AD) is the most common form of dementia, a group of conditions that gradually destroy brain cells and lead to progressive decline in mental function. In this study, two compounds which can be used in the treatment of AD, TLR-I-04 and memantine, were evaluated for toxic effects on MDCK cells at various concentrations. These cells are being used to mimic the blood brain barrier in order to determine the amount of drug that can be administered without significant side effects on these and other cells.

Individual wells of a 96 well plate were seeded with cell concentrations of 10,000 in 100 μ l of DMEM/F12 media supplemented with 10% fetal bovine serum and Penicillin/ Streptomycin, 100U/10 μ g per mL and incubated for 24 h at 37 °C / 5% CO₂. Cell were exposed to final concentrations of 0–500 μ M of each agent in triplicates for 30 min at 37 °C / 5% CO₂. The reaction was stopped by washing off chemicals with buffer and toxicity determined using AlamarBlue assay. Readings were measured at 0 hour and 3 hour time periods. Results show that TLR-I-04 and memantine have acceptable toxicity profiles on MDCK cells. Compared to \leq 5% DMSO controls, percent viability for TLR-I-04 treated cells increased, suggesting that TLR-I-04's effects were not masked by levels of DMSO employed in the study. Based on the results from this and similar studies, TLR-I-04 shows promise as a good anti-AD lead compound.

Category: Graduate Student/Research Associate

BEHAVIORAL EFFECTS OF COCAINE ARE ENHANCED BY STROMAL CELL DERIVED FACTOR 1 (SDF-1) IN RATS

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Stromal-cell derived factor 1 (SDF-1) is a chemokine that has been shown to play an important role in various biological processes including neuronal development, inflammation, and tumor pathogenesis. SDF-1 functions through a single receptor, CXCR4, which belongs to the family of seven trans-membrane G-protein coupled receptors. SDF-1 is detectable in both endothelial cells and neurons throughout the brain, including the amygdala, hippocampus, caudate, putamen, and medulla. Cocaine, a widely abused psychostimulant, binds to transport proteins and prevents the reuptake of dopamine, serotonin, and norepinephrine into presynaptic neurons. Exposure to cocaine in naïve animals results in an increase in ambulatory activity across a variety of doses. The present study determined the effect of SDF-1 on cocaine-induced locomotor activity. Twenty-nine male Sprague-Dawley rats underwent surgery to implant a cannula within the right cerebral ventricle and were allowed to recuperate for 4 days. After habituating in the locomotion chambers for 30 minutes, each group was given an injection of SDF-1 (100 ng/dose) or saline ICV, followed 15 minutes later by an IP injection of cocaine (15 mg/kg) or saline. The animals were monitored electronically for 60 minutes to evaluate ambulatory activity. Photocell break values were: sal/sal 283 (\pm 122), sal/coc 1646 (\pm 657), SDF-1/sal 566 (\pm 160), SDF-1/coc 2327 (\pm 695) respectively. Animals treated concomitantly with SDF-1 and cocaine showed a significant potentiation in activity as compared to those treated with cocaine (two-way ANOVA, $p < .0001$) or SDF-1 (two-way ANOVA, $p < .05$) alone. This study demonstrates a possible functional interaction between SDF-1 and cocaine allowing for future experimentation between chemokines and drugs of abuse. (This work was supported in part by T32 DA07237 and P30 DA13429.)

BASAL AND STIMULATED ENOS ACTIVITY IN HUMAN EA.HY926 CELLS

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The endothelium lining blood vessels plays a vital role in maintaining vascular tone through release of vasoactive compounds. One of these compounds is nitric oxide (NO), constitutively produced via the endothelial isoform of nitric oxide synthase (eNOS). Endothelial cells also contain varying amounts of an inducible form of NOS, the so-called iNOS. To explore the use of the EA.hy926 cells, a human endothelial cell hybridoma, in the study of factors that may modulate nitric oxide (NO) release, we have measured both basal and stimulated nitric oxide release into cell culture media under a variety of conditions. The advantage of using these cells to monitor modulation of NO output is their retention of many of the qualities of human endothelial cells *in vitro* coupled with immortality and ease in culture. Nitric oxide production was assayed using the classical Griess reaction, a measure of accumulated nitrite and nitrate degradation products of NO. EA.hy cell-derived NO is both cell number dependent and time dependent. The low level of NO production by these cells is inhibitable by N^w , Methyl-L-arginine Acetate salt (L-NMMA). Cellular NO production is stimulated by endothelial cell stimulators including bradykinin (1-10 μ M) and PMA (20-200 ng/ml). Future experiments to establish the potential of this cell model for the study of endothelial function and NO production are underway.

DESIGN AND SYNTHESIS OF NOVEL FLUORINATED PHENCYCLIDINE ANALOGS

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Selective non-competitive antagonists at the phencyclidine (PCP) binding sites of the N-methyl-D-aspartate (NMDA) receptor have potential as neuroprotective agents. During states of ischemia, over-excitation of neurons induces both necrosis and apoptosis in part because of influx of Ca²⁺. The designed agents are expected to bind inside of, and block the cation channel associated with NMDA receptors, preventing neuro-degeneration even in the presence of excitants. The purpose of this study was to synthesize several

designed compounds and evaluate their activities. Each of the target compounds was synthesized in four steps, and the net yields varied from 5 to 41%. Each compound was characterized by obtaining ^1H , ^{13}C , and ^{19}F -NMR spectra as well as MS, all of which were consistent with proposed structure. Binding studies on these compounds are pending. Anticonvulsant abilities of the compounds were evaluated by maximal electroshock test in mice. All the compounds exhibited neuroprotection at 100 mg/kg dose but showed signs of toxicity at 300 mg/kg. Acknowledgement: NIH Grant # 7R15NS36393-04.

CHARACTERIZATION OF SEROTONIN (5-HT)_{1A} AND 5-HT_{1B} RECEPTOR STIMULATION OF [^{35}S]GTP γ S INCORPORATION IN RABBIT BRAIN.

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The ability of 5-HT_{1A} and 5-HT_{1B} receptors to modulate second messenger production depends upon the efficacy of coupling to the Gi/o class of G-proteins which may change upon drug or physiological treatments. The present study characterized 5-HT_{1A} and 5-HT_{1B} receptor stimulation of [^{35}S]GTP incorporation into the G-proteins of Dutch Belted rabbit hippocampus and caudate membranes. In the hippocampus, the full agonist at 5-HT_{1A} receptors, (R)-(+)-OH-DPAT (DPAT) increased GTP γ S incorporation to a maximum of 90% of basal at 1-3 μM and an EC₅₀ of approximately 100 nM. The selective 5-HT_{1A} receptor antagonist, WAY100,635 eliminated this action, indicating that DPAT stimulates only the 5-HT_{1A} receptor. GR46,611, an agonist at 5-HT_{1A/1B/1D} receptors stimulated hippocampal G-protein coupling to a similar extent as DPAT and with an EC₅₀ of approximately 100 nM. However, analysis indicated that this stimulation occurs by an interaction with 2 sites. Consistent with this suggestion, WAY100,635 only partly inhibited the action elicited by GR46,611. The selective 5-HT_{1B} receptor antagonist, SB216,641 blocked the remaining, high-affinity, component of stimulation by GR46,611. Thus, we conclude that in the hippocampus, GR46,611 activates both the 5-HT_{1A} and 5-HT_{1B} receptors. In the caudate both DPAT and GR46,611 stimulated coupling to a similar extent (max. inc. 30-35%), but the EC₅₀ were 100 fold different (EC₅₀ DPAT = 1 μM ; EC₅₀ GR46611 = 10 nM). WAY100,635 failed to inhibit the stimulation produced by either DPAT or GR46,661. However, SB216,641 blocked the stimulation produced by both agonists, indication that rabbit caudate lacks 5-HT_{1A} receptors and the stimulation is due to activation of 5-HT_{1B} receptors. Future studies will use this information to monitor physiological or drug induced changes in 5-HT_{1A} and 5-HT_{1B} receptor function. Supported by NIDDK058669 to KJS.

IRREVERSIBLE ANTAGONISM OF μ -OPIOID RECEPTORS (MOR) IN THE LATERAL PARABRACHIAL NUCLEUS (LPBN) PREVENTS MOR-AGONIST STIMULATED CONSUMPTION OF A PALATABLE FOOD AND PERSISTENTLY DECREASES CHOW INTAKE.

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The LPBN contains endogenous opioids and opioid receptors and is involved in opioid-mediated feeding. Acute stimulation of MORs in the LPBN enhances consumption of standard chow, while acute antagonism of MORs attenuates this intake. The effects of chronic, irreversible antagonism of MORs in the LPBN on consumption of standard or palatable foods have not been elucidated. The irreversible MOR antagonist, β -funaltrexamine (β -FNA; 8.0nmol/0.5 were measured during a 4-h test for 5 days. Water and standard chow intakes (20h) were recorded. β -FNA persistently decreased consumption of standard chow by 34% compared to baseline for 5 days postinfusion; control intakes were unaffected. β -FNA did not affect intakes of either PAL or μl ; (N=7) or saline (0.5 μl ; N=6), were infused bilaterally in the LPBN of rats on Day 0 and intakes of a palatable (PAL) diet and water water compared to controls. To test whether β -FNA infusion on Day 0 prevents MOR-agonist stimulated feeding of PAL, the MOR agonist, DAMGO (2.0nmol/0.5 μl) was infused bilaterally into the LPBN on Days 6-7. DAMGO increased 4-h PAL intakes in controls by 79% compared to baseline. DAMGO did not affect PAL consumption in β -FNA-treated rats. The rats were sacrificed on Day 8 to quantify long-term regional loss of MOR G-protein coupling using [^{35}S] GTP γ S autoradiography. β -FNA decreased DAMGO-stimulated MOR coupling in the LPBN and was selective for MORs compared to κ -opioid receptors. These studies suggest that prevention of MOR G-protein coupling in the LPBN regulates consumption of a standard but not a palatable food. Supported by NIDDK067648 to KJS.

ALTERATIONS IN MOUSE CENTRAL NERVOUS SYSTEM GENE EXPRESSION INDUCED BY CHRONIC NICOTINE EXPOSURE

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Nicotine is the primary psychoactive/addictive component found in tobacco products, and it exerts many of its behavioral and physiological effects through alterations in brain circuitry. Region-specific changes in gene expression may underlie many of these alterations. We have used microarray technology to monitor nicotine-induced changes in gene expression in the mouse prefrontal cortex, nucleus accumbens, and ventral tegmental area. Nicotine (200 µg/mL (-)-nicotine free base in 2% saccharin) was administered *ad libitum* to male C57BL/6J mice for 35 days followed by total RNA isolation and RNA amplification from the aforementioned brain regions of treated and control mice. Probes were prepared and hybridized to oligonucleotide-based microarrays containing 13,443 unique gene sequences. Array slides were background-corrected and normalized within- and between-slides and gene expression levels from treated and control samples were determined using a linear model in the Limma analysis program. Genes were ranked by order of *B*-statistic (log odds that a gene is differentially expressed) and *p*-value (based on a modified *t* value and corrected for multiplicity) to determine significant changes in gene expression. A small number of genes (<1%) in each region were shown to be up- or down-regulated in a statistically significant manner, with the changes in the 0.58-1.8-fold range. The genes affected by the treatment were involved in many functional categories including cytoskeleton, regulation of gene expression, metabolic enzymes, and ubiquitin-associated processes. As expected, there were no observable changes in RNA levels for the various neuronal nicotinic acetylcholine receptor subunits, which although up-regulated by nicotine treatment, do so via post-translational mechanisms. Differentially expressed genes were verified by quantitative RT-PCR. Consistent with the microarray results, syntaxin binding protein 1 was shown to be down-regulated in response to nicotine. Future studies will involve examining time course changes in gene expression during exposure and recovery from chronic nicotine exposure. Supported by Pennsylvania Tobacco Formula Funds.

***KAPPA OPIOID ANTAGONISM OF ICILIN-INDUCED WET-DOG SHAKING AND GLUTAMATE STIMULATION IN THE DORSAL STRIATUM OF RATS IS REVERSED BY INFUSION OF NORBINALTORPHIMINE.**

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Icilin, the peripheral cold channel agonist, activates two transient receptor potential channels (TRPM8 and TRPA1) in dorsal root ganglia and trigeminal neurons of rats. Icilin was first investigated as a quasi-withdrawal inducing agent. Such agents can be structurally dissimilar from opioids but precipitate a range of overt behaviors reminiscent of opioid withdrawal. We have shown previously that icilin elicits robust wet-dog shakes in rats, that are antagonized by centrally acting mu (morphine and buprenorphine) and kappa (nalfurafine and U50,488H) opioid agonists, but not by ICI 204448, the peripherally directed kappa agonist. To investigate the mechanism of this icilin-evoked behavior, we studied glutamatergic changes within the dorsal striatum, a region implicated in habitual and stereotypic movement. Icilin (0.25, 0.5, 0.75 mg/kg, i.p.) produced a dose- and time-related increase in glutamate in the striatum that correlated with the incidence of shaking. It is known that kappa receptors are found presynaptically on axons in the striatum and, upon activation, modulate glutamate release. Pretreatment with nalfurafine (0.04 mg/kg, s.c.) blocked icilin (0.5 mg/kg, i.p.)-evoked glutamate increase in the striatum. To substantiate this, we infused norbinaltorphimine (100 nM), the kappa antagonist, into the striatum and effectively reversed nalfurafine (0.04 mg/kg)-mediated inhibition of icilin (0.5 mg/kg)-evoked behavior and glutamate stimulation. We show, for the first time, a neurochemical effect of icilin on the CNS of rats downstream of activation of TRPA1 and TRPM8 channels within the periphery, while providing a possible mechanism for kappa-mediated inhibition of icilin-induced wet-dog shaking. (T32DA07237).

THE JOHNS HOPKINS CLINICAL COMPOUND SCREENING INITIATIVE

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PURPOSE: In an effort to rapidly discover clinically useful angiogenesis and malaria inhibitors we created and screened a library of 2,600 existing drugs for inhibition of endothelial cell and *P. falciparum* proliferation. Because the clinical profiles of existing drugs are established, novel hits can rapidly be moved into the clinic.

RESULTS: The immunosuppressive drug mycophenolic acid (MPA) inhibits endothelial cell proliferation with an IC₅₀ of 100 ± 5.2 nM and causes G1/S phase cell cycle arrest. Inhibition and cell cycle arrest are overcome by addition of guanosine, suggesting the *de novo* nucleotide synthesis pathway, and more specifically, inosine monophosphate dehydrogenase (IMPDH), as the target of MPA in endothelial cells. MPA caused a significant decrease in VEGF/bFGF- and tumor-associated angiogenesis in two mouse models. The

non-sedating, orally administered anti-histamine astemizole inhibits proliferation of chloroquine sensitive and resistant *P. falciparum* (IC_{50} = 386 ± 10 nM and 332 ± 15 nM, respectively). During intraerythrocytic infection, *P. falciparum* parasites crystallize toxic heme released during hemoglobin catabolism, a process which is inhibited by chloroquine. Astemizole inhibits heme crystallization (IC_{50} = 8.69 ± 0.03 μ M) and concentrates in the food vacuole where this reaction occurs. In mice infected with *P. yoelii* astemizole at 100 mg/kg/day cured infection.

CONCLUSIONS: Previously, the IMPDH mediated *de novo* nucleotide synthesis pathway was thought to be specific to immune cells, however the predominant involvement of IMPDH-1 in endothelial cell cycle regulation presents an attractive target for specific inhibition of angiogenesis. Astemizole is a novel orally bioavailable pharmacophore for the development of potent inhibitors of heme crystallization that block growth of the malaria parasite *in vitro* and in animal models.

THE EFFECTS OF VIOXX IN THE STROKE PRONE-SPONTANEOUSLY HYPERTENSIVE (SHR-SP) RAT MODEL OF HYPERSENSITIVITY AND END-ORGAN DAMAGE.

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Introduction: Vioxx is a COX-2 selective, nonsteroidal anti-inflammatory drug (NSAID). Serious and potentially life-threatening side effects have been reported in patients taking Vioxx which include an increased risk in cardiovascular events. Therefore, the aim of this study was to determine if Vioxx, placed in a pre-clinical rat model of hypersensitivity and end-organ damage, exacerbated CV risk. **Methods:** 300 and 1000ppm Vioxx (30 and 100 mg/kg/day) was blended in a 24.5% fat rodent diet (N=12/dose). Drinking water consisted of a 1% salt solution. Additionally, 14 control rats were placed on compound-free 24.5% meal and 1% salt drinking water (high salt/fat diet or SFD) diet. N=12 rats remained on a normal rodent diet and tap water (Normal Diet or ND) and also acted as a control group. A Subgroup (N=6) of each group was implanted with telemetry devices for chronic hemodynamic evaluation. Morbidity was followed throughout the course of the study and 24 hour urine collections were collected bimonthly for eight weeks. Electrolyte, protein and microalbumin excretions were assessed across all treatment groups and compared to controls.

Results: There were minimal changes in electrolyte, protein and microalbumin excretion in animals fed a normal diet, with 100% survival in this group. Within the SFD and treatment groups, sodium and chloride had a greater than 10-fold increase from baseline at week two, which continued to remain elevated until the end of the study. The SFD and treatment groups showed a significant ($p<0.001$) increase in protein and microalbumin excretion, from the ND control with a $p<0.05$ significant increase of the treatment groups from the SFD control. There was no difference between the two treatments. Mean blood pressure, within the SFD and treatment groups, increased significantly ($p<0.05$) from the ND control on day 20 and by day 24 the blood pressure, from each treatment increased significantly ($p<0.05$) from the SFD control. This increase in mean blood pressure continued until the end of the study. In the SFD group 50% survived, 75% morbidity in the 300ppm Vioxx group, and 50% morbidity in 1000ppm Vioxx group at eight weeks. **Conclusion:** These data suggest that Vioxx exacerbates several risk factors associated with cardiovascular disease.

EFFECT OF AN IKs CHANNEL ANTAGONIST ON THE QTc INTERVAL IN ANESTHETIZED DOGS WITH VARYING DEGREES OF SYMPATHETIC TONE.

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Cardiac repolarization is mediated by fast (IKr) and slow (IKs) potassium rectifying currents and the role of each current may be influenced by sympathetic tone. For example, cardiac electrophysiologic studies *in vitro* show IKs has a greater role in repolarization when sympathetic tone is augmented (Han et al., *Am. J. Physiol* 280: H1075, 2001). In these studies, we examined the role of IKs in cardiac repolarization in pentobarbital-anesthetized dogs, a screening model for QTc prolongation, with normal autonomic tone and in dogs that were vagotomized (augmented sympathetic tone) or treated with a β -adrenoceptor antagonist (augmented parasympathetic tone). The IKs selective antagonist compound X (CX) was used in all studies to block of this current and increase the QTc interval. In anesthetized dogs with intact autonomic nerve function, CX (1, 3 & 10 mg/kg IV; 30 min infusion) produced dose-related QTc interval prolongation ($6 \pm 1\%$, $10 \pm 3\%$ & $12 \pm 2\%$, respectively) which indicates IKs blockade prolongs cardiac repolarization in this model. In vagotomized dogs (heightened sympathetic tone), the sensitivity to 1-10 mg/kg CX-induced QTc prolongation was unaltered and comparable to the intact group. In animals with cardioselective β -blockade (esmolol), QTc prolongation induced by 1 mg/kg CX was blunted, but the QTc prolongation observed at 3 and 10 mg/kg doses was not. In a follow up study, the delayed cardiac repolarization caused by 1 mg/kg/hr CX ($11 \pm 3\%$) was significantly blocked by esmolol infusion ($4 \pm 1\%$). These studies indicate that IKs has a tonic role in cardiac repolarization in both vagus-intact or vagotomized pentobarbital-anesthetized dogs and is sensitive to cardiac β -blockade. These findings clearly demonstrate that cardiac IKs current is modulated by sympathetic tone *in vivo*.

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KCNQ1/KCNE1 AS A PHARMACOLOGICAL MODEL OF CARDIAC IKs: DISCRIMINATION OF BLOCKING POTENCIES OF A DIASTEREOMERIC BENZODIAZEPINE ON RECOMBINANT VS. NATIVE CURRENTS.

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KCNQ1/KCNE1 transfected HEK cells were investigated as a recombinant model of the delayed rectifier potassium current IKs. Pharmacological inhibition of IKs, which plays an important role in the repolarization of cardiac myocytes, can prolong the QT interval and lead to potential proarrhythmic effects. To compare the pharmacological sensitivity of the recombinant versus native IKs currents from isolated guinea pig myocytes, we determined IC₅₀ values for all 4 diastereomers of a potent benzodiazepine. All currents were measured using the whole-cell variant of the patch clamp technique. HEK cells were held at a resting potential of -50mV and then depolarized to +50mV for 5 sec at 30-sec interpulse intervals, during control and in the presence of increasing concentrations of each diastereomer. Peak tail current amplitudes, expressed as fraction of control, were plotted as function of drug concentration and IC₅₀ values (Table) were determined by fitting the plots with a Hill equation. The potencies of each compound for inhibition of the KCNQ1/KCNE1 recombinant vs. the native current correlated well. Thus, KCNQ1/KCNE1 coexpressed in HEK cells serves as a highly predictive pharmacological model of cardiac IKs.

Inhibition of Native and Recombinant IKs by Benzodiazepine Diastereomers

COMPOUND #*	Stereochemistry*	Native IKs IC ₅₀ (nM)	KCNQ1/KCNE1 IC ₅₀ (nM)
39	(+) R	50	133
40	(-) R	0.08	0.1
41	(+) S	18	23
42	(-) S	0.4	0.7

* Salata, J.J., Selnick, H.G., and Lynch, J.J. (2004) *Current Med. Chem.* 11: 29-44.

✿ ISOFORM-SPECIFIC PROTEIN INTERACTION OF THE HUMAN PROSTAGLANDIN EP3 RECEPTOR

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Prostaglandin E2 is a metabolite of arachidonic acid which demonstrates a broad range of biological actions in various tissues through its binding to specific receptors on plasma membranes. PGE₂ exerts its actions through binding to four different G protein coupled receptors, EP1, EP2, EP3 and EP4, which differ in their signal transduction pathways. The EP3 receptor couples to inhibition of adenylyl cyclase (G_i) and exists as 8 isoforms that differ in carboxyl tail (C-tail) region. The isoforms show distinct properties including different levels of constitutive activity and agonist-induced internalization. The EP3 isoforms may serve different functions and contribute to the diversity of the actions of PGE₂. We hypothesized that the differences in the c-tails of the EP3 receptor isoforms point to differences among the isoforms in terms of binding partners, localization, trafficking and signaling. GEC1, an estrogen regulated protein, has been identified as a protein that binds to a particular motif in certain GPCRs that is found in isoform EP3.f, but in none of the other isoforms. Immunoprecipitation of the EP3.f c-tail with GEC1 protein showed interactions between the proteins. Deletion mutagenesis and site-directed mutagenesis were used to identify the GEC1 binding site on the c-tail of the receptor as the amino acid sequence FPAMS. Immunofluorescence microscopy was done to determine if GEC1 blocks internalization of the EP3.f receptor when agonist PGE₂ was present. We showed that when the GEC1 protein is present along with the EP3.f receptor, agonist-induced internalization is blocked. We hypothesize that GEC1 may be involved in trafficking the receptor throughout the cell.

SOMATOSTATIN REGULATES INTRACELLULAR SIGNALING IN RHEUMATOID ARTHRITIS SYNOVIOCYTES[§]

Frances Mae West*, Kari A. Belin and Allan D. Blake, Dept of Biology, Seton Hall University, South Orange, NJ 07079

Somatostatin (somatotropin release inhibitory factor, SRIF) is widely expressed in the body, where it controls cell proliferation and secretion via a family of highly homologous G protein-coupled receptors (GPCRs). SRIF analogs have demonstrated clinical utility in a range of endocrine, neuroendocrine and inflammatory disorders. We have investigated the role of SRIF in modulating the inflammatory response of the human synovioocyte, a critical cell in rheumatoid arthritis (RA). We utilized SRIF receptor-specific oligonucleotide primers to perform reverse transcriptase-polymerase chain reaction (RT-PCR) on synovial mRNA, thus identifying a molecular target for synovial SRIF action. Immunoblotting experiments with phospho-specific antiserum showed that SRIF controlled the ERK1/2 extracellular regulated kinases in rheumatoid synovioocytes. In addition, SRIF suppresses a sodium vanadate sensitive protein tyrosine phosphatase activity as measured with the fluorescent substrate, 6,8 difluor-4-methylumbelliferyll



phosphate (DiF MUP; Invitrogen, Carlsbad, CA). Taken together our results demonstrate that SRIF regulates intracellular signaling in rheumatoid synoviocytes.

[§]Supported by a Provost Challenge Grant from Seton Hall University

THE LOW MOLECULAR WEIGHT TPOR AGONIST, SB-497115, DOES NOT PRIME PLATELETS FOR ACTIVATION OR AGONIST-INDUCED AGGREGATION *IN VITRO*

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Objective: The thrombopoietin receptor (TpoR) is a therapeutic target for thrombocytopenia, as stimulation of this receptor results in enhanced megakaryocyte proliferation, differentiation, and ultimately platelet production. In addition to effects on megakaryocytes, thrombopoietin (TPO) directly stimulates platelet function. The objective of the present study was to examine the platelet activating potential of the small molecule TpoR agonist SB-497115 (currently in Phase II clinical trials).

Results: In signal transduction studies of washed human platelets, TPO activated Stats-1,3,5 and Akt. In comparison, SB-497115 partially activated Stats-3 and 5, with no/minimal activation of Stat-1 or Akt. In platelet aggregation studies, TPO acted in synergy with subthreshold/submaximal concentrations of ADP or collagen to induce maximal aggregation under all conditions examined. In contrast, SB-497115 induced weak and inconsistent activation of washed platelets; however, no synergy was observed when examined in PRP. Similar to aggregation results, platelet activation as examined via surface expression of CD62P was significantly enhanced by TPO as compared to SB-497115.

Conclusions: The present study demonstrates that the TpoR agonist SB-497115 has a limited capacity to induce human platelet activation, suggesting that potential platelet activation liabilities associated with TpoR agonists could be significantly attenuated via a small molecule approach, particularly in comparison to recombinant versions of TPO.

Category: Postdoctoral

✳️ CONSTITUTIVE COUPLING OF SMOOTHENED TO HETEROTRIMERIC GI PROTEINS.

Natalia A. Riobo*, Berangere Saucy, Cherisse DiLizio, and David R. Manning. Department of Pharmacology, University of Pennsylvania, Philadelphia, PA 19104

Smoothed (SMO) is a 7TM protein that transduces Hedgehog signaling in development, stem cell maintenance, and tumor formation. SMO constitutive activity is repressed by Patched, and binding of Hedgehog to Patched relieves that inhibition. Ultimately, Gli transcription factors are accumulated in the nucleus and turn on target genes. Despite SMO similarity to GPCRs, it is believed to signal independently of heterotrimeric G proteins. However, pertussis toxin (PTX) treatment of zebrafish embryos was reported to phenocopy some defects of SMO deficiency, suggesting that SMO could activate Gi proteins as a means to transduce Hedgehog signaling. In this study, we generated a baculovirus encoding mouse SMO for the controlled expression of SMO and different Gα subunits and Gβ1γ2 in Sf9 cells. This system provides a low background for 7TM receptors and Patched. Coupling, defined as GDP-GTP exchange, was assessed after extraction of Gα with non ionic detergents, immunoprecipitation of Gα-^[35S]GTP-γ-S, and scintillation spectroscopy. SMO increased ^[35S]GTP-γ-S binding of Gi1, Gi2, Gi3, Go and Gz (all members of the Gi family) by 2-8 fold, while it did not stimulate Gs, Gq or G12/13. Coupling was suppressed by the SMO inhibitor cyclopamine. Indeed, cyclopamine and two other inhibitors of SMO (SANT-1 and KAAD-cyclopamine) displayed a full inverse agonist capacity with rank order potency SANT-1 > cyclopamine ≥ KAAD-cyclopamine. Tomatidine, an inactive cyclopamine derivative, did not affect ^[35S]GTP-γ-S binding. In NIH 3T3 cells, PTX blocks activation of a Gli-luciferase reporter induced by Shh and SmoM2 (a Patched-insensitive oncogenic mutant). Moreover, Gli-luciferase induced by a dominant negative PKA is not affected by PTX, suggesting that SMO coupling to Gi proteins is required to decrease cAMP and PKA activity. In summary, we show that SMO is coupled to Gi proteins to induce Gli-dependent transcription and that SMO inhibitors are actual inverse agonists.

✳️ COMPARTMENTAL MODELING OF THE EFFECTS OF AN LXR AGONIST ON CHOLESTEROL HANDLING IN HAMSTERS

Karpagam Aravindhan^{1*}, Alan R. Olzinski², Michael C. Jaye², Robert N. Willette² and Beat M. Jucker². ¹Department of Applied Physics, College of Arts and Science, Drexel University, Philadelphia, PA 19104; ²Investigative and Cardiac Biology, Cardiovascular and Urogenital Center of Excellence in Drug Discovery, GlaxoSmithKline, King of Prussia, PA 19406

Multi-compartmental modeling was used to assess the effects of a potent, synthetic LXR (Liver X Receptor) agonist on cholesterol handling in the hamster following a bolus administration of 3,4-¹³C cholesterol. The effects of LXR agonist, GW683965A, on the

cholesterol exchanges were examined using a two, three or six compartmental model. The effect of a cholesterol synthesis inhibitor, Atorvastatin alone or in combination with an LXR agonist was also assessed. Therefore, four groups of animals were studied: Vehicle, GW683965A (10 mg/kg), Atorvastatin (10 mg/kg), and GW683965A+Atorvastatin (10 mg/kg) all dosed for 3 days (PO, sid). Significant changes in both plasma VLDL composition and LXR targeted tissue gene expression (ABCA1, ABCG1, ABCG5, ABCG8, SREBP-1c, FAS and CYP7a) were observed in the GW683965A and Atorvastatin treatment groups. The flux estimates from the two compartment minimal model describing free cholesterol in plasma and tissue pools was embedded into a three compartment model describing free cholesterol in plasma, hepatic tissue and extra-hepatic tissue pools and a six compartment model describing both unesterified and esterified cholesterol in plasma, hepatic tissue and extra-hepatic tissue pools. The six compartmental analysis of 3,4-¹³C cholesterol tracer in hamsters resulted in an increase, albeit non-significant, in free cholesterol efflux from the liver (60%) following treatment with the LXR agonist, a decrease in the free cholesterol efflux from the liver (30%) following treatment with Atorvastatin and an increase in the free cholesterol efflux from the liver (17%) following treatment with GW683965A+Atorvastatin. In summary, a comprehensive cholesterol exchange model to estimate the cholesterol flux through different tissue compartments was established and fluxes were shown to be modulated with both a LXR agonist and Atorvastatin.

✿ AGMATINE-INDUCED STEREOTYPED SCRATCHING IN MICE IS ANTAGONIZED BY NALFURAFINE, A KAPPA OPIOID AGONIST

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Agmatine, which is formed by decarboxylation of arginine, antagonizes NMDA receptor-dependent behaviors and inhibits nitric oxide synthase. Here, we describe a hitherto unreported behavioral effect of agmatine (excessive scratching in mice) and its attenuation by nalfurafine, a kappa opioid agonist. Male Swiss Webster mice (25-30 g, n=8) were acclimated in individual observation boxes for 2 hr, pretreated s.c. at -20 min with saline, then injected s.c. into the back of the neck with agmatine sulfate (Sigma, 2.5-160 mg/kg). Hindleg scratching movements directed at the neck were counted for 30 min. Agmatine-induced scratching started as soon as +1 min, predominated within +10 min, and was dose-dependent with an A50 value of 29 (15-44) mg/kg. Pretreatment of additional mice with nalfurafine (Adolor Corp., 0.02 mg/kg, s.c.) displaced the agmatine dose-response curve to the right and downwards to give an A50 value of 40 (21-75) mg/kg and maximal responding (with 80 mg/kg of agmatine) of 118 scratches rather than 250 scratches in 30 min. We conclude that (a) agmatine is an endogenous pruritic agent in mice and (b) based on this and previous work with other scratch-inducing compounds (GNTI, compound 48/80, chloroquine) nalfurafine may be regarded as a “universal” antipruritic in this species. (T32DA07237).

SHAPE SIGNATURES A NEW COMPUTATIONAL TECHNOLOGY FOR TARGETED APPROACHES TO CURRENT, NEW, AND FUTURE THERAPEUTICS: AN APPLICATION BASED PERSPECTIVE INCORPORATING CHEMISTRY, COMPUTATIONAL BIOLOGY, AND PHARMACOLOGY

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Lipinski's Rule of Five has proved an insightful observation in the race to identify new ligands for treatment of disease. The first approaches to apply the theory and obtain new leads was to synthesise vast numbers of compounds that conformed to these rules. With the advent of combinatorial chemistry, Lipinski's Rule did help to identify new leads and produced compounds of use to medicinal science. The method has not considerably increased the probability (0.001-0.0025%) to find suitable lead molecules among a library of candidate compounds. *In silico* screening methods incorporating rational drug design combined with known biological data have helped in this respect (e.g. antivirals Zanamivir, Amprenavir and Nelfinavir). The rapid expansion of ligand (natural product and medicinal) databases, structural databases, coupled with the burgeoning data from structural genomics and proteomics poses a huge problem. It is a pressing issue for current *in silico* methods to screen the available data faster. This large resource of key data cannot be ignored purely because it takes so long to screen and analyse. Our Shape Signature method screens compounds (at a rate of 1.4×10^9 per day per processor) and enriches databases for suitable leads by applying shape (or shape combined with electrostatic) descriptors quickly and accurately. Profiles of each molecule are generated (using a method akin to ray tracing), these databases can be rapidly screened time and time again. Shape Signatures is applied from a ligand or receptor-based perspective and build up an in-house database that can be multiply or singly screened as the need arises. Shape Signatures can be used by itself or in conjunction with current *in silico* techniques and applied to antibody, catalyst and purification technologies. A recent rational drug design success, Imatinib (Gleevec), that attenuates the c-Abl protein kinase oncogene responsible for chronic myelogenous



leukaemia, was used as query molecule. Shape Signatures identified analogues of Imatinib and created an enriched database for further laboratory analysis.

RECEPTOR MECHANISM INVOLVED IN ANTI-CONVULSANT EFFECT OF MELATONIN IN PTZ-INDUCED CONVULSIONS

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The major secretory product of the pineal gland is melatonin. The three subtypes of melatonin receptors are ML1, ML2 (neuronal distribution, found in mammals) and ML3 (birds). Melatonin has been proposed to be an endogenous anticonvulsant. Its precursor 5HT plays an important role in neuronal hyperpolarization, depolarization and excitation. GABA is a major inhibitory neurotransmitter in the CNS. The receptor(s) involved in the anticonvulsant effect of melatonin were studied on pentylenetetrazol (PTZ)-induced clonic-tonic convulsions in mice with the use of antagonists against ML1 (luzindole), ML2 (prazosin), 5HT2 (mianserin), 5HT3 (ondansetron) and GABA-A (bicuculline). We also studied effect of melatonin on PTZ-induced kindling (a model of epileptogenesis). The length of time was noted till subconvulsive dose of PTZ induced full clonic-tonic convulsions. Statistical analysis was done using one way ANOVA and Tukeys test at 5% level of significance. Results: Melatonin was seen to produce a dose-dependent decrease in duration of clonic-tonic convulsions. Enhancement of melatonin's anticonvulsant activity was seen with mianserin, ondansetron and luzindole. Reversal was seen with prazosin and bicuculline, implicating involvement of ML2 and GABA receptors in anticonvulsant effect of melatonin. Melatonin administration also delayed the development of kindled seizures (epileptogenesis).

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Category: Other (not in competition)

PRODRUG DELIVERY OF NOVEL PTP1B INHIBITORS TO ENHANCE INSULIN SIGNALING

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Continued increases in the occurrence of obesity, type 2 diabetes and the metabolic syndrome drive the need for pharmacologic therapies with improved efficacy and reduced side effects. One promising approach targets the tyrosine phosphatase, PTP1b, a negative regulator of signaling by two hormones crucial to long term energy storage: insulin and leptin. However, identification of potent, orally active, small molecule inhibitors of PTP1b has been elusive due to the principal challenge of designing a drug-like inhibitor to a very polar tyrosine phosphatase active site. Beginning with novel, reversible, competitive tyrosine mimetics, we have designed some of the most potent PTP1b inhibitors reported. However, the acidic nature of these compounds limits their intrinsic permeability and pharmacokinetics. Ester prodrugs of these inhibitors improve their drug-like properties with the goal of delivering nM inhibitors to the cytoplasm of cells within target tissues such as liver, muscle, and fat. The results show that we are able to design prodrugs to deliver active drugs into cells *in vitro* to inhibit PTP1b. Furthermore, these compounds can be further modified to gain a variety of cleavage properties. Different prodrug candidates were then tested *in vivo* for their ability to improve insulin sensitivity in *ob/ob* mice. Following four days of intra-peritoneal dosing, one compound lowered fasting blood glucose levels in the context of lowered fasting insulin levels. The considerable challenges to designing orally active compounds will be discussed along with a summary of the data for a panel of prodrug candidates.

NOVEL ANTIPROLIFERATIVE AGENTS SELECTIVE FOR P21 DEFICIENT CELLS- PYRAZOLO[1,5-A]PYRIMIDIN-7-YL PHENYL AMIDES

Dennis Powell*¹, Ariamala Gopalsamy¹, Yanong D. Wang¹, Hwei-Ru Tsou¹, Nan Zhang¹, Erick Honores¹, Steve Johnson¹, Biqi Wu¹, Carl Beyer², Carolyn M. Discafani², Miriam Miranda², John P. McGinnis², Sridhar K. Rabindran², Wendy Cheng¹, Girija Krishnamurthy¹, John W. Ellingboe¹. ¹Wyeth Chemical and Screening Sciences and ²Oncology, Pearl River, NY, 10977

A novel series of pyrazolo[1,5,a]pyrimidin-7-yl phenyl amides was discovered in a unique high throughput cell-based screen. In this screen, an isogenic pair of colon carcinoma cell lines (HCT116, p21waf1/cip1+/+ and p21waf1/cip1-/-)¹, ² was used to identify compounds that preferentially induce apoptosis in the p21-checkpoint deficient cells, compared to the p21-proficient cells. As a downstream effector of p53, p21 inhibits the cyclin-dependent kinases (CDKs) and arrests cell cycle progression in response to DNA damage and other environmental stresses. Disruption of this checkpoint results in the failure of the cell to arrest, leading to endoreduplication, and ultimately, apoptosis. The p21-deficient cells show increased chemosensitivity compared with the p21-

proficient cells, to a variety of clinically used antineoplastic drugs, validating the role of checkpoints in determining chemosensitivity. Compounds active in this assay are expected to target tumor cells that lack one or more checkpoints, a hallmark of cancer. Exploration of the SAR of the pyrazolopyrimidinyl phenyl amide series in the p21 paired cell lines will be described, as well as the potent inhibition of a panel of colon tumor cell lines by selected compounds.

DESIGN AND SYNTHESIS OF SUBSTITUTED 8-ARYLAMINO-2,3-DIHYDRO-1H-4-OXA-1,5-DIAZA-ANTHRACENE-7-CARBONITRILES AS ORALLY ACTIVE INHIBITORS OF THE EGFR TYROSINE KINASE

Hwei-Ru Tsou*, Elsebe G. Overbeek-Klumpers, William A. Hallett, Ramaswamy Nilakantan, Carolyn Discafani, Eric Upeslaci, and Sridhar Rabindran. Chemical and Screening Sciences and Oncology Research, Wyeth Research, Pearl River, NY 10965

Hyperactivation of the epidermal growth factor receptor (EGFR) family of receptors, leading to uncontrolled cell proliferation, is seen in a variety of cancers. Modulating the tyrosine phosphorylation event in this signaling pathway by small molecules, therefore, is an attractive strategy for inhibiting tumor growth. Earlier, we discovered a series of orally active, irreversible inhibitors of the EGFR kinase. Covalent binding was proposed to occur between the Michael acceptor-containing amide side chain of the compounds with the cysteine-773 residue located within the catalytic cleft of the enzyme. One of these compounds, EKB-569, a 4-anilinoquinoline-3-carbonitrile, achieved Phase II clinical trials.

We report here the design of a novel tricyclic series, 8-arylamino-2,3-dihydro-1H-4-oxa-1,5-diaza-anthracene-7-carbonitriles, where the 7-ethoxy group and the adjacent amide nitrogen of EKB-569 are tied together to form a ring. In contrast with EKB-569, the amide side chain containing the Michael acceptor function in these compounds is oriented at a fixed angle toward the cysteine-773 residue of EGFR. This configuration may facilitate the covalent interaction of the compound with EGFR, and is supported by molecular modeling studies. The synthesis of this new chemical series, the molecular modeling, and structure-activity relationships will be discussed, as well as the *in vivo* oral activity.

VALIDATION OF AN ATOMIC ABSORPTION RUBIDIUM EFFLUX ASSAY FOR KCNQ2/3 CHANNELS (M-CURRENT) USING THE ION CHANNEL READER (ICR) 8000.

E. Tseng*, D. M. Kowal, B. McIlvain, R. Shen, J. Q. Shan, S. Nawoschik, F. Jow, H. Zhang, Q. Lu, K. W. Wang and J. Dunlop. Discovery Neuroscience, Wyeth Research, CN 8000, Princeton, NJ 08543

KCNQ2/3 K⁺ channels have emerged as novel drug targets for a number of neurological disorders. The lack of direct high throughput assays combined with the low throughput of conventional electrophysiology (EP) has impeded a rapid screening and evaluation of K⁺ channel modulators. Development of a sensitive and efficient assay for the direct measurement of M-current activity is a critical step for the development of novel KCNQ2/3 channel modulators and subsequent investigation of their therapeutic potential. Using a stable CHO cell line expressing rat KCNQ2/3 channels, we have developed and validated a non-radioactive rubidium (Rb⁺) efflux assay which directly measures the activity of functional channels by atomic absorption spectroscopy. The Rb⁺ efflux assay was performed in a 96-well plate format using the automated Ion Channel Reader (ICR) 8000. KCNQ2/3 CHO cells were loaded with RbCl prior to challenge with an optimized K⁺ depolarization solution to stimulate maximal efflux of Rb⁺ through the channels. The stimulated Rb⁺ efflux was potentiated by the anticonvulsant retigabine (KCNQ channel opener), and was inhibited by the channel blockers XE991 and linopirdine. In-house compounds identified as KCNQ openers were further tested in this assay and their EC₅₀ values were compared with those obtained with EP. A positive correlation coefficient was achieved (r=0.60) between the two assays whereas no correlation was observed between FlexStation membrane potential and EP assays (r=0.11). In addition, four negative control compounds were found to possess no effect in both Rb⁺ efflux and EP assays. These results validate the atomic absorption Rb⁺ efflux assay for KCNQ2/3 channel activity.



IUPHAR Receptor Database Re-launch!

The International Union of Basic and Clinical Pharmacology (IUPHAR) has published authoritative compendia, review articles and online resources for biomedical researchers with an interest in receptor function for over 12 years. Already an established resource tool among scientists, the IUPHAR Receptor Database continues to evolve into a major global knowledge base for students, health-workers, scientists and drug discoverers. An updated version of this extensive receptor database is being launched in December 2005.

IUPHAR is a voluntary, non-profit association of national organisations that represents the interests of pharmacologists around the world. IUPHAR aims to foster international collaborations among pharmacologists, and provide updates on the nomenclature and pharmacology of receptors and ion channels via its publications, including a newsletter, scientific compendia and an online receptor database.

The IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) began work on the IUPHAR Receptor Database (IUPHARRD) in 2001 and released the database online in 2002. Formed in 1987, NC-IUPHAR is comprised of 17 international experts with established reputations in receptor and ion channel research. Subcommittees have been formed as a result of an expansion of activities; so far, there are over 50 subcommittees specialising in receptor and ion channel nomenclature.

A freely accessible resource, IUPHAR-RD is currently widely used among scientists and drug discoverers alike, and there are plans for additional growth. To date, IUPHAR RD offers detailed information on 150 G protein-coupled receptors (GPCRs) based on research data gathered from over 300 international experts. The goal is to provide information on all GPCRs, voltage- and ligand-gated ion channels and nuclear hormone receptors, on drugs that act on them, on specific targets in the body where they are found, and on diseases in which they may be involved.

Key Benefits

The IUPHAR Receptor Database offers:

- A catalogue of IUPHAR-approved nomenclature, known ligands and gene names for GPCRs (excluding sensory receptors and pseudogenes), with links to sequence and descriptive information in the Entrez Gene database.
- Detailed molecular, genomic and pharmacological properties of GPCRs and related proteins; including information on:
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 - Affinity values from radioligand-binding assays;
 - Signal transduction mechanisms;
 - Physiological functions and tissue distribution;
 - Functionally important splice variants and polymorphisms;
 - Phenotypes caused by mutations in man and in animals;
- An option to search the database via receptor names, gene symbols and receptor families.
- A freely available internet format, suitable for browsing on unsophisticated web browsers without a fast internet connection.
- A continuously evolving resource with frequent updates.

Resources

NC-IUPHAR meets every six months, under the funding of IUPHAR, to discuss a particular theme (e.g. ion channel classification, receptor databases) and to review the progress of each of the subcommittees.

IUPHAR-RD is now hosted by the University of Edinburgh, and is maintained and updated by two Research Associates. Funding for IUPHAR-RD has been provided in part by the International Council for Science (ICSU), through generous financial support from UNESCO; additional funding is provided by corporate sponsors.

To access the updated version of IUPHAR RD, go to:

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ASNS, ASPET)

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

🏆 ASPET's Centennial 🏆
Experimental Biology '08
San Diego, CA
Saturday-Wednesday
April 3-9, 2008